National Neonatology Forum, India

Evidence Based Clinical Practice Guidelines

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Foreword

There has been a long standing demand and felt need of NNF members for having management protocols suitable for Indian situations. It has also been felt that the existing publications are at the most only partially applicable to the available facilities in a large number of units in India. Present publication is an important step towards the solution of that problem. Clinical Practice Guidelines (CPG) answer various questions related to management in a large majority of clinical situations in neonatal practice. It also describes the available evidence for the recommended management approach. However, gaps in the evidence especially applicable to Indian situations have been brought out. We hope that these gaps will be filled through new researches in the near future.

Based on the facilities available in a particular neonatal unit, a locally applicable management protocol can be easily drawn from these CPG. We may keep it in mind that in the light of new research findings, availability of evidence continues to be a dynamic process. Hence, with the passage of time, CPG will keep on getting updated. Similarly, protocols too will get updated in the light of new CPG as well as improvement in the patient care facilities in a particular unit.

Dr. Praveen Kumar along with his committed editorial team and enthusiastic contributors need to be complimented in bringing out this stimulating and useful document which is bound to improve the neonatal care in the country. NNF secretariat under the able leadership of Dr Neelam Kler has done an admirable job in facilitating this important project.

Feedback from the users of these CPG will go a long way in the future modification and improvement of the document, so that we continue to progress.

O N Bhakoo
Ex-Professor and Head
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Message from NNF President & Secretary

There has been felt need to have Neonatal practice Guidelines which are evidence based relevant to our Country acceptable to our local needs and developed by a large group with wider representation. We hope NNF-practice guidelines will fulfill this gap.

Systematically developed statements to assist both practitioner and patient decisions in specific circumstances have become an increasingly familiar part of clinical care. Clinical Guidelines are viewed as useful tools for making care more consistent and efficient and for closing the gap between what clinicians do and what scientific evidence supports. In developed countries use of clinical guidelines is widely prevalent and part of international effort to provide quality care and improve outcomes by healthcare systems. There is ongoing interest in the developing countries for decreasing variations in health care system because some of these variations stem from inappropriate care. Identifying and appraising research evidence relevant to clinical practice is the process for developing clinical practice guidelines. There is evidence that this improves both the process and the outcomes of health care delivery making it more cost effective.

Over the last decade, the methods of developing guidelines have steadily improved, moving from solely consensus methods to methods that take explicit account of relevant evidence. The methods of developing NNF clinical practice guidelines are summarized by Dr Praveen Kumar Chair of Publication committee who has done excellent work on selecting the topics of clinical interest, selecting group of efficient ready to work experienced group of neonatologists from all over the country. NNF Clinical practice guidelines are devised to support pediatricians/Neonatologists working across the Country. These guide lines are developed following rigorous process to generate best evidence based on available research. While developing these guide lines an extensive survey has been conducted to find out prevalent practices. The important task remaining is to disseminate them widely and making sure they are being implemented.

We sincerely thank Dr Praveen Kumar chairperson Publication committee and his very dedicated group. Without their endless hard work this dream could not have become reality. We thank all the young members of writing group and senior experienced experts who helped with concepts, editing and reviewing. Our sincere thanks to Prof.ON Bhakoo Patron Advisor who was the sprit behind this work. Without his guidance and encouragement we could not have done this huge task. We hope and wish to God that these Clinical practice guidelines will help in improving health of large number of new born babies in our country. Our sincere gratitude to UNICEF for whole heartedly supporting this endeavor.

Neelam Kler
President
Sushma Nangia
Secretary
National Neonatology Forum

Preface

It has been a long standing demand of NNF members to have Clinical Practice guidelines for managing common situations. The task at hand was mammoth and the current output is a culmination of massive teamwork involving 66 authors,56 reviewers and their hard work of more than a year. A teamwork of this scale has not been achieved earlier in the history of NNF. The team comprised of most senior neonatologists of the country, the middle level neonatologists and the young brigade of dynamic DM neonatologists. In addition, expertise of specialists from allied disciplines was utilized for the review and writing process-including neonatal nurses, obstetricians, microbiologist, ophthalmologists, otorhinolaryngologist, radiologist , pediatric neurologists, geneticists and experts from pulmonary, transfusion and community medicines.

The process started more than a year ago with the formation of writing groups for twenty one topics. The groups were given guidance for raising questions, reviewing the evidence and putting up uniform drafts. The writing groups collected, reviewed and discussed the evidence and came out with draft write-ups. Each draft was peer reviewed anonymously by two experts. Subsequently a two day workshop was held on November 17-18,2009 at New Delhi where each draft was presented to the whole group and thrashed in depth. The groups went back and submitted revised documents after incorporating the suggestions. Thus each guideline has had the inputs from multiple experts.

The process of writing an evidence based guideline was a new learning experience for all the contributors. With repeated revisions, they have been able to come out with a high quality material. The process has also brought out the numerous gaps in evidence, especially as applicable to Indian situations. This helped generate many research ideas and questions which have been brought out as a special issue of the Journal of Neonatology. Creating guidelines is the first step. The next important task is to dissemination and for this, the guidelines are being supplied to all NNF members and stakeholders. They are also being made available on the website www.nnfpublication.org. In addition, it is expected that the writing groups will continue to be active and periodically update their write-ups as new evidence becomes available.

A task of this magnitude would not have been possible without the support of numerous well wishers. Amongst them, UNICEF stands out as the most sturdy and reliable pillar which facilitated and encouraged this activity. We welcome feedback from all to help us make improvements in subsequent updates of the guidelines.

Praveen Kumar
Chairperson, NNF Publication Committee
October 2010

Disclaimers

Due care has been taken to verify the accuracy of all the information in these Clinical Practice Guidelines. However, the contributors, editors or National Neonatology Forum are not responsible for errors or omissions or for any consequences from the application of information provided in this book and give no guarantee with respect to the completeness or accuracy of the contents. Application of the information in a situation different from that described in guidelines remains the professional responsibility of the concerned physicians. The guidelines do not endorse any particular brand of equipment or drug. The contributors, editors and NNF have no affiliation to any of the companies.

The contributors and editors have made great effort to ensure that all information is according to currently accepted recommendations. However, given the rapidity with which such information changes, the reader is urged to check the latest updates. This printed version is valid as of the date of publication i.e. October,2010. Updates as and when they occur, shall be posted on the website of the publication committee www.nnfpublication.org and published in the issues of the official journal of NNF, the Journal of Neonatology.

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How to use the guidelines

India is a vast country with huge diversity of healthcare set-ups, which are largely unregulated. Regionalization of care is virtually non-functional in our country and transporting a sick infant is arduous task. As a result, many of us have to often provide highest possible level of care in sub-optimal circumstances.

The guidelines are a broad umbrella of suggestions based on the currently existing best evidence adapted to most common local ground realities. However, it cannot be expected to meet individual and unit-specific requirements for each and every place. Individuals and units are advised to develop unit or situation specific protocols based on these guidelines.

Each guideline carries a Summary of Recommendations at the beginning which gives a gist of all recommendations pertaining to that topic. This is followed by a list of issues or questions which the guideline addresses. For each question, the evidence has been summarized and recommendations offered, often with grading of evidence. A comprehensive list of references has been provided at the end. Some of the guidelines also provide clinical algorithms for management and carry Annexures giving additional useful information helpful in day to day practice. For some guidelines, where more and lengthy information was available, it has been loaded on the website www.nnfpublication.org for interested readers.

Before applying the information given in the guideline, the readers should check for any updates on the website www.nnfpublication.org , where all updated guidelines shall be available for download and in the Journal of Neonatology. The updated versions would supersede the current publication.

Methods adopted by the groups for formulating the guidelines

Common methods were adopted by all groups and hence their details have been excluded from individual guidelines.

To address the questions of clinical interest , a search of medical literature using specific search terms was made using PubMed, Medline, Cochrane trial register, Google Scholar and 'Ovid'. Abstracts of the retrieved studies were inspected and selected studies were perused in detail and relevant data extracted. This search was conducted independently by the three authors in each group and the references were subsequently pooled to widen the reference base. In addition, relevant cross references were looked at in detail. Abstracts of conference proceedings of National and International meetings (NNF, IAP,PAS, ESPR) and recommendations of various professional bodies were also reviewed. A hand search of MD & DM dissertations and non-indexed journals like Journal of Neonatology was performed. Literature was assessed for appropriateness of study design, limitations in employed study design, inconsistency across different studies, and applicability to Indian neonates. Evidence provided by individual studies was classified as per standard recommendations. Based on evidence guidelines are provided for practice and research issues. GRADE recommendations were used to summarize evidence on therapeutic questions.

Following scheme of levels of evidence and grading of recommendations was used :

Level of evidence	**Type of study**
1a	Systematic review of randomized controlled trials
1b	Individual randomized controlled trial (with narrow confidence interval)
1c	All cases affected before intervention, some or none affected after intervention
2a	Systematic review of cohort studies
2b	Individual cohort study (including low-quality randomized controlled trial)
2c	'Outcomes' research
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles

Grades of recommendation	
Grade of recommendation	**Levels of studies**
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Care of the Normal Newborn

Summary of Recommendations

- **Care of a normal newborn at birth includes the components of essential newborn care such as prevention of asphyxia, prevention of hypothermia, early rooming-in and initiation of breast feeding.**
- **Each infant must have an identity band containing name of the mother, hospital registration number, gender and birth weight of the infant.**
- **All newborns should be weighed within first hour of birth and receive intramuscular vitamin K.**
- **First examination of a newborn should attempt to exclude transitional disturbances apart from identification of malformations.**
- **The health provider responsible for care at birth must communicate with the mother and family regarding time, weight at birth, gender and well being of the infant. The infant should be shown to the family with particular attention given to the fact that family members get to know the gender of the infant.**
- **Management in the first few days of life primarily focuses on cord care, eye care, exclusive breast feeding, evaluation of jaundice, vaccination and asepsis.**
- **Ideally, newborns should be discharged after 72-96 h when breast feeding has been established, mother is confident and baby has been observed for illness and jaundice.**
- **In case of early discharge, which is common because of overcrowded labor rooms, the newborn should be thoroughly examined and a discharge weight and visual (or transcutaneous) estimate of jaundice recorded. A follow up visit after 48 to 72 hrs should be arranged.**
- **Parents should be taught to recognize the danger signs and seek health care accordingly.**

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Introduction

A neonate experiences rapid change of physiology at birth and during initial few days of life. This is the period when many infants would fall sick and may even die.[1] Care at birth, first few days of life and during the remaining neonatal period is therefore very important and can lay a good foundation for a healthy childhood. This guideline is intended to provide evidence-based practice guidelines for care of a normal neonate at birth and beyond in health facility settings. A normal neonate for the purpose of this guideline has been defined as:

- Birth weight greater than or equal to 2500 g
- Gestation greater than or equal to 37 wk
- Birth weight between 10^{th} to 90^{th} percentiles on a standard intrauterine growth chart
- No need for assisted ventilation or beyond for resuscitation at birth
- Apgar score greater than or equal to 7 at 1 minute
- No postnatal illness such as respiratory distress, sepsis, hypoglycemia or polycythemia or requiring admission in neonatal unit

In this guideline an attempt has been made to address the following issues:

- What preparations must be done for care of the newly born?
- What are issues of concern in the first few hours of birth in normal newborn?
- What are issues of concern during initial few days of life ?
- When should normal newborn be discharged from hospital?
- What are signs and symptoms which predict mortality and suggest need for early referral ?
- Is there a role of vitamin supplementation for healthy newborns?

What preparations should be done for the care of the newly born?

Preparedness: The health facilities providing birthing services must have a proper newborn corner for care at birth in delivery room (DR) and maternity operation theater (MOT). The newborn corner must be located in the DR and MOT itself. There should be provision of a functional radiant warmer, basic resuscitation equipment of various sizes (bag & mask, laryngoscope, electrical or central suction device), oxygen, and autoclaved linen and ample supply of single use suction catheters, feeding tubes, endotracheal tubes, syringes, needles etc and drugs such as adrenaline, normal saline, & naloxone. Health professional caring for the baby should introduce herself or himself. The family should be counseled before the birth of baby. The family should be instructed to be ready with warm clothes and sheets to wrap the baby after birth.

Skilled birth attendance [2, 3]: At least one health professional (physician or nurse) trained in neonatal resuscitation must be physically available at time of birth of all infant irrespective of risk status (high or low) or mode of delivery (vaginal or cesarean). It is emphasized that this person must actually be present in delivery room before the birth of the baby. It is not good enough to have someone on call. The health professional must review the history of the mother and make adequate preparation. She or he should mobilize additional manpower if there is meconium stained liquor or difficult resuscitation is anticipated.

It is important to call out the time of birth loudly – this helps in accurate recording of the time and alerts other personnel in case any help is needed.

*Universal precautions***:** Health providers must exercise universal precaution in all cases while caring for infants at birth as per their hospital policy.[4] This should include wearing proper gowns, gloves, cap and face mask.

Asepsis at birth: It is important to prevent infection at birth by observing five cleans[5]- (1) clean hands after appropriate hand-hygiene and wearing sterile gloves (2) clean surface- use clean and sterile towel to dry and cover the baby (3) cut the umbilical cord by a clean and sterile blade/scissor (4) use a clean tie for the cord (5) do not apply anything to the cord.

*Prevention and management of hypothermia***:** Hypothermia at birth is common and has a detrimental effect on the health of the infant. Hypothermia should be prevented by paying special attention to temperature maintenance in the baby. The delivery room should be warm (at least 25^0C) and free from draft of air. The infant should be received in a *pre-warmed* sterile linen sheet. The infant should be dried thoroughly including the head and face areas.[6] The wet linen should not be allowed to remain in contact with the infant. The infant should be placed in skin-to-skin (STS) contact with the mother immediately after birth.[7] In addition to maintaining normal temperature of the infant, STS promotes early breastfeeding and decreases the pain and bleeding in the mother. The infant should be made to wear the caps and socks.

*Timing of umbilical cord clamping***:** Umbilical cord must be clamped after birth once cord pulsations have ceased. A meta-analysis of 15 controlled trials (1912 neonates) comparing early versus delayed cord clamping in neonates showed that delayed cord clamping was beneficial at 2 to 6 months of age in the form of improved hematologic status (hematocrit; weighted mean difference [WMD], 3.70%; 95% confidence interval [CI], 2.00%-5.40%), iron status as measured by ferritin concentration(WMD, 17.89; 95% CI, 16.58-19.21) and stored iron (WMD, 19.90; 95% CI, 7.67-32.13); and a clinically important reduction in the risk of anemia (relative risk (RR), 0.53; 95% CI, 0.40-0.70) [8]. Neonates with late clamping were at increased risk of experiencing asymptomatic polycythemia (7 studies [403 neonates]: RR, 3.82; 95% CI, 1.11-13.21; 2 high quality studies only [281 infants]: RR, 3.91; 95% CI, 1.00-15.36). However, the Expert Group felt that more evidence is required in this regard in view of high SGA (Small for gestational age) rates in India and delayed cord clamping may result in high rates of polycythemia in these infants.

*Method of clamping of the umbilical cord***:** Umbilical cord should be clamped either with the help of a commercially available clamp or a clean, autoclaved thread or a sterile rubber band. The rubber band could be a better option than a thread, as once cord starts shriveling; the rubber band would still maintain its grip while the thread might loosen up.[9] The length of cord left should 2-3 cm proximal and 2-3 cm distal to clamp/tie. Inspect the cord every 15-30 minutes for initial few hours after birth for early detection of any oozing from the cord.[10]

Assignment of Apgar score: Apgar score should be recorded at 1 and 5 minutes.[11] Extended Apgar scores at 10, 15 and 20 minutes should be recorded if initial scores are below 7.[12] Apgar score has a limited value for initial stabilization and prediction of subsequent outcomes.[13] However it does predict mortality on short term and help defining the need for nursery admission.

What are issues of concern in the first few hours of birth in normal newborn?

*Cleaning of the baby***:** All infants should be cleaned at birth with a clean, sterile cloth to remove blood clots and/or meconium present on the body. One should not attempt to remove vernix from the body by any means, as it can result in trauma to skin and increase chance of infections [14].

*Baby Identification marking***:** Each infant must have an identity band containing name of the mother, hospital registration number, gender and birth weight of the infant. [15] State of Maharashtra has adopted the system of biometric identification for the neonates. One should take into consideration the local requirement, directive from their State, if any and the costing to make a choice. If footprints of baby are being taken, the quality of print should be good and care should be taken to maintain cleanliness and hygiene. The footprints should always be taken on the mothers case record.

Recording of weight: All the infants should be weighed at within one hour of birth on a scale with at least 5 gm sensitivity. The weighing scale must be periodically calibrated. Place either a single-use paper towel or a sterile cloth towel on the weighing scale beneath the infant. Weight recording requires a considerable skill and therefore the health providers must be adequately trained to do so.[13]

*Administration of Vitamin K***:** Vitamin K in dose of 1 mg to term and 0.5 mg to preterm infants must be routinely administered intramuscularly to all neonates to prevent vitamin K deficiency bleeding. Oral preparation is unavailable in India and requires multiple dosing to prevent late onset vitamin K deficiency bleeding .

Stomach wash: There is no role of routine stomach wash after birth to prevent any kind of gastritis. If the infant is born through meconium stained liquor, the stomach may be aspirated to remove the content to prevent vomiting in early neonatal period.

*Examination at birth***:** The infant should be examined thoroughly for cardio-respiratory stability, malformation or trauma and determination of gestation at birth using a predesigned proforma (a sample copy is attached). There is no need for routine passage of catheter in the stomach for detection of esophageal atresia, in the nostrils for detection of choanal atresia or into the rectum for detection of anorectal malformation. Body temperature to the infant must be recorded by axillary route using electronic thermometer. If mercury thermometer is used, temperature should be recorded for three minutes. Use of rectal thermometer is associated with risk of trauma and infection and therefore must be avoided

*Prevention of tetanus***:** If mother has not received adequate tetanus immunization during pregnancy, the infant should be given a tetanus toxoid dose and concurrent tetanus immunoglobulin 250 IU intramuscularly to prevent tetanus neonatorum.[16]

Rooming in: There is no indication for separating a normal infant from the mother for routine observation in the nursery, irrespective of the mode of delivery. During initial couple of hours after birth, infants are awake and very active and this opportunity should be utilized for bonding and initiation of breastfeeding. Separation of a normal infant from the mother even for a couple of hours for 'observation' has a significant adverse impact on successful breastfeeding.[12]

Initiation of breastfeeding: The breastfeeding must be initiated as early as possible within one hour of birth. Health providers actually should assist the mother in helping her breastfeed the baby. Breastfeeding

counseling alone without actual physical support is unlikely to result into high rates of successful breastfeeding [17].

*Communication with the family***:** The health provider attending the birth of the infant must communicate with the mother and other family members regarding time, weight at birth, gender and well being of the infant. The infant should be shown to the family with particular attention given to the fact that family members get to know the gender and about the identity tag on the infant. This would avoid any confusion with legal implications regarding identity and gender of the infant.

What are issues of concern during initial few days of life?

Cord care: The umbilical cord must be kept open and dry. The nappy should be folded well below the umbilical stump [18, 19].

Eye care: Eyes of the infant must be cleaned with a sterile swab soaked in normal saline or sterile water. Clean from inner to outer canthus and use a separate swab for each eye. There is insufficient evidence to recommend routine antibiotic prophylaxis in Indian settings for prevention of ophthalmia neonatorum .

Exclusive breastfeeding: Successful breastfeeding requires a systematic approach to initiate, support and maintain breastfeeding. This amounts to educating mothers and families about the benefits during antenatal period, supporting the mother for initiation of breastfeeding soon after birth, appropriately managing various breastfeeding conditions during early postpartum period and psychological support to the mother. Provision of a dedicated lactation counselor significantly increases the chances of successful breastfeeding.

Oil massage: Oil massage is a low cost traditional practice well ingrained in Indian culture [20]. However, a paucity of data still exists as to what oil should be used for this purpose .

Evaluation for jaundice: All the infants must be examined for the development and severity of jaundice twice a day for first few days of life. Visual assessment in daylight is the preferred method. Transcutaneous assessment of jaundice using newer generation devices is helpful and may reduce the need for blood sampling.[21] However initial and running cost constitute an important barrier. American Academy of Pediatrics (AAP) recommends routine measurement of serum total bilirubin on a blood sample or by transcutaneous bilirubinometry in all neonates.[22] However, there is no data on cost-benefit of this approach. In view of the feasibility and cost involved, the same can not be recommended in Indian settings.

*Vaccination***:** All the infants must be offered the immunization at birth, before discharge, as per their state policy. Hepatitis B immunization at birth can prevent perinatal transmission of hepatitis B infection in majority of cases.[23]

*Bathing***:** Routine bathing in the hospital should be avoided in view of risks of cross infection and hypothermia.[24] The infant can be sponged, as required. Infant can be bathed at home once discharged from the hospital.

Sleep Position: There is at present substantial evidence of an association of prone position and SIDS, independent of other variables. However, no published report has suggested the converse-i.e., a reduced incidence of SIDS with the supine position. No studies were conducted in the hospital or facility setting.

No Indian study has looked into the sleep position of the healthy normal neonates and its relation to sudden infant death syndrome (SIDS). All healthy neonates who are born at term and have no medical complications should preferably be placed down for sleep on their back [25].

Traditional practices: A variety of traditional practices are common place in India. These can be beneficial such as oil massage, inconsequential such as putting black mark on forehead. However there are a variety of harmful traditional practices such as applying kajal/surma in eyes [26], putting oil in ear, putting boric acids in nostrils or applying substances such as cow dung on cord must be actively discouraged.

When should normal newborn be discharged from hospital?

Ideally infant should be discharged after 72-96 h once all the following criteria are fulfilled:

- Infant is free from any illness including significant jaundice
- The infant has been immunized
- Adequacy of breastfeeding has been established. This must be assessed in all infants and the same would be indicated by passage of urine at 6 to 8 times/24 hr, onset of transitional stools, baby sleeping well for 2-3 h after feeding. If there is any concern about adequacy of breastfeeding, the infant can be weighed on the same weighing scale that was used to weigh the infant at birth. Excessive weight loss (normal 8-10% of birth weight by 3-4 days of age) would indicate inadequate breastfeeding.
- Mother is free from any significant illness and confident to take care of her infant.

Early discharge (within first 24 to 48 h): This can be considered for non-primigravida mothers with prior breastfeeding experience and who fulfill the above mentioned criteria before discharge. However primigravida mothers should not be discharged before 72 hr in order to ensure adequate breastfeeding.

Key Points at discharge

- Every infant should have a routine formal examination before discharge. The examination should be performed with infant naked and in optimum light in presence of mother using a checklist (so as not to miss anything; sample proforma enclosed).
- Mother should be provided ample opportunity to ask questions and clarify all her doubts.
- Measure weight at discharge if there are concerns about feeding or problems to document if there is any significant weight loss. Normal weight loss is 7-8% by 3-4 days of age.
- There are no Indian studies reporting the readmission rates, breastfeeding failures, and morbidity characteristics, with which the early discharged babies get readmitted. However there is some information that breastfeeding inadequacy is a common occurrence that results in a variety of problems including high rates of jaundice requiring phototherapy in neonates. A Cochrane review has shown that the breastfeeding failure may be as high as 50% with readmission rates nearing 2% if the babies are discharged early. Therefore an early follow up visit (after 48 hr of discharge) is recommended for assessing adequacy of breastfeeding and examination for jaundice. This is particularly important for primigravida mothers and those who have been discharged before 48 h after birth.

What are signs and symptoms which predict mortality and suggest need for early referral ?

The Young infant study data done in the Indian setting presents the best possible scientific data on danger signs in neonates. Based on these most of the danger signs have a sensitivity and a specificity of more than 80%.

The following danger signs must be explained to the mothers at discharge:

i) Difficulty in feeding ii) convulsions iii) lethargy (movement only when stimulated) iv) fast breathing (respiratory rate of >60) v) severe chest in drawing vi) temperature of 37.5 degrees C or more or below 35.5 degrees C.

Is there a role for neonatal vitamin supplementation in healthy newborns?

A healthy newborn does not need routine supplementation of vitamins.

Role of Vitamin D supplementation

Various studies and survey in both developed and developing countries have reported 50 to 100% of the normal breastfed neonates to be deficient. Moreover, the mothers in developing countries like India are also deficient adding to the problem. Studies have showed routine vitamin D supplementation in a dose of 400 IU/day to exclusively breastfed neonates starting in the first month of life leads to a significant (100%) reduction in the biochemical deficiency of vitamin D, The results of the same can be logically extrapolated to our setting as the problem is more alarming. However, the Expert Group felt that in view of logistic difficulty in supplementing a large number of neonates, it would be prudent to wait for more evidence before universal supplementation can be recommended.

References

1. ICMR Report. Age profile of Neonatal deaths: ICMR young Infant study group. Indian Pediatric 2008;45:992-994.
2. Martines J, Paul VK, Bhutta ZA, Koblinsky M, Soucat A, Walker N, Bahl R, Fogstad H, Costello A. Neonatal survival: a call for action. Lancet 2005; 365:1189-97.
3. Sibley L and Ann Sipe T .What can a meta-analysis tell us about traditional birth attendant training and pregnancy outcomes? Midwifery 2004; 20: 51-60.
4. Sridhar MR, Bopathi S, Lodha R, Kabra SK. Standard precautions and post exposure prophylaxis for preventing infections. Indian J Pediatr 2004; 71:617-26.
5. Government of India-1993. Child Survival and Safe Motherhood programme- India. New Delhi: Ministry of Health and Family Welfare.
6. Dahm LS, James LS. Newborn temperature and calculated heat loss in the delivery room. Pediatrics 1972; 49:504-13.
7. Moore ER, Anderson GC, Bergman N. Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD003519. DOI: 10.1002/14651858.CD003519.pub2.

8. Hutton EK, Hassan ES. Late vs. Early clamping of the umbilical cord in Full-term Neonates: A Systematic review and meta-analyses of controlled trials. JAMA 2007; 297:1241-52.
9. Anderson JM, Phillip AGS. Management of the Umbilical Cord: Care regimens, Colonization, infection, and separation. Neoreviews 2004; 5:e155-63.
10. Neligan GA, Smith MC. Prevention of hemorrhage from the umbilical cord. Arch Dis Child 1963;38:471-75.
11. Behnke M, Eyler FD, Carter RL, et al. Predictive value of Apgar score for developmental outcome in premature infants. Am J Perinatol 1989; 6:18-21.
12. Pinheiro JMB.The Apgar cycle: a new view of a familiar scoring system.Arch. Dis. Child. Fetal Neonatal Ed.2009; 94: F70 - F72.
13. WHO Collaborating center for Training and Research in Newborn Care. Teaching Aids on Newborn Care. URL:http//www.newbornwhocc.org. Accessed on 10th October 2009.
14. Moraille R, Pickens WL, Visscher S B et al. A novel role for vernix caseosa as a skin cleanser. Biol Neonate 2005; 87:8-14.
15. Robus Jb et al. Guidelines on preventing abduction of infants from Hospital. National center for missing and exploited children. J Healthe Prot Manage 1992; 4:36-49.
16. Stanfield JP, Galazka A. Neonatal tetanus in the world today. Bull World Health Organ. 1984; 62:647-60.
17. Moore E R, Anderson G C. Randomized controlled trial of very early mother-infant skin-to-skin contact and breastfeeding status. Journal of Midwifery & Women's Health. 2007; 52:116–125.
18. Zupan J, Gamer P, Omari AA. Topical Umbilical cord care at birth. Cochrane Database Syst Rev. 2004(3):CD001057.
19. Lawn J, Cousens S, Bhutta ZA, Darmstadt GL, Martines J, Paul VK, Knippenberg R, Fogstadt H, Shetty P, Horton R.Why are 4 million newborn babies dying each year? The Lancet 2005; 364:399-401.
20. Bhutta ZA, Darmstadt GL, Hasan BS, Haws RA. Outcomes in Developing countries: A review of the evidence community-Based interventions for improving Perinatal and Neonatal Health. Pediatrics 2005; 115:519-617.
21. Maisels MJ, Kring E. Transcutaneous bilirubinometry decreases the need for serum bilirubin measurements and saves money. Pediatrics. 1997; 99:599-601.
22. American Academy of Pediatrics. Clinical practice guideline: management of hyperbilirubinemia in newborn infant 35 or more weeks of gestation. Pediatrics 2004; 114:297-316.
23. CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United State: recommendations of the Advisory Committee on Immunization Practices (ACIP), Part 1: Immunization of Infants, Children, and Adolescents, MMWR 2005; 54(RR-16).
24. Bergström A, Byaruhanga R, Okong P. The impact of newborn bathing on the prevalence of neonatal hypothermia in Uganda: a randomized,controlled trial. Acta Paediatr. 2005; 94:1462-7.
25. Kattwinkel J, Brooks J, Myerberg D; American Academy of Pediatrics, Task Force on Infant Positioning and SIDS. Positioning and SIDS. Pediatrics 1992; 89:1120–6.
26. Mehrotra SK, Maheshwari BB. Prevalence of ocular lesions in a rural community. Indian J Ophthalmol 1975;23:17-20.

Note: Details of the studies which were retrieved and reviewed for this guideline along with Summary of Evidence tables for all the issues addressed above are available on the website www.nnfpublication.org

Annexure

Sample Form for recording Examination of a Newborn

Department of Pediatrics, ABC Hospital, XYZ

Mother's name:	Registration No	Date Of Birth (dd/mm/yyyy)	Time Of Birth (--/--AM/PM)	Gender	Birth weight (g)

Significant events in previous pregnancies	Significant events in current pregnancy

Mode of delivery	Maximum resuscitation required	Apgar Score	Assigned gestation (in completed weeks)	SGA/LGA/AGA
	Routine care/initial steps/BMV/CC/adrenaline & more	1 min 5 min		

Any malformation	Any trauma

VITALS	**At Birth**	**At Discharge (Date)**
Temperature (^{o}C)		
Heart rate		
Respiratory rate		
Capillary refill time		
Femoral pulses		
EXAMINATION		
General Condition (Color, Cry, Tone, Activity)		
Head, fontanel, sutures		
Eyes (cataract, discharge)		
Ears, nose, mouth, palate		
Umbilical cord (discharge, redness, no. of arteries)		
Genitals (including hernia)		
Anal patency		
Spine (integrity etc)		
Abdomen (Liver, spleen, kidney, mass)		
Extremities (Clavicles, Hip)		
Skin (Rash, birthmark, hemangioma)		
Superficial infection (conjunctivitis/oral thrush/pustules)		

Jaundice (estimated levels/extent)		
Breastfeeding evaluation • Condition of breast & nipple • Position of baby • Attachment • Sucking		
Vaccination:	Urine passed: Y/N	Stool passed: Y/N
Record point of concerns, if any		**Examining doctor**

Management of Breast Feeding

Summary of Recommendations

- **Breastfeeding should be initiated within one hour of birth in all healthy infants.**
- **The frequency of breast feeding should be as often as the baby wants (demand feeding) for both day and night.**
- **A careful history and physical examination of the mother and baby should be performed, as well as observation of a breastfeeding session when there are concerns about inadequate breast milk.**
- **There should be a universal availability of skilled counselors for initiation of breastfeeding at birth, support during the stay in the hospital and at the time of discharge.**
- **Exclusive breastfeeding should be practiced during the first six months of life.**
- **Routine use of the multicomponent fortification of the breastmilk should be avoided. Their use should be restricted to infants <32 weeks gestation or <1500 g birth weight who fail to gain weight despite adequate breastmilk feeding.**

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Introduction

Scientific research during the last few decades has clearly proved that breastfeeding provides both short-term and long-term health benefits to infants, mothers, families, and society.[1-3] It is also known that breastfeeding is an exceptionally cost-effective strategy for improving child survival and reducing the burden of childhood disease However there is still a large gap between the knowledge and practice of breastfeeding. Further, the potential long term health benefits of breast feeding for mothers and babies, particularly in relation to obesity, blood pressure, cholesterol, and cancer are largely unknown. In spite of this knowledge, and the belief that breastfeeding culture comes naturally to Indian mothers, the rates of exclusive breastfeeding in India are dismal. This is evident from the National Family Health Survey-3 of India, which has documented that initiation of breastfeeding with in one hour of birth is only 24.5%, and exclusive breastfeeding up to six months of age is only 46.4%.[3] There are many barriers to initiate and continue breastfeeding during the neonatal period extending into infancy. This guideline attempts to answer the following questions of practical relevance related to breast feeding :

- When should breastfeeding be initiated?
- What should be the frequency of breastfeeding?
- How long should the breastfeeding be exclusive?
- What should be the duration of breastfeeding
- How to assess the adequacy of breastfeeding?
- How to breastfeed in maternal illness?
- How to use expressed breast milk ?
- How and when to fortify breastmilk ?
- What supplements are needed by breastfed VLBW?
- How shouldinsufficient milk supply be managed?
- What are the contraindications to breastfeeding?

When should breast feeding be initiated?

Evidence: Hospital practices surrounding labor and birth have been found to have great impact on the success of breastfeeding initiation. Education of nurses, physicians, and other health care professionals working with the nursing couplet regarding the dynamics of breastfeeding have a significant influence on initiation of breast feeding. Current international.[4,5] and national guidelines recommend initiation of breastfeeding within one hour of birth. Early initiation of breastfeeding is extremely important for establishing successful lactation as well as for providing 'Colostrum' to the baby. Ideally, the baby should receive the first breastfeed as soon as possible and preferably within one hour of birth. Early skin-to-skin contact immediately after delivery and the opportunity to suckle within the first hour after birth are both important. The Cochrane systematic review on early skin-to-skin contact for mothers and their healthy newborn infants concludes that the intervention may benefit breastfeeding outcomes, early mother-infant attachment, infant crying and cardio-respiratory stability, and has no apparent short or long-term negative effects.[6]. A study from Ghana has documented that 22.3% of all neonatal deaths could be prevented if all women could initiate breastfeeding within one hour of birth in a community. Even if breastfeeding is started within 24 hours after birth, 16% neonatal deaths can still be prevented.[7] Further, an

epidemiological evidence of a causal association between early breastfeeding and infection specific mortality in the newborn infants has also been documented.[8] After caesarean section under general anesthesia, initiation of breastfeeding may be delayed. In such situations, breastfeeding can be initiated within a few hours, as soon as the mother regains consciousness.[9] Healthy newborn infants are often separated from their mothers after delivery and may not be put to the breast for hours, or sometimes for days, waiting for breast milk to 'come in' or without any reason. This practice is detrimental to successful breastfeeding and must be discouraged.

Recommendation:

- Breastfeeding should be initiated within one hour of birth in all healthy infants**.**
- Healthy infants after the delivery should have immediate skin-to-skin contact with their mothers. Mothers and babies should remain together and "room-in" the same hospital room throughout their hospital stay to initiate early breast feeding.

What should be the frequency of breastfeeding?

Evidence: All mothers who are breastfeeding, should have no restrictions placed on the frequency or length of their babies' breastfeeds. They should be advised to breastfeed their babies whenever they are hungry or as often as the baby wants to feed (demand feeding) and they should wake their babies for breastfeeding if the babies sleep too long or the mother's breasts are overfull.[10] Scheduling feeds leads to breastfeeding problems and insufficient milk production which may cause mothers to start artificial feeding. Often baby rests a while during breastfeeding, as it is an active process, though remains attached with the breast. There is no need to 'wake up' the infant or remove from the breast. S/he will start suckling on its own till baby leaves the breast. Restricting length of the breastfeeding session may result in the baby getting less of the energy rich hind milk.[11] In a health facility, truly unrestricted breastfeeding is only possible with 24-hour rooming-in, and preferably bedding-in, which enables the mother to respond when her infant shows readiness to feed.

Recommendations: The frequency of breast feeding should be as often as the baby wants (demand feeding) during both day and night.

How to assess the adequacy of breast feeding?

Evidence: Exclusive breastfeeding is sufficient to support optimal growth and development for the first 6 months of life and provides continuing protection against diarrhea and respiratory tract infections.[12,13] However, the most common cause cited by the mother to give supplementary feeds along with breastfeed is her perception that she does not have enough breastmilk.[14] Even when a mother perceives her milk to be insufficient, the baby may get all the milk s/he needs. The fact is that the breastmilk production is determined by the amount that the baby draws from the breasts. Mothers who think that they do not have enough breastmilk need the help and support of a person skilled in breastfeeding management. After initial weight loss, if the neonate does not gain birth weight by two weeks of age, or the cumulative weight gain is less than 500 gm in a month or the infant is passing small amount of concentrated urine less than six times a day, while on the exclusive breastfeeding, one should be worried about the adequacy of the breastmilk.[15] Insufficient weight gain in a breastfed baby may occur because (i) the infant is not feeding effectively, (ii) the infant has a higher than expected calorie need, or (iii) mother has an insufficient milk supply. A practical approach for health workers to help the mothers in such a situation is

to follow three steps: First, decide whether the baby is getting enough milk or not. Second, if the baby is not getting enough breastmilk, decide why it is happening. Third, decide how to help the mother and the baby.[16] These mothers need additional support and counseling.

Signs of sufficient milk intake	
Infant	**Mother**
Audible swallowing heard during feeding Appears relaxed during feeding and satiated after feeding Has awake, alert, calm times between feedings Nurses 8–12 times in a 24-hour period Gains 20–30 g a day after day 3–5 of life	Breasts are full before a feeding and softer after a feeding May notice let-down reflex during feeding

Recommendation:

- A careful history and physical examination of the mother and baby should be performed, as well as observation of a breastfeeding session when there are concerns about inadequate breast milk.
- The adequacy of milk intake can be assessed by counting the number of wet diapers per day, the number and quantity of stools, and weight gain .

What are effective strategies to help mothers to breastfeed and maintain breastmilk supply during separation of mother-infant dyad?

Evidence: Breastfeeding is not a totally instinctive behavior, and the technique often needs to be learned. Hence the mother requires help and support for positioning and attachment of the baby to the breast. It has been reported that establishing of breastfeeding and relactation can be achieved in more than 90% mothers, who were unsuccessful in breastfeeding, within six weeks postpartum with support.[17,18]

A meta-analysis of 20 randomized or quasirandomized trials involving 23,712 motherinfant pairs (infants with any birth weight, four trials specifically excluded LBW), showed that professional support was effective in increasing the rates of any breastfeeding at 6 months (RR0.89, 95%CI 0.81 to 0.97), but its effect on exclusive breast feeding (EBF)was not significant. Lay support was effective in increasing EBF rates (RR0.66, 95%CI 0.49 to 0.69), but its effect on any breastfeeding was not significant. (Sikorski J et al.,2003).Breastfeeding counseling has generally not been included in the teaching-training curriculum of doctors, nurses or nursing aids, so they often lack the skills needed to assist, and help mothers for breastfeeding. They themselves require an appropriate skill based training to build their capacity to support mothers to initiate breastfeeding within one hour of birth and to manage breastfeeding difficulties and breast conditions. Availability of help from a skilled person soon after birth is very crucial.[13]

In the event of separation of the mother- infant dyad, mother should be taught expression of breast milk. The expressed breastmilk must be fed with a cup or spoon (bondla) in comparison to bottle, to

prevent nipple confusion and later problems of attachment of the baby to the breast.[19,20] Adequate technique and frequency of milk expression are necessary to achieve adequate lactation, and eventually to establish breastfeeding. Expression of milk should start as early as possible after birth, preferably on day one. Frequent expression, at least four times a day, leads to more production of milk; some experts recommend expression 8-12 times in the first week.[21,22]

There is not enough evidence to support routine use of galactogogues. Small trials report conflicting effects on increasing milk volume.(*Ehrenkranz RA,,1986, de Silva OP.2001, Hansen WF et al. 2005*)

Best practices to maintain lactation in mothers separated from their babies

1. **Provide information, educational materials, equipment, supplies during hospital stay.**

- Actively encourage and support breastfeeding
- Start milk expression in first 24 h after birth
- Aim for the first oral feedings to be at the breast
- Encourage milk expression 8 to 10 times per day
- Communicate about the progress of the baby and involve mother in day to day NICU babycare
- Respond to maternal concerns, stress, anxiety, or insomnia related to infant's changing condition
- Discuss identified maternal risk factors for lactation
- Avoid hormonal birth control during early postnatal period
- Make provision of hospital-grade breast pump and collection kit & storage containers
- Provide written educational information addressing common breatfeeding concerns
- Recommend specific medications to the mother that are compatible with lactation
- Educate new staff to support breastfeeding

2. Provide nonpharmacologic interventions in the NICU that optimize maternal milk volume during the infant's hospitalization.

- 24-hour visitation and access to infant
- Consistent message about the importance of human milk from all NICU clinicians
- Use of expression of breast milk at infant's bedside
- Daily skin-to-skin holding in the NICU
- Comfortable, supportive chairs should be available for mothers
- Daily "tasting" of milk (suckling at emptied breast) regardless of infant weight and gestation
- Peer support for expressing milk and other NICU-specific activities.
- Review of maternal milk volume records to identify expressing patterns.
- Observations of mother using manual expression or electric pump in the NICU to detect problems
- No free formula samples or other promotion of artificial feeding.
- Ensure the entire system supports breastfeeding

Adapted from Evidence-based Practices to Promote Exclusive Feeding of Human Milk in Very Low-birthweight Infants P. Meier, JL. Engstrom. *NeoReviews* 2007;8;e467-e477.

Recommendation:

- There should be an universal availability of skilled counselers for initiation of breastfeeding at birth, support during the stay in the hospital and at the time of discharge.
- In a situation of maternal separation from the infant, mother should be counseled and taught the technique of milk. She should also be taught how to feed breastmilk with cup or spoon.
- Encouragement and support from clinicians, education about the benefits of human milk, training and provision of breast pumps, and personal peer support have been shown to be effective methods of increasing breastfeeding rates.

How long should the breast feeding be exclusive?

Evidence: Exclusive breastfeeding has been defined by WHO as "the infant receives only breastmilk without any additional food or drink, not even water".[22]

Current international and national guidelines.[1,2] recommend exclusive breastfeeding for the first six months of life. In 2003, Lancet series on child survival[23] and later Lancet series on newborn survival[24] summarized that 13% to 15% of under-five deaths in resource poor countries could be prevented through achievement of 90% coverage with exclusive breastfeeding alone. The Cochrane review on optimal duration of exclusive breastfeeding concludes that infants who are exclusively breastfed for six months experience less morbidity from gastrointestinal infection in comparison to those who are mixed fed (breastfeeding plus other milk or food) during first six months of life, and also no growth deficits have been demonstrated among infants from either developing or developed countries who are exclusively breastfed for six months or longer.[25] Studies have shown that artificially fed infants have significantly higher rates of acute otitis media, non-specific gastroenteritis, severe lower respiratory tract infections, atopic dermatitis, asthma, sudden infant death syndrome (SIDS), and necrotizing enterocolitis. (*Gartner LM et al, 2005).*

Cochrane database concluded that commercial discharge packs containing samples of breast-milk substitutes, printed promotional materials on initiation and duration of breast-formula feeding have a detrimental effect on exclusive breastfeeding. (*Donnelly A,2000)*

The breastfeeding may not be able to meet all nutrients and energy needs of an infant after six months of age. Therefore, timely complementary feeds in appropriate consistency and amount should be introduced along with breastfeeding after baby completes six months of age.[26] Breastfeeding babies who are given food or drink other than breastmilk should have acceptable medical reasons.[13]

Recommendations:

- Infants should be exclusively breastfed during the first six months of life.
- The use of prelacteals should be strongly condemned and discouraged.

What are acceptable situations to use breast milk substitutes ?

Evidence: Almost all mothers can breastfeed successfully, which includes initiating breastfeeding within the first hour of life and breastfeeding exclusively for the first 6 months.[27] Nevertheless, a small number

of health conditions of the infant or the mother may justify recommending that she does not breastfeed temporarily or permanently.[28]Whenever stopping breastfeeding is considered, the benefits of breastfeeding should be weighed against the risks posed by the presence of the specific conditions listed.

Infants who should not receive breastmilk or any other milk except specialized formula

- Infants with classic galactosemia: a special galactose-free formula is needed.
- Infants with maple syrup urine disease: a special formula free of leucine, isoleucine and valine is needed.
- Infants with phenylketonuria: a special phenylalanine-free formula is needed (some breastfeeding is possible, under careful monitoring).

Infants for whom breastmilk remains the best feeding option but who may need other food in addition to breastmilk for a limited period

- *Infants born weighing less than 1500 g (very low birth weight)*
- *Infants born at less than 32 weeks of gestation (very preterm)*
- Newborn infants who are at risk of hypoglycemia by virtue of impaired metabolic adaptation or increased glucose demand (such as those who are preterm, small for gestational age or who have experienced significant intrapartum hypoxic/ischaemic stress, those who are ill and those whose mothers are diabetic[29]) if their blood sugar fails to respond to optimal breastfeeding or breast-milk feeding.

Maternal conditions that may justify temporary avoidance of breastfeeding

- Severe illness that prevents a mother from caring for her infant, for example sepsis, postpartum psychosis.
- Herpes simplex virus type 1 (HSV-1), chicken pox: direct contact between lesions on the mother's breasts and the infant's mouth should be avoided until all active lesions have resolved.
- Maternal medication[30]:
    - Cytotoxic drugs Cyclophosphamide, Methotrexate and Doxorubicin may interfere with cellular metabolism of the nursing infant hence incompatible with breastfeeding.
    - Radioactive compounds like Gallium 67 (^{67}Ga), Indium 111 (^{111}In), Iodine 131 (^{131}I), Technetium99m (^{99m}Tc), etc may lead to secretion of radioactive substance in breastmilk.

Maternal conditions during which breastfeeding can still continue, although health problems may be of concern

- Breast abscess: breastfeeding should continue on the unaffected breast; feeding from the affected breast can resume once treatment has started[31]
- Hepatitis B: infants should be given immunoglobulin at delivery and hepatitis B vaccine, within the first 48 hours or as soon as possible thereafter[32]
- Mastitis: if breastfeeding is very painful, milk must be removed by expression to prevent progression of the condition .

- Tuberculosis: Breast feeding can be continued . Mother and baby should be managed according to standard guidelines.[33]

Recommendation:

There are very few conditions in which temporary or complete avoidance of breastfeeding is required.

What is the role of multicomponent fortification of breast milk?

Evidence: A term normal weight does not require breastmilk fortification. According to the Cochrane review on "Multicomponent fortified human milk for promoting growth in preterm infants" supplementation of human milk with multi-component fortifiers is associated with short-term increases in weight gain, linear and head growth. There is no effect on serum alkaline phosphatase levels; it is not clear if there is an effect on bone mineral content. Nitrogen retention and blood urea levels appear to be increased. There are insufficient data to evaluate long term neuro-developmental and growth outcomes, although there appears to be no effect on growth beyond one year of life.[34] Safety concerns for such a product still remain unanswered. An increased osmolality, increased chances of bacterial contamination, and worsening of nonacid GER indices are some very important issues which may lead to an adverse outcome in the very low birth weight recipient of the breast- milk fortifiers.[35,36] It is started once the infant reaches 150 ml/kg/day of enteral feeds with expressed breastmilk in the dose recommended by the manufacturer (2g [1 sachet] human milk fortifier /50mL of expressed breastmilk).[37,38]The available research evidence[39] has revealed that the benefits of the multicomponent fortification of the breastmilk appear to be only short-term increases in growth, the safety is uncertain, and could be of more concern in developing countries with a greater risk of contamination. The review has thus expressed doubts on the routine use of multicomponent fortifiers, particularly in developing countries. Further research is needed to examine the role of multicomponent fortifiers in developing countries like India. There are no data examining the efficacy of multicomponent fortifier in infants of 32–36 weeks gestation or in term LBW infants.

Recommendation: Routine use of the multicomponent fortification of the breastmilk should be avoided. Their use should be restricted to infants <32 weeks gestation or <1500 g birth weight who fail to gain weight despite receiving full volumes of breastmilk which can be up to 180-200 ml/kg/day.

What nutritional supplements are needed by breastfed babies?

Evidence: Term healthy infants do not need any supplements during the first 6 months of life. Since intrauterine accretion of nutrients occurs mainly in the later part of the third trimester, preterm infants have low body stores at birth, requiring supplementation of various nutrients.[39]

Recommendation:

- Term healthy infants who are exclusively breastfed do not need any supplementation in first six months of life.
- Preterm/LBW infants in addition to breast milk need supplementation (see guideline on feeding of low birth weight infant).

Following are guidelines in clinical practice for successful breastfeeding:

At birth

- Enthusiastic support of breastfeeding by all health-care professionals
- Recommend human milk for all infants as the first choice for feeding.
- Healthy infants should be in direct skin-to-skin contact with their mothers immediately after birth
- Initiate breast feeding in the first hour of birth in all healthy infants
- Help mother with positioning and attaching the baby in first few attempts.

In Postnatal Care

- Enthusiastic support of breastfeeding by all health-care professionals
- Recommend human milk for all infants as the first choice for feeding.
- Mother and infant should sleep in proximity to each other
- Observe a breastfeeding session It involves observing and assessing feeding pattern, positioning and attachment, sucking behaviour, and breast fullness
- Implement baby friendly hospital initiative
- Avoid and discourage giving mothers commercial discharge packs containing formula or promotional material for formula milk
- Enforce the principles and aims of the International Code of Marketing of Breast-Milk Substitutes
- Support breastfeeding mothers and babies when confronted with medical needs that may jeopardize breastfeeding success
- Each mother at the time of discharge should demonstrate competence with nursing, including latching, identifying infant swallows and readiness to end a feeding, and identifying early feeding cues.

In NICU mothers

- Early, frequent and effective milk expression appears to be the most important factor in establishing lactation.
- When direct breastfeeding is not possible, expressed human milk should be provided
- Personal assistance that includes peer counselors, lactation specialist or peer support for mothers with insufficient breastmilk.,
- There are some simple practical ways of stimulating milk production. These include: Expressing milk in close proximity to the infant, Skin-to-skin (kangaroo) care, Non-nutritive suckling at the breast & Breast massage
- Developmentally supportive care

At Home

- Exclusive breastfeeds till first six months
- Demand feeding which is frequent and unrestricted breast feeding, day and night
- Water and other fluids should not be given to breastfeeding infants in first six months

- Continue breastfeeds upto 2 years and beyond in addition to complementary feeds from 6 months of age.
- Freshly expressed human milk can be used safely for up to 8 hours at room temperature

At Office practice

- Advocate, support and promote breastfeeding.
- See the baby within 1–2 days after discharge from the hospital or birthing center, and continue frequent visits until the baby is gaining weight adequately and mother appears confident
- Assess for adequacy of breastfeeding at every opportunity by the infant's weight, hydration status, and the presence or absence of jaundice
- Respond to parental concerns on feeding
- Prevention and early help with breastfeeding problems are crucial
- Most common infant and maternal health problems should not preclude breastfeeding, but mothers and infants will need support from knowledgeable health care professionals
- Each prescribing decision needs to take account of the risks and benefits to the individual mother and baby,
- Provide written or multimedia resources for patient education..

Special Circumstances:

- There are very few absolute contraindications for breastfeeding.
- Exclusive breast feeding for six months is recommended where no culturally acceptable, feasible, affordable, safe, and sustainable nutritional substitutes for breast milk are available.

To implement above mentioned guidelines, the unit needs to accomplish following actions:

- Have a policy on breastfeeding which Supports early initiation,Avoids pre-lacteal feeds,Practices rooming- in,Practices demand feed,Practices exclusive breastfeeding,Abjures supplemental feeds,Supports mother to maintain milk supply during separation,Supports mother in managing expressed breastmilk,Manages breast conditions,Avoids teats and dummies,Protects breastfeeding from commercial influence by implementing the Infant Milk Substitutes Feeding Bottles, and Infant Foods (Regulation of Production, Supply and Distribution) Act 1992 as amended in 2003, which prohibits all kinds of incentives to health workers from baby food companies.
- Ensure that all health workers do not accept any incentives from baby food industry or their allies, directly or indirectly
- Ensure appropriate training of the staff aimed at acquiring counseling skills to build confidence of the mother and practical skills to help mothers (see annexure).
- Provide post discharge support – To avoid breastfeeding failure and consequent morbidity and growth faltering, an institutional mechanism to support the mother-infant dyad during the follow up visits should be established. One such effective intervention could be to establish an infant and young child feeding counseling centre in the health facility.

References

1. Phatak A. Economic and ecological effects of breastfeeding. J Obstet Gynaecol India 1999; : 35-38.
2. Harit D, Faridi MM, Aggarwal A, Sharma SB. Lipid profile of term infants on exclusive breastfeeding and mixed feeding: a comparative study. Eur J Clin Nutr2008;62(2):203-209.
3. 3. International Institute of Population Sciences (IIPS) and Macro International. 2007. National Family Health Survey (NFHS - 3), 2005-06:India: Volume I. Mumbai:IIPS.
4. World Health Organization. What is the recommended food for children in their very early years? Available from: URL: http://www.who.int/features/qa/57/en/index.html. Accessed on August 3, 2009**.**
5. Ministry of Women and Child Development, Food and Nutrition Board, Government of India. National guidelines on infant and young child feeding, second edition, 2006.
6. Moore ER, Anderson GC, Bergman N. Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD003519. DOI: 10.1002/14651858.CD003519.pub2. Available at: http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003519/frame.html. on 14th August 2009.
7. Edmond KM, Zandoh C, Quigley MA, Amenga-Etego S, Owusu-Agyei S, Kirkwood BR. Delayed breastfeeding initiation increases risk of neonatal mortality. Pediatrics. 2006;117(3):e380-6.
8. Edmond KM, Kirkwood BR, Amenga-Etego S, Owusu-Agyei S, Hurt LS. Effect of early infant feeding practices on infection-specific neonatal mortality: an investigation of the causal links with observational data from rural Ghana. Am J Clin Nutr. 2007;86(4):1126-31.
9. World Health Organization. Evidence for the ten steps to successful breastfeeding. Available at: http://www.who.int/child_adolescent_health/documents/9241591544/en/index.html. Accessed on 14th August 2009.
10. Baby-friendly hospital initiative: Revised, Updated and Expanded for Integrated Care. Background implementation. January 2006; WHO and UNICEF. Available at: http://www.unicef.org/nutrition/index_24850.html. Accessed on 16th August 2009.
11. Woolridge MW, Baum JD () Recent advances in breast feeding. Acta paediatrica Japonica 1993, 35:1-12.
12. Kramer MS, Kakuma R. The Optimal Duration of Exclusive Breastfeeding. A Systematic Review. Geneva, Switzerland: World Health Organization; 2002.
13. Butte NF, Lopez-Alarcon MG, Garza C. Nutrient Adequacy of Exclusive Breastfeeding for the Term Infant During the First Six Months of Life. Geneva, Switzerland: World Health Organization; 2002.
14. Newman J. Breastfeeding: The problem of 'not enough milk'. Can Fam Physician. 1986 ; 32: 571–574.
15. Neifert MR. Prevention of breastfeeding tragedies. Pediatr Clin N Am 2001; 48 (2): 273-297.
16. World Health Organization . Not enough milk. Popline document no. 180857. Available at: www.popline.org/docs/1472/180857.html ; 1996. Accessed on 14th August 2009.
17. Banapurmath S, Banapurmath CR, Kesaree N. Initiation of lactation and establishing relactation in outpatients. Indian Pediatr 2003;40:343-347.
18. World Health Organization. Relactation: Review of experience and recommendations for practice. Department of Child And Adolescent Health and Development. Eds. Elizabeth Hormann and Felicity Savage Geneva PP: 1-38 WHO/CMS/CAH/98-14, 1998.
19. Huang YY**,** Gau ML**,** Huang CM**,** Lee JT**.** Supplementation with cup-feeding as a substitute for bottle-feeding to promote breastfeeding. Chang Gung Med J 2009; 32(4):423-31.
20. Meier P. Breast feeding the premature baby: a research review. News brief 1994; 9(1):2-5.
21. de Carvalho M et al. Frequency of milk expression and milk production by mothers of non-nursing premature neonates. American journal of diseases of children 1985; 139:483-485.
22. World Health Organization . Exclusive breastfeeding. Available at: http://www.who.int/nutrition/topics/exclusive_breastfeeding/en/. Accessed on September 27, 2009.

23. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris S S, and the Bellagio Child Survival Study Group. How many child deaths can we prevent this year? Lancet 2003; 362: 65–71.
24. Darmstadt GL, Bhutta ZA, Cousens S, Adam T, Walker N, de BL. Evidence-based, cost-effective interventions: how many newborn babies can we save? Lancet 2005; 365: 977–988.
25. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD003517. DOI: 10.1002/14651858.CD003517. Available at: http://www.cochrane.org/reviews/en/ab003517.html. Accessed on 10 August 2009.
26. WHO/UNICEF Global Strategy for Infant and Young Child Feeding, World Health Organization (WHO), 2002. Available at: http://www.who.int/child-adolescent-health/NUTRITION/global_strategy.htm
27. Baby-friendly hospital initiative: revised, updated and expanded for integrated care. Section 2, Strengthening and sustaining the baby-friendly hospital initiative: a course for decision makers. Produced by the World Health Organization, UNICEF and Wellstart International 2009. Available at: http://www.unicef.org/nutrition/files/BFHI_Revised_Section2.pdf. Accessed on 16th August, 2009.
28. Resolution WHA39.28. Infant and Young Child Feeding. In: Thirty-ninth World Health Assembly, Geneva, 5– 16 May 1986. Volume 1. Resolutions and records. Final. Geneva, World Health Organization, 1986 (WHA39/1986/REC/1), Annex 6:122–135. Available at: whqlibdoc.who.int/hq/2009/WHO_FCH_CAH_09.01_eng.pdf. Accessed on 16th August 2009.
29. World Health Organization. Hypoglycaemia of the newborn: review of the literature. Geneva, 1997 (WHO/CHD/97.1; Available at: http://whqlibdoc.who.int/hq/1997/WHO_CHD_97.1.pdf accessed on 15th August 2009.
30. American academy of pediatrics: Committee on drugs**.** The transfer of drugs and other chemicals into human milk. Pediatrics ; 108 (.3): 776-789.
31. World Health Organization. Mastitis: causes and management. Geneva, , 2000. Available at: http://whqlibdoc.who.int/hq/2000/WHO_FCH_CAH_00.13.pdf . Accessed on 14th August 2009.
32. CDC. Breastfeeding – Hepatitis B and C infection. Available at: http://www.cdc.gov/BREASTFEEDING/disease/hepatitis.htm. Accessed on 14th August 2009.
33. World Health Organization. Breastfeeding and maternal tuberculosis. Geneva, , 1998 (Update No.23). Aavailable at: http://www.who.int/child_adolescent_health/documents/breastfeeding_maternal_tb/en/index.html. Accessed on 15th August 2009.
34. Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants. From The Cochrane Library, Issue 2, 2005. Available at: http://www.nichd.nih.gov/cochrane/kuschel/kuschel.HTM. Accessed on 15th August 2009.
35. Aceti A, Corvaglia L, Paoletti V, Mariani E, Ancora G, Galletti S, Faldella G.Protein Content and Fortification of human milk influence gastroesophageal reflux in preterm infants. J Pediatr Gastroenterol Nutr. 2009 Jul 21. [Epub ahead of print].
36. Agarwal R, Singal A, Aggarwal R, Deorari AK, Paul VK. Effect of fortification with human milk fortifier (HMF) and other fortifying agents on the osmolality of preterm breast milk. Ind Pediatr 2004; 63 (41) : 63-67.
37. Sankar MJ, Agarwal R, Mishra S, Deorari AK, Paul VK. feeding of low birth weight infants. Ind J Pediatr, 2008;75:459-469.
38. Mukhopadhyay K, Narnag A, Mahajan R. Effect of human milk fortification in appropriate for gestation and small for gestation preterm babies: a randomized controlled trial. Indian Pediatr 2007;44(4):286-90.
39. Edmond, Karen, Bahl, R. WHO technical review on optimal feeding of low-birth-weight infants. 2006. Available at: http://www.who.int/child_adolescent_health/documents/9241595094/en/index.html. Accessed on 1st October 2009.

Supplementary References

1. Sikorski J, Renfrew MJ, Pindoria S, Wade A. Support for breastfeeding mothers: a systematic review. Paediatr Perinat Epidemiol. 2003 Oct;17(4):407-17.
2. Ehrenkranz RA, Ackerman BA. Metoclopramide effect on faltering milk production by mothers of premature infants. Pediatrics. 1986 Oct;78(4):614-20.
3. Hansen WF, McAndrew S, Harris K, Zimmerman MB. Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. Obstet Gynecol. 2005 Feb;105(2):383-9.
4. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, Eidelman AI; American Academy of Pediatrics Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2005 Feb;115(2):496-506.
5. Donnelly A, Snowden HM, Renfrew MJ, Woolridge MW. Commercial hospital discharge packs for breastfeeding women. Cochrane Database Syst Rev. 2000;(2):CD002075.

Annexure

1. Counseling of mother

Based on available scientific evidences exclusive breastfeeding should be done for initial six months of age and then breastfeeding should be continued for at least two years along with complementary feeding. Harmful socio-cultural practices, non observance of baby friendly hospital initiative in the health facilities, lack of support to the lactating mother by the family in particular and by the community in general and impact of unethical commercial strategies of the infant formula manufacturers make the breastfeeding difficult. It has been seen that counseling of the mother improves exclusive breastfeeding rates and duration of breastfeeding.

Counseling is a method to empower a person to take most appropriate decision. It is different from advising. It has three components; listening and learning skills, confidence building skills and checking understanding skills. Each of the three skills has six attributes.

a) Listening and Learning Skills:

1. Non-verbal communication-
    - Keep head at level
    - Remove barriers
    - Make eye contact
    - Keep appropriate distance
    - Show that you have time
    - Touch in culturally acceptable manner
2. Ask open questions
3. Show gestures and interest
4. Reflect back
5. Show empathy and not sympathy
6. Avoid using judging words

b) *Confidence Building Skills*

1. Accept what a mother thinks or feels
2. Praise what she is doing right
3. Give little practical help
4. Give relevant information
5. Use simple language
6. Give suggestions not commands

c) Checking Understanding Skills [please add six attributes of it from the minutes of meeting held for revising training tools]

Generally health care providers are not very efficient counselors. In spite of good intentions many of them are not able to help mother to overcome breastfeeding difficulties. They need training of breastfeeding counseling.

2. Syringe method for treatment of flat nipples

Explain that this method is for treating flat/inverted nipples postnatally, and to help a baby to attach to the breast. It is not certain whether it is helpful antenatally.

- *Show* the syringe to the mother that you have prepared, and explain how you cut off the adaptor end of the barrel.
- Put the plunger into the cut end of the barrel (that is, the reverse of its usual position).
- Use a *model* breast, and put the smooth end of the barrel over the nipple. Pull out the plunger to create suction on the nipple. (Explain that with a real breast, there is an airtight seal, and the nipple is drawn out into the syringe.)
- Explain that the mother must use the syringe herself.

Explain that you would teach her to:

- Put the smooth end of the syringe over her nipple, as you demonstrated.

- Gently pull the plunger to maintain steady but gentle pressure.

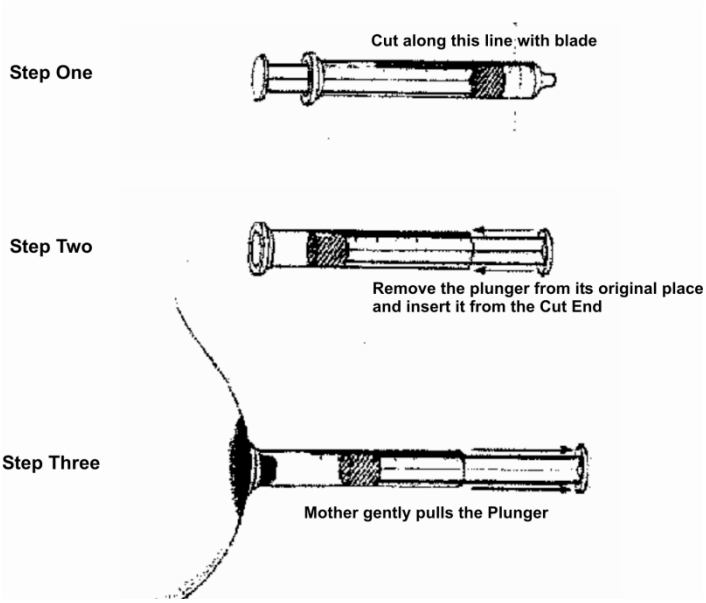
- Do this for 30 seconds to 1 minute, several times a day.

- Push the plunger back to decrease the suction, if she feels pain.

  (This prevents damaging the skin of the nipple and areola.)

- Push the plunger back, to reduce suction, when she removes the syringe from her breast.

- Use the syringe to make her nipple stand out just before she puts her baby to the breast.



Preparing and using a syringe for treatment of inverted nipples

(Source: BPNI 3-IN-1 training course on Infant and Young Child Feeding)

3.Troubleshooting for breastfeeding problems

.

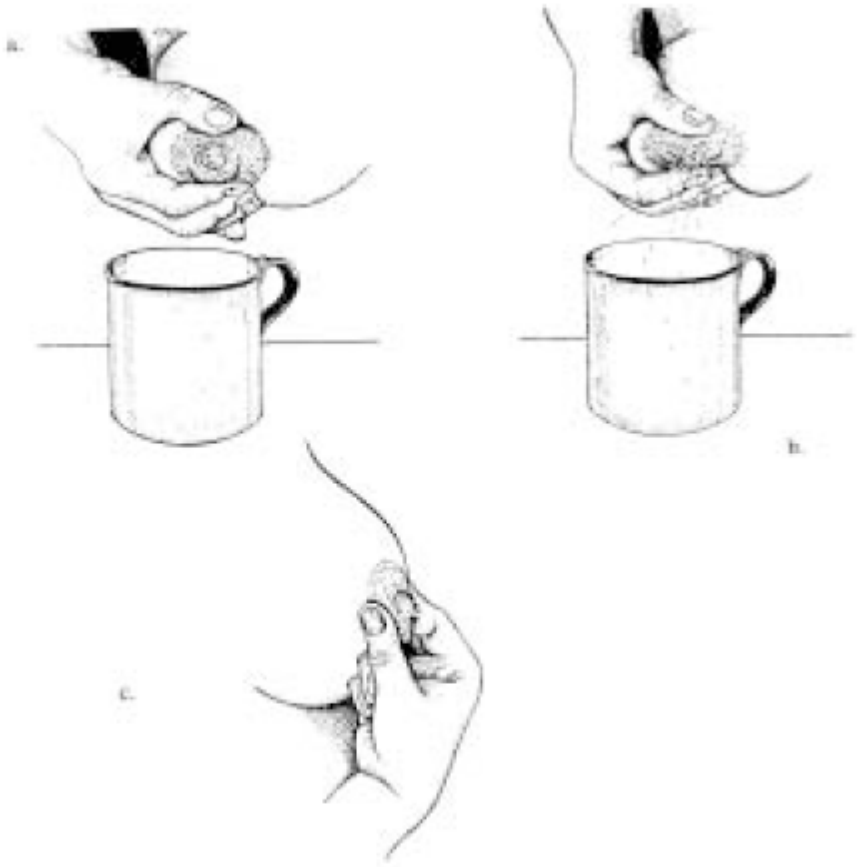
Problem	Characteristics	Management
Breast discomfort & Pain	May occur on days 2-7 when milk "comes in; if milk is not removed, milk production will diminish	Frequent unrestricted breast feeding, Analgesia compatible with breast feeding,; Breast massage; Hand expression if necessary; Cabbage leaves or cold compresses may help, but observed effects could be a placebo effect
Sore nipples	Trauma secondary to incorrect positioning, mothers or babies (or both) may have evidence of Candida albicans infection (thrush),	Correct positioning and attachment may prevent pain, Consider treating thrush infection, Topical nipple treatments, nipple shells, or nipple shields have not been shown to be effective; Evidence for the safety of nipple cream is weak
Mastitis	Caused by a blocked milk duct and poor milk drainage; signs and symptoms range from local inflammation with minimal systemic symptoms to abscess formation	Continue breast feeding or expressing milk, Analgesia compatible with breast feeding; increase fluid intake; Gently massage, If symptoms continue for more than a few hours of self management, seek professional advice to decide whether a β lactamase resistant antibiotic is indicated
Inverted or flat nipples	Require skilled help with positioning and attachment	Additional care and support, Not a contraindication to breast feeding.
Difficulty getting the baby to suck	May be effect of maternal drugs, anxiety, or stress	Assessment of effective breast feeding, Encourage Kangaroo care, Allay anxiety, stress or pain, Express milk.
Not gaining weight	Weight loss > 10% of babies weight	Assessment of effective breast feeding, Check urine output, stool frequency and character, observation for lethargy
Neonatal jaundice	Prolonged unconjugated jaundice, which lasts beyond 14 days, and the mechanism is unknown	Breast feed frequently, investigate jaundice persisting beyond 14 days
Multiple births	Ongoing struggles with the sheer intensity of the process of breast feeding	Intense maternal support, advice & counseling, Frequent feeding, Feed consecutively or simultaneously, Alternate breasts when breast feeding twins, Use cradle or foodball or combination position method, Even partial breast feeding may be beneficial.
Preterm Baby	Breastfeeding may be delayed for days or weeks.	Expressing milk, Mother-infant skin-to-skin contact as early as feasable, Fortified human milk for < 1500 grams who do not gain weight on adequate breast milk feed,s, Maternal support & counselling

Down's syndrome	Hypotonia, abnormal anatomic structure of the oral cavity, and significant congenital heart disease may affect breastfeeding	Suport, Feeding usually improves as the infant's muscle tone improves, prevalence of breastfeeding among patients who have Down syndrome is similar to that of the general population., Close monitoring for growth.
Cleft lip / palate	P roblems include inability to generate negative sucking pressure in the oral cavity, excessive air intake, nasal regurgitation, and fatigue leading to postnatal weight loss	Assistance in position and attachment, Breastfeeding offers several benefits over bottle-feeding
HIV	A route for transmission of the HIV virus from mother to infant	Individualized counseling,, screening for acceptable, feasible, a!ordable, sustainable and safe (AFASS) criteria, Promote and actively counsel on exclusive breastfeeding (EBF) for 6 months if ALL AFASS criteria not met,Avoid mixed feeding, early weaning, abrupt weaning.,Prepare for stopping BF at 6 months if AFASS criteria met

4. Manual Expression of Breast Milk

- Obtain a clean cup or container to collect and store the milk.
- Wash hands thoroughly.
- Ask the mother to sit or stand comfortably and hold the container underneath her breast.
- Support the breast with four fingers and place the thumb above the areola. Squeeze the areola between the thumb and fingers while pressing backwards against the chest.
- Express each breast for at least 4-5 minutes alternating breasts until the flow of milk stops.
- If the milk does not flow well –

a) Ensure the mother is using the correct technique.
b) Have the mother apply warm compresses to her breasts.
c) Have someone massage mothers back and neck.



Method of Expression of Breastmilk

5. Storing expressed breastmilk

Storage Location	**Temperature**	**Storage Duration**
Fresh milk, Countertop	Room	4–6 hours
Fresh milk, Refrigerator	35–40°F	5–8 days
Previously frozen milk, thawed in refrigerator	35–40°F	24 hours
Freezer section of refrigerator—freezer with common door	5°F	2 weeks
Freezer section of refrigerator—freezer with separate door	0°F	3–6 months
Stand-alone deep freeze	_4°F	6–12 months

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Management of Feeding in Low Birth Weight Infants

Summary of Recommendations

- **Mother's milk is the best feeding option for LBW infants. In case breastmilk feeding is not possible, it may be preferable to use pre-term infant formula for pre-term infants (< 2000 grams).**
- **Routine use of the multicomponent fortification of the breastmilk should be avoided. This option is best reserved for preterms infants <32 weeks gestation or <1500 g birth weight who fail to gain weight despite adequate breastmilk feeding.**
- **Enteral feeding should be initiated as early as clinically appropriate and minimal enteral nutrition should be provided, if volumes cannot be advanced.**
- **LBW neonates can be successfully fed with intragastric tubes or a variety of other traditional/culturally accepted devices.**
- **Non Nutritive Sucking and Kangaroo mother care are useful adjuncts to maintain and enhance breast feeding and nutrition.**
- **All LBW infants who are exclusively breastfed should receive supplements of vitamin D, calcium and phosphorous. Iron supplementation at 2-3 mg/kg/day at 6-8 wks , and as early as 2 wks in <1500 gms is effective in preventing anemia of prematurity.**
- **All LBW infants should be checked for weight (daily), head circumference (weekly) and length (weekly or fort-nightly) during their NICU stay.**

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Introduction

Optimal nutrition during the neonatal period is essential for growth and development throughout infancy and into childhood. Experience from both developed and developing countries has clearly shown that appropriate care of low birth weight (LBW) infants, with adequate attention to feeding can improve their survival. Nutritional needs of infants vary based on gestational age, metabolic state, and physiological complications. This guideline is an evidence based review on feeding of LBW infants and address the following issues:

- Feeding options for LBW baby
- Timing, volume and advancement of feeds in LBW infant
- Methods of enteral feeding
- Role of Minimal Enteral Nutrition
- Nutritional supplements
- Monitoring for nutrition and growth

What are feeding options for LBW baby? Which is the most ideal food for the LBW baby?

Evidence: The feeding options available for LBW baby are breast milk, expressed breast milk, donor human milk, preterm formula, term formula and animal milk.

Breast milk/ expressed breast milk: There is strong evidence that feeding a preterm with mothers own milk is associated with a lower incidence of infections and necrotizing enterocolitis, and improved neurodevelopmental outcome as compared with formula feeding, Un-supplemented human milk in preterms (< 32 weeks or < 1500 grams) has been associated with slower growth parameters. The implications of this slower growth are unclear.[1]

Donor human milk: Donor milk is obtained is obtained from lactating mothers. Feeding, with donor human milk results in slower growth[2]. There are insufficient data to assess the effects on long-term growth outcomes. There is currently no data on feeding fortified donor milk to LBW neonates. A study by Lucas etal[3] did however suggest that donor milk feeding was associated with advantages for later development that may have offset any potentially deleterious effects of its low nutrient content for preterm infants. A recent RCT found no short term benefit between donor milk and preterm formula, however in this study a significant number of neonates fed donor milk had to be switched over to preterm formula in view of poor growth.[4] A Cochrane review has found that feeding with formula compared to donor breast milk increases the risk of serious gut problems in preterm or low birth weight infants.[5]

Nutrient enriched breast milk and fortification: According to the Cochrane review on "Multicomponent fortified human milk for promoting growth in preterm infants" supplementation of human milk with multi-component fortifiers is associated with short-term increases in weight gain, linear and head growth.[6] There are insufficient data to evaluate long term neuro-developmental and growth outcomes, although there appears to be no effect on growth beyond one year of life.[7] The issues of concern in developing countries are higher prevalence of infections, a greater risk of contamination and high fortifier costs[8,9]. Therefore there are doubts on the routine use of multicomponent fortifiers, particularly in developing countries. There are no data examining the efficacy of multicomponent fortifier in infants of 32–36 weeks gestation or in term LBW infants. Few randomized studies exist regarding the

differences in different fortifiers. The optimal method for human milk fortification still remains to be determined. Further research is needed to examine the role of multicomponent fortifiers in developing countries like India. A Cochrane review[10] on Protein supplementation of human milk in relatively well preterm infants , showed an increase in short term weight gain, linear and head growth, with insufficient data to evaluate long term neurodevelopmental and growth outcome. The authors concluded that more research is needed to find the safest and most effective levels of protein supplementation. Another Cochrane review[11] on formula fed preterm infants has shown that higher protein intake (=> 3.0 g/kg/day but < 4.0 g/kg/day) from formula accelerates growth parameters in infants (weight gain: WMD 2.53 g/kg/day, 95% CI 1.62, 3.45, linear growth: WMD 0.16 cm/week, 95% CI 0.03, 0.30, and head growth: WMD 0.23, 95% CI 0.12, 0.35). The authors concluded that existing research is not adequate to make specific recommendations regarding formula with protein content more than 4.0 g/kg/day. A Cochrane review[12] on fat supplementation in preterms concluded that there is insufficient evidence to make recommendations for fat supplementation of human milk for promoting growth in preterm infants.

Preterm formula: No studies have examined the impact of preterm compared with standard infant formula on mortality rates or serious clinical disease in LBW infants. One large RCT examined the impact of term and pre-term formula on neurodevelopmental outcomes in pre-term infants.[13,14] Lucas et al(1990) reported significant advantages in psychomotor developmental scores at 18 months in infants fed pre-term formula. In a follow-up of participants of the same trial at 8 years of age, Lucas et al (1998) reported no significant benefit in overall IQ in the pre-term formula-fed infants. Only one study examined the long-term impacts of pre-term and standard infant formula on growth.[15] It reported significantly higher weight gain at hospital discharge in infants fed pre-term formula but no significant differences in weight, height or head circumference at 18 months and at 7½–8 years in infants who had been fed pre-term or standard infant formula.

Nutrient enriched formula: Two RCTs examined the impact of nutrient-enriched formula on neurodevelopmental outcomes, compared with standard infant formula.[16,17] Lucas et al[17] observed a a 2.8-point advantage in Bayley's psychomotor index subscale in infants fed nutrient-enriched formula when they had reached 18 months of chronological age, but this difference was not statistically significant. There was no difference in mental development scores in the two study groups.. Studies examining the impact of nutrient-enriched formula on growth outcomes had mixed results.

Animal milk: No studies were identified examining the impact of animal milk on clinical outcomes. No policy statements on the use of animal milk were located from international or national organizations.

***Recommendations*:** (GRADE A)

- Mother's milk is the best feeding option for LBW infants
- In case breastmilk feeding is not possible, it may be preferable to use pre-term infant formula for pre-term infants (< 2000 grams)
- Considering the weak evidence of benefits and substantially higher costs of nutrient enriched formula, its routine use cannot be justified in developing country settings .
- Routine use of the multicomponent fortification of the breastmilk should be avoided. This option is best reserved for preterms infants <32 weeks gestation or <1500 g birth weight who fail to gain weight despite full volumesof breastmilk feeding.

What is the role of prelacteal feeds in LBW feeding ?

Prelacteal feeds are any feeds given before the onset of lactogenesis, which is the onset of copious lactation that occurs within four days of birth.

Evidence: A systematic review[18] of effect of supplemental fluids or feedings during the first days of life on the overall breastfeeding duration and rate of exclusive breastfeeding among healthy infants showed that formula feeding was more in babies who were given prelacteal feeds with 5% glucose in the initial 3 days, than in the exclusively breast fed group. At 16 weeks, the percentage of mothers who continued breastfeeding, either exclusively or partially, was significantly lower in the group who received prelacteal feed than in the control group. In a population based cohort study from the Honduras both water- and milk-based prelacteal feeds were associated with a delayed milk arrival and a delay in the time at which the child was offered the breast for the first time. This study also suggests that in developing countries prelacteal feeds have an adverse effect on breast-feeding outcomes.[19]

***Recommendation*:** Prelacteal feeds have a negative outcome on breast feeding. The use of prelacteals should be strongly condemned and discouraged. (GRADE A)

When should enteral feeds be initiated?

Evidence: Milk feeding is generally initiated in stable infants >32 weeks gestation in the first 24 hours of life. However, the optimal timing of initiation of enteral feeding in infants <32 weeks gestation has been disputed. Practice differs considerably in developed and developing countries. A Cochrane review[20] which included three small trials in which a total of 115 very low birth weight infants participated with only a minority of participants being of extremely low birth weight or extreme preterm gestation, provided no evidence that delayed introduction of progressive enteral feeds affected the incidence of necrotizing enterocolitis.

Recommendation: There is evidence of benefit from initiation of early enteral feeding as early as clinically appropriate in stable low birth weight infants. (GRADE B)

What is the role of trophic feeds or minimal enteral nutrition?

Evidence: A Cochrane systematic review[21] summarized 10 trials of trophic feedings compared with no feedings in pre-term infants <33 weeks gestation, and one trial which compared trophic feedings with advanced feedings. They concluded that there is insufficient evidence to determine whether feeding very low birth weight infants small quantities of milk during the first week after birth (early trophic feeding) helps bowel development and improves subsequent feeding, growth and development. The same meta-analysis of nine studies with 650 participants showed no significant difference in the incidence of necrotising enterocolitis among infants given trophic feedings or no feedings. Nine studies (617 participants) included in this meta-analysis examined the role of trophic feeding on the number of days to reach full enteral feeding, and six studies (370 participants) examined the duration of hospital stay. Trophic feeding resulted in significant benefits in both these outcomes. The WMD in number of days to reach full enteral feeding was lower by 2.55 days in the trophic feeding group (95%CI 0.99 to 4.12). The duration of hospital stay was shorter by 11.44 days among infants in the trophic-feeding group.[22] Another RCT[23] determined the effects of trophic feeds in ventilated preterms from day3 of life (0.5ml-1ml/hr) along with parenteral nutrition found improved clinical outcome and no significant relative risk of any complications.

Recommendation: Trophic feeds (minimal enteral nutrition) decrease duration to reach full enteral feeds and duration of hospital stay without increasing the risk of NEC. (GRADE A)

What should be the volume of feeds? How rapidly should feeds be increased?

Evidence: Randomised controlled trials on enteral fluid intake of preterm infants are lacking as are studies comparing different fluid volumes providing identical nutrient intakes. A randomized controlled trial studied the effects of small volume feeds versus increasing feeding volumes on NEC, maturation of gut function and time to reach full feeds.[24] The authors concluded that neonatologists should consider using minimal feeding volumes until future trials assess the safety of advancing feeding volumes. A Cochrane meta-analysis on the topic included 3 RCTs and concluded that currently available data provide no evidence that slow advancement of enteral feed volumes prevent necrotizing enterocolitis in very low birth weight infants.[25]

Recommendation: The volume of feeds should be decided taking into consideration the gestational age, postnatal age and clinical status. The maximum volume of feeds may reach up to 180-200ml/kg/day (GRADE D). There is no evidence that slow progression of feeds decreases risk of NEC but this needs to be interpreted cautiously in ELBW infants.

What is the role of LCPUFA and DHA in LBW formula?

The long chain polyunsaturated fatty acids, arachidonic acid and docosahexanoic acid are critical for eicosanoid synthesis and cell membrane, retinal, and brain function. However, the synthesis of arachidonic acid and docosahexanoic acid may be limited in the preterm infant, and supplementation of preterm formula has been suggested.

Evidence: A randomized, masked, controlled trial found that those supplemented with LPUFA had better visual acquity , but no differences in Bayleys mental development index, or growth parameters like wt, length, or head circumference.[26] In a Cochrane review[27], most studies found no significant differences in any visual assessment between supplemented and control infants. There was no evidence that supplementation of formula with n-3 and n-6 LCPUFA impaired the growth of preterm infants. However conflicting results were seen in some studies.[28-30] A double blind multicentric RCT analysed the effect of high DHA (1% of total fatty acid) versus standard DHA (0.3% total fatty acid), found statistically no difference in Bayley mental develpoemental index (MDI) at 18 mo between them.[31C]

Recommendation*:* Developmental assessment trials of infants fed LCPUFA supplemented formulas have shown varied results, as have trials assessing the growth of infants fed such formulas. Further research is required to determine the overall balance of LCPUFA in the diets of preterm infants fed either human milk or infant formula. (GRADE A).

What is the role of Non nutritive sucking?

Evidence: Non nutritive suckling (NNS) was found to decrease significantly the length of hospital stay in preterm infants according to Cochrane metanalysis.[32] The review did not reveal a consistent benefit of NNS with respect to other major clinical variables (weight gain, energy intake, heart rate, oxygen saturation, intestinal transit time, age at full oral feeds) . No negative outcomes were reported in any of the studies. Studies have reported that oral stimulation enhances the oral feeding performance of preterm

infants born between 26 and 29 weeks' gestational age and also accelerates the transition to full oral feedings in preterm infants with greater intake of milk by the experimental group.[33,34] A randomised study by Rocha et al[35] has shown that sensory-motor-oral stimulation and non-nutritive sucking enhances the oral feeding performance of preterm infants in attaining earlier oral feeds and decreased length of hospital stay. The influence of non-nutritive sucking and oral stimulation on breastfeeding at discharge, at 3 and 6 month of corrected age in preterm infants with very low birth weight was analyzed through a randomized trial.[36] There was a statistically significant difference in breastfeeding at discharge with NNS group.

Recommendations: Non Nutritive Sucking accelerates the maturation of the sucking reflex and has been observed to shorten the transition time from gavage to breast feeding. NNS helps in initiation and maintanence, of successfull breast feeding, during hospital stay and after discharge. (GRADE A)

What is the role of Kangaroo Mother Care for LBW infant feeding?

Evidence: Kangaroo mother care (KMC), or "skin-to-skin contact" and its benefit on breastfeeding, early hospital discharge, psycho-emotional and neuro-sensory development have been reviewed by many studies. Cochrane metanalysis[37] has shown that KMC infants had more weight gain/day, and lower risk of nosocomial infection and lower incidence of respiratory infection at 6 months of age. However the weak methodology of the included trials precluded the authors from concluding that KMC was superior to conventional neonatal care. Two RCTs which evaluated the impact of KMC on breastfeeding rates[38,39] showed improvements in breast feeding rates and physiological stability.[40]A pilot test of a community-based feasibility of KMC has been reported from Bangladesh.[41] A study from our country has concluded KMC is safe in stable preterm babies and has a place in home care of LBW babies because of its simplicity which is of benefit in developing countries.[42]

Recommendation: Kangaroo mother care (KMC) is as effective as conventional care in stable LBW infants. There is evidence regarding its beneficial role in initiation and maintenance of breast feeding. KMC helps in better weight gain in LBW infants. (GRADE A).

What should be the method of enteral feeding for LBW infant ?

Evidence: Physiological immaturity and absence of the coordinated sucking and swallowing preclude premature infants less than 34 weeks form direct breast feeding. Before establishment of breastfeeding, milk feeding in these infants can be administered via different routes include: intragastric (nasogastric or orogastric) and oral feeding (cup, bottle, spoon, syringe or paladay).

Nasogastric Tube (NGT) Vs. Orogastric Tube (OGT) Feeding (Level II evidence) Both nasogastric and orogastric tubes feeding are used in neonatal intensive care units. There is not enough data to make any recommendation regarding the superiority of either routes of feeding.[1,43] In one RCT involving 70 VLBW (< 29 weeks) infants comparing NGT vs. OGT feeding, showed no difference in infant behaviour, gastrointestinal tolerance and time to achieve full enteral feeding.[44] There is no data available examining the mortality and long term morbidities. Both types of tubes are associated with pharyngeal, oesophageal, gastric and duodenal perforation with pneumomediastinum .[45] Nasogastric tube are easy to secure but there is some evidence to suggest that NGT feeding in infants < 2000 g may compromise respiratory functions and may increase work of breathing.[46] Therefore, some neonatal units prefer orogastric tube

feeding for infant < 2000 g. Orogastric tubes are easy to pass but may be associated with higher incidence of vagal stimulation, increased oral secretion and are difficult to secure. OG tubes are more prone for upward displacement with potential risk for aspiration.

Nasogastric Tube Vs Transpyloric Feeding: The system review[47] of nine trials showed no evidence of any added advantage with transpyloric feeding over nasogastric feeding. There is some evidence that transpyloric feeding was associated with a greater incidence of gastro-intestinal disturbance and increased mortality.

Oral Feeding Methods (cup, bottle, spoon, syringe or paladai): Cup feeding is recommended as a feeding method for sick and LBW infants by WHO and UNICEF.[1] Bottle feeding is not recommended. Most studies from developed countries comparing cup feeding with bottle feeding showed better physiological stabilities and higher breast feeding rate at discharge and at 3 and 6 months of age with cup feeding.[48,49] One Indian study compared cup, bottle and paladai and found better breast feeding rate at discharge with cup feeding .[50]

Recommendations:

- LBW infants with good suck should be directly breast fed.
- Feeding in LBW babies with no sucking capacity can be done using either indwelling nasogastric or orogastric tubes. There is no difference in tolerance/complications between indwelling nasogastric or orogastric tubes. However, in VLBW (<1500g) who have apnea or respiratory problems, orogastric route may be preferred.
- LBW neonates who have some sucking can be fed using a variety of devices – spoon, paladai, small cups or other traditional/culturally accepted devices.
- Routine feeding via the transpyloric route cannot be recommended.

What should be the frequency of feeds for LBW infants ?

Evidence: Bolus versus Continuous intragastric feeding- Naso or orogastric feeding can be given either as a bolus over 10 to 20 minutes or continuously using infusion pump. A Cochrane review[51] of the seven RCT involving 511 infants of < 1500 g found no difference in, time to achieve full enteral feeds, somatic growth and incidence of NEC between feeding methods. One study noted a trend toward more apneas during the study period in infants fed by the continuous tube feeding but faster weight gain. The potential for greater loss of nutrient (fat and protein)[52-54] and increased risk of bacterial contaminations[55] have been reported with continuous feeding than bolus feeding in laboratory model. All studies were conducted in developed countries. An additional issue in developing countries is that continuous feeding requires a syringe pump and frequent monitoring, which is often not possible in many maternity wards or neonatal units. On the other hand, bolus feeding requires only a gastric tube and monitoring of individual feeds which may be more feasible in these settings.

Two hourly versus three hourly feeding: One Indian study[56] has shown that a three hourly feeding schedule as compared to a two hourly schedule did not decrease the incidence of feed intolerance, nor increase the incidence of hypoglycaemia or apnea. For practical convenience the authors recommend a three hourly schedule over a two hourly one.

Feeding volumes and frequency

Birth Weight (g)	Starting volume (ml/kg/d)	Volume Increment each day (ml/kg/d)	Maximum volume (ml/kg/d)	Frequency of feeds
<1200	10-20	20	180	2 hrly
1200-1600	60	30	180	2 hrly
>1600	60	30	150	3 hrly

Recommendations *:* Frequency of feeding is decided by the gestational age, weight and the clinical condition of the baby (GRADE B).

What should be the infant positioning after feed?

Premature infants are nursed in variety of positions in NICU. It includes supine, prone, side-lying, and head up tilted position.

Evidence: Several studies demonstrated a variety of outcomes affected by different body positioning of preterm infants. van Wijk et al in there study concluded that a strategy of right lateral positioning for the first postprandial hour with a position change to the left thereafter promotes GE and reduces liquid GER in the late postprandial period and may prove to be a simple therapeutic approach for infants with GER disease**.** A comprehensive literature review by Monterosso et al [57] of period 1966-2000 found that the prone position is preferred for very low birth weight infants because it promotes development of pulmonary, cardiovascular, sleep state organizational, and gastrointestinal functions and facilitates the preterm infants recovering from the respiratory complications associated with immaturity. However several studies demonstrated a strong association between prone sleep position and Sudden Infant Death Syndrome (SIDS)[58]. Therefore, The Task Force of the American Academy of Pediatrics (AAP)[59] recommends the non-prone sleeping position for asymptomatic preterm infants to prevent SIDS.

Recommendation:Ideal position for LBW infants after feed is one which would promote gastric emptying, reduces gastroesophageal reflux (GER) and is developmentally appropriate**.** There is a strong association between prone sleep position and Sudden Infant Death Syndrome (SIDS) . Right lateral positioning after feed for 1 hour with a position change to the left there after may prove to be useful in infants with GER.

What are nutritional supplements needed for LBW babies?

Evidence: Elizabeth et al studied the umbilical cord blood nutrients in preterm and term LBW infants. Blood concentrations of all nutrients were lower in preterm LBW infants.[60] The breast milk of mothers who have preterm babies has higher concentrations of several nutrients such as energy, protein, calcium and folate, but there is no increase in the concentrations of phosphorus, magnesium, iron, zinc and vitamins A and D , and they need to be supplemented.

Vitamin D

Evidence: Breast milk alone is not sufficient to maintain newborn vitamin D levels within a normal range.[1,61] There is some evidence of reduced linear growth and increased risk of rickets in very low birth weight infants fed unsupplemented human milk.[62,63]No studies were located which examined the impact and clinical outcomes in infants who were fed unsupplemented and vitamin D-supplemented human milk. The American Academy of Pediatrics recommends supplementing all children who are exclusively breastfed with 400 IU of vitamin D from the first few days of life. The supplementation should continue until 1 year of age, when children begin ingesting vitamin D-fortified milk.[64,65] The ESPGHAN has recommended an intake of 800 – 1000 IU per day for LBW.[64] On a community level the WHO recommendations suggest no additional benefit of increasing the intake of vitamin D for VLBW infants from the usually recommended 400 IU per day.[1]

Calcium and Phosphorous

Evidence: Preterm infants are born with low skeletal stores of calcium and phosphorus. Preterm human milk provides insufficient calcium and phosphorus to meet their estimated needs. There are no data on the effect of phosphorus and calcium supplementation on key clinical outcomes in infants with a birth weight greater than 1500 g.[65] The benefit seems to be predominantly in the VLBW neonates. Three RCTs examined the impact of calcium and phosphorus supplementation as individual components (not as part of multicomponent fortification) on longer-term bone mineralization (after 2 years of age) , showed that it reduces the risk of metabolic bone disease in preterm infants .[66-68] ESPGHAN recommends calcium and phosphorous supplementation at at 120-140mg/kg/day (110-130 mg/100Kcal) and 60-90 mg/kg/day (55-80 mg/ 100Kcal) for the VLBW infants.[64]

Zinc

Evidence: There are no data on the effect of zinc on key clinical outcomes in pre-term infants. Data from two trials in developing countries suggest that term LBW infants in developing countries may have lower mortality and morbidity if they receive zinc supplementation.[69,70] There seems to be no evidence that zinc supplementation in these infants improves neurodevelopment or affects growth.

Iron

Evidence: No studies were located which examined the impact of oral iron supplementation on mortality, neurodevelopment and malnutrition in human-milk-fed LBW infants. Many observational studies have shown an association between iron deficiency anaemia and poor neurodevelopment in infants.[71] Aggarwal et al[72] & Lundstrom et al[73] examined the impact of iron supplementation at 6-8 wks of age in term LBW breast fed infants and found significant improvements in haemoglobin at 4 and 8 weeks. The optimal time to supplement iron has been widely studied. Franz etal[74] studied early versus late supplementation of Iron at 2mg/kg/day and found early iron supplementation was safe , feasible with reduced incidence of iron deficiency anemia and transfusions. Early iron supplementation has also been associated with improved neurocognitive development on followup [75].Since excess of iron intake has been shown to have adverse effects it is recommended that iron supplementation should be delayed in those neonates who have had multiple blood transfusions and high ferritin levels.

Recommendation: All LBW infants who are exclusively breastfed should receive 400 IU of vitamin D from the first few days of life.The supplementation should continue until 1 year of age. All VLBW infants

should receive calcium and phosphorous supplementation at 120-140mg/kg/day (110-130 mg/100Kcal) and 60-90 mg/kg/day (55-80 mg/ 100Kcal) respectively. There is no strong evidence to provide routine zinc supplementation to LBW infants. Iron supplementation at 2-3 mg/kg/day at 6-8 wks , and as early as 2 wks in <1500 gms is effective in preventing anemia of prematurity and needs to be continued till one year of age.

How to monitor growth of LBW infants ?

Evidence: Growth monitoring is a simple and objective tool of assessing the adequacy of feeding and nutritional wellbeing of low birth weight (LBW) infant. Serial growth monitoring allows early identification of growth faltering. Ideally speaking, adequate nutritional support should allow LBW infants to achieve growth velocity (GV) similar to in-utero GV (15 mg/kg/d) during their stay in NICU. However, studies have shown that most infants fail to achieve in-utero growth velocity and exhibit postnatal growth failure.[1] A data from the National Institute of Child and Human Development (NICHD) Neonatal Research Network indicates that 16% of extremely low birth weight infants are small for gestational age at birth, but by 36 weeks corrected age, 89% and by 18- 22 months 40% have growth failure. Postnatal weight loss and growth of low birth weight infant's depends on the degree of maturity, underlying clinical conditions and nutritional practices. Two types of growth charts are used to monitor growth in LBW and VLBW babies: Intrauterine and Postnatal. Both types of charts have merits and limitations. There are no comparative studies establishing superiority of one over the other. No population based in-utero or postnatal growth charts from India could be located.

Recommendation: All LBW infants should be checked for weight (daily), head circumference (weekly) and length (weekly or fort-nightly) during their NICU stay. Serial growth monitoring allows early identification of growth faltering. Fentons[3] growth charts can be used for preterm babies. WHO Growth charts (2006) should be used from corrected age of 40 weeks into childhood.

References

1. Edmond K and Bhal R. Optimal feeding of the low birth weight infants. Technical Review. World Health Organisation 2006; 1-130.
2. Quigley M, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD002971. DOI: 10.1002/14651858.CD002971.pub2
3. Lucas A, Morley R, Cole TJ, Gore SM.. A randomized multicentre study of human milk versus formula and later development in preterm infants. Arch Dis Child Fetal Neonatal Ed. 1994 Mar; 70(2):F141-146.
4. Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. Pediatrics, 2005; 116(2):400-6.
5. Henderson G, Anthony MY, McGuire W. Formula milk versus maternal breast milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD002972. DOI: 10.1002/14651858.CD002972.pub2McGuire W, Anthony MY.
6. Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD000343. DOI: 10.1002/14651858.CD000343.pub2

7. Mukhopadhyay K, Narang A , Mahajan R. .Effect of Human Fortification in Appropriate for Gestation and Small for Gestation Preterm Babies: A Randomised Control Trial. Indian Pediatr 2007; 44: 286-290.
8. Arslanoglu S, Moro GE, Ziegler EE Adjustable fortification of human milk fed to preterm infants: does it make a difference? J Perinatol. 2006 Oct;26(10):614-21.Epub 2006 Aug3.
9. Gathwala G, Chawla M, Gehlaut VS. Fortified human milk in the small for gestational age neonate.Indian J Pediatr. 2007 Sep;74(9):815-8.
10. Kuschel CA, Harding JE. Protein supplementation of human milk for promoting growth in preterm infants. Cochrane Database Syst Rev. 2000;(2):CD000433.
11. Premji SS, Fenton TR, Sauve RS. Higher versus lower protein intake in formula-fed low birth weight infants.low birth weight infants. Cochrane Database Syst Rev.2006 Jan;(1) :CD003959.
12. Kuschel CA, Harding JE, Kumaran VS. Fat supplementation of human milk for promoting growth in preterm infants. *Cochrane Database of Systematic Reviews* 2002, Issue 2. Art. No.: CD000341. DOI: 10.1002/14651858.CD000341**.**
13. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ 1998;317(7171):1481-7.
14. Lucas A, Morley R, Cole TJ, Gore SM, Lucas PJ, Crowle P, Pearse R, Boon AJ, Powell R. Early diet in preterm babies and developmental status at 18 months. Lancet. 1990 ;335(8704):1477-81.
15. Morley R, Lucas A. Randomized diet in the neonatal period and growth performance until 7.5-8 y of age in preterm children. Am J Clin Nutr. 2000 ;71(3):822-8.
16. Henderson G, Fahey T, McGuire W. Multicomponent fortification of human breast milk for preterm infants following hospital discharge. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD004866. DOI: 10.1002/14651858.CD004866.pub2
17. Lucas A, Fewtrell MS, Morley R, Singhal A, Abbott RA, Isaacs E, Stephenson T, MacFadyen UM, Clements H. Randomised Trial of nutrient enriched formula versus standard formula for post discharge preterm infants.Pediatrics.2001; 108(3):703-711.
18. Szajewska H , Horvath A ,Koletzko B, Marcin K. Effects of brief exposure to water, breast-milk substitutes, or other liquids on the success and duration of breastfeeding: A systematic review. Acta Pediatrica. 2007; 95(2) pgs 145-152.
19. Pérez-Escamilla R, Segura-Millán S, Canahuati J , Allen H. Prelacteal Feeds Are Negatively Associated with Breast-Feeding Outcomes in Honduras. J Nutr.1996; 126(11):2765-73.
20. Bombell S, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD001970. DOI: 10.1002/14651858.CD001970.pub2
21. Bombell S, McGuire W. Early trophic feeding for very low birth weight infants. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD000504. DOI: 10.1002/14651858.CD000504.pub3.
22. Tyson JE, Kennedy KA. Trophic feedings for parenterally fed infants. Cochrane Database of Systematic Reviews 2005; 5: CD000504.
23. McClure RJ, Newell SJ. Randomised controlled study of clinical outcome following trophic feeding. Archives Of Diseasein Childhood-Fetal and Neonatal Edition 2000; 82:F29-33.
24. Berseth CL, Bisquera JA, Paje VU. Prolonging small feeding volumes early in life decreases the incidence of necrotizing enterocolitis in very low birthweight Infants. Pediatrics. 2003; Mar; 111(3):529-34.
25. McGuire W, Bombell S. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD001241. DOI: 10.1002/14651858.CD001241.
26. O'Connor D L, HallR, Adamkin D, Auestad N**,**Castillo M etal. Growth and Development in Preterm Infants Fed Long-Chain Polyunsaturated Fatty Acids: A Prospective, Randomized Controlled Trial. Pediatrics. 2001; Vol.108 (2):pg 359-371.

27. Simmer K, Schulzke S, Patole S. Longchain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD000375. DOI: 10.1002/14651858.CD000375.pub3.
28. Henriksen C, Haugholt K, Lindgren M, Aurvåg AK, Rønnestad A, Grønn M, Solberg R, Moen A, Nakstad B, Berge RK, Smith L, Iversen PO, Drevon CA. Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid. Pediatrics. 2008 Jun; 121(6):1137-45.
29. Innis SM, Adamkin DH, Hall RT, Kalhan SC, Lair C, Lim M etal. Docosahexaenoic acid and arachidonic acid enhance growth with no adverse effects in preterm infants fed formula. J Pediatr. 2002 May; 140(5):547-54
30. Clandinin MT, Van Aerde JE, Merkel KL, Harris CL, Springer MA, Hansen JW, Diersen-Schade DA. Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and arachidonic acid. : J Pediatr. 2005 Apr;146(4):461-8.
31. Makrides M,Gibson R A, McPhee A J, Collins C T, Davis P G, Doyle LW, Simme K, Colditz P B, Morris S. Neurodevelopmental Outcomes of Preterm Infants Fed High-Dose Docosahexaenoic Acid *JAMA.* 2009;301(2):175-182.
32. Pinelli J, Symington AJ. Non-nutritive sucking for promoting physiologic stability and nutrition in preterm infants. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD001071. DOI: 10.1002/14651858.CD001071.pub2.
33. Simpson C, Schanler RJ, Lau C. Early introduction of oral feeding in preterm infants. Pediatrics. 2002 Sep;110(3):517-22.
34. Fucile S, Gisel E, Lau C. Oral stimulation accelerates the transition from tube to oral feeding in preterm infants.J Pediatr. 2002 Aug; 141(2):230-6.
35. Rocha AD, Moreira ME, Pimenta HP, Ramos JR, Lucena SL .A randomized study of the efficacy of sensory-motor-oral stimulation and non-nutritive sucking in very low birthweight infant.Early Hum Dev. 2007 Jun; 83(6):385-8.
36. Pimenta HP, Moreira MEL, RochaAD, Gomes JuniorSC, Pinto LW, Lucena SL. Effects of non-nutritive sucking and oral stimulation on breastfeeding rates for preterm, low birth weight infants:a randomized clinical trial;J Pediatr (Rio J). 2008; 84(5):423-427.
37. Conde-Agudelo A, Belizán JM. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD002771. DOI: 10.1002/14651858.CD002771
38. Charpak **N,** Ruiz-Peláez JG**,** Figueroa de Z, Charpak Y**.**Kangaroo Mother Versus Traditional Care for Newborn Infants 2000 Grams: A Randomized, Controlled Trial. Pediatrics. 1997Oct;100(4): 682-688.
39. Charpak N, Ruiz-Peláez JG, Figueroa de Z, Charpak Y . A randomized, controlled trial of Kangaroo Mother Care: Results of Follow-Up at 1 Year of Corrected Age. Pediatrics Vol. 108(. 5) 2001, pp. 1072-1079.
40. Bergman NJ, Linley LL, Fawcus SR. Randomized controlled trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization in 1200– to 2199–gram newborns. Acta Paediatrica, 2004, 93(6):779–85.
41. Quasem I et al. Adaptation of kangaroo mother care for community-based application. Journal of Perinatology, 2003, 23(8):646–51.
42. GuptaM, Jora R.,Bhatia R. Kangaroo mother care(KMC) in LBW infants- A Western Rajasthan experience. Indian J Pediatr2007; 74(8):747-749.
43. Hawes J. McEwan P, McGuire W. Nasal versus Oral route for placing feeding tubes in preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.:CD003952. DOI: 10.1002/14651858. CD003952.pub2
44. Dsilna A, Christensson K, Alfredsson L, Lagercratz H, Blennow M. Continuous feeding promotes gastrointestinal tolerance and growth in very low birth weight infants. J Pediatr. 2005 Jul; 147(1):43–9.

45. Sands T,Glasson M, Berry A. Hazards of nasogastric tube insertion in the newborn infant. Lancet ii, 1989; 680
46. Greenspan JS,Wolfson MR, Holt WJ, Shaffer TH. Neonatal gastric intubation: differential respiratory effects between nasogastric and orogastric tubes. Pediatric Pulmonology 1990; 8:254–8.
47. McGuire W, McEwan P. Transpyloric versus gastric tube feeding for preterm infants Cochrane Database Syst Rev. 2007 Jul 18 ;(3):CD003487
48. Collins CT, Makrides M, Gillis J, McPhee AJ. Avoidance of bottles during the establishment of breast feeds in preterm infants. Cochrane Database of Systemativ Reviews 2008, Issue 4. Art. No.: Cd005252. DOI: 10.1002/14651858. CD005252.pub2
49. Rocha N, Martinez F, Jorge S. Cup or bottle for preterm infants: effects on oxygen saturation, weight gain and breastfeeding. Journal of Human Lactation, 2002, 18:132–137.
50. Malhotra N,Viswambaran L, Sundaram KR, Narayanan I. A controlled trial of alternative methods of oral feeding in neonates. Early Hum Dev. 1999 Feb; 54(1):29–38.
51. Premji S, Chessell. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. Cochrane Database Syst Rev, 2004, May 25
52. Narayanan I, Singh B, Harvey D. Fat loss during feeding of human milk. Archives of Disease in Childhood, 1984, 59(5):475–7.
53. Stocks RJ, Davies DP, Allen F, Sewell D. Loss of breast milk nutrients during tube feeding. Arch Dis Child. 1985 Feb; 60(2):164–6.
54. Brooke OG, Barley J. Loss of energy during continuous infusions of breast milk. Archives of Disease in Childhood, 1978, 53(4):344–5.
55. Martin R, Fanaroff A, Walsh M (Eds). Fanaroff and Martin's Neonatal–Perinatal medicine: diseases of the foetus and infant. Elsevier 7th edition, p 593
56. Dhingra A., Agrawal S.K., Kumar P., Narang A. A randomised controlled trial of two feeding schedules in neonates weighing < 1750g. The Journal of Maternal-Fetal and Neonatal Medicine, March 2009; 22 (3):198-203.
57. Monterosso L, Kristjanson L, Cole J. Neuromotor development and physiologic effects of positioning in very low birth weight infants. J Obstetr Gyneco Neonat Nurs 2002; 31(2):138-46.
58. Willinger M, Hoffman HJ, Wu KT, Hou JR, Kessler RC, Ward SL,et al. Factors associated with the transition to nonprone sleep positions of infants in the United States. JAMA 1998; 280 (4):329-35.
59. American Academy of Paediatrics, Task Force on Infant Positioning and SIDS. Positioning and Sudden Infant Death Syndrome (SIDS). Paediatrics 1996; 98: 1216-8.
60. Elizabeth KE, Krishnan V, Vijayakumar T. Umbilical cord blood nutrients in low birth weight babies in relation to birth weight & gestational age. Indian J Med Res 2008; 128 : 128-33.
61. Lucas A, Brooke OG, Baker BA, Bishop N, Morley R. High alkaline phosphatase activity and growth in preterm neonates. Arch Dis Childhood 1989; 64 : 902-9.
62. Schanler R. Human milk. In: Tsang RC, Uavy RA, Koltez KoB, Zlotkin SH, editors. Nutrition of the preterm infant: scientific basis and practical guidelines, 2nd ed. Cincinnati, OH Ohio: Digital Educational Publishing, 2005.
63. 63.Robertson I. Follow-up study of clinical rickets in Cape Town infants. S Afr Med J 1970; 44 : 368.
64. 61.Slagle TA, Gross SJ. Effect of early low-volume enteral substrate on subsequent feeding tolerance in very low birth weight infants. J Pediatr. 1988; 113:526–53.
65. Dollberg S, Kuint J, Matzkereth R, Mimouni FB. Feeding tolerance in very low birth weight infants is affected by mode of feeding: a randomized clinical trial of intermittent versus continuous drip feeding. Pediatr Res. 1999; 45:280A
66. Dunn L, Hulman S, Weiner J, Kliegman R. Beneficial effects of early hypocaloric enteral feeding on neonatal gastrointestinal function: preliminary report of a randomized trial. J Pediatr. 1988; 112:622–629.

67. ESPGHAN committee on nutrition ; Enteral Nutrient Supply for Preterm Infants: Commentary From the European Society for Paediatric Gastroenterology, Hepatology,and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr, 2010; 50, 1: 1-9.
68. Kuschel CA, Harding JE, Kumaran VS. Calcium and phosphorus supplementation of human milk for preterm infants. Cochrane Database of Systematic Reviews 2001, Issue 4. Art. No.: CD003310. DOI: 10.1002/14651858.CD003310.
69. 66 .Backstrom MC et al. Randomised controlled trial of vitamin D supplementation on bonedensity and biochemical indices in preterm infants. Archives of Disease in Childhood Fetaland Neonatal Edition, 1999, 80:161–6.
70. Laing IA, Glass EJ, Hendry GM, Westwood A, Elton RA, Lang M, Hume R. Rickets of prematurity: calcium and phosphorus supplementation. Journal of Pediatrics, 1985, 106(2):265–8.
71. Holland PC, Wilkinson AR, Diez J, Lindsell DR. Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. Lancet, 1990, 335(8691):697–701.
72. Sazawal S, Black RE, Menon VP, Dinghra P,. Caulfield LE, Dhingra U, Bagati A. Zinc Supplementation in Infants Born Small for gestational age reduces mortality: a prospective, randomized, controlled trial . Pediatrics 2001, 108,1280-1286.
73. Taneja S, Bhandari N, Rongsen-Chandola T, Mahalanabis D, Fontaine O, Bhan MK. Effect of zinc supplementation on morbidity and growth in hospital-born, low-birth-weight infants. Am J Clin Nutr , 2009, 90: 385-391.
74. Lozoff B, Beard J, Connor J, et al. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev 2006;64:S34–43. discussion S72–S91.
75. Aggarwal D et al. Haematological effect of iron supplementation in breast fed term low birth weight infants. Archives of Disease in Childhood, 2005, 90(1):26–9.
76. Lundstrom U, Siimes AM, Dallman PR. At what age does iron supplementation become necessary in low birth weight infants? Journal of Pediatrics, 1977, 91:878–883.
77. Franz AR , Mihatsch WA**,** Sander S, Kron M, Pohlandt F. Prospective randomized trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams. Pediatrics, 2000, 106 (4) : pp700–706 .
78. Steinmacher J, Pohlandt F, Bode H, Sander S, Kron M, and Franz AR. Randomized Trial of Early Versus Late Enteral Iron Supplementation in Infants With a Birth Weight of Less Than 1301 Grams: Neurocognitive Development at 5.3 Years' Corrected Age.Pediatrics, 2007; 120(3): 538 – 546.

Annexure

1. Table 1. Developmental signs that show readiness for feeding

Behaviour at the breast	Response when offered expressed breast milk by cup	Range of gestational or post-menstrual age (weeks)	Feeding readiness	Range of birth weight
No definite mouthing	No extrusion of tongue, no licking	<28	No readiness IV feeding needed Intragastric tube may be possible	<1000g
Occasional, ineffective suckling attempts	Opening mouth, tongue out of the mouth, licking milk. Not able to co-ordinate breathing and swallowing well	28-31	First signs of oral readiness Intragastric feeding appropriate Can try small amount of direct expression or cup feeding to gain oral experience	1000-1500g
May root and attach to breast. Weak suckling attempts	Opening mouth, tongue forward, licking milk Able to co-ordinate breathing and swallowing well.	32-34	Can now use cup or other alternative feeding method for most feeds Allow baby to attach to breast for part of feed or for some feeds	1300-1800g
Able to root and attach to the breast. May have periods of organized suckling with long pauses	Opening mouth, tongue forward, licking milk, coordinating breasting and swallowing Co-ordinating breathing and swallowing well And now able to suck at the milk from the cup and other alternatives.	33-35	Breastfeed for part of feed or some complete feeds Cup or alternative supplement most feeds to ensure adequate intake	1600-2000g
Able to suckle effectively at the breast	Able to suck at milk from the cup and other alternative feeding methods	34-36	Breastfeed, and may need some supplements by cup or other alternative	1800-2200g

Abstracted from "The Optimal Feeding of Low Birth Weight Infant"-WHO document provided by Dr. Vinod K Paul

2. **Table 2. Feeding volumes for infants with birth weight 2000g to 2500 g whose mothers cannot or choose not to breastfeed**

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day7 onwards
Recommended fluid/feed intake (ml/kg/day)	60	80	100	120	140	150	160+
Amount of feed every 3 hours (ml)	17	22	27	32	37	40	42

3. **Table 3. Feeding an infant with birth weight 2000 to 2500 grams: summary**

Approximate age	Assessment of feeding readiness	What to feed	Feeding method and schedule
DAY 1	Clinically stable and able to suckle effectively at the breast	Breast milk *If mother cannot or chooses not to give her own breast milk, use standard infant formula**	Breastfeed every 2-3 hours (more frequent if the infant wants) *3 hourly feeds using alternative oral feeding method. 60 ml/kg/day divided into 8 feeds*
	Clinically stable, able to attach to the breast but not suckling effectively, able to accept feeds using an alternative feeding method	Breast milk *(if mother's breast milk is not available, as above)*	Every 3 hours: Allow infant to suckle at the breast Then give feed of expressed breast milk using an alternative oral feeding method. Offer the full volume: 60 ml/kg/day divided into 8 feeds
DAY 2-7	Clinically stable and able to suckle effectively at the breast. No vomiting or abdominal distension	Breast milk *(if mother's breast milk is not available, as above)*	Breastfeed every 2-3 hourly (more frequent if the infant wants) *Or 3 hourly feeds using alternative oral feeding method. Increase feeds by about 20 ml/kg/day until volumes of 160-180 ml/kg/day are reached.*

	Clinically stable, not able to suckle effectively at the breast. Able to accept feeds using and alternative feeding method. No vomiting or abdominal distension.	Breast milk *(if mother's breast milk is not available, as above)*	Every 3 hours: Allow infant to suckle at the breast before each feed Give expressed breast milk using an alternative oral feeding method. Give full volume. Increase feeds by 20 ml/kg/day up to 160-180 ml/kg/day.
DAY 8-28	Clinically stable and able to suckle effectively at the breast. Waking spontaneously for feeds, and showing signs of hunger. No vomiting or abdominal distension	Breast milk *(if mother's breast milk is not available, as above)*	Exclusive breastfeeding on demand *3hourly feeding using alternative oral feeding method. 160-180 ml/kg/day*
AT 2 MONTHS		Breast milk *if mother's breast milk is not available, as above)* Start iron supplements	Exclusive breastfeeding on demand Iron supplementation 2 mg elemental iron/kg/day, maximum total dose of 15 mg Fe/ day
AT 6 MONTHS		Breast milk *(if mother's breast milk is not available, as above)* Iron supplements Start complementary foods	Breastfeeding on demand Iron supplementation 2 mg elemental iron/kg/day, maximum total dose of 15 mg Fe/ day Apppropriate complementary feeding

** Strict guidelines must be followed in preparation and feeding of infant formula to reduce risks of infection.*

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Use of Parenteral Nutrition in the Newborn

Summary of Recommendations

- **Units providing intensive care for very low birth weight and sick babies should have facilities to provide parenteral nutrition.**
- **In the 'eligible' neonates, parenteral nutrition should be started at the earliest.**
- **The administration of parenteral nutrition requires the presence of trained personnel, due diligence, aseptic measures, automated calculations and careful monitoring for complications.**

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Introduction

Extrauterine growth retardation is a major clinical problem in preterm infants[1,2]. Recently it has become clear that small infants, especially VLBW, have special nutrition needs in early life. This underlines the importance of nutritional interventions immediately after birth. The limitations of enteral route during early life in preterm babies, makes parenteral nutrition (PN) essential component of nutritional management. However, the results of surveys conducted to assess nutritional practices in NICUs, indicate that the nutritional practices are variable, especially pertaining to PN[3]. The situation in India is quite serious. There is a lack of scientific approach towards PN in India, which is reflected by the limited research evidence from India[4-12]. It was found (through personal communication) that still many Indian neonatologists feel that PN is not an essential part of management. This attitude is surprising, but is responsible for PN not keeping up pace along with other interventions in neonatal care.

This guideline reviews the current evidence related to use of parenteral nutrition in the newborn and offers recommendations regarding issues related to indications, dosage, administration, monitoring and nutrient needs.

Which neonatal units should give PN?

Any neonatal units providing intensive care for small and sick neonates should have the facility for PN. Level II units can provide short term PN whereas level III units should be capable of providing PN for longer duration. These units should organize space for preparation and dispensing PN.

Which babies should receive PN [13-16]?

1. Prematurity <28 weeks gestation and/or <1000 grams
2. Prematurity <32 weeks gestation and/or <1500 grams who are unable to achieve reasonable enteral feeds by day 3.
3. Infants >32 weeks and/or >1500 grams who are unlikely to achieve at least 50% enteral feeds by day 5.
4. Necrotizing Enterocolitis
5. Surgically correctable gastrointestinal tract anomalies (exomphalus, gastroschisis, atresia of intestine, volvulus, short bowel syndrome etc)

Recommendation (GRADE A)***:***

- PN should be used when enteral feeding is impossible, inadequate, or hazardous. A duration of more than 4 to 5 days of "nil by mouth" is generally considered an indication for PN.
- PN is indicated where it is anticipated that the infant is likely to be receiving less than 50% of total energy requirement by day 7 of life.

When should PN be started [13-19]?

Evidence: Several controlled studies have demonstrated the efficacy and safety of amino acids initiated within the first 24 hours after birth. Concentrations of some key amino acids begin to decline from the time the cord is cut. Secretion of insulin depends on the plasma concentrations of these amino acids as

well as that of glucose. Early amino acid administration may stimulate insulin secretion consistent with the concept that forestalling the starvation response improves glucose tolerance. Many studies now show clearly that specific nutritional deficits at critical stages of development limit fundamental components of growth that have long-lasting influences.

Recommendation: Early introduction and more aggressive nutritional mangement has been shown to be safe and effective, even in the smallest and most immature infants as early as day 1.

What should be the protocol for initiating and increasing various constituents of PN (dosing regimens)?

a) Energy: The daily energy requirement for pretem infants is summarized in table 1. Minimal energy needs are met by 50-60 kCal/kg/day[20]. On parenteral nutrition energy needs for growth for preterm and term neonates are 110-120 kCal/kg/day and 90-100 kCal/kg/day, respectively. Energy is necessary for protein utilization and 30-40 kCal/kg/day are required for utilization of one gram of aminoacid (AA). A reasonable goal for energy accretion in preterm neonates is 25 kCal/kg/day, which is fetal energy accretion rate in third trimester[21].

Table 1 : Daily energy intake recommended for preterm infants

Committee	Recommended energy intake (kcal/kg/day)
American Academy of Pediatrics	105-130
Canadian Pediatric Society	105-135
European Society of Gastroenterology and Nutrition	98-128
Life Sciences Research Office	110-135

b) Dextrose: Dextrose is started on day 1. The dose of dextrose is calculated as glucose infusion rate (GIR) and not by percentage of dextrose ie: 5% or 10% Dextrose. Recommended GIR in preterm neonates on day 1 is between 4 to 8 mg/kg/min[22]. It is increased daily by 1-2 mg/kg/min till normoglycemia (blood glucose level between 45 to 150 mg/dL) is maintained. For babies on PN, minimum blood glucose desired is 60 mg/dL. Maximum GIR for preterm and term is 12 mg/kg/min and 13 mg/kg/min, respectively. [22,23] Glucose intake should cover 60-75% of non-protein calories(NPC). Insulin use should be restricted to conditions where reasonable adaptation of GIR does not control marked hyperglycemia.[24] The use of insulin typically is reserved for those infants who do not respond to a reduction in glucose delivery or continue to experience higher than desired serum glucose levels.[24] There is no threshold of glucose concentration adapted universally to initiate insulin therapy. Moreover, bacteremia should be ruled out when hyperglycemia develops in a baby receiving TPN at a dextrose concentration previously tolerated.

c) Amino acids (AA): Proteins are major structure and functional components of cells of body. Preterm neonates tolerate amino acid supplementation from day 1 of life and positive effects on protein metabolism are seen[14,15,25,27-28]. It has been shown in newer studies that newborns tolerate 3.5 g/ kg / d amino acids on first postnatal day[15]. Positive nitrogen balance is achieved at AA administration of 2.3 –

2.65 g/kg/d[25,27]. Others report that preterm babies can tolerate amino acid supplementation upto 3.9 g/kg/d[29]. Preterm infants without AA supplement excrete around 0.6 – 1.1 g/ kg / day protein[30-33]. For proper protein accretion 30 NPC per gram of amino acid are required. While prescribing amino acids Non-Protein Calorie: Nitrogen ratio should be calculated and maintained between 150 and 250. The nitrogen content varies with the protein preparation but in general, can be calculated by multiplying protein intake by 0.16. AA can be initiated on first or second second day of life in preterm neonates in a dose of 2.5 g/kg/d and increased to a maximum of 3.5 to 4 g/kg/d by day3 or 4.

The ideal quantitative composition of amino acid solutions is still controversial. AA solutions are available as 6% and 10% preparations. AA solution should contain essential (valine, leucine, isoleucine, methionine, phenylalanine, threonine, lysine and histidine) and conditionally essential (cysteine, tyrosine, glutamine, arginine, proline, glycine and taurine) AAs, should not have excess of glycine and methionine and should not contain sorbitol. Glutamine which is abundant in breast milk and is an essential amino acid for premature neonates, is not available in parenteral protein solutions due to stability issues. A review of literature demonstrated glutamine supplementation to a isonitrogenous study amino acid solution compared to a standard amino acid solution did not improve protein retention or weight gain, and did not reduce the risk of mortality or late onset sepsis in ELBW. Other amino acids which are not available in these solutions are tyrosine and cysteine. It has been shown that addition of cysteine can improve protein accretion. Cysteine hydrochloride which can be added just before delivery is available and the current recommendations are to add 40 mg/g of amino acid to a maximum of 120 mg/kg. However, this can result in metabolic acidosis, which can be taken care of by using acetate in parenteral solutions. In a meta-analysis, the supplementation of cysteine was associated with improved nitrogen balance, but did not significantly affect growth. No reliable tests are available for routine clinical use to evaluate Amino Acid tolerance.

d) Lipids: Lipid is energy dense source needed for cell metabolism and proper brain development. Generally lipid intake of 25 – 40% of NPC is recommended in fully parenterally fed neonate for maximal oxidation [30]. Lipid provides EFA like linoleic and linolenic acid. After one week of discontinuation of lipids, EFA levels go down. In order to prevent biochemical evidence of EFA deficiency, 0.25 g/kg/d linoleic acid should be given to preterm infants and 0.1 g/kg/d to term infants. In preterm neonates, lipids can be started on day 1 of life in a dose of 1 g/kg/d and increased by 1 g/kg/d to a maximum of 3 g/kg/d.[15,36]. Preterm neonates tolerate upto 3 g/kg/d of continuous lipid supply [15, 31,32]. However, in ELBW babies, this should be strictly monitored [33]. In term infants, the lipids can be increased up to 4 g/kg/d. Before initiation and prior to every increment of lipids serum levels of triglycerides should be checked and confirmed to be <200 mg/dL.

Lipid infusion can be given in patients with hyperbilirubinemia and thrombocytopenia[34,35]. It does not increase risk of bacterial sepsis[34,35] and it is not associated with increased sepsis related mortality[36] (if proper dosage and administration guidelines are followed). Thus, lipids do not have significant effect on short term adverse effects[32]. Lipids are available as 10% and 20% solutions but 20% lipid concentration is preferred because of the lower phospholipids : triglyceride ratio and thus leading to higher lipid clearance time. Lipids are potentially vulnerable to photo-oxidation leading to peroxide formation. Hence, the lipid emulsion should be covered with sterile opaque paper or aluminum foil**.** Carnitine is administered in neonates receiving PN for more than 2-4 weeks (8-10 mg/kg/d) to increase oxidation of fat [37]. A systematic review however found no evidence to support the routine supplementation of parenterally fed neonates with carnitine.

e) Vitamins: Parenteral vitamins are usually applied as a mixture of different vitamins. Vitamins should be added to lipid emulsion to increase stability and reduce peroxide formation[38,39]. Vitamin induced peroxide load can be reduced by shielding of tubing from light exposure[40]. Except vitamin K, all vitamins should be supplemented daily. Adult MVI is the only preparation available in our country. It contains benzoic acid as stabilizer which is not recommended for neonates and should be used with caution. The dose of adult MVI is 0.5 ml/kg (comparing parenteral vitamin supplement doses as suggested by ESPGHAN[41] with constitution of adult MVI). It is added on day 1. Pediatric MVI is currently not available in India. Separate preparations of fat-soluble and water-soluble vitamins suitable for neonates are not available in India.

f) Minerals: Sodium, Potassium and Chloride are essential minerals for survival. In VLBW infants, sodium intake should be restricted during first phase of fluid balance to reduce risk of bronchopulmonary dysplasia[42]. Till 6 – 10% of weight loss has occurred sodium should not be added to PN. Potassium should not be added till diuresis sets in. Sodium and potassium are added to PN usually from day 3 onwards, depending on serum levels. Sodium and potassium can be given as chloride, lactate, or phosphate salts. Infants who receive electrolytes solely as chloride salts may develop hyperchloremic metabolic acidosis. Chloride is generally given as sodium chloride. Estimated and advisable intakes are based on accretion studies and urinary and fecal losses from balance studies completed in the late 1970s. Trace elements (except Zinc and Copper) are necessary only for babies needing TPN for more than 2 weeks. Calcium, Phosphate and Magnesium should be added from day 1. The doses of various electrolytes and minerals are shown in table 2.

Table 2: Recommended doses of electrolytes and minerals

Electrolyte/Mineral	Recommended intake (mEq/kg/day)
Sodium	0 – 3*
Potassium	0 – 2
Chloride	0 – 5
Calcium (mg/kg/d)	32
#Phosphate (mg/kg/d)	14
Magnesium (mg/kg/d)	5

*the dose of sodium can be adjusted upto 10 mEq/kg depending on age and serum level. # Phosphate is currently not available in India

g) Trace elements: The 1988 American Society of Clinical Nutrition (ASCN) guidelines are given for term and preterm infants. Zinc is universally recommended from day one of TPN, whereas the other trace minerals are generally provided after two, four, or 12 weeks' of TPN without any appreciable enteral feeding. Copper, selenium, molybdenum, and iron can be delivered separately also. Copper and manganese are discontinued from TPN solutions with the complication of cholestasis, and amounts of chromium, selenium, and molybdenum are reduced or omitted when renal output is low.

When to stop PN?

Recommendation: Once the enteral nutrition is tolerated and baby takes 75-80% of the expected fluid volume by enteral route, PN can be stopped. (GRADE D)

Should we use 'standardized or individualized' solutions?

The use of standardized protocols in preterm neonates result in better provision of nutrients, weight gain and blood count profile compared with protocol prescribed by individual physicians[43]. Since manual compounding is associated with a greater risk of compounding errors and microbial contamination, the use of standard solutions might be a preferable alternative[44]. Hence it is desirable to have standardized solutions, which are not available at present in our country[12].

Which are the constituents suitable for neonates available in our country?

The market support for PN preparations in India is not very satisfactory. Vital preparations like phosphate, pediatric multivitamins and trace elements are not available. Amino acid and lipid preparations are available. The list of available PN preparations in Indian market is given in the Annexure.

Who should prepare the solutions and what are the guidelines for preparation?

PN can be prepared by pediatricians, neonatologists, pediatric residents, nursing staff and nutritionists, who are trained for PN preparation. A strict sterile aseptic technique is essential for preparation and administration of the PN. Use of Laminar flow is desirable with surgical scrubbing during preparation and administration. These applications reduce PN related complications[5].

Table 3: Dos and Don'ts of preparing PN

Dos	Don'ts
Strict asepsis, including surgical scrubbing and gowning	Use of gloves only during PN preparation
Sterile surface for mixing different constituents, use of Laminar flow is desirable	Continued use of prepared solution beyond 24 hours
Infusion sets to be changed every day	Administration of antibiotics and inotropes through line used for PN
Use of infusion pumps for administration	Untrained person preparing PN

It is advisable to have the nutrient ampoules and bottle surfaces sterilized for 30-45 minutes by switching on the UV light in the laminar air flow system. Surgical scrubbing is essential for setting up PN on the patient. Use of bacterial filters is recommended. Reuse of nutrient solutions is best avoided. However, the bottles can be shared between patients administered PN on the same day. It is advisable that the parenteral solutions should not be used for more than 24 hours.

What are the guidelines for doing the calculations?

Manual calculation of PN can be done following simple steps, as shown in annexure. Manual calculation is a demanding job, needs training and confirmation before execution of order. Automating of the process of writing repetitive tasks and tedious calculations should be aimed at, as PN prescription error rate is 27.9% and it can be reduced by interactive computerized PN worksheet[45,46]. Many softwares for PN calculation are now available (see website www.nnfpublication.org). These softwares are accurate, validated and reduce errors of compounding. They can be of use to keep track of patient's nutritional status.

What should be the routes and techniques of PN administration?

Route of PN delivery depends on energy needs, venous access, anticipated duration of support, and potential risks. PN can be administered through peripheral or central lines (umbilical or central venous route). Use of peripheral line is safer when PN is needed for less than 10 days[47].

PICC line is inserted to avoid phlebitis when[48]:

1. Concentrations of > 12.5% glucose are needed.
2. Osmolarity of solution is >900 mOsm/L.
3. Prolonged period of PN is anticipated.

The position of the tip of the catheter needs to be in a large vessel preferably the superior or inferior vena cava outside the heart with position confirmed by x-ray prior to use. Single lumen central lines are preferred over multiple lumen catheters due to less risk sepsis[49,50]. PN lines should be handled minimally and with all aseptic techniques. PICC use reduces number of catheters inserted and has not been associated with increased risk of infection [51]. Heparin should be added to the PN when PICC is the route of delivery.

Photo protection of PN: Peroxide formation in PN is now considered an important problem. Source of peroxide in PN are many viz amino acids (tryptophan, tyrosine, methionine, cysteine and phenylalanine), multivitamins (riboflavin), trace elements, lipid emulsion (PUFA) and additives used for stabilization of PN[52]. Photo protection of PN reduces peroxide load on the newborn[53]. Photo protection of PN reduces incidence of BPD[54].

How to monitor the nutritional status in babies on PN - What are the nutritional goals?

Nutritional monitoring should be an important part of neonatal management. Goal for the growing preterm infant has been to match the third trimester intrauterine growth. Postnatal body weight curves have been designed for less than 1000 gram babies on early enteral and parenteral nutrition[55,56]. Regaining birth weight earlier can be the first benchmark. This can be achieved early by setting up nutrition support guidelines[57].

How to monitor babies on PN?

Metabolic and sepsis related complications are most common. Catheter related problems and calculation errors need continuous vigilance. Certain problem like cholestasis is seen with prolonged PN. Following monitoring schedule[12] helps in minimizing PN related complications.

Table 4: Monitoring of a baby on PN

Parameter	Initial period (First 3-4 days)	Established PN
Weight (grams)	Same time each day	Same time each day
Length (cm)	-	Weekly
Head circumference (cm)	-	Weekly
Blood Sugar	Twice daily	Once daily
Urine sugar	Once daily	Once daily
Blood gas	Depending on hemodynamic stability	Once weekly
Serum sodium, Potassium, chloride	Every 24-48 hourly, can be done more frequently if clinical signs demand	Once weekly
Serum calcium, Phosphorous, Magnesium	Every 24-48 hourly, can be done more frequently if clinical signs demand	Once weekly
Urea, Creatinine	Every 48-72 hours	Once weekly
Serum Triglyceride	Before initiating and with increment of lipid dose	Once weekly
Liver function test	Before initiating lipids	Depending on clinical signs
Hemogram	Depending on clinical need	Once weekly

References

1. Grover A, Khashu M, Mukherjee A, Kairamkonda V. Iatrogenic malnutrition in neonatal intensive care units: urgent need to modify practice. J Parenter Enteral Nutr. 2008;32:140-4.
2. Ziegler E, Carlson S. Early nutrition of VLBW infants. J Maternal- Fetal Neonatal Med. 2009;22:191-197.
3. Lapillonne A, Fellous L, Mokthari M, Kermorvant-Duchemin E. Parenteral nutrition objectives for very low birth weight infants: results of a national survey. J Pediatr Gastroenterol Nutr. 2009;48:618-26.
4. Chaudhari S, Vaidya UV. Total parenteral nutrition in India. Indian J Pediatr. 1988;55:935-40.

5. Vaidya UV, Hegde VM, Bhave SA, Pandit AN. Reduction in parenteral nutrition related complications in the newborn. Indian Pediatr. 1991;28:477-84.
6. BhaveSA, VaidyaUV. Parenteral nutrition in the newborn:Technique and protocol. Bull Nat Neonatology Forum 1992, 6: 1-7.
7. Vaidya U, Bhave S, Pandit A. Parenteral nutrition in the management of severe protracted diarrhea. Indian J Pediatr. 1993;60:19-24.
8. Bhave SA, Vaidya UV. Parenteral nutrition in developing countries: Problems and Perspectives. In: Recent Advances in Pediatrics, Vol 4. Ed. Gupte S. New Delhi, Jaypee Publishers, 1993, pp 106-121.
9. Vaidya UV, Bhave SA, Pandit AN. Parenteral nutrition (PN) in the management of very low birth weight (VLBW) babies--a randomized controlled trial. Indian Pediatr. 1995;32:165-70.
10. Shenoi A, Sandesh Kiran PS, Latha TK, Karthik Nagesh N .Peripheral parenteral nutrition. J Neonatol. 2004;18:47.
11. Chaudhari S, Kadam S. Total parenteral nutrition in neonates. Indian Pediatr 2006;43:953-964.
12. Tagare A, Vaidya U. Parenteral nutrition: Current guidelines. J Neonatol 2007;21:186-188.
13. Koretz RL, Lipman TO, Klein S, American Gastroenterological Association. AGA technical review on parenteral nutrition. Gastroenterology 2001;121:970–1001.
14. Wilson DC,Cairns P,Halliday HL,Reid M,McClure G,Dodge J. Randomized controlled trial of an aggressive nutritional regimen in sick very low birth weight infants. Arch Dis Child Fetal Neonatal Ed 1997;77:F4-F11.
15. Ibrahim HM, Jeraidi MA, Baier RJ Dhanireddy R, Krouskop R. Aggressive early total parenteral nutrition in low birth weight infants. J Perinatol 2004; 24: 482-6.
16. Carr B, Denne S, Leitch C. Total energy expenditure in extremely premature and term infants in early postnatal life. Pediatr Res 2000; 47:284A.
17. Thureen PJ, Anderson AH, Baron KA, Melara D, Hay WW, Fennessey P. Protein balance in first week of life in ventilated neonates receiving parenteral nutrition. Am J Clin Nutr 1998; 68: 1128 – 35.
18. Saini J, Macmohan P, Morgan JB, Kovar IZ. Early parenteral feeding of amino acids. Arch Dis Child 1989;64:1362-1366.
19. Lloyd DA. Energy requirements of surgical newborn infants receiving parenteral nutrition. Nutrition 1998;14;101-104.
20. Thureen PJ, Hay WW. Intravenous nutrition and postnatal growth of the micropremie. Clin Perinatol 2000;27:197-219.
21. Ziegler EE, O'Donnell AM, Nelson S E, Nelson SE, Fomon SJ. Body composition of the reference fetus. Growth 1976;40:239 –241.
22. Kalhan SC, Kilic I. Carbohydrate as nutrient in the infant and child:range of acceptable intake. Eur J Clin Nutr 1999;53:S94-100.
23. Sunehag AL, Haymond MW, Schanler RJ Reeds PJ, Bier DM. Gluconeogenesis in very low birth weight infants receiving total parenteral nutrition. Diabetes 1999;48:791-800.
24. Chen SS, Donmoyer CM, Pearson DA, Poole A, Zhang Y, Lacy DB et al. Impact of infection on glucose dependent liver glucose uptake during TPN: interaction with insulin. Am J Physiol Endocrinol Metab 2004;286:E286-295.
25. Van Lingen RA, Van Goudoever JB, Luijendijk I H, Wattimena JL, Sauer PJ. Effects of early amino acid administration owing total parenteral nutrition on protein metabolism in preterm infants. Clin Sci (Lond) 1992; 82: 199 – 203.
26. Van Goudoever JB. Amino acid metabolism and protein accretion. In: Thureen PJ, Hay WW, Jr; editors. Neonatal nutrition and metabolism. 2nd ed 2006; Cambridge University Press.pp 115-121.
27. Thureen PJ, Melara D, Fennessey PV, Hay WW. Effect of low versus high intravenous amino acid intake on very low birth weight infants in the early neonatal period. Pediatr Res 2003;53:24-32.
28. Te Braake FWJ, Van den Akker CHP, Wattimena DJL, Huijmans JGM, van Goudoever JB. Amino acid administration to premature infants directly after birth. J Pediatr 2005;147:457-461.
29. Porcelli PJ, Sisk PM. Increased parenteral amino acid administration to extremely low birth weight infants during early postnatal life. J Pediatr Gastroenterol Nutr 2002;34:174-179.

30. Salas- Salvado J, Molina J, Figueras J, Marso J, Marti – Henneberg C, Jimenez R. Effect of quality of infused energy on substrate utilization in the newborn receiving total parenteral nutrition. Pediatr Res 1993; 33: 112 -7.
31. Drenckpohl D, McConnel C, Gaffiney S, Niehaus M, Macwan KS. Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life. Pediatrics 2008;122:743-751.
32. Simmer K, Rao SC. Early introduction of lipids to parenterally-fed preterm infants. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD005256. DOI: 10.1002/14651858.CD005256.
33. Brans YW, Andrew DS, Carrillo DW, Dutton EB, Menchaca EM, Puelo-Scheppke BA. Tolerance of fat emulsions in very-low-birth-weight neonates:effect of birth weight on plasma lipid concentrations. Am J Perinatol 1990;7:114-117.
34. Gilbertson N, Kovar IZ,Cox DJ, Crowe L, Palmer NT. Introduction of intravenous lipid administration on the first day of life in the very low birth weight neonate. J Pediatr 1991;119:615–623.
35. Brownlee KG, Kelly EJ, Ng PC, Kendall-Smith SC, Dear PR. Early or late parenteral nutrition for the sick preterm infant?. Arch Dis Child 1993;69:281–3.
36. Sosenko IR, Rodriguez-Pierce M, Bancalari E. Effect of early initiation of intravenous lipid administration on the incidence and severity of chronic lung disease in premature infants. J Pediatr 1993;123:975–982.
37. Christensen ML, Helms RA, Mauer EC, Storm MC. Plasma carnitine concentration and lipid metabolism in infants receiving parenteral nutrition. J Pediatr 1989;115:794-798.
38. Silvers KM, Darlow BA, Winterbourn CC. Lipid peroxide and hydrogen peroxide formation in parenteral nutrition solutions containing multivitamins. J Parenter Enteral Nutr. 2001;25:14-17.
39. Silvers KM, Sluis KB, Darlow BA McGill F, Stocker R, Winterbourn CC. Limiting light induced lipid peroxidation and vitamin loss in infant parenteral nutrition by adding multivitamin preparations to Intralipid. Acta Pediatr 2001;90:242-249.
40. Bassiouny MR, Almarsafawy H, Abdel-Hady H, Nasef N, Hammad TA, Aly H. A randomized controlled trial on parenteral nutrition, oxidative stress, and chronic lung diseases in preterm infants. J Pediatr Gastroenterol Nutr 2009;48:363-369.
41. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R for the Parenteral Nutrition Guidelines Working Group. 8. Vitamins. J Pediatr Gastroenterol Nutr 2005; 41:S47–S53.
42. Hartnoll G, Betremieux P, Modi N. Randomized controlled trial of postnatal sodium supplementation on body composition in 25 to 30 week gestational age infants. Arch Dis Child Fetal Neonatal Ed 2000;82:F24-F28.
43. Skouroliakou M, Koutri K, Stathopoulou M, Vourvouhaki E, Giannopoulou I, Gounaris A. Comparison of two types of TPN prescription methods in preterm neonates. Pharm World Sci. 2009;31:202-8.
44. Krohn K, Babl J, Reiter K, Koletzko B. Parenteral nutrition with standard solutions in Pediatric intensive care patients. Clin Nutr. 2005; 24: 274–280.
45. Puangco MA, Nguyen HL, Sheridan MJ Computerized PN ordering optimizes timely nutrition therapy in neonatal intensive care unit. J Am Diet Assoc. 1997; 97: 258–261.
46. Brown CL, Garrison NA, Hutchison AA. Error reduction when prescribing neonatal parenteral nutrition. Am J Perinatol. 2007; 24: 417–427.
47. Payne-James JJ, Khawaja HT. First choice for total parenteral nutrition: the peripheral route. J Parenter Enteral Nutr. 1993;17:468-478.
48. Kalhan S, Price P. Nutrition and selected disorders of the gastrointestinal tract.In: Klaus MH, Fanaroff AA. Care of High Risk Newborn 5th Ed 2001.WB Saunders Company. Pp 154.
49. Pemberton LB, Lyman B, Lander V, Covinsky J. Sepsis from triple vs single lumen catheters during total parenteral nutrition in surgical or critically ill patients. Arch Surg 1986;121:591-594.
50. Apelgren KN. Triple lumen catheters. Technological advance or setback? Am Surg 1987;53:113-116.
51. Ainsworth S, Clerihew L, McGuire W. Percutaneus central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD004219.
52. Sweeney B, Puri P, Reen DJ. Induction and modulation of apoptosis in neonatal monocytes by polyunsaturated fatty acids. J Pediatr Surg 2007 ;42:620-8.

53. Chessex P, Laborie S, Lavoie JC, Rouleau T. Photoprotection of solutions of parenteral nutrition decreases the infused load as well as the urinary excretion of peroxides in premature infants. Semin Perinatol. 2001;25:55-59.
54. Chessex P, Harrison A, Khashu M, Lavoie JC. In preterm neonates, is the risk of developing bronchopulmonary dysplasia influenced by the failure to protect total parenteral nutrition from exposure to ambient light? J Pediatr 2007;151:213-214.
55. Diekmann M, Genzel Boroviczency O, Zoppetti L, Von Poblotzki M. Postnatal growth curves for extremely low birth weight infants with early enteral nutrition. Eur J Pediatr.2005,164:714-23.
56. Pauls J, Baver K, Versmold H. Postnatal body weight curves infants below 1000g birth weight receiving early enteral and parenteral nutrition. Eur J Pediatr 1998.157:416-421.
57. Donovan R, Puppala B, Angst D, Coyle BW. Outcomes of early nutrition support in extremely low-birth weight infants. Nutr Clin Pract. 2006;21:395-400.

58. Annexure

1.Multi vitamins: Recommendations and dose modification of adult MVI

Vitamin	Daily requirement (per kg) (ESPGHAN[61])	Per ml content of adult MVI
Vitamin A (IU)	450-900	1000
Vitamin D (IU)	32	100
Vitamin E (mg)	2.8 – 3.5	0.5
Vitamin C (mg)	15 – 25	50
Thiamine (B1) (mg)	0.35 – 0.5	5
Riboflavin (B2) (mg)	0.15 – 0.2	1.4
Pyridoxine (B6) (mg)	0.15 – 0.2	1.5
Nicotinamide (mg)	4 – 6.8	10
Pantethol (mg)	1 – 2	2.5
Folic acid (mcg)	56	-
Vitamin B12 (mcg)	0.3	-
Biotin (mcg)	5 – 8	-

2.Market preparations required to give PN which are available in India

Constituent	**Preparation**	**Manufacturer**	**Availability (ml)**
Dextrose	Dextrose 5%,10%,25%,50%	*	25,100,500
Amino acids	Aminoven Infant 6%,10%	Fresinus Kabi India Pvt. Ltd.	100
	Primene 10%	Baxter Healthcare	100
Lipids	Intralipid 10% PLR	Fresinus Kabi India Pvt. Ltd	100
	Intralipid 20% PLR	Fresinus Kabi India Pvt. Ltd	100
	Clinoleic 20%	Baxter Healthcare	500
Sodium	3% NaCl	*	
	Concentrated Ringer Lactate	T. Walker's Pharmaceuticals Pvt Ltd	20
	0.9% Normal Saline	*	10,25,100,500
	Ringer Lactate	*	500
Potassium	Potassium Chloride	*	10
Calcium	Calcium Gluconate	*	10
Magnesium	Magnesium sulphate 25%, 50%	*	2
Vitamin	Multivitamin Infusion	*	10
Trace elements	Celecel 4, Celecel 5	Claris Lifesciences Ltd.	1,3,10

* many manufacturers distribute these products in different part of country

3. Manual PN calculation

Steps for calculation of TPN

I. Total fluid intake: ____mL/kg/d × ___kg = _____mL/d

II. Total TPN volume:
I – (Feed vol+ drug vol+ arterial line vol+ blood products) = _____mL/d

III. Fat volume: ___g/kg/d × ___kg ÷ 0.1* = _____mL/d
(*Lipid concentration per mL of 10% lipid, use 0.2 if using 20% lipid)

IV. Glucose-AA volume: II – III = _____mL/d

V. Glucose-AA volume to be prepared: IV × 1.2[#] = _____mL
([#]1.2 was multiplied to have 20% extra volume for wastage factor)

VI. Additive volumes:

a. AA ___g/kg/d × __kg × 10 × 1.2 = _____mL

b. Sodium ___mEq/kg/d × __kg × 6.6[$] × 1.2 = _____mL
([$] 6.6 mL of 0.9% NaCl = 1 mEq of Na, multiply by 2 if using 3% NaCl)

c. Potassium ___mEq/kg/d × __kg × 0.5 × 1.2 = _____mL

d. Calcium gluconate 8 mL/kg/d × __kg × 1.2 = _____mL

e. $MgSO_4$ 0.25 mL/kg/d × __kg × 1.2 = _____mL

VII. Total additive volume (a + b + c + d + e) = _____mL

VIII. Dextrose volume: = V-VII = _____mL

IX. Dextrose amount: __mg/kg/min × 60 × 24 ×1.2 = _____g/d

X. Dextrose concentration (VIII ÷ VII) × 100 = _____%

XI. Calculate the volumes of 10% & 25% dextrose to make VII volume with X conc.

10% Dextrose = _____ mL

25% Dextrose = _____mL

XII. Add 1 mL/kg/d of MVI in the fat volume = _____ mL

Final TPN order to infuse

Line 1: Lipids ____ mL/h for 24 h (III ÷ 24)

Line 2: Glucose-AA soln. _____ mL/h for 24 h (IV ÷ 24)

Management of Neonatal Hypoglycemia

Summary of Recommendations

- **Neonatal hypoglycemia is a common metabolic disorder and the operational threshold values of blood glucose < 40 mg/dL (plasma glucose< 45 mg/dL) should be used to guide management.**
- **All "at risk" neonates and sick infants should be monitored for blood glucose levels. Term healthy AGA infants without any risk factors need not be monitored routinely**.
- **Screening for hypoglycemia can be done by glucose reagent strips but confirmation requires laboratory estimation by either glucose oxidase or glucose electrode method. Treatment should not be delayed for confirmatory results.**
- **Asymptomatic hypoglycemia can be managed with a trial of measured oral feed if blood glucose is > 25 mg/dL and there is no contraindication to feeding.**
- **Symptomatic hypoglycemia should be treated with a mini-bolus of 2 ml/kg 10% dextrose and continuous infusion of 6 mg/kg/min of 10%dextrose.**
- **Refractory and prolonged hypoglycemia should be suspected and investigated if the glucose infusion requirement is > 12 mg/kg/min for more than 24 hours or the hypoglycemia persists > 5-7 days, respectively.**
- **Babies with hypoglycemia should be followed up for neurodevelopmental sequelae.**

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Introduction

As the neonate adapts to a state of intermittent enteral supply of glucose from that of continuous transplacental glucose supply of intrauterine life, hypoglycemia, especially in the early neonatal period, is a common event.[1] This tendency to develop hypoglycemia is accentuated by developmental immaturity of normal adaptive mechanisms like gluconeogenesis, hepatic glycogenolysis and ketogenesis.[2] The effect of neonatal hypoglycemia on the developing brain, with the potential for long term damage is of great concern.[3-6] Against this background, based on an extensive search of literature, an attempt has been made to address the following issues of practical relevance in the management of neonatal hypoglycemia:

- Operational threshold for management of neonatal hypoglycemia
- Screening for hypoglycemia
- Measurement of blood glucose
- Management of asymptomatic hypoglycemia
- Management of symptomatic hypoglycemia
- Diagnosis and evaluation of refractory and prolonged hypoglycemia
- Potentially best practices for prevention of hypoglycemia

Why should hypoglycemia in the newborn be managed aggressively?

Glucose is the predominant fuel for the newborn brain. Low blood glucose in the newborn period, in isolation as well as when associated with other morbidities, predisposes to long term neurological damage. The most common sequelae of hypoglycemia are disturbances of neurologic development and intellectual function, although minor deficits, especially spasticity and ataxia and seizure disorders can also occur. The occurrence of these may be related to etiology of hypoglycemia.

Evidence: A systematic review of literature reported inconclusive evidence on the effect of neonatal hypoglycemia on neurodevelopment.[7] In one series of 151 infants with neonatal hypoglycemia followed for 1-4 years the occurrence of seizures as part of the neonatal neurological syndrome was associated with a clearly abnormal outcome in 50% and with transient neurological abnormalities an additional 12%. In contrast, infants with neurological features without seizures did only marginal worse than those with no neurological features.[8] Findings from a large multicenter prospective study of preterm infants suggest that even moderate hypoglycemia (at least one daily value of plasma values <47 mg/dL) can have significant impact. There was a 30% incidence of neurodevelopmental sequelae if moderate hypoglycemia was present for 3 days or more and approximately 40% if present for 5 days or more.[9] Stenninger et al[10] reviewed the long-term, neurologic morbidity in 13 children with neonatal hypoglycemia, defined as blood glucose concentrations (< 27 mg/dL), compared with 15 children without neonatal hypoglycemia. Neurodevelopmental assessments were done at approximately 7.75 years of age. These investigators found that children with neonatal hypoglycemia had significantly more difficulties in a screening test for minimal brain dysfunction, and were more likely to be hyperactive, impulsive, and inattentive. These children also had lower developmental scores compared with controls. A recent Indian study by Udani and co-workers has concluded that neonatal hypoglycemia is the most common etiology of remote symptomatic infantile onset epilepsy.[11]

Recommendation: Neonates with hypoglycemia should be followed up for long term neurodevelopmental sequeale.

What should be the operational threshold for management for neonatal hypoglycemia?

Evidence: Hypoglycemia in neonates has been defined as blood glucose concentrations less than 40 mg/dL(Level 4), but there are several issues related to using a single cutoff of blood glucose in all neonates. Confusion exists due to the fact that the "normal" range of blood glucose is different for each newborn and depends upon a number of factors including birth-weight, gestational age, body stores, feeding status, availability of energy sources as well as the presence or absence of disease.[12-13] Cornblath et al suggested that 'hypoglycemia' is not readily defined for the individual neonate and that 'operational threshold' (concentration of blood glucose at which intervention should be considered) should be established.[14-15] Operational thresholds are different from therapeutic goals, do not define normal or abnormal but provide a margin of safety. Importantly however, such operational definitions do not address whether the threshold level of blood glucose for intervention represents the threshold level for neuronal injury.

Recommendation: For practical purposes and uniformity of definition, a blood glucose value of < 40 mg/dL (plasma glucose < 45 mg/dL) should prompt intervention for hypoglycemia in all newborns. There is no rational basis for the historical practice of distinguishing between term and preterm infants when setting threshold criteria for intervention.

Which neonates should be screened for hypoglycemia and what should be the screening schedule?

Evidence: The high risk group of neonates warranting routine screening for blood glucose are listed in table 1. Healthy term, appropriate for gestational age (AGA) neonates without any risk factors for hypoglycemia need not be monitored for blood glucose levels[16] except those with maternal fever during labor[12] (Level 3/4). While adjusting to postnatal life, transient self-correcting hypoglycemia in the first few hours after birth is common in full-term well infants with the nadir being reported at 1-2 hours postnatally.[16-19] Maternal oligohydramnios and a delay in initiation of breastfeeding beyond 2 hours have been reported as risk factors in one Indian study.[20]

There is a paucity of literature that looks into optimal timing and the intervals of glucose monitoring. Most studies indicate that 97% to 98% of hypoglycemic episodes occur within the first 24 hours of birth in asymptomatic neonates at risk.[21-23] In majority of studies, infants were screened at birth and thereafter 4 to 6 hourly till 24-48 hours of life. Holtrop et al[24] found that the average times for finding low glucose levels in large for gestational age (LGA) and small for gestational age (SGA) infants were 2.9 h (range 0.8 h to 8.5 h) and 6.1 h (range 0.8 h to 34.2 h), respectively. If mother's blood glucose is low which can happen if she has been starving, the baby can develop early hypoglycemia and in such situations, blood glucose should be tested even before 2 hours. One can infer that hypoglycemia usually occurs in LGA infants and IDMs within 12 h of birth, and screening beyond this period is not required provided blood glucose is maintained at > 45mg/dL and feeding has been established (Level 4). There is some suggestion that in the era of better glucose control in diabetic mothers, hypoglycemia is not detected beyond 2 hours[25](Level 3b). However it would not be appropriate to discontinue screening infants of diabetic mothers before 12 hours because diabetic control may not be optimum in Indian scenarios. Preterm and SGA infants may be vulnerable up to 36 h of age and perhaps later, particularly if regular feeds or intravenous infusions have not yet been established .[26]

Recommendation: All "at risk" neonates and sick infants should be monitored for blood glucose levels. Term healthy AGA infants without any risk factors need not be monitored routinely. All asymptomatic, at-risk neonates should be screened at two hours after birth and surveillance be continued 4-6 hourly thereafter, until feedings are well established and glucose values have normalized (generally till 48 hours of life). Monitoring before 2 hours may be required if mother has been starving or vomiting. The maximum risk for hypoglycemia is in first 24 hours but usually persists till 72 hours.

How should blood glucose be tested in neonates and when should a sample be sent to the laboratory for confirmation ?

Glucose values are affected by screening method, operator technique, associated disease process, and sample site. Glucose reagent strips are commonly used in the newborn nurseries to screen for low blood glucose concentration.

Evidence: Glucose meters show large variations in values compared to laboratory methods, especially at low glucose concentrations, and are of unproven reliability to document hypoglycemia in newborns. Hence, this method should only be considered as a screen and should not be used as the basis of diagnosis.[15-16] 'Glucose oxidase' (colorimetric method) or 'glucose electrode method' (as used in blood gas and electrolyte analyzer machine) are the two commonly used methods to assay blood glucose in the laboratory and are accurate and reliable. While testing the neonate's glucose, it is important to remember that the level in whole blood is about 10-15% less than in a plasma sample. Further, samples not analyzed immediately can show a falsely low reading as glucose levels fall by 14 to 18 mg/dL per hour of storage[27](Level 3b). Arterial glucose values are higher than capillary values, and capillary values are higher than venous values. Recently, subcutaneously inserted continuous glucose monitoring sensors have been used in very low birth weight infants to avoid repeated samplings.[28]

Recommendation: Glucose reagent strips are used to screen for hypoglycemia. If the values are low, a blood sample should be sent to the laboratory for confirmation by glucose oxidase or glucose electrode method. Treatment should be commenced on the basis of the screening test and should not be delayed till the laboratory results are available.

How should a neonate with asymptomatic hypoglycemia managed?

Babies with asymptomatic hypoglycemia are also at risk for developing long term neurodevelopmental sequelae and hence should be urgently treated.

Recommendation: In healthy asymptomatic hypoglycemic infants, initially a feed of measured breast milk can be given by spoon or gavage. If breast milk is not available, then formula milk may be used. Check blood glucose 30-60 min later before next feeding to ensure euglycemia. If repeat blood glucose is above 45 mg/dL, 2 -3 hourly feed is ensured with 4-6 hourly monitoring for glucose upto 48 hrs.

IV glucose infusion should be started in babies with asymptomatic hypoglycemia if :

a) Blood glucose is < 25 mg/dL
b) Blood glucose remains below 40 mg/dL despite one attempt of feeding breast milk.
c) Enteral feeding is contraindicated.
d) Baby becomes symptomatic.

How should a neonate with symptomatic hypoglycemia managed?

Symptomatic hypoglycemia can result in a high incidence of neuronal injury. Hence, in neonates with any symptoms suggestive of hypoglycemia accompanied by a low blood glucose value less than 45 mg/dl , the measures listed below should be instituted as an emergency.

i) A bolus of 2 mL/kg of 10% dextrose is given intravenously (after sending a sample to the laboratory for confirmation of the diagnosis) .[29]

ii) Following a bolus, an intravenous infusion of dextrose at a glucose infusion rate (GIR) of 6 mg/kg/min is started. This figure of the GIR is to strike a balance between the physiologic requirement of glucose and the risk of iatrogenic hyperglycemia followed by rebound hypoglycemia[30](Level2b).

iii) Blood glucose is re-checked after 15-30 min. If it remains well above 45 mg/dL, the frequency of checking can be gradually decreased from every hour to 4-6 hourly.

iv) If the blood glucose remains < 45 mg/dL, the GIR is increased in steps of 2 mg/kg/min every 15-30 min with repeat checks on blood glucose till the values are > 45 mg/dL.

v) Tapering of glucose infusion: Once the blood glucose values stabilize above 45mg/dL for about 24 hours, the infusion can be tapered off @ 2 mg/kg/min every 6 hours. Once a GIR of 4 mg/kg/min is reached, the infusion can be stopped if the neonate is euglycemic. In neonates who cannot be fed orally, the GIR is gradually brought down to the minimum at which euglycemia is maintained.

vi) If the neonate requires GIR of > 12 mg/kg/min, a diagnosis of resistant hypoglycemia should be entertained (after ensuring that there was no interruption in the glucose infusion) and investigations and management should be modified accordingly.

vii) Oral feeds: If there is no contraindication to feeding, oral feeds of breast or formula milk should be continued along with and their proportion increased as the intravenous infusion is tapered. Oral feeding ensures a more stable glycemic control.

Practice points

- Avoid using > 12.5% to 15% dextrose infusion through a peripheral vein due to the risk of thrombophlebitis.
- In addition to glucose infusion and monitoring, attention should be paid to reduce energy needs by correcting acidosis, maintaining a thermoneutral environment and treatment of other underlying conditions like sepsis.
- A continuous infusion of glucose should be ensured, preferably using a syringe infusion pump. Do not stop an IV infusion of glucose abruptly; severe rebound hypoglycemia may occur.
- Treatment of neonatal hypoglycemia with intermittent boluses alone is not logical; the need for such boluses is an indication for increasing the rate of continuous glucose infusion, and for considering other causes.

Recommendation: Symptomatic hypoglycemia should be treated intravenously by a mini-bolus of 2 ml/kg 10% dextrose followed by a continuous infusion of 6mg/kg/min. Oral feeding should be continued simultaneously unless contraindicated.

How should refractory and prolonged hypoglycemia be evaluated and managed?

Refractory and prolonged hypoglycemia should be suspected if GIR requirements are > 12 mg/kg/min for more than 24 hours or blood glucose levels remain unstable beyond 5 to 7 days, respectively. Refractory hypoglycemia in neonates is usually secondary to inappropriate and/or excessive insulin secretion or due to deficiency of one of the glucose regulatory enzymes of the liver.[31-33] Some important causes of resistant hypoglycemia are hyperinsulinemia, hypopituitarism, adrenal insufficiency and metabolic disorders like galactosemia, glycogen storage disease, organic acidemias and mitochondrial disorders. A consultation with a pediatric endocrinologist is recommended for management of refractory hypoglycemia. Investigations like plasma insulin, cortisol, thyroid profile, ammonia, lactate and urine for ketones and reducing substances are done initially. If initial investigations are not helpful or a specific etiology is suspected, second line investigations include 17-OHP, GALT assay, TMS, growth harmone and glucagon levels. Persistent Hyperinsulinemia(PHHI) is diagnosed if there is hyperinsulinemia (plasma insulin > 2 μU/mL, depending on sensitivity of insulin assay) in presence of documented laboratory hypoglycemia(< 50 mg/dL). In consultation with the endocrinologist, drugs like hydrocortisone, diazoxide, octreotide, nifedipine or glucagon may be prescribed.

What are the potentially best practices for prevention of neonatal hypoglycemia?

Some of the practices that help prevent neonatal hypoglycemia include:

(a) Support and promote early exclusive breastfeeds (or oral feeds of expressed breast milk) within first hour of life[34-35] in all healthy newborns. Delayed initiation of breast feeds is an important risk factor for hypoglycemia.[20] A controlled trial using sucrose fortified milk (5 g sucrose per 100 mL milk) fed orally has been shown to raise blood glucose levels and prevent hypoglycemia in small-for-gestational-age[36] as well as appropriate-for-gestational-age neonates[37] (Level 1b). However, this intervention is at the cost of compromising breastfeeding rates[38] and potential risk of contamination.

(b) Maintenance of thermoneutral environment helps prevent hypoglycemia and skin to skin contact of neonate with mother should be encouraged as a strategy for temperature maintenance.[16]

(c) Do not feed 5%, 10% or 25% dextrose as a substitute for breast milk. Plain dextrose feeding can induce vomiting and will cause increased insulin secretion, decreased glucagon, delayed gluconeogenesis and rebound hypoglycemia.[35]

(d) Ensure that there is no interruption in the intravenous glucose infusion by maintaining a good intravenous access and using a syringe infusion pump to deliver at a steady rate.

References

1. Haninger NC, Farley CL. Screening for hypoglycemia in healthy term neonates : effects on breastfeeding. J Midwifery Women's Health 2001;46:292-301.
2. Stanley CA, Baker L. The causes of neonatal hypoglycemia. (Editorial). N Engl J Med 1999;340:1200-01.
3. Pildes RS, Cornblath M, Warren I, Page-El E, di Menza S, Merritt DM, Peeva A. A Prospective Controlled Study of Neonatal Hypoglycemia. Pediatrics 1974;54:5-14.
4. Menni F, de Lonlay P, Sevin C, Touati G, Peigne C, Barbier V, Nihoul-Fekete C, et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. Pediatrics 2001;107:476-479.

5. Vannucci RC, Vannucci SJ. Hypoglycemic brain injury. Semin Neonatol 2001;6:147-55.
6. Kinnala A, Rikalainen H, Lapinleimu H, Parkkola R, Kormano M, Kero P. Cerebral magnetic resonance imaging and utrasonography findings after neonatal hypoglycemia. Pediatrics 1999;103:724-9.
7. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. Pediatrics. 2006 ;117:2231-43.
8. Koivisto M, Blanco-Sequeiros M, Krause U. Neonatal symptomatic and asymptomatic hypoglycemia : a follow up study of 151 infants. Dev Med Child Neurol. 1972; 14(5): 603-614.
9. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycemia. Br Med J. 1988; 297(6659): 1304-1309.
10. Stenninger E, Glink R, Eriksson b, Sahlen C. Long term neurological dysfunction and neonatal hypoglycemia after diabetic pregnancy. Arch Dis Child Fetal Neonatal Ed.1998; 79 (3) : 174-179.
11. Udani V, Munot P, Ursekar M, Gupta S. Neonatal Hypoglycemic Brain Injury – A Common Cause of Infantile-onset Remote Symptomatic Epilepsy. Indian Pediatr 2009; 46: 127-131.
12. Kalhan S, Sigal PW. Hypoglycemia : What is it for the neonate ? Am J Perinatol 2000;17:11-18.
13. Aynsley-Green A, Hawdon JM. Hypoglycemia in the neonate : current controversies. Acta Paediatr Jpn 1997;39 (Suppl 1): S12-6.
14. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, Kalhan SC. Controversies regarding definition of neonatal hypoglycemia : suggested operational thresholds. Pediatrics 2000;105:1141-5.
15. Cornblath M, Schwartz R, Aynsley-Green A, Lloyd JK. (Editors – A Ciba Foundation Discussion Meeting) Hypoglycemia in infancy : the need for a rational definition. Pediatrics 1990;85:834-7.
16. World Health Organization. Hypoglycemia of the newborn: review of the literature. Geneva, WHO/CHD/97.1;1997:1-55.
17. Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien L. Plasma glucose values in normal neonates: a new look. J Pediatrics 1986;109:114-7.
18. Tanzer F, Yazar N, Yazar H, Icagansioglu D. Blood glucose levels and hypoglycemia in full term neonates during the first 48 hours of life. J Tropical Pediatr 1997;43:58-60.
19. Hawdon JM, Ward Platt MP, Aynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. Arch Dis Child 1992;67:357-65.
20. Sasidharan CK, Gokul E, Sabitha S. Incidence and risk factors for neonatal hypoglycemia in Kelrela, India. Ceylon Med J 2004;49:110-3.
21. Kuhl C, Andersen GE, Hertel J, Molsted-Pendersen L. Metabolic events in infants of diabetic mothers during the first 24 hours after birth. Changes in plasma glucose, insulin and glucagon. Acta Paediatr Scand 1982;71:19-25.
22. Schaefer-Graf UM, Rossi R, Buhrer C, Siebert G, Kjos SL, Dudenhausen JW, Vetter K. Rate and risk factors of hypoglycemia in large-for-gestational-age newborn infants of non-diabetic mothers. Am J Obstet Gynecol 2002;187:913-7.
23. Bhat MA, Kumar P, Bhansali A, Majumdar S, Narang A, Hypoglycemia in small for gestational age babies. Indian J Pediatr 2000;67:423-7.
24. Holtrop PC. The frequency of hypoglycemia in full term and small for gestational age newborns. Am J Perinatol 1993;10:150-4.
25. Van Howe RS, Storms MR. Hypoglycemia in infants of diabetic mothers: experience in a rural hospital. Am J Perinatol. 2006 Feb;23(2):105-10.
26. Hume R, McGeechan A, Burchell A. Failure to detect preterm infants at risk of hypoglycemia before discharge. J Pediatr 1999;134:499-502.
27. Cowett RM, Damico LB. Capillary (heelstick) versus venous blood sampling for determining of glucose concentration in neonates. Biol Neonate 1992;62:32-6.
28. Beardsall K, Ogilvy-Staurt AL, Ahluwalia J, Thompson M, Dunger DB. The continuous glucose monitoring sensor in neonatal intensive care. Arch Dis Child Fetal Neonatal Ed 2005;90:F307-F310.
29. Lilien LD, Pildes RS, Srinivasan G. Treatment of neonatal hypoglycemia with minibolus and intravenous glucose infusion. J Pediatr 1980;97:295-8.
30. Kilegman RM. Problems in metabolic adaptation : Glucose, Calcium, and Magnesium. In Klaus MH, Fanaroff AA, eds: Care of the High-Risk Neonate (fifth edition)Philadelphia:WB Saunders, 2001, pp 301-9.

31. Thomas CG, Underwood LE, Carney CN, Dolcourt JL, Whitt JJ. Neonatal and infantile hypoglycemia due to insulin excess : New aspects of diagnosis and surgical management. Ann Surg 1977;185:505-16.
32. Glaser B. Hyperinsulinism of the newborn. Semin Perinatol 2000;24:150-63.
33. Sperling MA, Menon RK. Differential diagnosis and management of neonatal hypoglycemia. Pediatr Clin North Am 2004;51:703-23.
34. American Academy of Pediatrics Work Group on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 1997;100:1035-9.
35. Eidelman AI. Hypoglycemia and the breastfed neonate. Pediatr Clin North Am 2001;48:377-87.
36. Singhal PK, Singh M, Paul VK. Prevention of hypoglycemia : A controlled evaluation of sugar fortified milk feeding in small for date infants. Indian Pediatr 1992;29:1365-9.
37. Singhal PK, Singh M, Paul VK, Malhotra AK, Deorari AK, Ghorpade MD. A controlled study of sugar fortified milk feeding in prevention of neonatal hypoglycemia. Indian J Med Res 1991;94:342-5.
38. Jain A, Aggarwal R, Jeevasanker M, Agarwal R, Deorari AK, Paul VK. Hypoglycemia in the newborn. Indian J Pediatr 2008;75:63-7.
39. Narayan S, Aggarwal R, Deorari AK, Paul VK. Hypoglycemia in the newborn. Indian J Pediatr 2001;68:963-5.

Table 1: " At-risk" neonates for whom routine monitoring of blood glucose is recommended

- Preterm infants
- Small for gestation (SGA)
- Large for gestation (LGA)
- Infant of diabetic mother (IDM)
- Sick infants (eg: sepsis, asphyxia, respiratory distress)
- Post exchange blood transfusion
- Infants on intravenous fluids and parenteral nutrition
- Infants whose mothers received beta blockers , oral hypoglycemic agents or intrapartum dextrose infusion

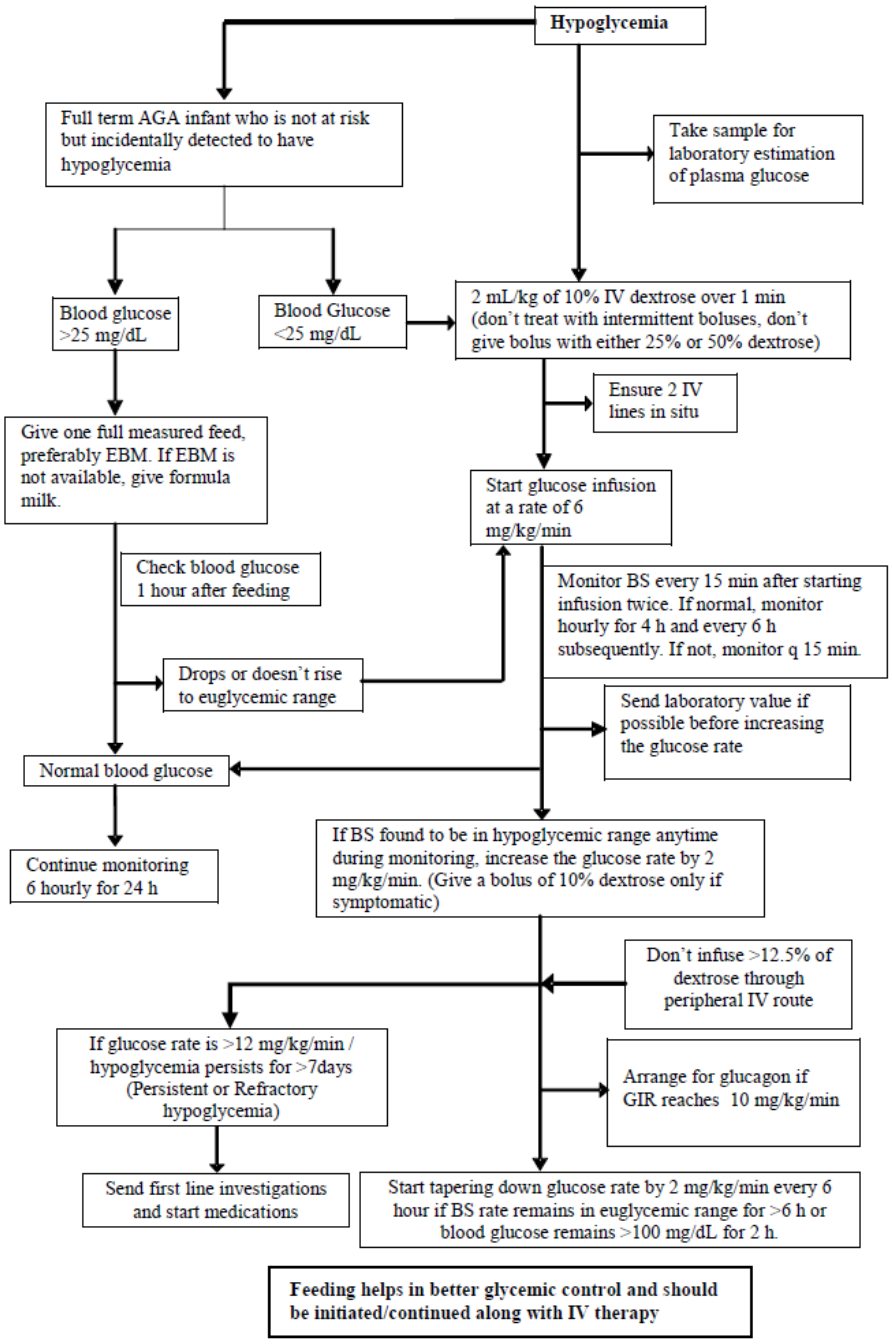

Fig 1: Management Algorithm for Hypoglycemia

Annexure

1. How to calculate the desired concentration of glucose in intravenous fluid and how to mix various solutions for creating a desired concentration of glucose in IV infusate?

The formula for preparing 100 mL of fluid with a desired concentration of glucose using 5% dextrose and 25% dextrose solutions is given by the formula **5X-25 = Y** where X is the required percentage of dextrose and Y is the amount of 25% dextrose (in mL) to be made up with 5% dextrose to make a total of 100 mL.

For example, to prepare 100ml of 10% dextrose from 5% dextrose and 25% dextrose, add 5x10-25=25ml of 25% dextrose to the remaining volume, i.e. 100-25 =75 ml of 5% dextrose.

To prepare 100 ml of 12.5% dextrose, add 5x12.5-25=37.5ml of 25% dextrose to 62.5 ml (100-37.5)of 5% dextrose.

2. How to calculate the glucose infusion rate (GIR) ?

Neonatal blood glucose concentrations correlate closely with glucose infusion rates. Glucose Infusion Rate (GIR) is expressed in terms of milligrams of glucose per kilogram body weight per minute (mg/kg/min). It can be calculated using one of the following formulae[39] :

(a) $\text{GIR (mg/kg/min)} = \dfrac{\text{\% of dextrose being infused} \times \text{rate of infusion (in ml/hr)}}{\text{Body weight (in kg)} \times 6}$

(b) $\text{GIR (mg/kg/min)} = \dfrac{\text{Rate of IV fluids (in ml/kg/day)} \times \text{\% of dextrose infused}}{144}$

(c) $\text{GIR} = \text{Rate of IV fluids (in ml/kg/day)} \times \text{\% of dextrose infused} \times 0.007$

Method 1 for calculating GIR (same as (b) above)

(a) Decide desired fluid intake of the neonate in mL/kg/day (24 hrs)
(b) Convert this to mL/kg/min by dividing the figure by 1440

(Since 24 hours have 1440 minutes)

If 10% dextrose is being used, multiply the figure obtained in (b) above by 100 to find out the Glucose Infusion Rate (GIR) in mg/kg/min.

(Since 10% Dextrose has 100 mg/mL of dextrose. Similarly, 5% dextrose has 50 mg/mL; 7.5% dextrose has 75mg/mL of dextrose and so on)

(c) Based on desired fluid intake and desired GIR, the concentration of dextrose in the IV infusate can be decided.

(d) Example

(i) Let the neonate's fluid intake be 80 mL/kg/day

(ii) This is 80/1440 = 0.055 mL/kg/min

(iii) If 10% dextrose is given, then the GIR is :

0.055 x 100 = 5.5 mg/kg/min

Method 2 for fluid rate and GIR (Using 10% dextrose only)[24]

Step1

(a) 100 mL of 10% dextrose has 10 gm or 10,000 mg of glucose

(b) If this 100 ml is given over 24 hours then GIR is

10,000/1440 = 6.95 mg/min; say 7.0 mg/min

(Since 24 hours have 1440 minutes)

(c) Therefore 1 mL/day of 10% dextrose will provide a GIR of 0.07 mg/min

(d) Based on the above, GIR for a neonate can be calculated as follows:

GIR (mg/kg/min) = IV fluid rate (mL/kg/day) x 0.07

Step 2 – Increasing GIR by 1mg/kg/min

(a) Add 2 mL/kg of 25% dextrose to the volume of fluid to be infused

over 8 hrs – see explanation below :

[i] 25% Dextrose has 250 mg/mL of dextrose; 2 mL/kg has 500 mg/kg

[ii] The 8 hour period has 8 x 60 = 480 minutes

[iii] 2 mL/kg of 25% dextrose over 8 hrs will increase the GIR by

500/480 or roughly 1 mg/kg/min

(b) Example

1. Let the neonate's fluid intake be 80 mL/kg/day
2. With 10% dextrose the GIR is 80x0.07 = 5.6 mg/kg/min
3. If GIR has to be increased by 1 mg/kg/min then add 2 ml/kg of 25% dextrose to the fluid to be infused over 8 hrs

(c) **Caveat :** For this formula to work, the GIR has to be kept at or below a tenth of the total fluid intake in mL/kg/day – e.g. if the total fluid intake is 100 mL/kg/day, you cannot increase GIR beyond 10 mg/kg/min using this formula – to increase GIR beyond this limit, fluid intake has to be increased.

3. How to convert gm/dL to mmol/L & vice versa ?

There are two main methods of describing concentrations: by weight, and by molecular count. Weights are in grams, molecular counts in moles.
To convert mmol/L of glucose to mg/dl, multiply by 18. To convert mg/dL of glucose to mmol/L, divide by 18 or multiply by 0.055.

4. How to calculate GIR in an infant on oral feeds along with simultaneous intravenous infusion of glucose?(also see Figures 2 and 3)

Glucose infusion needs to be calculated while giving feeding and can be done by the same formula

Glucose infusion rate while on feeding (mg/kg/min) =

[IV rate (ml/hr) x Dextrose conc (g/dl) x .0167 / wt (kg)] + [Feed rate(ml/hr) x Dextrose conc (g/dl) x .0167 / wt (kg)]*

Amount of dextrose in milk : *Breast milk = 7.1 gm/dL ,Term formula = 7.1gm/dL, Preterm formula = 8.5 gm/dL*

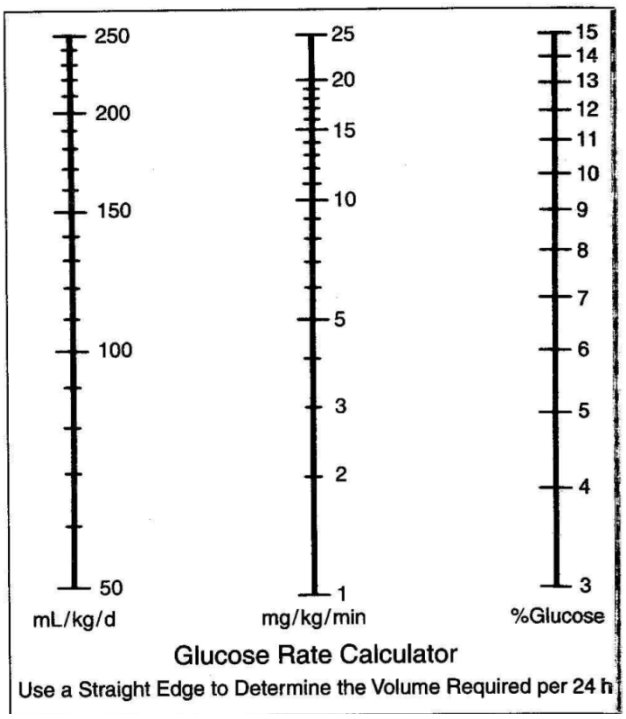

Figure 2: Calculating glucose concentration to be used based on amount of fluid and GIR

Use figures below:

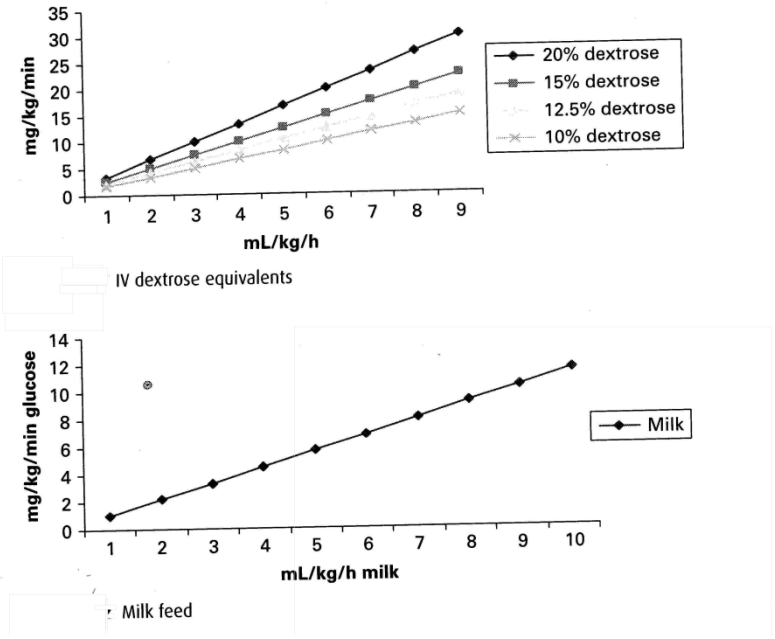

Figure 3 Calculation of GIR of baby on fluids and feeds (assuming breast milk or term formula)

Oxygen use in the Newborn

Summary of recommendations

- **For the babies needing higher FiO2s (>40%), the most comfortable and controlled method of providing supplemental oxygen is by Head-box.**
- **For the babies needing lower FiO2s (<40%), the most practical method of providing supplemental oxygen is by low flow nasal cannula.**
- **Heated humidifiers should be used whenever oxygen delivery system bypasses the nose or high flow rates (>1 Litre/min) are used.**
- **Supplemental oxygen must always be monitored. When administering supplemental oxygen, the relevant end point is not the FiO2 but the arterial oxygen tension (PaO2) or the arterial oxygen saturation (SpO2).**
- **Target saturation range of premature babies of <32 weeks gestation age should be 88 – 92% with alarm limits set at 86 – 94% till PCA of 34 weeks. Target SpO2 range of premature babies of >32 weeks gestation age should be 90-95 %.**
- **Oxygen is a drug and there should be a proper documentation in the neonate's records about the number of days on oxygen therapy.**

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Introduction

Oxygen is one of the most commonly administered drugs in the neonatal intensive care unit. The goal of oxygen therapy is to deliver adequate amount of oxygen to the tissues without causing oxygen toxicity. The delivery of oxygen to the tissue depends on fraction of inspired oxygen concentration (FiO2), lung ventilation, cardiac output, hemoglobin (Hb) concentration and dissociation of oxygen from Hb at the tissue level. Despite the exceedingly common use of supplemental oxygen in the neonates, there is little consensus as to the optimal mode of administration and appropriate levels of oxygen for maximizing short or long-term growth and development, while minimizing harmful effects. Data from our country is limited. This guideline answers the following important practical questions on oxygen therapy from the available literature and expert recommendations. It is restricted to various aspects of oxygen therapy in non-ventilated neonates and babies who are not receiving CPAP. Use of oxygen in neonatal resuscitation is not covered in this guideline.

- Indications for oxygen use
- Delivering appropriate concentration and humidification
- Saturation targets
- Assessment and Monitoring of oxygenation
- Sources of oxygen

What are the indications of oxygen therapy in a term and preterm neonate?

Oxygen therapy is the administration of oxygen at concentrations greater than that in ambient air with the intent of treating or preventing the symptoms and manifestations of hypoxia.[1] The clinical situation has to be kept in mind. A newborn with congenital cyanotic heart disease may not benefit by oxygen supplementation. The administration of supplemental oxygen to patients with certain congenital heart lesions (eg, hypoplastic left-heart, single ventricle) may cause an increase in alveolar oxygen tension and compromise the balance between pulmonary and systemic blood flow.

Evidence: The need for oxygen therapy is self-evident. The clinical effects of hypoxemia and tissue hypoxia have been well documented. [2]

Recommendations: Oxygen should be supplemented in the neonates in the following clinical situations:[1-3] Hypoxemia (O_2 saturation <87% and / or PaO2<50 mmHg in room air) and an acute situation with respiratory distress (respiratory rate >60/min and/or intercostal retractions and / or grunt and / or cyanosis in room air).

How to deliver appropriate oxygen concentration under various circumstances?

The administration of supplemental oxygen to neonatal patients requires the selection of an oxygen delivery system that suits the patient's size, needs, and the therapeutic goals. Oxygen delivery systems are categorized as either low-flow (variable performance) or high-flow (fixed performance) systems. Low-flow systems provide an FDO_2 (fractional concentration of delivered oxygen) that varies with the patient's inspiratory flow and are classified as variable-performance oxygen delivery systems. High-flow systems can deliver specific FDO_2 at flows that meet or exceed the patient's inspiratory flow requirement and are classified as fixed-performance oxygen delivery systems. High-flow systems are better when FiO2

requirements are high. Free Flow / blow by administration of oxygen (by holding oxygen supply tube near the infant's face), transtracheal catheters and tracheostomy oxygen adapters have not been discussed separately. As per the opinion of the Clinical Practice Guideline Steering Committee of AARC, nasopharyngeal catheters, partial-rebreathing masks and non-rebreathing masks are not appropriate for oxygen administration in the neonatal population.[4]

Evidence:

High Flow Systems

Oxygen hoods: Head box or oxygen hood are the transparent enclosures designed to surround the head of the neonate or small infant. Out of all the noninvasive oxygen delivery systems, this is the only one that allows the FiO2 to be determined precisely. FiO2 delivered depends upon the rate of flow, infant's minute ventilation, size of the hood and size and opening of side ports. Oxygen concentration in a hood can be varied from 0.21 to 1.0. Headbox oxygen is generally well tolerated, may be humidified and there is no increased risk of airway obstruction by mucus and gastric distension. Disadvantages include limitations on mobility, disturbance of enriched oxygen environment during nursing care procedures such as feeding or suctioning and risk of hypothermia due to high flow rate of cold gas. A gas flow of 2–3 L/kg/min is necessary to avoid re-breathing of carbon dioxide. It needs to be ensured that headbox size is appropriate to the size of the baby. One study involving newborns > 2 Kg found that flow rates of less than 4 L/min in small and 3 L/min in medium and large sized head boxes are associated with CO2 retention.[5] Another study which used a modified head box design showed no CO2 retention even at low flow rates of oxygen (1 L/min). The authors showed that this modified head box design could be used effectively in nursing the head end of the neonates without significantly altering the oxygen concentration.[6]

Closed incubators: Incubators are transparent enclosures that provide a temperature-controlled environment for small infants with temperature instability. Supplemental oxygen can be added to incubators to provide increased oxygen concentration. However it requires a very high flow of oxygen. Oxygen concentration gets altered with each opening of incubator for nursing procedures. Humidification is available through a baffled blow-over water reservoir; however, there is a high risk of infection associated with this humidification system. Opening any enclosure (oxygen hoods or incubators) decreases the O_2 concentration.

Low Flow systems

Nasal cannulas / prongs: Nasal cannulas provide low-level supplemental oxygen to the infant. Nasal cannulas or nasal prongs consist of two soft prongs (about 1 cm in length) that arise from oxygen supply tubing. The prongs are inserted into the patient's anterior nares, and the tubing is secured to the patient's face. Oxygen flows from the cannula into the patient's nasopharynx, which acts as an anatomic reservoir. Very low flow of oxygen (< 1 L/min) is used to provide oxygenation and for this flow-meters with ability to calibrate very low flow (250 – 500 ml/min) are required. Effective FiO2 delivery depends on the cannula flow rate, the FiO2 in the cannula gas flow, the relation between prong and nasal diameters, and the patient's body weight. Vain et al[7] measured the hypopharyngeal oxygen fraction (FHO2) in ten infants with weights 1780-4090 g receiving 0.5 or 1 L/min oxygen through nasal cannulae of 1 mm diameter. Mean FHO2 was 45% and 65% respectively. In premature infants, using 1 mm diameter nasal cannula, Wilson et al[8] found that measured FHO2 was 42 to 45% with flow rates of 0.2-0.5 L/min. They observed wide variation in the FHO2 readings for any given infant. Finer et al[9] were able to deliver a wide range of FHO2 values to premature and full term newborns using 100% oxygen and a low range flow meter (25–

200 ml/min). They found that measured FHO2 was dependent on the weight of the infant with lower values in larger infants at similar flow rates.

This mode ensures stable oxygen delivery during feeding and kangaroo mother care. There are decreased chances of displacement of device. Hence this is the preferred method of home oxygen therapy in infants. As the natural nasal mechanisms are heating and humidifying the inspired gases, there is no need for humidification (10). Unlike head box there is no danger of hypercarbia if the oxygen is turned off or the tubing disconnects. Changes in minute ventilation and inspiratory flow affect air entrainment and result in fluctuations in FiO_2.[7,9] Improper sizing can lead to nasal obstruction or irritation. Weber et al. observed complete nasal obstruction in eight out of 62 children (age range seven days to five years) with nasal cannulae.[11] Inadvertent CPAP may be administered depending upon the size of the nasal cannula, the gas flow, and the infant's anatomy .[11,12] Heated humidified high flow nasal cannula, using flow rates ≥1 L/minute), have been used increasingly in many NICUs and apparently have been accepted rapidly because of their ease of use and their ability to provide heated, humidified, oxygen/air gas mixtures.[13] There have been numerous reports of their use to treat apnea of prematurity, to prevent reintubation, and in some cases to replace conventional nasal CPAP therapy.

Finer[13] has described a regression equation for estimating nasal cannula FiO2 at flow rates of 1 – 3 L/minute

$$\text{Approximate FiO2} = (O_2 \text{ flow} \times 0.79) + [(0.21 \times V_E) / (V_E \times 100)]$$

V_E = minute ventilation (tidal volume × respiratory rate), O_2 flow = ml/min

Tidal volume assumed -5-6 ml/kg; directly applicable for infants <1500 grams

Infection Control: Universal Precautions must be adhered to at all times. Under normal circumstances, low-flow oxygen systems do not present clinically important risk of infection and do not require routine replacement on the same patient. There is no recommendation regarding the frequency of changing oxyhood and reservoirs while in use on the same patient .[4]

Recommendations:

For the babies needing higher FiO2s (>40%), the most comfortable and controlled method of providing supplemental oxygen in neonates is by Head-box.

- For the babies needing lower FiO2s (<40%), the most practical method of providing supplemental oxygen in neonates is by nasal cannula.
- Uncontrolled CPAP by using high flows through nasal cannulas is not recomended.
- Avoid using nasopharyngeal catheters, partial-rebreathing masks and non-rebreathing masks in neonates.

Is an air-oxygen blender essential to provide appropriate oxygen? Are there any other means of administering less than 100% oxygen? How to administer appropriate oxygen concentration?

Air-Oxygen blender, which mechanically blends pressurized oxygen and air, is the ideal way to provide appropriate delivered FiO2. O_2 concentration and flow rate are set as per the manufacturer's protocol. Dedicated blenders for O2 administration alone are not used frequently in our country presently; though the same are available as part of ventilators and CPAP systems. Except during an emergency resuscitation, 100% oxygen from a cylinder or piped source should not be used as pure oxygen is toxic to many tissues.

Other means of administering less than 100% oxygen

(a) *Venturi:* If a blender is not available, a venturi can be used. A venturi is cheaper than a blender but not as accurate. The venturi is a short plastic tube to which a pipe supplying oxygen is attached. The air entrainment mechanism is based on the principles described by Bernoulli.[14] Oxygen is forced through the jet orifice of venturi. The velocity increases causing a shearing effect distal to the jet orifice, which causes room air to be entrained. The FiO2 delivered is determined by the dimensions of the jet and the air entrainment ports. The opening of the jet orifice is adjustable and corresponds to graded markings of FiO2.

(b) *Air-Oxygen flow graph:* Air-oxygen blending at desired FiO2 may be obtained as mentioned in table1(annexure) The air-oxygen flow graph can be used for calculation and adjustment of flow rates to control the oxygen concentration (X axis – air; Y axis – oxygen). Oxygen and air from respective compressed sources are passed through flow-meters and mixed at pre-decided flow rates using a 'Y' piece to achieve targeted FiO2.

Recommendation: As evidence is not available in neonates, firm recommendations cannot be made on the use of air-oxygen flow graph or venturi devices in the administration of oxygen with concentration less than 100%.

How to give heated and humidified oxygen in a non-ventilated neonate? Are there any indigenous ways of heating and humidifying oxygen?

Medical gases have little water content at room temperature, and their delivery with various delivery systems in which the gases are not heated to body temperature and are not fully saturated with water, may increase heat loss and produce nasal drying effects, leading to mucosal barrier breakdown and increasing the risk for infection.[15] Cooling and loss of water from the airways may impair mucociliary transport, increase fluid osmolality, promote bronchospasm, and increase the viscosity of airway secretions. Moreover, considerable energy is required to heat and to humidify gas delivered into the nose, potentially interfering with optimal nutrition and growth.[16]

Evidence: On the basis of studies with very low birth weight infants undergoing ventilation, the delivery of non-humidified gas may lead to increases in air leaks, more severe chronic lung disease, impaired surfactant activity, and changes in pulmonary mechanics.[17] Hence humidification of respiratory gases is an essential requirement when using a device which bypasses respiratory tract especially at high flow rates (>1 L/min). Recommended humidity is at least 33 mg/L of absolute humidity (AH) with a relative

humidity (RH) of 70-100% .The minimum recommended gas temperature at the level of nostrils is 33^{o}C [International Organization for Standardization. Humidifiers for medical use (ISO 8185, 1997)]. Temperature should be monitored as near to the patient's airway opening as possible. Commonly used humidifiers include Unheated bubble humidifier, Heated humidifiers and Heat and moisture exchangers / filters (HME /HMEFs).

Unheated bubble humidifier: It is the simplest and cheapest of humidifiers used to add water vapour to the dry gas. Sterile or boiled water is added to the humidifier chamber or bottle and respiratory gases are bubbled through this chamber before delivery to patient. It has been shown that unheated bubble humidifier gives acceptable results when low flows of oxygen (0.5–1.0 L/min) are given in warm climates.[18] A bubble humidifier not only produces water vapour but also some aerosol capable of dispersing infectious particles. Bottle warmers may be used to warm the humidifier bottle. Monitoring of temperature of the water in humidifier bottle should be mandatory in such cases. This modality of providing heated humidified gases needs to undergo further studies in our country. Filling the humidifier bottle with hot water and changing hot water at some arbitrary intervals is unscientific. This practice, though appealing in a resource constrained setting, is not recommended.

Heated humidifiers: Water in the humidification chamber is warmed to a set target temperature leading to warming of the respiratory gases and addition of water vapors. A constant desired temperature is maintained via servo-controlled mechanism in an ideal humidification system while using high gas flow rates. These device use the process of vaporization, which generates a molecular distribution of water that is free of droplet water and provides vapor that is nearly 100% humidified at body and theoretically is unable to carry infectious agents. When a heated-wire patient circuit is used (to prevent condensation) on an infant, the temperature probe should be located outside of the incubator or away from the direct heat of the radiant warmer.

Heat and moisture exchangers / filters (HME /HMEFs): These use sponge like material of low thermal conductivity which absorbs heat of expired air and uses it for warming and humidification of inspired gases. Some of these are coated with bacteriostatic substances and are equipped with bacterial or viral filters. Data on their use in neonates is sparse and they have been tried only in ventilated newborns.[19,20]

Recommendations: Heated humidifiers should be used whenever oxygen delivery system bypasses the nose or high flow rates (>1 L /min) are used.

How to assess the oxygenation status while on oxygen therapy?

Clinical assessment including but not limited to cardiac, pulmonary, and neurologic status indicates the oxygenation status of the baby. In addition, we use oxygenation indices which act as indicators of disease severity in lungs of the newborn. One should be familiar with following terms while describing oxygenation indices :

FiO2 (Fraction of inspired oxygen concentration): It is the proportion of oxygen in the inspired gas. It is expressed as a percentage (e.g 70% O2) or in decimal form (e.g. 0.70 O2).

PaO2: Partial pressure of O2 in arterial blood is the amount of O2 physically dissolved in the arterial blood plasma and is expressed in millimeters of mercury (mmHg) or in torr. It is a useful indicator of the degree of O2 uptake through lungs.

PAO2: Partial pressure of O2 in alveolar gas is the amount of O2 present in the gas mixture delivered to alveoli.

Based on the above parameters, some useful blood gas derivatives (all of these basically indicate the severity of lung disease by matching PaO2 and FiO2 values in various ways) include:

1. Arterial to alveolar oxygen ratio (PaO2 / PAO2 or a/A ratio)
2. Alveolo-arterial O2 gradient or difference (A-a DO2)

A-a DO2 = PAO2 – PaO2 ($P_{Alveolar} - P_{arterial}$ oxygen)

= [PiO2 – PACO2] – PaO2

= [$(P_B - P_W) \times$ FiO2 – PaCO2] – PaO2

= [(760-47) × FiO2 – PaCO2] – PaO2

Example: Assuming a FiO2 of 40%, PaO2 of 60 mmHg, PaCO2 of 50 mmHg

[(713 × 0.4) – 50] – 60

[285.2 – 50] – 60

235.2 – 60

A-aDO2 = 175

Normal range in a newborn is 5 – 15 and >40 is definitely abnormal

3. PaO2/ FiO2

If $PaO2/FiO_2 < 300$ mmHg acute lung injury (ALI) is considered to be present.

If $PaO_2/FiO_2 < 200$ mmHg acute respiratory distress syndrome (ARDS) is considered to be present.

Recommendations: PaO2/FiO2, a/A ratio and A-aDO2 are some of the methods of assessing oxygenation status of a neonate while on oxygen therapy.

What are the ways of monitoring a baby on oxygen therapy?

Monitoring of oxygen therapy involves monitoring of the concentration of oxygen being administered to the baby (FiO2), percentage of Hb saturated with oxygen (SpO2) by pulse oximetry, partial pressure of oxygen in blood noninvasively (transcutaneously, PtcO2) or invasively by obtaining arterial blood (PaO2). Needless to say that noninvasive monitoring is easier and simple. Our further discussion on monitoring of oxygen therapy will be limited to noninvasive monitoring.

Evidence:

Oxygen analyzer: Amount of supplemental oxygen being administered (FiO2) to the baby should be monitored using Oxygen analyser (FiO2 monitor). It is a hand held portable equipment which employs a galvanic or teledyne cell with a long life sensor. The sensor has a quick response time and is kept in a horizontal position or with the tip directed downward during measurement. The Oxygen analyser should first be calibrated in room air where it should show FiO2 of 21 % and thereafter placed in the air-oxygen mixture being administered to the baby. FiO2 monitoring is essential for rational oxygen therapy. But it should be remembered that when administering supplemental oxygen, the relevant end point is not the FiO2 but the arterial oxygen tension (PaO2) or the arterial oxygen saturation (SpO2). In case of non availability of oxygen analyzer, flow rates of air and oxygen may be used to determine FiO2s, as shown in table 1.

Transcutaneous blood gas monitoring: Transcutaneous (tc) monitoring measures skin-surface P_{O2} to provide estimates of arterial partial pressure of oxygen (P_{aO2}). The devices induce hyperperfusion by local heating of the skin and measure the partial pressure of oxygen electrochemically.[21] Technical factors that may limit the performance of a tc monitor include need for heating the electrodes, prolonged stabilization time required following electrode placement, improper calibration, trapped air bubbles and damaged membranes. Clinical factors that may increase the discrepancy between arterial and tc PaO2 values include presence of hyperoxemia (PaO2 >100 mm Hg), a hypoperfused state (shock, acidosis), improper electrode placement or application and the nature of the patient's skin and subcutaneous tissue (skinfold thickness, edema). Arterial blood gas values should be compared to tc readings taken at the time of arterial sampling in order to validate the tc values. This validation should be performed initially and periodically as dictated by the patient's clinical state. A survey of tc blood gas monitoring among 41 European neonatal intensive care units showed that most units change the sensors every 3 hours; however, the recommended temperature of 44 degrees C is used in only 15% of units. In only 8% of units are arterial blood gases obtained to validate tc values. Large variations were found concerning the targeted level of PO2 [median upper limit: 70 mmHg (range 45-90 mmHg); median lower limit: 44 mmHg (range 30-60 mmHg)].[22] When direct measurement of arterial blood is not available or accessible in a timely fashion, P_{tcO2} measurements may temporarily suffice if the limitations of the data are appreciated. Transcutaneous blood gas monitoring should be continuous for development of trending data.[21] Transcutaneous oxygen monitoring has been largely supplanted by pulse oximetry due to ease of use and simplicity of pulse oximetry. However, above-mentioned survey of tc blood gas monitoring among European neonatal intensive care units showed that the use of transcutaneous monitors remains widespread among German speaking NICUs .[22]

Pulse oximetry: Pulse oximetry has become the primary tool for non-invasive oxygen monitoring in neonates. Pulse oximetry provides estimates of arterial oxyhemoglobin saturation (SaO2) by utilizing selected wavelengths (usually red and near infrared, which are absorbed differentially by oxygenated and reduced hemoglobin) of light, to noninvasively determine the saturation of oxyhemoglobin (SpO2).[23-25]

SpO2 is appropriate for continuous and prolonged monitoring and may be adequate when assessment of acid-base status and/or PaCO2 is not required. As pulse oximetry does not measure PaO2, it is insensitive in detecting hyperoxemia.[26-27] Due to the shape of the oxyhemoglobin dissociation curve, if SpO2 is> 95%, PaO2 is unpredictable (it could be 100 mmHg or it could be 200 mmHg or even higher); a factor which has guided the neonatologists in setting the alarm limits, as discussed subsequently in this topic. To help assure consistency of care (between institutions) based on SpO2 readings, probe selection and placement (the probe is attached to its intended site and the site needs to be rotated 4-6 hourly in ELBW babies) should be appropriate. For continuous, prolonged monitoring, the Hi/Low alarms should be appropriately set while complying with specific manufacturer's recommendations. While using the pulse oximeter, there should be an agreement between patient's heart rate as determined by pulse oximeter and by palpation or auscultation. Strength of plethysmograph waveform or pulse amplitude strength assures that the device is detecting an adequate pulse. The factors that may increase the discrepancy between arterial hemoglobin oxygen saturation and pulse oxymetry values include presence of a hypoperfused state (shock, acidosis), optical interference from external light sources, improper probe application and the nature of the patient's skin and subcutaneous tissue (skinfold thickness, edema).[23-25] Arterial blood gas values should be compared to pulse oxymetry readings taken at the time of arterial sampling in order to validate these values. This validation should be performed initially and periodically as dictated by the patient's clinical state .[28]

Recommendations:

- Supplemental oxygen must always be monitored. In Level III NICU there should be facilities for ABG analysis and Pulse oxymetry. In Level II NICU, there should be facility for Pulse oxymetry and access to ABG if oxygen use is prolonged or in high concentration.
- When direct measurement of arterial blood is not available or accessible in a timely fashion, P_{tcO2} measurements may temporarily suffice.

What are the sources for providing oxygen?

Oxygen supply systems include compressed gas cylinders, centralized piped gas supply and oxygen concentrators. Compressed gas cylinders provide a high-pressure source of 100% medical grade oxygen. It is most commonly used source of oxygen in small hospitals because of its lower costs and relatively easy availability in even small towns compared to the other systems. Gas cylinders also form a good back-up facility in case of a failure of other systems. Cylinders operate at pressures of 1800-2400 psi and need a down regulating valve before the flow-meter attachment. Splitters may be used to provide oxygen to two babies from the same cylinder. Centralized piped gas supply is suitable for large hospital to provide continuous source of oxygen. It should provide at least 50 psi pressure all the times. Oxygen concentrator is an electrical device that provides oxygen from the atmospheric air. It employs a molecular “sieve” that filters out the nitrogen molecules, water vapour and other trace gases.[29] The polymeric membrane concentrators can deliver 50% to 95% oxygen at flow rates of up to 10 L/min. Its main advantages are instant availability of medical oxygen by the flick of a switch, uninterrupted supply without the hassles of refill and delivery and ease of mobility. Portable oxygen concentrators usually can also be plugged into a vehicle DC adapter, and most have the ability to run from battery power as well.

Should all babies on oxygen be continuously monitored for oxygen saturation?

Continuous SpO2 monitoring may be indicated for detecting episodes of desaturation in an unstable patient with high FiO2 requirements whereas a spot check may suffice for evaluating the efficacy of continued oxygen therapy in a stable patient.[22] However, for newborns on oxygen therapy, continuous SpO2 monitoring remains the best option in a setting of no constraint of resources. There is no sufficient evidence to date to suggest what is the optimal oxygen saturation or PaO2 value in preterm infants on oxygen therapy; so as to avoid potential oxygen toxicity while ensuring adequate oxygen delivery to tissues.

Evidence: A systematic review of six trials[30] confirmed that policy of unrestricted, unmonitored oxygen therapy has potential harms without clear benefits. However, the question of what is the optimal target range for maintaining blood oxygen levels in preterm/LBW infants in the modern clinical setting from birth or soon thereafter was not answered by the data available for inclusion in this review. Most of the included studies were before 1970, during an early era of neonatal care, with therapies and practices quite different from modern "intensive" care. These studies included only small numbers of survivors with birth weights under 1000 g, the infants who carry the greatest mortality and morbidity burden today. The only recent study[31] in this systematic review included 358 infants < 30wks gestation who remained dependent on supplemental oxygen at 32 wks of postmenstrual age. The intervention group (standard oxygen) received supplemental oxygen to achieve SpO2 91-94%, while the control group (high oxygen) received supplemental oxygen to achieve SpO2 95-98%. There was no significant difference in the incidence of death between lower or higher oxygen saturation targeting when started in the later neonatal period. There were no statistically significant differences in the incidence of ROP (any stage) in survivors, the incidence of ROP > Stage 2 or ROP Stage 4 or 5 or blindness or the incidence of major developmental abnormality at 12 months corrected age between the infants receiving lower or higher oxygen saturation targeting. In relation to lung function, there was a significant reduction on the dependence of supplemental oxygen at 36 weeks of postmenstrual age with using a lower oxygen saturation target (RR 0.71, 95% CI 0.59-0.87).

We are mostly concerned with risk of development of ROP while giving supplemental oxygen to the premature neonates especially of <32 weeks of gestational age. ROP occurs most frequently at a postmenstrual age of 3-5 weeks postnatally[32].

Oxygen Saturation Targets During Phase 1 ROP

Sun and his colleagues collated data from Vermont Oxford Network, and compared the survival, chronic lung disease and severe retinopathy of prematurity of 1544 extremely low birth weight babies (500-1000 g) who were cared for in units that aimed to keep oxygen saturation at or below 95% and those that intended to keep saturations above 95% whilst these babies were in supplemental oxygen. They reported significantly lower incidences of chronic lung disease (27% vs. 53%) as well as stage III/IV ROP (10% vs. 29%) amongst babies cared for with targeted saturations of 95% or less. Survival rate was marginally higher in the low saturation group, but not statistically significantly (83% vs. 76%)[33].

Oxygen Saturation Targets During Phase 2 ROP

The STOP-ROP multicenter study group randomized 649 infants with prethreshold (moderately severe) ROP to receive supplemental oxygen to maintain SpO_2 of 89--94 percent (control) or 96--99 percent (treatment). More infants in the control group (46 percent) progressed to threshold disease than infants in the treatment group (32 percent). This suggests that liberalizing SpO_2 targets once an infant reaches prethreshold ROP may improve retinal outcomes. The study concluded, "The STOP-ROP data clearly demonstrate that oxygen at saturations of 96--99 percent does not increase the severity of ROP in eyes of infants with prethreshold ROP". However, it also showed a modest exacerbation of chronic lung disease and a lack of improvement in long-term growth and development at three months of age [34]. This study did not demonstrate that increased oxygen saturation levels are deleterious as far as established ROP is concerned. However, these data do not support the use of higher saturation levels for more immature infants where ROP is not already established. To date, the only randomised trial that has attempted to assess the effect of higher oxygen saturation target ranges on longer term growth and development (BOOST 2002) found no significant difference in growth, development or adverse eye outcomes for those targeting a higher oxygen saturation range[35].

Recommendations: There is no firm evidence to support any fixed saturation guidelines. Table 3 shows the proposed Oxygen saturation guidelines in newborns[31]. Apart from keeping these saturation ranges it is very important to avoid excessive fluctuation in the saturation.

Table: Oxygen saturation targets

Infants	PaO2 (mm Hg)	Saturation Range
Preterm <32 weeks	50-70	88-92%
Preterm ≥32 weeks	60-80	90-95%
Term and post term	60-80	90-95%
CLD and preterm PCA >36 weeks	60-80	90-95%

How should a baby be weaned from oxygen therapy?

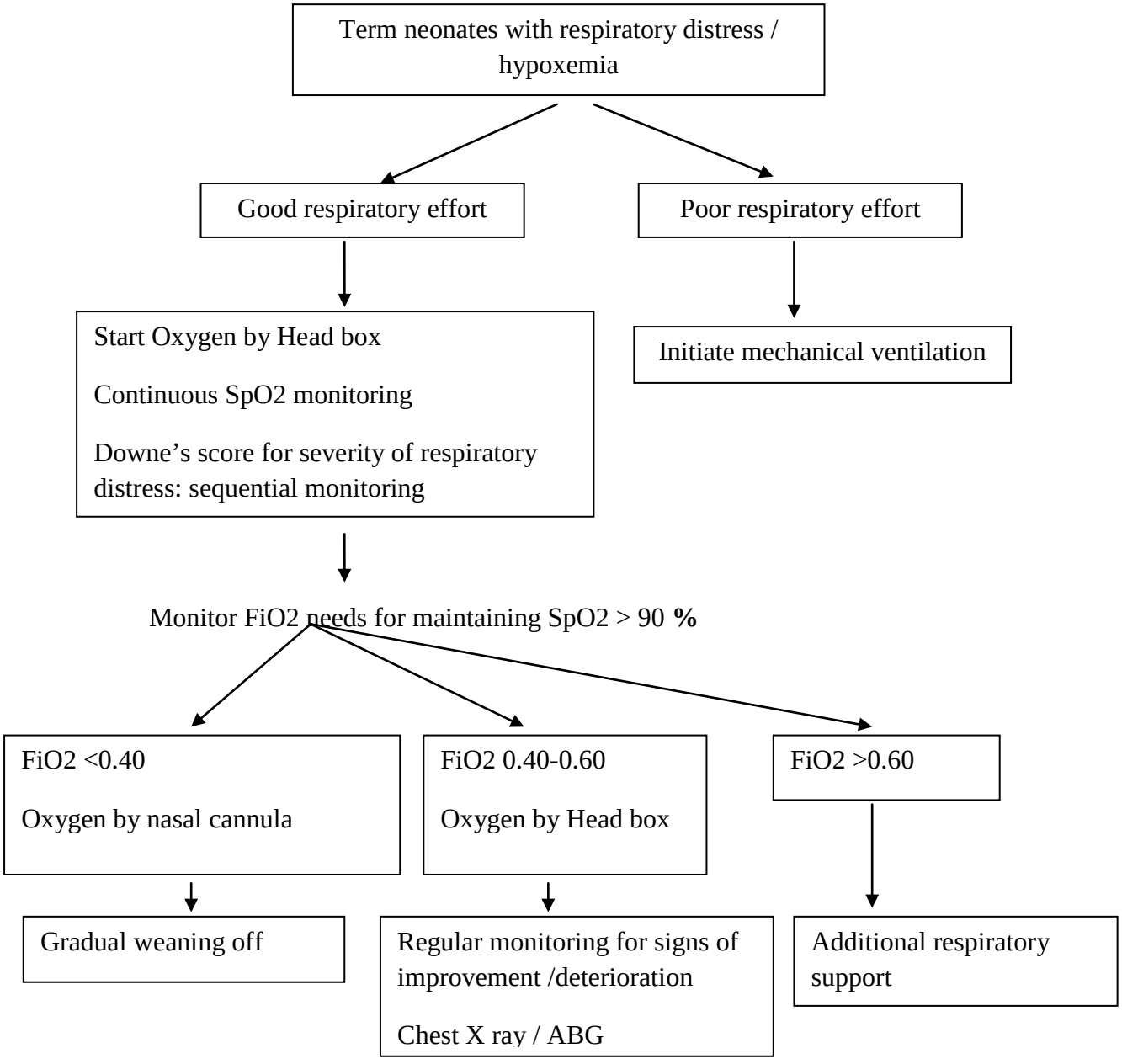
A baby may be weaned from supplementary oxygen gradually or abruptly. Studies of both humans and animal models on the effects of either method of oxygen cessation have shown mixed results on important infant outcomes[36].

Evidence: In a study by Bedrossian et al[37], there was an increased incidence in retrolental fibroplasia in low birth weight infants who had their oxygen therapy discontinued abruptly compared with those who had a stepwise reduction. This finding was independent of the duration of oxygen therapy. It is the only controlled trial in human babies that directly addressed the issue of gradual vs. abrupt oxygen weaning in preterm/LBW infants. Phelps and Rosenbaum[38] using a kitten model reported no difference in oxygen-induced retinopathy when supplemental oxygen was weaned gradually compared with abrupt discontinuation. However, Chan-Ling et al[39] showed in a kitten model that gradual oxygen withdrawal can significantly reduce retinal pathology.

Recommendation: Supplemental oxygen should be weaned gradually in newborn infants, making a stepwise reduction in FiO2, while monitoring the baby clinically and oxygen saturations.

Algorithm for oxygen therapy in newborns

The algorithm for term babies needing oxygen therapy has been mentioned below. The preterm babies with respiratory distress form a separate group, as they may need early CPAP and surfactant therapy.



References

1. Fulmer JD, Snider GL. ACCP-NHLBI National Conference on Oxygen Therapy. Chest 1984;86 (2):234-247.
2. Higgins TL, Yared J-P. Clinical effects of hypoxemia and tissue hypoxia. Respir Care 1993;38 (6):603-615.
3. American Association for Respiratory Care. AARC Clinical Practice Guideline: Oxygen therapy in the acute care facility -- 2002 revision and update. Respir Care 2002;47 (6):
4. American Association for Respiratory Care. AARC Clinical Practice Guideline: Selection of an Oxygen Delivery Device for Neonatal and Pediatric Patients -- 2002 revision and update. Respir Care 2002;47(6):707–716.
5. SK Jatana, S Dhingra, MNG Nair, G Gupta. Controlled FiO2 Therapy to Neonates by Oxygenhood in the Absence of Oxygen Analyzer. MJAFI 2007; 63: 149-153.
6. Mukta M. Jain, Arvind Shenoi and H. Paramesh. A new oxygen head box. Indian Pediatrics 2002; 39:842-846.
7. Vain NE, Prudent LM, Stevens DP, Weeter MM, Maisels MB. Regulation of oxygen concentration delivered to infants via nasal cannulas. Am J Dis Child 1989;143(12):1458-1460.
8. Wilson J, Arnold C, Connor R, et al. Evaluation of oxygen delivery with the use of nasopharyngeal catheters and nasal cannulas. Neonatal Netw 1996;15:15–22.
9. Finer NN, Bates R, Tomat P. Low flow oxygen delivery via nasal cannula to neonates. Pediatr Pulmonol 1996;21(1):48-51
10. Campbell EJ, Baker D, Crites-Silver P. Subjective effects of humidification of oxygen for delivery by nasal cannula. Chest 1988;93:289–93.
11. Weber MW, Palmer A, Oparaugo A, Mulholland EK. Comparison of nasal prongs and nasopharyngeal catheter for the delivery of oxygen in children with hypoxemia because of a lower respiratory tract infection. J Pediatr 1995;127(3):378-383.
12. Locke RG, Wolfson MR, Shaffer TH, Rubenstein SD, Greenspan JS. Inadvertent administration of positive end-distending pressure during nasal cannula flow. Pediatrics 1993;91(1):135-138.
13. Finer NN. Nasal cannula use in the preterm infant: oxygen or pressure? Pediatrics. 2005;116:1216–1217.
14. Scacci R. Air entrainment masks: jet mixing is how they work; the Bernoulli and Venturi principles are how they don't. Respir Care 1979;24(10):928-931.
15. Kopelman AE, Holbert D. Use of oxygen cannulas in extremely low birthweight infants is associated with mucosal trauma and bleeding, and possibly with coagulase-negative staphylococcal sepsis. J Perinatol 2003;23:94–97.
16. Schulze A. Respiratory gas conditioning in infants with an artificial airway. Semin Neonatol. 2002;7:369–377.
17. Tarnow-Mordi WO, Reid E, Griffiths P, Wilkinson AR. Low inspired gas temperature and respiratory complications in very low birth weight infants. J Pediatr. 1989;114:438–442.
18. Shann F, Gatchalian S, Hutchinson R. Nasopharyngeal oxygen in children. Lancet 1988;2:1238–40.
19. Bissonnette B, Sessler DI. Passive or active inspired gas humidification increases thermal staedy state temperature in anesthetised infants.Anesth Analg 1989;69:783-7.
20. Bissonnette B, Sessler DI, LaFlamme. Passive and active inspired gas humidification in infants and children. Anesthesiology1989;71:350-4.
21. American Association for Respiratory Care. Transcutaneous blood gas monitoring for neonatal & pediatric patients--2004 revision & update. Respir Care 2004 Sep;49(9):1069-72.
22. Rudiger M, Töpfer K, Hammer H, Schmalisch G, Wauer RR. A survey of transcutaneous blood gas monitoring among European neonatal intensive care units. BMC Pediatr. 2005;5:30.

23. Moran RF, Clausen JL, Ehrmeyer SS, Feil M, Van Kessel Al, Eichhorn JH. Oxygen content, hemoglobin oxygen, "saturation," and related quantities in blood: terminology, measurement, and reporting. National Committee for Clinical Laboratory Standards 1990; C25-P:10:1-49.
24. Huch A, Huch R, Konig V, Neuman MR, Parker D, Yount J, Lubbers D. Limitations of pulse oximetry. Lancet 1988;1:357-358.
25. Schnapp LM, Cohen NH. Pulse oximetry-uses and abuses. Chest 1990;98:1244-1250.
26. Tremper KK, Barker SJ. Pulse oximetry. Anesthesiology 1989;70:98-108.
27. Praud JP, Carofilis A, Bridey F, Lacaille F, Dehan M, Gaultier CL. Accuracy of two wavelength pulse oximetry in neonates and infants. Pediatr Pulmonol 1989;6:180-182.
28. American Association for Respiratory Care. Pulse oximetry. Respir Care 1992;37(8):891–897.
29. Gould GA, Hayhurst MD, Scott W, Flenley DC. Technical and clinical assessment of oxygen concentrators. Thorax1985; 40: 811-6.
30. Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.:CD001077. DOI: 10.1002/14651858.CD001077.pub2.
31. Askie, L. M., Henderson-Smart, D., Irwig, L., & Simpson, M. (2003). Oxygen-saturation targets and outcomes in extremely preterm infants. The New England Journal of Medicine, 349, 959-967.
32. Wheatley, D. M., Dickenson, J., Mackay, D., Craig, J., & Sale, M. (2002). Retinopathy of prematurity: Recent advances in our understanding. The British Journal of Ophthalmology, 86, 696-701.
33. Sun SC, Relation of target SpO2 levels and clinical outcome in ELBW infants on supplemental oxygen . Pediatric Res 2002; 51: A350.
34. STOP-ROP Multicenter Study Group. (2000). Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics, 105, 295-310.
35. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. The effect of differing oxygen saturation targeting ranges on long term growth and development of extremely preterm, oxygen dependent infants: the BOOST Trial [abstract]. In: Pediatr Res. Vol. 51. 2002:378A.
36. LM, Henderson-Smart DJ. Gradual versus abrupt discontinuation of oxygen In preterm or low birthweight infants.CochraneDatabase of SystematicReviews 2001, Issue 4.Art.No.:CD001075.DOI: 10.1002/14651858.CD001075.
37. RH, Carmichael P, Ritter J. Retinopathy of prematurity (retrolental fibroplasia) and oxygen. American Journal of Ophthalmology 1954;37:78–86.
38. Phelps DL, RosenbaumAL. Effects of variable oxygenation and gradual withdrawal of oxygen during the recovery phase in oxygen-induced retinopathy: kitten model. Pediatric Research 1987;22:297–301.
39. Chan-Ling T, Gock B, Stone J. Supplemental oxygen therapy. Basis for noninvasive treatment of retinopathy of prematurity. Investigative Ophthalmology and Visual Science 1995;36:1215–30.

Annexure

Table 1: Blending Air and Oxygen to Provide Controlled FiO2

O_2 / AIR L/min	0	1	2	3	4	5	6	7	8	9	10
0	*	20.8	20.8	20.8	20.8	20.8	20.8	20.8	20.8	20.8	20.8
1	100	59.5	47	41	38	34	32	30.5	28	27.5	26.5
2	100	74	59	53.5	48	44	41	38.5	35.5	34	32
3	100	82	70	60.5	56	51.5	48	43.5	40.5	39.5	38
4	100	86	74	66	60	57	54	48.5	45	44	42
5	100	88	78	71	66	59	57	53	49.5	48	46
6	100	90	82	74	70	65	59.5	56	53	51	49.5
7	100	92	84.5	77	72.5	68.5	64	60.5	56	54	52
8	100	93	86	79.5	75	71.5	67	62	59	57	55
9	100	94.5	87	82	76.5	73	69.5	64	62	60	57
10	100	96	88	84	78	75	71	66.5	64	62	60.5

X axis – air; Y axis - oxygen

Table2: Commonly Available Humidifiers: A Comparison

Feature	Unheated bubble humidifier	Heated humidifiers	HME/HMEF
Temperature	18-23 ^{o}C	36-38 ^{o}C	--
Absolute humidity	15-20 mg/L	42-44 mg/L	27-36 mg/L
Relative humidity	≤100 %	100%	--
General safety	Gas leakage	Electrical, equipment damage	Debris blockage
Microbiological safety	Reservoir contamination	Reservoir & circuit contamination	--

Use of Continuous Positive Airway Pressure in the Newborn

Summary of Recommendations

- **CPAP should be used at the earliest sign of respiratory distress in preterm infants at risk for RDS, unless there is a contraindication to its use. CPAP is also useful for apnea of prematurity and post-extubation respiratory support.**
- **Prophylactic CPAP in asymptomatic babies is not recommended.**
- **Surfactant administration can be done effectively by INSURE technique in babies requiring CPAP.**
- **Optimal pressures required to recruit the lung should be used. These vary in the range of 5 to 8 cm H_2O.**
- **A proportion of babies, especially extremely low birth weight, those with more severe disease and having no exposure to antenatal steroids may fail on CPAP. Alternative arrangements of mechanical ventilation should be made available for such babies.**
- **Short bi-nasal prongs are the best amongst the currently available patient interfaces.**
- **There are no clear cut demonstrable clinical advantages among various types of CPAP systems; a particular type may perform better in a particular setting.**

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Introduction

Continuous positive airway pressure (CPAP), a simple, low-cost, and non-invasive method of ventilating a sick newborn, could well be a boon for babies born in resource restricted countries. If used early and judiciously in infants with respiratory distress, CPAP can save many lives and reduce upward referrals.[1] Success of CPAP therapy lies in creation of a system with a team of committed health providers well versed in providing holistic care to sick newborn.

This guideline reviews the evidence and offers recommendations related to CPAP therapy in neonates for the following issues:

I. Clinical indications for CPAP

a. Respiratory distress syndrome (RDS)
   i. Evidence for use
   ii. Timing of initiation – early vs. late, prophylactic vs. delivery room CPAP
   iii. Optimal pressure to be used
   iv. Role of INSURE
   v. Weaning of CPAP
   vi. Failure of CPAP

b. Apnea of prematurity

c. Post-extubation setting

II. Equipment related

a. Pressure generators

b. Patient interfaces

A. Respiratory distress syndrome

i. Evidence for use

Evidence: Randomized trials evaluating use of CPAP were conducted mostly in the 1970's on more mature neonates using a wide variety of devices. Moreover, they were conducted before widespread use of antenatal corticosteroids and surfactant. The Cochrane review (2008) that included six trials concluded that use of CPAP is associated with a lower rate of failed treatment (death or use of assisted ventilation) [relative risk (RR): 0.65, 95% CI: 0.52, 0.81; number needed to treat (NNT): 5, 95% CI 4, 10], overall mortality [RR: 0.52, 95% CI: 0.32, 0.87; NNT: 7, 95% CI: 4, 25]. The use of CDP is, however, associated with an increased rate of pneumothorax [RR: 2.64, 95% CI: 1.39, 5.04; number needed to harm (NNH): 17, 95% CI: 17, 25][1]. A recent trial in infants born at gestation of >30 weeks in level two neonatal units with respiratory distress showed that CPAP resulted in a reduction in the need for transfer to a higher level of care but there was again a trend towards an increased risk of pneumothorax in the CPAP group.[1]

Recommendation*:* In preterm infants with RDS, application of CPAP is associated with reduced respiratory failure and reduced mortality. CPAP should therefore be used in all preterm infants with RDS, unless there is a contraindication to its use.

ii. Timing of initiation for respiratory distress in a preterm infant

Early versus late CPAP

Evidence: Use of CPAP in the course of respiratory distress syndrome (RDS) reduces the lung damage, particularly if applied early before atelectasis occurs. Early CPAP conserves the neonate's own surfactant stores and minimizes the stimulation of inflammatory cascade. The Cochrane review that compared early CPAP (initiated at randomization) and delayed initiation of CPAP (initiated at FiO2 of approximately 0.6) concluded that early administration of CPAP reduces the subsequent use of intermittent mandatory ventilation (IMV) [typical RR 0.55, 95% CI: 0.32-0.96; NNT: 6][2]. With early introduction of CPAP, there is a significant reduction in the duration of ventilator assistance (mean difference 33.7 hours) and need for mechanical ventilation (20.6%)[3]. In a recently published trial, early CPAP with use of selective surfactant was as effective as using prophylactic surfactant followed by CPAP in reducing the need for mechanical ventilation in infants born at 25 to 28 weeks' gestation[4]. Another recent trial that enrolled infants born between 24 and 27 weeks' gestation did not find any difference in the rate of BPD between the group initiated on CPAP in the delivery room and the group that received surfactant and mechanical ventilation within 1 hour of birth[5].

Recommendation: CPAP should be used early in the course of RDS, to reduce the need for mechanical ventilation unless there is a contraindication to use CPAP.

How early should CPAP be initiated- prophylactic (or) in delivery room (or) in NICU?

Evidence: A Cochrane meta-analysis evaluating the efficacy of prophylactic CPAP did not show any significant benefit in the rates of death, BPD, subsequent endotracheal intubation or intraventricular hemorrhage (IVH)[6]. Current available evidence does not support the use of prophylactic CPAP.

Most of the studies included in the meta-analysis by Ho et al initiated CPAP if the FiO_2 requirement was≥0.3 in the 'early CPAP group. [2] Finer et al documented the feasibility of delivery room CPAP even in ELBW infants.[7] In the recently published COIN trial, early CPAP was used from 5 minutes of life in neonates between 25 and 28 weeks**.** In the CPAP group the incidence of death/BPD is significantly less and surfactant use was halved in comparison to the ventilated group of neonates. The CPAP group received significantly fewer days of intubation and ventilation though the incidence of pneumothorax was more in the CPAP group as compared to the ventilated group (9% vs. 3% respectively).[8]

Recommendation: CPAP is not to be used prophylactically (i.e. before any sign of respiratory distress develops); it should, however, be initiated at the earliest sign of respiratory distress in neonates at risk for RDS. One of the arbitrary criteria could be FiO_2 requirement of ≥ 0.3. Some units also use respiratory distress scores – either Downe's or Silveman score – for initiation of CPAP (usually a score of >3 is used as the cut-off). CPAP can be initiated even in the delivery

room if delay in shifting to NICU is anticipated rather than withholding any form of respiratory support.

iii. Optimal pressure to be used

Evidence: The pressure required in an infant is best determined by the severity of the disease (chest retractions, FiO2 requirement) and lung expansion (clinical/radiological): a baby with severe RDS – relatively stiff lungs, a high FiO2, and a chest X-ray showing opaque lungs – would need a higher pressure than another baby with relatively mild disease.

While an initial pressure of 5 cm H_2O is used in most neonatal units, some units continue to use higher levels - often starting at 8 cm H_2O and going up to 10 cm H_2O.[9] A study of infants with mild RDS showed that the highest end expiratory lung volume and tidal volume, and the lowest respiratory rate and thoracoabdominal asynchrony were achieved with a pressure of 8 cm H_2O as compared to pressures of 0,2,4, and 6 cm H_2O.[10] Unfortunately, there is not much evidence in this regard and the optimal CPAP pressure to be used is yet to be ascertained.

Recommendation: A pressure of 5 cm H_2O is a good starting point. The pressure can be increased in increments of 1 cm H_2O – upto a maximum of 8 cm H_2O – if the infant shows evidence of severe lung disease.

iv. Role of surfactant with CPAP

INSURE technique refers to IN (Intubation) → SUR(Surfactant) →E (Extubation). This comprises of intubation only for the administration of exogenous surfactant, followed by immediate extubation to CPAP.

Evidence: Cochrane meta-analysis comparing early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation showed lower incidence of mechanical ventilation (typical RR 0.67, 95% CI: 0.57-0.79), air leak syndromes (typical RR 0.52, 95% CI: 0.28-0.96) and BPD (typical RR 0.51, 95% CI: 0.26-0.99).[11] The IFDAS trial was aimed to establish whether the early use of CPAP with prophylactic surfactant was an effective and safe in neonates of 27–29 weeks.[12] The authors concluded that the use of CPAP following prophylactic surfactant or CPAP alone was safe and reduced the need for mechanical ventilation when used as initial respiratory support, but did not demonstrate a reduction in BPD.

Recommendation: Current available evidence suggests that INSURE technique is to be followed if administration of surfactant is required and there is no other indication for continuing mechanical ventilation.

v. Weaning of CPAP

Weaning of CPAP is considered when the clinical condition for which it was initiated is passive and there are no other indications to continue.

Evidence: The optimal method of weaning an infant off CPAP remains uncertain. A survey of neonatal units in England showed that most units weaned by gradually increasing the time off CPAP.[13] A randomized trial comparing the strategy of weaning pressure with one of increasing time off CPAP showed a significant shorter duration of weaning with the 'pressure' strategy.[14]

Recommendation: If the infant is stable, first wean off the FiO2 to 30% (in steps of 5%) and then wean the pressure to 4 cm H2O (in steps of 1 cm). If the baby is comfortable – normal saturation and minimal retractions – at this setting, (s)he can be weaned off CPAP.

vi. Failure of CPAP and its predictors

The factors determining the success of CPAP are: choosing the right infant (weight and underlying disease process), applying it early rather than late, knowing the machine well, diligent and patient nursing care and the conviction of the team. In addition, the threshold or the criteria used to define failure will determine the CPAP failure rates. With increasing experience of the unit, the success rates are likely to improve.[15]

CPAP failure: Even on a CPAP of 7-8 cm H_2O and 70% FiO_2 if the neonate has excessive work of breathing or PCO_2 >60mmHg with pH <7.2 or recurrent apnea or hypoxemia (PaO_2 <50 mmHg), this should be considered as failure of CPAP.

Evidence: In a study by Koti J et al, 60 preterm neonates of gestation <35 weeks with respiratory distress and chest x- ray suggestive of RDS were enrolled.[16] CPAP failure was defined as infants requiring invasive ventilation in the first one week. The variables associated with failure were: no or only partial exposure to antenatal steroids, white out on the chest x-ray, Downe's score $\geq$ 7 at starting of CPAP and after 2 hours of CPAP , and $FiO_2 \geq 50\%$ after 2 hours of CPAP. In another study by Ammari A et al, 261 neonates of $\leq$ 1250 gms with RDS were enrolled.[17] The predictors of CPAP failure, as defined by requirement of ventilation by 72 hrs were: need for positive pressure ventilation (PPV) at delivery, alveolar-arterial oxygen tension gradient (A-a DO_2) >180 mmHg on the first arterial blood gas (ABG), and severe RDS on the initial chest x-ray. Another study from India reported high failure rates in babies who are born at lesser gestation and whose mothers did not receive antenatal steroids.[18]

Recommendation: The available evidence suggests that sicker and more immature a neonate is he/she is more likely to fail CPAP. Knowledge about the predictors of CPAP failure would help in early identification of neonates who are likely to fail CPAP and require mechanical ventilation. This would help the attending physician/staff to be more vigilant during CPAP administration and be prepared with the necessary facilities for mechanical ventilation and/or referral.

B. Apnea of prematurity

Evidence: CPAP has been shown to reduce the incidence and severity of mixed and obstructive apneas by preventing the collapse of pharynx and upper airways and by splinting the diaphragm. The Cochrane review that included a single study concluded that the face-mask CPAP is inferior to aminophylline for management of apnea.[19] The current methods of CPAP delivery including nasal prong CPAP have not been compared with methylxanthines. Evidence is now emerging that nasal intermittent positive pressure ventilation (NIPPV) is probably more effective than nasal CPAP in the management of apnea of prematurity.[20]

Recommendation: CPAP is typically used when clinically significant episodes of apnea persist despite optimal methylxanthine therapy.

C. Post-extubation

Evidence: The Cochrane review concluded that nasal CPAP reduces the incidence of respiratory failure (apnea, respiratory acidosis and increased oxygen requirements) indicating the need for additional ventilatory support [typical RR: 0.62, 95%CI: 0.51, 0.76; NNT: 6] when applied to preterm infants being extubated following intermittent positive pressure ventilation.[21]

Recommendation: Preterm VLBW infants extubated after a period of endotracheal intubation and ventilation are preferably managed with CPAP so as to reduce the incidence of reintubation and mechanical ventilation.

CPAP delivery systems

1. Pressure generators

The required CPAP pressure is usually generated by using one of these four devices:

a. Bubble CPAP
b. Ventilator/stand-alone CPAP
c. Variable flow devices (e.g. infant flow driver)
d. High flow nasal cannulae (HFNC)

Evidence: The authors of the Cochrane review on 'Devices and pressure sources for administration of CPAP' conclude that more studies are needed to determine the optimal pressure source for the delivery of nasal CPAP.[22] Two recent studies from India have reported very good results with bubble CPAP in preterm low birth weight infants with respiratory distress syndrome.[17, 19] The success rates (about 75 to 80%) in these studies were comparable to that of another study using ventilator derived CPAP (Personal communication). There are not enough studies regarding the use of other pressure generators. In a recently published study from United Kingdom, bubble CPAP was found to be as effective as IFD CPAP in the post-extubation management of infants with RDS; indeed, in infants ventilated for $\leq$14 days, bubble CPAP was associated with a significantly higher rate of successful extubation and reduced duration of CPAP support.[23]

***Recommendation*:** The evidence available at present does not permit us to choose a single best device for generating CPAP pressure. However, given the efficacy, ease of use/familiarity and the low cost, bubble CPAP device seems to be a better option than others.

Table 1 gives examples, approximate cost, and the relative merits and demerits of each of these methods.

Table 1: A comparison of CPAP devices used for pressure generation[24]

Device	Advantages	Disadvantages	Evidence	Remarks
1.Bubble CPAP	• Simple and inexpensive • Can identify large leaks at the nares (bubbling stops)	• Flow has to be altered to ensure proper bubbling and adequate pressure • Difficult to detect high flow rates that can lead to over distension of lungs	• While earlier studies indicated that the oscillations produced by bubbling facilitate gas exchange akin to HFV[25], later studies were not able to confirm it[26] • The results of two recent Indian studies seem to be encouraging (*vide Infra*)[11,13]	Stand-alone option makes it an easy and cost effective proposition in developing countries
2a. Conventional ventilator derived CPAP	• No need of a separate equipment • Can be easily switched over to mechanical ventilation, if CPAP fails	• Expensive • Difficult to know if the set flow is sufficient or not (insufficient flow can lead to increased WOB) • Standard flow of 5-8L/min may be insufficient in the presence of high leak	• A recent study from India found encouraging results in preterm neonates with RDS (Personal communication)	Of practical utility in units having neonatal ventilators
2b. Stand-alone CPAP machines ('Indigenous CPAP')	• Economical • Most have bubble CPAP option as well	• Most of them do not have proper blenders and/or pressure manometer	No studies are available yet	Though inexpensive, they have not been tested adequately; niggling issues observed with daily use
3. Variable flow devices	• Maintains more uniform pressure • Might decrease the WOB • Recruits lung volume more effectively	• Expensive • Requires more technical expertise	Though initial studies had shown superiority of IFD over constant flow devices in terms of decreased oxygen requirement, respiratory rates and lesser need for mechanical ventilation[27], recent studies have failed to reproduce these results[28]	Prohibitive cost and lack of evidence regarding its superiority preclude its widespread use
4. High flow nasal cannulae	• Easy to use	• Unreliable pressure delivery • FiO2 delivered may be high • Large leaks around the cannulae	Mainly tried in apnea of prematurity – paucity of data in other conditions	Still experimental

(WOB, work of breathing; HFV, high frequency ventilation; IFD, infant flow driver)

2. Patient interfaces

The devices used for CPAP delivery include:

1. Nasal prongs - single or double
2. Long (or) nasopharyngeal prongs
3. Nasal masks

Face mask, endotracheal, and head box are no longer used for CPAP delivery in neonates; endotracheal CPAP is not recommended because it has been found to increase the work of breathing (infant has to breathe 'through a straw'). The advantages and disadvantages of each of these devices have been summarized in *Table 2.*

Table 2: A comparison of common CPAP delivery systems

Delivery system	Advantages	Disadvantages	Evidence
Nasal prongs (single/binasal) Example: • Argyle, Hudson, Medicorp • IFD prongs • F & P prongs	• Simple device • Lower resistance leads to greater transmission of pressure • Mouth leak may act like a 'pop-off' mechanism	• Relatively difficult to fix • Risk of trauma to nasal septum and turbinates • Leak through mouth means end expiration pressure is variable	Studies have shown that short binasal prongs are more effective than nasopharyngeal prongs especially in post-extubation settings[29]
Nasopharyngeal prongs (e.g. using a cut endotracheal tube)	• Economical and easily available (if cut ET tube is being used) • Secure fixation	• Easily blocked by secretions • Likely to get kinked • Monitoring of local side effects is difficult	Though more economical and easily available, they are found to be inferior to short binasal prongs
Nasal masks	Minimal nasal trauma	• Difficulty in obtaining an adequate seal • Risk of injury to the junction of nasal septum & philtrum	New generation masks are yet to be studied in detail

(IFD, infant flow driver)

Evidence: The authors of the Cochrane review on devices and pressure sources for administration of CPAP conclude that "short binasal prong devices are more effective than single prongs in reducing the rate of re-intubation. Although the Infant Flow Driver appears more effective than Medicorp prongs, the most effective short binasal prong device remains to be determined. The improvement in respiratory

parameters with short binasal prongs suggests they are more effective than nasopharyngeal CPAP in the treatment of early RDS".[28] Few recent studies that have compared different CPAP delivery devices are available from either India or other countries.

***Recommendation**:* Among the CPAP delivery systems, short binasal prongs are preferred; however, there is not much evidence to choose a particular type of short binasal prong.

References

1. Ho JJ, Subramaniam P, Henderson-Smart DJ, DavisPG. Continuous distending pressure for respiratory distress in preterm infants. Cochrane Database Syst Rev 2002: CD002271.
2. Ho JJ, Henderson-Smart DJ, Davis PG. Early versus delayed initiation of continuous distending pressure for respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev 2002:CD002975.
3. Polin RA, Sahni R. Continuous positive airway pressure: old questions and new controversies. J Neonatal Perinatal Med 2008;1: 1-10.
4. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S, Pediatrics 2010;125:e1402-9. Epub 2010 May 3.
5. Early CPAP versus surfactant in extremely preterm infants. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, et al. N Engl J Med 2010;362:1970-9.
6. Subramaniam P, Henderson-Smart DJ, Davis PG. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. Cochrane Database Syst Rev 2005: CD001243.
7. Finer NN, Carlo WA, Duara S, et al. Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. Pediatrics 2004;114:651–57.
8. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB; COIN Trial Investigators.Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;358:700-8.
9. Davis PG, Morley CJ. Non-invasive respiratory support: An alternative to mechanical ventilation in preterm infants. In: Bancalari E (ed). The Newborn Lung. Neonatology questions and new controversies. 1st edn. Philadelphia: Saunders 2008: p. 361-76.
10. Elgellab A, Riou Y, Abbazine A, et al. Effects of nasal continuous positive airway pressure on breathing pattern in spontaneously breathing premature newborn infants. Intensive Care Med 2001; 27: 1782-7.
11. Stevens TP, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev 2007:CD003063.
12. Thomson M. Early continuous positive airway pressure (nCPAP) with prophylactic surfactant for neonates at risk of RDS. The IFDAS multicentre randomized trial. Pediatr Res 2002;51:379A.
13. Bowe L, Clarke P. Current use of nasal continuous positive airway pressure in neonates. Arch Dis Child Fetal Neonatl Ed 2005; 90: F92-3.
14. Bowe L, Smith J, Clarke P, et al. Nasal CPAP weaning of VLBW infants: is decreasing CPAP pressure or increasing time off the better strategy – results of a randomized controlled trial. Pediatric Academic Society Meeting, San Francisco (Abstract) 2006.
15. Aly H, Milner JD, Patel K, El-Mohandes AA. Does the experience with the use of nasal continuous positive airway pressure improve over time in extremely low birth weight infants? Pediatrics 2004;114:697-702.
16. Koti J, Murki S, Gaddam P, Reddy A, Reddy MD. Bubble CPAP for Respiratory Distress Syndrome in Preterm Infants. Indian Pediatr. 2010 ;47:139-43.
17. Ammari A, Suri M, Milisavljevic V, Sahni R, Bateman D, Sanocka U, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. J Pediatr. 2005;147:341-7.
18. Urs PS, Khan F, Maiya PP. Bubble CPAP - a primary respiratory support for respiratory distress syndrome in newborns. Indian Pediatr. 2009;46:409-11.
19. Henderson-Smart DJ, Subramaniam P, Davis PG. Continuous positive airway pressure versus theophylline for apnea in preterm infants. Cochrane Database Syst Rev 2001: CD001072.

20. Lemyre B, Davis PG, De Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity. Cochrane Database Syst Rev 2002: CD002272.
21. Davis PG, Henderson-Smart DJ. Nasal Continuous positive airway pressure immediately after extubation for preventing morbidity in preterm infants. Cochrane Database Syst Rev 2003: CD000143.
22. Sankar MJ, Sankar J, Agarwal R, Paul VK, Deorari AK. Protocol for administering continuous positive airway pressure in neonates. Indian J Pediatr. 2008;75:471-8.
23. Lee KS, Dunn MS, Fenwick M, et al. A comparison of underwater bubble continuous positive airway pressure with ventilator-derived continuous positive airway pressure in premature neonates ready for extubation. Biol Neonate 1998;73:69–75.
24. Kahn DJ, Courtney SE, Steele AM, Habib RH. Unpredictability of Delivered Bubble Nasal Continuous Positive Airway Pressure Role of Bias Flow Magnitude and Nares-Prong Air Leaks. Pediatr Res. 2007;62:343-47.
25. Mazzella M, Bellini C, Calevo MG, Campone F, Massocco D, Mezzano P, et al. A randomized control study comparing Infant Flow Driver with nasal CPAP in preterm infants. Arch Dis Child Fetal Neonatal Ed 2001; 85: F86-90.
26. Stefanescu BM, Murphy WP, Hansell BJ, Fuloria M, Morgan TM, Aschner JL. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics 2003;112:1031-8.
27. De Paoli AG, Davis PG, Faber B, Morley CJ. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. Cochrane Database of Syst. Rev. 2002: CD002977.
28. Gupta S, Sinha SK, Tin W, Donn SM. A randomized controlled trial of post-extubation bubble continuous positive airway pressure versus Infant Flow Driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. J Pediatr 2009;154:645-50.
29. Davis P, Davies M, Faber B. A randomised controlled trial of two methods of delivering nasal continuous positive airway pressure after extubation to infants weighing less than 1000g: binasal (Hudson) versus single nasal prongs. Archives of Disease in Childhood Fetal Neonatal Ed 2000;85:F82–5.

Surfactant Replacement Therapy

Summary of Recommendations

- **The diagnosis of Respiratory Distress Syndrome (RDS) should be based primarily on the clinical presentation of an at risk preterm neonate who has an early onset respiratory distress.**
- **Surfactant Replacement Therapy must be considered in all preterm infants with ≥28 week gestational age with a clinical suspicion of RDS. Use in infants of gestational age 24 to 27 weeks may be decided on a case-by-case basis.**
- **Early rescue therapy, where surfactant is administered early but after the onset of respiratory distress, is very effective in decreasing the incidence of RDS and mortality in preterm infants.**
- **An INSURE approach is recommended for surfactant administration. In extremely low birth weight infants intubation and mechanical ventilation may be considered if they have signs of fatigue.**
- **Surfactant must be administered only in units (level II or level III) with adequately trained personnel, appropriate equipment, monitoring facilities and infrastructure to provide comprehensive care to premature infants.**
- **Natural surfactant extracts seem to be the more desirable choice when compared to currently available synthetic surfactants**
- **Expanded use of surfactant remains investigational.**

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Introduction

Prematurity is a major cause of neonatal morbidity and mortality in India. Respiratory Distress Syndrome (RDS) is a common cause of mortality and morbidity in preterms. It is the commonest indication for ventilation in neonates in India.[1-3] Surfactant replacement therapy (SRT) for RDS is a major breakthrough that has revolutionized the survival of premature infants worldwide. A study from Narang A et al showed that SRT reduced mortality in Indian babies and was cost-effective in terms of reducing duration of ventilation and hospital stay [4]. Similarly, Sanghvi et al demonstrated better oxygenation in premature infants with respiratory failure following SRT [5]. However, there is lack of local data about optimal preparations of surfactant, dosage, ventilator strategy and indications suitable to different settings in our country. This guideline reviews the evidence regarding indications for SRT, available preparations, timing and mode of administration, and dosage and has been formulated to answer the following practical objectives:

- Indications for surfactant therapy in our country
- Diagnosis of RDS: practical versus ideal
- Timing of surfactant therapy
- CPAP versus mechanical ventilation for RDS
- Optimal dose, preparation, method of administration of surfactant
- Surfactant administration: role of level I vs. II vs. III units
- Contra-indications to SRT
- Cost-effectiveness and feasibility for a country like India

What are the indications for surfactant therapy in our country?

Evidence: Surfactant stabilizes alveoli, improves oxygenation, decreases the need for ventilator support, reduces the incidence of pulmonary air leaks and improves survival in infants with RDS between 24 and 34 weeks gestation.[5–8] The effect is significantly greater in infants less than 30 weeks gestation with birth weight <1250g.[7,8] However, studies from India have shown that SRT may not be as cost-effective in infants < 27 weeks gestation or < 1000g birth weight as it is in larger preterm neonates. This observation seems to have stemmed primarily due to limited resources for long term intensive care of these extremely preterm neonates.[9–11] The decision regarding SRT in these neonates depends on the background of the family, their willingness towards further care and economic viability of the individual families concerned.

Surfactant is also useful in larger late preterm infants with RDS. The incidence of late-preterm RDS has been increasing in view of elective cesarean sections and rising gestational diabetes in India.[12] Surfactant may also be indicated in severe cases of meconium aspiration syndrome, although more data is needed to make this a standard recommendation.[7,8,13]

Recommendation: SRT must be considered in all preterm infants with a strong clinical suspicion of RDS. SRT is more effective in the treatment of RDS in preterm infants > 28 weeks of gestation. In infants with a gestation range of 25 to 28 weeks, the decision may be made on an individual basis, after discussion with the family about the cost and prognosis. SRT may also be indicated in late-preterm infants with respiratory failure due to RDS. Major congenital anomalies, otherwise incompatible with life and neurologically devastated premature infants may not be considered for SRT.

How to diagnose RDS?: practical versus ideal

Evidence: Typically RDS is diagnosed using the following constellation of features: early onset respiratory distress (usually within the first 6 hours of life) in a preterm infant, history of absent or inadequate antenatal steroids, maternal complications such as antepartum hemorrhage and diabetes mellitus, and a suggestive postnatal gastric aspirate shake test. The diagnosis is supported by chest X-ray findings of low volume lungs (suggestive of under inflation), reticulo-granular opacities and air bronchograms.[7,8,13] Under ideal conditions, confirmation of diagnosis of RDS by performing a chest X Ray is desirable for diagnosing but is not essential for initiation of treatment. Many a times the CXR is delayed due to logistic reasons and hence may not help for the purpose of management. Though there are reports of use of biochemical tests for surfactant function such as bubble stability test to determine surfactant need in premature infants, this approach has not been validated in clinical trials. In addition, more reliable tests such as lecithin/ sphingomyelin ratio and presence of phospahtidyl glycerol are not readily available in India. [13]As these tests may not correlate well with the clinical severity of RDS, the degree of prematurity is considered a better indicator of the chance of developing RDS than the test itself.[13, 14]

Recommendation: The diagnosis of RDS is primarily based on the clinical presentation of a preterm neonate at risk for RDS who has an early onset respiratory distress. The diagnosis can be supported by certain historic information and a CXR. However, the decision of administering surfactant should not await a CXR.

What should be the timing of surfactant therapy?

Surfactant therapy has been divided in to a) prophylactic b) early rescue and c) late rescue based on the timing of the therapy. Prophylactic surfactant strategy is administration of surfactant to an infant who is at an increased risk for developing RDS even before the onset of symptoms. This is typically given within the initial 15-30 minutes of life but only after the infant has been resuscitated and stabilized. An early rescue strategy is defined as surfactant therapy to premature infants with respiratory distress suggestive of RDS and is typically administered within the initial 2 hours of life. A late rescue strategy is administration of surfactant any where beyond 2 hours of life to a preterm infant with respiratory distress suggestive of RDS. This is usually but not always administered within the first 12 to 24 hours after birth when certain specific threshold criteria for RDS are met.

Evidence: In general, earlier the administration of surfactant, better are the results in the form of reduction in the incidence and severity of RDS, reduction in mortality and pulmonary air leak.[7,8,13] The OSIRIS trial reported a reduction in mortality by 16% if the time to give surfactant was reduced from 3 hours to 2 hours of life.[15] A Cochrane systematic database review and meta-analysis showed that prophylactic surfactant administration to infants judged to be at risk of developing RDS (infants less than 30-32 weeks gestation), in comparison to selective use of surfactant in infants with established RDS, resulted in improved clinical outcomes. Infants who receive prophylactic surfactant have a decreased risk of air leaks and mortality. However, the review concluded that "it remains unclear exactly which criteria should be used to judge 'at risk' infants who would require prophylactic surfactant administration".[16] Several large clinical trials have demonstrated that early rescue surfactant therapy also significantly improves survival and reduces complications in RDS, and is highly cost-effective in comparison to no surfactant and late rescue surfactant.[7,8,13]

There is paucity of data on the incidence of RDS at various gestational ages in India. Asian babies reportedly have lower risk of RDS.[13] In addition, resources for tertiary neonatal care are limited in our country, and many infants are referred to other centers for treatment.[17] Hence, various Indian authors have suggested that rescue rather than prophylactic surfactant therapy will be more feasible and cost-effective in our country.[4-6] Also, guideline for prophylactic surfactant will vary depending on if antenatal steroids (ANS) have been used or not. Use of ANS in the mother between 24 to 34 weeks of gestation decreases the incidence of RDS by 40 - 50% by increasing the lung maturity [18]. Therefore, it might be prudent to wait till the symptoms develop in such cases and only then give the rescue therapy. There are no guidelines on how to manage infants with RDS referred to a tertiary center much later, e.g. on the second or third day of life. Many clinicians administer surfactant to infants with RDS admitted till 48-72 hours of postnatal age. This seems to be justified and acceptable as natural surfactant secretion improves by day 3 of life.[13, 19]

Recommendation: Early rescue therapy, where surfactant is administered early but after the onset of respiratory distress, is very effective in decreasing the incidence of RDS and mortality in preterm infants and is the recommended modality of SRT. Even though giving surfactant prophylactically may be more effective, it may not be recommended as a routine till we have Indian data available on the incidence of RDS at different gestations to enable one to calculate the gestation wise risk of RDS. Moreover, a study on the cost-effectiveness of prophylactic surfactant has to be planned before embarking on to routine practice. If early rescue therapy is not possible, surfactant must be given as soon as possible, after the diagnosis of RDS is established.

What should be the nature of respiratory support following surfactant administration?

Both prophylactic and early rescue surfactant administration are better than late rescue in terms of reduction in mortality as well as pulmonary air leaks. However, the preferred mode of respiratory support along with or following administration of surfactant is still an area of intense research. This is also complicated by the gestational age of the infant as more and more extremely preterm neonates are surviving and are being taken care of in the intensive care units.

Evidence: A recent observational study comparing the prevalence chronic lung disease (CLD, oxygen at 36 weeks postmenstrual age) at three large NICUs identified initiation of mechanical ventilation as the major risk factor associated with an increased risk of CLD among very low birth weight (VLBW) infants [20]. CPAP is a promising adjunctive or primary tool for treatment of RDS of moderate severity, in addition to surfactant therapy.[19-22] In infants who can be managed on CPAP, surfactant may be administered by INSURE technique (INtubate, give SURfactant and Extubate to CPAP within 3 to 5 minutes).[21-23] Recently, the successful use of Bubble CPAP in a select group preterm infants with RDS has been demonstrated in an Indian study.[22] Observational and cohort studies have shown that nasal CPAP followed by intubation and surfactant administration and later intubation and mechanical ventilation only if the failure criteria for nasal CPAP is reached reduced the need for mechanical ventilation as well incidence of BPD without increasing the mortality [24, 25]. A Cochrane meta-analysis comparing early surfactant administration with brief ventilation with selective surfactant and continued mechanical ventilation in preterm infants with or at risk for respiratory distress syndrome concluded that the former was associated with less need mechanical ventilation, lower incidence of BPD and fewer air leak syndromes [23]. However, a group of infants with respiratory failure due to RDS may be candidates for mechanical ventilation, in addition to surfactant replacement therapy without a CPAP trial. These candidates are tiny premature babies (<28 weeks gestation) with risk of easy fatigability[7,8,12]. A brief intubation for surfactant administration in newborns on nasal CPAP, the intubation-surfactant-extubation

(InSurE) method has also been investigated and resulted in a reduced need for MV in the first week of life when used early in RDS[13,18]. However a vast majority of these studies included less number of extremely preterm neonates.

A recent trial done in extremely preterm infants of 25-28 weeks gestation (COIN) comparing CPAP versus intubation and mechanical ventilation at 5 minutes of birth observed no difference in death or BPD between both the groups even though the neonates in the CPAP group had a decreased oxygen requirement at 28 days of life and fewer days of mechanical ventilation. [26]. Another trial compared early CPAP with early surfactant treatment versus intubation, surfactant and mechanical ventilation in extremely preterm infants [the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)] and observed no significant difference in the incidence of death or BPD at 36 weeks post-menstrual age [27]. Sandri F et al did not observe any significant difference when they compared prophylactic surfactant followed by nasal CPAP with early nasal CPAP application with early selective surfactant with respect to reduction in the need for MV in the first 5 days of life (CURPAP) [28].There are no large clinical trials comparing CPAP with and without surfactant therapy in RDS.

A recent RCT in preterm infants of gestational age of 27 - 31 weeks, treated with nasal CPAP early after birth, observed that the addition of very early surfactant therapy without mechanical ventilation decreased the need for subsequent ventilation as well as incidence of air-leak syndrome. Reduction in the need for mechanical ventilation is an important outcome when medical resources are limited and may result in less CLD in both developed and developing countries.[29] Another similar study has reported success with INSURE approach in babies between 23 to 29 weeks with 60% being managed with INSURE, 16% NCPAP alone and only 24% receiving MV.[30]

Recommendation: An INSURE approach is recommended for surfactant administration where intubation of the trachea is done only for administration of surfactant. Even in these preterm neonates an early CPAP should be initiated while planning and preparing for surfactant administration to facilitate alveolar recruitment. Extremely preterm neonates (<28 weeks gestation) should also be initiated on early CPAP with selective early rescue surfactant. Intubation and mechanical ventilation may be considered in them if they have signs of fatigability and they satisfy the criteria for CPAP failure. Prophylactic surfactant with early CPAP cannot be recommended as it has not been shown to be superior in terms of efficacy as well as safety in comparison to early CPAP with selective surfactant. CPAP with surfactant is more effective than intubation and mechanical ventilation as early CPAP may by itself eliminate the need for surfactant. But this hypothesis has to be tested in a well designed clinical trial comparing early CPAP with versus without surfactant before being translated in to a recommendation.

What should be the optimal dose, preparation and method of administration of surfactant?

Evidence: Exogenous surfactant is most effective when it is uniformly distributed within the lung. Surfactant distribution primarily depends on the proportion of surfactant protein B and phospatidyl glycerol (DPPG), the volume of surfactant, its rate of instillation and the position of the infant. The volume of surfactant to be given (3 to 5 mL/kg, depending on the preparation) has been determined by consideration of the normal surfactant pool size. However, the recommended dosage of surfactant for RDS varies from 50 to 200mg of phospholipids per kilogram of body weight. Porcine surfactant in a dose of 200 mg/kg has been shown to be more effective than 100 mg/kg (better oxygenation and fewer retreatment) [31]

Type of surfactant: Exogenous surfactants are of two types: natural and synthetic. Natural surfactants are either minced or lavaged extracts of animal lungs, which may be of either bovine or porcine in origin. A Cochrane review of eleven trials comparing animal derived surfactant extracts (natural surfactant) with synthetic surfactant in preterm infants with RDS has shown that the use of natural surfactant leads a significant reduction in the risk of pneumothorax and risk of mortality. The meta-analyses also support a marginal decrease in the risk of BPD or mortality associated with the use of natural surfactant preparations. The authors conclude that natural surfactant extracts would seem to be the more desirable choice when compared to currently available synthetic surfactants [32]. The major reason for the decreased efficacy of synthetics surfactants seems to be due to the absence of surfactant proteins (SP) especially SP-B. Lucinactant (KL-4) is a protein containing synthetic surfactant which, to some extent, may fill this lacuna. A Cochrane review on Protein containing synthetic surfactants versus animal derived surfactants extract for the prevention and treatment of RDS failed to identify any statistically significant clinical difference in death or CLD [33]. Prophylactic use of Lucinactant, a protein containing synthetic surfactant, is shown to be more effective than colfosceril palmitate (another synthetic surfactant) in reducing the incidence of RDS (39.1% vs. 47.2%). However Lucinactant did not differ when compared to beractant (Survanta). Sinha et al, reported that Lucinactant and poractant alfa were similar in terms of efficacy and safety when used for the prevention and treatment of RDS among preterm infants.[34]

Source of natural surfactant: Natural surfactants are primarily of bovine or porcine in origin. Ramanathan et al demonstrated that treatment with Poractant alfa (200 mg/kg initial dose) resulted in a rapid reduction in supplemental oxygen with fewer additional doses of surfactant in infants <35 weeks gestation with RDS, and significantly reduced mortality ($p<0.05$) than either beractant or poractant alfa (100 mg/kg initial dose) in infants≤32 weeks gestation with RDS. [35] Treatment with Curosurf (Poractant alfa) when compared to Survanta (beractant) was associated with faster weaning of supplemental oxygen, peak inspiratory pressure (PIP), and mean airway pressure (MAP) during the first 24 hours after treatment.[36] In a meta analysis of the type of surfactant, mortality was significantly lesser (OR 0.35, CI O.13-0.92, $p=0.002$) in the poractant alfa group in comparison to the beractant group[37]. The beneficial effects of poractant over beractant have also been reported in preterm infants ≤29 weeks in a recent study by Fujii et al.[38] These differences in outcome may be due to the differences in phospholipid and SP-B content, amount of antioxidant phospholipids, plasmalogens, anti-inflammatory properties and viscosity among these surfactants.[36] However, none of the studies reported any difference in long term clinical outcomes like death or BPD. Bovine Lung Extract Surfactant (BLES) is imported from Canada and marketed in India in the name of Neosurf. This is a calf lung lavage product whose head to head performance testing in terms of efficacy and safety in comparison to beractant and poractant is awaited.

Sources of synthetic surfactant: A major drawback of natural surfactants, especially in our country, is the high cost. At the same time synthetic surfactants are marred by the absence of surfactant proteins in them and hence leading to their poor spread as well as rapid inactivation in the alveoli. New synthetic surfactants containing proteins that mimic surfactant protein activity are under investigation. These products are quoted to be somewhat cheaper than natural surfactants. A recent meta-analysis showed similar outcomes in infants treated with newer protein-containing synthetic surfactants, compared to those treated with natural surfactants. However, the studies were not of adequate size and power.[32, 39] In the future, these may be economical and effective alternatives to natural surfactants.

Technique of administration: Although changing the position of the infant from side to side during and after administration theoretically allows gravity to produce a more uniform distribution, a two-position method appears equivalent to a four-position approach.[7,8,13,19] The current recommendation is to administer the entire dose in supine position in divided aliquots. The rate of administration is important;

the more slowly the surfactant is instilled, the more likely it is to go to more dependent areas; but too slow an instillation can lead to hypoxia. Hence, administration should be done over few minutes with each aliquot followed by few positive pressure breaths to ensure. The superiority of endotracheal tube with side port for surfactant administration (without the need for disconnection from ventilator) over direct instillation into the endotracheal tube is debatable. Other routes, like Laryngeal mask airway (LMA)[40,41] and nebulisation[42,43] for administration of surfactant are experimental at present and hence cannot be recommended for routine clinical use.

Repeat doses of surfactant: A single treatment dose of 100-200 mg/kg surfactant is very large relative to the surfactant pool size of an adult human (perhaps 5mg/kg) or a preterm animal without RDS (>4mg/kg) [44]. The slow catabolism and recycling of the treatment dose ensures a long persistence of the surfactant in the preterm lung, provided the lung is uninjured. Repetitive doses may be required to overcome the inhibitory effects on an injured lung. Repeated doses of surfactant given at intervals for predetermined indications have decreased mortality and morbidity compared with single surfactant dose.[13,45] A Cochrane meta-analysis on comparison of multiple versus single dose of animal derived surfactant suggested a significant reduction in the risk of pneumothorax and a trend towards reduction in the risk of mortality in the multiple doses group of preterm neonates [46]. No data exists on the long term neurological or pulmonary outcome following multiple doses of surfactant. Similarly, no complication was identified following multiple doses of surfactant.

Recommendations: The optimal dose of surfactant for RDS is 100 mg/kg body weight of phospholipids. Poractant alfa may be administered with an initial dose of 200mg/kg followed by 100 mg/kg of phospholipids. Natural surfactant extracts seem to be the more desirable choice when compared to currently available synthetic surfactants till cheaper, effective and safe synthetic surfactants are available. Even though, Poractant alfa has an edge over the other natural surfactants by decreasing the oxygen requirement faster, all the natural surfactants seem to be equally effective from long term outcomes point of view. Hence, one type of surfactant cannot be recommended over the other. Administration through the endotracheal tube is recommended. This should be in two to four aliquots (as per the manufacturer's recommendation), over a period of few minutes, with in between positive pressure breaths, with the neonate maintained in the supine position during the whole procedure. In general, as long as an infant continues to improve (decreased oxygen requirements, decreased ventilator support) after a dose of surfactant, a second dose is not indicated. A repeat dose of surfactant may be considered provided the neonate has satisfied a pre-decided criterion for second dose and had shown at least some response to the first dose. The frequency and interval of repetition of surfactant doses is not evidence based and is primarily driven by manufacturer's recommendations.

Who can administer surfactant: level I vs. II vs. III units?

Evidence: As administration of surfactant is a relatively simple procedure, one may tend to administer surfactant even in the absence of an adequate infrastructure. It is important to understand that preterm infants are at high risk for multi-organ dysfunction. In addition certain complication can result from the administration of surfactant like plugging of endotracheal tube by surfactant, cyanosis, bradycardia, tachycardia and apnea which may themselves be life-threatening. Hence, surfactant must be administered in units having the equipment and personnel to anticipate, recognize, and treat such complications.[7, 8] In addition, surfactant therapy is only part of the comprehensive care of premature infants. The importance of adequate infrastructure, asepsis and meticulous nursing care to optimise survival in surfactant-treated infants has been stressed in all Indian studies.[4-6] Costakos et al have demonstrated no benefit of pre-transport surfactant therapy with the pre-transport surfactant group having a longer hospital stay and

longer duration of ventilation[47]. National Neonatology Forum has published guidelines about the requirements and infrastructure for invasive ventilation and neonatal intensive care in our country.[48,49] In the absence of expertise and infrastructure to provide comprehensive care for premature infants, surfactant therapy in isolation will not be efficacious or cost-effective.

Recommendation: Surfactant must be administered in level II or level III units with appropriate trained personnel, equipment and monitoring facilities. Surfactant therapy is part of the comprehensive intensive care for RDS that includes appropriate ventilator and fluid management, adequate nutrition and maintenance of asepsis etc. In level I and level II units with inadequate facility, if surfactant administration has to be done prior to transport to a tertiary center, this must also be done by trained personnel from the transport team.

What are the contra-indications to SRT?

Evidence and recommendation: The available evidence does not point out to any absolute contraindication for SRT. Major congenital anomalies, otherwise incompatible with life and neurologically devastated premature infants may be considered as relative contraindications for SRT. Similarly, SRT may be abandoned in extreme preterm neonates (eg. <26 weeks of gestation) after a thorough discussion with the parents/caregivers about the chance of morbidity free survival and the social and economic impact the decision may bring to the family.

How cost-effective and feasible is SRT in India?

Evidence and *recommendation*: In India, it has been shown that there is a higher threshold to treat premature infants aggressively. Several Indian studies have shown that it is not cost-effective to save infants lesser than 28 weeks gestation or lower than 1000g birth weight, in view of limited resources. [9,10,11] Most of these observations are from the 1990s, and now with better infrastructure, technology and expertise in neonatal care along with increased inpatient neonatal facilities, there is a tilt towards saving infants less than 28 weeks gestation. The decision depends on the background, willingness and affordability of the individual families concerned.

How useful is surfactant therapy in diseases other than RDS?

Evidence: Surfactant function could be inhibited by proteinaceous pulmonary edema and other products of lung injury and result in a secondary surfactant deficiency type syndrome [50]. Other than injury caused by mechanical ventilation, meconium aspiration syndrome, BPD and sepsis/pneumonia have also been shown to cause lung injury in preterm neonates. A small RCT of surfactant treatment for MAS and other reports demonstrate that surfactant instillation can improve oxygenation in these infants [51, 52]. Surfactant lavage has been compared with routine care in several small series, and seemed to improve oxygenation in these neonates [53, 54]. However lavage has not been compared with more standard instillation in any of these trials. Similarly no robust RCTs are available on surfactant treatment in BPD as well as pneumonia.

Recommendation: Expanded use of surfactant still remains purely investigational. Even though this modality has found support in a case by case basis, more robust clinical trials are required to make this as a standard practice.

References

1. Kumar P, Kumar R, Narang A. Spectrum of neonatal respiratory distress at PGI. Bull NNF 1999; 13: 8-12.
2. Bhakoo ON. Assisted ventilation in neonates: The Indian perspective. Indian Pediatr 1995; 32: 1261-64.
3. Nangia S, Saili A, Dutta AK, Gaur V, Singh M, Seth A, Kumari S. Neonatal mechanical ventilation--experience at a level II care centre. Indian J Pediatr. 1998; 65:291-96.
4. Narang A, Kumar P, Dutta S, Kumar R. Surfactant Therapy for Hyaline Membrane Disease: The Chandigarh Experience. Recent Advances in Pediatric Care, 2001.
5. Sanghvi KP, Merchant RS et al. Single dose surfactant rescue therapy in neonatal RDS. Indian Pediatr 1995; 38:533-36.
6. Nagesh K, Bhat V, Kunikullaya S et al, Surfactant therapy in neonatal respiratory distress syndrome. Indian Pediatr. 1994; 31:971–77.
7. Engle WA et al. Surfactant-Replacement Therapy for Respiratory Distress in the Preterm and Term Neonate. Pediatrics 2008;121:419-32
8. AARC Clinical Practice Guideline. Surfactant Replacement Therapy. Respir Care 1994; 39:824-29
9. Miljeteig I, Sayeed SA, Jesani A, Johansson KA, Norheim OF. Impact of ethics and economics on end-of-life decisions in an Indian neonatal unit. Pediatrics. 2009; 124:e322-8.
10. Sundaram SR, PadmaPriya E, Shyamala J et al. Cost of neonatal intensive care. 1998. Indian J Pediatr 1998; 65:249-55.
11. Maiya PP, Vishwanath D, Hegde S et al, Ventilation of newborns. Indian Pediatr 1995; 32: 1275-280.
12. Seshiah V, Balaji V, Madhuri S, Balaji S, Sanjeevi CB, Green A. Gestational diabetes mellitus in India. The Journal of the Association of Physicians of India. 2004; 52:707-11.
13. Taeusch HW, Ramierez-Schrempp D, Laing IA. Surfactant treatment of respiratory disorders. In: Taeusch HW, Ballard RA, Gleason CA, eds. Avery's Disease of the Newborn. 8th ed. Philadelphia, PA
14. Smith ML, Curnock D, and Forshaw F. Value of the gastric aspirate shake test. Arch Dis Child. 1981; 56:230-31.
15. Early versus delayed neonatal administration of a synthetic surfactant--the judgment of OSIRIS. The OSIRIS Collaborative Group (open study of infants at high risk of or with respiratory insufficiency-the role of surfactant. Lancet. 1992; 340:1363-69
16. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane systematic database review 2001:CD000510
17. Singh M, Deorari AK, Paul VK, et al. Three year experience with neonatal ventilation from a tertiary care hospital in Delhi. Indian Pediatr 1993; 30:783-89
18. Osborn DA., Heather MM, Jeffery E. et al. Targeted Early Rescue Surfactant in Ventilated Preterm Infants Using the Click Test. Pediatrics 2000; 106:30
19. Jobe AH. Why surfactant works for RDS. NeoReviews. 2006; 7:95 – 106
20. Van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M, Susser M, Paneth N, Leviton A. Do clinical markers of barotrauma and oxygen toxicity explain inter hospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. Pediatrics 2000; 105:1194-201
21. Wung JT. Continuous positive airway pressure. In: Wung JT, Polin RA, eds. Respiratory Care of the Newborn: A Practical Approach. New York, NY: Babies and Children's Hospital; 2000.
22. Koti J, Murki S, Gaddam P et al, Bubble CPAP for RDS in preterm infants. Indian Pediatr 2009 May (E-pub ahead of print).
23. Stevens TP, Blennow M,Myers EH, Soll R. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003063. DOI: 10.1002/14651858.CD003063.pub3
24. De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. J Paediatr Child Health. 2001;37:161-67
25. Berger TM, Bachman II, Adams M, Schubiger G. Impact of improved survival of very low-birth-weight infants on incidence and severity of bronchopulmonary dysplasia. Biol Neonate. 2004; 86:124 –136
26. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008; 358:700-8

27. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus Surfactant in Extremely Preterm Infants. N Engl J Med 2010; 362:1970-79
28. Sandri F, Plavka R, Ancora G et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics 2010; 125:e1402-09
29. Rojas MA, Lozano JM, Rojas MX, Laughon M, Bose CL, Rondon MA, Charry L, Bastidas JA, Perez LA, Rojas C, Ovalle O, Celis LA, Garcia-Harker J, Jaramillo ML, for the Colombian Neonatal Research Network. Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized Controlled Trial. Pediatrics 2009; 123:137-142.
30. Dani C, Corsini I, Bertini G, Fontanelli G, Pratesi S, Rubaltelli FF. The INSURE method in preterm infants of less than 30 weeks' gestation. J Matern Fetal Neonatal Med. 2010 Feb 25.[Epub ahead of print]
31. Cogo PE, Facco M, Simonato M, Verlato G et al.Dosing of porcine surfactant: effect on kinetics and gas exchange in respiratory distress syndrome. Pediatrics 2009;124:e950-7. Epub 2009 Oct 12.
32. Soll R, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2001, Issue 2. Art. No.: CD000144. DOI: 10.1002/14651858.CD000144
33. Pfister RH, Soll RF, Wiswell T. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006069
34. Sinha SK, Lacaze-Masmonteil T, Valls i Soler A, Wiswell TE, Gadzinowski J, Hajdu J, Bernstein G, Sanchez-Luna M, Segal R, Schaber CJ, Massaro J, d'Agostino R; Surfaxin Therapy Against Respiratory Distress Syndrome Collaborative Group. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. Pediatrics. 2005; 115:1030-38
35. Ramanathan R, Rasmussen MR, Gerstmann DR, Finer N, Sekar K; North American Study Group. A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. Am J Perinatol. 2004; 21:109-19
36. Speer CP, O Gefeller, P Groneck et al. Randomized clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. Arch Dis Child Fetal Neonatal. 1995; 72:F8-13
37. Ramanathan R. Choosing a right surfactant for respiratory distress syndrome treatment. Neonatology. 2009; 95:1-5
38. Fujii AM, Patel SM, Allen R, Doros G, Guo CY, Testa S. Poractant alfa and beractant treatment of very premature infants with respiratory distress syndrome. J Perinatol. 2010 Mar 25. [Epub ahead of print]
39. Horbar JD, Wright LL, Soll RF, et al. A multicenter randomized trial comparing two surfactants for the treatment of neonatal respiratory distress syndrome. National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr. 1993; 123:757 -66
40. Trevisanuto D, Grazzina N, Ferrarese P et al .Laryngeal mask airway used as a delivery conduit for the administration of surfactant to preterm infants with respiratory distress syndrome. Biol Neonate. 2005; 87:217-20.
41. Micaglio M, Zanardo V, Ori C, Parotto M et al. ProSeal LMA for surfactant administration. Paediatr Anaesth. 2008; 18:91-92
42. E. Berggren. Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. Acta Pediatrica 2000; 89:460-64.
43. Donn SM, Sinha SK. Aerosolized lucinactant: a potential alternative to intratracheal surfactant replacement therapy. Expert Opin Pharmacother. 2008; 9:475-78.
44. Jobe AH. Pulmonary surfactant therapy. N Eng J Med 1993; 328:861-68
45. Zola EM, Gunkel JH, Chan RK, et al. Comparison of three dosing procedures for administration of bovine surfactant to neonates with respiratory distress syndrome. J Pediatr. 1993;122:453-59
46. Soll R, Özek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD000141. DOI: 10.1002/14651858.CD000141.pub2
47. Costakos D; Allen D et al. Surfactant therapy prior to the interhospital transport of preterm infants. American journal of Perinatology 1996;13:309-16
48. Narang A. Neonatal Ventilation. Recommendation of the NNF workshop held at PGIMER Chandigarh, 1993
49. Bhakoo ON, Dhall K, Vani S et al. Norms for accreditation of level II special care neonatal units. National Neonatology Forum, India, 1991

50. Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. Am Rev Respir Dis 1993; 147:218-33
51. Findlay RD, Taeusch WH, Walther FJ. Surfactant replacement therapy or meconium aspiration syndrome. Pediatrics 1996; 97:48-52
52. Auten RL, Notter RH, Kendig JW et al. Surfactant treatment of full term newborns with respiratory failure. Pediatrics 1991; 87:101-07
53. Wiswell TE, Knight GR, Finer NN, et al. A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. Pediatrics 2002; 109:1081-87
54. Chinese Collaborative Study Group for Neonatal Respiratory Diseases. Treatment of severe meconium aspiration syndrome with porcine surfactant: a multicentre, randomized, controlled trial. Acta Pediatr 2005; 94:896-902

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Management of Seizures in the Newborn

Summary of Recommendations

- **The diagnosis of seizures requires a high index of suspicion, careful clinical observation and often electroencephalography(EEG).**
- **Seizures in the newborn are usually secondary to hypoxia ischemia, intracranial hemorrhage, intracranial infections and metabolic disturbances.**
- **Metabolic investigations, cranial ultrasound, EEG and lumbar puncture form the first line of investigations in most cases.**
- **Conventional EEG is the gold standard for diagnosis of seizures while Amplitude Integrated EEG(aEEG) has poor accuracy and low sensitivity.**
- **All clinical seizures with EEG correlates and all EEG seizures should be aggressively treated with anticonvulsants.**
- **Phenobarbitone is the drug of first choice for treatment followed by fosphenytoin/phenytoin.**
- **The optimal duration of anticonvulsant should be based on neurological examination at discharge, cause of seizures and associated background EEG abnormalities.**
- **Neonates with seizures should be followed up for neurodevelopmental sequelae at least till 12-18 months.**

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Introduction

Neonatal seizures constitute a medical emergency**.** A seizure is defined clinically as a paroxysmal alteration in neurologic function, i.e. motor, behavior and/or autonomic function. Neonatal seizures contribute a significant burden to the neonatal morbidities/mortality and also to adverse neurodevelopment including motor and cognitive disabilities in the childhood. Although experience in evaluation and management of neonatal seizures is vast, evidence is incomplete or absent for most relevant issues. Data from our country is limited to few published case series and unpublished research. In this guideline attempt has been made to answer important practical issues related to evaluation and management of seizures :

- Types of seizures
- Diagnoses and confirmation of seizures
- Common causes of neonatal seizures
- Investigations following seizures : EEG, aEEG, LP, Neuroimaging
- First line and Second line of drugs
- Duration of anticonvulsants
- Prognosis and Follow-up

Clinical seizure types

Seizures in the newborn are classified into 4 clinical types : clonic movements (focal or multifocal or generalized), myoclonus (multifocal or generalized), tonic movements (focal or generalized), and motor automatisms / subtle seizures.

Evidence: Only one study has observed that babies with subtle and generalized tonic seizures had a significantly higher prevalence of epilepsy, mental retardation and cerebral palsy in comparison with those of other seizure types.[1] No data exists to support the use of clinical classification to identify the underlying etiology and outcome primarily due to the varied presentation of neonatal seizures.

Recommendation: Clinical classification of seizures has limited diagnostic / prognostic value.

Diagnoses and confirmation of seizures

The clinical expression of seizures in a neonate is quite variable, poorly recognized and often subtle. Neonatal seizures are not stimulus sensitive, not abolished by restraint or repositioning, are often associated with autonomic changes and ocular phenomena, are usually stereotypic and repetitive, and the interictal examination is often abnormal. Moreover, neonatal seizures are associated with electro-clinical dissociation making their diagnosis even more difficult.

Evidence : Making a confident diagnosis based on seizure semiology alone is difficult due to the wide variety of atypical movements exhibited by neonates.[2] Experts recommend EEG monitoring to confirm clinical events as seizures and to detect electrographic events without clinical correlates. Newborns frequently demonstrate electrographic seizures without clinical movements and vice versa. Mizrahi et al, using bedside electroencephalography (EEG) / polygraphic / video monitoring, showed that focal clonic seizures, some forms of myoclonic seizures and focal tonic seizures were consistently associated with

electrical seizure activity whereas most subtle seizures, all generalized tonic seizures and some forms of myoclonic seizures were either not associated with electrical activity or had an inconsistent relationship.[3] Clancy et al demonstrated that only 21% of seizures seen on EEG monitoring had a clinical correlate.[4] ''Electrographic-only'' events occur most commonly after anticonvulsants, or in infants with exceedingly frequent discharge or status epilepticus.

Recommendations: Diagnosing subtle seizures requires a high index of suspicion. Hence, neonates who are at risk for seizures (e.g. hypoxic ischemic encephalopathy, intraventricular hemorrhage) must be under careful clinical observation by an experienced nurse / doctor for abnormal movements. Whenever feasible suspected seizure like clinical events should be confirmed with EEG monitoring and / or Video EEG.

Common causes of neonatal seizures

Hypoxic ischemic encephalopathy (HIE), intracranial infections, metabolic disorders such as hypoglycemia, hypocalcaemia, hyponatremia, intracranial hemorrhages (ICH), inborn errors of metabolism (IEM) and epileptic syndromes are the common causes of neonatal seizures.

Evidence: In a study of 89 term infants with clinical seizures, Tegkul et.al observed that an etiology could be identified in 77 infants (87%). The common etiologies were HIE (global & focal) and ICH. Cerebral dysgenesis, metabolic disturbances (hypoglycemia, hypocalcemia), infections and IEM individually formed a lesser proportion of cases.[5] Volpe JJ observed that HIE was the most common followed by intracranial infections and ICH and developmental defects as underlying etiologies for seizures.[6] In a study from PGI, Chandigarh, India (M.D. Thesis; unpublished data) HIE was found to be the commonest cause of seizures followed by meningitis, ICH, transient metabolic disturbances (hypocalcemia, hypoglycemia) and cerebral infarction.

Recommendations: The common underlying etiologies for neonatal seizures are HIE, ICH, intracranial infections and metabolic disturbances (in decreasing order of frequency). A detailed history and a complete clinical examination and neuroimaging will identify cause of seizures in most neonates.

Investigations following seizures

Neonatal seizures are rarely idiopathic. Investigations for neonatal seizures are done to confirm the diagnosis, to identify the etiology, to plan the management with anticonvulsant drugs (ACD) and to prognosticate.

Evidence : Tegkul et al, could identify etiology in 77/89(7%) neonates with EEG, neuroimaging (mostly MRI), serum glucose and electrolyte levels, cerebrospinal fluid studies, and arterial blood gas. Serum ammonia, urine and serum organic and amino acid analysis and lactate and pyruvate levels, coagulation studies and an echocardiography were performed only when indicated.[5]

Recommendations: Investigations for neonatal seizures may be prioritized as follows:

- First line (mandatory): Blood glucose, serum ionized/total calcium, serum sodium and blood gas.
- **Add-on (situational): (**a) Sick neonates with seizures: Investigations for sepsis (complete hemogram & blood culture), intracranial infection (CSF studies for bacterial and viral etiology),

intracranial hemorrhage (cranial ultrasonography & CT scan) and IEM (serum ammonia, lactate and pyruvate , urine and serum organic and amino acid analysis). The choice of investigation should largely depend on the clues obtained from history, clinical examination as well as from the first line investigations. At places where facilities for these tests (tandem mass spectrometry, urine gas chromatography/ mass spectrometry, high performance liquid chromatography) are not available, the blood and urine samples can be taken on filter papers, dried and then sent to centers/ laboratories where these tests are available. It is important to take the samples before interventions. The timing is important for correct diagnosis of inborn errors of metabolism.

- A conventional EEG should be considered in all neonates for diagnosis, classification and for prognostic purposes.
- Neuroimaging: man**d**atory for persistent focal clonic or tonic seizures and to look for infarcts (arterial or venous). But the need for a neuroimaging has to be assessed on a case by case basis.

Electroencephalography

An EEG may be useful to diagnose seizures, to prognosticate the outcome, assess the severity of brain dysfunction and to decide the duration of anticonvulsant drugs.

Evidence:

EEG in suspected seizures: As newborns frequently demonstrate electrographic seizures without clinical correlates, EEG becomes an essential investigation. Unfortunately EEG technology is limited to very few specialized centers due to the need of a specially trained technician and electroencephalographer to record and interpret neonatal EEG.[7] Major value of initial EEG in the evaluation of neonatal seizures is to determine whether the infant with subtle clinical phenomena is experiencing electrographic seizures and to determine whether the paralyzed infant is experiencing electrographic seizures. No data is available whether EEG adds value when the clinical presentation is typical of seizure.

Type of EEG: Conventional EEG using the International 10-20 system (channels) modified for neonates with concurrent video is the gold standard for monitoring and recording seizures in the newborn.[8] Limited channel (2-channel) bedside EEG in combination with 'amplitude integrated EEG (aEEG)' has been compared with a continuous conventional EEG and was found to have a sensitivity of 76% and a positive predictive value of 78% for detection of neonatal seizures. Using either a 2-channel (C3-P3 and C4-P4) EEG or an aEEG separately did not achieve adequate sensitivity in comparison to conventional EEG.[9] A conventional EEG should preferably be a portable apparatus with a skilled technician and a dedicated electroencephalographer should perform and interpret a neonatal EEG.

EEG for diagnostic purposes: EEG tracings during seizure episodes provide valuable information regarding the presence of true epileptic phenomenon. However, diagnostic and therapeutic maneuvers should not be deferred for the purpose of obtaining an ictal tracing as evidence indicates that some epileptic discharges may not be detectable by surface EEG studies.[6] No data is available regarding when to do an EEG for diagnosis of seizures after the suspected clinical phenomena has aborted.

EEG for prognostic purposes: The interictal pattern of EEG is of value in establishing prognosis in neonatal seizures.[6] Neurologic sequelae are unusual when EEG correlates occur on a normal background. In contrast, severe background abnormalities are associated with neurological sequelae in 90% of cases.[10]

Recommendations:

- Considering the fact that the availability of neonatal bedside EEG facilities are limited in our country, an EEG tracing may be deferred in seizure types those have an unequivocal clinical presentation and have a very good EEG correlation, like focal clonic seizures, some forms of myoclonic seizures and focal tonic seizures.
- All neonates with an equivocal clinical presentation (clinically suspected seizures) should preferably have a conventional EEG recorded during or as close to the seizure episode as possible. All EEG recordings should be continuous for at least 1 hour duration. Always attempt to record with the neonate asleep as well as awake for better interpretation.
- Neonates who are at risk for seizures (e.g. asphyxiated neonates and sick neonates who are paralyzed) should preferably undergo continuous EEG monitoring.
- A conventional 10-20 channels continuous EEG is recommended for neonatal seizures. The EEG should be performed by a trained technician and reported by a physician trained in interpretation of neonatal EEG.
- In neonatal EEG, identification of the background activity and maturation of the EEG are more important than the epileptiform abnormalities per se.

Lumbar puncture

Lumbar puncture(LP) is done in neonatal seizures to rule out bacterial and viral infections. It may also help in the diagnosis of nonketotic hyperglycinemia (NKH) or certain rare entities like GLUT1 deficiency.

Evidence: About 5-10% of neonatal seizures are due to intracranial infections, predominantly due to congenital viral and protozoal infections. Acquired bacterial infections (meningitis and meningoencephalitis) form a small proportion.[11] Some experts recommend a LP in all neonates with perinatal asphyxia to rule out meningitis acting as an inciting factor for asphyxia.[6]

***Recommendations*:** A lumbar puncture should be performed on sick neonates following seizures, once their cardiorespiratory status is stable. Neonates who are well before and after a seizure, and have transient metabolic disturbances like hypoglycemia and hypocalcaemia may not require a LP.

Neuroimaging

Neuroimaging following neonatal seizures may help in diagnosing the etiology of the seizures and measuring the extent of the cerebral insult. Apart from cranial ultrasound(CUS), other neuroimaging modalities require transfer of the sick neonate to a dedicated place to perform the procedure.

Evidence: We could not identify any study that has specifically investigated the role of routine neuroimaging in neonates with seizures. Hence, we extrapolated the data available for neuroimaging in preterm very low birth weight (VLBW) neonates and term infants with encephalopathy and formulated the following recommendations:[12]

***Recommendations*:**

- All sick neonates with seizures irrespective of gestation should undergo a bedside CUS to rule out intracranial hemorrhage, major malformations and abscesses. Some estimate of cerebral edema can also be made on CUS.
- In term infants with seizures and encephalopathy, significant birth trauma, and evidence of low hematocrit and/or coagulopathy, a non contrast CT scan should be performed to look for hemorrhage.
- A MRI is not generally indicated during the acute phase of the seizures but may be required later to prognosticate and to further investigate the etiology.

Treatment of neonatal seizures

Neonatal seizures should be treated, as seizures per se can cause brain injury leading to poorer outcome.[13] Immediate management of seizures includes stabilization, identification of the cause and specific treatment, and if required, administration of an anticonvulsant drug (ACD) to prevent seizure recurrence. Electro-clinical uncoupling of neonatal seizures creates dilemma about which seizures warrant ACD therapy.

Evidence : Decision regarding aggressive treatment of seizures should take into consideration the underlying etiology and the presence of associated inflammation and metabolic compromise. The therapeutic goal should be elimination of electrical only and electro-clinical seizures to reduce the risk of brain injury.[13] In an observation by Toet et al, a strikingly lower incidence of post neonatal epilepsy (9.4%) was observed in term infants who received treatment for both clinical and sub-clinical (aEEG) seizures, compared with an incidence of 20-50% reported in other studies which treated 'clinical only' seizures.[14] Many clinicians do not aggressively treat 'clinical-only' events due to the potential cardio-respiratory toxicity of ACDs. However, considering the possibility of an electro-clinical dissociation in clinical-only seizures, a prolonged EEG recording of at least 1 hour is warranted close to a clinically suspected seizure episode.[13]

Recommendations: All clinical seizures with EEG correlates and all EEG seizures should be aggressively treated with ACDs. However, diagnostic and therapeutic maneuvers should not be deferred for the purpose of obtaining an ictal tracing. The priority should be stabilization of vital functions and exclusion or rapid treatment of correctable metabolic conditions.

First line drug of choice

Traditionally Phenobarbital is the drug of choice for treatment of neonatal seizures. Ease of administration, availability in oral and intravenous form, knowledge of its side effects and efficacy are quoted as the reasons for preferring Phenobarbital in neonatal seizure management. But recent reports based on various animal and human studies have suggested a high risk- benefit ratio for this drug.

Evidence:

Efficacy: There is little evidence from randomized controlled trials to support the use of any of the anticonvulsants currently used in the neonatal seizures. Painter et al observed that fewer than half of the patients treated with either Phenobarbital or Phenytoin had adequate seizure cessation.[15] They suggested

that Phenobarbital should be administered intravenously (IV), with a 20 mg/kg loading dose as an infusion that should be no faster than 1 to 2 mg/kg per min. It is preferable to use monotherapy (single drug) for control of seizures. In another study on efficacy, Gal and colleagues studied Phenobarbital monotherapy and reported ultimate seizure control in 85%, with effective concentrations between 10.1 and 46.4 mg/L. Up to 90% of the neonates who responded did so at serum levels between 20 and 30 mg/L. Phenytoin administered as 15 to 20 mg/kg loading dose resulted in effective therapeutic levels. They suggested that Phenytoin should be infused no faster than 1 mg/kg per minute to avoid cardiac arrhythmias or hypotension, and the cardiac rate and blood pressure should be continuously monitored while the infusion is on. [16] In a similar study by Tegkul et.al, seizure control was achieved in 78% with cumulative loading dose of Phenobarbital up to 40-50mg/kg with the rest (22%) requiring either Phenytoin or lorazepam.[5]

Safety: Infants and toddlers randomized to prophylactic phenobarbital therapy for febrile seizures had a lower intelligence quotient that outlasted the duration of development.[17] Safety of antiepileptic drugs has been questioned with a more recent animal study showing apoptotic neurodegeneration following the use of Phenobarbital, Phenytoin and Diazepam in rats (18). Moreover, phenytoin was shown to run the risk of unpredictable serum levels and risk of cardiotoxicity.[19] The impact of therapeutic doses of these agents on neurodevelopmental outcomes in newborns with seizures is not known. Fosphenytoin, a phosphate ester prodrug of Phenytoin, has proved to be a major advance in therapy of status epilepticus in neonates, children and adults.[20,21] The drug, in contrast to phenytoin, is highly water soluble, compatible with standard intravenous solutions, has a pH value close to neutral, safe for intramuscular administration, does not cause tissue injury following intravenous extravasation, and allows a faster rate of administration.[22] The effective dose of Fosphenytoin, in phenytoin equivalents (1.5 mg of Fosphenytoin yields approximately 1.0 mg of Phenytoin), is essentially identical to that described for phenytoin.

Recommendation:

- Phenobarbital currently remains the drug of first choice to treat neonatal seizures, till further evidence accumulates regarding the long term neurodevelopmental outcome of Phenobarbital therapy and till such time that alternate first line agents for treatment of neonatal seizures with a high therapeutic safety margin are available.
- Care should be taken to avoid the cumulative loading dose of Phenobarbital to exceed 40mg/kg and that of phenytoin beyond 30mg/kg.
- In neonates with hepatic dysfunction, the maximum dose should be restricted to 20mg/kg.
- Wherever feasible, use of Fosphenytoin should be preferred over Phenytoin due to its clinical advantages.

Alternate second line drugs

Alternate drugs that have been tried in the management of neonatal seizures are pyridoxine, lorazepam, midazolam, lidocaine, and newer ACDs like topiramate, lamotrigine and levetiracetam. .

Evidence : Midazolam and lidocaine have been tested in small studies for the potential utility of second line anticonvulsants in neonates who failed Phenobarbital and Phenytoin. Two retrospective studies comparing use of Midazolam and lidocaine showed no difference[23] or a trend towards improved efficacy of lidocaine.[24] In the only randomized trial comparing the two as second line agents for neonatal seizures, there was a trend towards better efficacy of lidocaine, though both groups had a poor outcome at 1 year of

age.[25] Anecdotal reports have used lorazepam, thiopentone, sodium valproate and lamotrigine to treat neonatal seizures without evidence of their safety and efficacy. Newer antiepileptic drugs like levetiracetam and topiramate have been used as add-on agents due to their possible lower side effect profile, better tolerability and equivalent efficacy but await additional safety, pharmacokinetic and efficacy data from rigorous clinical trials.[26] There are 2 published reports describing therapeutic use of levetiracetam in 4 infants, each of whom had adequate seizure control and no adverse effects.[27,28]

Recommendations: Experience with second line drugs in the newborn is very limited. Lidocaine or Midazolam may be used as second line agents for neonatal seizures refractory to phenobarbital or phenytoin. It is recommended to exercise caution while administering these drugs due to their unproven safety profile and narrower therapeutic window.

Amplitude Integrated EEG (aEEG)

Amplitude integrated EEG (aEEG) is a bedside cerebral function monitor. The advantage of 'aEEG' is its immediate availability, appropriateness for bedside long-term monitoring, ease of application and interpretation. Due to the use of only a single EEG channel, seizures in the centroparietal region can be readily detected but those originating in other areas and asymmetries may be missed.

Evidence: Several studies suggest that 'aEEG' has a low accuracy for seizure detection in comparison to conventional EEG.[9,14] They also suggest that brief, low voltage or focal seizures are easily missed by 'aEEG'. Hence, the clinical impact and utility of 'aEEG' in neonatal seizure detection remains unproven. A single study comparing 'aEEG' alone to 'aEEG' plus 2- channel EEG showed that including the EEG data when evaluating for seizures greatly improves the sensitivity and specificity of the test.[8]

Recommendations: Limited accuracy and low sensitivity of 'aEEG' for neonatal seizure detection warrants larger studies with improved technology especially using automated 'aEEG'. Till such time, conventional EEG stays as a gold standard for seizure detection and an 'aEEG' may be used to complement a conventional EEG but not alone to detect neonatal seizures.

Prognosis

Even though the incidence of death following neonatal seizures has decreased over the years, the risk of neurodevelopmental disability remains high.

Evidence: There are limited number of population based studies that address outcomes of neonates with seizures. Gabriel et al. prospectively followed 82 babies with neonatal seizures in a population-based setting and found that of the survivors, 17 (27%) developed epilepsy, 16 (25%) had cerebral palsy, 13 (20%) had mental retardation, and 17 (27%) had learning disorders. They suggested that a Sarnat stage III or equivalent severe encephalopathy, cerebral dysgenesis, complicated intraventricular hemorrhage, infections in the preterm infants, abnormal neonatal EEGs, and the need for multiple drugs to treat the neonatal seizures were associated with poor prognosis.[29] A pure clonic seizure without facial involvement in term infants suggested favorable outcome, whereas generalized myoclonic seizures in preterm infants were associated with an increased risk of mortality. Iype et al observed that an abnormal EEG (presence of spike waves) was the only predictor of a poor outcome at 2-8 months of age in a NICU cohort.[30] Another group observed that underlying etiologies like severe HIE, cerebral dysgenesis, and intraventricular hemorrhage, seizures within 12 hours of life, or lasting for more than 30 minutes to one hour, recurrent seizures lasting for more than 48 hours, generalized myoclonic, generalized tonic and

subtle seizures and severe background abnormalities on EEG are associated with a poor prognosis.[29] A study from PGI, Chandigarh observed that seizures with onset within 72 hours of life, tonic seizures, seizures due to ICH, and neonates with background EEG abnormalities had an invariably poor outcome (M.D Thesis; unpublished data). Preterm babies, early onset seizures in HIE, prolonged seizures, repeated difficult to control seizures, subtle seizures, myoclonic seizures, abnormal neurological status, attenuation of background activity, discontinuous record with significantly prolonged inter burst interval, burst suppression pattern on EEG and deep grey matter / multifocal or diffuse cortical involvement on neuroimaging indicate poor prognosis.

Recommendations: To assess prognosis, take into consideration the gestation, onset, type and cause of seizures, neurological examination and results of EEG and neuroimaging.

Duration of Anticonvulsants

Duration of ACD primarily rests on the likelihood of recurrence of seizure if the drugs are discontinued. Evidence suggests that recurrence of seizures can adversely affect outcomes.[31] Hence, prevention of recurrence by use of ACD should improve outcomes. However, there is little agreement about when to stop ACD.

Evidence: Risk of seizure recurrence varies from 10 to 30% in different studies.[32,33] A study from PGI, Chandigarh done in 31 infants with seizures observed a recurrence rate of 13% (M.D Thesis, 1988; unpublished). The likelihood of seizure recurrence depends primarily on the neurological examination at discharge, cause of seizures, and the background EEG abnormality. At least two studies on asphyxiated neonates have shown a 50% risk of recurrence when the neurological examination at discharge was abnormal emphasizing the prognostic value of a discharge neurological examination.[34,35] Similarly, seizures following perinatal asphyxia and cortical dysgenesis have a recurrence risk of 50% and 100% respectively after the drug has been stopped whereas a benign cause like late onset hypocalcemia is associated with a negligible risk.[6] Watanabe et al observed that in a cohort of 54 asphyxiated infants none with a normal or minimally abnormal EEG background activity developed subsequent epilepsy.[34] No randomized controlled trials could be identified addressing this issue.

Recommendations : The optimal duration of ACD should be based on neurological examination after seizures or at discharge, cause of seizures and associated background EEG abnormalities. In those infants where the ACD therapy is continued beyond discharge, the need for ongoing treatment should be reviewed again at 1 and 3 months of age due to the potential long term adverse effects of the drug per se.

Follow-up for sequelae

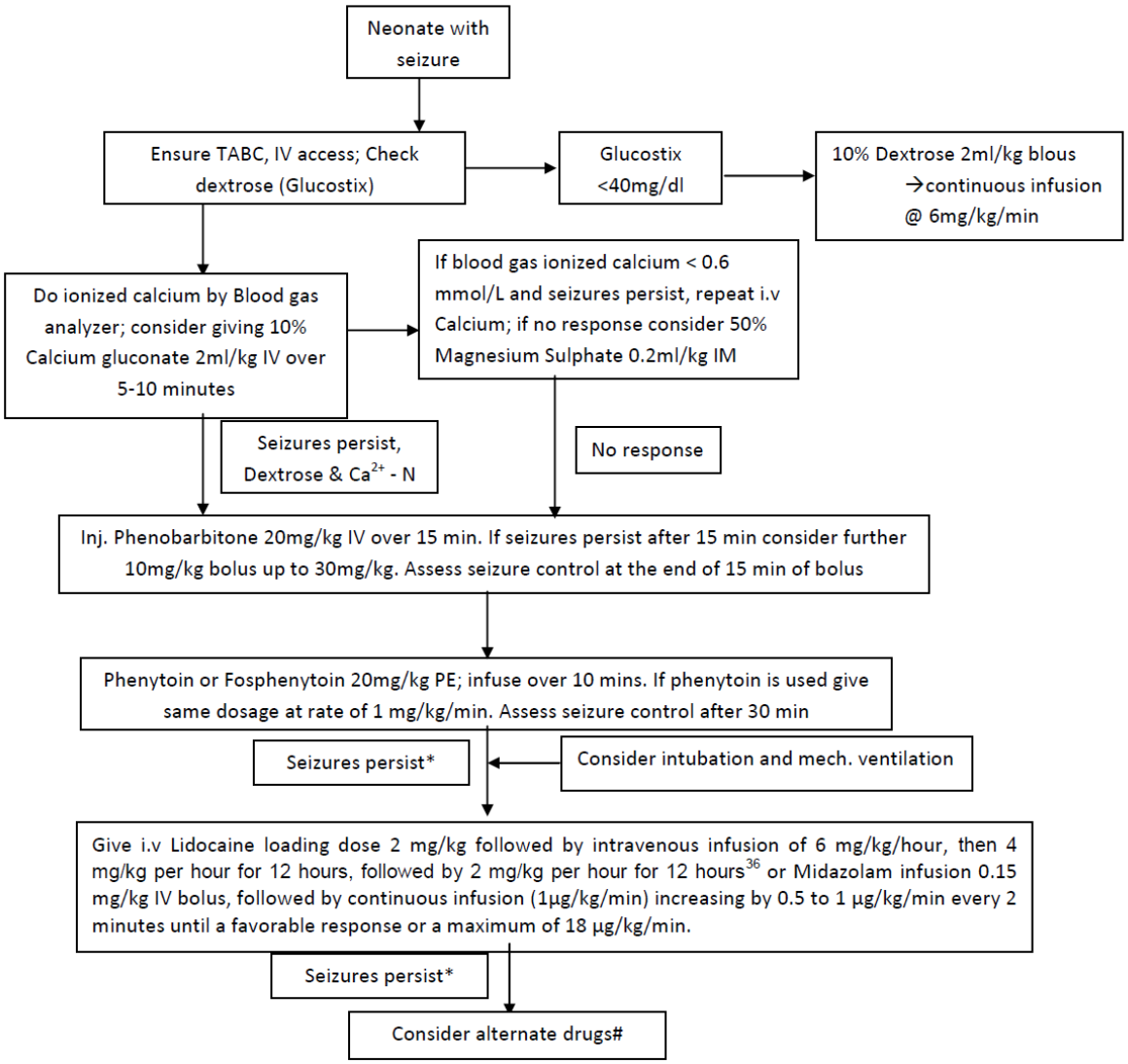
Babies discharged with a diagnosis of neonatal seizures are at increased risk of seizure recurrence and neurodevelopmental disability and the recurrence usually occurs in the early infancy. A 12-18 month follow up will recognize most babies with major disability – cerebral palsy, mental retardation or hearing problems. Longer follow up till school age and older age can additionally recognize learning and behavioral problems.

Evidence : Infants discharged from a single unit with a diagnosis of neonatal seizures over 12 years were reviewed for outcomes. Of the 132 babies 24 % had a seizure recurrence and 16 % had multiple recurrences treated as epilepsy. There were babies in the study group who had first recurrence at 2 years also.[32] Similarly, Ronen et al reported 27% epilepsy, 25% cerebral palsy, 20% mental retardation, and

27% learning disorders in their study neonates. They suggested these learning problems may be evident only when the child is followed to school age . [29]

Recommendation : Neonatal seizures are associated with increased risk of seizure recurrence and neurodevelopmental problems. Such neonates should be followed up at least till 12-18 months and preferably through early school years.

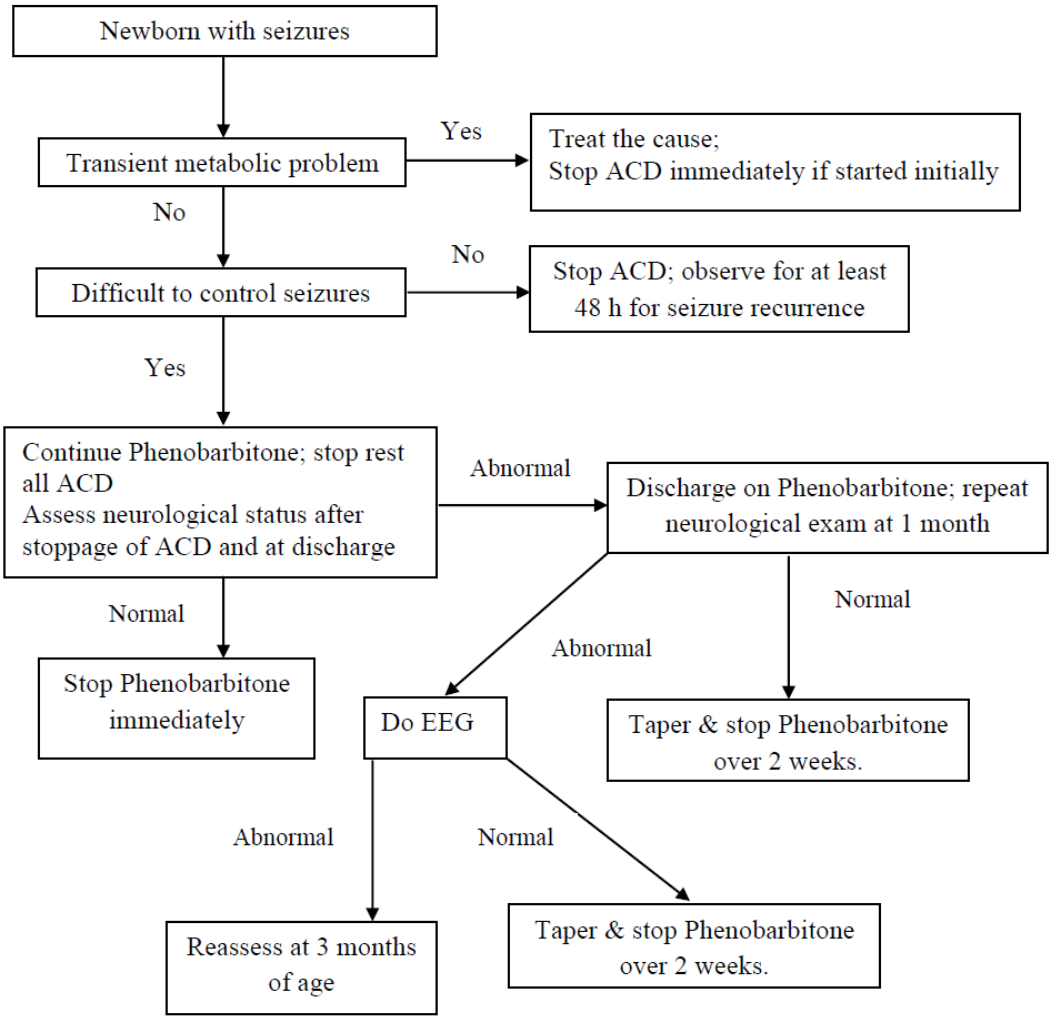
Fig 1: Flow chart for management of acute neonatal seizures



#Levetiracetam, Topiramate

Note: Calcium step is considered in case of IDM, IUGR, preterm and a sick neonate. A second dose of Phenobarbital 10m/kg is optional before giving Fosphenytoin. *Consider using pyridoxine at these steps.

Fig 2: Suggested guideline for weaning from ACDs



References

1. Brunquell PJ, Glennon CM, DiMario FJ Jr, Lerer T, Eisenfeld L. Prediction of outcome based on clinical seizure type in newborn infants. J Pediatr 2002;140:707-12.
2. Weiner SP, Painter MJ, Geva D, Guthrie RD, Scher MS. Neonatal seizures: electroclinical dissociation. Pediatr Neurol 1991; 7:363-68.
3. G Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. Neurology 1987; 37:1837-44.
4. Clancy RR, Legido A, Lewis D. Occult neonatal seizures. Epilepsia 1998;29:256-261.
5. Tekgul H, Gauvreau K, Soul J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics. 2006;117:1270-1280.
6. Volpe JJ. Neonatal seizures. In: Volpe JJ, ed. Neonatal Neurology. 5th ed. Philadelphia: WB Saunders; 2008:203-244.
7. Shah DK, Mackay MT, Lavery S, Watson S, Harvey S, Zempel J, Mathur A, Inder TE. Accuracy of bedside electroencephalography monitoring in comparison with simultaneous continuous conventional electroencephalography for seizure detection in term infants. Pediatrics 2008; 121:1146-54
8. Cherian PJ, Swarte RM, Visser GH. Technical standards for recording and interpretation of neonatal electroencephalography in clinical practice. Ann Ind Acad Neurol 2009; 12:58-70.
9. Shellhaas RA, Shoita AI, Clancy RR. Sensitivity of amplitude integrated electroencephalography for neonatal seizure detection. Pediatrics 2007; 120:770-77.
10. Menache CC, Bourgeois BFD, Volpe JJ. Prognostic value of neonatal discontinuous EEG. Pediatr Neurol 2002; 27:93-101.
11. Zupanc ML. Neonatal seizures. Ped Clin North America 2004; 51:961-78.
12. Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA, Martin JP, Rivkin M, Slovis TL. Practice parameter: Neuroimaging of the neonate. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002; 58:1726-38.
13. Glass HC, Wirrell E. Controversies in neonatal seizure management. J Child Neurol 2009; 24:591-99.
14. Toet MC, van der Meij W, de Vries LS, Uiterwaal CS, van Huffelen KC. Comparison between simultaneously recorded amplitude integrated electroencephalogram (cerebral function monitor) and standard electroencephalogram in neonates. Pediatrics. 2002; 109:772-779.
15. Painter MJ, Scher MS, Stein AD et al. Phenobarbital compared with Phenytoin for the treatment of neonatal seizures. N Engl J Med 1999; 341:485-89.
16. Gal P, Toback DJ, Boer HR, Erkan NV, Wells TJ. Efficacy of phenobarbital monotherapy in treatment of neonatal seizures—relationship to blood levels. Neurology 1982; 32:1401.
17. Sulzbacher S, Farwell JR, Temkin N, Lu AS, Hirtz DG. Late cognitive effects of early treatment with phenobarbital. Clin Pediatr (Phila). 1999; 38:387-394.
18. Bittigau P, Sifringer M, Genz K et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci U.S.A 2002; 99:15089-15094.
19. Boylan BG, Rennie JM, Pressler RM, Wilsopn G, Morton M, Binnie CD. Phenobarbitone, neonatal seizures and video EEG. Arch Dis Child Fetal & Neonatal Ed 2002; 86:F165-70.
20. Morton LD, Rizkallah E, Pellock JM. New drug therapy for acute seizure management. Semin Pediatr Neurol 1997; 4:51-63, Morton LD. Clinical experience with Fosphenytoin in children. J Child Neurol 1998; 13:S19-22.
21. Kriel RL, Cifuentes RF. Fosphenytoin in infants of extremely low birth weight. Pediatr Neurol 2001; 24:219-221.
22. Riviello JJ. Drug therapy for neonatal seizures. Pharmacol Rev 2004; 5:e215-220.
23. Yamamoto H, Aihara M, Niijima S, Yamanouchi H. Treatments with Midazolam and lidocaine for status epilepticus in neonates. Brain Dev 2007; 29:559-64.
24. Shany E, Benzaqen O, Watemberg N. Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. J Child Neurol 2007; 22:255-59.
25. Boylan GB, Rennie JM, Chorley G, et al. Second line anticonvulsant treatment of neonatal seizures: a video EEG monitoring study. Neurology 2004; 62:486-88.

26. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of new antiepileptic drugs I: treatment of new onset epilepsy: Report of Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society Neurology 2004; 62:1252-1260.
27. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. J Child Neurol. 2007; 22:95-98.
28. Hmaimess G, Kadhim H, Nassogne MC, Bonnier C, van Rijckevorsel K. Levetiracetam in a neonate with malignant migrating partial seizures. Pediatr Neurol. 2006; 34:55-59.
29. Ronen GM, Buckley D, Penney S, Streiner DL. Long-term prognosis in children with neonatal seizures: a population-based study. Neurology. 2007;69:1816-1822.
30. Iype M, Prasad M, Nair MP, Geeta S, Kailas L. The newborn with seizures -- a follow-up study. Indian Pediatr 2008;45749-52.
31. Clancy RR, Legido A. Postnatal epilepsy after EEG confirmed neonatal seizures. Epilepsia 1991; 32:69-76.
32. Guillet R, Kwon J. Seizure recurrence and developmental disabilities after neonatal seizures: outcomes are unrelated to use of phenobarbital prophylaxis. J Child Neurol 2007; 22:389-95.
33. Hellstrom-Westas L, Blennow G, Lindroth M, Rosen I, Svenningsen NW. Low risk of seizure recurrence after early withdrawal of antiepileptic treatment in the neonatal period. *Arch Dis Child* 1995;**72**:F97-101.
34. Watanabe K, Hara K, Miyazaki S, Hakamada S et al. Apneic seizures in the newborn. Am J Dis Child 1982; 136:980-84.
35. Corsellis JAN, Meldrum BS: Epilepsy. In: Blackwood W, Corsellis JAN (eds.). Greenfields Neuropathology. Edward Arnold, London, 1976.
36. Carin M.A. Rademaker and Linda S. de Vries. Pharmacology Review: Lidocaine for Neonatal Seizure Management. NeoReviews 2008;9;e585-e589.

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Use of Blood Components in the Newborn

Summary of recommendations

- **Transfusion in the newborn requires selection of appropriate donor, measures to minimize donor exposure and prevent graft versus host disease and transmission of Cytomegalovirus.**
- **Component therapy rather than whole blood transfusion, is appropriate in most situations.**
- **A clear cut policy of cut-offs for transfusions in different situations helps reduce unnecessary exposure to blood products.**
- **Transfusion triggers should be based on underlying disease, age and general condition of the neonate.**

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Introduction

Blood forms an important part of the therapeutic armamentarium of the neonatologist. Very small premature neonates are amongst the most common of all patient groups to receive extensive transfusions. The risks of blood transfusion in today's age of rigid blood banking laws, while infrequent, are not trivial. Therefore, as with any therapy used in the newborn, it is essential that one considers the risk- benefit ratio and strive to develop treatment strategies that will result in the best patient outcomes. In addition, the relatively immature immune status of the neonate predisposes them to Graft versus Host Disease (GVHD), in addition to other complications including transmission of infections, oxidant damage, allo-immunization and so on. Since neonatal physiology varies with the maturity, age, weight and the presence of morbidities, it is difficult to formulate one parameter to guide all transfusion decisions. This guideline addresses the following issues:

- What specific pretransfusion processing is performed before transfusing blood products to neonates?
- What are the indications for the use of various blood products?

Foe some of the indications, there is robust evidence but many are based on biological principles, expert recommendations and consensus statements.

Pre-transfusion Issues: *Recommendations*

1. Donor selection
    a. Avoid blood donation from first and second degree relatives.
    b. In addition to routine screening tests, the donor should be seronegative for Cytomegalovirus (CMV).
2. Pre-transfusion testing of donor blood
    a. Blood typing errors can result from
        i. Weak expression of red blood cell(RBC) antigens in neonates
        ii. Presence of maternal antibodies that can mask the corresponding antigens.
        iii. Umbilical cord samples contaminated by maternal blood/ Wharton's jelly.
    b. When indicated following tests should be performed before selecting the right donor blood
        i. Mother's blood: ABO/Rh blood group and irregular antibodies against RBCs using the indirect antiglobulin test (IAT).
        ii. Neonate's blood: ABO/Rh blood groups, (when possible, confirmed on a second sample). Direct antiglobulin test (DAT) and, if positive, elution of any antibody and its identification.
3. Leucodepletion: Whole blood, Packed RBC and platelet concentrates should be leucodepleted ($<5 \times 10^6$ leucocytes per pack). This may be done in the blood bank (pre issue) or using online filters at the bedside (post issue).
4. Hematocrit: Reconstituted blood should have a hematocrit 0.5 ± 0.05
5. Gamma irradiation: It renders donor lymphocytes effete and unable to mount a graft versus host reaction on the immunologically incompetent neonate. The dosage required is 25-50 gray (2500-5000 rads). Irradiation of packed RBC should be done within 14 days of collection of the cells;

once irradiated packed RBC should be transfused within 48 hours. Irradiation does not change the shelf-life of platelet concentrates. Irradiation is indicated for

i. Intrauterine transfusion of packed RBC and platelets
ii. Transfusion of packed RBC and platelets (also in blood exchange transfusion) after intrauterine transfusion
iii. Transfusion of RBC and platelets in neonates with birth weight < 1500grams and/or gestation at birth < 30weeks
iv. Donations from first or second degree relatives
v. Neonates with congenital or acquired immunodeficiency.

6. Prevention of Cytomegalovirus infection: This can be achieved by using CMV seronegative donors and leucodepletion. CMV negative blood is indicated for
   i. Intrauterine transfusion of packed RBC and platelets
   ii. Neonates with birth weight <1500 grams and/or gestation < 30weeks
   iii. Neonates with congenital or acquired immune deficiency;
7. Use of satellite (piggyback) bags: This reduces wastage and exposure to multiple donors. Blood banks should be encouraged to use these for all blood components.
8. T activation: T antigens (and the closely related Th, Tk and Tx antigens) are present on the neonate's RBC surface and get activated in certain clinical situations (e.g. Necrotizing enterocolitis and Septicemia) when RBC get exposed to bacterial or viral enzymes (neuraminidase). This leads to polyagglutination of the RBCs (unexpected agglutination on testing with sera from ABO compatible donors) and thereby hemolysis. In high risk situations avoid all plasma or plasma products as most adults have anti T antibodies due to prior exposure to bacteria and vaccines. If unavoidable use plasma with low titres of anti T antibody to prevent hemolysis.
9. Reconstitution of packed cells for exchange transfusion: At present, in India no regulatory guidelines exist for reconstitution of blood. In the West, the FDA clearly states that although reconstitution of blood can be done either at the blood bank or at the ward, whoever reconstitutes the blood must be registered with the FDA.[1]
10. Single vs multiple donors: Preterm infants frequently require multiple blood transfusions. A unit of blood with additional satellite packs ordered for each infant and used up to its expiry date, allows up to eight transfusions from a single donation, reducing the number donor exposures .[2]

Recommendations on use of blood products in neonates

a. Characteristics: Blood for transfusion should be less than 5 days old, irradiated, CMV negative, warmed and have a hematocrit of 0.5 to 0.6.
b. Reconstituted blood: Reconstituted whole blood is obtained by combining packed RBC with fresh-frozen plasma (FFP). Ideally FFP should be from the same donor bag from which the packed RBC was produced. Otherwise AB group FFP from a different donor may be used. The final product should be used within 24h of reconstitution and has the same characteristics as whole blood except for reduced platelets.

c. Indications of whole blood:

- Exchange transfusion
- Replacement of blood loss in massive hemorrhage
- Cardiac surgery

Exchange transfusion: The choice of donor blood group is dependent on the mother and infant's blood and Rh grouping.

a. Rh incompatibility:

   Blood arranged prior to birth: O negative cross matched against mother

   Blood arranged after birth: Rh negative of baby's ABO group cross matched against infant and mother

b. ABO incompatibility: Rh matched O group cross matched with mother
c. Other indications (non-hemolytic): Blood group of infant cross matched against infant and mother

To avoid the risk of hyperkalemia, use fresh whole blood (<5 days of age) and reconstitute blood using washed packed red cells. Saline wash if available can reduce the risk of hyperkalemia and also reduce the antigen load on the RBC.

Packed red blood cell (PRBC) transfusions

Oxygen delivery to the tissues is dependant upon multiple factors such as stroke volume, level and type of hemoglobin (Hb), arterial oxygen tension, oxygen extraction fraction, and tissue consumption of oxygen. Thus for a given hemoglobin level, isovolaemic anemia (e.g. anemia of prematurity), is better tolerated than hypovolemic anemia (acute hemorrhage). While various markers for tissue oxygenation (fractional extraction of oxygen, serum lactate levels, echocardiographic parameters), other than hemoglobin (or Hematocrit-PCV) have been studied to guide transfusion thresholds, none are as easily/quickly evaluated in clinical practice. The current recommendations on RBC transfusions in neonates have, therefore, remained related to values of Hb (or PCV), in relation to the clinical state of the neonate and any bone marrow erythropoietic compensation.

Evidence: Many centers have introduced restrictive transfusion policies for preterm infants in recent years. The benefits and adverse consequences of allowing lower hematocrit levels have not been systematically evaluated. The limited evidence regarding the use of restrictive hematocrit levels to guide RBC transfusion are as follows[3-5]:

- The results of trials studying clinically relevant outcomes of restrictive transfusion practices are conflicting. While some authors[4] caution against the use of restrictive guidelines due to higher incidence of major adverse neurologic events (parenchymal brain hemorrhage, periventricular leukomalacia, or both) and significantly more frequent apnea (and potentially adverse long term neurodevelopmental outcome), others[5] found no difference in the frequency of complications. As

such, there is an urgent need to study the short and long term repercussions of using restrictive threshold for the use of red cell transfusions.

- Hb limited oxygen unloading capacity to the tissues is rare even in the intensive care setting The practice of following local guidelines results in fewer transfusions.
- Neurodevelopmental follow up of infants with severe hemolytic disease of the newborn for a period of 62 months were performed using Gesell Developmental schedule and McCarthy's Scales of Children's abilities. There were no delay in mean developmental quotient or mean cognitive index among patients with lowest fetal hematocrit of 0.20 ± 0.078, peak fetal bilirubin 7.1 ± 2.1 mg/dL or with hydrops fetalis (45%) and mean gestational age at delivery being 35.6 ± 2.2 weeks[6.]
- The PINT trial showed a significantly higher cognitive delay in the group of ELBW assigned to receive restricted transfusions.[7]

Recommendations:

Considering the limited evidence, the RBC guidelines are based on the available expert recommendations[8-11] and the need to restrict donor exposure in neonates. Despite hematocrit being an imperfect surrogate marker for oxygen delivery, various guidelines propose cut off values to trigger transfusion. It is worthwhile to bear in mind that the overall clinical picture rather than a particular figure should be considered in the decision to transfuse a neonate. Transfusion triggers vary with etiology, age and general condition of the neonate.

- *Severe anemia of antenatal onset*: Anemia occurring before birth, characterized by Hb < 8/dL at birth, requires prompt transfusion, as specified below
    a. In severe anemia associated with congestive heart failure (due to immunohemolysis, chronic feto-maternal or feto-fetal hemorrhage) the most appropriate treatment is "partial" exchange transfusion (PET) with packed RBC with the aim of correcting the anemia while avoiding volume overload.
    b. In severe anemia with hypovolaemic shock (placenta previa, abruption placentae, rupture of the cord), the intravascular volume must be restored and the anemia corrected.
- *Early neonatal anemia*: For anemia developing after birth or in the first week of life, in which the values of Hb are moderately decreased, transfusion treatment is necessary in the case of severe cardio-pulmonary diseases, in order to maintain the PCV greater than 0.35 to 0.40.
- *Late neonatal anemia*
    a. **Acute blood loss** greater than 10% of blood volume with features of decreased oxygen delivery or greater than 20% of blood volume.
    b. **PCV < 30%:** Moderate or significant mechanical ventilator support [MAP >8 cm , FiO2 >0.40 with conventional ventilation or MAP >14 and FiO2 > 0.40 with High frequency ventilation-HFV]
    c. **PCV < 25%**: Minimal mechanical ventilator support [MAP < 8 cm, FiO2 < 0.40 on conventional ventilation or MAP <14 and/or FiO2 0.40 on HFV]
    d. **PCV < 20%**: Supplemental oxygen not requiring mechanical ventilatory support plus the presence of one or more of the following :
        i. Tachycardia >180/minute or Respiratory rate > 60 for ≥ 24hours
        ii. Doubling of the oxygen requirement in last 48 hours
        iii. Lactate > 2.5 mEq/L or acute metabolic acidosis with pH <7.20

iv. Weight gain less than 10 grams/kg/day over 4 days while receiving 120 kcal/kg/day

v. If the infant will undergo major surgery within 72 hours

e. **PCV< 18%:** Consider transfusion for asymptomatic infants with absolute reticulocyte count of < $100x10^3/\mu L$ ($100x10^9/L$) or < 2 percent.

Platelet transfusions

Evidence: Asymptomatic thrombocytopenia occurs in about 1% of term and 25% of preterm neonates. Characteristics of platelet transfusions used in the NICUs have been studied[12-14]. Platelet transfusions are common in the NICU, being administered to 2% - 9.4% of neonates admitted to NICUs. Majority of platelet transfusions were used prophylactically in non-bleeding neonates with platelet counts in the range of 30 to 50 x 10^9/L. Repeated platelet transfusions were common with more than 50% infants receiving more than one platelet transfusion during their NICU stay. Thrombocytopenic neonates who receive platelets are up to 10 times more likely to die than neonates who do not receive platelet transfusion (usually to causes unrelated to severe hemorrhage). Andrew et al[14] found no benefit in terms of hemorrhage when maintaining a normal platelet count by platelet transfusion in a study of preterm neonates compared with controls with moderate thrombocytopenia (platelets (50 to 150 x 10^9/L).

Recommendations:

Platelets (x10^9/L)	**Bleeding**		**Immune status**	
	Yes	**No**	**AITP***	**NAIT****
<30	Transfuse	Consider platelet transfusion	Transfuse if bleeding/ IVIG not available	Transfuse if bleeding
30 to 49	Transfuse	Transfuse if Weight <1000grams *or* postnatal age <1week *or*Unstable (IVH Gr3-4) *or* associated coagulopathy *or* Surgery required	Transfuse, if unstable, bleeding	Transfuse if bleeding
50 to 99	Transfuse	Do not transfuse	Do not transfuse	Transfuse if bleeding
> 99	Do not transfuse			

**AITP: Autoimmune thrombocytopenia, **NAIT: Neonatal alloimmune thrombocytopenia ,IVH: Intraventricular hemorrhage*

Fresh frozen plasma and Cryoprecipitate

Recommendations for use of Fresh frozen plasma:

- Indications
    a. Severe clotting deficiency (including DIC) with bleeding
    b. Severe clotting deficiency in a neonate undergoing an invasive procedure
    c. Vitamin K deficiency with bleeding
    d. Dilutional coagulopathy with bleeding
    e. Severe anticoagulant protein deficiency
    f. Reconstitution of packed RBC for exchange transfusion
- Incorrect indications for which FFP is often prescribed but should not be used[16]
    a. Prevention of intraventricular hemorrhage in premature neonates
    b. Volume replacement in the management of sepsis
    c. As an adjunct in the management of thrombocytopenia
    d. To "correct" prolonged indices of coagulation

***Recommendations for Factor VIII/ cryoprecipitate*:**

Congenital factor deficiencies are rare in the neonatal period. While treating bleeding neonates, cryoprecipitate is often considered an alternative to FFP because of its small volume. However, cryoprecipitate contains only factors VIII, XIII and fibrinogen and is not effective in treating the more extensive clotting factor deficiencies.

Practice points

- Use components wherever feasible/ available.
- Follow guidelines: It is difficult to obtain clear scientific evidence on the criteria to use for the administration of PRBC in premature VLBW neonates, who constitute the category of patients with the highest transfusion needs.[17-18] It however, has been demonstrated that transfusing according to agreed criteria limits both the number of neonates undergoing transfusion and the number of donors to which each neonate is exposed.[19-20] The use of "local" transfusion protocols in the various Neonatal Intensive Care Units is, therefore, recommended (Level of evidence Ib, grade of recommendation A).
- Treat patient/ not lab values: Fallacies arise in the collection and processing of blood samples, and in the reporting and interpretation of laboratory results. The final guide for a particular treatment strategy is finally based upon the clinical condition of the patient.
- Awareness of complications of blood transfusions: Homologous blood transfusion is associated with the risk of transmission of infections such as HIV, hepatitis B and C, cytomegalovirus, syphilis, and malaria. The rates of transfusion associated infection increase when multiple transfusions from multiple donors are given. Other transfusion related complications of a non-infectious nature may also occur in neonates and include fluid overload, graft-versus-host disease, electrolyte and acid base disturbances, iron overload, increased susceptibility to oxidant damage and allo-immunisation.

References

1. 2007 Ask the FDA Transcript" (http://www.aabb.org/Content/Programs_and_Services/Government_Regulatory_Issues/fdatranscripts2007.htm) accessed on 09 Mar 2010
2. Bifano EM. The effect of hematocrit (HCT) level on clinical outcomes in extremely low birthweight (ELBW) infants. Pediatr Res. 2001;49 :311A
3. Bell EF, Strauss RG, Widness JA. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics. 2005;115 :1685
4. Kirpalani H, Whyte RK, Andersen C. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr. 2006;149 :301
5. Hudon L et al. Long-term neurodevelopmental outcome after intrauterine transfusion for the treatment of fetal hemolytic disease. American Journal of Obstetrics and Gynecology; 179(4):858-863
6. Whyte RK et al. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics. 2009 Jan;123(1):207-13
7. Fetus and Newborn Committee, Canadian Paediatric Society (CPS). Red blood cell transfusions in newborn infants:Revised guidelines Paediatrics & Child Health 2002;7(8):553-8
8. Boulton F. Transfusion guidelines for neonates and older children. Brit J Haemat, 2004; 124: 433–453
9. Shannon KM, Keith JF 3rd, Mentzer WC, et al. Recombinant human erythropoietin stimulates erythropoiesis and reduces erythrocyte transfusions in very low birth weight preterm infants. Pediatrics. 1995;95
10. Ohls R.K. Transfusions in the Preterm Infant NeoReviews 2007; 8(9): e377
11. Murray NA, Howarth LJ, McCloy MP, et al. Platelet transfusion in the management of severe thrombocytopenia in neonatal intensive care unit patients. Transfus Med 2002;12:35–41.
12. Garcia MG, Duenas E, Sola MC, et al. Epidemiologic and outcome studies of patients who received platelet transfusions in the neonatal intensive care unit. J Perinatol 2001;21:415–20.
13. Del Vecchio A, Sola MC, Theriaque DW, et al. Platelet transfusions in the neonatal intensive care unit: factors predicting which patients will require multiple transfusions. Transfusion 2001;41:803–8
14. Andrew M, Vegh P, Caco C, et al. Randomized controlled trial of platelet transfusions in thrombocytopenic premature infants. J Pediatr 1993; 123; 285-91
15. Strauss RG, Levy GJ, Sotelo-Avila C, et al. National survey of neonatal transfusion practices. II. Blood component therapy. Pediatrics 1993;91:530–6
16. Strauss RG. Controversies in the management of the anemia of prematurity using single-donor red blood cell transfusions and/or recombinant human erythropoietin. Transfus Med Rev 2006; 20: 34-44.
17. Ross MP, Christensen RD, Rothstein G et al. A randomized trial to develop criteria for administering erythrocyte transfusions to anemic preterm infants 1 to 3 months of age. J Perinatol 1989; 9: 246-53.
18. Pupella S, Girelli G, CasadeiAM, et al. Protocollo operativo per la terapia trasfusionale del neonato: risultati preliminari. La Trasf del Sangue 1999; 44: 298-303.
19. Miyashiro AM, dos Santos N, Guinsburg R, et al. Strict red blood cell transfusion guideline reduces the need for transfusions in very-low-birth weight infants in the first 4 weeks of life: a multicentre trial. Vox Sang 2005; 88: 107-13.
20. Wood A, et al. Reducing donor exposure in preterm infants requiring multiple blood transfusions. Arch Dis Child Fetal Neonatal Ed 1995;72:F29-F33

Annexure

1.Whole blood/ reconstituted whole blood

- Collection and storage: Total volume of blood collected is 450-500 ml. Anticoagulant used is CPD (Citrate, Phosphate, and Dextrose). Blood can be stored for three weeks in CPD containing 25grams/litre of dextrose. Adenine which retards glycolysis in the RBC is added to CPD and increases storage to 35 days. Other nutrient solutions for extended storage of RBCs upto 42 days include Adsol (AS-1), Nutricel (AS-3) and Opticel (AS-5). The ratio of blood to anticoagulant is maintained at approximately 7:1.
- Biochemical changes that occur in the stored blood are
    - fall in pH due to accumulation of pyruvate and lactate
    - fall in extracellular sodium levels and rise in potassium levels
    - depletion of 2,3 DPG
    - loss of platelet and factor VII function after 48hours.

2.Whole blood for Exchange transfusion

a. In neonates exchange transfusion is used for the severe jaundice mostly due to Rh and ABO isoimunisation, severe anemia leading to cardiac dysfunction and in some special situations such as septicemia, inborn errors of metabolism, and disseminated intravascular coagulation.
b. Double volume exchange transfusion is the standard in management of severe hyperbilirubinemia in neonates (weight x 80ml x 2). This removes nearly 90% of red cells and approximately 50% of circulating bilirubin. There is a risk of hyperkalemia in the neonate after or during the exchange transfusion as the serum potassium levels in blood bag can reach 50mEq/L after storage for 42 days.

3. Packed Red blood cells

Dosage: The dose to be infused depends upon the desired and actual hematocrit of the infant.

$$\text{Packed RBC volume to be infused} = \frac{\text{Blood volume} \times \text{desired PCV} - \text{actual PCV}}{\text{PCV of packed RBC being transfused}}$$

The rate of infusion should not exceed 10ml/kg/hour in the absence of cardiac failure and 2ml/kg/hour in its presence. A dose of intravenous frusemide (1-2mg/kg) may be administered during the infusion to prevent fluid overload.

Preparation and characteristics: A unit of packed red blood cells made allowing cells in a bag of whole blood to separate by centrifuging or by gravity. It has a volume of about 250ml and a hematocrit of 0.7-0.8 and contains all types of cells including platelets and leucocytes.

4.Platelet concentrate

- Preparation and characteristics: Platelets separated by centrifugation are pooled to make random donor platelet packs which have a volume of 50-60 ml and contain about 5 to 7 x 10^{10} platelets. Platelets obtained by aphaeresis from a single individual (single donor platelets) provides about 3 to 4 x 10^{11} platelets. Platelet packs contain leucocytes, plasma and some red cells.
- Storage: platelet packs are stored at 22°C with continuous agitation of the bag.
- Typing: Platelet specific antigen and antibody testing has bearing on the management of alloimmune thrombocytopenia but it is not readily available. All platelet packs are contaminated with some RBCs, plasma and leucocytes, theoretically leading to ABO and Rh group incompatibility if similar group is not used. Ideally, therefore, group specific platelets should be used. However, unless repeated transfusions are required, different group platelets may be used in an emergency.
- Dosage: One unit of random donor platelets per 10 kg body weight increases the platelet count by 40-50 x 10^9/L. This can be achieved by infusion of 5-10 ml/kg of standard donor platelets.
- The goal of platelet transfusion is to raise the platelet count to 100 x 10^9/L.
- Frequency of transfusion: Normal half life of stored platelets is 3-5 days. In vivo life span is shorter, especially if there is platelet consumption. A repeat platelet count should be performed after 12 hours of transfusion.

5.Fresh frozen plasma

- Preparation & characteristics: FFP is made by freezing plasma obtained by centrifugation of fresh whole blood. It contains albumin and factors II, VII, X and XI. Antibodies and Factors V, VIII and XIII are also present, but in insignificant quantities, thus precluding the use of FFP as replacement for these substances.
- Storage and viability: FFP is stored at -20°C. After thawing it should be used immediately as there is a rapid fall in the concentration of clotting factors.

Management of Neonatal Hyperbilirubinemia

Summary of Recommendations

- **All neonates should be monitored clinically for appearance of jaundice during first postnatal week .**
- **In cases of discharge before 72-96 h from the hospital, a thorough assessment of risk factors for severe jaundice should be done in all babies. This assessment should include a clinical examination and if feasible, a biochemical screening.**
- **In neonates with significant jaundice, investigations should include blood groups of mother and baby, a Coomb's test, evidence for hemolysis and G6PD assay in areas known to have high prevalence of G6PD deficiency.**
- **The decision to initiate phototherapy or exchange blood transfusion should be based on gestation, postnatal age, risk factors and clinical status.**
- **Phototherapy units should be of proven safety and provide maximum irradiance to maximum possible surface area.**
- **Neonates with significant hyperbilirubinemia should be followed up for hearing loss and other neurodevelopmental sequelae.**

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Introduction

Hyperbilirubinemia is a common problem in neonates with an incidence of 70-80%.[1] A significant proportion of these neonates develop pathological hyperbilirubinemia (defined as hyperbilirubinemia requiring treatment) during the first week of life.[2-4] Premature babies have much higher incidence of neonatal jaundice requiring therapeutic intervention more commonly than term newborns.[5] Although the outcome for the majority is benign, infants with untreated, severe hyperbilirubinemia (defined as serum total bilirubin level >20 mg/dL) can develop signs of acute bilirubin encephalopathy (ABE). If not treated immediately, they might go on to develop kernicterus, a chronic, neurologically devastating condition resulting from bilirubin toxicity. Management of hyperbilirubinemia includes detection of at-risk neonates, investigating the cause of pathological hyperbilirubinemia, deciding thresholds for starting and stopping treatment and follow-up of neonates with severe hyperbilirubinemia.

This guideline reviews the evidence for the following issues :

- Optimum timing for discharge & follow-up and assessment policy
- Pre-discharge stratification for risk of developing significant jaundice
- Universal serum or transcutaneous bilirubin estimation for risk assessment
- Laboratory investigations to be conducted in a baby needing treatment
- Use of phototherapy (PT) & blood exchange transfusion (BET) for treatment
- Monitoring of a baby with jaundice and assessment of response to treatment
- Additional therapies in prevention/treatment of jaundice
- Long term morbidities and follow-up plan of baby with jaundice

Optimum timing for discharge & follow-up and assessment policy to minimize the risk of severe hyperbilirubinemia and kernicterus

In India, healthy neonates are usually discharged within 24-48 h after a normal delivery. Due to continuing rise of bilirubin and absence of supervision for ensuring optimal feeding, neonates discharged home before completing 48-72 h of age are at high risk of developing undetected significant jaundice. In India, this risk may further be aggravated due to the absence of any formal system of follow-up home-visits by health care personnel (e.g. public health nurse) and due to traditional practice of confinement of mother-baby dyad at home for first few weeks after delivery.

Evidence: There is no prospective population-based or birth cohort-based study on epidemiology (rise, peak and fall of bilirubin) of significant jaundice in Indian neonates. Therefore it is difficult to define the time-period during which newborn needs to be followed up for significant jaundice. American Academy of Pediatrics (AAP) recommends follow-up of all neonates based on the postnatal age at discharge. This strategy also helps in assessment of newborn for feeding adequacy. Although desirable, this approach may not be feasible uniformly in India due to relative shortage of health care personnel and inability of some families to return for follow-up. Therefore follow-up plan may be devised based on pre-discharge risk assessment (Table 1).

Table 1: Suggested follow-up policy

Scenario	Age at discharge	Follow-up
None of risk factors* present	24-72 h	48 h after discharge
	>72 h	Follow-up optional
Any risk factor* present	24-48 h	24 h after discharge**
	49-72 h	48 h after discharge**
	73-120 h	48 h after discharge

*Risk factors: History of jaundice needing treatment in previous sibling, setting of blood group incompatibility, visible jaundice at discharge, gestation <38 completed weeks, high prevalence of G6PD deficiency, primipara mother, weight loss at discharge >3% per day or >7% cumulative weight loss

**may need a repeat visit depending on physician's assessment

Recommendation: Discharge and follow up plan should be optimized and individualized by a thorough pre-discharge assessment for risk factors for severe jaundice.

Pre-discharge stratification for risk of developing significant jaundice

Assessment and follow up of all the infants may not be feasible especially from a developing country point of view. Hence a pre-discharge stratification of the neonates based on the risk of developing significant jaundice is essential.

Evidence: Visual assessment alone for the presence and extent of jaundice is less accurate. Risk stratification for significant jaundice has been done by measuring bilirubin load (absolute levels or rate of rise of serum total bilirubin or transcutaneous bilirubin), bilirubin production (exhaled carbon monoxide) and identifying underlying biological cause. In India, prospective studies have not been able to assign a definite biological cause in about one-third to half of the cases of significant jaundice[6]. The American Academy of Pediatrics (AAP) – Subcommittee on Hyperbilirubinemia has outlined certain clinical and epidemiological risk factors in newborn infants of 35 weeks and more gestation in order to identify the at risk neonates before discharge[7]. Similarly, Bhutani et al suggested the use of an hour specific nomogram for pre-discharge risk stratification in healthy term neonates using total serum bilirubin (TSB). However, the generalizability of these guidelines in an Indian set-up may be difficult due to a different set of risk factors like higher prevalence of G6PD deficiency, more neonates with a low albumin state at birth and a significant role played by seasonal variation[6]. Nevertheless, these shortcomings do not mitigate the need for risk stratification as even in the presence of a known underlying etiology, risk factors may further modify the incidence and severity of significant jaundice.

Recommendations: Pre-discharge objective assessment for risk of developing significant jaundice should be done if neonates are being discharged from hospital within 72-96 h of birth and universal follow-up is not possible. This assessment should include a thorough clinical assessment and if feasible, a biochemical screening.

Universal serum or trans-cutaneous bilirubin estimation for risk assessment

Evidence: In a study conducted on term and near term infants without Rh hemolytic disease, Agarwal et al found that absence of TSB >6 mg/dL at 24±6 h of age virtually ruled out the possibility of subsequent significant jaundice (likelihood ratio of negative test 0.07) within 5 days of birth.[8] In another Indian study, a cut off of 3.99 mg/dL at 18-24 h was found to have sensitivity and specificity of 67% each for prediction of subsequent bilirubin level >15 mg/dL.[9] However, in both the studies only those neonates who stayed in the hospital, either due to their illness or due to certain maternal indications, were followed up. Moreover about 50% of infants, who were healthy and thus discharged early, were not followed up. As serum total bilirubin (TSB) estimation is invasive and relatively labor-intensive, non-invasive transcutaneous bilirubin (TcB) assessment has been investigated and was reported to correlate and agree closely with TSB in European and American origin infants.[7] Reports from India suggest heterogeneous performance with declining accuracy at TSB >13 mg/dL.[10] However, TcB used judiciously may serve as a good screening tool for jaundice prediction during first 24-48 of life in neonates with relatively lower levels of bilirubin. Bhat YR et al have reported good predictive ability of TcB index using cut-off of 7 at 24 h and 10 at 48 h of age in healthy term breastfed neonates.[11]

Hour-specific serum bilirubin nomogram published by Bhutani et al has been recommended by the APP for a pre-discharge risk assessment and are used widely in the Western population.[12] However, direct extrapolation of this nomogram to Indian neonates may not be possible as <1% of the neonates included in this study were of Asian origin. Mishra et al have provided normative data for TcB in healthy term and late-preterm Indian neonates during first 72 h of age using a multiwavelength reflectance transcutaneous bilimeter[13]. However, the diagnostic utility of this nomogram for predicting hyperbilirubinemia needs to be tested in a separate validation cohort.

Recommendations: Universal measurement of serum total bilirubin or transcutaneous bilirubin may help in identifying and stratifying neonates based on their risk of developing significant jaundice. However, more studies are required in this regard from a wider population base especially involving Indian neonates and the feasibility of this approach at the community level remains to be evaluated .

Laboratory investigations to be conducted in a baby needing treatment

Evidence: Laboratory investigations primarily intend to identify the presence of clinically significant jaundice, the severity of jaundice, the underlying etiology and possible adverse effects due to therapy. Literature search has not revealed any particular set of investigations universal for all infants. Investigations should be designed based on the region, risk factors present and clues from examination. Consensus opinion from the subcommittee for hyperbilirubinemia of the AAP has outlined investigations which are, to a large extent, applicable to Indian infants. Table 2 depicts a list of proposed investigations in an infant with jaundice. Other rare causes like galactosemia, hypothyroidism and intrauterine infections may be looked for depending on the clinical presentation. Bacterial infections have been implicated as a cause in 5-7% cases of significant jaundice.[6] However, with the present body of evidence, in absence of others sign(s) indicative of bacterial infection, investigations for sepsis is not warranted in a jaundiced infant.

Some of the investigations to diagnose presence of hemolysis may not be available round-the-clock in some settings. For the purpose of clinical management significant jaundice should be assumed to be due to hemolysis in following circumstances: mother blood group not known or O positive, high prevalence of G6PD deficiency, onset of jaundice within first 24 h after birth and presence of signs of Bilirubin Induced

Neurological Damage (BIND). Universal screening for G6PD deficiency in communities with high prevalence of this enzyme deficiency (eg. Panjabis in North India & Lambani tribal population in South India) needs to be investigated.

Recommendations: Baby's and mother's blood group, direct Coombs' test, reticulocyte count, peripheral blood smear for evidence of hemolysis and G6PD levels must be obtained in neonates with significant jaundice (table 2).

Table 2: Laboratory assessment in infants with significant jaundice

Indications	**Assessments**
Jaundice in first 24 hours	Measure TSB and / or TcB
Jaundice appears excessive for the infant's age	Measure TSB and / or TcB
Infants receiving PT	Measure TSB and / or TcB; blood type and DCT (if mother is 'O' or Rh negative); G6PD status; peripheral smear and reticulocyte count
TSB rising rapidly and unexplained by history and physical examination	Blood type and DCT ; G6PD status; peripheral smear and reticulocyte count; albumin (optional); measure direct bilirubin
TSB approaching exchange levels or not responding to PT	Blood type and DCT ; G6PD status; peripheral smear and reticulocyte count; albumin (optional)
Elevated direct (conjugated) bilirubin level	Urinalysis, urine culture, investigate for sepsis (as clinically indicated), thyroid profile (T3, T4, TSH)
Jaundice in a sick infant or present beyond 3 weeks of age	Total and direct bilirubin, evaluate for cholestasis (if direct bilirubin is elevated), thyroid profile, urine for reducing substances (galactosemia), urinalysis, urine culture, investigate for sepsis (as clinically indicated)

Source: Modified from table 2 in reference no. 7

Use of Phototherapy(PT) and Blood Exchange Transfusion(BET) for treatment

a) When to start PT and BET?

For neonates born at ≥35 weeks of gestation

Evidence: Due to lack of any population- or hospital-based data or registry, incidence of severe hyperbilirubinemia (TSB>20 mg/dL) or kernicterus cannot be estimated. However, neonates presenting in hospital emergencies with established BIND are not uncommon. In contrast to Western data, kernicterus has been reported at lower levels of peak TSB in India. In a study at a tertiary care center in northern

India, 21.8% neonates with non-hemolytic jaundice and TSB≥18 mg% had kernicterus when brought to the hospital.[14] In another study from the same hospital, about 10% neonates with TSB of 20-25 mg/dL presented with established BIND.[15] In a study on term infants with hyperbilirubinemia of mixed etiology, 10 out of 15 neonates with TSB of 21-25 mg/dL developed transient abnormalities in brainstem auditory evoked response (BERA) and 11% had developmental delay at 1 year of age.[15, 16] In a large cross-sectional study, kernicterus was identified as the underlying cause in 16.7% cases of cerebral palsy.[17] Reasons for increased propensity to BIND in Indian neonates need to be investigated. Proposed mechanisms include prolonged exposure to high TSB due to late referrals, concomitant morbidities, higher incidence of glucose-6-phosphate dehydrogenase (G6PD) deficiency, increased production of bilirubin and genetically altered blood-brain barrier permeability. Need for PT and BET should ideally be based on estimates of risk: benefit and cost: benefit ratio. Unfortunately, there is little such evidence on which to base these recommendations. As a result, treatment guidelines rely more on uncertain estimates and extrapolations.

Factors which may modify the risk of BIND in Indian neonates include:

1. Possible differences in genetic make-up including higher incidence of G6PD deficiency in certain geographical areas of India: In areas with documented higher incidence of BET, all neonates should be considered to be G6PD deficient unless proven otherwise and therefore risk-stratification for PT/BET must be done accordingly. Similarly, history of sibling with unexplained neonatal jaundice requiring treatment should be considered as a risk factor while deciding treatment.
2. Significantly higher proportion of small-for-gestation age (SGA) neonates: About two-thirds of low birth weight neonates born in India are born SGA.[18] However, there is no data regarding their differential risk of BIND. In the absence of supporting evidence it is not possible to formulate guidelines for this group of neonates. However, it may be prudent to consider them for appropriate treatment based on their birth weight rather than gestation.
3. Non-availability of intensive PT in many neonatal units: AAP recommends use of intensive PT with irradiance in blue-green spectrum of at least 30µW/cm2 per nm and delivered to as much of the infant's surface area as possible.[7] However, this seems to be very difficult to achieve in Indian scenario. In a study done on 58 PT units across 24 centers in India, it was observed that only 9% of the units are of the special-blue lights and 31% of the units were giving irradiance of at least 15 µW/cm2 per nm.[19] Although, standard-light fluorescent tubes have been demonstrated to be as efficacious as special blue compact fluorescent lamps (CFL) in moderate hyperbilirubinemia[20], their efficacy has not yet been demonstrated in hyperbilirubinemia nearing threshold for BET.

For neonates born at <35 weeks of gestation

Evidence: Several physiological differences from term infants indicate an increased risk for bilirubin toxicity in the immature newborn. It is therefore generally recommended to treat hyperbilirubinemia at lower levels in low birth weight (LBW) infants in comparison to term infants. The general guide is to start PT when TSB is 0.5% & 0.75% of the body weight in healthy and sick infants respectively and to do a EBT when TSB is ≥ 1% of the body weight in grams (table 3). However, it is important to remember that most of the algorithms do not take into consideration the lower concentration of albumin and the diminished albumin binding ability in a sick preterm neonate. More aggressive approach towards starting PT in extremely low birth weight (ELBW) neonates has not demonstrated benefit in terms of improvement in composite outcome of death and neurodevelopment impairment.[21]

Recommendations:

1) The postnatal age, gestation and risk based recommendations by AAP for starting PT and doing BET in infants ≥35 weeks of gestation thus can be used, but need certain modifications according to the Indian scenario.
2) In using the guidelines for PT and BET, one should use TSB. The direct reacting or conjugated bilirubin level should not be subtracted from the total bilirubin unless it is greater than 50% of the total. Immediate EBT is recommended if infant shows signs of ABE or if TSB is ≥5 mg/dl above the recommended lines.
3) AAP guidelines present PT and BET thresholds up to seven days of post natal age. Due to ongoing maturation of blood brain barrier, the thresholds for treatment are expected to be higher as post natal age advances. However due to lack of outcome studies, thresholds presented on seventh day may be used for rest of the neonatal period.
4) The PT and BET recommendations for preterm infants <35 weeks of gestation is given in table 3 .

Table 3: Indications for PT and BET in LBW babies

Birth Weight (grams)	Guidelines for PT* (mg/dL)		Consider BET (mg/dL)
	Healthy Infant	Sick Infant	
<1000	5-7	4-6	10-12
1000-1500	7-10	6-8	12-15
1501-2000	10-12	8-10	15-18
2001-2500	12-15	10-12	18-20

*Martin & Fanaroff. Neonatal-Perinatal Medicine, 8th Edition p1450

b) Role of prophylactic PT in preterm babies

Curtis-Cohen et al in a randomized controlled trial (RCT) observed that prophylactic PT does not offer any clinical benefit in the course of hyperbilirubinemia.[22] In a prospective unblinded study done at New Delhi on 50 newborns weighing <1250gm, it was concluded that prophylactic PT is unnecessary and of no benefit.[23] In a RCT comparing aggressive (routine PT within 12 hr of life) vs. conservative PT (starting when TSB is above 8.8 mg/dL) done on 95 VLBW neonates, it was concluded that no significant difference in adverse long-term outcome is observed between the two groups.[24]

c) Administration of PT

Three types of PT units are in common use:

i) Special blue tube-lights (PHILIPS TL52, 20W)
ii) Special blue CFT lamps (OSRAM 18 W)
iii) High intensity gallium nitride blue light emitting diode (LED)

In a multi-centric, open-label RCT comparing efficacy of single surface LED vs. CFT lamps, it was concluded that both were equally efficacious in the management of non-hemolytic hyperbilirubinemia in healthy term and late-preterm neonates.[25] In an another RCT done at a level III tertiary newborn center, it was concluded that CFT PT has no superiority over standard tube-light PT in terms of efficacy and adverse effects on the neonate and effects on nursing staff.[20] There is no evidence to support one above the other in moderate hyperbilirubinemia. Intensive PT must be ensured for neonates nearing BET threshold. It is not necessary to measure spectral irradiance before each use of PT; however it is important to perform periodic checks of PT units to make sure that an adequate irradiance is being delivered. Double surface PT should be started whenever possible and there is evidence to suggest its superiority over single surface PT.[26] Use of locally made wooden devices/devices without electrical fitting certification has been associated with fatal accidents and is therefore strongly discouraged.

d) Increasing the delivered irradiance

Irradiance can be increased by decreasing the distance between baby and the PT unit to as low as 10 cm (only if using CFL/LED lamps). Sides of bassinet, incubator or warmer can be lined with aluminum foil or white material to increase the irradiance, but the evidence for clinical benefit is not conclusive. In a RCT done at a tertiary care centre it was concluded that, though hanging of white reflective sling on sides of CFT PT equipment resulted in marginal increase in irradiance, it did not decrease the duration of PT.[27] However in an another RCT done at Malaysia on term newborns with uncomplicated neonatal jaundice it was concluded that hanging white curtains around PT units significantly increases efficacy of PT in the treatment of neonatal jaundice without evidence of increased adverse effects.[28]

e) Stopping of PT

PT may be discontinued when serum bilirubin level has fallen below 2mgs/dL lower than the PT threshold for that postnatal age. Discharge from the hospital need not be delayed to observe the infant for rebound provided investigations have shown a non-hemolytic etiology for the jaundice and an early follow up after discharge is assured. If PT is used for infants with hemolytic diseases or is initiated early and discontinued before the infant is 3 to 4 days old, a follow-up bilirubin measurement within 24 hours after discharge is recommended. For infants who are readmitted with hyperbilirubinemia and then discharged, significant rebound is rare, but a repeat TSB measurement or follow-up 24 hours after discharge is an option. In a prospective observational study it was observed that post-PT neonatal bilirubin rebound to clinically significant levels may occur, especially in cases of prematurity, direct Coombs test positivity, and those treated $\leq$ 72 hours. These risk factors should be taken into account when planning post-PT follow up.[29]

f) Care of newborns under PT

Breastfed infants should continue breastfeeding every 2-3 hourly. Infants with inadequate oral intake, excessive weight loss (>10%), or clinical or biochemical evidence of dehydration should receive supplemental breast milk or formula. Intravenous fluids should be given if enteral feeding is unsuccessful and the infant is dehydrated. The infant should be nursed naked except for diapers (use diapers and nappy pads only if deemed necessary and cut them to the minimum possible size), and the eyes should be covered with an opaque cloth (soft, preferably made of cotton) to reduce the risk of retinal damage. Older data suggested that PT was associated with increased insensible water loss; therefore, many clinicians have routinely added a certain percentage to the infant's estimated basic fluid requirements. Newer data suggest that if temperature homeostasis is maintained, fluid loss is not significantly increased by PT. Rather than instituting blanket increases of fluid supplements to all infants receiving PT, fluid supplementation should be tailored to the infant's individual needs, as measured through evaluation of daily weight, urine output measurements, urine specific gravity, and fecal water loss supplemented by biochemical tests, wherever essential.

g) Failure of PT

Failure of PT has been defined as an inability to observe a decline in bilirubin of 1-2 mg/dL after 4-6 hours and/or to keep the bilirubin below the BET level. BET is recommended if the TSB rises to these levels despite intensive PT. For readmitted infants, if the TSB level is above the exchange level, intensive PT should be started pending arrangement for BET. One may consider a repeat TSB measurement just prior to the procedure to confirm the TSB levels are still above the exchange level. However, a BET should be performed at the suspicion of bilirubin encephalopathy irrespective of the bilirubin value.

h) Indications for a BET

The decision to do exchange is based on the TSB value for that postnatal age, level of sickness of the baby, the likely etiology of jaundice, and presence or absence of bilirubin encephalopathy. Important risk factors to consider exchange at lower TSB levels include presence of **A**cidosis, low **A**lbumin level, **B**lood brain barrier disruption (e.g. intracranial hemorrhage, asphyxia, sepsis, meningitis), **C**oomb's positive jaundice, G6P**D** deficiency, **D**isplacers of bilirubin (e.g. FFA from intralipid, ibuprofen, ceftriaxone) and **E**ncephalopathy.

One should consider an early BET in case of hydrops (may require a initial partial exchange followed by a double volume BET), history of previous sibling requiring exchange because of Rh isoimmunisation, cord Hb <11 gm/dL, cord TSB >5mg/dL, rate of rise of TSB >1mg/dL/hr despite PT or rise >0.5mg/dL/hr despite PT if Hb is between 11-13gm/dL, any TSB >12mg/dL in first 24hrs and TSB >20mg/dL in the neonatal period.

i) Procedure of BET

Type and volume of blood*:* For 'Rh' isoimmunization, the best choice would be O negative packed cells suspended in AB positive plasma. O negative whole blood or cross-matched baby's blood group (Rh negative) may also be used. For 'ABO' isoimmunization, O group (Rh compatible) packed cells suspended in AB plasma or O group whole blood (Rh compatible with baby) should be used. In other situations baby's blood group should be used. All blood must be cross matched against maternal plasma.

Blood volume: 2 x (80-100 ml/kg) x birth weight in Kg. In a prospective observational study done at a tertiary care centre it was concluded that BET with G6PD-deficient donor blood leads to a lesser drop in post-exchange TSB.[30] It prolongs the duration of PT and increases the need for repeat BETs. However, due to absence of round the clock availability of the G6PD measurements in most of health facilities, routine screening of donor blood cannot be recommended at present.

Single versus double volume BET*:* A recent Cochrane review on the topic concluded that there was insufficient evidence to support or refute the use of single volume BET as opposed to double volume BET in jaundiced newborns.[31] A change from the current practice of double volume BETs for severe jaundice in newborns infant, cannot be recommended based on current evidence.

Route of exchange (peripheral vs. umbilical)*:* A retrospective study done to compare the efficiency and safety of BET by using peripheral arteries and veins with that of conventional BET via the umbilical vein in treating neonatal pathologic hyperbilirubinemia, concluded that BET using peripheral arteries and veins is efficient and effective in reducing serum bilirubin from circulation and is associated with few adverse events.[32] However, placing a peripheral arterial line may require more expertise in comparison to an umbilical venous line.

Intravenous albumin infusion before blood exchange: In an RCT done on intravenous albumin infusion before blood exchange on south Iranian term neonates, it was concluded that infusion of 20% albumin (1g/kg) one hour prior to blood exchange can significantly reduced the post exchange total serum bilirubin and duration of PT. However there are concerns about safety of this approach and routine use of albumin cannot be recommended based on the current evidence.

j) Complications of BET

Death associated with BET has been reported in approximately 3 in 1000 procedures. Significant morbidity (apnea, bradycardia, cyanosis, vasospasm, thrombosis, necrotizing enterocolitis) occurs in as many as 5% of BETs, and the risks associated with the use of blood products must always be considered.[7] Incidence of complications may be higher in developing countries. Hence BET should be performed only by trained personnel in a neonatal nursery with full monitoring including ECG and resuscitation capabilities.

Recommendations:

1. PT and BET cut off should be decided based on the baby's gestation/birth weight, hours of life and presence or absence of risk factors (using cut-offs published by AAP).
2. Intensive PT covering maximum possible surface area should be used in cases of TSB approaching critical levels.
3. Use of locally made wooden devices/devices without certified electrical fittings has been associated with fatal accidents and is therefore strongly discouraged.
4. Different light sources including standard length tube-lights, CFT lights and LED lights may be used as long as the desired irradiance is delivered and source-specific precautions are followed.
5. There is no role of prophylactic PT in preterm neonates.
6. BET should be done by central or peripheral route aiming replacement of double the baby's blood volume and should be done by skilled personnel in a well-equipped centre.

Monitoring for progression of jaundice and response to treatment

Assessment of the severity of jaundice

a) **Clinical assessment:** Clinical judgment, which is widely used for the initial assessment of jaundice, is based on the cephalo-caudal progression of jaundice (Kramer's rule). Visual assessment of jaundice should be performed in an adequately illuminated room (day light or white fluorescent light). Skin should be blanched by digital pressure, revealing the underlying color of skin and subcutaneous tissue. Level of total serum bilirubin (TSB) is based on extent of yellowish discoloration (light or deep) and dermal zone of icterus.[33] Extent of jaundice thus detected gives a rough estimate of serum bilirubin. Once bilirubin levels are more than 15 mg/dl, it results in staining of soles and palms. But questions have been raised about the utility of clinical assessment especially in dark colored infants or when TSB is more than 15 mg%. In a study by Lodha R et al, clinical examination was found to have a sensitivity of 52.2% in detecting hyperbilirubinemia >13 mg%.[10] AAP advises frequent clinical assessment during early neonatal period but cautions against completely relying on the clinically assessed level of TSB.[7] World Health Organization (WHO) in its guide for managing newborn problems relies heavily on clinical assessment for deciding need for starting PT or referral. Guidelines label jaundice as severe if it appears on day 1, involves arms and legs on day 2 and hands and feet on day 3 or thereafter.[34] These guidelines may be useful in certain settings like assessment during home visits by peripheral health workers or in a district hospital/first referral unit when facility for TSB measurement is not available during 'off-hours'. However, validity and reliability of clinical assessment of bilirubin in different cadres of health workers needs testing.

b) **Transcutaneous bilirubin (TcB) estimation**

Transcutaneous bilimeter although an objective method of assessing the degree of jaundice cannot substitute for TSB estimation particularly for babies with serum bilirubin >13 mg/dl.[10] When used as screening tool TcB measurement has been shown to reduce the need of blood sampling in healthy term and near-term north Indian neonates.[35] Further studies are needed to assess cost-effectiveness of this strategy, especially in Asian neonates.

c) **Total Serum Bilirubin (TSB) estimation**

TSB estimation can be done by various methods including laboratory dependent High Performance Liquid Chromatography (HPLC) or Diazo methods and bedside estimation using a spectrophotometer. Later method uses very small amount of blood sample, is rapid and accurate if routine calibrations are carried out. Till now, the laboratory estimation by HPLC is considered to be the gold standard followed by estimation by Diazo method.

Monitoring response to therapy

Studies performed on Indian neonates under PT for moderately high levels of TSB due to non-hemolytic significant jaundice have demonstrated a rate of decline of about 0.2 mg/dL/h.[20, 25, 27]. In neonates with higher TSB levels this decline may be faster. If initial TSB levels are near BET range, repeat measurement may be done after 4-6 h of intensive PT. Once a declining trend has been documented and levels are no longer near BET threshold, TSB may be monitored every 8-12 h. Due to blanching of skin, clinical assessment and TcB measurement are not useful when baby is under PT.

Rebound rise in bilirubin has been reported in about 7% neonates after stopping PT.[29] Neonates with gestation at birth<35 weeks, birth weight<2000 gm and onset of jaundice at <60 h of postnatal age are at higher-risk.[29] Post-PT discharge and follow-up planning should take these risk factors into account.

Recommendations:

1. All neonates should be monitored clinically for appearance of jaundice during first postnatal week. Frequency of monitoring should be twice daily during first 72 h and daily thereafter.
2. TcB measurements can reduce the need for estimating TSB. TSB measurement should be considered if clinical and/or TcB assessment is within 2-3 mg/dL or 80% of age-specific threshold for starting PT. If TcB is use, a value of >13 mg/dL should be confirmed with a TSB estimation.
3. A point of care testing instrument e.g. a spectrophotometer which negates the effect of hemoglobin and other serum solutes while estimating TSB should be available in neonatal nurseries.
4. WHO clinical criteria for severe jaundice (outlined above) may be used by peripheral health workers for assessment during home visits or while deciding the need of treatment/referral if facility for TSB measurement is not available.
5. During PT, depending on severity of hyperbilirubinemia, TSB should be monitored every 4-12 h.
6. Post-PT discharge and follow-up planning should take into account the possibility of rebound rise in bilirubin after stopping PT.

Role of additional therapies in prevention/treatment of jaundice

In addition to PT and BET various other pharmacological agents/approaches have been investigated to prevent or treat significant jaundice. These include phenobarbitone, immunoglobulin, tin mesoporphyrins, clofibrate, zinc and fluid supplementation. These therapeutic modalities either decrease the peak TSB or the duration of hyperbilirubinemia thereby decreasing the duration of PT and the need for EBT. In addition, a decrease in interventions may decrease morbidities like fluid and electrolyte imbalance, patent ductus arteriosus, intraventricular hemorrhage and nosocomial infection.

a) Phenobarbitone: Phenobarbitone induces the activity of uridine-di-phosphate glucuronyl transferase (UDPGT) enzyme. Three RCTs (one conducted in Indian neonates) have investigated the efficacy of phenobarbitone in very low birth weight (VLBW) neonates.[36] A meta-analysis of these three studies has concluded that phenobarbitone reduces peak serum bilirubin, duration and need of PT and need of BET in preterm VLBW neonates.[37] Although no major adverse events have been reported, reporting on neurodevelopmental outcome is lacking. Arya et al investigated use of prophylactic phenobarbitone in neonates with cord bilirubin >2.5 mg/dL and did not find any difference in the need of PT or incidence of bilirubin level >13 mg/dL.[38] Similarly, Murki S et al studied the role of prophylactic phenobarbitone in neonates with G6PD deficiency and did not observe any significant difference in need of PT or BET.[39]

b) Fluid supplementation: Subclinical dehydration due to evaporative losses and poor intake of breast milk can lead to an increased incidence and severity of jaundice in newborns. In the only published RCT, Mehta S et al have investigated role of intravenous fluid supplementation in treating extreme hyperbilirubinemia in term neonates and they observed a decrease in the need of BET and duration of PT [40]. These findings and incidence of severe hyperbilirubinemia attributable to dehydration need to be confirmed in further studies. Furthermore, IV fluid administration has been reported to be a risk factor for development of nosocomial infection, though in this study, there was no increase in sepsis rates.

c) **Intravenous immunoglobulins (IVIG):** IVIG therapy inhibits hemolytic breakdown of red blood cells by causing non-specific blockade of Fc receptors in the reticulo-endothelial system. Significant reduction in maximum TSB and the need for BET has been reported in a meta-analysis which included 3 studies that investigated the role of IVIG in hemolytic anemia.[41] However, there was a trend towards increased need for packed cell transfusion due to anemia after first week of life. No significant difference was observed in a small RCT comparing 0.5 and 1.0 gm/kg dose of IVIG.[42] With present body of evidence use of IVIG can be recommended if TSB is reaching exchange threshold (within 2-3 mg/dL) in proven cases of iso-immune hemolytic anemia (positive direct Coomb's test). If neonate is not already under PT, a trial of intensive PT for 4-6 h may obviate the need of IVIG therapy. In addition, it must be emphasized that not all newborns with a positive DCT will necessarily develop hyperbilirubinemia and IVIG should not be administered until it is apparent that hyperbilirubinemia is progressing. There are limitations in design of published studies and short- and long-term benefits/harms of IVIG need to be investigated in a well-designed RCT. Furthermore, there are many other unanswered questions regarding optimum timing (prophylactic after or before BET or when bilirubin levels are reaching exchange threshold) and the optimal dose of IVIG.

d) **Other agents**: These include Clofibrate, tin-mesoporphyrins, agar and zinc. Due to lack of consistent effect or concern about long-term side effects, these agents are not recommended at present.

Recommendations:

1. IVIG may be used in the dose of 0.5-1g/kg for decreasing the need of EBT in neonates with proven isoimmune hemolytic jaundice (established hyperbilirubinemia with positive direct Coomb's test or hydrops fetalis). In case BET is imminent, IVIG may be given after completing the procedure.
2. Supplemental intravenous fluids in neonates presenting with severe hyperbilirubinemia in the emergency may have a role in decreasing the need of BET but needs careful monitoring for potential complications.
3. Other agents like phenobarbitone and clofibrate are not recommended due to either lack of efficacy or concerns regarding medium and long term adverse effects.

Long-term morbidities associated with pathological hyperbilirubinemia and followup plan

Major long-term morbidities associated with pathological hyperbilirubinemia include sensori-neural hearing loss (SNHL) and cerebral palsy. Transient abnormalities in brainstem auditory evoked response has been observed during severe hyperbilirubinemia, usually with levels >20 mg/dL.[16,43] With rapid institution of treatment, these changes were usually reversed. Similarly, early clinical markers of BIND may be observed during severe hyperbilirubinemia and were reversed as TSB falls with institution of treatment. In absence of overt signs of BIND, significant jaundice has not been associated with other 'milder' forms of brain damage like intellectual function, learning disability or behavioral changes.

Recommendations:

1. Based on the existing evidence, it is recommended that all neonates with peak TSB > 20 mg/dL or where there was a need for BET should be followed up and screened for SNHL and abnormalities of tone, posture and movements.
2. Hearing screening should preferably be conducted before 3 months of age by BAER as oto-acoustic emission may be normal in some cases.

3. Clinical examination for motor dysfunction should be conducted at 3, 6, 9, 12 and 18-24 months of age.

References

1.Ip S, Chung M, Kulig J, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004;114:e130-53
2.Report 2002-2003: National Neonatal Perinatal Database Network. New Delhi: National Neonatology Forum of India; 2004.
3.Report 2002-2003: National Neonatal Perinatal Database Human Reproduction Research Centre Network. New Delhi:National Neonatology Forum of India; 2006.
4.Report 2000: National Neonatal Perinatal Database Network. New Delhi: National Neonatology Forum of India; 2001.
5.Narang A, Kumar P, Kumar R. Neonatal jaundice in very low birth weight babies. Indian J Pediatr 2001;68:307-9.
6.Narang A, Gathwala G, Kumar P. Neonatal jaundice: an analysis of 551 cases. Indian Pediatr 1997;34:429-32.
7.Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:297-316.
8.Agarwal R, Kaushal M, Aggarwal R, Paul VK, Deorari AK. Early neonatal hyperbilirubinemia using first day serum bilirubin level. Indian Pediatr 2002;39:724-30.
9.Awasthi S, Rehman H. Early prediction of neonatal hyperbilirubinemia. Indian J Pediatr 1998;65:131-9.
10.Lodha R, Deorari AK, Jatana V, Paul VK. Non-invasive estimation of total serum bilirubin by multi-wavelength spectral reflectance in neonates. Indian Pediatr 2000;37:771-5.
11.Bhat YR, Rao A. Transcutaneous bilirubin in predicting hyperbilirubinemia in term neonates. Indian J Pediatr 2008;75:119-23.
12.Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999;103:6-14.
13.Mishra S, Chawla D, Agarwal R, Deorari AK, Paul VK. Indian J Pediatr 2010; 77:45-50
14.Murki S, Kumar P, Majumdar S, Marwaha N, Narang A. Risk factors for kernicterus in term babies with non-hemolytic jaundice. Indian Pediatr 2001;38:757-62.
15.Dhaded SM, Kumar P, Narang A. Safe bilirubin level for term babies with non-hemolytic jaundice. Indian Pediatr 1996;33:1059-60.
16.Agrawal VK, Shukla R, Misra PK, Kapoor RK, Malik GK. Brainstem auditory evoked response in newborns with hyperbilirubinemia. Indian Pediatr 1998;35:513-8.
17.Banerjee TK, Hazra A, Biswas A, et al. Neurological disorders in children and adolescents. Indian J Pediatr 2009;76:139- 46.
18.State of India's Newborns. National Neonatology Forum of India and Save the Children US. Washington DC; 2004.
19.Pejaver RK, Vishwanath J. An audit of PT units. Indian J Pediatr 2000;67:883-4.
20.Sarin M, Dutta S, Narang A. Randomized controlled trial of compact fluorescent lamp versus standard PT for the treatment of neonatal hyperbilirubinemia. Indian Pediatr 2006;43:583-90.
21.Morris BH, Oh W, Tyson JE, et al. Aggressive vs. conservative PT for infants with extremely low birth weight. N Engl J Med 2008;359:1885-96.
22.Curtis-Cohen M, Stahl GE, Costarino AT, Polin RA. Randomized trial of prophylactic PT in the infant with very low birth weight. J Pediatr 1985;107:121-4.
23.Tripathi S, Saili A. Effect of prophylactic PT on neonatal hyperbilirubinemia of prematures. Indian J Med Sci 2006;60:385-7.
24.Jangaard KA, Vincer MJ, Allen AC. A randomized trial of aggressive versus conservative PT for hyperbilirubinemia in infants weighing less than 1500 g: Short- and long-term outcomes. Paediatr Child Health 2007;12:853-8.
25.Kumar P, Murki S, Malik GK, et al. Light-emitting diodes versus compact fluorescent tubes for PT in neonatal jaundice: A multi-center randomized controlled trial. Indian Pediatr 2009:PII:S097475590800565-1.

26.Sarici SU, Alpay F, Unay B, Ozcan O, Gokcay E. Double versus single PT in term newborns with significant hyperbilirubinemia. J Trop Pediatr 2000;46:36-9.
27.Sivanandan S, Chawla D, Misra S, Agarwal R, Deorari AK. Effect of sling application on efficacy of PT in healthy term neonates with nonhemolytic jaundice: a randomized conrolled trial. Indian Pediatr 2009;46:23-8.
28.Djokomuljanto S, Quah BS, Surini Y, et al. Efficacy of PT for neonatal jaundice is increased by the use of low-cost white reflecting curtains. Arch Dis Child Fetal Neonatal Ed 2006;91:F439-42.
29.Bansal A, Jain S, Parmar V, Chawla D. Bilirubin rebound after intensive PT for neonatal jaundice. In: XXVIII Annual conference of National Neonatology Forum of India; 2008; Kolkata; 2008.
30.Samanta S, Kumar P, Kishore SS, Garewal G, Narang A. Donor blood glucose 6-phosphate dehydrogenase deficiency reduces the efficacy of BET in neonatal hyperbilirubinemia. Pediatrics 2009;123:e96-e100.
31.Thayyil S, Milligan DW. Single versus double volume BET in jaundiced newborn infants. Cochrane Database Syst Rev 2006:CD004592.
32.Chen HN, Lee ML, Tsao LY. BET using peripheral vessels is safe and effective in newborn infants. Pediatrics 2008;122:e905-10.
33.Kramer LI. Advancement of dermal icterus in the jaundiced newborn. Am J Dis Child 1969;118:454-8.
34.Managing newborn problems: A guide for doctors, nurses, and midwives. Geneva: World Health Organization; 2003.
35.Mishra S, Chawla D, Agarwal R. Comparison of transcutaneous bilirubinometry and visual assessment of level of jaundice in term and near-term neonates of deciding the need for blood sampling: A randomized trial and economic evaluation. In: XXVII Annual conference of National Neonatology Forum of India; 2007; Pune; 2007.
36.Kumar R, Narang A, Kumar P, Garewal G. Phenobarbitone prophylaxis for neonatal jaundice in babies with birth weight 1000-1499 grams. Indian Pediatr 2002;39:945-51.
37.Chawla D, Parmar V. Phenobarbitone for prevention and treatment of unconjugated hyperbilirubinemia in preterm neonates: A systematic review and meta-analysis. Indian Pediatr 2009:PII:S097475590800485-1.
38.Arya VB, Agarwal R, Paul VK, Deorari AK. Efficacy of oral phenobarbitone in term "at risk" neonates in decreasing neonatal hyperbilirubinemia: a randomized double-blinded, placebo controlled trial. Indian Pediatr 2004;41:327-32.
39.Murki S, Dutta S, Narang A, Sarkar U, Garewal G. A randomized, triple-blind, placebo-controlled trial of prophylactic oral phenobarbital to reduce the need for PT in G6PD-deficient neonates. J Perinatol 2005;25:325-30.
40.Mehta S, Kumar P, Narang A. A randomized controlled trial of fluid supplementation in term neonates with severe hyperbilirubinemia. J Pediatr 2005;147:781-5.
41.Alcock GS, Liley H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. Cochrane Database Syst Rev 2002:CD003313.
42.Girish G, Chawla D, Agarwal R, Paul VK, Deorari AK. Efficacy of two dose regimes of intravenous immunoglobulin in Rh hemolytic disease of newborn: a randomized controlled trial. Indian Pediatr 2008;45:653-9.
43.Deorari AK, Singh M, Ahuja GK, et al. One year outcome of babies with severe neonatal hyperbilirubinemia and reversible abnormality in brainstem auditory evoked responses. Indian Pediatr 1994;31:915-21.

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Management of Neonatal Sepsis

Summary of Recommendations

- **In India, both early and late onset sepsis are caused by similar organisms with similar antibiotic sensitivities.**
- **Clinical features of neonatal sepsis are non-specific and any unexplained clinical deterioration should be investigated for sepsis.**
- **There is no role of performing sepsis screen in early onset neonatal sepsis.**
- **Lumbar puncture (LP) for CSF examination must be performed in all symptomatic neonates being initiated on antibiotics, with the exception of premature neonates presenting with respiratory distress at birth with no risk factors for sepsis.**
- **The traditional cut-offs for interpretation of cerebrospinal fluid values are based on relatively old studies with methodological problems. A new set of guidelines for interpretation is proposed.**
- **Routine urine culture in all neonates with non-specific symptoms is not recommended.**
- **Every newborn unit must have its own antibiotic policy based on the local sensitivity patterns and the profile of pathogens.**
- **Apart from appropriate antibiotics, the survival of a sick septic newborn often depends upon aggressive supportive care.**
- **There may be a potential role of intravenous immunoglobulins in treatment of neonatal sepsis but larger studies are required. There is currently no role for the use of colony stimulating factors.**

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Introduction

Neonatal infections are estimated to cause about 1.6 million deaths worldwide and 40% of all neonatal deaths due to sepsis occur in developing countries. Even though neonatal care has dramatically improved over the last decade, the overall as well as gestation specific mortality due to sepsis has not changed much due to more and more smaller babies surviving in the intensive care units. This guideline includes the following issues related to identification and management of neonatal sepsis :

- Presentation of neonatal sepsis according to the time of onset
- Clinical signs associated with neonatal sepsis
- Approach to a neonate with suspected early onset sepsis (EOS)
- Approach to a neonate with suspected late onset sepsis (LOS)
- Pre-requisites for blood culture
- Interpretation of cerebro-spinal fluid (CSF) examination
- Symptoms and management of urinary tract infections (UTI) in neonates
- Antibiotic therapy – empirical, upgradation and modification
- Duration of antibiotic therapy
- Supportive care of a sick and septic neonate

Presentation of neonatal sepsis according to the time of onset

Evidence: Neonatal sepsis can broadly classified in to Early-onset sepsis (<72 hours) and Late onset sepsis (>72 hours). Early onset sepsis (EOS) often presents as a fulminant, multi-system illness within 72 hours of delivery and is mainly due to bacteria acquired before and during delivery whereas late onset sepsis (LOS) is due to bacteria acquired after delivery (nosocomial or community sources) and can present as either a fulminant or a smoldering infection. EOS presents with prominent respiratory signs while LOS has more varied presentations. In the Indian subcontinent, the distinction between EOS and LOS is somewhat blurred [1]**.** The clinical presentations of EOS and LOS are different and the risk factors are different, but the organisms causing the EOS and LOS are similar and so are their antibiograms [2, 3]

Recommendations: Even though conventionally neonatal sepsis has been classified as EOS and LOS with 72 hours of life as a common demarcation, the clinical information available from the Indian subcontinent suggests similar type of organisms associated with both types of sepsis with respect to clinical presentation, severity and antibiotic sensitivity.

Clinical signs associated with neonatal sepsis

A neonate responds in a stereotyped way to a variety of stressors. Therefore the possibility of sepsis must be considered with any clinical deterioration unless the event is readily explained by other causes.

Evidence: Six studies addressing the issue of clinical signs in nosocomial sepsis were located. Three of these are from developing countries [4-6]. Of them, Okascharoen et al included all hospitalised neonates [4], Singh et al included all neonates admitted to the neonatal intensive care unit (NICU) [6] and Rosenberg et al limited their study to neonates ≤33 weeks of gestation [5]. The signs include lethargy/hypotonia, tachycardia, fever, abdominal distension, increased aspirates, retractions, grunting, hypotension/delayed

capillary refill, pallor, jaundice, hepatomegaly, apnea, abnormal skin color, bradycardia and increased ventilator requirements. There is no evidence that the signs are different in preterm and term infants. Late clinical signs are indicative of severe septicemia: sclerema, shock, features of disseminated intravascular coagulation, pulmonary hemorrhage, collapse.

Recommendations: The available evidence indicates a list of clinical signs which are more specific for neonatal sepsis. However, any neonate with an unexplained clinical deterioration of any form should be investigated and managed in the lines of sepsis unless proven otherwise.

Approach to a neonate with suspected EOS

Evidence:

a) *Role of sepsis screen in EOS*: There is no rationale for performing a "sepsis screen" (i.e. CRP, hematological parameters, micro ESR) in suspected EOS. The negative predictive value (NPV) of various sepsis screen parameters is too low to confidently rule out EOS [7, 8]. Procalcitonin and IL-6 are more promising than the standard screen for the diagnosis of EOS, but they are currently not easily available on the bedside and are not considered standards of care.

b) *Symptomatic neonates*: Neonates who turn symptomatic within 72 hours must be clinically assessed for probability of sepsis. Twenty percent of symptomatic neonates in India suspected to have EOS are blood culture positive [8].

The following neonates need not be immediately started on antibiotics but their clinical course must be carefully monitored:

- Those who are born *without* any of the known risk factors of sepsis [preterm, premature rupture of membranes (pPROM), prolonged rupture of membranes (PROM) >18 hrs, spontaneous preterm onset of labor (SPTOL), clinical chorioamnionitis, foul smelling liquor, unclean vaginal examinations, maternal fever, maternal urinary or other systemic infections, frequent (>3) per vaginal examinations in labor, perinatal asphyxia, and maternal recto-vaginal group B *Streptococcus* carriage], AND
- Chest X ray is *not* suggestive of pneumonia AND
- Have alternative reasons to explain the symptoms.

Those symptomatic neonates with any of the known risk factors or who have a chest X-ray suggestive of pneumonia or do not have any alternate explanation for the signs, must be immediately started on antibiotics after drawing a blood culture. Lumbar puncture (LP) for CSF examination must be performed in all symptomatic neonates, with the exception of premature neonates presenting with respiratory distress at birth with no risk factors for sepsis [9, 10]. The decision for performing LP should not be based on sepsis screen results or blood culture results.

c) *Asymptomatic neonates with presence of risk factors for sepsis*:

All neonates, especially those who are premature, must be evaluated for presence of risk factors of EOS, as elucidated above. It must be appreciated that most of these risk factors were described in studies where no intra-partum antibiotic prophylaxis had been given to the mothers. In the presence of intra-partum antibiotic prophylaxis, many of these may get modified or cease to be risk factors

altogether. However, in the absence of intra-partum antibiotic prophylaxis, all the above risk factors are pertinent.

A number of risk scores have been devised for asymptomatic neonates at risk of EOS [11-14]. Risk factors identified in these studies were: birth asphyxia, unclean vaginal examination, foul smelling liquor, labor >24 hrs, DROM >24 hrs, birth weight <2 kg, prematurity, maternal fever, gastric polymorphs >20/high power field and meconium stained liquor. These published scores have several drawbacks: weightage was allotted arbitrarily, multi-variable analysis was not performed, and the issue of maternal antibiotics was ignored.

To circumvent these drawbacks, a risk score was generated based on the multi-variable analysis of data from a prospective cohort study of 600 mother-infant dyads in a setting where there was a routine policy to give intrapartum antibiotic prophylaxis for known risk factors; and this score was later validated in a RCT [15, 16]. The independent risk factors among neonates <35 weeks of gestation, who remain asymptomatic until 2 hours of life, are as follows: Intra-partum per vaginal examinations ≥3, clinical chorioamnionitis*, birth weight <1.5 kg, male gender, not received intrapartum antibiotics** and gestation ≤30 weeks.

*Clinical chorioamnionitis: intra-partum fever (>37.8°C) with ≥2 of the following features: fetal tachycardia, uterine tenderness, malodorous vaginal discharge, maternal leucocytosis (TLC > 15,000).

**Antibiotics started <4 hours prior to delivery also classified as "Not received antibiotics"

Neonates with extreme risk factors (a) very prolonged rupture of membranes (≥72 hours), (b) very prolonged labor (≥24 hours), (c) foul smelling liquor, (d) unclean per vaginal examinations, (e) maternal septicemia or other systemic infections, must be started on empirical antibiotics, irrespective of the score.

Recommendations:

- There is no role for performing a "sepsis screen" in suspected EOS.
- Neonates who turn symptomatic within 72 hours but have no risk factor for sepsis or CXR is not suggestive of pneumonia or the symptoms can be explained by other illnesses need not be started on antibiotics immediately. Instead the clinical course of these neonates should be continuously monitored. On the other hand, symptomatic neonates with presence of either of the above supportive features should be started on antibiotics.
- Asymptomatic neonate with risk factors for sepsis may be evaluated using any one of the risk factors scoring system to take a decision regarding starting antibiotics.

Approach to a neonate with suspected LOS

Evidence:

a) Neonates who become symptomatic after 72 hours must be evaluated for LOS. The clinical signs mentioned above can be used as a guide. Overall, 30% neonates clinically suspected to have LOS in an NICU setting have positive blood culture. [6]

b) A single episode or transient presence of one of the above signs may not warrant any action. The more persistent the sign the more likely it is associated with LOS. [17]

c) Based on clinical assessment the neonate must be categorized into those with low probability of sepsis or high probability of sepsis. The rule of thumb is "low probability" represents situations where the clinician would be willing to withhold antibiotics if the sepsis screen is negative. Those assessed to have a low probability of sepsis (eg. single episode of apnea or vomiting, but otherwise well) should undergo a sepsis screen. The purpose of the sepsis screen is to rule out sepsis rather than to rule in sepsis. Traditionally, the sepsis screen consists of 4 items: C-reactive protein (CRP), absolute neutrophil count (ANC), immature to total neutrophil ratio (ITR) and micro-erythrocyte sedimentation rate (µ-ESR).

- CRP: Quantitative CRP assayed by nephelometry is superior to CRP by ELISA and semi-quantitative CRP by a latex agglutination kit. Cut-off value for quantitative assay is10 mg/L.
- ANC: It must be read off Manroe's charts or Mouzinho's chart, depending on whether it is a term baby or a preterm baby respectively [17, 18]
- ITR: Value above 27% in term babies is considered positive.[18] For preterms, it is considered to be 20%. ITR is defined as

$$\frac{\text{Immature neutrophils (band forms, metamyelocytes, myelocytes)}}{\text{Mature + immature neutrophils}}$$

- µ-ESR. Value (in mm in first hour) of more than 3+ age in days in the first week of life or more than 10 thereafter is considered positive.

d) Two systematic reviews on sepsis screens reached the same conclusions- that there is no ideal test or combination of tests which achieves an $LR^+ \geq 10$ or $LR^- \leq 0.1$, which are the benchmarks of an excellent test [19-21]. Overall, the studies on sepsis screen are of poor methodological quality, and the results are too heterogenous to be combined in a meta-analysis. Among the various tests, quantitative CRP is the best, followed by qualitative CRP and immature to total neutrophil ratio.

e) If all the parameters of the sepsis screen are negative in a neonate assessed to have low probability of LOS, antibiotics may not be started and the neonate must be monitored clinically. The screen must be repeated after 12-24 hours. Two consecutive completely negative screens are suggestive of no sepsis. [6]

f) Several authors have evaluated various combinations of screen parameters. Many of our assumptions about the standard sepsis screen are based on the following two studies which were performed in the 1980s (table 1). The practice of designating the screen positive if ≥2 parameters are positive finds its origin in these studies.

Table 1: Diagnostic ability of sepsis screen in neonates

Author	Year	Test	Sensitivity	Specificity	LR^+	LR^-
Philip[25]	1980	Any 2 + ve of: ITR>0.2, WCC<5000, CRP >8 mg/l, ESR >15 mm/1st hr, Haptoglobulin >25 mg/dl	93	88	7.8	0.08
Gerdes[26]	1987	Any 2 + ve of: WCC <5000/mm3, ITR >0.2, and CRP > 1 mg/dL	100	83	5.9	0

g) Since we now realize that CRP is the key parameter in the sepsis screen, a pragmatic approach would be that if the quantitative CRP alone is positive or any two parameters of the sepsis screen are positive, a blood culture must be drawn and empirical antibiotics must be started. A CSF examination must be performed. Meningitis occurs in 3.4% cases of suspected LOS and 25% cases of culture positive LOS [22, 23]

h) Neonates assessed to have a high clinical probability of sepsis (for which the clinician is convinced that antibiotics must be started) may not be subjected to a sepsis screen, because a negative screen would not alter the decision to start antibiotics. A CSF examination must be performed. In recent years, procalcitonin has attracted interest. Head-to-head comparisons with CRP have shown that procalcitonin is superior. [24-26]

Recommendations:

- All neonates who become symptomatic after 72 hours of life with the symptoms suggestive of sepsis must be evaluated for LOS. Evaluation involves categorization of these neonates into those with low probability or high probability of sepsis.
- Perform a sepsis screen in neonates with a low probability for sepsis. If all the parameters of the screen are negative, antibiotics may not be started and the neonate must be monitored clinically. However the screen must be repeated after 12-24 hours. A negative repeat screen strongly indicates against starting antibiotics whereas a positive repeat screen with persistence of symptoms may warrant antibiotics.
- A sepsis screen is not warranted in neonates with a high probability for sepsis. Instead these neonates should be directly started on antibiotics pending blood culture.
- A CSF examination must be performed in all neonates with a high probability of sepsis as well as in those neonates with a low probability of sepsis with a positive sepsis screen .

Pre-requisites for blood culture

Evidence:

The volume of blood inoculated in the culture bottle significantly influences the blood culture positivity. The chance of growing an organism effectively increases following inoculation of 0.5 ml venous blood in a pediatric blood culture bottle or 1 ml in an adult blood culture bottle (if the pediatric bottle is not available) [27-29]. Use of umbilical venous catheters, indwelling arterial lines or capillary blood samples for culture increase the risk of contamination. If catheter-associated sepsis is suspected, a culture should be obtained through the catheter as well as through a peripheral vein. In a prospective observational study from India, 101 cases of suspected neonatal sepsis were used to compare the manual method of blood culture with an automated BacT/Alert system for detection of neonatal septicemia. The mean times to positivity with the manual and BacT/Alert 3D systems were 53.1 h and 14.3 h, respectively ($p < 0.001$). [30] With conventional methods the detection rate is 89.1% by day 2 and 99.5% by day 4.

Recommendations: Inoculation of 0.5 ml of blood is recommended for adequate and appropriate growth in a pediatric blood culture bottle. The physician should ensure a proper aseptic technique before collecting blood to avoid contamination. Automated BacT/Alert systems are equally efficacious in correctly identifying a bacterial growth and they do so in a significantly shorter time.

Performing and interpreting a cerebro-spinal fluid (CSF) examination

Evidence:

Performing a lumbar puncture (LP):

- In an unstable neonate, the LP can be deferred, until stabilization is achieved. The cellular and biochemical abnormalities in the CSF of older patients with bacterial meningitis persist for up to 3 days. Gram positive bacteria clear in 36 hours of appropriate therapy whereas gram negative bacteria may take up to 5 days.
- In a neonate with meningitis not showing clinical recovery after institution of antibiotics, LP should be repeated after 48 hours. If the LP is traumatic, the CSF should be sent for gram stain and culture.
- The concentration of glucose is not significantly altered by a traumatic lumbar puncture. Therefore a low CSF glucose in the setting of a traumatic LP is abnormal. Nothing much is gained by using the various formulas for adjusting the WBC count in a traumatic CSF, based on the RBC counts. Adjustment merely results in a loss of sensitivity with marginal gain in specificity. [31]
- Ideally, the WBC cell count must be performed within 30 minutes of drawing the sample. It must be noted that CSF WBC and glucose rapidly fall with time, giving spurious results. [32]

Interpretation of CSF findings:

- Apart from culture and gram stain, 4 parameters are commonly evaluated: total WBC count (per micro L), percentage neutrophil count, glucose and protein. Traditionally, the following cut-offs have been used: 30 cells, more than 60% of polymorphs, glucose less than 50% of blood glucose, protein more than 150 mg/dL in term babies and 180 mg/dL in preterm babies. These cut-offs are no longer acceptable as they are based on old normative data, and represent an over-simplified approach based on single cut-off points derived from 2 standard deviation values.

- Little data is available on the hospital-based incidence of culture-proven meningitis among cases of suspected sepsis in developing countries. The WHO Young Infant Study had reported that 7.9% lumbar punctures yielded a positive culture among symptomatic infants <3 months of age in a community setting.[33] A hospital-based study from Bangladesh pegged this figure at 4.7%.[34] Therefore, for purposes of deriving a post-test probability of meningitis, a prevalence of 5% among hospitalized cases of suspected sepsis in India can be assumed.
- Among preterm infants, none of the above CSF parameters is satisfactory for the rapid diagnosis of meningitis. In a large study on 4632 preterm infants [35], the area under the ROC curve for CSF WBC count was 0.8 (95% CI 0.73, 0.86), followed by CSF protein 0.72 (0.64, 0.8) and CSF glucose 0.63 (0.54, 0.70). Only tests with an area above 0.8 are considered good tests. The performance of the tests at various cut offs is depicted below, with the derived probability of having meningitis in Indian neonates (table 2).

Table 2: Performance of various CSF parameters in diagnosis of meningitis in preterm infants

	Criterion for positive test	Sensitivity	Specificity	LR^+	LR^-	Probability of meningitis if test (+)	Probability of meningitis if test (-)
1	WBC >10	80	67	2.4	0.3	11	2
2	WBC >20	73	79	3.5	0.3	16	2
3	WBC >25	69	82	3.9	0.4	17	2
4	WBC >100	51	91	5.7	0.5	23	3
5	Glucose <10	18	99	23	0.8	55	4
6	Glucose <24	32	96	8	0.7	30	4
7	Protein >90	96	18	1.2	0.2	6	1
8	Protein >170	61	75	2.4	0.5	11	3
9	#3 and #6 and #8 positive	26	97	8.7	0.8	31	4
10	#3 or #6 or #8 positive	78	65	2.2	0.3	10	2

- Similarly, in a large study among 9111 term neonates, none of the above CSF parameters is satisfactory for the rapid diagnosis of meningitis [36]
- The performance of the tests at various slabs of test results for term babies is depicted in the table below, with the post-test probability of meningitis having been derived for Indian babies (table 3):

Table 3: Performance of various CSF parameters in diagnosis of meningitis in term infants

No.	Result criterion	Sensitivity	Specificity	LR of the test result	Post-test probability of meningitis
1	WBC= 1 to 8	97	11	1.09	5
2	WBC= 9 to 21	83	61	2.1	10
3	WBC= 22 to 100	79	81	4.2	18
4	WBC >100	66	94	11	37
5	Glucose <20	44	98	22	54
6	Glucose 20-60	89	20	1.1	5
7	Protein= 41 to 89	100	2	1.02	5
8	Protein= 90-120	84	28	1.2	6
9	Protein >120	76	63	2	10

- Meningitis being a dangerous disease, one may assume that any neonate with ≥10% probability of having meningitis must be treated and only those with ≤3% probability can be left alone.

Recommendations:

- *Preterm infants*: Treat if CSF WBC count ≥10 OR glucose <24 OR protein >170. Do not treat if "CSF WBC count <25 AND glucose ≥25 AND protein <170". For in-between results, clinical judgment will have to be used, keeping in mind clinical features (seizures, degree of altered sensorium, fullness of fontanelles) and prematurity (the lower the gestation, lower should be the threshold for diagnosis).
- *Term infants*: Treat if CSF WBC count >8 OR glucose <20 OR protein >120. There is no safe cut-off at which one can recommend "do not treat". Clinical judgment as above would have to be used.

Symptoms and management of urinary tract infections (UTI) in neonates

Evidence:

- The signs of UTI in neonates are nonspecific and varied. The common clinical signs in cases of UTI in neonates are - failure to thrive (50%), fever (39%), vomiting (37%), diarrhoea (25%), cyanosis (23%), jaundice (18%) and irritability & lethargy (17%). The yield of a routine urine culture is very less [37, 38].
- Routine urine microscopy has poor correlation with culture and must not be relied upon for diagnosing UTI. More accurate microscopic analysis of uncentrifuged urine can be performed with a hemocytometer and reporting cells per cubic millimeter. With hemocytometer, a cutoff of ≥10 WBCs/mL has a sensitivity of 82%, specificity 94%, LR^+ 12.7 and LR^- 0.19 [39].

- Urine culture must always be performed on a sample obtained by a supra-pubic puncture or by a fresh bladder catheter. In neonates, use of ultrasound guidance simplifies supra-pubic aspiration and improves the diagnostic yield of obtaining a urine specimen from 60% to almost 97% [40].

Recommendations:

- Routine urine culture in all neonates with non-specific symptoms is not recommended.
- Neonates with the above clinical signs, or septic neonates with LOS or who are VLBW or have known urinary tract anomalies or have had previous or on-going bladder catheterization or visibly turbid urine should be investigated for UTI.
- Urine analysis should be performed with a hemocytometer on uncentrifuged urine and the cells should be reported as number per cubic millimeter.
- Supra pubic aspiration is the ideal method of sample collection in cases of suspected UTI. Bag sample and free flow sample are highly prone for contamination and may increase the diagnostic dilemma of the clinician and hence should be avoided.

Antibiotic therapy – empirical, upgradation and modification

Evidence *and Recommendations*:

There is generally no distinction in the choice of empirical antibiotics, be it suspected EOS or LOS as the bacterial and sensitivity profile in India seems to be is similar in both situations. [1 - 3].

Starting empirical antibiotics

As the profile of organisms is similar for EOS and LOS, the following policies can be used irrespective of whether it is EOS or LOS.

Policy for community acquired sepsis [41]

- Ampicillin + Gentamicin/Amikacin (empirical)
- If evidence of staphylococcus : Cloxacillin + Gentamycin/Amikacin
- If evidence of meningitis: Add Cefotaxime

Policy for nosocomial sepsis

It is not possible to suggest a single antibiotic policy for use in all newborn units. Every newborn unit must have its own antibiotic policy based on the local sensitivity patterns and the profile of pathogens. Preferably choose Penicillin plus an Aminoglycoside combination. Cephalosporins rapidly induce the production of extended spectrum β-lactamases (ESBL), cephalosporinases and fungal colonization.

Upgradation of empirical antibiotics

- Empirical upgradation must be done if the expected clinical improvement with the ongoing line of antibiotics does not occur. At least 48-72 hours period of observation should be allowed before

declaring the particular line as having failed. If any new sign appears and/or the existing signs fail to begin remitting, it would be considered that the expected clinical improvement has not occurred. Current evidence does not support the use of serial quantitative CRP as a guide for deciding whether or not antibiotics should be upgraded empirically.

- In case the neonate is extremely sick or deteriorating very rapidly and the treating team feels that the neonate may not able to survive 48 hours in the absence of appropriate antibiotics, a decision may be taken to bypass the first line of antibiotics and start with the second-line of antibiotics.

Antibiotic therapy once culture report is available

- It must first be assessed whether the positive blood culture is a contaminant. The following are suggestive of contamination: growth in only one bottle (if two had been sent), growth of a known non-pathogen: eg. aerobic spore bearers , mixed growth of doubtful significance and onset of growth beyond 96 hours in the absence of a history of prior exposure of antibiotics in the 72 hours before sending the blood culture. This must be discussed with the microbiologist because certain slow growing organisms may have onset of growth beyond 96 hours.

- If the growth is a non-contaminant, the antibiotic sensitivity must be assessed to decide whether antibiotics need to be changed or not. The following guidelines would allow a rationale use of antibiotics:

    - If the organism is sensitive to an antibiotic with a narrower spectrum or lower cost, therapy must be changed to such an antibiotic, even if the neonate was improving with the empirical antibiotics and/or the empirical antibiotics are reported sensitive.
    - If possible, a single sensitive antibiotic must be used, the exception being Pseudomonas for which 2 sensitive antibiotics must be used.
    - If the empirical antibiotics are reported sensitive, but the neonate has worsened on these antibiotics, it may be a case of *in vitro* resistance. Antibiotics may be changed to an alternate sensitive antibiotic with the narrowest spectrum and lowest cost.
    - If the empirical antibiotics are reported resistant but the neonate has improved clinically, it may or may not be a case of *in-vivo* sensitivity. In such cases are careful assessment must be made before deciding on continuing with the empirical antibiotics. One must not continue with antibiotics with *in vitro* resistance in case of Pseudomonas, Klebsiella and MRSA; and in cases of CNS infections and deep-seated infections.
    - If no antibiotic has been reported sensitive, but one or more has been reported ‘moderately sensitive’, therapy must be changed to such antibiotics at the highest permissible dose. Use a combination, in such cases.

Duration of antibiotics

Evidence and *Recommendations:*

Culture positive sepsis: Give sensitive antibiotics for total duration of 10-14 days**.** There is no definitive published literature regarding the optimum duration of antibiotics for neonatal sepsis. In a RCT, it was shown that neonates infected by Staphylococcus aureus require 14 days of antibiotics. In those neonates who are infected by non-Staphylococcus aureus organisms, without meningitis or deep-seated infections, and who become completely asymptomatic by day five, one may consider a shorter duration of antibiotics

[42]. Some authors suggest the use of quantitative CRP assay to decide on stoppage of antibiotics but based on the current evidence this cannot be recommended as a standard practice [43].

Culture negative sepsis: If the blood culture is reported sterile at 48 hours, the following guidelines must be adhered to:

- Asymptomatic neonate at risk of EOS: stop antibiotics
- Suspected EOS or LOS and the neonate becomes completely asymptomatic over time: stop antibiotics
- Suspected EOS or LOS and the neonate improves but does not become asymptomatic: repeat a CRP assay [44-47]
    - If CRP + ve: continue antibiotics
    - If CRP –ve: stop antibiotics
- Suspected EOS or LOS and the neonate have not improved or have worsened: upgrade antibiotics as per the empiric antibiotic policy. Simultaneously, alternative explanations for the clinical signs must be actively sought for.

Culture-proven meningitis: Gram stain-proven meningitis or meningitis suspected on CSF examination: give total of 21-day course of parenteral antibiotics that cross uninflamed meninges. Anti-meningitic doses must be used throughout the course and use only antibiotics with a proven *in vitro* sensitivity.

Monitoring protocol following diagnosis of meningitis:

- At least twice weekly head circumference monitoring
- Input/Output monitoring, daily weight monitoring (for SIADH)
- Daily neurological examination (focal neurological deficits).
- Hearing screen after 4-8 weeks
- Ultrasound head in the first week and at the end of antibiotic therapy (look for ventricular size, ventricular wall enhancement, midline shift, intraventricular debris). Ventriculitis may require 6 weeks of antibiotics.
- CECT head may be required in case of rapidly rising OFC with suspicious USG, focal seizures, focal neurological deficits or infection with *Citrobacter koseri* and *Enterobacter sakazakii*

UTI: May be treated for 7-14 days. This duration has no evidence to back it. There is extensive literature to support shorter duration of antibiotics in older children, but not in neonates. Start empirical treatment with Cefotaxime/Ceftriaxone plus Amikacin, and modify as per culture report. Nalidixic acid or nitrofurantoin should not be used to treat UTI since they do not achieve therapeutic concentrations in the renal parenchyma and blood stream. UTI occurring in the setting of generalized septicemia may not be associated with VUR or malformations. However, an isolated UTI could be associated with these conditions. Hence, after treatment of isolated UTI, all cases must be started on Amoxycillin 10 mg/kg once a day oral prophylaxis, till such time that a renal ultrasound, MCU and DMSA scan are performed to exclude VUR or malformations.

Proven bone or joint infections: Must be treated for at least 6 weeks. Start empirical treatment with Cloxacillin or Vancomycin (plus an aminoglycoside for first 1-2 weeks) and modify as per culture report. Of this, at least 4 weeks must constitute parenterally administered antibiotics. The rest of the course may be enterally administered.

Supportive care of a sick & septic neonate

General supportive care

Evidence and *Recommendations:*

The survival of a sick septic newborn often depends upon aggressive supportive care. Neonates should be nursed in a thermo-neutral environment taking care to avoid hypo/hyperthermia thereby reducing oxygen consumption. Aggressive nutritional support is needed to combat the catabolic state associated with sepsis. We could not find any specific evidence in relation to supportive care of a septic neonate. Hence, we have attempted to provide certain general guidelines mainly derived from expert opinions and anecdotes:

- Oxygen saturation should be maintained in the normal range and mechanical ventilation may be required in case of increased work of breathing.
- Volume expansion with crystalloids/colloids and judicious use of inotropes are essential to maintain normal tissue perfusion and blood pressure.
- Anemia, thrombocytopenia, and disseminated intravascular coagulation are treated with appropriate transfusions. Packed red cells and fresh frozen plasma might have to be used in the event of anemia or bleeding diathesis.
- Newborn infants are vulnerable to heat loss and should be nursed under a radiant warmer or an Incubator and be in a thermoneutral environment.
- Hypoglycemia is defined as a whole-blood glucose level of less than 45 mg per dL. Septic infants should be screened for hypoglycemia. Treat hypoglycemia with an initial bolus of 10% glucose at the rate of 2 mL per kg, followed by an intravenous infusion of 6 to 8 mg per kg per minute, with frequent monitoring.
- Management of Septic Shock in a neonate [48]: Fluid resuscitation with isotonic boluses (20 ml/kg over 15 minutes each) to a maximum volume of 60 mL/ kg may be accomplished. In addition, hypoglycemia and hypocalcemia should be corrected. Hypocalcemia must be treated with slow IV administration of calcium gluconate at a dose of 2 ml/kg. If shock persists, central venous and arterial access should be obtained and vasoactive agents should be started, with dopamine as a first-line agent. If after the first hour circulation is not restored with further pressor support, a possibility of adrenal insufficiency should be considered and hydrocortisone therapy should be initiated.

Adjunctive therapies

Evidence *and Recommendations:*

a) Intravenous immunoglobulins (IVIG):

In the Cochrane meta-analysis on the use of immunoglobulins in cases of suspected and proven neonatal infections, 6 studies (n = 318) reported on mortality in patients with clinically suspected infection. The results showed a reduction in mortality [typical RR 0.63 (95% CI; 0.40, 1.00)] of borderline statistical significance. The updated Cochrane review (2010) shows a narrower confidence interval, but results from the large INIS trial are still awaited. Treatment with IVIG in cases of subsequently proven infection (seven trials, n = 262) showed a statistically significant reduction in mortality [typical RR 0.55 (95% CI; 0.31, 0.98)], but with a very wide confidence interval, approaching unity [49]. In the Cochrane review on sepsis and septic shock, the subgroup analysis of neonates showed that the decrease in mortality was not significant (n=241; RR= 0.70; 95% CI 0.42, 1.18) [50]. There are two Indian trials on the use of immunoglobulins in neonatal infections, but none showed any benefit [51, 52].

***Recommendations**:* The currently available evidence does not support the use of IVIG. The currently undergoing International Neonatal Immunotherapy Study is expected to be provide some important and definitive information in this aspect [53].

b) Colony stimulating factors

From the Cochrane review, there is no evidence that the addition of Granulocyte-CSF (G-CSF) or Granulocyte Monocyte-CSF (GM-CSF) to antibiotic therapy in preterm infants with suspected systemic infection reduces mortality [54]. No significant survival advantage was seen at 14 days from the start of therapy [typical RR 0.71 (95% CI 0.38, 1.33)]. All treatment studies were small, the largest recruiting only 60 infants. A subgroup analysis of 97 infants who, in addition to systemic infection, had neutropenia (<1700 per micro L) showed a significant reduction in mortality by day 14 [RR 0.34 (95% CI 0.12, 0.92)], but the sample size was too small and confidence interval was very wide. Prophylaxis studies have not demonstrated a significant reduction in mortality in neonates receiving GM-CSF [RR 0.59 (95% CI 0.24, 1.44)]. In another multi-centre study on prophylaxis, there was no reduction in sepsis among extremely preterm, small-for-gestational age neonates [55].

***Recommendations**:* There is currently no evidence to support the use of colony stimulating factors either as a treatment modality or as a prophylaxis therapy.

c) Blood Exchange Transfusion (BET)

Double volume BET has been used as a modality for managing sepsis for several decades, but large, well-conducted RCTs are still lacking. The earlier trials were uncontrolled and showed impressive improvements in neutrophil counts, immunoglobulin levels, recovery from sclerema and less mortality compared to historical experiences [56-58]. In a small RCT from India, conducted on septicemic neonates, there was a non significant reduction in mortality [7/20 versus 7/10; RR 0.5 (95% CI 0.24, 1.03)], but there were significant improvements in total leucocyte count, absolute neutrophil count and neutrophil functions in the BET group [59]. In another small RCT on sclerematous neonates from the same centre, BET resulted in a significant reduction in mortality [50% versus 95%; RR 0.53 (95% CI 0.34, 0.83)] and significant improvement in immunoglobulin levels [60]. In a non-randomized, controlled trial from Turkey,

BET was compared with IVIG and controls [61]. There was a non-significant reduction in mortality both in the BET and IVIG groups compared to controls and a significant rise in IgM levels in the BET group.

Recommendations: BET may be performed in a case of deteriorating sepsis with sclerema provided the general condition of the baby allows the procedure .

References

1. Sundaram V, Kumar P, Narang A. Bacterial profile of early versus late onset neonatal sepsis in a North Indian tertiary care centre: Heading towards a change. J Pediatr Infect Dis 2009; 4: 241-245
2. Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. Lancet 2005; 365:1175-88.
3. NNPD network. National Neonatal Perinatal Database- report for the year 2002-2003. NNF NNPD network. 2005. New Delhi. Ref Type: Report
4. Okascharoen C, Sirinavin S, Thakkinstian A, Kitayaporn D, Supapanachart S. A bedside prediction-scoring model for late-onset neonatal sepsis. J Perinatol 2005; 25:778-83.
5. Rosenberg RE, Ahmed AN, Saha SK, Chowdhury MA, Ahmed S, Law PA et al. Nosocomial Sepsis Risk Score for Preterm Infants in Low-resource Settings. J Trop Pediatr 2009; Jul 21:Epub ahead of print.
6. Singh SA, Dutta S, Narang A. Predictive clinical scores for diagnosis of late onset neonatal septicemia. J Trop Pediatr 2003; 49:235-9.
7. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics 1998; 102:E41.
8. Mahale R, DuttaS, Ahluwalia J, and Narang A. Baseline illness severity does not alter accuracy of neonatal sepsis screen. 2005. Postgraduate Institute of Medical Education and Research, Chandigarh. 2005. Ref Type: Thesis/Dissertation
9. Eldadah M, Frenkel LD, Hiatt IM, Hegyi T. Evaluation of routine lumbar punctures in newborn infants with respiratory distress syndrome. Pediatr Infect Dis J 1987; 6:243-6.
10. Weiss MG, Ionides SP, Anderson CL. Meningitis in premature infants with respiratory distress: role of admission lumbar puncture. J Pediatr 1991; 119:973-5.
11. Bergqvist G, Eriksson M, Zetterstrom R. Neonatal septicemia and perinatal risk factors. Acta Paediatr Scand 1979; 68:337-9.
12. Kumari S, Pruthi PK, Mehra R, Gujral VV. Infection scoring in early neonatal infection. Indian J Pediatr 1983; 50:177-81.
13. Singh M, Narang A, Bhakoo ON. Predictive perinatal score in the diagnosis of neonatal sepsis. J Trop Pediatr 1994; 40:365-8.
14. Takkar VP, Bhakoo ON, Narang A. Scoring system for the prediction of early neonatal infections. Indian Pediatr 1974; 11:597-600.
15. Reddy R, Dutta S, and Narang A. Multi-variate analysis of risk factors of early onset neonatal sepsis in preterm infants. 2004. Postgraduate Institute of Medical Education and Research, Chandigarh. 2004. Ref Type: Thesis/Dissertation
16. Sheikh S, Dutta S, Kumar P, and Ray P. Comparison of the new PGI perinatal risk score versus the standard PGI perinatal risk score for deciding antibiotic treatment of asymptomatic premature neonates at risk of early onset neonatal sepsis: a randomized controlled trial. 2008. Postgraduate Institute of Medical Education and Research, Chandigarh. 2008. Ref Type: Thesis/Dissertation
17. Kudawla M, Dutta S, Narang A. Validation of a clinical score for the diagnosis of late onset neonatal septicemia in babies weighing 1000-2500 g. J Trop Pediatr 2008; 54:66-9.
18. Mouzinho A, Rosenfeld CR, Sanchez PJ, Risser R. Revised reference ranges for circulating neutrophils in very-low-birth-weight neonates. Pediatrics 1994; 94:76-82.
19. Schelonka RL, Yoder BA, desJardins SE, Hall RB, Butler J. Peripheral leukocyte count and leukocyte indexes in healthy newborn term infants. J Pediatr 1994; 125:603-6.

20. Da Silva O, Ohlsson A, Kenyon C. Accuracy of leukocyte indices and C-reactive protein for diagnosis of neonatal sepsis: a critical review. Pediatr Infect Dis J 1995; 14:362-6.
21. Fowlie PW, Schmidt B. Diagnostic tests for bacterial infection from birth to 90 days--a systematic review. Arch Dis Child Fetal Neonatal Ed 1998; 78:F92-F98
22. Fielkow S, Reuter S, Gotoff SP. Cerebrospinal fluid examination in symptom-free infants with risk factors for infection. J Pediatr 1991; 119:971-3.
23. Kumar P, Sarkar S, Narang A. Role of routine lumbar puncture in neonatal sepsis. J Paediatr Child Health 1995; 31:8-10.
24. Malik A, Hui CP, Pennie RA, Kirpalani H. Beyond the complete blood cell count and C-reactive protein: a systematic review of modern diagnostic tests for neonatal sepsis. Arch Pediatr Adolesc Med 2003; 157:511-6.
25. Philip AG, Hewitt JR. Early diagnosis of neonatal sepsis. Pediatrics 1980; 65:1036-41.
26. Gerdes JS, Polin RA. Sepsis screen in neonates with evaluation of plasma fibronectin. Pediatr Infect Dis J 1987; 6:443-6.
27. Brown DR, Kutler D, Rai B, Chan T, Cohen M. Bacterial concentration and blood volume required for a positive blood culture. J Perinatol 1995; 15:157-9.
28. Connell TG, Rele M, Cowley D, Buttery JP, Curtis N. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. Pediatrics 2007; 119:891-6.
29. Jawaheer G, Neal TJ, Shaw NJ. Blood culture volume and detection of coagulase negative staphylococcal septicaemia in neonates. Arch Dis Child Fetal Neonatal Ed 1997; 76:F57-F58.
30. Hasana AS, Uppal P, Aryab S, Capoora MR, Naira D, Chellani H et al. Comparison of BacT/lert microbial detection system with conventional blood culture method in neonatal sepsis. Journal of Pediatric Infectious Diseases 2008; 3:21-5.
31. Greenberg RG, Smith PB, Cotten CM, Moody MA, Clark RH, Benjamin DK, Jr. Traumatic lumbar punctures in neonates: test performance of the cerebrospinal fluid white blood cell count. Pediatr Infect Dis J 2008; 27:1047-51.
32. Rajesh NT, Dutta S, Prasad R, Narang A. Effect of Delay in Analysis on Neonatal Cerebro-Spinal Fluid Parameters. Arch Dis Child Fetal Neonatal Ed 2009; Aug 10:Epub ahead of print.
33. The WHO Young Infant Study Group. Clinical prediction of serious bacterial infections in young infants in developing countries. Pediatr Infect Dis J 1999; 18:S23-S31.
34. Ahmed AS, Chowdhury MA, Hoque M, Darmstadt GL. Clinical and bacteriological profile of neonatal septicemia in a tertiary level pediatric hospital in Bangladesh. Indian Pediatr 2002; 39:1034-9.
35. Smith PB, Garges HP, Cotton CM, Walsh TJ, Clark RH, Benjamin DK, Jr. Meningitis in preterm neonates: importance of cerebrospinal fluid parameters. Am J Perinatol 2008; 25:421-6.
36. Garges HP, Moody MA, Cotten CM, Smith PB, Tiffany KF, Lenfestey R et al. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? Pediatrics 2006; 117:1094-100.
37. DiGeronimo RJ. Lack of efficacy of the urine culture as part of the initial workup of suspected neonatal sepsis. Pediatr Infect Dis J 1992; 11:764-6.
38. Tamim MM, Alesseh H, Aziz H. Analysis of the efficacy of urine culture as part of sepsis evaluation in the premature infant. Pediatr Infect Dis J 2003; 22:805-8.
39. Lin DS, Huang SH, Lin CC, Tung YC, Huang TT, Chiu NC et al. Urinary tract infection in febrile infants younger than eight weeks of Age. Pediatrics 2000; 105:E20.
40. Buys H, Pead L, Hallett R, Maskell R. Suprapubic aspiration under ultrasound guidance in children with fever of undiagnosed cause. BMJ 1994; 308:690-2.
41. Paul VK, Agarwal R. Neonatal sepsis. In: Mondkar J, Pejavar RK, editors. NNF Manual of Neonatal Care. Bangalore: Prism Publishers; 2004. p. 121-34.
42. Chowdhary G, Dutta S, Narang A. Randomized controlled trial of 7-Day vs. 14-Day antibiotics for neonatal sepsis. J Trop Pediatr 2006; 52:427-32.
43. Couto RC, Barbosa JA, Pedrosa TM, Biscione FM. C-reactive protein-guided approach may shorten length of antimicrobial treatment of culture-proven late-onset sepsis: an intervention study. Braz J Infect Dis 2007; 11:240-5.
44. Ehl S, Gering B, Bartmann P, Hogel J, Pohlandt F. C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics 1997; 99:216-21.

45. Engle WD, Jackson GL, Sendelbach D, Ford D, Olesen B, Burton KM et al. Neonatal pneumonia: comparison of 4 vs 7 days of antibiotic therapy in term and near-term infants. J Perinatol 2000; 20:421-6.
46. Saini SS, Dutta S, Ray P, and Narang A. Comparison of 4-day and 7-day antibiotic courses for probable neonatal sepsis. Early Human Development 84[1], S64. 2008. Ref Type: Abstract
47. Squire EN, Jr., Reich HM, Merenstein GB, Favara BE, Todd JK. Criteria for the discontinuation of antibiotic therapy during presumptive treatment of suspected neonatal infection. Pediatr Infect Dis 1982; 1:85-90.
48. Carcillo JA, Fields AI. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. Crit Care Med 2002; 30:1365-78.
49. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database Syst Rev 2010; Mar 17;(3):CD001239.
50. Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. Cochrane Database Syst Rev 2002;CD001090.
51. Samatha S, Jalalu MP, Hegde RK, Vishwanath D, Maiya PP. Role of IgM enriched intravenous immunoglobulin as an adjuvant to antibiotics in neonatal sepsis. Karnataka Pediatric Journal 1997; 11:1-6.
52. Shenoi A, Nagesh NK, Maiya PP, Bhat SR, Subba Rao SD. Multicenter randomized placebo controlled trial of therapy with intravenous immunoglobulin in decreasing mortality due to neonatal sepsis. Indian Pediatr 1999; 36:1113-8.
53. The INIS Study. International Neonatal Immunotherapy Study: non-specific intravenous immunoglobulin therapy for suspected or proven neonatal sepsis: an international, placebo controlled, multicentre randomised trial. BMC Pregnancy Childbirth 2008; 8:52.
54. Carr R, Modi N, Dore C. G-CSF and GM-CSF for treating or preventing neonatal infections. Cochrane Database Syst Rev 2003;CD003066.
55. Carr R, Brocklehurst P, Dore CJ, Modi N. Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicentre, randomised controlled trial. Lancet 2009; 373:226-33.
56. Christensen RD, Hill HR, Anstall HB, Rothstein G. Exchange transfusion as an alternative to granulocyte concentrate administration in neonates with bacterial sepsis and profound neutropenia. J Clin Apher 1984; 2:177-83.
57. Dalvi R, Rao S, Rangnekar J, Fernandez A. Exchange transfusions in neonatal sepsis. Indian Pediatr 1991; 28:39-43.
58. Vain NE, Mazlumian JR, Swarner OW, Cha CC. Role of exchange transfusion in the treatment of severe septicemia. Pediatrics 1980; 66:693-7.
59. Mathur NB, Subramanian BK, Sharma VK, Puri RK. Exchange transfusion in neutropenic septicemic neonates: effect on granulocyte functions. Acta Paediatr 1993; 82:939-43.
60. Sadana S, Mathur NB, Thakur A. Exchange transfusion in septic neonates with sclerema: effect on immunoglobulin and complement levels. Indian Pediatr 1997; 34:20-5.
61. Gunes T, Koklu E, Buyukkayhan D, Kurtoglu S, Karakukcu M, Patiroglu T. Exchange transfusion or intravenous immunoglobulin therapy as an adjunct to antibiotics for neonatal sepsis in developing countries: a pilot study. Ann Trop Pediatr 2006; 26:39-42.

Annexure

Definitions

Neonatal sepsis: Defined as the presence of generalized systemic features of sepsis associated with pure growth of organisms from one or more sites. This includes septicemia, pneumonia, meningitis, urinary tract infection, dysentery, osteomyelitis, septic arthritis and deep-seated infections.

Probable sepsis: clinical and laboratory findings consistent with bacterial infection without a positive culture.

Severe Sepsis: Sepsis associated with organ dysfunction, hypoperfusion abnormalities, or hypotension. Manifestations of hypoperfusion include but are not limited to prolonged capillary refill time, lactic acidosis, oliguria or an acute alteration in sensorium.

Septic Shock: Sepsis-induced hypotension despite fluid resuscitation plus hypoperfusion abnormalities.

Multiple Organ Dysfunction Syndrome (MODS): Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Surveillance for Healthcare Associated Infections

Summary of Recommendations

- **Each neonatal unit should have a systematic surveillance system for healthcare associated infections.**
- **All units should use same definitions and weight stratifications for reporting. Currently CDC definitions are universally accepted.**
- **Existing nursing and paramedical staff can be trained effectively to perform surveillance activities.**
- **Umbilical catheters, central lines, ventilator, CPAP and peripheral lines should be monitored for device associated infection rates.**
- **It will be cost effective to monitor for blood stream infection, pneumonia, fungemia and MRSA sepsis in the initial phase .**
- **Routine surface cultures have no role in the NICU.**

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Introduction

A major proportion of the 1.6 million global deaths due to neonatal infections is hospital acquired or Healthcare Associated Infections (HAI) [1,2]. As per National Neonatal Perinatal Database (NNPD) 2002-03, systemic infections (18.6%) are the second most common cause of neonatal deaths in India[3]. HAI contribute significantly to patient morbidity, prolonged hospital stay, increased costs and mortality. Neonates represent a unique and highly vulnerable patient population due to their immature immune system, altered cutaneous barrier and frequent invasive diagnostic and therapeutic interventions.

Systematic surveillance is an integral part of all approaches to decrease nosocomial infections (NI). A systematic review of published reports by Harbarth, to find the preventable proportion of NIs suggested that a great potential exists to decrease NIs by 10 to 70% depending on setting, baseline infections rate and type of infections[4]. In another report by Pawa et al, the incidence of nosocomial sepsis from a Delhi based hospital was 16.8/100 patient days and 1.9/1000 device days[5].

Current reporting system in our country and its disadvantages

Majority of the units in our country regularly calculate the incidence of late-onset sepsis (LOS) (manifesting after 48 or 72 hours of age) as proportion of live births or NICU admissions. These reports as well as the largest report of neonatal data from our country, the NNPD, do not take "at-risk population" and the presence of risk factors like central lines and ventilation into account. Moreover, no standard definition of hospital acquired or health care associated infections are followed. When admissions or live births are used as denominator, every patient is assumed to be at equal risk of infection with no account of exposure to important risk factors. Because of this, it is not possible to have benchmarking and fair comparison between units or between different time periods within the same unit, as the sickness level and exposure to risk factors could vary between units and over time.

Origin and evolution of surveillance systems

In a Surveillance system uniform definitions and specific methods are used. Importance of Surveillance was realized in seventies which provided the basis for development of National Nosocomial Infection Surveillance (NNIS) of Center for Disease Control (CDC) in the USA) [6]. Initially, most of the data in hospital wide surveillance was collected from infected patients (numerator data) but this is of limited value since it is not able to measure the influence of exposure to significant risk factors for nosocomial infections. Over time, the importance of denominator data (i.e. patients at risk of becoming infected) was realized and the patients were categorized according to weight and the exposure to various risk factors for HAIS. Another surveillance system, KISS (Krankenhaus Infections Surveillance System), was established in Germany in 1997 as National Surveillance system for nosocomial infections [7]. KISS is a patient based system in which data for individual patients is collected separately. For neonates, peripheral vascular catheters and CPAP were recorded as devices in NEO-KISS while they are not recorded as devices in NNIS. In NEO-KISS only neonates with birth weight less than 1500gm are monitored and modified CDC definition for BSI and Pneumonia is used. This guideline will address various issues in relation to nosocomial surveillance pertaining to neonates. The guidelines for sepsis surveillance have to be flexible. No generalized guidelines can be recommended as each unit is different with respect to their patient population, risk of infection, availability of resources and priorities. Scientific evidence is available for very few questions while most of the other recommendations are mainly based on anecdotal experience gained over last 40 years of surveillance of HAIs.

This guideline reviews the evidence and offers recommendations for the following issues:

- Role of surveillance in decreasing nosocomial infection rate
- Definitions to be used for hospital acquired infections
- Weight categories to be monitored for HAIs
- Devices to be monitored for HAIs
- Unit based versus patient based surveillance
- Timing of conducting surveillance
- Type of data collection and type of infections for surveillance
- Role of routine surface cultures in surveillance

Role of surveillance in decreasing nosocomial infection rates

Evidence: Surveillance decreases the HAI rate by itself. Gastmeier P et al had shown that participation in KISS (German National surveillance system) was associated with a significant reduction in Ventilator Associated Pneumonia (VAP), Central Venous Catheter related Blood Stream Infection (CR-BSI) and surgical site infection (SSI) rate. Comparing the rates in third year of surveillance with first year, the relative risk for VAP, CR-BSI and SSI was 0.71 (0.66-0.76), 0.80 (0.72-0.90) and 0.72 (0.64-0.80) respectively[8]. Similar results were found by Schwab. F et al in NICUs with at least three years participation in NEO-KISS (Surveillance system for NICU VLBW patients). The incidence of BSI decreased significantly by 24% (8.3/1000 days to 6.4/1000 days) in first and third years respectively. The year of participation was an independent risk factor for BSI but not for pneumonia[9].

Recommendations: A diligent surveillance by itself leads to decrease in the NI rates. Hence every unit should have a proper surveillance system in place.

Definitions to be used for hospital acquired infections

Evidence: Most of the surveillance studies have used CDC definitions given for <1 year old patients. Modified definitions are used in German NI surveillance system to incorporate as many objective criteria as possible and make them applicable to special population of neonates. Gastmeier P et al found high level of agreement between CDC and modified CDC (German) criteria for CR-BSI rate (kappa=0.92) and a good agreement for VAP (kappa=0.79)[8]. In surveillance study for NIs in a Dutch neonatal intensive care unit by Vander Zwet WC et al, 32% of BSI cases detected with modified definitions would not have been identified on application of CDC definitions. Similarly, 12.5% of pneumonia cases would not have been detected by CDC definitions that were detected by the modified definition[10].

Recommendations: Even though modified definitions used by the German NI surveillance system performed better in detection of BSI and pneumonia in comparison to the CDC definitions, the latter is more universally used and accepted. Till specific definitions for neonates are available and are well validated, the CDC definitions should be used for surveillance.

Weight categories to be monitored for HAIs

Evidence: NNIS collects data for 5 different weight group i.e. <750gm, 751-1000gm, 1001-1500gm, 1501-2500gm, and >2500 gm. In German surveillance system only neonates with birth weight less then 1500 gm are monitored and neonates with birth weight <500 gm are considered as a special category. In our country as the infection rate is quite high even in bigger weight babies, we need to monitor all neonates and not only VLBW infants.

Recommendations: All neonates admitted in the nursery / intensive care unit should be monitored for infections. In order to facilitate comparison, weight-wise stratification of babies should be done.

Devices to be monitored for HAIs

Evidence: Device associated infection rate is calculated for central venous catheters, with a separate mention about umbilical venous catheters and ventilators. In addition to these devices CPAP and peripheral vascular catheters are also considered as devices in the German surveillance system. In India, infection rate is very high and vascular line management needs improvement. Thus we need to monitor peripheral vascular line and CPAP as devices and calculate device associated HAI for them also.

Recommendations: Umbilical catheters, central lines, ventilator, CPAP and peripheral lines are the devices to be monitored for device associated infections.

Unit based versus patient based surveillance

Evidence: Decision regarding having a unit based versus patient based surveillance primarily depends on the resources. NNIS is a unit based system while KISS is patient based system. Patient based system is more labor intensive and requires more time and manual power.

Recommendations: In resource limited situations, unit based approach is more cost-effective as all babies need to be monitored.

Timing and personnel for conducting surveillance

Evidence: The job of data collection for surveillance can be ascribed to staff nurses for collection of denominator data i.e. to record daily patient days and device days and resident doctors for the numerator data i.e. any new episode of HAI. Although active surveillance, data collection by trained personnel like an Infection Control Practitioner (ICP), is better, with limited resources it may not be possible for all units. The newborn unit in PGIMER, Chandigarh has successfully adopted this approach of surveillance by training the existing staff in their unit (Praveen Kumar; personal communication).

Recommendations: Ideally dedicated infection control nurses are required for surveillance data collection. In resource constrained settings, available nursing and paramedical staff can be trained effectively.

Type of data collection and type of infections to be included for surveillance

Evidence: The data should be collected prospectively and approach should be priority directed i.e. specific infections, like Blood Stream Infections (BSI) and pneumonia should be followed over time. Various studies have proved that BSI and pneumonia are the commonest NIs. Couto R et al in a prospective 10 year follow-up open cohort study involving six Brazilian NICUs found the frequency of various HAIs as primary BSI (45.9%), conjunctivitis (12.1%) skin infections (9.6%) and pneumonia (6.8%)[11]. Jeong SI et al reported most common infections as pneumonia (28%), BSI (26%) and conjunctivitis (22%) in a South Korean NICU[12]. Contreras-Cuellar GA in their prospective surveillance study in a Columbian NICU found BSI (72%) and pneumonia (18%) to be the most frequent NIs[13]. So it will be cost effective to start surveillance for BSI and Pneumonia in a priority directed manner. Similarly it will be worthwhile to record fungal infection and methicillin resistant staphylococcus aureus (MRSA) as separate categories. The incidence rate of fungal infection will help in determining prophylactic fluconazole protocol for a given NICU. If the incidence of MRSA is high, it will help in taking specific prophylactic measures, for e.g. use of chlorhexidine scrubs. Any infection within 48 hours of hospital discharge should be considered as HAI. Some systemic infections like osteomyelitis, septic arthritis and fungal balls can present as late as 4-6 weeks after hospital discharge in NICU graduates and thus should be considered as nosocomial in origin.

Recommendations: The data should be collected prospectively and prioritization for most common and fulminant infections should be done. It is cost effective to collect data for BSI, pneumonia, fungemia and MRSA sepsis in the starting phase of surveillance.

Role of routine surface cultures in surveillance

Evidence: Untargeted bacteriological surveillance of superficial and deep body sites is frequently performed in clinical settings. This practice is based on the assumption that early identification of surface microbial flora might be predictive of organisms that will later cause invasive disease and that it may consequently assist in guiding empirical antibiotic therapy. Evans et al found such cultures to be of little value in predicting the organisms causing true sepsis even if taken at the time of suspected sepsis[13]. Fulginiti and Ray describe surface culturing for the individual infant as an 'exercise in futility, wastefulness and inappropriate practice'. [14] Yu VY did a questionnaire survey in 20 NICUs in Australia to study the pattern of neonatal bacterial infection, its management and the types of infection control policy and found that out of twenty, 6 NICUs were routinely doing surface cultures in neonates and seventeen NICU were sending routine endotracheal culture in ventilated babies[15]. Dobson et al collected prospective data on infection in their neonatal intensive care unit for seven years. During the first four year period, six surface cultures were routinely sent for neonates with suspected early and late onset neonatal sepsis (LONS). In the next three years the numbers of surfaces cultures were reduced to two surface areas only. Reduction in surface cultures did not alter the rate of systemic infection, choice of antibiotics in LONS and decision regarding the duration of antibiotic course.[16] Issacs et al studied the correlation of LONS and surface culture in twenty seven newborns. Colonization with the organism causing sepsis could be documented only in 10 cases. They also cast doubt on the value of eliminating colonizing organisms by expensive infection control measures[17]. In a comprehensive review of the literature by Glupczynski Y, the authors found that the clinical value and cost-effectiveness of such practices are unproven in most conditions and situations where they are routinely advocated[18].

Recommendations: Clinical value and cost effectiveness of routine surface cultures in the NICU is unproven.

References

1. WHO. Perinatal mortality. Report No.: WHO/FRH/MSM 1967. Geneva: WHO, 1996.
2. Zaidi AK, Huskin WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital acquired neonatal infections in developing countries. Lancet 2005; 365:1175-1188.
3. Report of the National Neonatal Perinatal Database (National Neonatology Forum, India) 2002-2003.
4. Harbarth S. The preventable proportion of nosocomial infections: an overview of published reports. J Hosp Infect 2003; 54:258.
5. Pawa AK, Ramji S, Prakash K, Thirupuram S. Neonatal Nosocomial Infection: Profile and risk factors. Indian Pediatrics 1997; 34:297-302.
6. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309-32
7. Gastmeier P, Geffers C, Schwab F, Fitzner J, Obladen M, Ruden H. Development of surveillance system for nosocomial infections: the component for neonatal intensive Care Unit in Germany. J Hosp infect 2004; 57:126-31
8. Gastmeier P, Geffers C, Schwab F, Fitzner J, Obladen M, Ruden H. Development of surveillance system for nosocomial infections: the component for neonatal intensive care unit in Germany. J Hosp Infect 2004; 57:126-131.
9. Schwab F, Geffers C, Barwoiff S, Ruden H, Gastmeier. Reducing neonatal naosocomial bloodstream infections through participation in a national surveillance system. J Hosp Infec 2007; 65:319-325.
10. Van der Zwet WC, Kaiser AM, Van Elburg RM, Berkhof J, Fetter WP, Perlevliet GA, Vandenbroucke-Grauls CM. Nosocomial infections in a Dutch neonatal intensive care unit: surveillance study with definitions for infection specifically adapted for neonates. J Hosp Infec 2005; 61:300-311.
11. Couto R, Carvalho E, Pedrosa E, Pedrosa MA. 10 years prospective surveillance of nosocomial infections in neonatal intensive care units. Am J Infect Control 2007; 35:183-189.
12. Jeong IS, Jeong JS, Choi EO. Nosocomial infection in a newborn intensive care unit (NICU), South Korea. BMC Infect Dis. 2006; 6:103.
13. Evans ME, Schaffner W, Federspiel CF, et al. Sensitivity, specificity and predictive value of body surface cultures in a neonatal intensive care unit. JAMA 1988;259:249-53.
14. Fulginiti VA, Ray CG. Body surface cultures in the newborn infant. Am J Dis Child 1988; 142:19-20.
15. Yu VY. Neonatal sepsis and infection control policies in Australia. : J Paediatr Child Health. 1990; 26:252-56.
16. Dobson SRM, Isaacs D, Wilkinson AR, Hope PL. Reduced use of surface cultures for suspected neonatal sepsis and surveillance. Arch Dis Child 1992; 67:44-47
17. Isaacs D, Wilkinson AR, Moxon ER. Surveillance of colonization and late-onset septicaemia in neonates. J Hosp Infect. 1987; 10:114-19
18. Glupczynski Y. Usefulness of bacteriological surveillance cultures for monitoring infection in hospitalized patients: a critical reappraisal. Acta Clin Belg. 2001; 56:38-45.

Annexure

General guideline for surveillance in NICU

1. Assess the population and select the outcome (e.g. blood stream infections, pneumonia, fungemia & MRSA sepsis) and process of interest, which are likely to be a risk factor for infection e.g. ventilation, central line insertion, peripheral vascular line & CPAP.
2. Determine the time period for which surveillance is to be done and decide the surveillance methodology.
3. Ideally surveillance should be conducted by infection control professionals in an active, patient based, prospective and priority directed manner but in resource limited settings, staff nurses and resident doctors can also collect the data. Infection rate has to be calculated per 1000 central line days, per 1000 ventilation days, per 1000 peripheral vascular line days and per 1000 patient days for each weight category i.e. <750 g, 751-1000 g, 1001-1500 g, 1501-2500 g and > 2500 g.
4. Monitor for outcome or process using standardized definitions for all data collected. For definitions of HAIs CDC definitions can be used for the process of surveillance. Epidemic is defined by CDC as the occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time
5. Numerator data (data of infected patients) to be collected include name, birth weight, gestation, date of birth, gender, hospital identification number, infection site and date of onset, devices used in last 48 hours, preceding infection, procedures, organisms isolated and their antibiogram, X-ray, CT Scan and MRI reports. Sources of data include admission/discharge records, microbiology lab records, ward visits and discussion with caregivers, patient charts and notes. Ward rounds are essential for surveillance, prevention, control activities and to complete HAI data collection forms/screens as data sources are reviewed. Also record the number of nurses in each shift to calculate nurse patient ratio.
6. Denominator data (patients at risk of being infected) include counts of the cohorts of patients at risk of acquiring HAI. For device associated HAIs record total number of patients and total number of ventilator days, central line days, peripheral line days & CPAP days etc in the patient care area(s) under surveillance on a daily basis, sum these daily counts at the end of the surveillance period for use as denominators. Sources of denominator data include visits to patient care areas, to obtain daily counts of the number of patients admitted and the number of patients with each of the devices (i.e. central line, ventilator, urinary catheter, peripheral line, CPAP). We should also calculate antibiotic days in each weight category and include it in denominator, since it will help us in long term to rationalize our antibiotic policy. Also record the name of antibiotic being used.
7. Definitions of key terms: As per NNIS any infection is labeled as ICU associated that was not present or incubating at patient's admission to ICU but became apparent during ICU stay or within 48 hours after transfer from ICU. Device associated infection is defined as any infection in a patient with a device (ventilator, peripheral vascular line or central line) that was used within 48 hour period before onset of infection. If interval is longer than 48 hours, then there must be compelling evidence that infection was associated with device use. There is no minimum time period for which the device must be in place to label the infection as device associated.
8. Calculation of device associated infection rates and device utilization ratio: Device Associated Infection Rate (DAIR) is calculated per 1000 device days using the following formula:

$$\text{DAIR} = \frac{\text{Number of device associated infections for an Infection site} \times 1000}{\text{Number of device days}}$$

Device utilization ratio (DUR) reflects the proportion of patient days, for which the patients are on devices like ventilators or central lines. Indirectly this tells about the sickness level in a unit. A unit with sicker and smaller babies will have higher device utilization and hence may have higher infection rates. DUR is calculated with the following formula:

$$\text{DUR} = \frac{\text{Number of device days}}{\text{Number of patient days}}$$

Collection of data involves daily calculating the total number of patients of each weight category that will amount to patient days of each weight category and calculate the number of patients who are on devices like peripheral vascular line, ventilator, CPAP or central lines that will amount to devices days of each weight category. Total number of babies who are on antibiotics will also be recorded to calculate antibiotic days in each weight category. Further, the person collecting the data will actively look for any new episode of HAIs and whether it fulfills the definitions which are being used for HAIs. For each episode of HAIs we need to record all the devices which were in place in the preceding 48 hours of infection to label it as device associated and record all the signs and symptoms and the antibiotic sensitivity pattern of any organism isolated.

DAILY SIN sheet (Surveillance Information Notesheet)

DATE: AREA :

	Birth wt. / Total	<750 g	750-1000g	1000-1500 g	1501-2500 g	>2500 g
No. of babies						
No. on Invasive ventilation (intubated)						
CPAP						
NIMV						
UVC						
PICC						
UAC						
PAC						
PN						

Signatures and Name: STAFF NURSE SENIOR RESIDENT

CPAP:Continuous positive Airway Pressure **NIMV**:Nasal Intermittent mandatory ventilation, **UVC**:Umbilical venous catheter, **PICC**:Peripherally inserted central catheter, **UAC**:Umbilical arterial catheter, **PAC**:Peripheral arterial catheter, **PN**: Parenteral nutrition

NOSOCOMIAL INFECTION EPISODE DESCRIPTION

Date of enrolment Name CR No

Gestation Birth Weight DOB TOB

Date and time when this episode was suspected

Is this 1st episode ? Y/N If No, Episode no. Previous episode date

Areas of stay till the time of onset of this episode

	Stay begin		Stay end	
	Date	Time	Date	Time

BSI (Clinical Manifestations) (Tick wherever applicable)					
CDC		**Modified definitions**			
Fever		Tachycardia		Abdominal distension	
Hypothermia		Increased O2 requirement (intubation)		Coagulopathy	
Apnea		Prolonged CFT		Sclerema	
Bradycardia		Unexplained metabolic acidosis		Unstable general status	
		New hyperglycemia		Skin color	
		Biochemical signs		Any other	
		Temp instability			
		Apathy			

Pneumonia(Tick wherever applicable)					
CDC				**Modified definitions**	
Apnea		Consolidation		Fluid in lobar fissure	
Tachypnea		Pleural effusion		Worsening of gas exchange	
Wheezing		Increased respiratory secretions		Dyspnea (retractions, grunt, nasal flaring)	
Bradycardia		Histopathological evidence		Tachycardia	
Rhonchi		Isolation of pathogen in respiratory secretions		Purulent tracheal secretions	
Cough		New sputum or change in character		Temp instability	
Infiltrates		Organisms cultured from blood or increased antibody titre		CRP 1:2 Positive	
Cavitation				Immature:total neutrophil ratio >0.2	

Devices in place in preceding 48 Hrs (Tick below wherever applicable)

IV Fluid	Invasive ventilation	CPAP	NIMV	UVC	UAC	PICC	PAC	TPN

Cultures (Blood, CSF and Urine)

	Date when sample taken	Report*
Blood		
CSF		
Urine		

*Mention complete name and species, including for fungi. If it is a preliminary report, final report should be collected

Culture sensitivity(In case of multiple organisms, write the name & sensitivity of different organisms with different color inks)

Drug	Sensitive	Resistant	Intermediate	Not tested
Cefotaxime				
Ceftazidime				
Cefetriaxone				
Ceftizoxime				
Cefoperazone				
Cefepime				
Cefotaxime sulbactum				
Ceftriaxone sulbactum				
Cefoperazone sulbactum				
Gentamycin				
Amikacin				
Netilmycin				
Ciprofloxacin				
Imipenam				
Meropenem				
Vancomycin				
Methicillin				
Erythromycin				
Piperacillin				
Drug	**Sensitive**	**Resistant**	**Intermediate**	**Not tested**
Piperacillin tazobactum				
Ticarcillin clavulanic acid				
Aztreonam				
Amoxycillin				
Chloramphenicol				

Fluconazole				
Amphotericin B				

Outcome: Died/Recovered/LAMA

If Died, **Cause of death**

Date of Discharge/Death

Signature

Final Diagnostic Label (To be completed by SR responsible for sepsis data)

Is it Nosocomial sepsis ? Y/N

If Yes, diagnostic labels (please see the CDC definitions)

LCBI(Lab confirmed bloodstream infection)	
CSEP(Clinical Sepsis)	
MEN(Meningitis or Ventricultis)	
PNU(Pneumonia)	

Signature

Perinatal Human Immunodeficiency Virus(HIV) Infection

Summary of Recommendations

- **Early diagnosis of HIV infection in a pregnant woman followed by counseling optimizes her medical and psychosocial care, and also decreases the incidence of Mother to Child Transmission (MTCT).**
- **For prevention of Mother to Child HIV Transmission, updated NACO/WHO guidelines should be followed. Follow testing strategy according to NACO program for diagnosis as well as presumptive diagnosis of HIV in infants.**
- **Use of antiretroviral drugs other than ZDV is not recommended in premature infants due to lack of pharmakokinetic and safety data.**
- **Exclusive breastfeeding is recommended for HIV-infected mothers for the first six months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe.**
- **When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended. At six months, if replacement feeding is still not possible, continuation of breastfeeding with additional complementary foods is recommended.**
- **All breastfeeding should stop once a nutritionally adequate and safe diet (without breast milk) can be provided.**
- **HIV-1 exposed infants should be considered for Pneumocystis carinii prophylaxis beginning at 4 to 6 weeks of age by administration of TMP-SMZ (5mg/kg/day) given till 1 year of age.**
- **All routine infant immunizations may be given to HIV-1 exposed infants.**

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Introduction

In the pandemic of HIV infection mother to child transmission accounts for over 90% of HIV infections in children below the age of 15 years. With approximately 27 million babies born in our country every year and given 0.7% prevalence rate of HIV infections in pregnancy, the estimates are about 1,89,000 HIV infected women deliver in India and as per the NACO 2005 estimates, approximately 60,000 HIV infected infants are added to the existing load each year. [1] Over 50% of such babies die undiagnosed before their second birthday. Almost 10% of world's burden of vertical transmission of HIV infection comes from India. Unfortunately, less than 4% of pregnancies avail—Prevention of Parent to Child Transmission (PPTCT)—services, less than 7% of such exposed mother-baby couples are put in—Prevention of Mother to Child Transmission (PMTCT) —regimen of single dose NVP and less than 3.5% of such babies are actually prevented from getting infected from their mothers.[2] This is far less than United Nations General Assembly Special Session (UNGASS) goals of 20% reduction in MTCT, which was to be achieved by 2005. It is equally important to provide support to those, who are infected in spite of best efforts. This is huge task for a country like India.

These evidence-based clinical practice guidelines will address the following questions:

- What would be the best treatment practices for prevention of Parent to Child Transmission (PPTCT)?
- What is the management of HIV exposed babies in the following scenarios ?:
    - Infants born to HIV-infected women already receiving ART
    - Infants born to HIV infected pregnant women who do not require treatment for their own health i.e.Antiretroviral prophylaxis (ARV) prophylaxis.
- What is the management of HIV exposed baby immediately after birth?
- What are the current Infant Feeding Guidelines?
- How is HIV infection diagnosed in infants?
- Can presumptive diagnosis be made, if there is no testing available?
- What are the issues with respect to pneumocystis *carinii* pneumonia (PCP) prophylaxis?
- What is the advice for immunization?

What would be the best treatment practices for PPTCT?

Early diagnosis of HIV infection in a pregnant woman decreases the incidence of mother-to-child transmission. In addition, it optimizes her medical and psychosocial care. The pediatrician can play a major role in reducing MTCT. MTCT is reduced by effective administration of antiretroviral therapy (ART) to mother, administration of ART to newborn baby, and by appropriate infant-feeding counseling. In the absence of any intervention, the risk of perinatal transmission is 15-30% in non-breastfeeding population. Breastfeeding by an infected mother increases the risk by 5-20% to a total of 20-45%.[3] The risk of MTCT can be reduced to <2% by certain interventions. These interventions include ARV to pregnant mother and infant,[4] elective caesarean section prior to rupture of membranes,[5] and complete avoidance of breastfeeding. [6] Elective caesarean section (ECS)is an effective intervention for the prevention of MTCT among HIV-1-infected women, not taking ARVs or taking only zidovudine (Cochrane meta-analysis).[5] The risk of post partum maternal morbidity is higher with ECS than vaginal delivery. Among HIV-1-infected women, more advanced maternal HIV-1 disease stage and concomitant

medical conditions (e.g., diabetes) are independent risk factors for post partum maternal morbidity. The association of risk of MTCT among HIV-1-infected women with low viral loads with mode of delivery is unclear. The low viral load could be due to initial stages of disease, or secondary to ARV. However Public Health Service Task Force guidelines 2009 recommend ECS at 38 weeks if plasma HIV RNA remains > 1000 copies / mL.

What is the management of HIV exposed babies in the different scenarios?

Definition of HIV exposure: Infants and children born to mothers living with HIV, until HIV infection is reliably excluded and the infant or child is no longer exposed through breastfeeding.

The currently implemented NACO guidelines are presented here followed by the latest WHO 2009 recommendations. The different strategies may be appropriate depending upon various prevailing local conditions.

- **National AIDS Control Organization (NACO) guidelines:**

  These guidelines are based on the WHO 2006 guidelines on ART in infants & children in resource limited setting: towards universal access, recommendations for public health approach in as well as review of current literature on HIV & children.[7]

  - **Pregnant women living with HIV infection who are already on Highly Active Antiretroviral Therapy (HAART):** Infant to be treated with single dose Neverapine (NVP) (2mg/kg) as soon as possible after birth (within 72 hours) and oral AZT (2mg/kg/dose) four-times a day for 7 days.
  - **Pregnant HIV infected women with indications for ARV therapy presenting before active labour:**

    - **If pregnant woman has received at least four weeks of AZT before labour:** Infant should be treated with single dose NVP (2mg/kg) immediately after birth (within 72 hours) and oral AZT (2mg/kg/dose) four times a day for 7 days.
    - **If pregnant woman has received less than four weeks of AZT before labour:** Infant should be treated with single dose NVP (2mg/kg) immediately after birth (within 72 hours) oral AZT (2mg/kg/dose) four times a day for 4 weeks.

  - **Pregnant HIV infected women with no indication for ART (ARV prophylaxis for the prevention of MTCT**
    - **Pregnant woman presents during pregnancy:** Infant to be treated with single dose oral NVP (2mg/kg) immediately after birth (within 72 hours) and oral AZT (2mg/kg/dose) four times a day for 7 days.
    - **Pregnant woman who has not received antepartum prophylaxis:** Infant to be treated with single dose oral NVP (2mg/kg) immediately after birth (within 72hours) & oral AZT (2mg/kg/dose) four times a day for 4 weeks.
    - **Pregnant woman who has not received either antepartum or intrapartumprophylaxis:** Infant to be treated with single dose oral NVP (2mg/kg)immediately after birth (within 72 hours) and oral AZT (2mg/kg/dose) four a day for 4 weeks.

- **WHO 2009 recommendations:**

With the availability of significant amount of new research indicating the benefits of starting ARV prophylaxis for PMTCT earlier during pregnancy, and new data indicating that extended ARV prophylaxis to mothers or infants is effective in substantially decreasing the risk of HIV transmission through breastfeeding, revised WHO guidelines have been published online in November 2009 with the objective to simplify and standardize current recommendations, and to provide updated normative guidance for more effective PMTCT interventions in both resource-limited settings and globally.[8] Once implemented, these recommendations are expected to reduce MTCT risk to less than 5% in breastfeeding populations.

- **Infants born to HIV-infected women receiving ART for their own health should receive:**
  - **Breastfeeding infants*:** Daily NVP from birth until 6 weeks of age
  - **Non-breastfeeding infants**: Daily AZT / NVP from birth until 6 weeks of age

  * Continued regimen of triple therapy is recommended through the end of the breastfeeding period.

- **ARV-prophylaxis options recommended for HIV-infected pregnant women who do not need treatment for their own health**

Option A:	**Option B:**
Mother	**Mother**
AZT	Triple ARV prophylaxis starting from as early as 14 weeks of gestation until all breastfeeding has ended
Infant	**Infant**
Breastfeeding infant	***Breastfeeding infant***
Daily NVP from birth until one week after all exposure to breast milk has ended	Daily NVP from birth to 6 weeks
Non-breastfeeding infant	***Non-breastfeeding infant***
AZT or NVP for 6 weeks	AZT or NVP for 6 weeks

- **US Public Health Service Task Force Recommendations (November 2009):**

These recommendations have been developed for use in the United States. Alternative strategies may be appropriate in other countries.

- **If the mother has received Highly Active Antiretroviral therapy (HAART): (Mother with indication for ART or receiving HAART for PMTCT):** The infant should be treated with Zidovudine (AZT) (4mg/kg/dose twice a day) starting within 6-12 hrs after birth for 6 weeks.[9]

- ZDV should be dosed differently for premature infants <35 weeks, (2mg/kg/dose twice a day), advancing to 8 hrly doses at 2 weeks of age if > 30 weeks gestation at birth, or at 4 weeks of age if < 30 weeks gestation at birth. [9]
- Use of antiretroviral drugs other than ZDV is not recommended in premature infants due to lack of dosing and safety data.

    - **If the mother has not received optimal antepartum and intrapartum prophylaxis:** The infant should be treated with AZT (4mg/kg/dose twice a day) for 6 weeks. [9]
        - If mother has received Sd NVP during labour, the infant should be treated with single dose NVP (2mg/kg) after birth (within 72 hours) + The infant should be treated with AZT (4mg/kg/dose twice a day) for 6 weeks.

    Note: Nevirapine dose should be repeated in situations where the woman takes the drug during false labour and the woman / baby vomits within 30 minutes of taking the drug.[8,9] (AZT syrup available in the market with strength of 50 mg/5ml & NVP syrup available in the market with strength of 50 mg/5ml)

What is the management of HIV exposed baby immediately after birth?

The guidelines include the following

- Maintain universal precautions throughout.
- The baby's mouth and nose should be wiped as soon as the head is delivered.
- The baby should be handled with gloved hands until all the blood and maternal secretions have been washed off.
- The cord should be clamped soon after birth and milking should be avoided. Cover the cord with gloved hand and gauze before cutting blood splashing.
- Use suction only when meconium stained liquor is present. Avoid routine suctioning.
- Initiate feeding within 1 hour of birth according to mother's informed choice. Mother should be counselled prior to onset of labour regarding the choices of infant feeding.

Note: There are no evidenced based guidelines for a HIV exposed baby related to timing of the first baby bath after birth.

What are the steps of Infant Feeding Counselling?

All HIV-infected mothers should receive counselling, during the antenatal as well as postnatal period. This includes provision of general information about the risks and benefits of various infant feeding options, and specific guidance in selecting the option most likely to be suitable for their situation. Good counselling involves assisting an HIV-infected woman to choose an infant feeding option, such as exclusive breastfeeding or complete avoidance of breastfeeding ,that is appropriate and safe for her situation and to which she is more likely to adhere to Whatever a mother decides, she should be supported in her choice. Counselling on complementary feeding should also be provided once the baby is 6 months old. Steps of the feeding counselling are provided in Annexure 1.

Counsel mothers about advantages and disadvantages of different feeding options.

Benefits of Breastfeeding

Mothers need to be counselled that breast milk provides complete nutrition for an infant for the first six months of life. The numerous anti-infective factors protect babies from a wide variety of infections and growth factors stimulate the development of the infant's gut. Breast fed infants have much lower rate of diarrhoeal diseases, pneumonia, ear and other infections compared to artificially fed infants. Breastfeeding promotes the emotional relationship, or bonding, between mother and child.

Risks of Breastfeeding for an HIV positive Mother

Risk of MTCT exists as long as the HIV infected mother breastfeeds. Family may pressurize the mother to give water, other liquids, or food to the infant. Mixed feeding increases the risk of transmission further.

Replacement feeding is feeding used for infants who are receiving no breast milk. During the first six months of life, replacement feeding should be with a suitable breast-milk substitute. After six months the suitable breast-milk substitute should be complemented with other foods.

Benefits of Replacement feeding for HIV Positive Mothers:

There is no risk of transmitting HIV to the infant through replacement feeding. Other family members can help feed the infant.

Risks of Replacement Feeding

Replacement feeding is expensive. The mother or caretaker must make fresh replacement milk for each feed both day and night which is tedious. Safe preparation of commercial formula requires clean water boiled for ten minutes. Home-prepared formula does not contain all the nutrients that infants need. Replacement feeds do not contain protective factors; hence babies are more likely to get sick from diarrhoea, pneumonia and may develop malnutrition leading to much higher child mortality. A continuous and reliable supply of replacement feeds is required to prevent malnutrition. The mother must stop breastfeeding completely or the risk of transmitting virus may increase. Mothers need to be told about using a cup and spoon rather than feeding with a bottle.

The risk of MTCT should be explained to the HIV positive mother.

Postnatal transmission of HIV-1 through ingestion of human milk from a mother with HIV-1 infection is well documented, with rates as high as 9% to 15% with prolonged breastfeeding.[10] The cumulative risk of transmission increases from 3.5%-13% by 5 months to 10.3% to 21% at the end of 23 months.[11] HIV-1 can be detected in human milk as both cell-free virus and cell-associated virus with the prevalence being higher in mature milk (47%) than in colostrum (27%).[12] A higher human milk viral load is associated with a higher risk of mother-to-child transmission. Similarly, a higher plasma viral load is associated with higher probability of breastfeeding transmission per liter of milk ingested by the infant.[13] Mothers acquiring HIV when they are still breastfeeding are twice as likely to transmit the virus through breast-milk than those infected before or during pregnancy because of viremia associated with primary infection with HIV-1 and the presumably high viral load concomitantly in human milk.[14]

Estimated risk of HIV transmission is significantly higher for those who receive mixed feeding before 3 months compared to those exclusively breastfed to 3 months (24.1 vs 14.6 %,). By 15 months of age, children who ever breastfed are more likely to become HIV-1-infected (31.6%) than children who have never breastfed (19.4%). Of children who ever breastfed, those who exclusively breastfed until at least 3 months of age but no longer than 6 months of age had a lower estimated transmission point estimate than did those with mixed feeding. [15] Recent studies confirm that exclusive breastfeeding for up to six months was associated with a three- to four-fold decreased risk of transmission of HIV compared to breastfeeding that was non-exclusive in three large cohort studies conducted in Côte d'Ivoire, South Africa and Zimbabwe. [16] Maternal immunosuppression defined by low CD4 cell count <500 per µl, although strongly correlates with plasma RNA viral load, is an independent risk factor for transmission of infection through breastfeeding.[17] Studies in South Africa, infants born to mothers with CD4 cell counts less than 200 per µl were almost four times more likely to acquire HIV or die than were those born to mothers with CD4 cell counts greater than 500 per µl.[18] The maternal breast problems like subclinical mastitis, breast abscess, fissured nipples, as well as infantile problems like oral thrush or intestinal lesions, have been identified as contributors to MTCT.

Current United Nations Infant Feeding Guidelines: Recognizing the need to minimize the risk of MTCT to infants while simultaneously avoiding increasing the risk of other morbidity and mortality due to malnutrition and infection, WHO, UNAIDS ,and UNICEF have issued the following recommendation:[19]

- **"** For mothers who are HIV negative or do not know their HIV status, exclusive breastfeeding for the first six months and continued breastfeeding for upto two years or longer with addition of complimentary food after six months is recommended.
- Exclusive breastfeeding is recommended for HIV-infected mothers for the first six months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time. (Details in Annexure 2)
- When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended.
- At six months, if replacement feeding is still not acceptable, feasible, affordable, sustainable and safe, continuation of breastfeeding with additional complementary foods is recommended, while the mother and baby continue to be regularly assessed.
- All breastfeeding should stop once a nutritionally adequate and safe diet without breast milk can be provided."

Breastfeeding options for an HIV positive mother

A child may be exclusively breastfed with expressed human milk from his mother, a breast milk donor or from a milk bank or from a known HIV negative wet nurse. Only if a woman expresses interest in another option (expression and heat treatment, wet nursing), should the counsellor discuss it in detail.

- **Exclusive breastfeeding with early cessation (Cessation at or before six months):** If complete avoidance of human milk is not 'AFASS', early weaning from human milk (at or before 6 months of age), if feasible, would limit exposure to HIV-1-infected human milk while allowing the child to experience benefits of breastfeeding. HIV positive mothers who chose to do so must be helped to do so as safely as possible and the transition time from exclusive breastfeeding to exclusive replacement feeding should be minimized as there are concerns about the possible increased risk of HIV

transmission with mixed feeding during the transition period between exclusive breastfeeding and complete cessation of breastfeeding.

Smooth transition is also possible by gradually getting the infant accustomed to less frequent feeding from the breast and to drinking *expressed breast milk* by cup or wati-spoon. **Once the infant has been weaned off the breast, shift from expressed milk to replacement milk feeds.** Replacing milk feeds with family foods should be tried only after transition to replacement milk feeding has been achieved and the infant is growing well. All efforts should be done to avoid mixed feeding in such cases.

In many settings, the risk of infant morbidity and mortality due to malnutrition and infectious disease may be higher than that due to HIV when infants are no longer breastfed.[1] Early breastfeeding cessation at four months was associated with reduced HIV transmission but also with increased child mortality from 4 to 24 months in preliminary data presented from a randomized trial in Zambia.[20] Breastfeeding of HIV-infected infants beyond six months was associated with improved survival compared to stopping breastfeeding in preliminary data presented from Zambia and Botswana.[20,21] Hence counselling should be appropriate to the local circumstances.

As per WHO 2009 guidelines, in resource constrained settings, mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided. Mothers known to be HIV-infected who decide to stop breastfeeding at any time should stop gradually within one month. Mothers or infants who have been receiving ARV prophylaxis should continue prophylaxis for one week after breastfeeding is fully stopped. Stopping breastfeeding abruptly is not advisable.

- **Using expressed heat-treated milk**. Removing the milk from the breasts manually or with a pump, then heating it to kill is another method by which HIV positive mothers may opt to feed their babies. Pretoria pasteurization is a simple low cost method which has been shown to inactivate HIV in breast milk.[22] The method uses passive transfer of heat from 450 ml of water heated to boiling point in which the container of expressed milk is placed. Milk temperatures of 56-62.5 degree Celsius are maintained for 15 -30 minutes.

  As per WHO 2009 guidelines, mothers known to be HIV-infected may consider expressing and heat-treating breast milk as *an interim feeding strategy* under following situations.

  - In special circumstances such as when the infant is born with low birth weight or is otherwise ill in the neonatal period and unable to breastfeed; **or**
  - When the mother is unwell and temporarily unable to breastfeed or has a temporary breast health problem such as mastitis; **or**
  - To assist mothers to stop breastfeeding; **or**
- If antiretroviral drugs are temporarily not available.

- **Using a Wet Nurse:** having another woman breastfeed an infant; ensuring that the woman is HIV negative. The wet nurse must be available to breastfeed the infant frequently throughout the day and night and she must protect herself from HIV infection till she is breastfeeding.

- **Human milk banks:** A centre where donor milk is pasteurized and made available for infants is another source of providing human milk.
- **Use of anti retroviral therapy along with breastfeeding:** Antiretroviral drugs (ARV) reduce viral replication and can reduce mother-to-child transmission of HIV either by lowing plasma viral load in pregnant women or through post-exposure prophylaxis in their newborns. Highly active antiretroviral therapy (HAART) has reduced the vertical transmission rates to around 1-2%, but HAART is not yet widely available in developing countries. In the MITRA PLUS study (Tanzania), in which women were treated with ZDV/3TC/NVP during late pregnancy from 34 weeks of gestation, the infants received ZDV/3TC for one week after birth and mothers counselled on exclusive BF and encouraged to stop at six months, the cumulative proportion of HIV-1 infected infants was 5.0% at 6 months.[23]

Providing post-exposure prophylaxis to the infant is the second approach of use of ARV regimens to prevent MTCT during breastfeeding. In the Mashi Study,[21] mothers received short-course ZDV antenatally and during labor. Mothers and infants were randomized to receive sdNVP or placebo. Infants were randomized to 6 months of BF and ZDV or formula feeding and ZDV for one month. The 7-month HIV infection rates were 9.0% in the first group and 5.6% in the second (p=0.04), but the cumulative mortality was higher in the second group. Both strategies had comparable HIV-free survival at 18 months.

The WHO 2009 guidelines of continuing ART to mother or baby during the period of breastfeeding is a useful strategy particularly for developing nations.

Replacement Feeding options to HIV positive mother

The infant feeding options for replacement feeding include:

• **Commercial infant formula:** specially formulated milk for infants and sold in shops or provided through programmes designed to prevent vertical HIV transmission.

• **Home modified animal milk:** fresh or processed animal milk that is modified by adding water, sugar and micronutrient supplements. WHO 2006 & 2009 guidelines no longer recommend home-modified animal milk as a replacement feeding option to be used for all of the first six months of life as it does not provide all the nutrients that an infant needs. For women who choose replacement feeding, home-modified animal milk should only be used for short times when commercial infant formula is not available.

For infants six months of age and older, undiluted animal milks can be added to the diet, and serve as a suitable substitute for breast milk. The recommended volumes are 200–400 ml per day if adequate amounts of other animal source foods are consumed regularly, otherwise 300–500 ml per day.

How to diagnose HIV infection in infants?

For children < 18 months old, both breastfed and non breastfed, born to a HIV positive mother – the following testing strategy applies according to NACO program.[24]

- The first HIV DNA PCR should be conducted at 6 weeks of age. If the test is positive, the test is to be repeated immediately (or as early as possible) for confirmation.
- If the first PCR is negative in a non-breastfed baby, confirm with a second PCR test at 6 months.

- If the child is breastfed and initial PCR test at 6 weeks is negative, PCR testing should be repeated at 6 – 8 weeks after cessation of breastfeeding to rule out HIV infection.
- In case of mixed feeding the same strategy to be applied as for a breastfed baby.
- If symptoms develop any time, the child should be tested appropriately (PCR or ELISA) at that age.
- A report of HIV positive is given when 2 PCR tests are positive and a report of HIV negative is given when 2 PCR tests are negative.

Can presumptive diagnosis be made when there is no testing available?

A presumptive diagnosis of severe HIV disease is made if

- The infant is confirmed HIV antibody positive

And

- Diagnosis of any AIDS indicator condition can be made

Or

- The infant is symptomatic with 2 or more of the following: Oral thrush, severe pneumonia, severe sepsis

Other factors that support the diagnosis of HIV disease in an HIV seropositive infant include

- Advanced HIV disease in mother
- Recent HIV related maternal death
- CD4 < 20%

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

What are the specific management issues for PCP prophylaxis ?

Pneumocystis carinii pneumonia (PCP) is the most common serious opportunistic infection in HIV-1–infected infants and children especially during the first year of life, with cases peaking at 3 to 6 months of age Chemoprophylaxis is highly effective in the prevention of PCP. HIV-1 exposed infants should be considered for prophylaxis beginning at 4 to 6 weeks of age[25] by administration of TMP-SMZ (5mg/kg/day) which should be given until 1 year of age, at which time reassessment is made on the basis of age-specific $CD4^+$ T-lymphocyte count/percentage thresholds. Trimethoprim/sulfamethoxazole is the drug of choice for prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum. Infants with indeterminate HIV-1 infection status should receive prophylaxis starting at 4 to 6 weeks of age until they are deemed to be presumptively or definitively uninfected.

What is the advice for Immunization?

All routine infant immunizations may be given to HIV-1–exposed infants.[25] If HIV-1 infection is confirmed, then guidelines for the HIV-1–infected child should be followed.[26] All inactivated vaccines can be administered safely to HIV-1–infected children regardless of whether the vaccine is a killed whole organism or a recombinant, subunit, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine.The usual doses and schedules are recommended. Persons with severe cell-mediated immunodeficiency should not receive live-attenuated vaccines. However, children with HIV-1 infection are at increased risk of complications of varicella, herpes zoster, and measles compared with immunocompetent children. On the basis of limited safety, immunogenicity, and efficacy data among HIV-1–infected children, varicella and measles-mumps-rubella vaccines can be considered for HIV-1 infected children who are not severely immunosuppressed (those with $CD4^+$ T-lymphocyte percentages of $\geq$15%). Combined measles-mumps-rubella-varicella (MMRV) vaccine is not recommended for use in children with HIV-1.

References

1. Draft Treatment Guidelines for Pediatricians on HIV care & treatment including ART. NACO, March 2006.
2. Shah NK, Mehta K, Manglani MV. Prevention of mother to child transmission of HIV. Ind J Pract Pediatr 2003; 5(4): 337-347.
3. De Cock KM, Fowler MG, Mercier E, de Vincenzi I, Saba J, Hoff E, Alnwick DJ, Rogers M, Shaffer N. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. JAMA 2000; 283:1175-82.
4. Volmink J, Siegfried NL, van der Merwe L, Brocklehurst P. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev 2007;(1):CD003510.
5. Read JS, Newell MK. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. Cochrane Database Syst Rev. 2005;(4):CD005479.
6. Horvath T, Madi BC, Iuppa IM, Kennedy GE, Rutherford G, Read JS. Interventions for preventing late postnatal mother-to-child transmission of HIV. Cochrane Database Syst Rev. 2009;(1):CD006734.
7. WHO Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants; towards universal access. 2006.
8. Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants, November 2009. Available at http://www.who.int/hiv/pub/mtct/advice/en/. Accessed (11March2010) [page number 13,15] .
9. Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. April 29, 2009; pp 1-90. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed (26 Sep 2009) [page number 75].
10. Read JS; American Academy of Pediatrics, Committee on Pediatric AIDS. Human milk, breastfeeding, and transmission of human immunodeficiency virus type 1 in the United States. Pediatrics 2003;112 (5):1196 – 1205.
11. Working Group on Mother-to-Child Transmission of HIV. Rates of mother-to-child transmission of HIV-1 in Africa, America, and Europe: results from 13 perinatal studies. J Acquir Immune Defic Syndr Hum Retrovirol 1995; 8:506-10.
12. Koulinska IN et al. Transmission of cell-free and cell-associated HIV through breastfeeding. Journal of Acquired Immune Deficiency Syndrome 2006; 41:93–99.
13. European Collaborative Study. HIV-infected pregnant women and vertical transmission in Europe since 1986. AIDS 2001;15(6):761–70.

14. Mayaux MJ, Dussaix E, Isopet J, et al. Maternal virus load during pregnancy and the mother-to-child transmission of human immunodeficiency virus type 1: the French Perinatal Cohort Studies. J Infect Dis 1997 ;175(1):172-5. http://www.ncbi.nlm.nih.gov/pubmed/8985214.
15. Coutsoudis A, Pillay K, Spooner E, Kuhn L, Coovadia HM. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. South African Vitamin A Study Group. Lancet 1999; 354(9177):471-6.
16. Coovadia HM et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding: the first six months of life. Lancet 2007, 369:1107-16.
17. Willumsen JF et al. Breastmilk RNA viral load in HIV-infected South African women: effects of subclinical mastitis and infant feeding. AIDS 2003; 17(3):407–14.
18. The Breastfeeding and HIV International Transmission Study Group (BHITS) (2004). Late postnatal transmission of HIV in breast-fed children: an individual patient data meta-analysis. Journal of Infect Dis 189(12):2154–66.
19. HIV and infant feeding : update based on the technical consultation held on behalf of the Inter-agency Team (IATT) on Prevention of HIV Infections in Pregnant Women, Mothers and their Infants, Geneva, 25-27 October 2006.
20. Sinkala M et al. for the Zambia Exclusive Breastfeeding Study (ZEBS) Team. No benefit of early cessation of breastfeeding at 4 months on HIV-free survival of infants born to HIV-infected mothers in Zambia: the Zambia Exclusive Breastfeeding Study.
21. Thior I et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. Journal of the American Medical Association, 2006, 296: 794-805.CROI 2007, Session 24, Abstract 74.
22. WHO, UNICEF, UNFPA and UNAIDS. HIV Transmission Through Breastfeeding .A Review of Available Evidence. An Update from 2001 to 2007. Available at http://www.unfpa.org/public/op/edit/publications/pid/2046. Accessed Sept 30,2010.
23. Kilewo C, Karlsson K, Ngarina M, Massawe A, Lyamuya E, Lipyoga R, Msemo G, Swai A, Mhalu F, Biberfeld G. Prevention of mother-to-child transmission of hiv-1 through breastfeeding by treating mothers prophylactically with triple antiretroviral therapy in Dar es Salaam, Tanzania - the Mitra Plus Study IAS Conf HIV Pathog Treat 2007 Jul 22-25;4th: Abstract No. TUAX101. Available at http://www.aegis.com/conferences/iashivpt/2007/TUAX101.html. Accessed Sept 30, 2010.
24. Guidelines for HIV care & treatment in infants & children. NACO. Nov. 2006. Available at http://www.nacoonline.org/upload/Policies%20&%20Guidelines/4-%20Guidelines%20for%20HIV%20care%20and%20treatment%20in%20Infants%20and%20children.pdf. Accessed Sept 30, 2010.
25. Havens PL, Mofenson LM, and the Committee on Pediatric AIDS. Evaluation and Management of the Infant Exposed to HIV-1 in the United States..Pediatrics 2009;123(1):175-87.
26. Mofenson LM, Brady MT, Danner SP, Dominguez KL, Hazra R, Handelsman E, Havens P, Nesheim S, Read JS, Serchuck L, Van Dyke R; Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America; Pediatric Infectious Diseases Society; American Academy of Pediatrics. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep. 2009 Sep 4;58(RR-11):1-166.

Annexure

1.Steps of Infant Feeding Counselling

Step 1: The risk of MTCT should be explained to the HIV positive mother.
Step 2: The advantages and disadvantages of different feeding options starting with the mother's initial preference should be provided.
Step 3: The counsellor should explore with the mother her home and family situation and help her to choose an appropriate feeding option.
Step 4: Once selected, the counsellor should help with demonstration how to practice the chosen feeding option.
Step 5: Provide counselling and support throughout.

2.AFASS

The terms Acceptable, Feasible, Affordable, Sustainable and Safe (AFASS) are defined as follows:

Acceptable: The mother perceives no cultural or social barrier to replacement feeding. She is under no social or cultural pressure not to use replacement feeding; and she is supported by family and community in opting for replacement feeding, and she can deal with possible stigma attached to being seen with replacement food.

Feasible: The mother (or family) has adequate time, knowledge, skills and other resources to prepare the replacement food and feed the infant up to 12 times in 24 hours. She can understand and follow the instructions for preparing infant formula, and with support from the family can prepare enough replacement feeds correctly day and night.

Affordable: The mother and family, with community or health-system support if necessary, can pay the cost of purchasing/producing, preparing and using replacement feeding, including all ingredients, fuel, clean water, soap and equipment, without compromising the health and nutrition of the family. This concept also includes access to & cost of medical care.

Sustainable: Availability of a continuous and uninterrupted supply and dependable system of distribution for all ingredients and products needed for safe replacement feeding, for as long as the infant needs it, up to one year of age or longer. Another person is available to feed the child in the mother's absence, and can prepare and give replacement feeds.

Safe: Replacement foods are correctly and hygienically prepared and stored, and fed in nutritionally adequate quantities, with clean hands and using clean utensils, preferably by cup. There should be access to a reliable supply of safe water

Note: In a huge country like ours with population of diverse backgrounds with respect to affordability of replacement feeding, education of mothers and their capacity to understand the importance of cleanliness in preparation of replacement feeds, availability of safe drinking water etc, it is not feasible to have a single policy of avoidance of breastfeeding to minimize transmission.

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Assessment and Management of Pain in the Newborn

Summary of Recommendations

- **Neonates, including preterms experience pain like older children and adults.**
- **Almost all procedures create undesirable stress responses in neonates.**
- **PIPP (Premature Infant Pain Profile) can be used to assess acute pain and N-PASS (Neonatal Pain Agitation and Sedation Scale) for prolonged pain.**
- **Comfort measures such as skin to skin contact, facilitated tucking, swaddling, containment and a quiet environment are effective strategies for pain management.**
- **Amongst the pharmacological measures, sucrose, dextrose and paracetamol are effective for minor procedures. Opioids should be used selectively, when indicated by clinical judgment and evaluation of pain indicators.**
- **Benzodiazepines cannot be recommended for routine sedation in ventilated neonates. Similarly, none of the barbiturates can be recommended for sedation or analgesia in neonates.**
- **Topical anesthetics are useful for invasive procedures.**

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Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is important to understand that the inability to communicate verbally or nonverbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment[1]. Pain can be acute, established, or chronic. It can further be classified as physiologic, inflammatory, neuropathic, or visceral, with each of these categories further divided according to the degree of severity. Pain in newborns is very commonly overlooked, under recognized, and under-treated. Health care providers must evaluate, recognize, prevent and manage pain in the newborn infant. The following guideline is meant to help the health care provider assess and manage pain in the newborn and has attempted to answer the following issues:

- Pain perception & effects of inadequately treated pain
- Manifestations of pain in neonates
- Procedures and events that cause pain and discomfort
- Technique & tools for objective assessment of neonatal pain
- Management of pain in neonates – non-pharmacological methods
- Management of pain in neonates – pharmacological methods
- Prevention / minimization of pain

Do newborn babies perceive pain and what are the effects of inadequately treated pain?

Evidence: The anatomic and physiological basis for nociception is present even in very preterm neonates. Infants who are cared for in the intensive care neonatal unit experience pain frequently, and for prolonged periods of time. Newborn infants have an increased sensitivity to pain and are more sensitive to pain than older children and adults and are vulnerable to long-term effects related to pain [2, 3]. Preterm infants have mature pain perception pathways that render them capable of perceiving pain. However immature descending neural pathways render any pain modulation relatively ineffective, resulting in a greater magnitude of pain that lasts for a longer period of time [4].

Research has shown that failure to reduce pain in preterm infants may lead to permanent changes in brain processing and maladaptive behavior later [4-6]. Pain may also have certain detrimental effect on the subsequent ability of the infant to learn and remember new information. Prolonged stress due to pain also results in the irreversible depletion of hippocampal dendrites[7]. Repetitive pain and/or stress affect this apoptosis action more profoundly [7, 8]. Minimal anesthesia during surgery has been associated with an increased incidence of intra-operative and postoperative complications leading to poor surgical outcomes [9, 10]. Trials have shown that improved pain control during neonatal surgery leads to improved clinical outcome, decreased postoperative morbidity and a lower mortality rate [11, 12]

Recommendation: Neonates experience pain from the same interventions or clinical conditions as older children and adults. Available physiological studies suggest that newborn infants are more sensitive to pain in comparison to older children and adults. Moreover, the pain invoked and its sequelae last for a longer period of time. Prevention and effective reduction of pain in neonates will help in reducing the immediate and long-term effects including altered pain sensitivity and reactivity and other clinical outcomes.

What are the manifestations of pain in neonates?

Evidence: Numerous studies have documented responses of a neonate to pain. The newborn infant may respond to pain through various physiologic, behavioral and biochemical changes (table 1).

Recommendation: The ways of expression of pain is very varied in a newborn ranging from subtle physiologic changes to late and persistent changes in the biochemical parameters.

Which are the procedures and events that cause pain and discomfort?

Evidence: Pain in newborns is a ubiquitous phenomenon and all newborns are routinely subjected to pain from very early in lives. Babies in NICU are subjected to frequent invasive and potentially noxious procedures (table 2 & 3). They may be exposed up to 10 to 14 painful procedures per day. Stevens et al described an average of 134 painful procedures within the first two weeks of life for each of 124 preterm neonates he studied with a gestational age of 27–31 weeks [13]. In a study by Simons et al, among 151 neonates, an average of 14 ± 4 painful interventions were recorded during the first 14 days of life within a period of 24 hours. Critically ill and preterm neonates may experience more than 700 painful procedures by the time of discharge from the NICU. It was also observed that the highest exposure occurred during the first few days of admission and in those neonates who were receiving respiratory support [14].

Recommendation*:* Almost all procedures may create undesirable stress responses in neonates. The degree of risk related to stress depends on the severity of pain, its duration, and the maturity of the infant

What are the techniques and tools available for objective assessment of neonatal pain?

Evidence: Pain in a neonate is primarily due to procedures, varying from minor to major. They may experience pain as a result of undergoing a single or repeated procedure for diagnostic or therapeutic and/or surgical reasons (table 2). This is true for neonates of all gestational ages in all hospital settings[16]. Additionally, mechanically ventilated neonates are subjected to multiple invasive and procedural interventions that may be particularly painful. Sedation alone does not alleviate pain[17]. A number of scales for measuring neonatal pain have been designed and validated to varying degrees (table 3). The manifestations of pain will differ across the different types of pain, the intensity or duration. Thus, it may be impractical to develop a universal scale for assessing pain in all newborns.

On systematically analyzing the literature, we could identify 35 different pain assessment tools. Of these 18 were uni-dimensional and 17 were multi-dimensional. Uni-dimensional methods evaluate one parameter eg: Neonatal Facial Coding System (NFCS) and multidimensional methods include physiologic, behavioral, and contextual parameters. As per the current evidence there is no “gold standard” for evaluating neonatal pain (especially in ELBW neonate).

Pain assessment tools have certain limitations like:

- Subjective evaluation by observers leading to inter-observer variability
- Requires mandatory training of the staff to improve inter-observer reliability
- Most assessment tools may not detect prolonged pain, pain in ELBW infants (birth weight <1000 g), critically ill, neurologically abnormal or those receiving paralytic medications or infants with persistent/chronic pain.

- Influenced by hunger, fatigue, noxious stimuli like light, sound etc.
- A behavioral score is not the same as a pain intensity score. Behavioral scores are useful in telling us whether pain is present or not but does not indicate about the severity of pain

Recommendation*:* Assess pain on admission, when pain is suspected, before and 10-30 min after additional pain medication and when infant's condition changes substantially.[18] Acute procedures does not require scoring and one should focus on performing the procedure optimally. However, severe painful events such as newborns with NEC with distended abdomen, after vacuum extraction, those with fractures, those with extended hematoma (e.g. after breech extraction), those following intestinal surgery related to necrotizing enterocolitis (NEC) and cardiac surgery may require frequent evaluation. Ideal pain assessment tool for acute pain is the PIPP (Premature Infant Pain Profile) whereas one should use the N-PASS (Neonatal Pain Agitation and Sedation Scale) for prolonged pain [19-21]

Practice point: The provider must remember that a lack of response to pain does not indicate lack of pain. None of the existing instruments have fulfilled all criteria for an ideal measure. The choice of the assessment pain tool is dependent upon the neonatal population to be assessed and the different types of pain that need to be evaluated. Because of the limited ability to detect and quantify neonatal pain, it is desirable that pain control measures should routinely be administered to prevent or reduce pain due to known noxious stimuli.

How can one manage pain in neonates utilizing non-pharmacological methods?

Non-pharmacological pain intervention is a prophylactic and complementary approach to reduce pain. A number of non-pharmacologic therapies have been shown to be beneficial in the management of mild to moderate pain in neonates. These therapies include non-nutritive sucking (NNS) both with and without sucrose, breast milk, breastfeeding, swaddling or facilitated tucking, kangaroo care, music therapy, and multi-sensorial stimulation[22]. Effective coping strategies, such as 'maternal touch', 'NNS' and 'kangaroo care', may elicit activation of neuropeptides systems, such as cholecystokinin (CCK). CCK is an opioid-modulating substance that promotes stressor adaptability and can achieve an analgesic effect through the potentiation of opioid activity[23]

Breastfeeding: Breastfeeding was associated with reduction in changes in the heart rate, duration of crying, percentage time crying and improvement in validated and non-validated pain measures when compared to placebo/no intervention/positioning in neonates[24]. Breastfeeding was equally effective when compared to higher concentrations of glucose/sucrose with respect to duration of crying and PIPP score. However, these findings are applicable only to term babies and for procedures such as heel prick and venepuncture. Breastfeeding is better than sucrose solutions for procedural pain in term neonates [25, 26]. However, it is impossible to delineate the role of different components of breastfeeding or the mechanisms behind the analgesic effect of sucrose solutions, skin-to skin contact, holding, oro-tactile stimulation because of oral liquid, or oro-gustatory stimulation [25].

Recommendation: Breastfeeding or supplemental breast milk should be used to alleviate procedural pain in neonates undergoing a single painful procedure. The role of breastfeeding or supplemental breast milk in cases of repeated painful procedures has not been established [24]

Non Nutritive Sucking (NNS): A total of 4 RCTs and one meta-analysis have been conducted on the effects of NNS [23]. In all of them pacifiers were used alone or along with sucrose/glucose. There are no studies published of NNS being used on an empty breast to prevent/reduce pain. Sucking on a pacifier or

a cotton wool stick which had been sprinkled with distilled water, 10% glucose, or 24% sucrose resulted in a reduction in pain. A statistically significant reduction in pain response was achieved by sucking on a pacifier with distilled water. Sucking on a pacifier with 10% glucose was more effective than sucking on a pacifier with distilled water.

Recommendation: Pacifiers are not recommended for our country primarily due to risk of infection and negative effect on breastfeeding promotion. Hence, it is recommended to use empty breast nipples or a gloved finger dipped in sucrose or breast milk or glucose solution and inserted in baby's mouth for NNS. Use of NNS should be restricted to infants above 28 weeks of gestation or those who have developed a suck response [25]

Kangaroo Care: One RCT and one meta-analysis evaluating kangaroo mother care (KMC) for pain relief during minor procedures like heel lancing, have concluded that KMC is beneficial in reducing pain during heel lances. This is true for term babies [26] and preterm babies (28 weeks to 36 [6/7] weeks) [27-30]. The pain assessment tool varied in these studies.

Recommendation: KMC reduces pain during minor procedures like heel prick. KMC is an excellent tool applied at least for 15 minutes before the heel prick with continuation during the procedure and the recovery phase.

Music: Two RCTs have shown beneficial effect of music on pain response such as lowering of heart rate and rise in oxygen saturation and a reduction in excitation state. These studies were done in infants more than 31 weeks of gestation and in one of them music was combined with NNS. The authors concluded that music should not be provided for longer than 15 min per intervention due to the risk of sensory overload. Various types of music like intrauterine sounds, instrumental music or Capella singing were used in these studies [31]

Recommendation: Music may have a calming effect even in newborns but is not standardised and more studies need to be done to confirm the result

Facilitated tucking: 'Facilitated tucking' was tested in three studies with randomised samples of 30–40 preterm infants. In tucking, a nurse or a parent holds the infant in the side-lying, flexed fetal-type position. This posture gives the infant an opportunity to control his/her own body which may increase the infant's ability to control pain. Adding simultaneous skin contact to postural support may result in synergistic effect in pain control. 'Facilitated tucking' leads to a significant reduction in the heart rate. Time to first quieting and total crying time were also reduced significantly. With regard to oxygen saturation, however, this intervention had no effect. Among a group of 40 intubated and ventilated preterm neonates between 23 and 32 weeks gestation, 'Facilitated tucking' during endotracheal suctioning achieved significant pain relief [23].

Recommendation: Facilitated tucking is useful in neonates between the age groups of 25 to 36 weeks and should be used during endotracheal suctioning or other painful procedures.

Swaddling: 'Swaddling' involves wrapping the neonate in a fabric cloth. 'Swaddling' after a painful intervention is associated with a clear reduction in the heart rate. 'Swaddling' also has an effect on oxygen saturation for all age groups. The preterm neonates demonstrate a significantly faster increase in oxygen saturation, and in the process attain stability more rapidly than a control group. The behaviour-oriented indicators, such as facial mimicry, body language and crying, are attenuated as a result of

'swaddling'. In a meta-analysis with a random sample of 108 term and preterm neonates, a pain-relieving effect was also recorded, the effect being maintained, interestingly, for a longer time among term infants (up to 4 min). Among preterm infants, the effect was also present but lasted for a significantly shorter time [23]

***Recommendation**:* Swaddling is recommended during procedures to reduce pain along with other measures.

Positioning: Laying the neonate in a prone position is a frequent measure in everyday practice as it is expected that the counter-pressure of the mattress will relieve the pain being experienced. Furthermore it promotes better breathing and a decrease of oxygen needed. The moderate to large effect of 'positioning' continued throughout the post stick period. In contrast the effects of 'swaddling' (in both full term and preterm neonates) and of 'maternal holding and touching' tended to decrease over time.

***Recommendation**:* Evidence for the effect of 'positioning' remains inconclusive [23]. Positioning may be useful to reduce pain and anxiety along with other measures.

Olfactory and multi-sensorial stimulation: A familiar odour might be effective in relieving distress associated with painful stimuli in preterm infants. This odour could be the odour of breast milk or of vanilla or any other experiential flavour. Olfactory intervention is probably only effective in cases of slight to moderate pain [23].

Recommendation: Currently, this method cannot be depended upon for pain relief as a sole option but can be co-opted with other interventions.

How to manage pain in neonates utilizing pharmacological methods?

Evidence:

Sucrose: Small amounts of sweet solutions placed on to the neonate's tongue have been shown to mediate an increase in endogenous opioid release, reduce procedural pain and minimize crying following the procedure [32]. The recommended sucrose concentration is a 24% solution. When breastfeeding is not possible, oral sucrose has been found to be effective for repeated painful procedures during an infant's hospitalization in term and preterm neonates [33, 34]. The oral administration of sucrose is a safe and effective form of analgesia for short-duration procedures and may be given for repeated procedures [17, 33, 34]. The effect of sucrose on pain is mediated via its gustatory effect (taste), and therefore, doses are given onto the tongue (buccal). No benefit has been demonstrated when administered via a gastric tube [35]. Two minutes prior to the painful procedure, administering a small amount of the dose onto the neonate's tongue using a syringe or pacifier [32, 35] have a lesser risk of poor developmental outcomes in one small study. The long-term effects of sucrose use for short-duration procedures are unknown; therefore, sucrose should be used with caution for neonates hospitalized for a prolonged period of time, in particular, neonates of less than 32 weeks gestation [36]. It should be used in conjunction with environmental and behavioral measures to relieve pain. A dose dependent effect is noted with increasing analgesic effect. Even tiny amount of 0.05 ml may provide some relief.

Recommendation: The most effective dose and concentration of sucrose is 2ml of 24% solution. In infants requiring intensive care, administration of 0.1 ml of 24% sucrose solution orally will be effective. Similarly, premature infants (32 to 36 wks) on full oral feeds and term infants should be given 0.5 to 1 ml

and 1 to 2 ml orally respectively for optimal effect. Until readymade preparations are available, freshly prepared sterile solutions may be used (dose: 0.12-.48 grams sucrose).

Paracetamol & other NSAIDs: Paracetamol (Acetaminophen) acts primarily by inhibiting the COX enzymes in the brain and has been well studied in newborns, particularly for mild procedural pain or fever reduction after immunizations. However, it has limited efficacy for procedures such as circumcision[37] or heel prick[38]. Rectal or intravenous formulations (propacetamol) have been studied in neonates and infants, with minimal adverse effects shown clinically[39]. Limited data are available on the pharmacokinetics of acetaminophen (paracetamol) in newborns. There are no studies in the newborn on the effectiveness and safety of ketorolac or ibuprofen to reduce pain

Recommendation: Paracetamol can be recommended for pain reduction in immunization as well as for mild procedures like circumcision. It cannot be recommended as the sole agent for pain reduction in other conditions. It should be used with caution in neonates with renal or liver impairment

Opioids: Among the opioids, fentanyl, morphine, alfentanil and methadone seem to be used more commonly in neonates. Adequate safety and efficacy data are not available for most opioid analgesics, owing to the lack of validated pain assessment measures and large well-designed clinical trials.

Fentanyl: Fentanyl is used frequently because of its ability to provide rapid analgesia, maintain haemodynamic stability, block endocrine stress responses and prevent pain-induced increases in pulmonary vascular resistance[40]. Fentanyl is highly lipophilic, crosses the blood–brain barrier rapidly, accumulates in fatty tissues and causes less histamine release compared with morphine. Searches of Medline, EMBASE, the Cochrane Controlled Trials Register and Pediatric Research abstracts yielded only three trials of fentanyl in ventilated preterm neonates that met the inclusion criteria for a meta-analysis[41-43] These studies reported markedly lower heart rates, behavioural stress scores and pain score for infants receiving fentanyl versus those receiving placebo, but at 24 h, higher ventilator rates and peak inspiratory pressures were required for infants receiving fentanyl. Side effects of fentanyl include vagal bradycardia, chest wall rigidity and opioid tolerance after prolonged therapy. Despite case reports of chest wall rigidity, a prospective study of rapid fentanyl infusion showed no adverse effects on dynamic respiratory system compliance in infants [44]

Morphine: Placebo-controlled RCTs with blinded assessments showed no differences in pain scores between placebo and morphine groups before and after tracheal suctioning or heel sticks. A recent meta-analysis, that included 13 studies with 1505 infants of fair to good quality, reported that infants given opioids showed reduced Premature Infant Pain Profile (PIPP) scores compared to the control group. Heterogeneity was significantly high in all analyses of pain [45]. Meta-analyses of mortality, duration of mechanical ventilation and long-term and short-term neurodevelopmental outcomes showed no statistically significant differences. Very preterm infants given morphine took significantly longer to reach full enteral feeding than those in control groups. One randomized trial, comparing infusions of fentanyl (1.5 mg/kg/h) versus morphine (20 mg/kg/h) in ventilated neonates has reported similar pain scores, catecholamine responses and vital signs in the two randomized groups [46]

Recommendation*:* There is insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns. Opioids should be used selectively, when indicated by clinical judgment and evaluation of pain indicators. If sedation is required, morphine is safer than midazolam. More studies are required to test the efficacy and safety of newer opioids like alfentanyl in neonates

Benzodiazepines: Midazolam and lorazepam are used extensively in neonates, but diazepam is used infrequently because of its limited metabolism in neonates. Despite several studies examining its use in ventilated preterm neonates[47-49], a recent Cochrane report[50] noted that the results of these three RCTs could not be combined for analysis. Two studies reported increased sedation with midazolam, but one reported an increased incidence of poor neurological outcomes (IVH, PVL or death), with longer hospital stay[47]. Another study using midazolam for intubation noted side effects, causing early termination of the trial[51]; intravenous boluses of midazolam can lead to changes in cerebral blood flow, although long-term outcomes after neonatal midazolam therapy have not been reported. Lorazepam is also used in the intensive care nursery because of its prolonged duration of action (8–12 h) and potent anticonvulsant effects. Lorazepam was used successfully for seizure control in neonates who were refractory to phenobarbital and phenytoin, despite its potential neuronal toxicity[52].

Recommendation: Midazolam has been associated with adverse effects without any significant advantage in ventilated neonates. Hence benzodiazepines cannot be recommended for routine sedation in ventilated neonates

Barbiturates: Barbiturates such as phenobarbital and thiopental have been used extensively in neonates for sedation and seizure control. The barbiturates are hypnotic agents with no analgesic effects and are metabolized in the liver. Like the benzodiazepines, phenobarbital is often used in conjunction with opioids to provide sedation, and for reducing excitability in the neonatal abstinence syndrome [53] Thiopental is a short-term barbiturate used primarily for anaesthetic induction. A placebo-controlled RCT showed that it prevents the blood pressure and heart rate changes associated with tracheal intubation, although clinical outcomes such as IVH or neurodevelopmental outcome were not studied[54]. Despite its theoretical advantages as a potent analgesic, sedative and amnestic agent, ketamine has been minimally studied in neonates; thus, it should be used mostly in approved research protocols. Similarly, Propofol has gained increasing popularity as an anaesthetic agent for neonates, but with very little data to support its use in this population[55]. Although there are pharmacokinetic data on children, these data are lacking in neonates.

Recommendation*:* As per the current evidence, none of the barbiturates can be recommended for sedation – analgesia of neonates. More research is needed involving safer drugs like propofol in neonatal population with pain relief and mortality as primary short term outcomes.

Local anesthetics: Local anesthetics effectively reduce procedural pain in neonates. Injectable lidocaine and topical creams have both been studied in various neonatal populations. Lidocaine is used commonly for dorsal penile nerve block in neonatal circumcision, but a head-to-head comparison reported ring block to be more effective than either dorsal penile block or topical anesthetics[56]. Lidocaine infiltration is not effective for lumbar puncture in neonates[57] although handling, immobilization and pain from dural puncture may over-ride the effects of local anesthesia. Complications of therapy include case reports of seizures and changes in brain stem auditory response with lidocaine injection. Various topical anesthetics have been tried in neonates with variable success. The first of these, EMLA (Eutectic Mixture of Local Anesthetics) cream, was studied extensively in neonates for procedural pain[58] although newer agents have a shorter onset of action and may be more effective. For example, the pain from heel pricks, the most common skin-breaking procedure in neonates, is not affected by EMLA cream[59]. Although multiple studies have shown its efficacy for venepuncture, lumbar puncture or immunizations, it was less efficacious than sucrose for venepuncture or lidocaine blocks for circumcisions[40]. Complications of topical anesthetics include methemoglobinemia from the prilocaine component if EMLA cream is not applied correctly, or transient skin reactions from various agents.

***Recommendation**:* In summary, topical anesthetics are useful for invasive procedures in neonates, but they must be used correctly and cautiously in preterm neonates.

What are the methods to prevent or minimize pain in a newborn?

Evidence & *recommendation:*** Consideration of the least painful method of undertaking specific procedures is important[16]. It also important to provide information to the parents that emphasizes that breastfeeding or oral sucrose is effective for short duration procedures and the administration may be repeated for subsequent procedures[33, 34] Comfort measures such as positioning, swaddling, containment; a quiet environment; pacifiers; and a familiar odor reduce the effects of extraneous stimuli and are effective strategies for pain management[27]

Painful or stressful procedures should be minimized and when appropriate, coordinated with other aspects of the neonate's care. Special consideration is required for infants less than 30 weeks gestation as they may not tolerate clustered cares following a stressful intervention[13] A sweet-tasting solution, such as a breastfeed or sucrose, is given prior to painful procedures.

Opioid infusions are used at the lowest effective dose and minimum duration based on clinical assessment. The use of opioid for infants with ongoing pain or post-operative pain is recommended and weaned as soon as possible to avoid narcotic dependence and withdrawal, and pain assessments should be undertaken regularly. Premature infants, specifically those less than 28 weeks gestation, require particular attention as opioids can be harmful and their behavioral responses can be altered[60]

Small amounts of mother's EBM, if available, have been found to be effective for painful procedure management in newborns unable to suckle at the breast. A small amount of EBM should be placed on the tongue prior to and during a painful procedure. The effectiveness of repeated doses over time has not been evaluated as yet.

Pain assessments should be carried out by health professionals at least once per shift for all neonates following surgery, those receiving mechanical ventilation and those in intensive or special care nurseries who are subjected to painful procedures. A lack of behavioral responses (including crying and movement) does not necessarily indicate a lack of pain[16]. Infants at risk of neurological impairment also respond to painful stimuli. Assessment of pain and distress in ventilated preterm infants presents special challenges[60].

Useful indicators of persistent pain in ventilated preterm infants may include facial expression, varied activity, poor response to routine care and poor ventilator synchrony. Pain should be assessed as frequently as other vital signs.

References

1. Merskey H. IASP Pain Terminology. Seattle, WA: IASP Press; 2001
2. Slater, R, Cantarella, A, Gallella, S, et al. Cortical pain responses in human infants. J Neurosci 2006; 26:3662
3. Bartocci, M, Bergqvist, LL, Lagercrantz, H, Anand, KJ. Pain activates cortical areas in the preterm newborn brain. Pain 2006; 122:109

4. Anand K. Pain, plasticity, and premature birth: A prescription for permanent suffering? Nature Medicine 2000; 6:971–73
5. Anand K, and Hickey P. Pain and its effects in the human neonate and fetus. New England Journal of Medicine 1987; 317:1321–29.
6. Anand K, and Scalzo F. Can adverse neonatal experiences alter brain development and subsequent behavior? Biology of the Neonate 2000; 77:69–82
7. Weinstein S. Periventricular leukomalacia in premature infants: Implications for developmental specialists. Paper presented at Developmental Interventions in Neonatal Care Conference, 2001, November 4, Washington, DC.
8. Buskila D, Neumann L, Zmora E, et al. Pain sensitivity in prematurely born adolescents. Arch Pediatr Adolesc Med 2003; 157:1079
9. Anand KJS. Relationships between stress responses and clinical outcome in newborns, infants, and children. Crit Care Med. 1993; 21(9 suppl):S358–S359.
10. Bouwmeester NJ, Anand KJS, van Dijk M, Hop WC, Boomsma F, Tibboel D. Hormonal and metabolic stress responses after major surgery in children aged 0–3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth. 2001;87: 390–99
11. Anand KJ, Sippell WG, Aynsley-Green A. Randomized trial of fentanyl anesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet 1987; 1:62.
12. Anand KJ, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 1992; 326:1.
13. Stevens B, Johnston C, Franck L, Petryshen P, Jack A, Foster G. The efficacy of developmentally sensitive interventions and sucrose for relieving procedural pain in very low birth weight neonates. Nurs Res 1999; 48:35–43
14. Simons S, van Dijk M, Anand S, Roofthooft D, van Lingen R, Tibboel D. Do we still hurt newborn babies? Arch Pediatr Adolesc Med 2003; 157:1058–64
15. Fitzgerald M. The development of nociceptive circuits. Nat. Rev. Neurosci. 2005; 6:507–20
16. Anand KJ. International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. Arch. Pediatr. Adolesc. Med. 2001; 155:173–80
17. Suresh S, Anand KJ. Opioid tolerance in neonates: a state-of-the-art review. Pediatr. Anesth. 2001; 11:511–21
18. Hummel P, van Dijk M Pain assessment: current status and challenges. Semin Fetal Neonatal Med. 2006; 11:237-45.
19. Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. Clin J Pain 1996; 12:13.
20. McNair C, Ballantyne M, Dionne K, et al. Postoperative pain assessment in the neonatal intensive care unit. Arch Dis Child Fetal Neonatal Ed 2004; 89:F53.
21. Anand KJS, Aranda JV, Berde CB, et al. Analgesia and anesthesia for neonates: study design and ethical issues. Clin Ther 2005; 27:e43
22. Brenda Golianu, Elliot Krane, Jeannie Seybold, Chris Almgren, and K. J. S. Anand. Non-pharmacological techniques for pain management in neonates. Semin Perinatol. 2007; 31:318-22
23. Cignacco E, Hamers JP, Stoffel L, van Lingen RA, Gessler P, McDougall J, Nelle M. The efficacy of non-pharmacological interventions in the management of procedural pain in preterm and term neonates. A systematic literature review. Eur J Pain. 2007; 11:139-52
24. Shah PS, Aliwalas LL, Shah VS. Breastfeeding or breast milk for procedural pain in neonates. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD004950. DOI: 10.1002/14651858.CD004950.pub2
25. Codipietro L, Ceccarelli M, Ponzone A Breastfeeding or oral sucrose solution in term neonates receiving heel lance: a randomized, controlled trial. Pediatrics. 2008; 122:e716-21.
26. Larry Gray, Lisa Watt and Elliott M. Blass Skin-to-Skin Contact Is Analgesic in Healthy Newborns. Pediatrics 2000; 105:e14
27. Johnston CC, Stevens B, Pinelli J, et al. Kangaroo Care Is Effective in Diminishing Pain Response in Preterm Neonates. Arch Pediatr Adolesc Med. 2003; 157:1084-88
28. Ludington-Hoe SM, Hosseini R, Torowicz DL. Skin-to-Skin Contact (Kangaroo Care) Analgesia for Preterm Infant Heel Stick. AACN Clin Issues. 2005; 16:373-87.

29. Johnston CC, Filion F, Campbell-Yeo M, et al. Kangaroo mother care diminishes pain from heel lance in very preterm neonates: a crossover trial. BMC Pediatr. 2008; 24:13.
30. Castral TC, Warnock F, Leite AM, Haas VJ, Scochi CG. The effects of skin-to-skin contact during acute pain in preterm newborns. Eur J Pain. 2008; 12:464-71.
31. Hartling L, Shaik MS, Tjosvold L, et al. Music for medical indications in the neonatal period: a systematic review of randomized controlled trials. Arch. Dis. Child. Fetal Neonatal Ed. 2009; 94: F1-F7.
32. Stevens B, Yamada J, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst. Rev.2004; 3: CD001069. DOI: 10.1002/14651858.CD001069.pub2
33. Stevens B, Yamada J, Beyene J et al. Consistent management of repeated procedural pain with sucrose in preterm neonates: is it effective and safe for repeated use over time? Clin. J. Pain 2005; 21:543–48
34. Harrison D, Loughnan P, Manias E, Johnston L. The effectiveness of repeated doses of oral sucrose in reducing procedural pain during the course of an infant's prolonged hospitalization. J Paediatr Child Health 2007; 43 (Suppl. 1):A20
35. Ramenghi LA, Evans DJ, Levene MI. 'Sucrose analgesia': absorptive mechanism or taste perception? Arch. Dis. Child. Fetal Neonatal Ed.1999; 80:F146–7
36. Johnston C, Filion F, Snider L et al. How much sucrose is too much? Pediatrics 2007; 119:226
37. Howard CR, Howard FM, Weitzman ML. Acetaminophen analgesia in neonatal circumcision: the effect on pain. Pediatrics 1994; 93:641–46
38. Shah V, Taddio A, Ohlsson A. Randomized controlled trial of paracetamol for heel prick pain in neonates. Arch Dis Child Fetal Neonatal Ed 1998; 79:F209–211
39. van Lingen RA, Deinum JT, Quak JM, et al. Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates. Arch Dis Child Fetal Neonatal Ed 1999; 80:F59–63
40. Anand KJS, Hall RW. Pharmacological therapy for analgesia and sedation in the newborn. Arch Dis Child Fetal Neonatal Ed 2006; 91:F448-53
41. Orsini AJ, Leef KH, Costarino A, et al. Routine use of fentanyl infusions for pain and stress reduction in infants with respiratory distress syndrome. J Pediatr 1996; 129:140–45
42. Guinsburg R, Kopelman BI, Anand KJS, et al. Physiological, hormonal, and behavioral responses to a single fentanyl dose in intubated and ventilated preterm neonates. J Pediatr 1998; 132:954–59
43. Lago P, Benini F, Agosto C, et al. Randomized controlled trial of low dose fentanyl infusion in preterm infants with hyaline membrane disease. Arch Dis Child Fetal Neonatal Ed 1998; 79:F194–97
44. Irazuzta J, Pascucci R, Perlman N, et al. Effects of fentanyl administration on respiratory system compliance in infants. Crit Care Med 1993; 21:1001–4
45. Bellu R, de Waal K, Zanini R. Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2010; 95:F241-51
46. Saarenmaa E, Huttunen P, Leppaluoto J, et al. Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: a randomized trial. J Pediatr 1999; 134:144–50
47. Anand KJS, McIntosh N, Lagercrantz H, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Arch Pediatr Adolesc Med 1999; 153:331–8
48. Arya V, Ramji S. Midazolam sedation in mechanically ventilated newborns: a double blind randomized placebo controlled trial. Indian Pediatr 2001; 38:967–72
49. Jacqz-Aigrain E, Daoud P, Burtin P, et al. Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. Lancet 1994; 344:646–50
50. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit [update of Cochrane Database Syst Rev 2000;2:CD002052; PMID: 10796280]. Cochrane Database Syst Rev 2003; 1:CD002052
51. Attardi DM, Paul DA, Tuttle DJ, et al. Premedication for intubation in neonates. Arch Dis Child Fetal Neonatal Ed 2000; 83:F161
52. McDermott CA, Kowalczyk AL, Schnitzler ER, et al. Pharmacokinetics of lorazepam in critically ill neonates with seizures. J Pediatr 1992; 120:479–83
53. Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants [update of Cochrane Database Syst Rev 2002; 3:CD002053; PMID: 12137641]. Cochrane Database Syst Rev 2005; 3:CD002053
54. Bhutada A, Sahni R, Rastogi S, et al. Randomized controlled trial of thiopental for intubation in neonates. Arch Dis Child Fetal Neonatal Ed 2000; 82:F34–7

55. Davis PJ, Galinkin J, McGowan FX, et al. A randomized multicenter study of remifentanil compared with halothane in neonates and infants undergoing pyloromyotomy. I. Emergence and recovery profiles. Anesth Analg 2001; 93:1380–86
56. Lander J, Brady-Fryer B, Metcalfe JB, et al. Comparison of ring block, dorsal penile nerve block, and topical anesthesia for neonatal circumcision: a randomized controlled trial. JAMA 1997; 278:2157–62
57. Porter FL, Miller JP, Cole FS, et al. A controlled clinical trial of local anesthesia for lumbar punctures in newborns. Pediatrics 1991; 88:663–9
58. Taddio A, Ohlsson A, Einarson TR, et al. A systematic review of lidocaine prilocaine cream (EMLA) in the treatment of acute pain in neonates. Pediatrics 1998; 101:E1
59. Stevens B, Johnston C, Taddio A, et al. Management of pain from heel lance with lidocaine-prilocaine (EMLA) cream: is it safe and efficacious in preterm infants? J Dev Behav Pediatr 1999; 20:216–21
60. Boyle EM, Freer Y, Wong CM, McIntosh N, Anand KJ. Assessment of persistent pain or distress and adequacy of analgesia in preterm ventilated infants. Pain 2006; 124: 87–91

Table 1: Manifestations of untreated pain in neonates

Physiologic Changes	Behavioral Changes	Biochemical Changes
Increased heart rate	Increased facial grimacing	Increased serum cortisol level
Increased respiratory rate	Crying	Increased epinephrine
Increased intracranial pressure	Increased body movements	Increased norepinephrine
Increased blood pressure	Rapid changes in mood	Increased growth hormones
Decreased oxygen saturations	Fussiness	Decreased prolactin production
Decreased heart rate variability	Sleeplessness	Protein catabolism
Apnea		Hyperglycemia
Bradycardia		
Palmar sweating		
Skin color changes		

Table 2: Classification of procedures based on the intensity of pain

Mild	Moderate	Severe	Chronic
Physical examination	Lumbar puncture	Surgical correction	NEC
Heel prick	Inter-costal tube insertion		Mechanical ventilation
Venepuncture	Endotracheal suction		Meningitis
Arterial puncture	Elective endotracheal intubation		Osteomyelitis
Feeding tube insertion	Eye examination for ROP		
SC/IM injection	Ventricular tap		
Handling for X ray	PICC/Central lines insertion & removal		
Umbilical catheterization	Suprapubic puncture		
Adhesive tape removal	Chest physiotherapy		
Gavage tube insertion	Dressing change		

Table 3: Commonly used measures of pain in neonates

Measure	Variables included	Type of pain	Psychometric testing
PIPP (Premature Infant Pain Profile)	Heart rate, oxygen saturation, facial actions; takes state and gestational age into account	Procedural, postoperative (minor)	Reliability, validity, clinical utility well established
NIPS (Neonatal Infant Pain Score)	Facial expression, crying, breathing patterns, arm and leg movements, arousal	Procedural	Reliability, validity
NFCS (Neonatal Facial Coding System)	Facial actions	Procedural	Reliability, validity, clinical utility, high degree of sensitivity to analgesia
N-PASS (Neonatal Pain, Agitation, and Sedation Scale)	Crying, irritability, behavioral state, facial expression, extremity tone, vital signs	Postoperative, procedural, ventilated	Reliability, validity, includes sedation end of scale, does not distinguish pain from agitation
CRIES (Cry, Requires oxygen, Increased vital signs, Expression, Sleeplessness)	Crying, facial expression, sleeplessness, requires oxygen to stay at_95% saturation,increased vital signs	Postoperative	Reliability, validity

Annexure

1. For acute pain (step ladder approach)

Type of pain	Useful Agent
Mild pain	Oral Sucrose, Breast milk*
Moderate pain	Oral or rectal Paracetamol
Severe pain	Opioids like fentanyl or morphine
Local pain relief	Local infiltration of Lignocaine / Topical analgesic creams

* If breast milk or sucrose is not available, 25% dextrose may be used

2. Recommended non-pharmacologic methods of pain relief in newborns

Intervention	Procedures
Modification of environmental stimuli	Shade infant's eyes Cover isolette/crib with blankets Close doors gently Avoid loud noises/voices Set telephone ring at lowest volume possible Decrease amount of noise Cluster nursing-care activities Allow periods of undisturbed rest Gentle manipulation of tubes and lines Careful removal of tape from skin
Positioning	Swaddling Nesting using blanket rolls to tuck around sides/back/feet and head to promote boundaries Hugging Holding—kangaroo care (skin-to-skin contact) Proper body alignment
Touch	Stroking, rocking, caressing, cuddling and massaging. Simple massage or rubbing of painful areas can relieve pain and spasm and mobilize contracted muscles
Pacifier/sucrose	Give sucrose via pacifier 2minutes before painful procedures
Distraction	Use materials that have auditory and visual stimulation such as music, colored objects, and mobiles Rhythmic rocking

3. Recommended pharmacological therapies for common procedures	
Procedure	**Pharmacotherapy**
Venous or arterial puncture	EMLA or ametope
Lumbar puncture	EMLA cream
Circumcision	Ring block or dorsal penile nerve block with Lidocaine
Intubation	Not known; consider fentanyl 2 mg/kg and midazolam 0.2 mg/kg
Tracheal suction	Not known; consider midazolam, sucrose
Mechanical ventilation	Not known; consider morphine load at 100 mg/kg (if not hypotensive and over 26 weeks gestational age) or midazolam 0.1 mg/kg with drip at 0.05 mg/kg/h or lorazepam 0.1 mg/kg every 4–6 h
ROP Screen	Pupils are dilated with Phenylephrine 2.5% and Tropicamide 1.0%. One drop of Tropicamide is to be instilled every 10-15 minutes up to 4 times starting 1 hour before the scheduled time for examination. This is followed by phenylephrine, one drop just before examination. Phenylephrine is available in 10% concentration; it should be diluted 4 times before use in neonates.
Laser therapy for ROP	Nil by mouth 3 h prior to procedure. Start on intravenous fluids. Put on vital sign monitor. Warmer for maintaining temperature. Dilatation of pupil is done by using 1% tropicamide and 2.5% phenylephrine as for ROP Screening. Use local anesthesia & topical anesthetic drops. Post procedure start feeds if stable.

4 Procedure for administration of sucrose solution for pain relief

Using a syringe, drop directly on the anterior portion of the tongue (90% of taste buds are present in the anterior 2 cm of tongue) or dropped on a gloved finger which can then be placed into the mouth to suck as a pacifier.

For all infants commence administration 2 minutes before the procedure.

If procedure is prolonged (> 5 min) a repeat dose can be considered up to a total of 2 ml.

- **Contraindications:**

Infants not established on enteral feeds.

Hereditary Fructose Intolerance

Infants whose mothers are taking Methadone

Infants of less than 32 weeks of gestation (risk of hyperglycemia, necrotizing enterocolitis)

- **Other precautions:**

  In cases with respiratory distress or sedation/ depression, doses more than 0.1 ml should be used with caution because of the dangers of aspiration and choking.

  Two minutes prior to the painful procedure administer a small amount of the dose, about one drop, onto the neonate's tongue using a pacifier or syringe. If necessary, repeat giving a drop of sucrose onto the infant's tongue during the procedure.

  Use the smallest amount of sucrose to provide pain relief, and if necessary, administer in small drops until the maximum recommended volume is achieved.

  Sucrose is more effective if given in conjunction with NNS.

  Intubated infants can be given oral sucrose using a syringe and placing a drop on the tongue, caution is taken to avoid gagging or choking, use one drop at a time.

  Comfort measures, such as facilitated tucking, rocking, skin to skin care and swaddling, may be used in conjunction with the sucrose during the procedure.

  Using glucose solutions in the dose range of 1 to 2 ml of 10 to 30% has been a useful, but less effective substitute for sucrose solution.

- **Please visit the website www.nnfpublication.org for Pain assessment tools and comparison of various pain relieving agents.**

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Follow up of High Risk Newborns

Summary of Recommendations

- **All health facilities caring for sick neonates must have a follow up program. It requires establishment of a multidisciplinary team.**
- **The level of follow up can be based on anticipated severity of risk to neurodevelopment. The frequency of follow up and the type of tests depend on "intensity or level of follow up" assigned. The schedule for follow up must be planned before discharge from birth admission.**
- **Prior to discharge, a detailed medical and neurological assessment, neurosonogram, ROP screen and hearing screen should be initiated. A psychosocial assessment of the family should also be done.**
- **The follow up protocol should include assessment of growth, nutrition, development, vision, hearing and neurological status.**
- **Formal developmental assessment must be performed at least once in the first year and repeated yearly thereafter till six years of life. In Indian context, DASII is the best formal test for developmental assessment (till 2 year 6 months).**
- **Ideally, the follow up should continue till late adolescence, at least till school as many cognitive problems, learning problems and behavioral problems that are more common in at-risk neonates are apparent only on longer follow up.**
- **Early intervention programme (early stimulation) must be started in the NICU once the neonate is medically stable.**
- **Timely specific intervention must be ensured after detection of deviation of neurodevelopment from normal.**

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Introduction

Last two decades have witnessed a steady improvement in the quality of perinatal care in India. In the last 2 decades, the neonatal care has improved and more VLBW and ELBW babies are surviving in our country. (89 % survival of the 14.5 % preterm babies and 70 % survival of 3.4 % VLBW babies, NNPD 2002-3) Close Neonatal - Obstetric collaboration, successful implementation of NALS programs, better understanding of pathophysiology and management of neonatal problems, technological advances in neonatal care and above all the concern of pediatricians to enhance the intact survival of newborn babies have contributed to this increased survival of high risk newborns. These improvements have been most dramatic in infants born ELBW (<1000g) and at extremes of viability (22-25 weeks) .[1-3, 5-8] Even though there has been a substantial improvement in neonatal survival, the incidence of chronic morbidities and adverse outcome in survivors continues to be high.[2, 4-7, 9-15] The incidence of severe disabilities like Cerebral palsy has remained quite unrelenting at 4.5-10% over the past two decades.[16] This is also associated with reports of increasingly high incidence of neuro-sensory impairment (blindness and deafness), cognitive, learning disabilities and behavioral problems like ADHD and depression.[16-18] Perinatal risk factors and course of neonatal illness define a group of neonates at increased risk of neurodevelopmental disability. Timely and appropriate intervention can prevent or modify many of these disabilities (example – laser photocoagulation for ROP, timely hearing aid for hearing impaired). There is a lack of knowledge among neonatal specialists, primary health care providers, lack of coordination among health care providers and lack of parent understanding of need for follow up. Structured follow up programme can result in improvement of implementation and compliance of the multidisciplinary follow up.

Importance of follow up care

Surveillance: The mission of a neonatal follow up program is to provide a continuum of specialized care to sick babies discharged from NICUs. The objective is to identify early deviation of growth, development or behavior from normal and provide support and interventions as indicated. The neonate "at-risk" of neurodevelopmental disability must be identified before discharge from birth admission. A discharge summary must be provided to primary care provider and parents, the discharge summary should describe the prenatal and perinatal risk factors, neonate's hospital course and therapies that can increase the risk of neurodevelopmental disability. (Level 2 evidence).

Bench marking: Auditing of perinatal care practices: It is now known that short term outcomes of survival or absence of major anomalies in early infancy are not sufficient to assess efficacy and safety of therapies. Long term follow up will enhance understanding of association between risk factors, therapies and intact survival. There is increasing awareness of the importance of reporting long-term outcomes in RCTs studying interventions and not just survival or short term medical outcomes. There is also an increased recognition of the potential disconnect between perinatal outcomes and long-term outcomes. There is lack of evidence based data on the sequelae of these at - risk newborns and most therapies used in neonatal period.

Data base helps in anticipatory counseling of parents/ health planning: In India, we have no systematic database of outcomes of at-risk neonates. The NNPD provides only a database of sick neonates, illnesses and survival. A uniform structure of follow up will go beyond improving care of these at–risk babies, will allow a database that will guide regional and national health care planners. These databases will also allow objective anticipatory guidance of parents based on actual local scenario, rather than information obtained from more equipped and developed world.

Efforts to improve compliance to follow up programs: Parents must be informed of the risk factors for neurodevelopmental disability and the need for follow up. Structured follow up programme will result in improvement of implementation and compliance with the multidisciplinary follow up.

- Integrate multi-disciplinary follow up: Assessments at various points are done by a team of Neonatologist/Pediatrician (coordinator), developmental pediatrician / therapist, ophthalmologist, ENT specialist, audiologist, physiotherapist / occupational therapist, pediatric neurologist, clinical psychologist, orthopedician etc. Effort must be made to integrate the developmental follow up with health visit for immunization or routine care. A social worker / a public health nurse must integrate the multidisciplinary team, facilitate parent communication and improve patient confidence. The date of subsequent visits / purpose / place of next visit for developmental assessment must be explained and documented.
- Communication: Address, phone numbers and emails of parents must be recorded and updated. The parents and primary care physicians must be provided contact phone numbers for clarification and emergency.
- Continuity of care must be ensured. The primary care physician must be identified before discharge. He must be communicated regarding the risk factors and follow up plan.

Recommendations:

- All health facilities caring for sick neonates ("at-risk" of neurodevelopmental disability) must have a follow up program.
- Make efforts to improve compliance to follow up programs.

Who needs follow up and assigning the level of follow up?

The "at –risk" neonates may seem healthy and can be missed on a routine follow up. An active surveillance is necessary, both at ***birth admission and in follow up*** for pointers to abnormal neurodevelopmental outcome. Timely and appropriate screening or assessment must be offered even before symptoms or signs of disability appear.

1. Identify at-risk infants: The neonate "at-risk" of neurodevelopmental disability must be identified before discharge from birth admission. Prenatal, Perinatal risk factors, course of neonatal illness and therapies identify a group of "at – risk" neonates - at increased risk of neurodevelopmental disability. It is important to prospectively record the risk factors and communicate them to parents and document them in the discharge summary. **Documentation:** discharge summary must have gestation, birth weight, discharge weight and discharge head circumference, feeding method and dietary details, diagnosis (medical problems list), medications and references to other departments, days on oxygen and gestation when baby went off oxygen, date and findings of last hematological assessment, metabolic screen, ROP screen, hearing screen, thyroid screen, ultrasound cranium, immunization status, and assessment of family.

   A. Biological risk factors Prematurity, Low birth weight, Asphyxia, Shock, Need for ventilation, CLD, Sepsis, Jaundice, PDA, NEC , Malformations
   B. Interventions – e.g. post natal steroids/ hypocarbia
   C. Socio – economic

Various risk factors have been identified for adverse developmental outcome in NICU graduates. Biggest factor among them is probably gestational age and birth weight. There has been remarkable improvement in survival of VLBW and ELBW babies,[1,3,7,11,23,24] but this improvement has not been associated with a similar improvement in neurodevelopmental outcome. Hence most centers treat neurodevelopmental outcome as a measure of success and undertake follow up of preterms.[2,4-7,9-15]

Neonatal sepsis is another recognized risk factor for neurodevelopmental impairment (NDI). Stoll et al have described in a large cohort from NICHD Neonatal Research Network that infants with neonatal infections were more likely to have lower mean developmental index (MDI) scores, lower psychomotor development index, visual problems and cerebral palsy.[25] Moreover incidence of CNS damage is present in 20 to 60% cases of neonatal meningitis and incidence of hearing loss is 15% in case of gram negative meningitis while 30% suffer disorder ad developmental delay.[26]

In a meta-analysis of infants with NEC overall, 45% of children who had neonatal NEC were neuro-developmentally impaired. Infants with NEC were significantly more likely neurodevelopmentally impaired than infants of similar age and gestation who did not develop NEC, including a higher risk of cerebral palsy (1.5 (1.2 to 2.0), p = 0.001), visual (2.3 (1.0 to 5.1), p = 0.04), cognitive (1.7 (1.4 to 2.2), p<0.0001) and psychomotor impairment (1.7 (1.3 to 2.2), p<0.0001). The odds ratio of neurodevelopmental impairment was also 2.3 times higher in neonates with Bell's stage III disease or requiring surgery ((1.5 to 3.6), p = 0.0001) .[27]Schulke and colleagues have described that the risk of long-term neurodevelopmental impairment was significantly higher in the presence of at least stage II NEC vs no NEC (odds ratio, 1.82; 95% confidence interval, 1.46-2.27). Significant heterogeneity (I^2 = 47.9%; *P* = .06) between the studies indicated variations in patient, illness, and intervention characteristics and in follow-up methods. Patients with NEC requiring surgery were at higher risk for neurodevelopmental impairment vs those managed medically (odds ratio, 1.99; 95% confidence interval, 1.26-3.14).[28]

Invasive ventilation alone has been described as a risk factor for NDI. Marlow and colleagues who studied neurological and respiratory outcomes at 2 year of age of babies ventilated with either high frequency ventilation (HFOV) or conventional ventilation (CV) found at 24 months of age, severe neurodevelopmental disability was present in 9% and other disabilities in 38% of children, but the prevalence of disability was similar in children who received HFOV or CV (relative risk 0.93; 95% confidence interval 0.74 to 1.16).[29] Infants with BPD-2 were found to have a lower mean developmental quotient (comparison group: 97.4 (15.0) vs BPD-1: 97.9 (11.6) vs BPD-2: 90.7 (19.3).[30] Teberg et al [31] and Gray and coworkers [32] concluded that VLBW and preterm infants with BPD present a higher risk of neurodevelopmental delay but that risk is associated with neonatal brain lesions and not respiratory problems. Neonatal jaundice associated with prematurity, birth weight<1000g and bilirubin encephalopathy were likely to have an adverse outcome.[33-35] Also therapeutic interventions like prolonged postnatal steroid therapy to prevent or ameliorate BPD seems to be associated with negative CNS outcomes.[36,37–39]

Recommendations for at risk newborn follow up :

Social class also has a role to play. In a review of social class and developmental outcomes in 37 studies conducted in 2000,[40] low social class as determined by several different means, was associated with poorer growth, greater academic difficulties including reading and spelling problems, lower IQ, poorer language skills, poorer fine motor skills, more aggression and externalizing behavior, more depression and other psychiatric disorders, poorer sibling relationships, and poorer social development[40]. Accordingly

these risk factors can be broadly classified into biological risk, interventions and social/environmental risk[41].

The frequency of follow up and the type of tests used would depend on "intensity or level of follow up" assigned. Determinants of level of follow up include – severity of perinatal risk factors, interventions required at birth admission to NICU, demographic factors of the family, and resources of the follow up service.

High Risk:

1. Babies with <1000g birth weight and/or gestation <28 weeks
2. Major morbidities such as chronic lung disease, intraventricular hemorrhage, and periventricular leucomalacia
3. Perinatal asphyxia - Apgar score 3 or less at 5 min and/or hypoxic ischemic encephalopathy
4. Surgical conditions like Diaphragmatic hernia, Tracheo-oesophageal fistula
5. Small for date (<3rd centile) and large for date (>97th centile)
6. Mechanical ventilation for more than 24 hours
7. Persistent prolonged hypoglycemia and hypocalcemia
8. Seizures
9. meningitis
10. Shock requiring inotropic/vasopressor support
11. Infants born to HIV-positive mothers
12. Twin to twin transfusion
13. Neonatal bilirubin encephalopathy
14. Major malformations
15. Inborn errors of metabolism / other genetic disorders
16. Abnormal neurological examination at discharge

Moderate Risk:

1. Babies with weight – 1000 g- 1500g or gestation < 33 weeks
2. Twins/triplets
3. Moderate Neonatal HIE
4. Hypoglycemia, Blood sugar<25 m/dl
5. Neonatal sepsis
6. Hyperbilirubinemia > 20mg/dL or requirement of exchange transfusion
7. IVH grade 2
8. Suboptimal home environment

Mild Risk:

1. preterm, Weight 1500 g - 2500g
2. HIE grade I
3. Transient hypoglycemia
4. Suspect sepsis
5. Neonatal jaundice needing PT
6. IVH grade 1

Risk factors for NDD - Assign the baby to the highest level indicated by risk

Mild risk for NDD	Moderate risk for NDD	High-risk for NDD
Prenatal risk factors	Abnormal Fetal growth	Fetal distress
≥37 weeks	33 – 36	< 33 weeks
>2500 gms	1500 - 2500	<1500 grams
Booked pregnancy / intramural baby	Sub optimal perinatal care	Sub optimal transport (extramural)
Completed course of ANS	Incomplete course of ANS	No ANS
No need for resuscitation	Need for resuscitation at birth	APGAR < 3 at 5 min Encephalopathy, Multi-organ injury
Levene grade 1	Levene grade 2	Levene grade 3
Not required ventilation	Uncomplicated course of ventilation	Ventilation more than 7 days, Hypocarbia, Pneumothorax Apnoea requiring resuscitation
No shock	Shock	Refractory shock Hemodynamically significant PDA
Transient hypoglycemia	Hypoglycemia, blood sugar < 25 mg / dL, > 3 days	Symptomatic hypoglycemia, seizure
Suspect sepsis (screen negative)	Sepsis (culture +ve / clinical and screen +ve)	Meningitis
Neonatal jaundice needing phototherapy	Neonatal jaundice leading to Exchange transfusion	Kernicterus
NICU admission	(Complex course – NEC & PDA (needing surgery)	CLD
Preterm IVH grade 1 or 2 , no abnormality at 40 wks	Intra-Ventricular Hemorrhage (IVH) > grade 2 on Neurosonogram	Ventriculomegaly and / or cystic periventricular leukomalacia (at 40 weeks), hydrocephalus
Normal neurologic exam at discharge	Severe / prolonged encephalopathy Any cause	Abnormal neurologic examination at discharge / Suspect development
Good home environment + optimal follow up	Sub-optimal Home Environment (Parent coping poor/ low socio-economic)	Parent concern for NDD

Where should the baby be followed up and who should do the follow-up?

Place of follow up should be easily accessible to the parents and the directions to the place should be mentioned in the discharge card. Low risk infants can be followed up at a well baby clinic. Moderate and High risk infants should be followed up in or near to a facility providing Level II and Level III NICU care respectively due to multidisciplinary approach required and increased frequency of ongoing illness in these cohorts.

A comprehensive follow up program requires a multi disciplinary approach involving a team of experts who include a pediatrician, a child psychologist, pediatric neurologist, ophthalmologist, audiologist, occupational therapist, social worker and a dietician all under one roof.

1. Low risk: follow up with pediatrician / primary care provider with objective to screen for deviation in growth and development.
2. Moderate risk: follow up with neonatologist and developmental pediatrician: screen for developmental delay, manage intercurrent illnesses
    - Developmental pediatrician
    - Developmental therapist
    - Radiologist
    - Ophthalmologist
    - Audiologist
    - Physiotherapist
    - Social worker
    - Dietician
3. For babies with high risk of Neurodevelopmental delay: Neonatologist: supervise and screen for developmental delay

    Team as for Moderate risk and

    - Pediatric neurologist
    - Geneticist
    - Occupational therapist
    - Speech therapist
    - Endocrinologist
    - Pediatric surgeon
    - Orthopedician

Recommendations:

- A discharge summary must be provided to primary care provider and parents, the discharge summary should describe the prenatal and perinatal risk factors, neonate's hospital course and (and therapies) that can increase the risk of neurodevelopmental disability. (level 2 evidence)

- The frequency of follow up and the type of tests used would depend on "intensity or level of follow up" assigned. Determinants of level of follow up – severity of perinatal risk factors, interventions required at birth admission to NICU, demographic factors of the family, and resources of the follow up service.

Active surveillance is required before discharge from NICU and in follow up.

Pre-discharge

A) Medical examination
B) Neurobehavior and Neurological examination
C) Neuroimaging
D) ROP screening
E) Hearing screening
F) Screening for congenital hypothyroidism
G) Screening for metabolic disorders
H) Assessment of parent coping and developmental environment

Follow up

I) Medical examination - nutrition and growth, Immunization
J) Neurological examination
K) Development assessment
L) Ophthalmologic assessment – squint and refraction
M) Hearing and Language and speech
N) Function
O) Behavioral, cognitive and intelligence status

Recommendations:

- An active surveillance is necessary, both ***Pre-discharge and in follow up*** for pointers to abnormal neurodevelopmental outcome.
- The schedule for follow up must be planned before discharge from birth admission. The "at-risk" neonates must be followed till at least one year age (follow up into school years is desirable)

Medical examination – physical examination, nutrition and growth, Immunization, unresolved medical issues, laboratory tests (Hemoglobin, Calcium, Phosphate, Alkaline phosphate)

Head circumference (OFC)

- Head circumference (OFC) is the most important and simple tool that can predict abnormal brain growth. (level 2)
    - OFC centile < (microcephaly) / > length centile (hydrocephalus)
    - Static / dropping centile of OFC in relation to length centile on serial follow up

- Growth – weight and length potted on growth chart and compare centiles
    - Birth weight and discharge weight must be compared. Weight centile must be interpreted against length centile.
    - Poor growth may be a pointer to medical problems (can affect Neuro – development)
    - Poor growth is also often seen in babies with NDD (as the feeding is not optimal)
- A complete physical examination must look for common anticipated medical problems some of which may have impact on developmental outcomes – e.g hip examination, dysmorphism, signs of IU infections, neuro-cutaneous markers etc.
    - Hip examination – risk group – breech, oligohydramnios, and girl, family h/o DDH – look for asymmetry
- In preterm babies use special growth chart for preterm babies/ corrected age after the baby is "term"
- Unresolved medical problems must be addressed and medications reviewed
    - Chronic lung disease
    - Gastro-esophageal reflex disease
    - Reactive airway disease

Neurobehavioral and Neurological examination

Neurobehavioral assessment and neonatal neurological examination must form a part of routine clinical examination of a newborn infant. When carefully performed, it is of great value in predicting subsequent abnormality. Several tools have been found effective—Hammersmith neonatal neurological screener, neurodevelopmental risk examination, Amiel-Tison—all examine different domains eg. tone, reflexes, sensory and behavioral responses. They are useful predictors of neurodevelopmental disability on follow up.

Neurobehavioral assessment

Although predictive power of isolated neurological signs is not great, certain abnormal findings are associated with greater frequency with abnormal outcomes. In a large population study, as a part of the Collaborative perinatal project of NIH, when infants who developed cerebral palsy (mostly term) were compared with those who did not, certain neurological abnormalities were valuable predictors.

Neurological signs in neonate (mostly term)	Increased risk of CP
Abnormal Tone – limb, neck, trunk	12-15 fold
Diminished cry for > one day	21 fold
Weak or absent suck	14 fold
Need for gavage or tube feeding	16-22 fold
Diminished activity > one day	19 fold

Similarly, severity of neonatal neurological insult in neonatal period is a predictor of abnormal outcome. Perinatal asphyxia - Levene's modification of Sarnat & Sarnat score.

Grade 1	Grade 2	Grade 3
No seizure	Seizure	Prolonged seizure
Irritable	Lethargy	Comatose
Hypotonia mild	Marked tone abn	Severe hypotonia
Poor sucking	Requires Tube feed	Needs ventilation*

* Fails to maintain spontaneous respiration

In preterm babies - NAPI (neurobehavioral assessment of preterm infants)- It can be used for babies between 32 weeks gestation and term.

Requires training, it includes assessment of

- Motor development & vigor
- Scarf sign
- Popliteal angle
- Alertness & orientation
- Irritability
- Vigor and crying
- Percentage sleep ratings

Also score rating scales for quality of spontaneous movements, crying and visual behavior.

VLBW and ELBW babies, who had CP, had low scores of NAPI.

Neurological examination

Hammersmith neonatal neurological examination (screener) is a simple test. It is best used for evaluation of term born "normal" neonates in maternity ward/ first follow-up in a busy follow up clinic. If two items are in "blocked/ shaded area, the neonate should have a detailed assessment.

The full Hammersmith test evaluates a baby in following areas-

- Posture and tone
- Tone patterns
- Reflexes
- Movements
- Abnormal signs or patterns
- Orientation / behavior

An optimality score is generated in the full test. It is mostly used as a research tool.

Neuroimaging – USG/CT/MRI

Neuroimaging is a very important complement to clinical assessment in the management of preterm and term neonates with encephalopathy. It serves 2 purposes (1) diagnosis of brain pathology for appropriate immediate management and (2) detection of those lesions which are associated with long term neurodevelopmental disability. Problems associated with imaging are the choice of right technique, timing, risk of radiation, need for sophisticated machines and trained manpower etc. Many of these babies are quite often sick and testing outside the NICU may not be possible. The growing brain differs in maturity and interpretation of MRI / ultrasound images requires a sound knowledge of "normal" at various gestations and postnatal ages.

Currently the most widely used and available modalities are

1. Ultrasound
2. CT Sacn
3. MRI

Recommendations:

- All preterm babies born before 32 weeks and < 1500 grams birth weight must undergo screening neurosonograms at 1-2 weeks and 36 – 40 weeks corrected age.
    - Ultrasounds may be performed more often if the preterm baby has a catastrophic event like seizure, frequent apnea that may reflect IVH.

- With limited facility available, it is advisable to have at least one ultrasound at ~ 40 wks of gestation in preterm babies.
- Babies with ventriculomegaly and cystic PVL have a very high incidence of cerebral palsy as compared to those with a normal neurosonogram. The sonographic assessment of brain injury is a better predictor of neuromotor outcome than gestation and perinatal risk factors.
- MRI is more sensitive in detection of preterm brain injury, but, ultrasound has similar specificity in detection of severe lesions (ventriculomegaly, cystic PVL and grade 3, 4 IVH).

- Encephalopathy in term born babies
  - Suspected hemorrhagic encephalopathy – pallor, raised anterior fontanel, history of birth trauma – CT scan is the preferred imaging modality. CT is better in detection of intracranial calcifications.
  - MRI is the diagnostic imaging modality in all babies with encephalopathy if ICH is not suspected.

  Limitations – USG is operator dependant, CT has risk of radiation exposure and MRI requires sedation and monitoring is not possible during the procedure unless monitors that are MRI compatible are available.

Follow up protocol

Schedule for follow up of infants is driven by several factors such as developmental milestones at a given age, availability and applicability of appropriate test instruments at specific ages, and cost and feasibility of follow up of a cohort of patients.

Initial weekly examination is done to ascertain whether the infant has settled in the home environment and if he is gaining weight or not. The neuromotor examination at discharge and at 1 and 3 months of age has been used to predict CP at 1 year of age. [44] At 12 months of Corrected age, environmental factors are less influential and a broad range of cognitive and behavioral processes can be assessed. Neuro assessment at 12 months can be used to predict cognitive performance at 36 months. [45] Indices of neurodevelopment in infants and toddlers are less stable over time and, at least before 24 months, lack substantial predictive validity for later morbidity. This is partly because of the means by which infants are able to express their cognitive abilities (i.e., primarily through sensorimotor acts) and the lack of continuity in response modalities from infancy to older childhood and adolescence.[46] By 24 months of age, environmental factors begin to exert influence on the test results and there is improved prediction to early school performance. At 3-4 years intelligence can be assessed and later IQ scores predicted. School achievement can be assessed at 6 years and IQ, neurophysiological functions and school performance at 8 years.[47]

Medical follow up

A. Growth and Nutrition

Growth: It is a well established fact that preterm very low birth weight babies grow poorly in postnatal period. During postnatal life though the target growth is to achieve intrauterine growth rate as well as to maintain fetal body composition, however in reality they grow very poorly due to several factors like sickness and inadequate nutrition which contribute to their poor growth. According to NICHD reports,[8] 97% of all VLBW babies and 99% of ELBW babies had weights $<10^{th}$ centile at 36 weeks PMA. These babies subsequently also continue to grow poorly throughout childhood. This growth restriction is believed to persist in adult life as shown by some researchers and they[55] found VLBW infants are twice as

likely to have a height less than 3rd centile at 20 years of age than that of normal birth weight controls. Hence there is a need for early and aggressive nutrition policy to prevent significant catabolic losses and early catch up growth.

Data regarding post discharge growth of VLBW infants scanty in our country. In our follow up study (abstract presented in Pedicon 2008)[56] we found the similar trend of growth failure till corrected age (CA) of 1 yr. At 40 wks CA, 85% VLBW babies were less than <10th centile. They showed some catch up growth by 6 months but again by CA 1 year 78% were <10th centile probably due to delayed weaning.

The growth failure is more marked in SGA babies as described in various studies. A report from Hongkong [57] observed in a cohort of their LBW (<2500 g) babies that one third of their babies were SGA who were term or near term. At 6-12 months, 33-35% babies were still short as compared to 7-12% of AGA babies. Probably this reflects poor fetal growth has a long term impact on long term growth potential.

The standard anthropometric measurements which are followed in routine practice are as follows

- Weight
- Length
- Head circumference

Other anthropometric measurements which are mostly used for research purposes are

- Mid arm circumference
- Triceps skin fold thickness
- Weight for length ratio
- Growth velocity
- Energy intake and energy expenditure
- Bone density

Which chart to follow?

There is controversy about which chart to use in the neonatal period as both have merits and demerits.

- Intrauterine growth chart or
- Postnatal growth chart

The IU growth charts are based on reference fetal growth.[58] However this can not be used as these data based on a small sample and based on chemical composition and the optimal weight gain was calculated based on body weight obtained at different gestations. Though the actual measurement of body composition would give an accurate assessment of optimal growth but a large number of fetuses to be studied for this and practically it will be difficult.

There are several other intrauterine growth charts.[59,60,61] Though currently they are taken as gold standards for ideal postnatal growth but it does not take into account of postnatal weight loss, sickness and

metabolic losses. In addition many of these growth charts are from US and Canada and there is a need for developing our own chart which should be multicentric by keeping in mind the wide variation in ethnicity and in babies who are born to mothers with no antenatal problem and from upper socio economic status.

Though intrauterine growth standards are still the gold standard but one needs to keep in mind that weight gain is not the only criteria but the body composition is important consideration to prevent metabolic syndromes in later life. It has been found that aggressive nutrition does improve the nutrition status but it is not clear whether it will have any adverse metabolic effect in later life or not.

Due to above problems with IU growth chart, some like to use postnatal growth charts which represent the longitudinal growth of VLBW neonates. The advantages of these charts are that they take into account the postnatal weight loss. However, the disadvantages are that postnatal illness are not uniform and policies of nutrition are very variable and also one needs to take into account the intrauterine growth status and multiple gestations while developing such charts. There are several postnatal growth charts which have been developed in last 2-3 decades.

Which postnatal chart to follow?

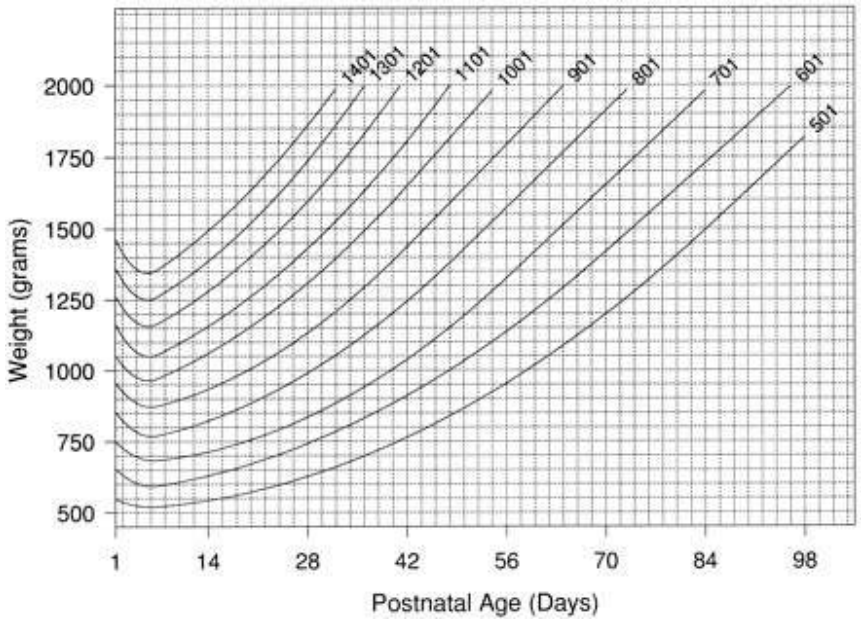
There are several postnatal growth charts with relative merits and demerits.[62,63] We propose to use either Kelly-Wright chart[62] or NICHD growth chart.[63] Kelly Wright's chart involves all 3-parameters (weight, length and HC) and up to 105 postnatal days but it gives data only for singleton AGA babies, where as NICHD growth chart includes SGA babies and well and sick babies as well. After 40 weeks, one can use CDC growth charts. However in CDC charts, VLBW babies were not included and as is is known that VLBW babies grow differently than normal birth weight babies, to develop a new reference to compare the growth of VLBW babies is the need of the hour, specially in our country due to our genetic and environmental differences from that of western countries.CDC charts can be used throughout childhood and the growth status percentiles and/or Z scores are easily available on the CDC website. (www.cdc.gov/growth charts)

There is a new growth chart (Fenton TR. A new growth chart for preterm babies: Babson and Brenda's chart updated with recent data and a new format. BMC Central 2003; 3: 13) hich is an updated version of original Bebson and Brenda's chart, beginning at 22 weeks upto 50 weeks which is based on a meta analysis of published reference studies though like other graphs the validity is limited by the heterogeneity of the data sources. For post 40 weeks section, CDC growth chart was used.

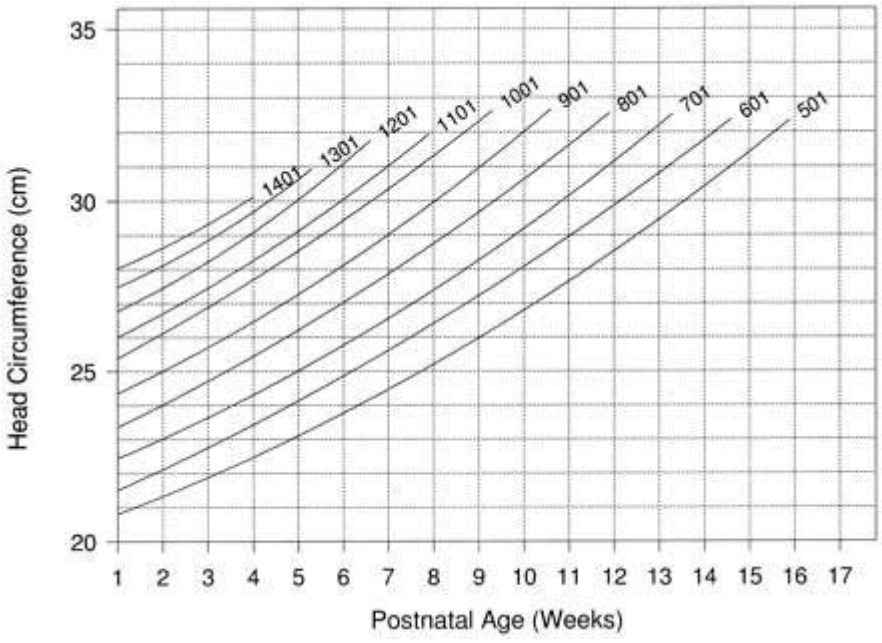
Recommendations

- Use a standard Intrauterine growth chart to plot centiles for weight, length and HC
- Follow with an appropriate postnatal growth chart

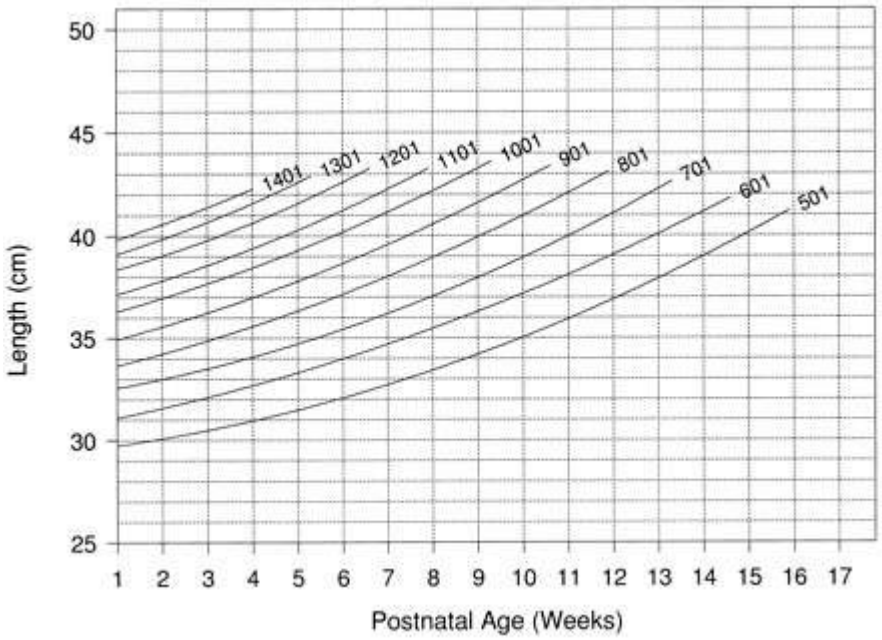
Growth charts for VLBW (Ehrenkranz)



Average daily body weight versus postnatal age in days for infants



Average weekly head circumference versus postnatal age in weeks



Average weekly length versus postnatal age in weeks for infants

Recommendations:

- OFC must be recorded and plotted serially every health visit till two years age. (Level 2 evidence) It must be assessed in context of length of the baby.
- Weight and length must be plotted at every health visit till 6 years of age. (Level 3 evidence)

Nutrition

Post discharge nutrition

Though the in hospital growth affects significantly the nutritional status at discharge, post discharge feeding and nutrition issues have not been researched as much as pre-discharge nutrition issues. The conventional diet after discharge has been unfortified human milk or term formula once the baby reached 2 -2.5 kg however from mid 90's the issues regarding post discharge nutrition has gained lot of attention due to significant growth failure during follow up.

Human milk fortifier: As evident from the previous data that preterms and VLBW babies continue to grow poorly, post discharge nutrition remains a major issue during follow up. Fortification of human milk remains debatable after discharge. Because of their poor postnatal growth there is a need for continuation of higher energy intakes. Though post discharge enriched formulas are available for formula fed babies, there are no reference data available for breast fed babies after discharge. On one hand premature babies

may be unable to take breast feed ad libitum to maintain growth and on the other side for a fully breast fed baby; it is a difficult proposition to express the milk and add fortifiers. Some studies have reported un-supplemented human milk feeding after discharge resulted in slower accretion of both radius and whole body bone mass compared with infants fed standard formula.[64,65] The risk of continued fortification is that concentration of nutrients may be excess when the baby reaches corrected age term and beyond. The post discharge follow up of premature babies found no differences in growth either during their first year or at 8 years (both remaining below 50th centile) whether fed human milk or term formula. Thus close observation is mandatory for the babies who show poor growth on full breast feeds or have biochemical abnormalities in the form of low levels of blood urea nitrogen, albumin, phosphorus and high alkaline phosphatase. This group forms a special at risk group and may need some fortification or extra mineral supplements. Deficiencies have been described with nutrients like Vitamin A, E, D, Iron, Zinc, Copper etc and most of these needs to be supplemented in preterm diet either by fortification or using preterm formula as they are deficient in preterm mature milk.

The most extensively studied metabolic deficiency state is osteopenia of prematurity which manifests after 6 -8 wks of life due to poor bone mineralization arising due to deficiency of calcium and phosphate and sometimes due to vitamin D deficiency in the diet of a VLBW and ELBW infants.[66] Mineral fortified diet and adequate vitamin D intake can help to minimize this complication. The preterm babies are also at risk of developing late hyponatremia due to massive sodium (Na) loss in the urine due to tubular immaturity. Preterms babies may need extra Na supplements during the growing phase. By 34 weeks nephronogenesis is complete and tubules become more mature and hence the Na loss continues to decrease and by the time the baby is discharged, hyponatremia gets corrected. Iron supplementation should be started by 4-6 weeks of postnatal life and continued till 1-2 years. Recommended dose is 3 mg/kg per day of elemental iron.

Supplementary feeding of preterm neonates: There are no standard guidelines regarding age of starting supplementary feeding in preterm babies. In general it is decided by readiness of eating semisolids by these babies. Some prefer to start it by corrected age of 4 months however one should not be in a hurry of starting semisolids too early as it can compromise weight gain.

Recommendation:

- Ensure adequate postnatal nutrition.
- Ensure adequate vitamin, minerals and Iron supplementation
- Start supplementary feeding as per baby's readiness

B. Immunization

The preterm/VLBW babies should be immunized according to chronological age and as per guidelines for full term newborns. For Hepatitis B, one should wait till the baby is 2000 g.[107]

Combined follow up and immunization schedule

Age / Date	Immunization	Given	Dev test	Interpretation
Hep B at birth (if mothers status is HBSAg positive or unknown) HBIG at birth if mother HBSAg +ve				
1 – 2 week after discharge	BCG after 34 weeks corrected age OPV		Medical exam including growth Neuro behavior Neonatal neuroexam OAE (if not done before) /BERA ROP follow up if not completed	
2 months	DTaP / DTP HIB hep B OPV / IPV PCV			
4 months	DTaP / DTP HIB hep B OPV / IPV PCV		OAE (if not done before) Medical exam including growth Neuorological exam • Hammersmith • Amiel tison Development test • TDSC / CDC grading • DDST • DASII	
6 months	DTaP / DTP HIB hep B OPV / IPV PCV			
9 months	Measles			
12 months				
15 months	MMR			
18 months	DTaP / DTP HIB OPV / IPV PCV			
Yearly till 5 years				
Adolescence				
Adult				

Medical examination

Date / age				
Urine stream - boys				
Murmur				
Hepatosplenomegaly				
GERD				
HRAD				
Hernia: Umbilical/ Inguinal				
Hemangioma				
Undescended testis				
Hb				
Iron				
Ca / P / ALP				
Calcium supplement				
Multivitamin supplement / HMF				
Change from LBW to term formula (if not exclusively breast fed)				
Unsorted medical problems				
Medications				
Squint / refraction				

An assessment of refraction and examination for squint, other visual problems must be performed at least at 1 year and yearly thereafter till school age (5 years). Squint and refraction: test at 9 mo – 1year age for babies born at 32 weeks or less.

Neurological examination

The neurological examination of infant, toddler and child is an integral part of follow up care. Infants with mild or moderate abnormalities may improve with time. This is known as transient neuromotor dysfunction and in growing brain with plasticity, many infants become normal. The infants with severe early neurologic dysfunction is unlikely to make complete recovery and likely to have worst neurodevelopmental outcome.[72]

Amiel Tison Scale[73]

Evaluation of the tone is a fundamental part of this assessment. There is a definite pattern of development of tone in neonates which is gestation dependent which needs to be considered while assessing tone. From 28 to 40 weeks the acquisition of muscle tone and motor function proceeds in a caudo-cephalic direction. After 40 weeks, the process is reversed, so that relaxation and motor control proceed downward for the next 12-18 months. (cephalocaudal)

The assessment is done under the following headings:

1. Neuromotor
    - Tone in upper limb , lower limb and axial
2. Neurosensory
    - Hearing and vision
3. Neurobehavioural
    - Arousal pattern, quality of cry, suckling , swallowing
4. Head growth
    - Head circumference and also skull for sutures, size of anterior fontanel

Following parameters are recorded for evaluation of tone

1. Spontaneous posture
2. Passive tone
3. Active tone

Spontaneous posture is evaluated by inspecting the child while he or she lies quiet

Passive tone is evaluated by measuring the angles at extremities. The resistance of the extremity to these maneuvers is measured as angle as given below

Adductor and Popliteal angles are best studied. Adductor and popliteal angle measured with a goniometer.

Months	**3**	**6**	**9**	**12**
Adductor angle	40-80	70-110	100-140	130-150
Popliteal angle	80-100	90-120	110-160	150-170

Test schedule - 3, 6, 9, 12 months

Tone abnormalities

- Normal tone
- Hypotonia (mild / severe)
- Hypertonia (mild / severe)

a. Pattern of tone abnormalities

- Diplegia
- Hemiplegia
- Differential extensor tone against flexor tone

Look for asymmetry

- Assessment of Passive tone (Amiel Tison) in the first year of life is a useful tool in early detection of motor developmental disability**.** (comparable to BSID at 3, 6, 9 months).

  Word of caution – it has been seen that, tight angles at 4 months (<2000 gm birth weight) do not always predict abnormal outcome, many of which become normal, where as persisting hypertonia at 8-12 months is associated with poor outcomes.

  Active tone is assessed with the infant moving spontaneously in response to a given stimulus.

- *For extremities it is assessed by looking at posture resting and posture recoil and for the axial tone (neck and trunk tone), it is assessed by response to pull to sit or pull to stand.*
- In addition deep tendon reflexes, abnormal persistence of primitive reflexes, like ATNR, fisting and cortical thumb are also recorded.
- Amiel –Tison scale is a good screening test for neuromotor assessment, the predictive value at 3 months examination for normal outcome at 12 months is 93%. The main draw back of using this solely is that this scale does not take into account the mental development. Hence one still needs to do a formal development tests as developmental delay can be present in a baby with normal neurological examination.

a. Primitive reflexes at 3 months
   - Palmar grasp
   - Automatic walking
   - Moro reflex
   - Asymmetric tonic neck reflex

All disappear by 3 months in Indian infants

Primitive reflexes are difficult to interpret even by experts. In infants with diffuse bilateral cerebral injuries, stronger, sustained reflexes with no signs of habituation (stereotyped, not decreasing with repeated elicitation) are obtained.

b. Postural reflexes at 9 months

- Parachute
- Lateral propping

Postural reactions are relatively easier to interpret, and a slow appearance indicates delay in acquiring postures and hence, CNS injury. Vojta's system of kinesiological diagnosis (based on the evaluation of 7 postural reactions) enables one to identify infants at risk for neurodevelopment delay as early as 3 months of age with 100 % accuracy when 3 reactions were abnormal.

Recommendations:

A structured, age-appropriate Neuro-motor assessment should be performed by corrected age at least once during the first 6 months, once during the second six months, and once yearly.

- Assessment of neurobehavior in neonatal period may have great predictive value and can guide further imaging, intervention planning.
- Neurological Assessment by Amiel –Tison scale, Hammersmith neonatal / infant neurological examination at discharge and periodically as indicated
- Assessment of severity of disability (function) by GMFCS at 2 years

Developmental assessment

Each baby follows his or her own schedule of development (acquiring skills) within fairly broad limits of age. Development assessment in infancy is not a predictor of intelligence and has limited ability in predicting eventual normal neurodevelopment. Deviations from normal identify an at-risk group of babies/ children who may require further evaluation and intervention. Developmental tests must be performed in conjunction with medical examination to identify the cause of deviation and plan the interventions. The interpretation of the developmental test must be discussed with parents.

General principles

Parental concerns regarding development must be recorded and respected. Development may be assessed by

- Developmental history (assessment by report)
- Direct observations and interaction with examiner - Administration of specific tests

Factors that may affect development

Prematurity - **How long to use corrected age (CA)?**

Though there is controversy about how long to use CA most of the researchers correct completely for prematurity up to 2-3 years for neuro developmental assessment.

- Assess child's environment and developmentally relevant stimulation
- Medical illness that may interfere with normal development

Developmental Tests: Various development scales which are used commonly are

1. DOC with CDC grading
2. Trivandrum Developmental Screening Chart (TDSC)
3. Denver Development Screening Test (DDST) / Denver II
4. Development Assessment scale for Indian Infants (DASII)

Babies at mild / no risk may be followed by primary care physician in the clinic along with well baby care / immunization visits

- Development observation card
- Trivandrum development screening chart

Development observation card (DOC) (with CDC grading)

DOC is a self-explanatory card that can be used by parents. Four screening milestones

- Social Smile by 2 months
- Head holding by 4 months
- Sit alone by 8 months
- Stand-alone by 12 months
- Make sure the baby can see, hear and listen

Further grading of each milestone helps in defining stage of development accurately.

Trivandrum development screening chart (TDSC)

TDSC is a simple screening test. There are 17 items taken from Bayley Scale of Infant development. The test can be used for children 0-2 years age. No kit is required. Anybody, including an Anganwadi worker can administer the test. Place a scale against age line; the child should pass the item on the left of the age-line. Currently TDSC is being validated for children till 6 years of age.

For at- risk babies (moderate / severe)

A multidimensional development-screening test (Denver development screening test (DDST / Denver II) should be documented using standardized instruments (LOE 3)

- At least once during first 6 months
- At least once during next 6 months
- Once every year till 5 years.

A formal developmental evaluation Development assessment scale for Indian infants –DASII and diagnostic work up and intervention should be performed within 2 months of parental concern / abnormal screening test for development / once every year in babies at moderate – high risk of disability

Denver development screening test (DDST)

The Denver Developmental Screening Test is a simple, clinically useful tool for early detection of ***children with serious developmental delays***. The test is best used for apparently normal children (asymptomatic, but, having perinatal risk factors), confirming suspicions with objective tool and in monitoring children with developmental problems, serially. The test compares the index child against children of similar age. The test is ***not designed to derive a developmental or mental age***, nor a development or intelligence quotient; it is to be ***used only to alert professional child workers to the possibility of developmental delays*** so that appropriate diagnostic studies may be pursued. The parents should be informed that DDST ***is not an IQ test but a developmental screening device to obtain an estimate of the child's level of development***.

DDST has 4 sectors – gross motor, fine motor, language and social. All 4 are to be treated as independent tests and interpreted separately. This allows diagnosis of the probable differential diagnosis of developmental disability.

The test has been developed for use by people who are not trained in psychological testing.

Recommendations:

- In settings where formal developmental tests cannot be performed or in mild/ moderate risk neonates, a multi-dimensional screening test for development must be performed at 0- 6 months age, preferably 4 months corrected age between 6-12 months preferably 8 months corrected age and yearly thereafter till at least 6 years age. DDST is a simple screening test. CDC grading is a test validated on Indian population.
- In case a development screening test is abnormal or in case of parental concern, a formal test for development assessment must be performed within 2 months.
- Formal development assessment must be performed at least once in the first year and repeated yearly thereafter till six years of life. In Indian context, DASII is the best formal test for development assessment (below 30 months).

Squint and refraction assessment

By 9-12 months age, irrespective of ROP.

Language and speech assessment

Babies with risk factors for hearing loss, who have passed the newborn hearing test, must have a repeat diagnostic hearing test at 12 months age- retesting of hearing by behavioral audiometry at 1 year. Comprehensive assessment of speech and language must be done between one and two years age using Language Evaluation Scale Trivandrum (0-3). Reference TEENS. Adequate receptive and expressive language is fundamental for communication, adaptative behavior, academic success and literacy. Assessment is not easy as different skills emerge at different ages. For complete assessment of language, both receptive and expressive language as well as organization and grammars are required. Various test batteries are available to test the above parameters.

Recommendation:

Language assessment at 9 months and 18 months using LEST (0-3)

Gross motor functioning

Gross motor function is an important adjunct to the neurologic assessment. A gross motor functional classification scale[74] (GMFCS) is used in many western centers. This scale can be used from 18 months and up to 12 years and this scale contains a scoring system for gross motor skill levels by direct observation. It has 5 levels, starting from normal category to severe disability and this way it not only reports rate of CP but also severity of CP.

How long to follow up?

Most follow up studies follow the infant for a short term (18-24 months). The problems with longer follow up are challenges of cost, tracking, and feasibility. But there is now increasing evidence of adverse outcomes into school age and adolescence.[48-49] Currently, in India there is no standardized guideline for follow up services for high risk infants.

A recent meta analysis[98] reported that very preterm and/or VLBW children have moderate to severe deficits in academic achievement, attention problems, and internalizing behavioral problems and poor executive function and all these adverse effects were strongly correlated with their maturity at birth. During transition to young adulthood these children continue to lag behind term born peers.

Ensure follow up till late adolescence, at least till school. Many cognitive problems, learning problems, behavioral problems that are commoner in at-risk neonates are apparent only on longer follow up.

In our country large number of dropout happens due to movement and most of the high risk babies born in the tertiary care are usually referred from far off places leading to drop out in follow up. In cases of expected drop out, the follow up can be continued up to at least 3 years when an IQ check and behavioral assessment can be performed.

Motor outcomes of high risk infants can range from transient dystonia to cerebral palsy. At school age, low birth weight infants are more likely to have subtle neurologic impairment than their normal birth weight peers.[61,70]

On examination, 10% to 11% of low birth weight infants have neurologic soft signs, a twofold increased risk compared with their normal birth weight peers.[23,71] Soft signs are defined as deviations in speech, balance, coordination, gait, tone, or fine motor or visual motor tasks that do not signify localized brain dysfunction. These soft signs are associated with an increased the risk of subnormal IQ, learning disabilities, attention deficit disorder, and internalizing and externalizing behaviors at 6 and 11 years.[71]

Learning (psycho-educational) problems

Other than neuromotor disabilities and developmental delay, the preterm VLBW babies are also at a high risk of learning difficulties.[96] Though these babies may be neurologically normal, have age appropriate adaptive skills and activities of daily living, they often have poor school achievement and behavioral difficulties as compared to their same age controls and these are even worse in ELBW babies especially in mathematics.[97]

In Pune low birth weight study [99] 180 high risk babies weighing less than 2000 g were followed up till 12 years and assessed for cognitive and educational abilities along with 90 controls of normal birth weight. The mean IQ (89.5 ±16.9) was in normal range in study group though it was significantly lower ($p<0.05$) than normal controls (97.2 ± 14.1).Preterm SGA had the lowest IQ (85.4 ±17.7). Visuo-motor perception and motor competence were poor in study group and they had writing and mathematics learning disability, poor academic achievement especially preterm SGA and VLBW group.

Hence all VBW and ELBW babies should be followed up till adolescence for early identification of school difficulties and development of intervention strategies to improve the outcome.

Cognition

Cognitive impairment is the most common impairment among high risk infants defined as scores that are 2 standard deviations below the mean on standardized cognitive testing. Average score for ELBW infants at 18 to 22 months corrected age in the NICHD is 76 [20] (mean score 100). Like rates of neurodevelopmental impairment, rates of cognitive impairment vary worldwide, and are inversely proportional to gestational age and birth weight. Worldwide rates of cognitive impairment throughout childhood range from 14% to 39% at 24 weeks, 10% to 30% at 25 weeks,[2] 4% to 24% at less than 26weeks, and 11% to 18% at less than 29 weeks.[5,14] Mean IQ for ELBW and VLBW at school age ranges from 82-105 which though is within normal range it is significantly lower than their normal birth weight peers.[22-24,41-43] Children born VLBW or ELBW have relative impairments of executive functioning,[29,41,60,61] visual-motor skills,[61] and memory,[29,41] especially verbal memory.[32] They score lower on tests of academic achievement,[29,30,42] perceptual-organizational skills,[31,41] visual processing tasks,[31,41] and adaptive functioning [29,41] compared with their normal birth weight peers. A group of NICU cohorts comprising LBW followed in Pune had significant cognitive impairment at school age with learning difficulties and went to have poor IQ scores at 12 year of age with the study group having poor skills in mathamatics.[48] Saroj Saigal et al[49] found significantly higher scores for depression and ADHD on questioning parents of teens born ELBW on parents questionnaire however there was no difference in self esteem in between the two groups.

Malin's Intelligence Scale for Indian Children (MISIC), Seguin Form Board (SFB) and Vineland Social Maturity Scale (VSMS) are freely available tools)

1. The scales which can be used to assess cognitive and functional status are Weschler's intelligence scale –revised (WISC-R)[100]- This is the most commonly used intelligence scale all over the world for school age children. An Indian adaptation by MC Bhatt is also available. It has 11 subtests and gives a separate verbal and performance score. It must be administered in a quiet room by a trained psychologist and takes about one and half hours. An intelligence quotient of below 70 is considered mental retardation, between 70-84 as borderline intelligence, between 85-109 as average and 110 or more above average intelligence.
2. Bender- Gestalt Test (BG) [101]This assesses the visuo- motor perception which is important for reading and writing. It consists of 9 figures characterized by their patterning and the child is instructed to copy the figures. This is scored as age appropriate, below normal (9-11 years), and poor (below 9 years).
3. Wide range achievement test (WRAT)[10] This test assesses the basic codes of reading, writing and mathematics. When used in conjunction with an IQ test like WISC, it can detect specific learning disabilities.
4. Human figure drawing: Emotional state of the child can be assessed by asking the child to draw a human figure on a prescribed piece of paper .Koppitz[103] has described 30 emotional indicators which can be interpreted from the drawings. The presence of 3 or more indicators is considered abnormal.
5. School performance: In addition to above tests, parents can be asked to bring the child's report which shows the child's school performance.

Behavioral assessment

High risk infants have been associated with a wide array of behavioral and psychological disabilities. Recent concern has arisen that rates of Autism Spectrum Disorder (ASD) may be higher in ELBW infants than previously thought. Although low birth weight (<2500 g) may result in a two- to threefold increase in the risk of ASD,[76,77] At 14 and 17 years of age, VLBW children score significantly lower on measures of self-esteem.[43,44] They report less confidence in their athletic, school, romantic, and job-related abilities.[44] At the age of 20 years, VLBW adults report lower rates of alcohol and drug use, sexual activity, and pregnancy than adults born normal birth weight.[46,49]

For behavioral assessment, CBCL scale can be used. CBCL[104] (Achenbach Child behavior checklist) which is based on parental perception of children's behavior designed to assess the social competence and behavioral problems and can be used from 1.5-5 years aged children.

Fetal Onset Adult Diseases:

Comparative cross sectional analysis of two groups of cohorts followed-up at 1 year and 16 years of age at Child Development Centre (CDC), Kerala showed that high triglyceride values and overweight/obesity were significantly more in LBW adolescents when compared to NBW adolescents. This has policy implications in planning adolescent nutrition and care programs in India. Nair MKC . Life Cycle Approach to Child Development. Indian Pediatr Suppl 2009;46: S7-S11)

Recommendations:

- Ensure follow up till late adolescence, at least till school entry. Many cognitive problems, learning problems, behavioral problems that are commoner in at-risk neonates are apparent only on longer follow up.
    - Behavioral assessment can be done after one year age
    - Formal cognitive development, IQ is tested by 3 years
    - BP, BMI and Lipid Profile at school exit

Children born below 28 weeks or 1000 grams birth weight must be referred for a Psycho-educational testing (pre-school assessment) to detect learning

Early intervention – do we need/ when/ how ?

The problems associated with at - risk infants are often identified very late when little can be done. No Drug has been conclusively proven to be effective in improving outcome in post-asphyxial encephalopathy. Pyritinol was not found useful in improving the neurodevelopmental status of babies with post-asphyxial encephalopathy at one year of age.

Hence, developmental follow up and early intervention is the answer to this problem.[19] The early intervention institute at Utah University reviewed 316 articles reporting results of 162 early intervention efficacy studies showing that there is compelling evidence in 150 of them that early intervention has immediate positive effect on one third to one half.[20] A recent Meta analysis showed that early intervention improved cognitive outcome at infant age (0-2 years).[21] Although, there is no uniform agreement as to the ideal group of babies who would benefit maximally from early intervention, the neonatal nursery graduates would probably form the best captive population for providing early stimulation. CDC model of 'early stimulation therapy' was effective at one year. The beneficial effect also persisted at two years, without any additional interventions in the second year. A reduction of 40% in poor performance could be achieved by early intervention in LBW babies in Trivandrum.[22]

A sick neonate in NICU experiences significant adverse environment and separation from mother which is very stressful and can lead to abnormal sensory input resulting in abnormal brain structure and function and as a result can develop developmental disabilities. Developmental supportive care is an intervention for preterm infants that focuses on environment and is designed to minimize the stress of the neonate in NICU environment. Interventions aiming at enhancing parent – infant relationship focuses on sensitizing the parents to infant cues and teach appropriate and timely response to the infant's needs. There is evidence that early parent- infant interaction positively influences cognitive and social development in children.[108] NIDCAP (The Newborn Individualized Developmental Care and Assessment Program) is one developmental care framework. There are several NIDCAP based RCT which showed positive effects in the short term as well as long term outcome in the form of less disability specially mental delay in BSID scale.[109]

The Cochrane review published in 2007[110] which looked at the pooled result of 16 randomized controlled studies involving 2379 patients. Intervention was started within the first 12 months, in babies less than 37 weeks of gestation, either in hospital or after discharge. Meta analysis concluded that intervention improved cognitive outcomes at infant age, preschool age, however this effect was not sustained at school age though there was significant heterogeneity between studies for cognitive outcome at infant and school

ages. There was little evidence of an effect of early intervention on motor outcomes in the short, medium and long term but there were only 2 studies reporting outcome beyond 2 years.

Hence based on above evidence, it is recommended to start early intervention while the baby is still in NICU

Early intervention after discharge from NICU

Who should be initiated on an early stimulation programme?

Babies at risk of Neurodevelopmental disabilities based on risk factors & Initial assessment

When can early stimulation be started?

As soon as baby is medically stable in the NICU

In the NICU

- Optimize lighting
- Reduce noise, gentle music
- Club painful procedures, allow suck sucrose / breast milk , hold hand
- Tactile stimulation – touch, gentle massage
- Kangaroo Mother Care
- Non-nutritive sucking
- Passive exercises

Motivate the parent to stimulate the baby with appropriate stimuli; the parents of an at-risk baby are likely to be demoralized & at-risk of not being involved in stimulation of the child.

What is done in early stimulation?

- Assess parenting –skills and educate
- Stimulate the child in all sectors of development – motor, cognitive, Neuro-sensory, language
- Developmentally appropriate - through the normal developmental channel (stimulate to achieve the next “mile-stone” rather than age-based)
- Physical stimulation – passive exercises to prevent development of hypertonia
- Caution – avoid over-stimulation (has shown negative effects on development when many inputs of different nature are simultaneously started)

At Home

- Bold patterns with strong contrasts / parent faces / moving objects
- Talk to the baby / music
- Touch - Rocking, walking and swinging

- Massage

Recommendations:

- Early intervention programme (early stimulation) must be started in the NICU itself once the neonate is medically stable and continued till at least till 1 year of age

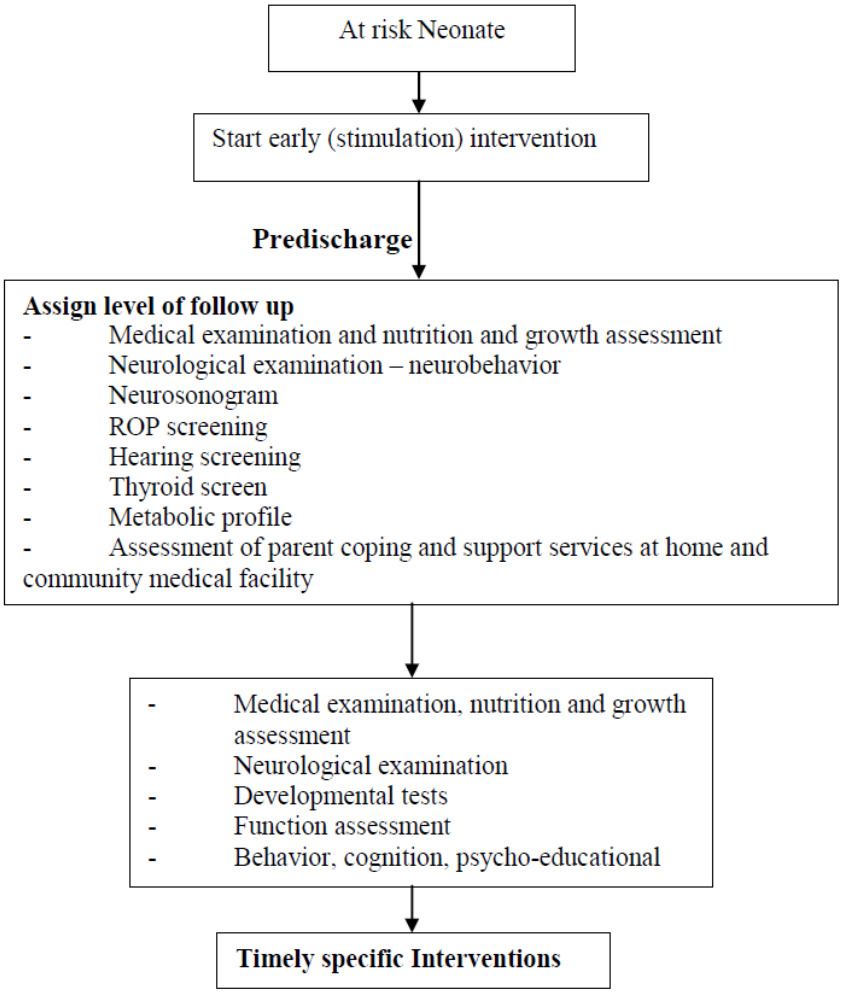
Specific interventions

- Motor impairment / Hypertonia – medications and physiotherapy
- Physiotherapy and occupational therapy
- Speech therapy
- Seizures
- DDH and other Orthopedic
- Squint correction
- Behavior therapy and pharmacotherapy for behavioral disorders
- Therapy for learning disabilities

Recommendations :

Timely specific interventions and compliance must be ensured after detection of deviation from normal.

Algorithm for follow up of at-risk neonates



References

1. Fanaroff AA, Hack M, Walsh MC. The NICHD neonatal research network:changes in practice and outcomes during the first 15 years. Semin Perinatol 2003;27(4):281–7.
2. Hack M, Fanaroff AA. Outcomes of children of extremely lowbirthweight and gestational age in the 1990s. Semin Neonatol 2000;5(2):89–106.
3. Hintz SR, Poole WK, Wright LL, et al. Changes in mortality and morbiditiesamong infants born at less than 25 weeks during the post-surfactant era. Arch Dis Child Fetal Neonatal Ed 2005;90(2):F128–33.
4. Wilson-Costello D, Friedman H, Minich N, et al. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics 2005;115(4):997–1003.
5. Emsley HC, Wardle SP, Sims DG, et al. Increased survival and deteriorating developmental outcome in 23 to 25 week old gestation infants, 1990–4 compared with 1984–9. Arch Dis Child Fetal Neonatal Ed 1998;78(2):F99–104.
6. O'Shea TM, Klinepeter KL, Goldstein DJ, et al. Survival and developmentaldisability in infants with birth weights of 501 to 800 grams, born between 1979 and 1994. Pediatrics 1997;100(6):982–6.
7. Lorenz JM, Wooliever DE, Jetton JR, et al. A quantitative review of mortality and developmental disability in extremely premature newborns. Arch Pediatr Adolesc Med 1998;152(5):425–35.
8. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001;107(1):E1.
9. Blaymore-Bier J, Pezzullo J, Kim E, et al. Outcome of extremely low-birth-weight infants: 1980–1990. Acta Paediatr 1994;83(12):1244–8.
10. Hack M, Friedman H, Fanaroff AA. Outcomes of extremely low birth weight infants. Pediatrics 1996;98(5):931–7.
11. Piecuch RE, Leonard CH, Cooper BA, et al. Outcome of extremely low birth weight infants (500 to 999 grams) over a 12-year period. Pediatrics 1997;100(4):633–9.
12. Wilson-Costello D, Friedman H, Minich N, et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000–2002. Pediatrics 2007; 119(1):37–45.
13. Hintz SR, Kendrick DE, Vohr BR, et al. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993–1999. Pediatrics 2005;115(6):1645–51.
14. Vohr BR, Msall ME. Neuropsychological and functional outcomes of very low birth weight infants. Semin Perinatol 1997;21(3):202–20.
15. Vohr BR, Wright LL, Poole WK, et al. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. Pediatrics 2005;116(3):635–43.
16. Sudha Chaudhari. Learning problems in children who were "high-risk" at birth. Indian Pediatr 1994; 31:1461-64.
17. John M. Lorenz, Diane E. Wooliever, James R Jetton; Nigel Paneth. A quantitative review of mortality and developmental disability in extremely premature newborns. Arch Pediatr Adolesc Med 1998;152:425-35
18. Saroj Saigal, Janet Pinelli, Lorraine Hoult, M. Marie Kim, Michael Boyle. Psychopathology and social competencies of adolescents who were extremely low birth weight. Pediatrics 2003;11:969-71.
19. MKC Nair. Early intervention symposium. Indian J Pediatr; 1992:59:657-659.
20. White K, Casto G. an integrative view of early intervention efficacy studies with at risk children. Implication for the handicapped. Analysis and intervention in developmental disabilities.1985;5:7-31
21. Spittle AJ, Orton AJ, Doyle LW, Boyle R. Early developmental intervention program pot hospital discharge to prevent motor and cognitive impairments in preterm infants. Cochrane Database syst Dev.2007;2:CD005495.
22. Nair MKC, Early stimulation CC Trivandrum Model. Indian J Pediatr; 1992;59:663-7.
23. Narayan S Aggarwal R Upadhyay A, Deorari AK, Singh MK, Paul VK. Survival and morbidity in extremely low birth infants. Indian Pediatr 2003;40(2):130-5.

24. Jerold F. Lucey, Cherise A. Rowan, Patricia Shiono, Andrew R. Wilkinson, Sarah Kilpatrick, Nathaniel R. Payne, Jeffrey Horbar, Joseph Carpenter, Jeannette Rogowski, Roger F. Soll. Fetal Infants: The Fate of 4172 Infants With Birth Weights of 401 to 500 Grams—The Vermont Oxford Network Experience (1996–2000). Pediatrics 2004;113:1559-66.
25. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004; 292:2357–65.
26. Unhanand M, Mustafa MM, McCracken GH Jr, Nelson JD. Gram negative enteric bacillary meningitis: a twenty one year experience. J Pediatr 1993;122:15-21.
27. Clare M Rees, Agostino Pierro, Simon Eaton.Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. Archives of Disease in Childhood - Fetal and Neonatal Edition 2007;92:F193-F198.
28. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. Arch Pediatr Adolesc Med 2007;161:583-90.
29. N Marlow, A Greenough, J L Peacock, L Marston, E S Limb, A H Johnson, S A Calvert. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. Arch Dis Child - Fetal and Neonatal Ed 2006;91:F320-F326.
30. Marie-Claude Gre´goire, Francine Lefebvre, Jacqueline Glorieux. Health and Developmental Outcomes at 18 Months in Very Preterm Infants With Bronchopulmonary Dysplasia. Pediatrics 1998;101:856-70.
31. Teberg AJ, Pena I, Finello K, Aguilar T, Hodgman JE. Prediction of neurodevelopmental outcome in infants with and without bronchopulmonary dysplasia. Am J Med Sci 1991;301:369–74.
32. Gray PH, Burns YR, Mohay HA, O'Callaghan MJ, Tudehope DI. Neurodevelopmentaloutcome of preterm infants with bronchopulmonary dysplasia. Arch Dis Child 1995;73:128–34.
33. Thomas B. Newman, Petra LiljestrandRita J. Jeremy., Donna M. Ferriero, Yvonne W. Wu, Esther S. Hudes, Gabriel J. Escobar. Outcomes among Newborns with Total Serum Bilirubin Levels of 25 mg per Deciliter or More. NEJM ;354:1889-1900.
34. Okumura, A., Kidokoro, H., Shoji, H., Nakazawa, T., Mimaki, M., Fujii, K., Oba, H., Shimizu, T. (2009). Kernicterus in Preterm Infants. *Pediatrics* 123: e1052-e1058
35. Eichenwald, E. C. (2006). Neurodevelopmental Outcomes of Newborns with Severe Neonatal Jaundice. AAP Grand Rounds 16: 16-16
36. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. *Pediatrics* 2000;105:12-16.
37. Jobe AH. Glucocorticoids in perinatal medicine: misguided rockets? *J Pediatr.*2000;137:1–3.
38. Yeh TF, Lin YJ, Huang CC, et al. Early dexamethasone therapy in preterm infants: a follow-up study. *Pediatrics*1998;101(5):13-20.
39. American Academy of Pediatrics, Committee on Fetus and Newborn. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics*2002;109:330-38.
40. Bradley RH, Corwyn RF. Socioeconomic status and child development. Annu Rev Psychol 2002;53:371–99.
41. Follow up Care of High Risk Infants; Pediatrics 2004;114;1377-97.
42. Kadam A, Pandit A. Developmental Screening in High Risk Newborns Through Infancy. J Neonatol 2005;19:100-6.
43. Nair MKC, Jain N. The High Risk Newborn. 1st Edition;207-208,231-235.
44. Chaudhari S. Learning problems in children who were "high risk" at birth. Indian Pediatr 1994:31:1461-64.
45. Giannì ML, Picciolini O, Vegni C, Gardon L, Fumagalli M, Mosca F. Twelve-Month Neurofunctional Assessment and Cognitive Performance at 36 Months of Age in Extremely Low Birth Weight Infants. Pediatrics 2007;120:1012-9.
46. Bhutta AT, Cleves MA, Casey PH, et al. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002;288(6):728–37.
47. Doyle LW, Anderson PJ. Improved neurosensory outcome at 8 years of age of extremely low birthweight children born in Victoria over three distinct eras. Arch Dis Child Fetal Neonatal Ed 2005;90(6):F484–8.
48. Taylor HG, Klein N, Minich NM, et al. Middle-school-age outcomes in children with very low birthweight. Child Dev 2000;71(6):1495–511.

49. Saigal S, Stoskopf BL, Streiner DL, Burrows E. Physical growth and current health status of infants who were of extremely low birth weight at adolescence. Pediatrics 2001;108(2):407-15.
50. Rickards AL, Kelly EA, Doyle LW, et al. Cognition, academic progress, behaviour and self-concept at 14 years of very low birth weight children. J Dev Behav Pediatr 2001;22(1):11–8.
51 Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. Pediatrics 2008;121(6):1155–64.
52. Grunau RE, Whitfield MF, Fay TB. Psychosocial and academic characteristics of extremely low birth weight (< or5800 g) adolescents who are free of major impairment compared with term-born control subjects. Pediatrics 2004;114(6):e725–32.
53 Hack M, Flannery DJ, Schluchter M, et al. Outcomes in young adulthood for very-low-birth-weight infants. N Engl J Med 2002;346(3):149–57.
54. Hack M, Youngstrom EA, Cartar L, et al. Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. Pediatrics 2004;114(4):932–40.
55. Hack M, Flannery DJ, Schluchter M, Cartar L, Barowski E , Klein N . Outcomes in young adulthood for very low birth weight infants. New Eng J Med 2002; 346(3):147-157.
56. Mukhopadhyay K, Narang A, Majajan R. Growth in the 1st year of life of very low birth weight and extremely low birth weight babies – Indian experience. Abstract presented in Pedicon 2009.
57. Lam B,Karlberg J, Low LC, Yeung CY.Incomplete catch up growth in low birth weight Chinese infants in Hongkong.J Paediatr Child Health 1995;31:428-34.
58. Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. Growth 1976;40:329-41.
59. Lubchenco, usher- Mc lean, 1.Lubchenco LO, Hansman C, Boyd E. Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. Pediatrics 1966; 37:793-80.
60. Lubchenco LO, Hansman C, Dressler M. Intrauterine growth as estimated from live born birth weight data at 24 to 42 weeks of gestation Pediatrics 1963;32:793-9.
61. Usher R, McLean F. Intrauterine growth of live born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 to 44 weeks of gestation. J Pediatr 1969; 74: 901-910.
62. Wright K, Dawson JP, Fallis D, Vogt E, Lorch V. New postnatal growth grids for very low birth weight infants Pediatrics 1993;91:922-26.
63. Ehrenkranz RA, Younes L, Lemons JA, Fanaroff AA, Donovan EF, Wright LL, Katsik , Shankaran S, et at. Longitudinal growh of hospitalized very low birth weight infants. Pediatrics 1999; 104: 280-289.
64 . Chan GM. Growth and bone mineral status of discharged very low birth weight infants fed different formulas or human milk. *J Pediatr* 1993;123:439-43.
65. Rubinacci A, Sirtori P, Moro G, Galli L, Minoli I, Tessari L. Is there an impact of birth weight and early life nutrition on bone mineral content in preterm born infants and children ? *Acta Paediatr* 1993;82: 711-13.
66. Brooke OG, Lucas A. Metabolic bone disease in preterm infants. Arch Dis Child 1985;60:682-5.
67. Vohr B, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, et al. Neurodevelopmental and functional outcome s of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. Pediatrics 2000;105(6):1216-26.
68. Platt MJ, Canns C, Johnson A, Surman G, Topp M, Torrioli G et al. Trends in cerebral palsy among infants of very low birth weight (< 1500 g) or born prematurely (<32 wks) in 16 European centres : a database study. The Lancet 2007;369:43-50.
69. Hagberg B, Hagberg G, Beckung E,Uvebrant P. Changing panorama of cerebral palsy in Sweden.VIIII. Prevalence and origin in the birth year period 1991-94. Acta Pediatr 2001; 2001; 90: 271-77.
70. Finnstrom O, Otterblad Olausson P, Sedin G et al . Neurosensory outcome and growth at three years in extremely low birth weight infants: follow up results from the Swedish national prospective study. Acta Pediatr 1998; 87:1055-60.
71. Chaudhari S, Kulkarni S, Pajnigar F, Pandit AN, Deshmukh S. A longitudinal follow up of development of preterm infants. Ind Pediatr 1991;28:873-80.
72. Drillien C. Abnormal neurologic signs in the 1st year of life in low birth weight infants: possible prognostic significance. Dev Med Child Neurol 1997;55:803-9.

73. Amiel-Tison C, Grenier A (Eds) Neurological assessment during the First year of life. New York: Oxford University press 1986:96-145.
74. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39(4):214-23.
75. Frankenburg WK. The Denver approach to early case finding. In : Frakenburg WK, Emde RN,Sullivan JW, eds. Early identification of children at risk. New York , NY; Plenum Press ; 135-158.
76. Frankenburg WK, Dodds J ,Archer P,Shapiro H, Bresnick B. The Denver II: A major revision and restandardization of the Denver Development screening test. Pediatrics 1992; 89 (1); 91-97.
77. Nair MKC, George B, Philip E. Trivandrum Development Screening Chart. Indian Pediatr 1991; 28: 869-872.
78. Pathak AT, Khurana B.Baroda Developmental Screening test for infants. Indian Pediatr 1991; 28: 869-872.
79. Bayley N. Bayley scale of Infant development II. San Antonio,TX: Psychological corporation ; 1993.
80. Pathak P. Baroda norms of motor and mental development of Indian babies from 1 to 30 months. Psychological studies 1993; 38(3): 142-149.
81. Mason JA, Herrmann KR. Universal hearing screening by Automated Auditory Brainstem Response Audiometry. Pediatrics 1998 : 101 (2) : 221-228
82. Year 2000 position statement : Principle and Guidelines for early hearing detection and intervention program . Jt Committ Infant Hearing Pediatr 2000;106(4):798-817.
83. Nelson HD, Bougatsos C, Nygren P ; 2001 US Preventive Services Task Force . Universal Newborn Hearing Screening: Systematic review to update the 2001 US Preventive Services Task Force Recommendation. Pediatrics 2008; 122(1):e 266-76.
84. Nagapoornima P, Ramesh A, Srilakshmi, Rao S, Patricia PL, Gore M, Dominic M, Swarnarekha. Universal Hearing Screening. Indian J Pediatr 2007;74 (6);545-9.
85. Hussain N, Clive J , Bhandari V. Current incidence of Retinopathy of Prematurity . Pediatrics 1999; 104(3): e26. 2.Mathew MR, Fern AI, Hill R. Retinopathy of prematurity : Are we screening too many babies? Eye 2002;16(5):538-42
86. Teed RG, Saunders RA. Retinopathy of prematurity in extremely premature babies. J AAPOS 2009;13:370-3.
87. Valcamonico A, Accorsi P, Sanzeni C, Martelli P, La Boria P, Cavazza A, Frusca T. Mid term and longterm outcome of extremely low birth weight (ELBW) INFANTS : an anlaysis of prognostic factors. J Matern Fetal Neonatal Medicine 2007; 20(6) : 465-71. 88.Tommiska V, Heinonen K, Ikonen S, Kero P, Pokela M, Renlund M, Renlund M et al . A national short term follow up study of extremely low birth weight infants born in Finland in 1996-1997.Pediatrics 2001 Jan; 107(1): E2.
89. Ho SF, Mathew MR, Wykes W, Lavy T, Marshall T. Retinopathy of prematurity : an optimum strategy.J AAAPOS 2005; 9(6): 584-8.
90. Rekha S, Battu R . Retinopathy of prematurity : Incidence and risk factors. Indian Pediatr 1996;33: 999-1003.
91. Charan R, Dogra MR, Gupta A, Narang A. The incidence of Retinopathy of Prematurity in a neonatal care unit. Indian Journal of Opthalmology 1995;43:123-6.
92. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of Prematurity in Asian babies weighing greater than 1250 gms at birth: Ten year data from a tertiary care centre in a developing country. Indian J opthalmol 2007;55:331-6.
93. Aggarwal R, Deorari AK, Azad RV, Kumar H, Talwar D, Sethi A, Paul VK. Changing profile of retinopathy of prematurity . J Trop Pediatr 2002;48:239-42.
94. Schalij-Delfos NE , de Graaf ME, Treffers WF, Engel J, Cats BP. Long term follow up of premature infants : detection of strabismus, amblyopia, and refractive errors. Br J Opthalmol 2000;84:963-7.
95. Theng JT, Wong TY, Ling Y. Refractive errors and strabismus in premature Asian infants with and without retinopathy of Prematurity. Singapore Med J 2000;41:393-7.
96. Hack M, Fanaroff AA, Merkatz IR. The low birth weight infant: Evolution of changing outlook. N Eng J Med 1979;301:1162-5.
97. Saigal S. Follow up of very low birth weight babies to adolescence. Semin Neonatol 2000;5(2):107-18.
98. Aarnoudse- Moens CSH, Goudoever JB, Oosteriaan J. Meta analysis of Neurobehavioral outcome in very preterm and/or very low birth weight children. Pediatrics 2009;124:717-28.

99. Chaudhari S, Otiv M, Chitale A, Pandit A, Hoge M. Pune low birth weight study – Cognitive abilities and Educational Performance at twelve years. Indian Pediatr 2004;41:121-8.
100. Wechsler D. The Wechsler Intelligence scale for children. 4th edition . San Antonio, TX: The Psychological corporation; 2003.
101. Koppitz EM.The Bender Gestalt test for young children , New York , Grune and Stratton 1963.
102. Jastak S, Wilkinson GS.Wide Range Achievement Test (WRAT). Janak Associates Inc, Cincinati, 1984.
103. Koppitz EM. Psychological evaluation of Children's Human figure drawings II . New York , Grune and Stratton 1963.
104. Achenbach TM. Integrative guide for the 1991 CBCL /4-18 YSR and TRF profiles. Burlington VT. University of Vermont, Dept of Psychiatry;1991.
105. Pinto-Martin JA, Whitaker AH, Feldman J, Van Rossem R,Paneth N. Relation of cranial ultrasound abnormalities in low birth weight infants to motor or cognitive performance at ages 2, 6 and 9 years. Dev Med Child Neurol 1999;41:826-833.
106. Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA et al. Practice parameter : Neuroimaging of the neonate . Report of the quality standards subcommittee of the American Academy of Neurology and the practice committee of the child neurology society. Neurology 2002;58:1726-1738.
107. Saari TN. Immunization of preterm and low birth weight infants. Clinical report – guidance for the clinician in rendering pediatric care. American Academy of Pediatrics. Pediatrics 2003:112:193-8.
108. Melnyk BM, Alper-Gillis, Fischbeck –Feinstein N, Fairbanks E, Czarniak-Schultz N et al. Improving cognitive development of low birth weight premature infants with the COPE program: a pilot study of the benefit of early NICU intervention with mothers. Research in Nursing and Health 2001;24:373-89.
109. Peters KL, Rosychuk RJ, Hendson L, Cote JJ, McPherson C, Tyebkhan JM. Improvement of short and longterm outcomes for very lowbirth weight infants : Edmonton NIDCAP trial. Pediatrics 2009;124:1009-1020
110. Spittle AJ, Orton J, Doyle LW, Boyd R. Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants. Cochrane Database of Systematic Reviews 2007, Issue 2. Art n**o:** CD005495. DOI: 10.1002/14651858.CD005495.pub2.
111. Bavdekar A, Yajnik CS, Fall CHD, Bapat S, Pandit AN, Despande V et al. Insulin resistance syndrome in 8 year old children – small at birth, big at 8 years or both? Diabetis 1999;48:2422-2429.
112. vanWalraven C, Seth R, Austin PC, Laupacis A. Effect of discharge summary availability during post-discharge visits on hospital re-admission. J Gen Inern Med 2002;17:186-92.
113. Hospital discharge of the high risk neonate – proposed guide-lines. American Academy of Pediatrics on Fetus and Newborn. Pediatrics 1998;102:411-417.
114. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effwct of very low birth weight and subnormal head size on cognitive abilities at school age. N Engl J Med 1991;325:231 – 237.
115. Recommendations for Preventive health care. American Academy of Pediarics committee on practice and ambulatory medicine. Pediatrics 2000;105:6.

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Retinopathy of Prematurity

Summary of Recommendations

- **Retinopathy of prematurity (ROP) is emerging as one of the leading causes of preventable childhood blindness in India.**
- **Screening for ROP should be performed in all preterm neonates who are born < 34 weeks gestation and/or < 1750 grams birth weight; as well as in babies 34-36$^{6/7}$ weeks gestation or 1750-2000 grams birth weight if they have risk factors for ROP.**
- **The first retinal examination should be performed not later than 4 weeks of age or 30 days of life in infants born ≥ 28 weeks of gestational age. Infants born < 28 weeks or < 1200 grams birth weight should be screened early, by 2-3 weeks of age, to enable early identification of AP-ROP.**
- **The retinal findings should be classified and documented based on the International Classification of Retinopathy of Prematurity guidelines (ICROP).**
- **Follow up examinations should be based on the retinal findings and should continue until complete vascularization or regressing ROP is documented or until treated based on the ETROP guidelines.**
- **Laser photocoagulation delivered by the indirect ophthalmoscopic device is the mainstay of ROP treatment.**
- **The responsibility of recognition of infants for screening lies with the pediatrician/neonatologist.**
- **Communication with the parents regarding timely screening for ROP, seriousness of the issue, possible findings and consequences is extremely important.**

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Introduction

The incidence of ROP in India is reported to vary between 38 – 51.9 % in low birth weight infants.[1-3] Out of the approximate 26 million annual live births in India, approximately 8.7% of newborns in India are < 2000 grams[4] in weight. This would imply that almost 2 million newborns are at risk for developing ROP. The fundamental pathological process underlying ROP stems from incomplete vascularization at birth. Normal retinal vascularization progresses in-utero from the disc margin (16 weeks) and reaches the nasal ora serrata (by 36 weeks) and then temporally (by 39-41 weeks) to complete a mature vascular retina.[5] Term infants have completely vascularized retina and hence are not at risk for developing ROP. Premature infants have avascular or incompletely vascularized retina at birth; ROP evolves over 4-5 weeks after birth. This relatively slow evolution gives a small window of opportunity to effectively conduct retinal examinations and timely interventions to improve visual outcome and avoid irreversible blindness due to retinal detachment from progressive untreated ROP. In this guideline an attempt has been made to address the following issues:

- Which neonates should be screened for ROP?
- When should such screening be initiated?
- How frequently should the infants be screened?
- When is the screening complete?
- Where and how should the examinations be done?
- When is treatment of ROP indicated?

Which infants should be screened for ROP?

Evidence: The American Academy of Pediatrics (AAP) guidelines [6, 7] state that infants with a birth weight of less than 1500 g or gestational age of 30 weeks or less (as defined by the attending neonatologist) and selected infants with a birth weight between 1500 and 2000g or gestational age of more than 30 weeks with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk, should have retinal screening examinations. In India, the gestational age of infants is not always known or accurate; in addition, ROP has been reported in larger babies with a birth weight between 1500 and 2000 grams. There have been several anecdotal reports from ophthalmologists of babies between 1750 and 2000 grams being diagnosed with ROP. However, there is a paucity of population based data of ROP in these larger neonates.

There is a concern that screening all infants with a birth weight of < 2000 g will considerably increase the number of eligible infants; this is unlikely to be feasible in the current scenario of limited access to trained ophthalmologists. Hence, a birth weight of less than 1750 grams and/or gestational age of less than 34 weeks may be used as a cut-off for performing retinal screening examinations. Babies with a gestational age of 34 to 36[6/7] weeks gestation or a birth weight between 1750 and 2000 grams should also be screened if risk factors for developing ROP are present.[6-10] The traditional risk factors considered are mechanical ventilation, prolonged oxygen therapy and hemodynamic instability. It should be remembered that lack of taking these factors into serious consideration may inadvertently exclude the infants at risk for significant ROP and careful review for risk factors should be undertaken by the pediatrician.

***Recommendation**:* Screening for ROP should be performed in all preterm neonates who are < 34 weeks gestation and / or < 1750 grams birth weight. Apart from these infants, those preterm infants between 34 to $36^{6/7}$ weeks gestational age or a birth weight between 1750 and 2000 grams with risk factors for ROP should also be screened. Risk factors for ROP in larger infants have not been clearly established. Multi-centre studies need to be undertaken to determine the incidence, risk factors and natural course of ROP in the larger preterm infants.

When should the first screening be done?

Evidence: The timing of first screening usually depends on the infant's postnatal age. The convention is not to delay the first screening later than 4 weeks of age or 30 days of life for infants born at or more than 28 weeks of gestation.[6, 9] Infants may be screened as early as 3 weeks of age. For infants born less than 28 weeks of gestation, the first screening should take place at 31 weeks of postmenstrual age (PMA) (gestational age at birth plus postnatal age in weeks) as per AAP guidelines. Some studies have shown serious ROP to be more related to PMA rather than to just postnatal age alone.[6] It has also been well documented that very low birth weight babies may develop early and aggressive posterior ROP (AP-ROP).[5,9] It is relatively common in Indian babies and may have a worse prognosis compared to classical ROP.[11,12] This rapidly progressive type of ROP that can lead to retinal detachment without treatment, needs earlier screening.[9] Infants <1200 grams or < 28 weeks gestational age may be strongly considered for screening at 2-3 weeks of life in view of the significant incidence of the AP-ROP in these infants.

***Recommendation**:* The first screen should be performed not later than 4 weeks of age or 30 days of life in infants ≥ 28 weeks of gestational age. They may also be screened by the third week of life to enable diagnosis of AP-ROP. Infants <28 weeks or <1200 grams birth weight should be screened early at 2-3 weeks of age, to enable early identification of AP-ROP.

How frequently should the infants be screened?

Evidence & *Recommendation*: Follow up examination intervals are based on the retinal findings; these findings are classified according to the revised International classification of ROP (ICROP).[13] The major changes from the previous ICROP classification are the description of aggressive posterior ROP (AP-ROP), the inclusion of pre-plus disease and a practical guide to measuring the extent of zone I. Based on the retinal findings, the follow up examination schedule (Table 1) is suggested.[6]

When should the screening be terminated?

Evidence & *Recommendation:*** Retinal examinations may be terminated based on postmenstrual age or retinal findings. The following are the recommendations to guide when to stop further examinations: [6, 9]

a) Full retinal vascularization; this usually occurs at about the 40^{th} week of postmenstrual age and mostly completes by the 45^{th} week [5]
b) Regression of ROP noted

It is advisable to screen the baby every 1-2 weeks at least until the infant is 38-40 weeks of postmenstrual age. [9]

Where and how should the examinations be done?

Evidence & *Recommendation:* The ideal setting for screening is under a radiant warmer in the NICU, under the guidance of the neonatologist. Discharged and stable babies may be screened in the trained ophthalmologist's clinic or in the NICU itself. The treating team should not forget to communicate with the parents regarding the risk of ROP; the need for screening preterm babies must be addressed along with the initial admission counseling itself. The possible findings and consequences must be explained prior to the initial examination. Documentation of such a communication is highly desirable.

The baby should be swaddled and preferably fed one hour prior to examination. Incubator dependant babies can be screened (and even treated) within the incubator itself through the slanting wall without disturbing the equilibrium of the infant.[14] Pupillary dilatation should be performed about an hour prior to screening. A combination of cyclopentolate 0.5% and phenylephrine (2.5%) drops is used two to three times about 10-15 minutes apart. Tropicamide 0.5-1% is an alternative to cyclopentolate. Atropine should not be used for dilatation. Excess eye drops should be wiped off to prevent systemic absorption though the cheek skin. Over dosage carries the risk of tachycardia and hyperthermia and must be avoided. A non-dilating pupil could indicate the presence of tunica vasculosa lentis and must be confirmed by the ophthalmologist before undue excess medication for dilatation is administered.

The examination is carried out under topical anesthesia without any sedation, using the indirect ophthalmoscope and a 20 D or 28 D condensing lens. Recordings of the findings should be done in the chart or card using standard notations. The date of subsequent follow-up should be clearly stated, and the neonatologist and parent counseled about the same. It must be remembered that retinal examinations are stressful and may be even painful to the infant. Swaddling the infant firmly in a thin blanket and administering 0.5-1 ml of 24% sucrose orally by syringe 1-2 minutes prior to the examination will help to provide comfort and relieve pain. Apnea and bradycardia may rarely develop during the examination in very premature babies. Resuscitation measures should be readily available.

When is treatment of ROP indicated?

Evidence: Prior to December 2003, the CRYO-ROP[15] treatment guidelines were followed. Only a more advanced proliferative stage termed as 'threshold disease' was treated. This was defined as "at least 5 contiguous or 8 cumulative clock hours of stage 3 ROP in zone I or II in the presence of plus disease." The Early Treatment for Retinopathy of Prematurity study (ETROP) [16] study showed that early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcomes to a clinically important degree. Ablative therapy is indicated for high risk ROP or type 1 ROP, defined as any of the following: a) Zone I, stage 1 to 3 ROP with plus disease, b) Zone I, stage 3 ROP without plus disease and c) Zone II, stage 2 or 3 ROP with plus disease.

Recommendation: The guidelines from the above study are the currently recommended indications for ablative treatment and are summarized in table 2. AP-ROP also needs early and aggressive laser treatment, often in multiple sessions to prevent retinal detachment [11, 17]

How should ROP be treated ?

Evidence & *Recommendation*: The aim of the treatment is to ablate the entire avascular retina up to the ora serrata in a near confluent burn pattern getting as close to the edge of the ridge as possible.[18, 19] Treatment should be carried out in the NICU or in a setting where monitoring and resuscitation facilities

and trained personnel are readily available. Laser photocoagulation delivered by the indirect ophthalmoscopic device is the mainstay of ROP treatment. Laser has supplanted cryotherapy due to better structural and functional outcomes. It is a safer and a more controlled procedure. Laser therapy can be done under topical anesthesia (0.5% proparacaine HCl, 4% xylocaine), general anesthesia or sedation. Laser treatment, using the ETROP guidelines, has a greater than 90% successful outcome.

Post-treatment recommendation: The child can be fed after about 30 minutes following completion of the procedure. Vital signs must be monitored. It is preferable that the child be under the supervision of the neonatologist or an anesthesiologist for at least 2-3 hours following the procedure. Post-treatment hypothermia and hypoglycemia are common and must be prevented. Mild conjunctival chemosis and hyperemia following the procedure may last for a few days and the parents must be counseled regarding this.

Follow-up visits recommendation: This may be typically scheduled after week 1, 2, 4 and 12 following treatment based on the findings recorded by the treating ophthalmologist. Long-term follow up for development of visual problems is also essential.[20]

How should retinal detachment be treated?

Stage 4 or 5 ROP requires vitreo-retinal surgical intervention; retinal detachment carries a high risk of irreversible blindness. Lens sparing vitrectomy is the procedure of choice in stage 4A and subtypes of 4B.[21, 22] Timely lens sparing surgery may in fact result in reasonable to fairly good visual outcomes. A lensectomy–vitrectomy may be performed in stage 5. The prognosis is guarded and results continue to be poor.[23] Visual rehabilitation must be offered to all visually challenged ROP babies.

How should the long term follow up of these infants be planned?

Evidence: Infants with ROP, regardless of whether they have required treatment, are at risk for developing visual disorders such as strabismus, amblyopia, myopia and cataract;[6, 20] Retinal detachment may also occur during adulthood in infants with ROP. Moreover, prematurity may itself predispose to refractive errors, strabismus and lenticular opacities. Appropriate follow-up for these potential problems after discharge from the NICU is essential.[6, 9]

Recommendation: Following development of ROP, babies need to be under more intensive follow up for the first 6 months followed by a less intensive follow up schedule until young adulthood period to identify long term complications promptly.

What is the future of ROP screening and what is the role of Photo-documentation and Tele-ophthalmology in ROP screening?

The use of retinal wide field digital imaging (WFDI) using a portable pediatric fundus camera such as the RETCAM II, III and RETCAM shuttle (Clarity MSI, CA, USA) has become a useful adjunct to the documentation of ROP and as a screening and teaching tool.[24] The PHOTO-ROP study reports have shown that WFDI compares well with indirect ophthalmoscopy with a high diagnostic sensitivity.[17, 25] In India, an on-going Tele-ROP trial using non-physician imagers cum graders is being validated against ophthalmologists; preliminary results are encouraging.[26] In our country where trained ophthalmologists for ROP management are so few in number when the need is much more, the role of tele-ophthalmology

in screening infants in peripherally situated semi-urban and rural centers by ROP experts in the tertiary care centers seems promising. This may enable timely referral of the affected infants to appropriate centers for further evaluation and treatment.

References

1. Charan R, Dogra MR, Gupta A, Narang A. The incidence of retinopathy of prematurity in a neonatal care unit. Indian J Ophthalmol 1995; 43:123-26.
2. Gopal L, Sharma T, Ramchandran S, Shanmugasundaram R, Asha V. Retinopathy of prematurity. A study. Indian J Ophthalmol 1995; 43:50-61.
3. Varughese S, Jain S, Gupta N, Singh S, Tyagi V, Puliyel JM. Magnitude of the problem of retinopathy of prematurity. Experience in a large maternity unit with a medium size level-3 nursery. Indian J Ophthalmol 2001:49:187-88
4. National Neonatalogy Forum of India. National Neonatal Perinatal Database. Report for year 2003-2003. New Delhi 2005
5. Quiram PA, Capone A. Current understanding and management of retinopathy of prematurity. Current Opinion in Ophthalmology 2007, 18:228–234
6. American Academy of Pediatrics, Section on Ophthalmology. Screening examination of premature infants for retinopathy of prematurity. Pediatrics ; 117: 572-576.
7. Erratum for Section on Ophthalmology et al., AAP Policy 117 (2) 572-576**.** Pediatrics;118:1324.
8. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: ten year data from a tertiary care center in a developing country. Indian J Ophthalmol. 2007 Sep-Oct; 55(5):331-6.
9. Jalali S, R Anand, H Kumar, Dorgra MR, Azad EV, Gopal L. Programme planning and screening strategy in retinopathy of prematurity. Indian J Ophthalmol 2003; 51:89-97
10. Jalali S, Hussain A, Matalia J, Anand R. Modification of screening criteria for Retinopathy of Prematurity in India and other middle-income group countries. Am J Ophthalmol 2006; May 141 (5): 966-968
11. Sanghi G, Dogra MR, DAS P, Vinekar A, Gupta A, Dutta S. Aggressive posterior retinopathy of prematurity in Asian Indian Babies: Spectrum of Disease and Outcome after Laser Treatment. Retina. 2009 Jul 1. [Epub ahead of print]
12. Shah P, Narendran V, Saravanan VR, Raghuram A, et al. Fulminate retinopathy of prematurity - Clinical characteristics and laser outcome. Indian J Ophthalmol 2005; 53:261-265
13. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123:991–999
14. Dogra MR, Vinekar A, Viswanathan K, Sangtam T, Das P, Gupta A, Dutta S. Laser treatment for retinopathy of prematurity through the incubator wall. Ophthalmic Surg Lasers Imaging. 2008 Jul-Aug; 39(4):350-2.
15. Cryotherapy for retinopathy of prematurity cooperative group. Multicentre trial of cryotherapy for retinopathy of prematurity: three month outcome. Arch Ophthalmol 1990;108:195-204
16. Early treatment of Retinopathy of Prematurity cooperative group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment of Retinopathy of Prematurity Randomized trial. Arch Ophthalmol. 2003;121:1684-1696.
17. Vinekar A, Trese MT, Capone A Jr; Photographic Screening for Retinopathy of Prematurity (PHOTO-ROP) Cooperative Group. Evolution of retinal detachment in posterior retinopathy of prematurity: impact on treatment approach. Am J Ophthalmol. 2008 ;145(3):548-555.
18. Banach MJ, Ferrone PJ, Trese MT. A comparison of dense versus less dense diode laser photocoagulation patterns for threshold retinopathy of prematurity. Ophthalmology 2000; 107:324-327
19. Capone A. Jr, Vinekar A. Treatment of advanced retinopathy of prematurity: peripheral retinal ablation. In Retina and Vitreous Surgery, Bhavsar A (Ed), Saunders, 2008;pp17.

20. Dhawan A, Dogra M, Vinekar A, Gupta A, Dutta S. Structural sequelae and refractive outcome after successful laser treatment for threshold retinopathy of prematurity. J Pediatr Ophthalmol Strabismus 2008 ; 45(6):356-61.
21. Bende P, Gopal L, Sharma T, Verma A, Biswas RK. Functional and anatomical outcomes after primary lens sparing pars plana vitrectomy for stage 4 ROP. Indian J Ophthalmol 2009; 57(4):267-71.
22. El Rayes EN, Vinekar A, Capone A Jr. Three-year anatomic and visual outcomes after vitrectomy for stage 4B retinopathy of prematurity. Retina. 2008 Apr; 28(4):568-72 .
23. Gopal L, Sharma T, Shamnmugham M, Badrinath SS, Sharma A et al. Surgery for stage 5 ROP: the learning curve and evolving technique. Indian J Ophthalmol 2000; 48(2):101-6.
24. Trese MT. What is the real gold standard for ROP screening? Retina. 2008 ; 28(3 Suppl):S1-2.
25. Photographic Screening for ROP Cooperative Group. The Photographic Screening for ROP study. Retina 2008; 28:S47-54.
26. Vinekar A. The ROP challenge in Rural India: Preliminary report of a telemedicine screening model. (In) International Experience with photographic imaging for pediatric and adult eye disease. Retina Physician 2008; Supplem 9-10.
27. Filho JBF, Bonomo PP, Maia M, Procianoy RS. Weight gain measured at 6 weeks after birth as a predictor for severe Retinopathy of prematurity: study with 317 very low birth weight preterm babies. Graefes' Arch Clin Exptl Ophthalmol 2009; 247: 831-36.
28. Filho JBF, Bonomo PP, Maia M, Procianoy RS. Weight gain measured at 6 weeks after birth as a predictor for severe Retinopathy of prematurity: study with 317 very low birth weight preterm babies. Graefes' Arch Clin Exptl Ophthalmol 2009; 247: 831-36.

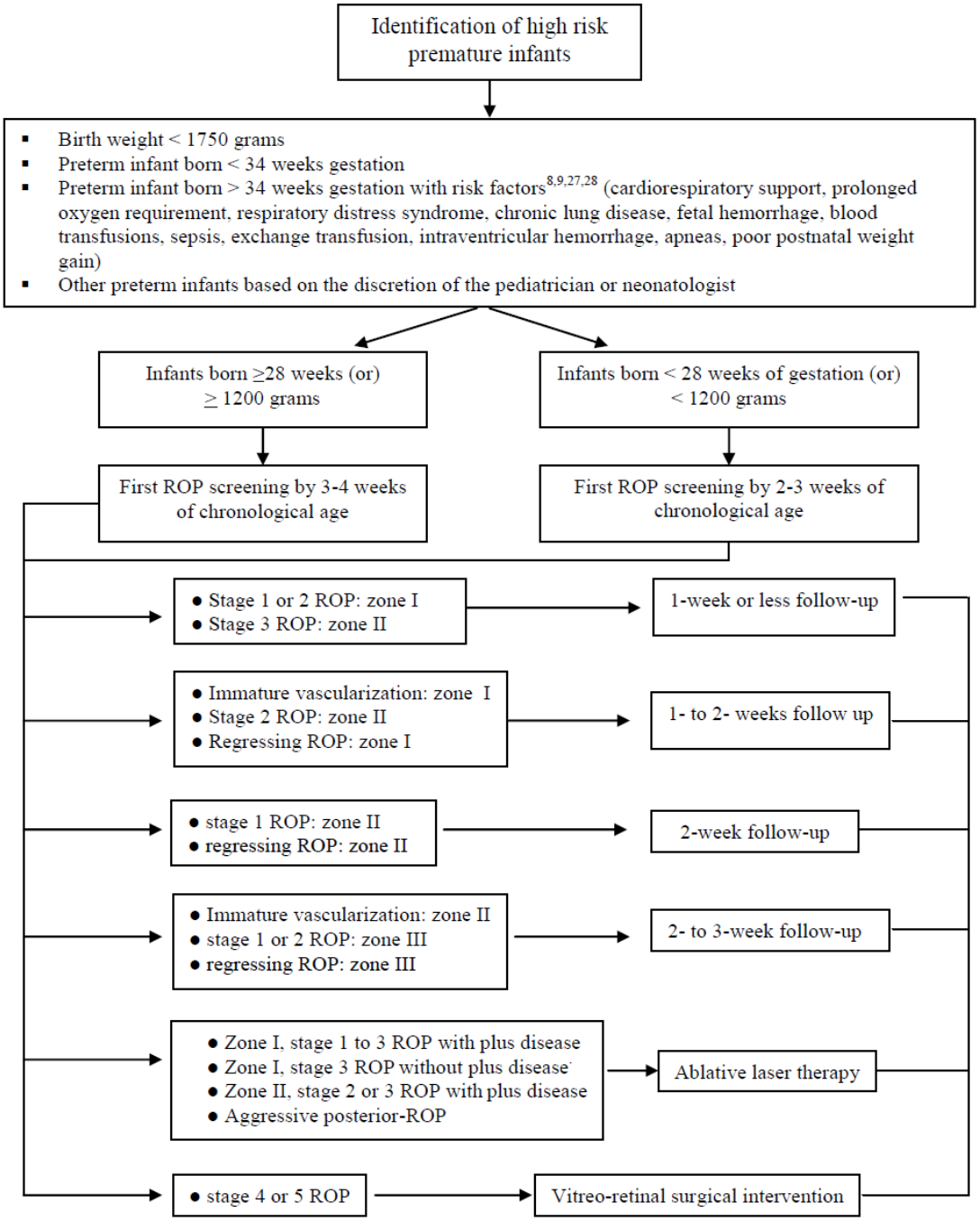
Table 1. Follow up examination schedule based on retinal findings

Zone of retinal findings	*Stage of retinal findings*	*Follow up interval*
Zone 1	Immature vascularization	1-2 weeks
	Stage 1 or 2	1 week or less
	Regressing ROP	1-2 weeks
Zone 2	Immature vascularization	2-3 weeks
	Stage 1	2 weeks
	Stage 2	1-2 weeks
	Stage 3	1 week or less
	Regressing ROP	1-2 weeks
Zone 3	Stage 1 or 2	2-3 weeks
	Regressing ROP	2-3 weeks

Table 2: Treatment guidelines for ROP adapted from the current ETROP guidelines. [16]

ZONE 1	NO PLUS	Stage 1	Follow
		Stage 2	Follow
		Stage 3	Treat
	PLUS	Stage 1	Treat
		Stage 2	Treat
		Stage 3	Treat
ZONE 2	NO PLUS	Stage 1	Follow
		Stage 2	Follow
		Stage 3	Follow
	PLUS	Stage 1	Follow
		Stage 2	Treat
		Stage 3	Treat

Fig 1: Algorithm for management of Retinopathy of prematurity



Annexure

Staging of ROP

ROP is described based on the 1) location of retinal involvement by zone 2) extent of retinal involvement by clock hour, and 3) stage of the disease at the junction of the avascular and vascular retina.

Location of the disease

Zones are centered around the optic disc and not the macula.

Zone I (innermost) is a circle, the radius of which extends from the center of the optic disc to twice the distance from the center of the optic disc to the center of the macula.

Zone II extends centrifugally from the edge of zone 1 to the nasal ora serrata.

Zone III is the residual crescent of retina temporal to zone 2.

Extent of the disease

The extent of the retinal involvement is recorded as hours of the clock or as 30 degrees sectors.

Stage of the disease

The clinical appearance of the stages of ROP is related to the appearance of the retinal vessels at the avascular-vascular junction. More than one stage may be present in the same eye; staging then is determined by the most severe manifestation present.

Immature or incompletely vascularized retina: this is seen prior to the development of ROP and is characterized by dichotomously branching retinal vessels of normal caliber.

Stage 1: A flat demarcating line is seen delimiting vascularized retina from the anterior avascular retina. Abnormal branching or arcading of vessels is seen leading up to the demarcation line.

Stage 2: The demarcation line develops into a ‘ridge’. This ridge is raised and has ‘volume’.

Stage 3: Extra-retinal neovascularization into the vitreous is seen with the development of abnormal shunt vessels at the ridge.

Stage 4: ROP associated with retinal detachments are classified into stage 4A (partial retinal detachment, not involving the macula) and stage 4B (involving the macula).

Stage 5: Total retinal detachment is usually tractional and funnel shaped and presents as a leucocoria or white pupillary reflex.

Plus disease: refers to venous dilatation and arteriolar tortuosity of the posterior retinal vessels in at least two quadrants of the eye. Engorgement of iris vessels, pupillary rigidity and vitreous haze may also be seen. A plus symbol is added to the ROP stage number to designate the presence of plus disease.

Pre-plus is the term used to denote vascular abnormalities of the posterior retina that are insufficient for the diagnosis of plus disease, but that cannot be considered normal.

Aggressive-posterior ROP (AP-ROP) (previously called type II ROP and 'rush disease'): is a rapidly progressing, severe form of ROP which if untreated progresses to stage 5 ROP. The features include posterior location (zone I and sometimes posterior zone II), prominence of plus disease, ill-defined nature of the retinopathy, flat network of neovascularization and hemorrhages. The earliest phase of this disease shows abnormal closed-loop vessels (and not the normal dichotomous branching pattern) with mild tortuosity that can develop into the full-blown picture in less than a week. The disease does not proceed from the classical stages of 1 through 3. Diagnosis can be made on a single visit and does not require evaluation over time.

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Hearing Screening

Summary of Recommendations

- **Ideally, efforts should be made to organize Universal newborn hearing screening because up to 42% of profoundly hearing impaired children may be missed using only risk-based screening .**
- **Short of universal screening, high risk screening should be mandatory. Known risk factors for hearing loss include genetic abnormalities, cytomegalovirus infection, asphyxia, hyperbilirubinemia, meningitis and premature infants necessitating a stay in the neonatal intensive care unit.**
- **Screening modalities include oto-acoustic emission and automated brainstem response. Oto-acoustic emissions alone are not a sufficient screening tool in infants who are at high risk.**
- **Newborns with positive screening tests should be referred for definitive testing and intervention services.**
- **Early intervention in hearing-impaired children improves language and communication skills. Identification and intervention for hearing impairment should occur before 6 months of age.**

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Introduction

Hearing loss is one of the most common congenital anomalies, occurring in approximately 2-4 infants per 1000 live births [1-3]. If congenital hearing loss is not recognized and managed, a child's speech, language, and cognitive development are often severely delayed. Universal screening for hearing loss is a preferred strategy over selective screening of at-risk groups. More than 50 percent of hearing impairment in children is thought to be genetic and not related to infectious, anatomic or other non-inherited causes [3, 4]. This guideline aims to give an evidence base about newborn hearing screening, with special focus on following questions:

- What is the critical age for hearing screening for preventing abnormalities in communication skills?
- Should the hearing screening be risk factor based or universal?
- What are the equipments for performing hearing screening?
- How frequently should children with risk factors be screened?

What is the critical age for hearing screening for preventing abnormalities in communication skills?

Evidence: Screening for hearing loss in newborns is based on two concepts. First, a critical period exists for optimal language skills to develop, and earlier intervention produces better outcomes [5, 6]. Second, treatment of hearing defects has been shown to improve communication [7]. Children with hearing loss typically experience significant delays in language development and academic achievement. Although the impact of a severe or profound hearing loss is well recognized, children with mild or moderate hearing loss also experience deficits in speech and language development.

Several studies by Yoshinaga-Itano and her colleagues have shown that when children are identified with hearing loss at birth and receive intervention before 6 months of age, they ''catch up'' with their normal-hearing peers and demonstrate essentially normal language development by 5 years of age [8-10]. Conversely, children who are identified with hearing loss later in life and receive intervention after 6 months of age, especially those with severe to profound hearing loss and with multiple handicaps, struggle to catch up with their normal-hearing peers. Moreover, children identified later than 6 months of age may lag in their speech, language, and auditory development well into early and later elementary years.

In 1994, Bess and Paradise challenged the need for earlier identification and intervention, stating that no evidence support the notion "that outcomes in children with congenital hearing loss are more favorable if treatment is begun early in infancy rather than later in childhood" [11]. In 1995, Apuzzo and Yoshinaga-Itano found that infant's identified when they were younger than 2 months had significantly higher language scores than those identified when they were older than 2 months, despite similar interventions in both groups [12]. In 1995, Robinshaw reported that children who were identified and who wore hearing aids by the age of 6 months acquired age-appropriate vocal communicative and linguistic skills well before children who were identified at a later age [13]. Although all of the above studies demonstrate the importance of early identification and intervention, a study conducted in 1998 at the University of Colorado truly established the critical period of early identification and intervention, namely, younger than 6 months [8, 14]. Yoshinaga-Itano and Sedey et al reported that even children identified as early as age 7-12 months had lower receptive and expressive language quotients than those of children identified by

age 6 months. No significant difference was found between children identified at age 7-12 months and those identified at age 25-30 months [8].

Recommendation: Identification and intervention before age 6 months can have a significant impact on the development of expressive and receptive language.

Should the hearing screening be risk factor based or universal?

Evidence: The Joint Committee on Infant Hearing (JCIH) first published a set of risk indicators for hearing loss in 1971, which were used primarily for screening infants in the neonatal intensive care unit (NICU), because most infants with risk factors were found in the NICU [15]. However, subsequent studies reported that 19 to 42 percent of profoundly hearing-impaired children would be missed with targeted, risk factor–based screening [16]. In 1999, Finitzio and Crumley reported that, according to the identification rates currently reported from various screening programs, approximately 8,000-16,000 newborns are born with hearing loss each year [17]. Of these, 50% are discharged home from the well-baby nursery with no known risk factors for hearing loss, according to the National Institutes of Health [18]. Although higher risk among NICU graduates should not be ignored, a program in which only neonates meeting the high risk criteria are screened was found to exclude as many as 50% of newborns with significant congenital hearing loss. This led to the initiation of the universal newborn hearing screening program in USA, and in 1999, the American Academy of Pediatrics estimated that 1 to 3 per 1000 infants born in well-baby nurseries may have permanent hearing loss sufficient to interfere with normal speech and language acquisition [19]. AAP suggests that when parents voice concerns about possible hearing loss, the pediatrician needs to assume that such is true until the child has been evaluated objectively. [20]

Recommendation: A high risk criterion can be used to identify children who are at risk for hearing loss. Nonetheless, if feasible based on logistics, **all newborns** should be screened, regardless of risk. Highest on the high risk group is parental concern; if universal screening is not feasible, the newborns in the high risk category (Table 1) should definitely undergo hearing screening [21, 22]. If a newborn passes the newborn hearing screening but has an identified risk for sensorineural and/or conductive hearing loss, these infants should be closely monitored for any changes in hearing status.

What are the modalities for performing hearing screening?

Auditory brainstem response (ABR), otoacoustic emissions (OAEs), and automated ABR (AABR) testing have been used in newborn hearing-screening programs. A modified screening version of the ABR test, called the AABR test, has been available for screening since approximately 1987. The discovery of OAEs by David Kemp in 1978 allowed the development of an alternative screening technology that has become common place in hospitals [23].

Evidence: OAEs are used to assess cochlear integrity and serve as a fast objective screening test to evaluate the function of the peripheral auditory system, primarily the cochlea, which is the area most often involved in sensorineural hearing loss. The presence of evoked OAE responses indicates hearing sensitivity in the normal to near-normal range [24]. The effectiveness of OAEs is reduced by contamination with low-frequency ambient noise in a busy nursery, vernix in the ear canal, or any middle ear pathology.

AABR is an electrophysiologic measurement that is used to assess auditory function from the eighth nerve through the auditory brainstem [25]. Most AABR systems compare an infant's waveform with that of a template developed from normative ABR infant data. A pass or fail response is determined from this

comparison. Most commercially available systems can be used as an effective screening tool in infants younger than 6 months. The AABR method produce a simple pass or fail result without requiring interpretation and the test can be conducted in the presence of background noise. However, it lacks frequency-specific information and requires increased preparation time prior to testing.

Diagnostic ABR testing is generally not used in universal newborn hearing screening programs because of the length of the procedure, the cost, and the need for an audiologist to perform the test and interpret the results [25]. Unlike the AABR test, which elicits a response to a fixed 35-dB HL click, the intensity of the stimulus is varied in the manual ABR test to determine the lowest level required to evoke a clear and repeatable response. While AABR has been used for years on infants falling under the high-risk register (HRR), OAE screening has been shown to be a highly cost-effective tool. Several papers have described a combined AABR and OAE screening technique as an effective tool for maintaining low referral rates [26-28]. Although OAE screening continues to be cost effective in the well-baby nursery, OAE screening followed by AABR is a reliable protocol that results in low referral rates [29].

Recommendation (see Figure 1): The initial screening can be performed using OAE/ AABR or both. OAEs alone are not a sufficient screening tool in infants who are at risk for neural hearing loss (e.g., auditory neuropathy/dyssynchrony, infants with jaundice/ asphyxia). Hence, any infant in the NICU or in the hospital for more than 5 days should undergo an ABR screening also, so that the presence of auditory neuropathy is not missed. Both ears should be screened individually. The initial screening should consist of 2 attempts maximum on each ear. The re-screening is a second hearing screening that can be performed if an infant does not pass the initial hearing screening in one or both ears and it should be performed prior to 1 month of age. In India, it would be practical to do the second test at 6 weeks when the infant comes for immunization. If an infant does not pass the re-screening or if results cannot be obtained in one or both ears, he should be referred for diagnostic audiological evaluation which should involve diagnostic BERA.

How frequently should children with risk factors be screened?

Evidence: Children with risk factors should be screened not only at birth but also throughout childhood. The Joint Committee on Infant Hearing recommends continued surveillance of these children because they may be at risk of progressive hearing loss [20, 21]. This recommendation includes audiologic testing every six months until three years of age. In low-risk children, a repeat hearing screening is recommended at 6 months and then, before entry into kindergarten [25].

Recommendation: NICU graduates should undergo first screening prior to discharge while normal newborns, it may be delayed to a post discharge visit (usually at 6weeks when the child presents for immunization). Infants who do not pass an initial hearing screening at birth should return for follow-up testing within 1 month. Diagnostic OAE and ABR testing is recommended for any infant who does not pass the second screening session. Both tests are necessary to differentially diagnose an infant's hearing impairment. In addition, children with risk factors for hearing loss who have a negative hearing screen at birth should undergo audiologic testing every six months until three years of age to look for any progressive hearing loss.

Most patients with hearing loss benefit from amplification. In a patient with a conductive hearing loss, consideration usually is given to correction of the loss, medically or surgically. If the patient is an unsuitable surgical candidate or has significant residual loss after medical or surgical therapy, a hearing aid should be strongly considered. Those with sensory neural hearing loss also usually benefit from a

hearing aid, although the fitting of an appropriate instrument may be more difficult, depending on the magnitude of loss and degree of associated distortion. Patients with bilateral severe to profound SNHL who do not benefit significantly from conventional hearing aids often are candidates for cochlear implantation.

What are the limitations of hearing screening?

The newborn hearing screening produces a large number of false-positive test results. Both AABR and TEOAE can be influenced by motion artifact and therefore are more specific if performed on a sleeping child in a quiet room. The rate of false positives ranges from more than 30 percent for one-step programs using TEOAE [28] to less than 1 percent with a two-step process, such as retesting a child before discharge if the initial test is positive. Increased parental anxiety may result from a false-positive test, although this finding has not been demonstrated consistently in all studies [30, 31]. Qualitative studies indicate that negative parental emotions may be addressed with more systematic education before and after screening [32].

References

1. Nagapoornima, P., A. Ramesh, et al. (2007). Universal hearing screening. Indian J Pediatr 74(6): 545-9.
2. Centers for Disease Control and Prevention. National Center on Birth Defects and Developmental Disabilities. Hearing loss. Accessed at: http://www.cdc.gov/ncbddd/dd/ddhi.htm
3. Hadad J Jr. Hearing loss. In: Behrman RE, Kliegman R, Jenson HB, eds. Nelson Textbook of Pediatrics. 17th Ed. Philadelphia, Pa.: Saunders, 2004:2129-34.
4. Yoshinaga-Itano C, Sedey AL, Coulter DK, Mehl AL. Language of early- and later-identified children with hearing loss. Pediatrics 1998;102:1161-71
5. Lim G, Fortaleza K. Overcoming challenges in newborn hearing screening. J Perinatol 2000; 20:S138-42.
6. Ruben RJ. Early identification of hearing impairment in infants and young children. NIH Consensus Statement 1993; 11:17-9.
7. Yoshinaga-Itano C, Sedey AL, Coulter DK, et al. Language of early- and later-identified children with hearing loss. Pediatrics 1998; 102(5):1161–71.
8. Downs MP, Yoshinaga-Itano C. The efficacy of early identification and intervention for children with hearing impairment. Pediatr Clin North Am 1999; 46(1):79–87.
9. Yoshinaga-Itano C. Early intervention after universal neonatal hearing screening: impact on outcomes. Ment Retard Dev Disabil Res Rev 2003; 9(4):252–66.
10. Bess FH, Paradise JL. Universal screening for infant hearing impairment: not simple, not risk-free, not necessarily beneficial, and not presently justified. Pediatrics. Feb 1994; 93(2):330-4.
11. Apuzzo ML, Yoshinaga-Itano C. Early identification of infants with significant hearing loss and the Minnesota Child Development Inventory. Semin Hearing. 1995; 16:124-37.
12. Robinshaw HM. Early intervention for hearing impairment: dif ferences in the timing of communicative and linguistic development. Br J Audiol. Dec 1995; 29(6):315-34.
13. Yoshinaga-Itano C, Apuzzo ML. Identification of hearing loss after age 18 months is not early enough. Am Ann Deaf. Dec 1998; 143(5):380-7.
14. Committee on Fetus and Newborn. Joint statement on neonatal screening for hearing impairment. Pediatrics 1971; 47(6):1085.
15. Thompson DC, McPhillips H, Davis RL, Lieu TL, Homer CJ, Helfand M. Universal newborn hearing screening: summary of evidence. JAMA 2001; 286:2000-10.
16. Finitzo T, Crumley WG. The role of the pediatrician in hearing loss. From detection to connection. Pediatr Cl in North Am. Feb 1999; 46(1):15-34, ix-x.
17. NIH. Early identification of hearing impairment in infants and young children. NIH Consensus Statement. Mar 1-3 1993; 11(1):1-24.

18. Erenberg A, Lemons J, Sia C, Trunkel D, Ziring P. Newborn and infant hearing loss: detection and intervention. American Academy of Pediatrics. Task Force on Newborn and Infant Hearing, 1998-1999. Pediatrics 1999; 103:527-30.
19. JCIH. Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs.
20. Joint Committee on Infant Hearing, American Academy of Audiology, American Academy of Pediatrics, American Speech-Language-Hearing Association, and Directors of Speech and Hearing Programs in State Health and Welfare Agencies. Pediatrics. Oct 2000;106(4):798-817.
21. Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention program. Pediatrics 2007; 120(4):898–921.
22. Kemp DT. Stimulated acoustic emissions from within the human auditory system. J Acoust Soc Am. Nov 1978;64 (5):1386-91.
23. Hall JW 3rd, Smith SD, Popelka GR. Newborn hearing screening with combined otoacoustic emissions and auditory brainstem responses. J Am Acad Audiol. Jun 2004; 15(6):414-25.
24. American Speech-Language-Hearing Panel. Guidelines for audiologic screening. Rockville, Md.: American Speech-Language-Hearing Association, 1997.
25. Stewart DL, Mehl A, Hall JW 3rd, Thomson V, Carroll M, Hamlett J. Universal newborn hearing screening with automated auditory brainstem response: a multisite investigation. J Perinatol. Dec 2000;20 (8 Pt 2):S128-31.
26. Gorga MP, Preissler K, Simmons J, Walker L, Hoover B. Some issues relevant to establishing a universal newborn hearing screening program. J Am Acad Audiol. Feb 2001; 12(2):101-12.
27. Norton SJ, Gorga MP, Widen JE, Folsom RC, Sininger Y, Cone-Wesson B. Identification of neonatal hearing impairment: a multicenter investigation. Ear Hear. Oct 2000; 21(5):348-56.
28. Lin HC, Shu MT, Lee KS, Lin HY, Lin G. Reducing False Positives in Newborn Hearing Screening Program: How and Why. Otol Neurotol. Sep 2007; 28(6):788-792.
29. Clarke P, Iqbal M, Mitchell S. A comparison of transient-evoked oto-acoustic emissions and automated auditory brainstem responses for pre-discharge neonatal hearing screening. Int J Audiol 2003;42:443-7
30. Russ SA, Kuo AA, Poulakis Z, Barker M, Rickards F, Saunders K, et al. Qualitative analysis of parents' experience with early detection of hearing loss. Arch Dis Child 2004;89:353-8.
31. U.S. Preventive Services Task Force. Recommendations and rationale: newborn hearing screening. Accessed at: http://www.ahrq.gov/clinic/uspstf/uspsnbhr.htm.
32. Thompson DC, McPhillips H, Davis RL, Lieu TL, Homer CJ, Helfand M. Universal newborn hearing screening: summary of evidence. JAMA 2001; 286:2000-10.

Table 1: Risk factors associated with higher likelihood of hearing loss (From 2007 JCIH risk indicators)

- Caregiver concern for hearing, speech, language, or developmental delay
- Family history of permanent childhood hearing loss
- Infants requiring neonatal intensive care for more than 5 days, including administration of
    - Extracorporeal membrane oxygenation (ECMO),
    - Assisted ventilation,
    - Ototoxic medications,
    - Hyperbilirubinemia requiring exchange transfusion
- Postnatal infections such as Meningitis, Encephalitis, Sepsis, and Herpes
- In utero infections, including cytomegalovirus, herpes, rubella, syphilis, and toxoplasmosis
- Craniofacial anomalies including cleft palate or lip, anomalies of the pinna or ear canal, ear tags, ear pits, or temporal bone anomalies
- Syndromes associated with hearing loss (or a family history of same)
    - Neurofibromatosis
    - Osteopetrosis
    - Waardenburg syndrome
    - Pendred syndrome
    - Jervell syndrome
    - Lange-Nielsen syndrome
    - Alport syndrome
    - Usher syndrome
    - Treacher-Collins syndrome
- Head trauma (especially involving basal skull or temporal bone)

Table 2: Key Recommendations for Practice

Clinical recommendation	Evidence rating	References
Universal newborn hearing screening should be used to accurately diagnose moderate to severe sensorineural hearing loss.	C	18, 20
Children with risk factors for hearing loss who have a negative hearing screen at birth should undergo audiologic testing every six months until three years of age.	C	18, 20, 23
Identification of hearing loss before six months of age improves language development and communication skills.	B	31, 32

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series.

Table 3: Tips for hearing screening

- Visually inspect the ear canal for debris
- Seat the ear phone probe gently
- If the baby does not pass on the first try:

    a. Remove the probe and check for debris
    b. Replace tip if needed
    c. Clean probe

- Reposition probe and repeat
- When to screen

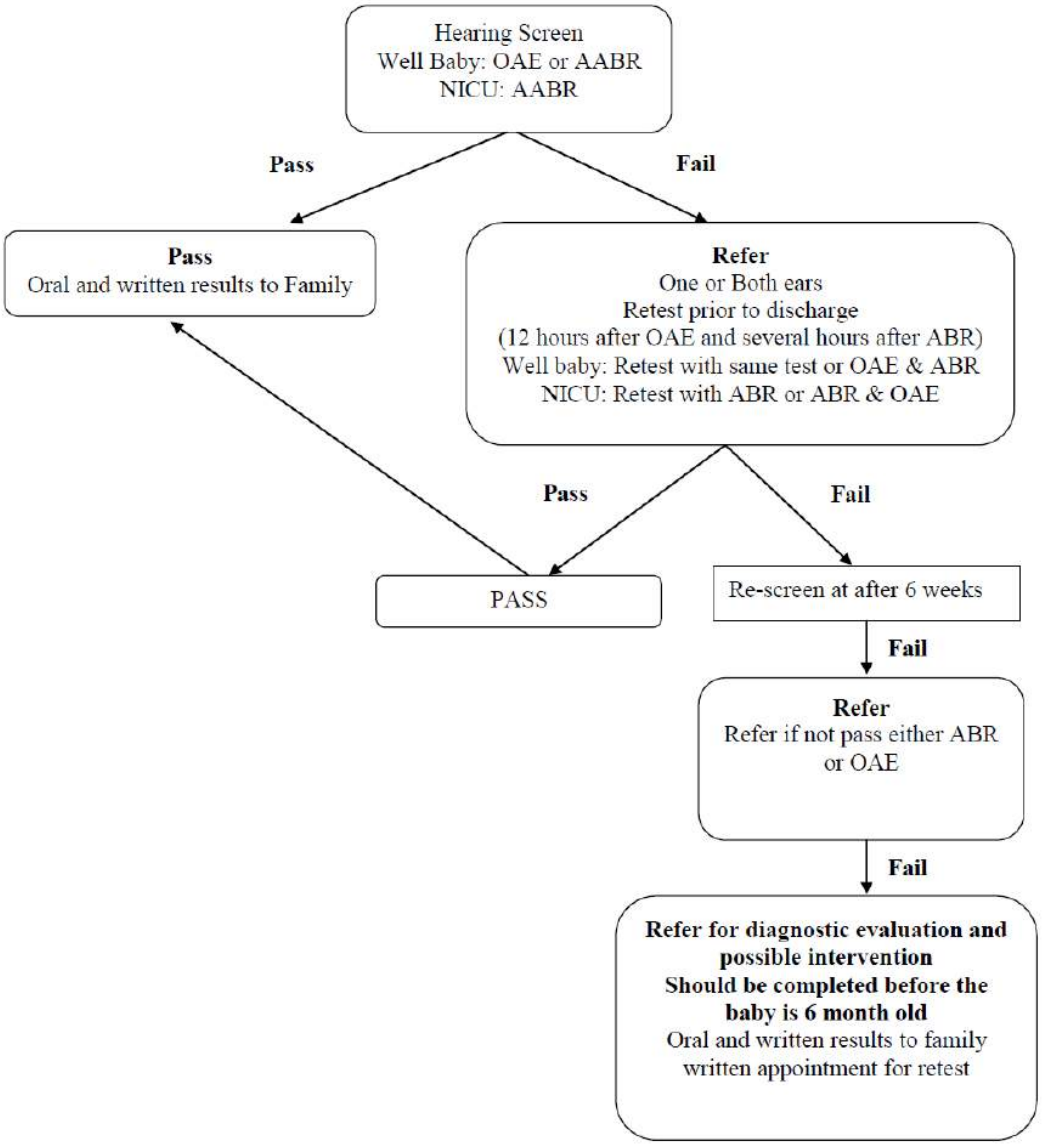
    a. Testing should be done as close to discharge as possible
    b. It is preferable to screen between 24 – 72 Hrs of life.
    c. False positive rates decreases after 12 – 24 hrs of life
    d. After infant completes nursing or feeding
    e. Screen after 34 week of gestation.
    f. Antibiotic therapy should not be reason for missed screen.
    g. Screen can be done during phototherapy.
    h. Test time, 3–6 min per baby depending on type of equipment and co-operation.
    i. Should return for 2nd screen within 6 weeks

- Neonatal Intensive Care unit

    a. AABR is preferred method of screening for all NICU infants; OAE an alternative
    b. Initial screen: Two attempts may be conducted on each ear before considering referral
    c. Second screen: Separate time of the day than the initial screen. Two attempts may be conducted on each ear before referral.
    d. Maximum: Do not screen more than 2 times in each ear at either the initial or second screen.
    e. NICU infants admitted for greater than 5 days should have auditory brainstem response (ABR) included as part of their hearing screening so that neural hearing loss will not be missed.

    f. Infants who do not pass the automated ABR should be referred directly to an audiologist for re – screening/ diagnostic ABR

Fig 1: Algorithm for Newborn Hearing Screening



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Cranial Ultrasonography in the Newborn

Summary of Recommendations

- **Cranial ultrasonography (CUS) is the best point of care neuroimaging method available for premature and sick babies.**
- **The ultrasound machine should be portable, should have presets for neonatal CUS and there should be facility to print and store the images. The transducer should be of 5-8 Mhz multi-frequency sector probe and its head be small enough to fit the windows.**
- **The sonographer should have knowledge about the brain anatomy, maturation, common neurological morbidities and the art of handling such fragile patients.**
- **A systematic structured approach should be followed to detect cerebral pathology and the same should be documented methodically.**
- **Periventricular hemorrhage, cystic periventricular leukomalacia and ventricular dilatation can be accurately detected and followed by CUS.**
- **Routine screening cranial US should be performed on all infants with birth weight < 1250grams or gestation < 30 weeks. However, this is mainly based on evidence from western countries. Data from multiple centers across India needs to be collated to validate these cut-offs.**
- **Screening cranial US should be performed at 7 to 14 days of age and repeated at 36 to 40 weeks postmenstrual age.**
- **Role of gray-scale CUS in term asphyxiated babies is not proven. However measurement of CBF by Doppler helps in predicting the neurodevelopmental outcome in hypoxic ischemic encephalopathy.**

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Introduction

Neonatal Care in India is advancing at an impressive phase at the level of the community as well as in tertiary care units. The concept of 'survival' of the newborn has predictably given way to the importance of 'intact survival' of the high risk infant, prompting initiation of strategies to identify neurological sub-normality at the earliest. Advances in imaging techniques have contributed significantly to early detection of abnormalities of the brain. Ultrasonography, which is now ubiquitously available, is an ideal tool for the primary screening of the neonatal brain. Despite the wide availability of ultrasound machines in the hospitals, the penetration of cranial ultrasonography (CUS) in Indian NICU's is still very little. In this guideline, an attempt has been made to answer the following issues related to the use of cranial ultrasonography (CUS) in the newborns:

- Role of CUS in the newborn
- Characteristics of the ultrasound equipment
- Technical aspects of performing the ultrasound examination
- Indications of doing CUS in preterm and term neonates
- Objective grading of lesions and prognostic significance

Why imaging of brain is required in neonatal units?

CUS helps in demonstration of cerebral pathologies in premature and sick newborn babies like hemorrhage, ischemia and ventricular dilatation. Also, knowledge of cerebral pathology aids in predicting neurological outcome according to the grade of injury. Sometimes, CUS helps to assess the timing of brain injury. For instance, in a baby with neonatal encephalopathy, an early cranial USG may help us in determining as to whether the injury was antenatal or postnatal[1].

Why should CUS be used as a tool for neonatal brain imaging?

CUS in neonates is safe and radiation free. Safety of sonography is well established in fetuses and infants except for transcranial doppler where there can be local rise of tissue temperature and cavitation if performed for long duration[1]. CUS can be easily performed at the bedside. CUS done with a portable ultrasound machine, conveniently in the NICU meets the definition of point-of-care testing (POCT)[1]. It is reliable for commonly occurring neonatal events like hemorrhages, cystic lesions, major malformations and fluid collections. CUS can be initiated even immediately after birth and hence suitable for screening. It can be repeated as often as possible without any adverse affects and hence helps in proper follow up of babies with neurological problems. Lastly, CUS is a significantly cheaper modality of neuroimaging compared with other techniques[1].

What are the requirements for a Cranial Ultrasound Machine?

The following are the minimum requirements of an ultrasound machine to perform a good quality cranial ultrasonography[1].

a. Should be easily transportable to the bedside in the NICU.
b. The settings and knobs should be easy to operate.

c. It is ideal to have color and doppler also in the machine as it helps in measurement of vascular resistance and cerebral blood flow.
d. There should be special software and presets for neonatal CUS, therefore making the procedure easier and consistent.
e. Should have the ability to store images for later reproducibility.
f. There should be facility to print images and generate reports.

For detailed technical specifications, refer to the NNF Equipment committee website www.nfequipment.org

What are the transducer requisites for good quality neonatal brain imaging?

Ultimately, transducer probe is the one which captures the images. An ultrasound machine can have several probes, which can be changed according to need. However, the following are the minimum requirements of a transducer to perform cranial ultrasonography in neonates[5].

a. Sector or a curved linear probe
b. Ideal frequency is 5-8MHz, usually as a multifrequency probe. Higher frequencies have better near-view resolution but loose penetration.
c. Transducer head should be appropriately sized to fit the anterior fontanelle.
d. Transducer gel (warm medium) should always be used for good contact between the probe and skin.

Who should do the CUS in neonates?

CUS can be performed by a caregiver having good knowledge of the brain anatomy, maturational changes and common pathologies at various gestational ages. Either a pediatric radiologist with experience of CUS in the newborn or a neonatologist with special training and experience in neonatal CUS may perform the procedure. In either case, the images should be stored for records, review and confirmation. During the procedure these vulnerable babies need to be handled gently, should avoid procedure related hypothermia and follow standard asepsis protocols in the unit.

Which windows in the skull are useful for CUS examination?

Several windows in the un-fused skull of a neonate give the opportunity to look into various parts of the brain with a reasonable degree of accuracy and detail[5].

- Standard or conventional views are those obtained through anterior fontanelle (AF). *Coronal planes*: The probe is swept from orbits to occiput to take six views keeping the marker on the right. *Saggital planes*: The probe is swept from midline to either side till sylvian fissures and insulae. A midline and two views on either side are recorded. The posterior part of probe is angled a little laterally to get a complete view of the lateral ventricles. Be careful to mark as to which side is being scanned.
- Supplemental windows (Posterior, Mastoid and Temporal fontanelle): Other smaller windows help us to visualize structures closer to the windows in a better way as the probes are usually of higher frequencies. But these additional windows need skill and expertise and hence cannot be

used initially during the learning process. These views may be useful in suspected cerebellar hemorrhage / posterior fossa abnormalities (baby with respiratory instability, stridor, neck retraction or suspicion on a standard CUS), in IVH to rule out occipital or cerebellar extension or in ventricular dilatation of unknown origin.

What would be a systematic approach in the procedure of CUS?

A systematic approach is required in any procedure in order to avoid missing any useful information. The following points need to be considered when doing a CUG[5].

a. Are the anatomical structures distinguishable and do they appear normal? It is essential to identify the following structures – ventricular system, interhemispheric fissure, corpus callosum, sylvian fissure, thalamus and basal ganglia.
b. Does the maturation of the brain appear appropriate for the gestation? Look at the degree of cortical folding on the cortical surfaces and along the interhemispheric fissure.
c. Are the basal ganglia and thalami prominently echogenic?
d. Is there normal echogenicity and homogeneity of periventricular and subcortical white matter?
e. Does the size, lining and the echogenicity of ventricular system appear normal?
f. In case of ventricular enlargement, the ventricles should be measured and compared with nomograms.
g. Are there any extra-axial collections such as subarachnoid hemorrhage or subdural effusion?
h. Is there a midline shift?

The findings should be recorded in a structured performa. (Annexure).

What are the indications of doing CUS in a neonate?

a. Screening CUS in a premature baby
b. Clinical suspicion of intracranial hemorrhage
c. Neonatal seizures
d. Evaluation of large or rapidly enlarging head
e. Serial follow up of post hemorrhagic hydrocephalus
f. Hypoxic Ischemic encephalopathy

Which lesions in the newborn are accurately detected by CUS?

Evidence : In four studies[13-16] reporting results of a total of 87 autopsies performed on PT infants, US was 76% to 100% accurate in detecting grade 1 lesions of > 5 mm and grade 3 and grade 4 hemorrhages. Detection of grade 2 hemorrhages was much less accurate. Correlation of US findings of cystic periventricular leukomalacia(PVL) with neuropathologic data was evaluated in three studies.[16-18] Each study found 100% correlation between US findings and neuropathologic data. Ultrasound is also particularly useful in detecting some important congenital malformations such as cystic leisons (hydrocephalus, porencephalic cysts, Dandy-Walker cysts complex, holoprosencephaly, choroid plexus cysts and arachanoid cysts), corpus callosal agenesis and aneurysm of vein of Galen (color Doppler).

Recommendation : Cranial Ultrasound is useful in detecting intraventricular hemorrhage, cystic PVL and ventriculomegaly besides important congenital malformations such as hydrocephalus, corpus callosum agenesis and others.

Screening CUS in a premature baby

Who should be screened?

Screening cranial ultrasonography is done in premature infants to detect intraventricular hemorrhage, cystic periventricular leucomalacia and ventriculomegaly. Detection of agenesis of corpus callosum, cystic lesions, and vein of Galen malformation are chance findings.

Evidence : In a study by Perlman et al.[1] screening ultrasound in VLBW neonates identified abnormalities in 57% of neonates. Of the 318 infants screened the US was normal in 156 neonates (49%) and abnormal in 161 (57%). The principal abnormalities included intraventricular hemorrhage (IVH) (n=74), periventricular echogenicity (PVE) (n=68), ventriculomegaly (n=7), and solitary cysts (n=9). Seven studies evaluated the need for screening cranial US in low BW preterm infants.[1-7] Review of these studies suggests that although CUS in infants with BW of < 1500 grams or GA of < 33 weeks shows some abnormalities in 12% to 51% of infants in the first 2 weeks of life, major US abnormalities such as grades 3 and 4 IVH or bilateral cystic PVL occur in < 20% of infants. In only four studies, the data were presented by specific GA and/or BW groups.[1,2,4,6] In these studies, grades 3 and 4 IVH was noted in 11% of infants with BW of <1,000 grams and in 5% of infants with BW of 1,000 to 1,250 grams; Likewise, cystic PVL was noted in 5% to 26% of infants weighing <1,000 grams, compared with 1% to 5% of infants with BW of >1,000 grams. Ventriculomegaly was described in 5% to 7% of infants weighing <1,000 grams. In a study from North India, 31 of the 97 VLBW infants had PVL during the course of hospital stay and only 5(5%) infants developed cystic PVL and one had ventriculomegaly (1%).[8]

Recommendations: Routine screening cranial US should be performed on all infants with birth weight < 1250grams or gestation <30weeks, irrespective of symptoms and signs .

What should be the timing of screening CUS?

Ultrasonographic evidence of injury to the developing brain varies with time. Grades 3 and 4 IVH, which may alter medical management, may be detected as late as the third postnatal week. Cystic PVL and ventriculomegaly, which may alter prognosis and treatment programs, may be first seen by US at term. Furthermore, these lesions may be detected in many infants after previously normal US findings. Screening US is done to identify lesions which help in acute management or in prognostication. The ideal time of screening could vary from day 1 of life to discharge from hospital or at term corrected age

Evidence : Multiple studies performed before 1990 suggested that > 90% of all IVH cases in VLBW PT infants were detected during postnatal days 4 to 5.[9-12] In one study,[1] 248 infants with BW of <1,500 grams underwent regular US at predefined times (1–5 days, 10–14 days, 28days, and term). Approximately 65% of IVH cases were detected within the first week. The other cases occurred in the second and third postnatal weeks, and one infant developed severe IVH after postnatal day 28. When BW was < 1,000 grams, severe IVH was detected in 10 (77%) of 13 infants on days 1 to 5; 13 (100%) of 13 cases of severe IVH were detected on day 28. In a study designed to assess changes in US findings across time,[5] 144 infants with BW of < 1,500 grams or GA of < 33 weeks underwent US between days 1 and 7 and then between days 10 and 14. Fifteen infants (10%) had significant changes in US findings from the

first to the second scan. Thirteen infants whose first US showed normal results or grades 1 and 2 IVH were found to have major abnormalities (i.e., grades 3 and 4 IVH and/or PVL) at the time of the second scan. For two infants, US findings changed from a major abnormality during the first US (i.e., PVL) to either normal results or a minor abnormality (i.e., grade 2 IVH) during the second US.

Cystic PVL has been detected in infants without previous US abnormalities as late as postnatal day 104.[3,6,7] In one report,[1] Cystic PVL and ventriculomegaly were found in 8 (3%) of 256 neonates after previously normal US findings. For infants weighing < 1,000 grams, 3 (50%) of 6 cases of PVL were noted at 36 to 40 weeks' postmenstrual age

The timing at which US can detect injury in the developing brain may be changing. Grades 3 and 4 IVH, which may alter medical management and prognostic information, may be detected as late as the third postnatal week. Cystic PVL and ventriculomegaly, which may alter prognosis and treatment programs, may be first seen by US at term. Furthermore, these lesions may be detected in many infants after previously normal US findings. Levene's Index is the used in premature babies to measure ventriculomegaly and is measured as a distance between falx (or interhemispheric fissure) to the lateral tip of lateral ventricle in the plane of third ventricle

Recommendation:

- Screening cranial US should be performed on all infants with GA of < 30 weeks at 7 to 14 days of age and should be optimally repeated at 36 to 40 weeks' postmenstrual age. This recommendation is designed to detect clinically unsuspected IVH and also PVL/ventriculomegaly[8].
- In babies <28 weeks a cranial ultrasound may be done on day 1 of life to rule out severe IVH and antenatal brain injury. This may facilitate decision making for aggressive management of such extreme infants.
- Apart from screening US, cranial ultrasound in preterm infants is required in the following clinical situations
    - Neonatal seizures (major malformations, intracranial hemorrhage)
    - Clinical suspicion of intracranial hemorrhage
    - Unexplained Congestive cardiac failure (Vein of Galen and AV malformations)

What is the ability of CUS to predict long-term neurodevelopmental outcome in VLBW infants?

One of the aims of screening neonatal CUS is to identify neonates at risk of long term neuro-developmental outcome such as cerebral palsy, lower developmental quotient, lower IQs and sensory impairments or motor handicaps**.**

Evidence : Six studies[24-29] compared US findings with the incidence of CP for almost 2,250 VLBW PT children at ages 2 to 9 years. Significant associations between grades 4 IVH, PVL, and/or ventriculomegaly and CP were noted in all six studies. In the largest of these studies, both grade 4 IVH and PVL were associated with CP (odds ratio [OR], 15.4; 95% CI, 7.6–31.1); any grade IVH alone was also associated with CP (OR, 3.14; 95% CI, 1.5–6.5). When the same groups assessed[25-27,] the correlation of neonatal US findings with the developmental quotient, grade 4 IVH and moderate to severe ventriculomegaly were strongly associated with the risk of mental retardation at 2 to 9 years of age. In

these prospective studies, OR ranged from 9.97 to 19.0. In addition, Whitaker et al.[28] demonstrated that for infants with BW of 500 to 2,000 grams who had grade 4 IVH and/or moderate to severe ventriculomegaly, the OR for the development of any neuropsychiatric disorder at the age 6 years was 4.4.

Recommendations:

- For VLBW infants, CUS can be used to predict long-term neurodevelopmental outcome.
- The findings of grades 3 and 4 intraventricular hemorrhage, periventricular cystic lesions, and moderate to severe ventriculomegaly are all associated with adverse outcome.

Is CUS useful in term babies with encephalopathy?

The following pathologies may be detected by careful ultrasound examination in a term baby with encephalopathy[9]:

a. *Basal ganglia injury* may be evident as echodense (hemorrhagic necrosis) or as echolucent lesions (non-hemorrhagic necrosis).
b. *Focal ischemic lesion* may be evident as echodensity in an area of vascular distribution associated with loss of pulsations in the affected vessel.
c. *Periventricular Injury*, like in a premature baby, may show up periventricular flare, cyst formation and progressive ventricular dilatation.

Ultrasound cannot detect other forms of injury seen in HIE such as selective neuronal necrosis (cortical and brainstem) and parasaggital injury. It may detect indirect evidence of cerebral edema in the form of chinked ventricles. CUS can easily detect various forms of intracranial bleed such as cerebellar, parenchyma and intraventricular hemorrhage associated with asphyxia.

Evidence : In one study,[29] CUS was performed on 104 encephalopathic term neonates and 70 control term neonates on the first postnatal day. A diffuse increase in echogenicity of the cerebral parenchyma and slit-like ventricles were significantly more common in infants with encephalopathy than in controls. (39% versus 1% [$p < 0.001$] and 44% versus 9% [p <0.00l], respectively), but the investigators found no correlation between US findings on the first postnatal day and neurodevelopmental status at 1 year of age. Similar results were noted in a study evaluating term infants with neonatal encephalopathy on the first postnatal day.[30] In the same study, analysis of simultaneous Doppler US demonstrated resistive indices (resistive index =peak systolic velocity minus end diastolic velocity divided by peak systolic velocity) of <0.60 for all children with adverse neurodevelopmental outcome. In another study,[31] grayscale US, Doppler US, and CT were performed on infants with neonatal encephalopathy. Gray-scale US was not predictive of outcome, but a resistive index of < 0.5 in the middle cerebral artery was associated with adverse neurodevelopmental outcome at 1 to 2 years (sensitivity, 82%; specificity, 89%). In addition, CT demonstrating generalized decreased density had 91% sensitivity and 100% specificity for adverse outcomes. Three studies[32-34] compared early US and MRI studies for infants with neonatal encephalopathy. An abnormal MRI signal in the basal ganglia in association with an abnormal US result for the basal ganglia was most frequently associated with an adverse neurodevelopmental outcome including CP, seizures, and developmental delay at 1 year of age, while normal findings of US and CT or US and MRI had low negative predictive values.

Recommendations: At present evidence does not support the role of routine grey scale CUS in the diagnosis and management of term neonate with encephalopathy. However in cases of encephalopathy, a screening ultrasound may occasionally detect structural malformations, ischemic insults such as porencephalic cysts and hemorrhagic manifestations such as intra-cerebral hemorrhage.

What is the role of Doppler in CUS?

Doppler assessment helps in measurement of cerebral blood flood velocity (cerebral hemodyanamics). The main indication for Doppler in CUS is to measure the CBF velocity in babies with HIE. The cerebral blood flow velocities initially increase due to hyperperfusion and later decrease in those who develop HIE.

Evidence : Liu J et al evaluated 40 term neonates with HIE and 30 healthy controls. Color Doppler ultrasound was performed at the bedside within 24 h after birth. The transducer was placed on the temporal fontanelle to detect the hemodynamic parameters of bilateral middle cerebral arteries. The results showed that infants with HIE had significant cerebral hemodynamic disturbance. The cerebral blood flow velocity decreased or increased markedly as resistive index (RI) decreased or increased markedly, which usually suggested the diagnosis of HIE, RI < 0.50 or RI > 0.90 usually occurred in severe patients, while RI > 1.0 would be associated with later brain death. In the study by Gray H et al Resistivity index (RI) can be measured on any cerebral vessel and a value < 0.5-0.6 has been associated with poor outcome[10]. It may be abnormal from around 24-72 hours after the insult. If the RI in a baby with encephalopathy is abnormal on day 1, this suggests that an insult occurred in the 1-2 days preceding birth.

Asymmetry in the MCA Doppler is seen in infants with unilateral MCA infarction. Arterial, venous or arterio-venous malformations/thrombosis can also be detected by transcranial Doppler study.

Recommendations : RI < 0.50 or >0.90 in the cerebral blood vessels is associated with immediate and long term poor outcome, but the current evidence is inadequate to suggest routine Doppler screening of HIE infants.

What are the limitations of CUS?

Evaluation of superficial structures just beneath the probe is often difficult, but can be obviated by using a high frequency probe or could be viewed by a different window. Visualization and precise delineation of posterior fossa structures is often not possible unless one gets perfection to use supplemental windows. Extracerebral hemorrhages are not well delineated (SAH, SDH, EDH). Damage to basal ganglia is not precisely detected and ischemia is difficult to detect compared to the hemorrhages.

What are the next best imaging techniques if CUS information is inadequate?

CUS, CT and MRI are complimentary neuro-imaging modalities in modern neonatology. The main drawback of CT and MRI is that these require the babies to be shifted to another place (therefore not POCT) , are significantly more expensive than CUS, CT carries the risk of radiation and monitoring of babies during MRI/CT is difficult. However, they have a role in some specific instances as mentioned below.

Evidence : Three studies compared results of cranial US and MRI performed during the newborn period for PT infants.[19-21] Maalouf et al.[19] performed paired MRI and US studies on the same day for 32 infants with GA of < 30 weeks. US accurately detected the presence of germinal matrix, IVH, and parenchymal hemorrhage confirmed by MRI (positive predictive values of 0.8, 0.85, and 0.96, respectively). However, in this study and others,[20,21] white matter injury detected by MRI was less well predicted by US (sensitivity of 0.56–0.89). Additional information provided by MRI included depiction of hemorrhagic lesions in 64% of infants and more numerous or extensive cysts in infants with PVL diagnosed by US.[21] To date, there has not been correlation with neurodevelopment follow-up. Compared with US performed on the same day, MRI of PT neonates detects more white matter abnormalities in the first week of life, more hemorrhagic lesions, and more numerous or extensive cysts. There are insufficient data from follow-up studies to indicate whether these additional findings provide more information about the neurodevelopmental prognosis.

CT brain

CT is extremely sensitive to detect all forms of intracranial hemorrhage including subdural and subarachnoid hemorrhages. It also detects cerebral calcifications and cystic malformations easily. CT can be performed rapidly and without sedation of the neonate. Some studies assessed the value of CT for encephalopathic term neonates. Two studies suggested that low attenuation in the basal ganglia and/or thalami indicates severe injury consistent with HIE. But CT exposes the baby to heavy radiation.

MRI brain

MRI brain is very sensitive in early detection of hypoxic ischemic injury. The diffuse and non-cystic lesions are better depicted. It precisely delineates cortical dysplasia[9]. However, MRI is time consuming and cannot be repeated frequently. A recent study did not support the routine use of MRI in very preterm babies[11].

Recommendations: Currently, data available from class II studies do not provide sufficient evidence that routine MRI should be performed on all very low birth weight (VLBW) infants for whom results of screening cranial US are abnormal.

Conclusions

Cranial ultrasonography is the best initial neuroimaging technique in newborns. The quality of CUS imaging and its diagnostic accuracy, as with any other imaging technique, depends on many factors. These include not only the suitability of the equipment for neonatal cranial work and the use of appropriate settings and probes, but also scanning at appropriate times depending on the pathology being sought, the use of different acoustic windows and not least the experience and expertise of the examiner. But unlike other modalities like CT or MRI which can be done by technicians, CUS has to be learnt by the physicians in a diligent manner in order to avoid subjective errors.Finally, individualized protocols need to be laid down in the NICU for CUS in neonatal units based on the neonatal work load and the available resources.

References

1. Bracci R, Perrone SN, Buonocore G. The Timing of Neonatal Brain Damage. Biol Neonate 2006;90:145–155.
2. BMUS. British Medical Ultrasound Society. October 2007. http://www.bmus.org/about-ultrasound/au-safetystatement.asp
3. Kost GJ. Goals, guidelines and principles for point-of-care testing. In:Principles and practice of point-of-care testing. Philadelphia: Lippincott Williams and Wilkins 2002 Chapter 1, pp3-12.
4. Van Wezel-Meijler G. Neonatal cranial ultrasonography: guidelines for the procedure and atlas of normal ultrasound anatomy. Berlin: Springer; 2007. Heidelberg.
5. Steggerda S, Leijser L, Walther FJ, Van Wezel-Meijler G. Neonatal cranial ultrasonography: How to optimize its performance. Early Human Development 85 (2009) 93–99.
6. Trounce JQ, Fagan D, Levene MI. Intraventricular haemorrhage and periventricular leukomalacia: ultrasound and autopsy correlation. Arch Dis Child 1986;61:1203–1207.
7. Behar R, Coen RW, Merrit TA, et al. Focal necrosis of the white matter (periventricular leukomalacia): sonographic, pathologic, and electroencephalographic features. AJNR Am J Neuroradiol 1986;7:1073–1080.
8. L. R. Ment, H. S. Bada, P. Barnes, P. E. Grant, D. Hirtz, L. A. Papile, J. Pinto–Martin, M. Rivkin and T. L. Slovis.Practice parameter: Neuroimaging of the neonate: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2002;58;1726-1738
9. Volpe JJ. Hypoxic-ishemic encephalopathy: clinical aspects. In. Neurology of the newborn. WB saunders, Philadelphia. 5th edition, 2008, pp 400-480.
10. Gray PH, Tudehope DI, Masel JP, et al. Perinatal hypoxic-ischemic brain injury: prediction of outcome. Dev Med Child Neurol 1993;35:965– 973.
11. Leijser LM, de Bruïne FT, Steggerda SJ, van der Grond J, Walther FJ, van Wezel-Meijler G.Brain imaging findings in very preterm infants throughout the neonatal period: Part I. Incidences and evolution of lesions, comparison between ultrasound and MRI. Early Human Development 85 (2009) 101–109.
12. Volpe JJ. Intraventricular hemorrhage in premature infants-current concepts II. Ann Neurol 1989, 25:109-116.
13. De Vries LS, Eken P, Dubowitz LM et al. The spectrum of Leukomalacia using cranial ultrasound. Behav Brain Res 1992, 49: 1-6.
14. Mack LA, Wright K, Hirsch JH, et al. Intracranial hemorrhage in premature infants: accuracy in sonographic evaluation. AJR Am J Roentgenol 1981;137:245–250.
15. Pape KE, Bennett-Britton S, Szymonowicz W, Martin DJ, Fitz CR, Becker LE. Diagnostic accuracy of neonatal brain imaging: a postmortem correlation of computed tomography and ultrasound scans. J Pediatr 1983;102:275–280.
16. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child 1981, 56: 900-904.
17. Virkola K. The lateral ventricle in early infancy. Thesis, Helsinki, 1988 (ISBN; 952-90012-9-0)
18. Stark JE, Seibert JJ. Cerebral artery Doppler ultrasonography for prediction of outcome after perinatal asphyxia. J Ultrasound Med 1994;13:595–600.

Annexure

Sections of normal brain anatomy and illustrated line diagrams with representative CUS images have been provided on the website www.nnfpublication.org

PVH-IVH grading[12]

Grade 1	GMH with no or minimal IVH (<10% of ventricular area on parasaggital view)
Grade 2	IVH (10-50% of ventricular area on parasaggital view)
Grade 3	IVH (>50% of ventricular area on parasaggital view)
IPE	Concomitant periventricular echodensity
PHVD	Mention separately if present

IPE-Intraparenchymal echodensity PHVD-Post Hemorrhagic Ventricular Dilatation

PVL Grading[13]

Grade 1	Transient echodensities persisting for> 7 days
Grade 2	The above evolving into small localized frontoparietal cyst
Grade 3	Extensive cystic lesions
Grade 4	Extending to deep white mater

Ventriculomegaly[14,15]

Mild	0.5-1.0 cm
Moderate	1.0-1.5 cm
Severe	>1.5 cm

Methods of measurement of lateral ventricles

It is important to measure the size of the lateral ventricles in a proper method to define enlargement of ventricles, to monitor the progression of ventriculomegaly, to minimize interobserver variations and for the purpose of proper documentation.

Levene's Index[16]

Mostly used in premature babies and is measured as a distance between falx to the lateral tip of lateral ventricle in the plane of third ventricle.

Ventricular Head Ratio (VHR)[17]

In full term babies the ventricular size is measured as a ratio between combined coronal ventricular width to combined hemispheric width.

Doppler Vascular Measurements[18]

The Doppler vascular measurement can be made on all cerebral vessels. The vessels that are the easiest to access are the anterior cerebral artery (ACA), best seen through the anterior fontanelle in the sagittal plane and the middle cerebral artery (MCA) best seen through the temporal window in the axial plane.

The Resistivity index (RI) can be calculated using the following equation:

$$\frac{PS - ED}{PS}$$

Where PS= peak systolic velocity and ED = end diastolic velocity. The normal range for the PI is about 0.65 - 0.90. Values below 0.5 or above 0.9 are abnormal.

Sample CUS Reporting Form (This and another sample form are available at www.nnfpublication.org)

Name of the baby ID Number Date
Date of birth Birth weight Gestational age...
Diagnosis and Indication of scanning (screening/follow-up/neurological problem) .....
Postnatal age..... Post conceptional age .....
Place of scan (nursery/radiology deptt).....Performed by …….
Machine:..... Transducer used.....
USG findings:

		1st Scan	Serial scans with dates		
		Postnatal/ Gest.age	***Postnatal/ Gest.age***	***Postnatal/ Gest.age***	***Postnatal/ Gest.age***
1)	Anatomical structures distinguishable? Normal?				
2)	Cortical folding (maturation of the brain) appropriate for gestational age?	Y/N			
4)	Cortical grey matter echogenicity (IPE)?	Y/N			
5)	Sub cortical white matter appears normal?	Y/N			
6)	Thalami and basal ganglia echogenicity normal?	Y/N			
7)	a. Ventricular system? a. Size (width) dilated /slit like(ventricular index) b. asymmetry c. lining d. Intraventricular haemorrhage (give grade and laterality) e. Mention if having PHVD	Y/N			
8)	PVL ; If yes, grade and laterality	Y/N			
9)	Evidence of calcifications? If yes, whether a)Periventricular or b) intracerebral	Y/N			
10)	Corpus callosum present?	Y/N			
11)	A midline shift present?	Y/N			
12)	Any suggestion of cortical atrophy?	Y/N			
13)	Do posterior fossa structures appear normal?	Y/N			
14)	Subarachnoid space normal or increased?	Y/N			
15)	Any extracerebral collection; If Y, area of collection.	Y/N			
16)	Any gross structural malformation.	Y/N			
17)	Any other finding.	Y/N			
	Date of Procedure				
	Signature & Name & Designation of Sonographer				
	Special Comments				

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Newborn Screening

Summary of Recommendations

- **Universal newborn screening should be introduced in phases in our country.**
- **Screening should be done after 2 days and before 7 days of age . Infants screened before 24 hours of life should be re-screened by 2 weeks of age to detect possible missed cases. Sick and premature babies should also have metabolic screening performed by 7 days of life.**
- **The disorders to be screened our country have been classified into three groups, depending on availability of resources.**
- **A positive screening test should always be followed with parental counseling, confirmatory test, genetic counseling and early dietary or other interventions.**
- **There is a need for comprehensive planning for NBS at state and national levels .**

Glossary

NBS- Newborn Screening ,IEM--Inborn Errors of Metabolism, PKU - Phenylketonuria, T4--- Thyroxine, CH - Congenital Hypothyroidism, TSH- Thyrotropin, CAH- Congenital Adrenal Hyperplasia, TMS- Tandem Mass Spectrometry, MS/MS- Mass spectrometry/Mass spectrometry, RNA—Ribonucleic acid, DNA--- Deoxy Ribonucleic acid, CDC- Centre for Disease Control, UNICEF- United Nation Children's Fund, IMR- Infant Mortality Rate,G6PD- Glucose -6 – Phosphate Dehydrogenase Deficiency, HCY - Homocystinuria, MSUD -Mayple syrup urine disease, ELISA- Enzyme Linked Immunosorbent Assay, KEM- King Edward Memorial Hospital, MELAS- Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke, GSD- Glycogen storage disorders, MMA - methylmalonic academia, UCD - urea cycle disorders, ICMR- Indian Council of Medical Research, IEF - Isoelectric Focusing, HPLC- High Performance Liquid Chromatography , HB- Hemoglobins, ACMG -American Centers for Medical Genetics, m/Z - mass-to-charge ratio, GC/MS- Gas chromatography/mass spectrometry,TPN- Total Parenteral Nutrition, SCAD- Short-chain acyl-coenzyme A (CoA) dehydrogenase deficiency, MSUD- Mayple Syrup Urine Disease, MCAD- Medium chain acyl CoA dehydrogenase deficiency, VLCAD- Very Long Chain acyl-CoA dehydrogenase, LCHAD- Long-chain acyl CoA dehydrogenase deficiency,CPT-II - Carnitine palmitoyltransferase deficiency type II TSH- Thyroid stimulating Hormone, NICCD- Neonatal Intrahepatic Cholestasis caused by Citrin Deficiency, IRT- Immunoreactive Trypsinogen,DELFIA- Dissociation-Enhanced Lanthanide Fluorescent Immunoassay, EIA- Enzyme Immunoassay, FIA- Flouroimmunoassay, AIIMS- All India Institute of Medical Sciences, GA- Gestational Age, GALT- Galactose-1-Phosphate Uridyltransferase, CF- Cystic Fibrosis, IUGR- Intrauterine Growth Retardation

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Introduction

Newborn Screening refers to the process where babies are subjected to simple blood test a few days after birth to see if they have a genetic or metabolic disorder. The conditions screened for in Newborn Screening (NBS) may be life threatening and/or cause intellectual disability or physical disability.[1] These conditions are often referred to as Inborn Errors of Metabolism (IEM). The aim of NBS is to detect the conditions before the onset of symptoms so treatment can be started early to reduce the effect of the condition.[1] This form of testing is known as screening because it involves testing a whole population - in this case, newborn babies. All babies are tested even if they do not have any obvious signs of a condition that affects their metabolism. The neonatal screening tests are not diagnostic. They separate a population of newborn infants into two groups: one made up of those who may have a given disease, the other by those who probably do not have it.[2]

This guideline reviews the scientific literature with respect to metabolic screening in newborns especially in the Indian context and tries to address the following issues:

Why is NBS needed?

As per recent data 140 million children are born every year around the world, out of which 4 million children are born with some congenital problem of which thousands die of definable and non-definable reasons , referred to as Sudden Infant Death Syndrome, out of which at least 25-30% babies are expected to have Inborn Error of Metabolism. Recent data suggest that the overall incidence of metabolic disorder around the world is a good,1:1350 [2] .Universal screening for metabolic disorders is mandatory in US, Europe and many other countries across the world. Though screening is a cost-intensive exercise, the benefits far exceed the costs as it helps in reducing the morbidity & morbidity of the disease.[3] Screening is a process of filtration. Today, neonatal screening is the best known and most widely used genetics-related preventative pediatric public health initiative in the world.[1]About 5 to 15 % of all sick neonates in NICU are expected to have some Inborn Error of Metabolism, which may be transient or permanent.

Should routine Newborn Screening be done mandatorily for all babies born in India?

Evidence: The success of the blood spot newborn screening in the USA led to early screening efforts in parts of the Asia Pacific Region from the mid-1960s onward. [7] Though the exact incidence and prevalence of most of the disorders is not known as we do not have large population based studies, some information is available to have an idea about the disease burden in India. A pilot newborn screening project was carried out on 1,25,000 newborns.[9] Homocysteneimia, hyperglycinemia, MSUD, PKU, hypothyroidism and G6PD deficiency were found to be the common errors. Another pilot expanded newborn screening was started in 2000 at Hyderabad to screen amino acid disorders, CH, congenital adrenal hyperplasia (CAH), G6PD deficiency, biotinidase deficiency, galactosemia and cystic fibrosis. Testing a total of eighteen thousand three hundred babies, the results revealed a high prevalence of CH (1 in 1700). The next common disorder was congenital adrenal hyperplasia followed by G6PD deficiency. Aminoacidopathies as a group constituted the next most common disorder. Interestingly, a very high prevalence of inborn errors of metabolism to the extent of 1 in every thousand newborn was observed. The authors stressed the importance of screening in India, necessitating nation-wide large-scale screening[11]. All this data suggest that collectively inborn errors of metabolism do have significant incidence in India which may lead to significant morbidity and mortality. All major Inborn Errors of Metabolism have been reported in the Indian literature[8, 9, 10]. Recent data from Kerala has suggested congenital hypothyroidism to be about 2.1 per 1000 live inborn babies[12]. The emergence of newer

technologies including Tandem Mass Spectrometer (TMS, MS/MS) in India in the recent few years has opened up the opportunities to further clearly assess the incidence of other IEM's more accurately . There are currently about 5 laboratories in India who are providing this technology. It is not surprising that in the newborn population in NICUs catering to the sick babies in India the incidence of IEM is as high as 74 per 1000 babies screened. Most of them seem to have Organic Acidemias or Aminoacidopathies. But the data on "Universal Newborn Screening" from the state of Goa suggests that the overall incidence of IEM is as high as 6 per 1000 live births!

Recommendations **:** Considering the available Indian data, there is a need for universal newborn screening for all newborns in India. We can start from states where the NMR & IMR due to other conditions is low, generate model programs and gradually implement all over the country. The financial implication and logistics however need to be worked out.

What is the ideal age for doing the NBS?

Evidence: Most data suggest that the samples be taken between 3 and 7 days of age.[26,30,45]. In general cord blood is not suitable for newborn screening because it is taken before the baby has taken breast milk and hence the toxic metabolites and byproducts in IEM's cannot be detected biochemically until at-least 12 hours after the baby has taken feeds. In the case of screening for CH the huge variations in the levels of TSH in the first 48 hrs after birth make it sensible to do a TSH screening only after 48 to 72 hrs of birth. Other variables such as prematurity, blood transfusion, parenteral nutrition also influence the timing of newborn screening.

Recommendations:

- Screening should be done after 2 days of age and before 7 days. This would enable screening results to be obtained at the earliest and by two weeks of age, the baby could be started on specific therapy or special elimination diets if positive.

- Infants screened before 24 hours of life should be re-screened by 2 weeks of age to detect possible missed cases.
- Postnatal age at which the newborn screening is done should be mentioned while sending the sample.

What should be the recommendation for NBS in Preterm/LBW babies?

Evidence: The summary of all the evidence suggests that for preterm/LBW, NBS considerations are not different from that of the term average weight newborn. But, it is important to mention the gestational age of the baby when sending the sample, as the cutoffs of some metabolites are different in preterm neonates (e.g. tyrosine levels, 17-OHP levels are higher in preterm & sick neonates).[5]

Recommendation:

- It is recommended that all sick babies and premature babies should have metabolic screening performed by 7 days of life.
- Gestational age and birth weight is to be documented while sending the samples.

Which disorders should be screened?

Evidence: worldwide the diseases most often screened include phenylketonuria, congenital hypothyroidism, sickle-cell anemia and other hemoglobinopathies, cystic fibrosis, galactosemia, biotinidase deficiency, G6PD deficiency, congenital adrenal hyperplasia, maple syrup urine disease, medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD) and tyrosinemia. Information on the panels of diseases tested for in many different parts of the world is available on the website of the International Society for Neonatal Screening (ISNS).[3] In general, state screening policies all over the world generally follow the recommendations of Wilson and Jungner concentrating on cost-beneficial outcomes resulting from treatable disorders of relatively high population prevalence. [5] The literature review suggests that there are about 27 million births India annually , of which 8 lakh are born with congenital malformation, 3.5 lakh with glucose 6 phosphate deficiency (G6PD), 25,000 with metabolic disorders, 20,000 with Down Syndrome, 15,000 with congenital hypothyroidism,14,000 with thalassemia and 5,000 with sickle cell anemia. Screening of cases of mental retardation revealed that 5.75% cases were due to various IEM. This makes the case for routine universal NBS in India. In the High risk categories such as critically ill neonates, those with positive previous family history, babies with mental retardation/ cerebral palsy / anamoly, in recurrent abortions, in situations of neonatal sibling deaths with undetermined cause or consanguinity, it becomes necessary to screen the baby for IEM.

Recommendation:

- **Group A (all newborns): Congenital hypothyroidism, Congenital Adrenal Hyperplasia, G 6 PD Deficiency disorder are** the disorders that can be strongly recommended in the **routine newborn** metabolic screening in our country due to following reasons (High incidence, easily missed at birth, definitive treatment available, definitive test available to diagnose the conditions, cost of diagnosis would be only around Rs.250 to 300, If missed early in the neonatal period , the child could end up having irreversible damage (CH, CAH), In case of G 6 PD deficiency the drugs provoking the hemolysis could be avoided, treatment of these disorders is affordable in most settings in the present scenario)

- **Group B (Screening In the High Risk Population):** The following disorders can be screened in the **high risk population (**Previous children with unexplained mental retardation, seizure disorder, previous unexplained sibling deaths with features suggestive of IEM, critically ill neonates, newborns/ children with symptoms/signs/ investigations suggestive of IEM and consanguinity)
    - Phenylketonuria
    - Homocystinuria
    - Alkaptonuria
    - Galactosemia
    - Sickle-cell anemia and other hemoglobinopathies,
    - Cystic fibrosis*
    - Biotinidase deficiency
    - Maple syrup urine disease
    - Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency (MCAD)
    - Tyrosinemia
    - Fatty Acid Oxidation Defects

*The screening for CF could be restricted to the high risk neonate with Meconium ileus in the neonatal period or previous sibling with cystic fibrosis.

There are many metabolic disorders that can be diagnosed in neonatal period, however currently the treatment options are not easily available in our country. Many of these disorders require special diet and long term monitoring for preventing complications. However the detection of these disorders early in life is useful in genetic counseling of the affected family, which in turn can help prevent the recurrence of similar births. Currently efforts are being made to modify Indian diet to treat the metabolic disorders; the results are still far from satisfactory. Screening all the newborns for the above disorders may not be cost effective.

- **Group C (Screening in Resource Rich Settings):** 'Expanded Newborn screening' for 30-40 inherited IEM's done by TMS can be offered to the 'well to do' especially in urban settings where facilities for sending samples to the TMS laboratory are available.

What is follow up action if a screening test is positive?

When results are positive, the time at which treatment is started is crucial to preventing morbidity, mortality and sequelae. Families must be informed of abnormal results as quickly as possible so that confirmatory diagnostic tests can be carried out, as outlined in the annexure specifically for each disorder. The family should be supported by a pediatrician who should explain the significance of positive screening results and the possibility of false positives and arrange referral for confirmatory testing. [1] Negative result must also be provided as quickly as possible. The policy that no news is good news must not be adopted.[1] Performing screening arouses expectations in families and they have the right to know the results as quickly as possible. Pediatricians will need to be guided by metabolic specialists and, very often will refer their patients for treatment over the long term. In a large proportion of these diseases multidisciplinary follow-up is needed in addition to regular care by the referring pediatrician, who has more opportunities for contact with the patient and their family. Therefore, the pediatrician will need to keep informed of pathophysiologic, clinical and psychosocial features of the disease.

Recommendations:

- On receiving abnormal screening results, the first action a pediatrician should take is to confirm whether the child is well and asymptomatic. Any child who is not well should be urgently assessed and may need to be admitted to hospital for support or specific treatment[46]
- Diagnostic test should follow the positive screening test
- Genetic counseling is also part of this stage, including the detection of other carriers in the family, the recurrence risk, and the possibilities for prenatal diagnosis in couple's future pregnancies
- For specific nutrition requirement and availability for a particular disorder one can review the website (http://www.icmrmetbionetindia.org/Nutritiousnews.aspx)

Is there a case for planning region specific screening depending on the incidence of the disorder?

Evidence: In view of ethnicity, race , percentage of consanguineous marriages certain disorders can be more prevalent in one part of the country than at other regions.G6PD Mediterranean is the most common deficient variant in the caste groups whereas, G6PD Orissa is more prevalent among the tribals of India. The third common variant seen in India is G6PD Kerala-Kalyan. The prevalence varies from zero to 27% in different caste, ethnic and linguistic groups. Also, G6PD deficiency is more common in the northern states and western part of India.[8,14,16,22.] Hemoglobin disorders are considered to be a serious health problem by WHO. In India, the carrier frequency of beta thalassemia varies from 1-17% (mean 3.3%). It is estimated that about 10,000 babies affected with beta thalassemia are born every year. Sickle cell disease is predominantly found in tribal communities in India, which constitutes about 8% of total population of India.[55] In a study by Balgir, *et al.*,[56] it was seen that the most common hemoglobin disorders observed of 1015 cases were: sickle cell trait (29.8%), sickle cell disease (7.5%), sickle cell-beta-thalassemia (1.7%), betathalassemia trait (18.2%), thalassemia major (5.3%), thalassemia intermedia (0.9%), Hb E trait (0.9%), Hb E disease (0.3%), E-beta-thalassemia (0.7%), Hb D trait (0.2%) and SD disease (0.2%). With the available Indian data, a sickle cell belt could be mapped out in the country. Studies on prenatal diagnosis are also very few.

Recommendations:

- It is recommended that routine NBS should definitely include screening for CH and G6PD in the northern states in the country. MSUD prevalence has been reported high in the north as well[14,15] and hence it is recommended that this disorder be definitely included for screening in the Group-B and Group-C screening categories in these states.
- Screening for sickle cell disease using HPLC of hemoglobin variants should be undertaken in pockets of high incidence.

What should be a comprehensive plan of NBS at state/national level to cover all delivered babies?

The planning for NBS at state / national level will be a difficult task in our country with only about 60% deliveries being in the institutions. There is a need to integrate the NBS program to the existing health infrastructure.

Recommendations

Hospital deliveries: It would be easy to plan for the NBS program at a hospital level. The lab could form a liaison with one of the nearest referral metabolic laboratory for NBS. One nursing staff / paramedic staff can be designated to collect the samples. The samples can be collected at around 3-4 days of life for all the newborn and samples could be pooled and sent on a particular day of the week to the lab by courier. The abnormal reports could be informed to the primary physician, who in turn could contact the parents and inform about the reports. With availability of the internet facility with most of the hospitals, reports could be emailed to the physician. The cost of the metabolic screening could be borne by the parents or insurance or the employing company as the case may be.

State level: It would be a herculean task for any state government to plan for a comprehensive universal newborn screening for all the newborns delivering in the state. It requires a lot of co-ordination between the hospital / government agency and the referral metabolic lab to achieve the universal NBS. Recently, the state of Goa was able to successfully complete one year of the universal metabolic screening for all the babies delivered in the state.[13]

All the major government hospitals, where majority of deliveries occur could be networked to collect the samples and send it to a common nodal center designated to collect the samples and then send it to the referral metabolic laboratory. The center could be responsible to collect and dispense the reports to the respective hospitals. The nodal center could be manned by paramedical staff. The nodal center could have personnel who could visit all the networked hospitals on a fixed day of a week to collect the samples and dispense the reports. At the community level, the trained Dai / anganwadi worker could be made responsible to collect the samples for the babies delivered at home and send the samples to the nodal center (Fig.1).

The cost of the metabolic screening and maintenance of the nodal center could be borne by the state government/NGO. Awareness needs to be created for NBS through the media / newspapers.

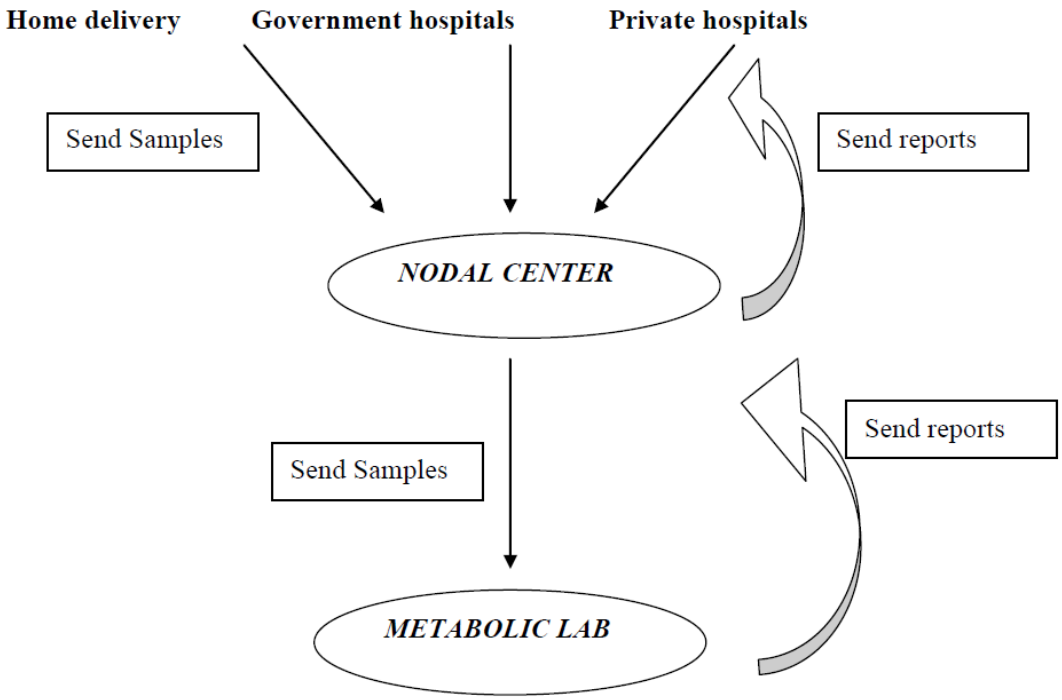

Fig.1;Diagrammatic representation of planning for NBS at the state level

Setting up an Advisory Committee for management of the IEM

Evidence: Recent developments in tandem mass spectrometry (MS/MS), which is now capable of multi-analyte analysis in a high throughput capacity, has enabled newborn screening to include many more disorders detectable from a newborn blood spot. Unlike measuring one analyte at a time, MS/MS allows measurement of >40 analytes, in a few minutes with the use of a single assay. Currently, MS/MS is being used for the identification of several amino acid, organic acid and fatty acid disorders [46,47]After the introduction of expanded screening by MS/MS in the United States, a great deal of follow-up was carried out on pediatricians and family doctors to evaluate their roles. These investigations found that, although these specialists demonstrated interest and many of them were actually involved in the expanded screening, their knowledge about the diseases involved was scant and they were not prepared for treatment and management of the children found to be screen positiveby screening.[1] The Newborn Screening Expert Group found a clear disparity between the information available and the information needed by the primary care physician (pediatricians and family doctors) to ensure an immediate response to positive screening tests and so recommended that professional training should be the responsibility of the screening system. They also developed a list of actions (ACT sheets) to be taken in the event of a positive diagnosis for each of the diseases proposed for testing.[1]

Recommendations:

- It is recommended that to facilitate early confirmatory diagnosis and therapy for the IEM,a 'Special Advisory Board' be constituted in each zone/state of the country to help the treating Pediatrician and the family in confirming the diagnosis and providing advice on therapy.The board can also keep a check on the quality and validity of the testing facility. The Advisory board should constitute Pediatric Metabolic Specialist,Endocrinologist, Intensivist,Biochemist, Geneticist and a Nutritionist. The team should be available for specialist advice at all times through phone or/and email. Just screening without treatment, counselling and effective follow up isn't right.

Is the NBS program cost- effective ?

Evidence: Cost effectiveness for newborn screening programme depends upon the health burden of a particular disease on the society in the form of morbidity, mortality, diagnostic procedures, and treatment modalities. It has been found that Universal Routine Newborn Screening is very cost effective if the diseases recommended for screening are found to be of high incidence and treatment modalities are available if diagnosed early. The screening tests for Group A are cheap and easily available all over India. Government could take a step for directing all labs including private labs to perform these tests (included in groupA) at a uniform and affordable cost. This would be helpful in building public private partnerships. TMS screening at present usually costs around Rs.3000-4000 depending upon the number of disorders to be screened. The cost can be further decreased if the custom's duty on the import of the Spectrometer (15% for Private labs.) can be decreased as well as duty on the filter papers (30%) can be decreased. At present, the TMS machine costs around Rs.1.5 crore and creating a full laboratory setup costs a capital investment of around Rs.4 crore to Rs.5 crore depending upon the area. If the number influx of samples can be increased to each laboratory to about, 1000/month, then the cost of TMS screening can be decreased to about Rs.1200 per test approximately in private laboratories[13, 22]. Also, the Government can finance part of cost as has been done in Goa.[13] Most of the responding Neonatologists in our questionnaire survey have suggested that the right price for the basic screen should be not more than Rs.500.

Recommendation: NBS is cost effective. The Government should help initiate more aggressive NBS through reducing custom's duty on equipment and consumables as also, by subsidizing the cost . Also, insurance companies can help by part funding the tests. Group A screening tests for CH,CAH and G6PD are very inexpensive and all efforts should be made by every Pediatrician to incorporate these screening tests in his package of care for the neonate under his treatment.

References

1. Letícia Lima Leão,Marcos José Burle de Aguiar. Newborn screening: what pediatricians should know. J Pediatr (Rio J). 2008;84(4 Suppl):S80-90:
2. Simone Albers, Harvey l. Levy; Newborn Screening, Avery's disease of Children, 8th edition, p 338-47.
3. Jailkhani R, Patil VS, laxman HB. Selective screening for inborn errors of metabolism in children: single center experience from Karnataka. Journal of Clinical and Diagnostic Research [serial online] 2008 Aug; (2): 952-958.
4. Anil B.J. Neonatal screening for IEM. Nirman (Document on internet). Available from http://jalananil.tripod.com/NIRMAN/id14.html, p. 104–115
5. Bridget Wilcken and Veronica Wiley. Newborn Screening. Pathology February; 2008 (2),Pp. 104–115
6. Bradford LT & John A.Newborn screening in North America J Inherit Metab Dis 2007; 30:447–465
7. Carmencita DP & Bradford L. Therrell.Newborn screening in the Asia Pacific region.J Inherit MetabDis 2007; 30:490–506.
8. Kumta.NB. Inborn error of metabolism-An Indian perspective. Indian J Pediatr 2005;72(4);325-332.
9. Devi AR, Rao NA, Bittles AH Newborn screening for aminoacidopathies in South India. In: Naruse H, Irie H, eds.Neonatal Screening. Amsterdam: Elsevier Science Publishers, 1983, 493–494
10. Rao NA, Devi AR, Savithri HS, Rao SV, BittlesAH.Neonatal screening for amino acidaemias in Karnataka, South India. ClinGenet 1988;34: 60–63.
11. Devi AR, NaushadSM. Newborn screening in India.Indian Journal of Pediatrics 2004; 71: 157–160.
12. Sanghvi U and Diwakar KK. Universal Newborn Screening for Congenital Hypothyroid. Indian Pediatrics , 2008;Volume 45__April 17.
13. Kariappa R. Incidence of IEM in samples screened by TMS (2007-2009, Neogen labs , Bangalore) Unpublished data , Personal communication (Reproduced with permission)
14. Kaur Manjeet, Ganesh Prasad Das, IshwarChanderVerma.Inborn Errors of Amino Acid Metabolism in North India.J. Inher. Metab. Dis. 17 (1994) 230-233.
15. ICMR Publication, 'Clinical Manual for Inborn errors of Metabolism', Editors ;Kalra.V.,Kabra.M.,Kapoor.S.,2008
16. Jain S, Kaur G, Chawla D, Jyoti, Rajeev, Chavan BS. 21 Months Experience of a Newly Set Neonatal Genetic Screening Program in a teaching hospital in India, Government Medical College and Hospital, Chandigarh ,May 2007 till January 2009.(unpublished data, personal communication)
17. Donald H. C, Theodore AK, Edwin W N. Use of Tandem Mass Spectrometry for Multianalyte Screening of Dried Blood Specimens from Newborns.Clinical Chemistry. 2003; 49:1797-1817
18. Donald HC. Tandem mass spectrometry and new born screening. Save Babies (document on internet). Available from http://www.pediatrixscreening.com/
19. Michael SW., Marie YM,, Michele AL. Newborn Screening Towards A Uniform Screening Panel And System(Executive Summary). Genet Med 2006:8(5, Supplement):1S–11S
20. Andreas S; Martin L; Dirk K et al.Expanded Newborn Screening for Inborn Errors of Metabolism by Electrospray Ionization-Tandem Mass Spectrometry: Results, Outcome, and Implications. Pediatrics2003; 111:1399 –1406;
21. Leong A .Is There a Need for Neonatal Screening ofGlucose-6-Phosphate Dehydrogenase Deficiency inCanada? MJM 2007 10(1):31-34.
22. Kaur M. Pitfalls and Errors in the interpretation of TMS in neonates.(unpublished data, Personal communication). HOD of Genetics department Dr.Lalpath Laboratory, New Delhi,2009, Sept.
23. Jain V, Agarwal R, Deorari AK, Paul VK. Congenital hypothyroidism; Indian J Pediatr. 2008 Apr; 75(4):363-7.
24. Büyükgebiz A. Newborn screening for congenital hypothyroidism. J Pediatr Endocrinol Metab. 19(11):1291-8.
25. Foley T, Kaplowitz PB, Kaye CI, Sundararajan S, VarmaSK ,American Academy of Pediatrics, Rose SR; Section

on Endocrinology and Committee on Genetics, American Thyroid Association, Brown RS; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society,. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics. 2006 Jun;117(6):2290-303.
26. Rockville, MD. Screening for Congenital Hypothyroidism; Topic Page. U.S. Preventive Services Task Force. March 2008. Agency for Healthcare Research and Quality, http://www.ahrq.gov/clinic
27. Perrin C. White .NatureReviews; Endocrinology September 2009;5, 490-498.
28. Frank JE. Martin Army Community Hospital, Fort Benning, Georgia. Diagnosis and Management of G6PD Deficiency; American Academy of Family Physicians. 72/ No.7 ,October 2005; 72:1277-82.
29. Mohanty D, Mukherjee MB, Colah RB. Glucose-6-phosphate dehydrogenase deficiency in India; Indian J Pediatr. 2004 Jun; 71 (6) : 525-9.
30. U.S. Preventive Services Task Force. Screening for Phenylketonuria (PKU): U.S. Preventive Services Task Force Reaffirmation Recommendation Statement. AHRQ Publication No. 08-05110-EF-2, March 2008. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/clinic/uspstf08/pku/pkurs.htm
31. Kishnani PS, Chen YT. Defects in galactose metabolism, Nelson's Textbook of Pediatrics, Ed; 18th.Ed.Kliegman,Behrman,Jenson and Stanton,2008.P609-610.
32. Schweitzer S; Newborn mass screening for galactosemia; European J Pediatrics;1995,154, (Suppl 2) ,S37-S39.
33. Ahuja A S, Kabra S.K. Cystic Fibrosis- Indian experience.Indian Pediatrics 2002; 39:813-81.
34. Kabra M, Kabra SK, Ghosh M, Khanna A, Arora S, Menon PS, *et al.* Is the spectrum of mutations in Indian patients with cystic fibrosis different? Am J Med Genet 2000; 93:161-163.
35. Kabra SK, Kabra M, Ghosh M, Verma IC. Cystic fibrosis-an Indian perspective on recent advances in diagnosis and management. Indian J Pediatr 1996; 63: 189-198.
36. Kabra SK, Madhulika, Connett GJ, Rolles CJ. Diagnosis of cystic fibrosis: Indian perspective. Indian J Pediatr 1999; 66: 923-928
37. Kabra SK, Kabra M, Ghosh M, Khanna A, Pandey RM. Cystic fibrosis in Indian children: clinical profile of 62 children. PediatrPulmonol 1999, 19 (supplement): 337 (Abstract)
38. Kevin W Southern, Marieke M. E. Mérelle, Jeannette E Dankert-Roelse, Ad Nagelkerke.Newborn screening for cystic fibrosis.Cochrane Database of Systematic Reviews, Issue 3, 2009.
39. Accurso FJ, Sontag MK, Wagener JS. Complications associated with symptomatic diagnosis in infants with cystic fibrosis. J Pediatr. 2005;147(3 suppl) :S37 –S41.
40. Wilcken B, Chalmers G. Reduced morbidity in patients with cystic fibrosis detected by neonatal screening. Lancet. 1985;2(8468) :1319 –1321.
41. Siret D, Bretaudeau G, Branger B, et al. Comparing the clinical evolution of cystic fibrosis screened neonatally to that of cystic fibrosis diagnosed through clinical symptoms: a 10-year retrospective study in a French region (Britanny). PediatrPulmonol. 2003;35 :342 –349.
42. Koscik RL, Lai HJ, Laxova A, et al. Preventing early, prolonged vitamin E deficiency: an opportunity for better cognitive outcomes via early diagnosis through neonatal screening. J Pediatr. 2005;147(3 suppl) :S51 –S56.
43. Lai HJ, Cheng Y, Cho H, Kosorok MR, Farrell PM. Association between initial disease presentation, lung disease outcomes, and survival in patients with cystic fibrosis. Am J Epidemiol. 2004;159 :537 –546.
44. Doull IJ, Ryley HC, Weller P, Goodchild MC. Cystic fibrosis-related deaths in infancy and the effect of newborn screening. PediatrPulmonol. 2001;31 :363 –366.
45. Peter A. Lane M.D.Director, Colorado Sickle Cell Treatment and Research Ctr.University of Colorado Health Sciences CtrJanuary 9, 2001 http://sickle.bwh.harvard.edu/screening.html
46. Celia I. Kaye, MD, PhD, and the Committee on Genetics Introduction to the Newborn Screening Fact Sheets ,Pediatrics, Volume 118, Number 3, September 2006.
47. MMWR Morb Mortal Wkly Rep. Centers for Disease Control and Prevention (CDC). Impact of expanded newborn screening--United States, 2006; 2008 Sep 19; 57(37):1012-5.
48. Garg U, Dasouki M. Expanded newborn screening of inherited metabolic disorders by tandem mass spectrometry: clinical and laboratory aspects;ClinBiochem. 2006 Apr; 39(4):315-32. Epub 2006 Mar 23.
49. Toublanc JE, Comparison of Epidemiological Data on Congenital Hypothyroidism in Europe with Those of Other Parts in the World Horm Res 1992;38:230-235 49.
50. Rosenthal M,Addison GM, Pric DA. Congenital hypothyroidism: increased incidence in Asian families.Archives of Disease in Childhood 1988;63:790-793.
51. Desai MP, . Colaco MP, Ajgaonkar AR, et al. Neonatal screening for congenital hypothyroidism in a developing country: problems and strategies. Indian Journal of Pediatrics.July 1987; Volume 54 Number 4.

52.Meena P. Desai. Disorders of thyroid gland in India. Indian Journal of Pediatrics.January 1997; Volume 64 Number 1.
53.Songya Pang MD[1], Michael A. Wallace PhD[1], Lindsay Hofman PhD. Worldwide Experience in Newborn Screening for Classical Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. Pediatrics June 1988; Vol. 81 No. 6, pp. 866-874.
54.Abhilasha, Shaila B. Incidence of Congenital Adrenal Hyperplasia in a Hospital in 500 Newborns. Unpublised data.Thesis submitted to Kathmandu university for award of MD Degree in Pediatrics,2008.
55.Seema Kapoor and Madhulika Kabra .Newborn Screening in India: Current Perspectives. Indian Pediatrics ,March 2010; Volume 47,pp.219-224
56.Balgir RS. Spectrum of hemoglobinopathies in the state of Orissa, India: a ten years cohort study. J Assoc Physicians India 2005; 53: 1021-1026

Annexure

A lot of information related to data on IEM from India, the technologies related to metabolic testing, techniques of sample collection and a list of laboratories offering these services in India is available on the website : www.nnfpublication.org

Sample Collection for TMS/ CH /CAH

1. Special filter papers are usually available with the referral metabolic lab to collect the sample for Biochemical assay or TMS. Labs can be contacted to procure the filter papers.
2. Ensure that the heel is warm. Warming the heel will enhance the blood flow.
3. Clean the site with alcohol and wipe it dry with sterile gauze
4. Puncture heel with a sterile lancet. Wipe away first blood drop with sterile gauze pad. Allow another large blood to form
5. Lightly touch filter paper to large blood drop. Allow blood to soak through and completely fill circle. Apply blood to one side of the filter paper only
6. Dry blood spots on a dry, clean, flat non absorbent surface for a minimum of four hours. When a wet sample is put inside paper envelop, paper fibers get attached to the blood sample. These fibers can clog tandem mass spectrometer.
7. Put the blood specimen card in a paper envelope. Put this again in a second paper envelope and the sample should be couriered to the referral metabolic lab.
8. Dried paper can be stored at ambient temperature (away from sunlight) or in the refrigerator for upto 10 days.

Transportation of dried blood spot specimens.

Dried blood spot specimens that have been packed as described above have to be transported through the mail / courier every day if possible or twice a week .If samples are not being transported the same day, the cards should be kept in the collection centers in refrigerators and protected from moisture.

Common Sample Collection Problems

Ensure good quality of samples. Poor quality sample will be labeled as invalid sample for testing and you will get request to send second sample. Poor quality samples cause unnecessary trauma to the newborn (and parents) and could potentially delay the detection and treatment of an affected infant.

1. Insufficient blood (not filling all circles); not enough sample to perform tests or repeat tests.
2. Milking or squeezing the puncture site can cause hemolysis and mixing of tissue fluids with blood.
3. Layering or applying successive drops of blood (double collection) in the same printed circle causes caking and /or non-uniform concentrations of blood.
4. If the blood flow diminishes, such that circles are not completely filled, then repeat the sampling technique in a new circle.
5. Do not put many blood spots in same printed circle.
6. Ensure that blood soaks through. Do not apply blood on both sides.

7. Contamination of sample during collection, drying, or mailing with urine samples will render the results unreliable. Such samples will be labeled invalid and will not be tested.
8. Inadequate or inappropriate drying.

- Humidity and moisture adversely affect the quality of sample and analyte recovery
- Excess heat or sunlight bakes the sample

Details of taking samples and how to send it with proper documentation can be found on the website, http://www.icmrmetbionetindia.org/protocols.aspx .

Pitfalls and Fallacies in the Interpretation of NewBorn Screening Results[22]

Neonates with positive screening require close clinical correlation (in case the baby has developed symptoms), with the medication the mother is taking, Prematurity status, feeding status (breastfeeds or TPN) to establish true positives and to exclude false positives. Depending upon whether the abnormal value obtained is just above the cutoff or is several folds higher than the cut off, the true positive result can be considered into three categories-1).low probability, 2).moderate probability, and 3).high probability. Babies landing into the high probability category should be immediately evaluated by a metabolic specialist.Recommendation for further repeat testing or confirmation by other test should be done only for those falling into low or moderate categories, although some intervention should be done in moderate probability cases (depending upon the anormal analyte detected) without waiting for the repeat filter paper test result. For instance immediate intervention and checking of serum ammonia is required for abnormal markers of urea cycle disorders before the deviation increases over time. Some markers, for instance, of glutaric acidemia type 1 and fatty acid oxidation disorders may decrease over time even in affected neonates. Multiple aminoacids elevation seen in hyperalimentation should be checked on repeat samples after discontinuation of the hyperalimentation. The world of newborn screening revolves around emotions. Misunderstanding of results can cause emotional disturbance in families and also wrong or delayed management. Results of each marker should be critically analysed in terms of the clinical picture and in combination with values of all markers. TSH can be seen elevated inspite of normal thyroid function if the sample is collected when the child is sick, or has symptoms of poor feeding or hypotonia. Elevated TSH can be due to congenital hypothyroidism as also, transient rise can occur due to illness, iodine excess or deficiency, maternal medications or maternal thyroid disease. What is termed “false positive newborn thyroid screen “may predict future subclinical hypothyroidism.G6PD value may be overestimated in the presence of active hemolysis. A false normal value can be obtained if the test is carried out on sample collected shortly after the hemolytic crisis. G6 PD value can be falsely deficient if the sample is collected from an anemic baby with red blood cells count lower than normal. As much as 55% of G6PD deficient newborns did not require phototherapy at all. This implies that without newborn screening to identify asymptomatic G6PD deficient enzyme, these infants run a risk of unexpected hemolytic anemia[21]. Accurate detection of all IEMs can be achieved only if the child is screened by an expanded newborn screening instead of doing only a smaller panel including TSH, G6PD, Galactosemia , 17OHP, IRT,and Biotinidase. Biotinidase deficiency is very common in India-both profound and partial deficiency,as per data on screening available with us. Neonate exposed to prolonged antibiotic therapy & anticonvulsant drugs can develop secondary biotinidase deficiency .This if not treated in time can hinder normal neurodevelopment.High IRT levels (the biomarker for cystic fibrosis) have been also associated with perinatal asphyxia & in sick infants. A thorough dietary history is essential to avoid subjecting patients to a fruitless search for nonexistent metabolic disorder. What the mother eats can reflect in the

breastfed newborn's screening result.Elevated citrulline levels in the neonate for example, can be related to heavy consumption by the lactating mother of watermelon, a fruit containing high free citrulline and arginine concentrations. Fatty acid oxidation disorders can be missed if the sample is collected after intravenous fluid hydration with dextrose Pivalocarnitine can give a false negative result for isovaleric academia in a newborn whose mother is on treatment with pivoxilsulbactum containing antibiotics . Results of test conducted on cord samples can be a mixture of false negative results. Most essential message to hence convey is to collect the right kind of sample at the right time. Some disorders may be mild or have a variant with likelihood of showing clinical manifestations only during later age. The availability of the Expanded Newborn Screening by Tandem Mass Spectrometry in India now,hence allows for the presymptomatic diagnosis of more than 30 disorders of inborn errors of metabolism. [22]

Transport of a Sick Neonate

Summary of Recommendations

- **The development of efficient transport systems is crucial to the implementation of regionalization of perinatal care.**
- **Transportation of the sick or preterm babies to a centre with expertise and facilities for the provision of multi-organ intensive care improve outcomes.**
- **Neonates needing special or intensive care should preferably be transported by a skilled transport team through an organized teamwork.**
- **Appropriate equipments and vehicle customized for neonates should be available for safe transport.**
- **Pre-transport stabilization is the most vital step in the whole process of transport.**
- **Adequate and timely communication with the family, referring hospital and the support group is essential.**

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Introduction

Treatment of the sick neonate in specialized neonatal intensive care units (NICU) has been associated with decrease in mortality and morbidity. In the early 1960s, neonatal transport was first used to make intensive care accessible to those neonates who needed it.[1] Subsequently, organized emergency neonatal transport systems developed and became an important component in the regionalization of perinatal care.[2-5] In utero transfer is the safest transfer but unfortunately, preterm delivery, perinatal illness and congenital malformations cannot always be anticipated, resulting in a continued need for transfer of babies after delivery.[6] These babies are often critically ill, and the outcome is partly dependent on the effectiveness of the transport system.[7] Facilities for neonatal transport in India are dismal. Most neonates are transported without any pre-transport stabilization or care during transport. Any available vehicle is used, which often takes long hours and place where to take the baby is also not well recognized. There is an acute shortage of neonatal beds and majority of the sick neonate in need of urgent admission are dumped in pediatric wards with inadequate infrastructure. Often, these neonates are shunted from one health facility to another.[8]

With less experienced staff, the risk of adverse events on such transports can be greater than with well equipped and trained staff.[9-11] Many of the babies thus transported are cold, blue and hypoglycemic and 75% of the babies transferred this way have serious clinical implications.[12-14] Mathur et al in a study to evaluate WHO classification of hypothermia observed that in sick extramural neonates, the presence of weight less than 2000 g, associated illness (birth asphyxia, neonatal sepsis and respiratory distress) and physiological derangements (hypoxia, hypoperfusion and hypoglycemia) were associated with higher mortality and suggested that these factors should be considered adverse factors in hypothermic neonates. Their presence should classify hypothermia in the next higher category of severity in WHO classification.[15]

In this guideline, an attempt has been made to address the following questions regarding neonatal transport:

- Why transport of sick neonates is necessary?
- What is the difference between self transport and organized transport?
- Which babies need transport?
- What are different types of transports?
- How to organize a Neonatal Transport System?
- What special care needs to be given for a sick neonate requiring transport?
- What are the different modes of transport?
- What are the situations which need special precautions during transport?
- How should one communicate for neonatal transport?
- What are the medico-legal issues related to neonatal transports?
- How the family should be supported while transport?
- What are the alternative transport modalities?

Why is transport of sick patients necessary?

In India, majority of the deliveries still occur at home (approximately 60% in rural areas as per NFHS 3). Although hospital based deliveries need to be promoted, delivery of sick neonates needing special care will still take place at places with extremely limited resources, necessitating need for transport. Transportation of the sick or preterm babies to a centre with expertise and facilities for the provision of multi-organ intensive care has been shown to improve outcomes.[16] Prematurity, asphyxia and sepsis are the most common cause of neonatal mortality in our setting.[17] many of these are easy to correct and a significant decrease in neonatal mortality can occur if specialized care can be made available to these neonates. With the initiative of state governments in developing Special Care Newborn Units (SCNU) at District Hospitals, many of the sick neonates can be provided better newborn care if they are timely transported in a stable condition. Also transport from these SCNU to higher center should be made possible when necessary.

What is the difference between self transport and organized transport?

Organized transport service provides almost the same level of monitoring and the quality of care during the transport that is available in the advanced care facility. Ideally it should have the ability to provide mechanical ventilation, multiple fluid infusion therapy and cardio-respiratory monitoring. In India, most sick neonates are transferred by their parents or paramedical personnel either in private vehicles or poorly equipped ambulance. There is currently no dedicated neonatal transport service provided by the states in India.

Evidence: There is enough data to suggest that the transport by a skilled organized team reduces neonatal mortality and morbidity.[18-19] Some innovative models for transport are being tried in few states like Tamil Nadu, Kerala, Andhra Pradesh and Madhya Pradesh. In a retrospective analysis done over a period of 33 months from an experience on a regionalized transport network in and around 250 kms of Hyderabad, biochemical and temperature disturbances were more common in babies transported on their own as compared to specialized neonatal transport service. Neonates transported by the hospital team had significantly higher survival as compared to those who came on their own.[20] Some of the private hospitals in the country offer neonatal transport services; however, it is quite expensive.

Recommendation: Neonates needing special or intensive care should preferably be transported by a skilled transport team through an organized effort

Which babies need transport?

Infants requiring advance medical and/or nursing care exceeding what is available in their current settings will need transfer to a higher health facility. Example is a preterm neonate with respiratory distress (severe retractions and grunt) but facilities for respiratory support (CPAP, mechanical ventilation) are not available. The broad indications for which neonatal transport should be considered are given in table 1[21]:

What are different types of transports?

The need for transport could be from home to a health facility or from a lower health facility to a higher health facility or a referral center.

Neonatal transfers can be categorized as follows:

1. From Home to Hospital
2. Intra-hospital transport (including delivery rooms, operation theatres, neuroimaging and special procedures)
3. To facilitate specialist management of the neonate (movement to a regional center for cardiac, neurological, renal or surgical opinion)
4. Retrieval from a peripheral hospital for ongoing intensive care (when mothers deliver prematurely without warning)
5. Returning infants to local neonatal units following care elsewhere (either locally or long distance) – *Reverse Transport.*[22]

How to develop a neonatal transport system?

The Committee on Perinatal Health proposed a system for regionalized perinatal care and defined three levels of hospital care, which served throughout the 1970s and 1980s as a national model for the rapid development of neonatal referral centers.[23] This model required the development of a neonatal transport system, which was associated with a significant reduction in the US neonatal mortality rate. The American Academy of Pediatrics (AAP) formed a Task Force on Inter-hospital Transport and developed guidelines.[24]

Evidence: In India, neonatal health care delivery is unregulated, patchy and not standardized.[25] Many smaller centers attempts to provide Level II or III with inadequate staffing and equipments resulting in deficiencies in the quality or constancy of care. The existing evidence from the developed countries indicates that better regionalization of neonatal care is associated with better outcomes.[26-28]

Recommendation*:* There is need to develop perinatal regionalization with special care newborn units at district level and referral centers at state level. To make this operational we need to create a neonatal transport system.

The key components of a Neonatal Transport System are:

- Human Resource
- Vehicles and equipments
- Communication and Family Support
- Documentation and consent form
- Feed back to Referring unit

Human Resource: The doctor or nurse in organized neonatal transport service or accompanying person in case of community transport which could be ASHA worker, ANM a paramedic trained / untrained or a family member should be trained in essential newborn care during transport, identification of danger signs and their immediate remedy.

A. Leadership:

1. Medical director: A physician with specialty training in neonatology or equivalent expertise.
2. Manager: Works closely with the medical director and controls day to day management, budget and maintenance of equipment. The manager may be a nurse or paramedic personnel.

B. Team members:

Most transport teams in western countries have a neonatal-trained nurse. Other programs use anesthetists, respiratory therapists, paramedics or a combination of these three disciplines.[29] Physicians are frequently added to the basic team depending on the needs of the patient and the competency of team members.

Evidence: No difference in outcomes has been observed when neonates are transported by trained paramedics / RN or physicians.[30, 31] In a recent study a Physician-Nurse and Nurse-Nurse teams for neonatal transport were compared to study mortality, transport-related morbidity, overall transport times and outcome of procedures performed by transport nurses. Outcomes for the 2 types of teams were equivalent. Non-physician teams responded more quickly and spent less time at the referring facility.[32]

Recommendation*:* Trained nurses or paramedics for transport services are not available in India. Most units involved in organized neonatal transport utilize the services of residents and fellows working in neonatology for this purpose. However, we need to develop a cadre of nurses and paramedic personnel for more effective neonatal transport.

C. Vehicle and Equipments:

An ideal design of the vehicle and equipments for transport should have consideration of weight, fixation, power and gas requirements.

Transport vehicle:

The ambulance used for neonatal transport should, at a minimum, meet the requirements for a basic life support ambulance.[33] In order to accommodate neonates the ambulance must provide:

1. Secure fixation of the transport incubator to the cot rails.
2. Secure fastening of other equipment (e.g. Oxygen and air tanks, monitoring equipment)
3. Independent power source to supplement equipment batteries to guarantee uninterrupted operation of the incubator and other monitoring and supportive equipment.
4. Necessary adapters to access the ambulance power source should be readily available.
5. Environmental conditions that reduce the risk of temperature instability, excessive noise and vibration, infection.
6. Rapid and safe transport without compromising safety.

Design of Ambulance: Unlike adult ambulances there are no specific guidelines available for the design of neonatal ambulances. An ideal ambulance would be clinically efficient and would provide safety for the patient and the transport staff. Ambulance design should be based on ergonomics principle of clinical activities inside the ambulance and local road and weather conditions. It should provide adequate width

and height to accommodate Neonatal System (built in unit that has stretcher with incubator/ ventilator, monitoring devices, oxygen cylinders), suction apparatus and minimum two seats for transport staff. Following are the general principles/ recommendations, based on experience and not on scientific evidence, should be consider in ambulance designing.

Types of Vehicle: Most ambulances in India are the makeshift of commercial vehicles like van, SUV or mini truck, modified to the designed and specification of the purchaser.

Van or Mini-truck:

- Distance: up to 300 km (6-10 hours)
- Advantage:
    a. Adequate room (height and width) for Neonatal System (transport incubator) and transport staff for seating and monitoring.
    b. Neonatal system can be customize to the need of the purchaser
    c. In emergency, enough room to perform procedure like endotracheal intubation.
    d. Family member can accompany with transport team and patient
- Disadvantage: High Cost

Long SUV or Minivan:

- Distance: up to 100-150 km
- Advantage: Easily available, cost effective
- Disadvantage: require removal of back seat, front seat can be turn backward and can be utilized next to Neonatal System for staff for monitoring. Not enough space to perform any emergency procedure. Family member cannot accompany the patient

For ongoing treatment and care during journey a relatively larger vehicle is preferable, for full access to the neonate especially in an incubator. Speed and stability (lateral roll and front–back impact on braking) of the vehicle is very important. The quality of the new generation of chassis cabs has improved performance in terms of acceleration, cruising speed, braking. However, most of the commonly used vehicles for transport in India are highly inadequate for smooth travel.

Trolley / Incubator position: Offside mounting of incubator as compared to transverse mounting is quick and easy to load and enables more staff to be seated by the side with clear vision of the baby. Offside mounting is better fixed to the ambulance and provides more straightforward access for re-intubation if needed.

Fixation of equipment: In the event of a collision, as a result of severe deceleration forces, unsecured items or people in the rear of the ambulance may suffer severe collision, resulting in severe injury. Unsecured items of equipment may become projectile and also cause severe injury or death. To overcome this, various fixation devices have been developed. European Committee for Standardization has produced standards for the securing of all persons, items and transport incubators in ambulances.[34, 35] The entire system should be able to withstand a 10 G force in 5 directions (forward, rearward, left, right and vertical). This 10 G represents the forces encountered when a vehicle travelling at moderate speed is

involved in a collision resulting in rapid deceleration (e.g. a vehicle travelling at 50 kmph coming to a complete halt in 1 m, or a vehicle travelling at 30 mph coming to a complete halt in 3 ft).

Speed of Vehicle: The speed limit guidelines for the ambulances are variable and depend on the traffic and road conditions. The National Health Service (NHS) permits a higher speed for medical ambulances, approximately 10 – 20 mph above the permissible speed limits on various motorways. However, considering the road and traffic conditions in our country, it may be advisable to keep strictly to permissible speed limits and may be lower, especially where the traffic congestion is too high and road conditions are poor and bumpy. Over speeding in our conditions may be associated with higher risk of accidents and destabilization of patient. Adequate stabilization and preparation for anticipated complications (eg chest tube drainage for pneumothroax and adequate sedation for the baby with PPHN) before transport will avoid temptation for over-speeding.

Recommendation: Speed of the ambulance should not be more than 15-20 km/hr over the posted speed limit.

Equipment

The transportation of neonates requires several equipments (table 2):

Power backup: All the equipment in use should have a battery back and should be kept fully charged in anticipation of transport request. An alternating current 240 V power source can be provided in the ambulance by two methods, a dedicated generator or an inverter. Sufficient adaptors should be available to make quick changeover to available mode of power supply.

Gas supplies: Make sure the cylinders are filled prior to onset of journey and will last the duration of transport. In case of long journeys, keep spare cylinders and equipment to change the cylinders. Most of the cylinders with the transport incubator last for not more than 2 hours. The ambulance should have large oxygen and air cylinders which can last for the duration of transport. Adaptors to fit these both type of cylinders should be available and the personnel accompanying the transport should be well versed with technique of changing the cylinders.

Specific equipment items

Ventilators: Ventilators or T-piece device or self / flow inflating resuscitation device is an essential equipment as most babies are referred for respiratory support. Some of the commercially available transport systems have ventilators that are integral to the incubator system (Air-Shields Globetrotter TI500, Draeger Medical) or standalone systems (Pneupac® babyPAC™, Smiths Medical). These systems are now capable of functioning well at the full range of rates and inspiratory times required for neonatal practice

Transport Incubators: Some of the available transport incubator systems which provide adequate temperature control even in extreme conditions are (Airborne 750i, GE Healthcare; Air Shields Globetrotter TI 500, Draeger Medical). Active warming consumes considerable amounts of power. Make sure the incubator has its own battery and also works well on available external power sources. A new solution to assist warming during transport is the use of phase-change gel mattresses which very effectively warm infants through release of latent heat of crystallisation. With correct temperature activation, these devices can be an alternative method to warm a cold infant during transfer.[36]

It is important to secure the neonate inside the incubator. A rearward facing seat with a 5-point body harness has been used in adults which is inappropriate for a premature neonate with respiratory failure. Placing a belt over the top of a neonatal patient will provide some protection if the ambulance drops vertically, but provides virtually no protection to a supine or prone patient in the event of a head-on collision. Neonatal harnesses are now commercially available (Neo-restraint, Paraid Medical) which consists of a series of foam wedges and straps, than can be adjusted to the position and size of the infant within the transport incubator

Syringe Infusion Pumps: For neonatal transport, syringe infusion pumps are probably the best suited to deliver both maintenance fluids and drug infusions. Most pumps work on 240 V power source and many work with an internal rechargeable battery that last for 4 hours, but the batteries may be unreliable. Only few function from an external 12 V DC power source. However, there is risk of extravasation, unless the device has variable pressure alarms which are specific for neonatal use.

Monitors: A multi-parameter monitor is preferable. However, a lightweight portable pulse-oximeter is a good alternative. Most of the conventional probes are very sensitive to motion and give fallacious readings. Pulse oximeters and monitors which use Massimo technology would minimize or eliminate such artifacts. Although end-tidal CO2 (ETCO2) monitoring yields consistent quantitative errors in neonates, trend information may be helpful. ETCO2 monitor can be very useful in determining the placement and patency of an endotracheal tube.

How to organize a neonatal transport system?

The preparation would depend whether the transport is from Home to Health facility or Pick from a Health Facility by an organized transport team.

Once a decision for transport is taken the principles of neonatal transport are

- Assessment
- Stabilization before transport
- Care during transport

Principals of transport remain same for any type of transport.[43]

*Pre-transport stabilization***:** Available models for pre-transport stabilization and care during transport are:

- STABLE: **S**ugar, **T**emperature, **A**rtificial breathing, **B**lood pressure, **L**aboratory work, **E**motional support.[37]
- SAFER: **S**ugar, **A**rterial circulatory support, **F**amily support, **E**nvironment, **R**espiratory support.[38]
- TOPS: **T**emperature, **O**xygenation (Airway & Breathing), **P**erfusion, **S**ugar[39]

Evidence: Hypoglycemia, hypothermia, poor perfusion and oxygenation have been shown to be associated with high mortality in transported neonates.[40] TOPS, a simplified assessment of neonatal acute physiology gives a good prediction of mortality in these neonates.[39] Prior stabilization and adequate care during transport results in decreased of hypoglycemia, acidosis and mortality.[19] Innovative techniques like thermocol boxes have been shown to be low cost and effective method for neonatal transport.[41] Plastic

wraps or bags, skin-to-skin care and transwarmer mattresses all keep infants warmer, leading to higher temperatures on admission to neonatal units and less hypothermia.[42]

***Recommendations**:* Stabilization of sick neonates before and care during transport to maintain euglycemia, normothermia, adequate oxygenation and perfusion should be the utmost priority.

Step 1: Assess the baby and depending on facilities available check for Temperature, airway, breathing, circulation and sugar

Step 2: Temperature: Correct hypothermia if present before transport – KMC, provide warm clothing or under radiant warmer at stabilization unit or referring centre, as most transport incubators are not able to actively warm the hypothermic baby

Step 3: Airway: Assess airway for presence of any secretions (suction if present) and position of neck (place shoulder roll)

Step 4: Breathing: Assess for respiratory distress; assess whether baby requires ventilation (PPV device such as self inflating bag)

Step 5: Circulation: Check Heart rate, CRT, Urine output, Blood pressure (if feasible); Assess the need of fluid bolus; Check what fluids baby is getting and whether baby is on inotropes; Adjust infusion of inotropes as per need

Step 6: Sugar: Check sugar with glucometer; If Blood glucose < 40 mg/dl, give 2 ml/kg of 10% Dextrose through intravenous line; Check the patency of iv cannula and start IV fluids; Laboratory workup: Check all investigations of baby; Check all the medications received.

Step 7: Transport personnel: Mother/ Attendant/ ASHA from community or basic health facility. Trained nurse, paramedic or physician at the referring hospital

Step 8: Equipment: Ambulance if available or any other vehicle preferably drought free

What care should be given during transport?

Temperature maintenance: Use a transport incubator if available. Kangaroo mother care (KMC) by mother or attendant is a useful way to maintain temperature. Kangaroo mother care is a good method of temperature maintenance during transport especially in resource limited conditions when transport incubators are not available [44]. Other methods like adequately covering the baby, and using improvised containers (thermocol box, basket, polythene covering) may help in maintaining temperature

Airway and breathing: Keep neck of the baby in slight extension position; if airway is unstable, it is better to intubate and transport; if intubation is not considered necessary / possible, short PPV or CPAP can be provided using a T-piece resuscitator.

Circulation: Assess perfusion for warm peripheries, capillary refill time of ≤3 seconds, tone and activity, and blood pressure. Stabilize perfusion before moving the baby to the ambulance. Syringe pumps are required to use inotropes with accuracy.

Check oxygenation: Continuous Pulse oximeter monitoring is preferable; observe for central cyanosis; if possible perform blood gas analysis before and during transfer

Communication: Inform SCNU / NICU to arrange and organize baby cot and keep the over head radiant warmer on.

Feeds: It is best to not attempt feeding sick babies with abnormal sensorium or severe respiratory distress before or during transfer. A well baby at risk of hypoglycemia may be fed in addition to IVF; if baby can accept provide breast feeds; if not give expressed breast milk (EBM) with spoon or paladai; if EBM not available give any available milk continue IV fluids if the baby is sick.

What are the different modes of transport?

The choice of vehicle will depend upon clinical urgency, traveling distance, weather conditions and its availability. Published data comparing the efficacy and safety of road vs. air transport are scanty.

Road Ambulance*:*

Indications: For distance from 10- 200 kms
Advantages:

- Relatively easily available, lower costs, least influenced by weather
- More space, better patient access
- Can be stopped or diverted to the nearest hospital if necessary for any emergency interventions

Disadvantages:

- Retrieval time is influenced by speed limitations, traffic delays and road conditions

Rotary Wing (helicopter):

Indication: For distance from 50- 300 kms

Advantage:

- Speedy retrieval, better utilizations of medical staffs (less travel time and out of hospital)

Disadvantages:

- High costs, limited space, may be influenced by weather conditions, require a landing site close to the hospital, limited patients access, high noise and vibration levels
- Not pressurized: altitude generally 2000-3000 feet (not less than 500)

Fixed Wing Aircraft:

Indication: For distance from greater than 200 km

Advantage:

- Good for long distance retrievals, reasonable space and access to patient, family can travel with their baby

Disadvantages:

- Require near by airport, immigration clearance, longer retrieval time and assistance with road transport

Problems with Air Transport: There are certain issues related to air transport, which need to be taken into account.

High altitude: The barometric pressure in a standard airline carrier is 565 mm Hg as compared to 760 mmHg at sea level resulting in reduction of partial pressure of oxygen. Every effort therefore must be made to maximize oxygen delivery in hypoxic infants by other means before an air transfer by maintaining an adequate systemic blood pressure and hemoglobin concentration.[45] Air expands at high altitude and innocuous air leaks at sea level are likely to become significant. Even trivial air leaks should be drained before embarking on air transport. Infants at risk of air leaks, like meconium aspiration syndrome, should be transported with cabin altitude set at sea level.

Take off and landing: Rapid acceleration during take off, with the infant secured head forward, theoretically results in reduced cerebral perfusion. Conversely, on landing, rapid deceleration may cause a sudden rise in venous cerebral perfusion. There is provisional evidence that premature infants undergoing transfer may have a higher incidence of intraventricular bleeding.[46, 47] However, the clinical effect of these controllable events requires clarification.

Thermal issues: There is a temperature drop of 2°C for every 300 m of altitude, and in unheated military helicopters this may put high demands on the transport incubator system (TIS). A reliable method of measuring infant temperature during transport must be used. Reducing heat loss and conservation of battery power on the TIS include use of Isocovers, Transwarmer mattresses, bubble wrap, and hats. The incubator used for air transport must always have fully charged batteries at the beginning of a transfer. DC power cables suitable for both the aircraft and the ambulance should be taken.

Noise and vibration: Vibration is not usually detrimental to the infant, but can dislodge lines and tubes and adversely effect monitoring equipment.[48] Consideration should be given to equipment specifically designed to minimise the effect of movement artifact such as pulse oximetry using Masimo or Oxismart technology. During transport all lines should be secure and visible, particularly arterial lines, to allow observation without the need to open the incubator. Visual rather than audio alarms should be used where possible. The long term effects of exposure of the newborn infant to excessive sound remain unclear.[49, 50]

Transport in specific conditions

Respiratory distress syndrome: Transport issues in babies with RDS (HMD, MAS, Congenital diaphragmatic hernia or others) depend on management of primary condition. If baby requires ventilation depending on clinical judgment he/she should be ventilated. Oxygenation, perfusion should be maintained throughout the transport. Ventilation should also be well supported during transport in babies with apneas,

birth asphyxia. Primary aim should be to maintain adequate oxygenation and prevent hypoxemia. If there are minimal oxygen needs, oxygen may be supplemented with nasal catheters with a flow rate of less than 2l/min. However, in cases of moderate to severe respiratory distress or high oxygen needs, CPAP may be considered.

Air leak syndromes: Even mild pneumothoraces may worsen during transport due to vibrations and bumps of the ride, resulting in erratic ventilatory pressures. Hence, it is advisable to drain the pneumothorax adequately and preferably keep a chest tube in place before departure. During transport, underwater seal systems are bulky and difficult to manage in ambulance. The pleural drainage may depend on a continuous suction being applied to the system. Moreover, the chest tube and its connections may move and get dislodged with the movement or vibrations of the ambulance. Management of pulmonary interstitial emphysema should include using minimal ventilatory pressures to maintain sufficient oxygenation.

Esophageal atresia: A continuous suction with the help of two catheters (one attached to suction and the other left open to air) should be done during transport in babies with esophageal atresia to prevent pulmonary aspiration.

Meningomyelocele: The exposed swelling on the back should be covered with guaze piece soaked in normal saline and baby should lie on the side and not back during transport.

What is the role of CPAP during transport?

Evidence: Although CPAP therapy is now widely accepted therapy for acute respiratory failure within NICU setting, limited evidence is available for its safety and efficacy during transport. Bomont and Cheema.[51] in a retrospective study showed that Nasal CPAP appears to be a safe method of respiratory support for a carefully selected group of infants during land based ambulance transfers. Out of 100 patients (84 patients by doctor led and 16 patients by nurse led team) 5 patients (2=intubation and 3=stimulation and reposition of prongs) required intervention during transport. The integral Babylog 2000 ventilator was used to generate CPAP during transport. Authors in this study emphasized that experience with nasal CPAP and familiarity with equipment is essential for transport team before it is used on transport. One of the author of this guideline had used Bubble CPAP safely in selected patients (RD with FiO2 less than 40%,) during both air and land transport in Australia. There are no reports of safety and efficacy of CPAP during transport in Indian context.

Recommendation*:* CPAP therapy during transport is recommended when the transport team has sufficient clinical experience to CPAP therapy and familiarity with CPAP equipment in NICU setting, the team is led by pediatrician and / or registrar trained in ET intubation and resuscitation and the ambulance is fully equipped with adequate space to perform necessary procedures. Nasal CPAP cannula commonly used may be unstable during transport and frequent dislodgement is common. Nasopharyngeal CPAP may be an effective alternative with properly inserted endotracheal tube through the nostril into the posterior pharynx. This technique may be more easily fixed and effective during transport. However, if the neonate is unstable on CPAP, intubation may be necessary to provide mechanical ventilation / PPV.

What is the role of intubation before transport?

Decision to intubate before transport is determined by underlying pathophysiology, potential for deterioration and travel distance. For example a patient with severe meconium aspiration syndrome with

respiratory distress and high oxygen requirement should be intubated for potential of developing PPHN and pneumothoraces. Following are general indications where ET intubation is preferable before transport:

- Respiratory distress worsening with increasing oxygen requirement (FiO2 of more than 70%)
- Recurrent apnea
- Recurrent seizures
- Congenital heart disease on prostaglandin E1 infusion of more than 0.05 microgram /kg/min (risk of apnea)
- Congenital diaphragmatic hernia
- Limited space and skills to perform any resuscitation

Elective intubation of babies with significant distress is favored by most; however there is no data to support that elective intubation is needed in all infants with respiratory distress. If neonatal transport ventilator is not available, T piece resuscitator or Neopuff can be considered which in addition to PPV breaths will also deliver PEEP. However, if T-piece resuscitator is not available, bag and tube ventilation may be provided. Positive pressure ventilation can be accomplished by hand-bag ventilation for transports of short duration. Studies in adult patients have revealed that bag-valve ventilation was as effective as with transport ventilation; however there is no similar data in neonates.[52]

What is the role of administering surfactant before transport?

Evidence: Surfactant therapy is one of the seminal discoveries in neonatology which has been shown to decreased mortality and morbidities in preterm infant with hyaline membrane disease (HMD). Many aspects (rescue vs. preventive, synthetic vs natural, single or multiple doses) of its use have been extensively studied in NICU context, but limited data are available for its use before or during transport. Two retrospective studies found surfactant therapy before transport to be safe with no different in mortality and one study found lower oxygen requirement and fewer mechanical ventilations days compare to control group.[53,54] (Level 3b) Unnecessary delay of surfactant therapy may worsen the outcomes. The OSIRIS study[55] found that even short delay (mean age of 3 hours instead of 2 hours) in surfactant treatment increases risk for death or BPD by 11%. The studies of early surfactant therapy (prophylactic or few hours) showed that it reduces incidence of pneumothrorax. This potential benefit has more relevance for transporting a patient with HMD as given the difficulty in management of pneumothoraces during transport.

The factors which will determine surfactant therapy includes severity of the underlying disease, distance from receiving hospital, competence of transport team and cost. Traditionally in western model of full stabilization before transport, surfactant therapy is recommended if there is radiological evidence of hyaline membrane disease with oxygen requirement of more than 40% at the referring hospital

Following are some of the important points one should consider before use of surfactant therapy by transport team

1. Competence of transport team staff in intubation
2. Efficiency in management of immediate complication of surfactant therapy (desaturation, pulmonary hemorrhage, tube block)

3. Understand the changes in lung physiology (compliance) and ventilator management following surfactant therapy
4. Availability of x ray and blood gas (optional) at referring hospital. The hospital where x-ray and blood gas facilities are limited and the travel distance is short, surfactant therapy is best delayed.

Recommendation*:* Intubated infants with severe RDS should receive exogenous surfactant therapy before transport if transport team is led by pediatrician efficient and experienced in surfactant therapy.

What should be done in case the neonate deteriorates during transport?

Evidence: Evidence regarding the most appropriate action for the patient who deteriorates during transport is scanty. The most appropriate action depends on the level of skills of transport team in resuscitation, space and equipments available in the ambulance, and the distance from the receiving hospital.

Recommendation*:* The two major strategies can be used in case of acute deterioration are:

- Stop the vehicle and resuscitate: If skills and space is available stop the vehicle and resuscitate (ET intubation or chest tube insertion for pneumothorax).
- Don't perform procedure in a moving vehicle; get to the nearest hospital, stabilize, before proceeding.

How should one communicate during transport?

Success of transport process depends on the effective communication between the referral (sending) and receiving institute. A dedicated communication centre or telephone line at the receiving institute to contact the transport team or neonatologist will enhance transport process. Ideally, a dedicated communications centre with mobile help lines operating 24 hours a day, 7 days a week should be developed to allow for constant communication during the triage process and transport. An alternative method of initial contact is for the referring physicians to call the NICU directly and have the unit personnel place them in contact with the appropriate transport team, which could be from the referral hospital or a dedicated transport team.

Communication for neonatal transport before, during and after reaching referral centre:

Subsequent to decision for transport – communication with parents and family:

a. Nature and severity of illness and the need for transport
b. Facilities available at Referral hospital including infrastructure, details of key personnel. Give examples of previous successful transfers and outcomes
c. Type and mode of transport and time needed to reach the referral hospital
d. Names and contact numbers of key personnel at Referral hospital
e. Possible need for emergency procedures during transport
f. The availability of bed should be asked before starting transport and referred hospital should be informed in advance.

g. If referred hospital refuses to accept patient due to some reasons, bed facility should be asked in other health care facilities and baby should be transported by same team to the place where bed should be available.
h. Till the time of admission of baby to referred health care facility, the transportation team should not leave that health care facility.
i. Responsibilities of Referring Institute:

- Patient demographic details (name, age, sex, gestational age and weight, place and name of referring hospital)
- Reason for transfer
- Detail perinatal history, labor and delivery, neonatal resuscitation
- Current patient status, therapy and laboratory data (eg CBC, blood sugar)
- Potential for deterioration and need for advance therapy like mechanical ventilation and exchange transfusion or diagnostic evaluation
- Referral note with Provisional diagnosis and treatment given so far
- Consent form from parents

Communication during transport: Mobile telephones should be made available to contact referring or referral hospital in case of any emergency or breakdown. It also helps to inform approximate time the transport team is likely to reach the referral hospital. This helps especially when the NICU is away from the emergency services where the transport vehicle is likely to reach. To avoid destabilization, the team from the referral centre should preferably receive the neonate at entry to the hospital.

Communication between the treating team at the referral centre and the transporting team: Information regarding condition of the neonate and treatment details before and during transport should be documented and handed to treating team. After initial stabilization at the NICU, the treating team should communicate with the family and attending personnel, explain about condition of the baby, likely diagnosis, prognosis, duration of stay and approximate finances involved. Family attendants should also be helped with place to stay, closer to the hospital. If the mother has accompanied the baby, it helps to admit her in the maternity wards.

Feed back communication with Referring centre: Team at Referral centre shall call or send a written communication to the members of referring regarding the condition of the baby with details of medical illness, likely diagnosis, prognosis and likely duration of stay. Once improved and stable, the infant may be transported back (reverse transport) for ongoing care with written details of treatment details and its duration.

What are the medico-legal issues associated with transport? [57]

Most medico-legal problems are a result of poor communication and provision of inadequate information. The condition of baby, risks involved during transport and financial implications of transport and treatment at the referral centre should be discussed with family and documented and the case record. If baby dies during transport:

- The ambulance should be stopped and CPR should be performed as per NRP guidelines

- If baby dies on the way, he/she should be first taken to the higher health facility
- Casualty admission should be done. Parents should be explained and death certificate made by the medical personnel of higher health care facility
- It's the responsibility of transporting team to make death certificate of baby

How should the family be supported during transport process?

Families of the sick newborn are under considerable stress, and the transport team can provide sensitive support. Parents need accurate information about the newborn's clinical condition and prognosis, and an opportunity to ask and have questions answered by the team. They need information about the anticipated time frame of the transport and about the receiving hospital (location, contact telephone numbers, personnel). Information can be shared about anticipated procedures, operations or clinical studies. Parents should see and have an opportunity to touch their baby prior to the transport. Parents should preferably accompany the baby during transport. If the mother is accompanying the baby, then her medical needs during transfer and after reaching referral hospital must be addressed.

What are the indigenous ways to transport a sick neonate in the absence of ambulances and transport equipment?

In absence of availability of proper ambulance and equipment for the transfer of a sick neonate, some innovative methods used in the past can be used. Thermocol boxes have been used to maintain neonate's body temperature.[41] However, it needs to be of appropriate size to accommodate the infant and have enough ports to maintain air circulation and observe the baby. Even though this low cost intervention was found to be effective, one needs to be careful as the sick may neonate may suddenly deteriorate. The accompanying care provider should be familiar with the danger signs and immediate actions to be taken, if neonate deteriorates. In today's era of air-conditioned cars and taxis, ambient temperatures inside the vehicle can be maintained between 26 – 28^{o}C. The accompanying person could provide kangaroo mother care during transport, to maintain euthermia.[44] The infant should be given direct breast feeding or supplemental feeds with spoon or paladai during transport so as to prevent hypothermia. The vehicle should be halted during feeding.

Table 1: Indications for transport

- Very Low birth weight Infants especially below 1250 g
- Prematurity: Gestational age $\leq$ 32 wks
- Respiratory distress or apnea
    - Requires supplemental O_2
    - Apnea requiring bag and mask ventilation
- Cyanosis persisting despite oxygen therapy
- Hypoxic ischemic encephalopathy
    - Requires intubation and assisted ventilation
    - Develops seizures activity
    - Multi-organ involvement
- Sepsis with signs of systemic infection
- Jaundice with potential for exchange transfusion
- Active bleeding from any site
- Infant of diabetic mother or Hypoglycemia unresponsive to recommended treatment
- Surgical conditions
- Congenital heart disease (antenatal diagnosis or suspected)
- Heart failure or arrhythmia
- Suspected metabolic disorder
- Severe electrolytes abnormalities
- Infants requiring special diagnostic and/or therapeutic service

Table 2: Equipments required for neonatal transport

Thermal support equipment and supplies:

- Transport incubator
- Thermometer and/ or temperature monitor and probes
- Plastic wrap, Insulating blankets, Heat shield

Respiratory support equipment:

- Oxygen and air cylinders with appropriate indicators of in – line pressure and gas content
- Flow meters, Oxygen tubing and adapters
- Oxygen hood, neonatal size masks and cannula
- Oxygen analyzer, Pulse oximeter
- Neonatal positive pressure bags
- Continuous positive airway apparatus: nasal prongs, endotracheal tube
- Mechanical ventilator with back up circuit
- Endotracheal tubes: 2.5, 3.0, 3.5, 4.0 mm
- Laryngoscope with size 00, 0 and 1 blades
- Laryngoscope batteries and extra lamps
- Endotracheal tube holders and tape to secure ET tube

Suction equipment:

- Mucus suction trap, Suction catheters (5, 6, 8, 10, 12 F)
- Regulated suction with gauge limiting < 100 mm Hg
- Feeding tube (8 Fr) and 20 ml syringe for oro-gastric decompression
- Sterile gloves, Sterile water for irrigation

Monitoring equipment

- Stethoscope, cardiac monitor, pulse oximeter
- Glucometer for blood sugar evaluation

Parenteral infusion equipment

- Intravenous catheters (24, 26 guaze)
- Syringes (2, 5, 10, 20, 50 ml)
- Splint, Transparent dressings or micropore
- Three way stopcocks, IV chamber sets / Micro drip sets
- Intravenous administration tubing compatible with infusion pump

Medications

- Calcium gluconate 10%
- Epinephrine (1:10000) prefilled syringes, Sodium bicarbonate
- Dopamine, dobutamine, Morphine, Midazolam
- Normal saline, Phenobarbitone, Surfactant

References

1. Segal S. Transfer of a premature or other high-risk newborn infant to a referral hospital. Pediatr Clin N Am 1966;13:1195.
2. Segal S, editor. Manual for the transport of high risk newborn infants. Canadian Pediatric Society, 1972.
3. Recommended standards for maternity and newborn care.Health and Welfare Canada.
4. Family centred maternity and newborn care. National Guidelines. Health and Welfare Canada, 1988
5. Guidelines for perinatal care. 5th ed. American Academy of Pediatrics/American College of Obstetricians and Gynecologists, 2002.
6. Kempley ST, Sinha AK. Census of neonatal transfers in London and the South East of England. Arch Dis Child Fetal Neonatal Ed 2004; 89: F521-F526.
7. Rashid A, Bhuta T, Berry A. A regionalized transport service, the way ahead? Arch Dis Child 1999; 80:488-492.
8. Mathur NB. Comprehensive neonatal care in India: Experiences in planning and implementation. Journal of Neonatology, 2006; 20: 204–205.
9. Cornette L. Contemporary neonatal transport: problems and solutions Arch Dis Child Fetal Neonatal Ed 2004; 89: F212.
10. Cornette L. Transporting the sick neonate. Current Pediatr 2004; 14: 20-25.
11. Parmanum J, Field D, Rennie J, Steer P. National census of availability of neonatal intensive care. BMJ 2000; 321: 727-729.
12. Britto J, Nadel S, Maconochie I, Levin M. Morbidity and severity of illness during interhospital transfer: impact of a specialized pediatric retrieval team. BMJ 1995;311:836-839.
13. Agostino R, Fenton AC, Kollée LAA. Organization of neonatal transport in Europe. Prenat Neonatal Med 1999;4:20-34.
14. Leslie AJ, Stephenson TJ. Audit of neonatal intensive care transport: closing the loop. Acta Pediatr 1997; 86: 1253-1256.
15. Mathur NB, Krishnamurthy S, Mishra TK. Evaluation of WHO classification of hypothermia in sick extramural neonates as predictor of fatality. J Trop Pediatr. 2005 Dec; 51(6):341-345.
16. Orr RA, Felmet KA, Han Y, McCloskey KA, Dragotta MA, Bills DM, et al. Pediatric specialized transport teams are associated with improved outcomes. Pediatrics 2009 Jul;124(1):381-383.
17. Bang AT, Bang RA, Baitule SB, Reddy MH, Deshmukh MD. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. Lancet 1999; 354:1955–61.
18. Chance G, Matthew J, Gash J, Williams G, Cunningham K, Neonatal transport: A controlled study of skilled assistance. J Pediatr 1978;93(4):662-66
19. Hood J, Cross A, Hulka B, Lawson E. Effectiveness of the neonatal trasnport team. Crit Care Med 1983;11(6):419-23.
20. Kumar P, Kumar C, Venkatlakshmi A. Long distance neoantal transport - the need of hour. Indian Pediatr 2008;45:920-922.
21. Newborn Emergency Transport Service: Indications for neonatal transfer. Available from http://www.rch.org.au/nets/transport/emergency_services/index.cfm?doc_id=1447
22. Boxwell G (Ed) (2000) Neonatal intensive care nursing. Routledge, London.
23. March of Dimes Birth Defect Foundation. Toward Improving the Outcome of Pregnancy: The 90's and Beyond. 1993.
24. AAP Committee on Fetus and Newborn & ACOG Committee on Obstetric Practice. Interhospital Care of the Perinatal Patient. In: CJ Lockwood, JA Lemons. Guidelines for Perinatal Care. 5th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2002:57-71.
25. Agrawal S, Banot A, Sangar K. Neonatal care and Transport Among the Urban Poor: Challenges and Options. J of Neonatology 2005;19(4):347-352.
26. Johansson S, Montgomery SM, Ekbom A, Olausson PO, Granath F, Norman M, et al. Preterm delivery, level of care, and infant death in Sweden: a population-based study. Pediatrics 2004;113(5) 1230-1235.
27. Paneth N, Kiely JL, Wallenstein S, Marcus M, Pakter J, Susser M et al. Newborn intensive care and neonatal mortality in low-birth-weight infants: a population study. N Engl J Med 1982;307(3):149–155.
28. Yeast J, Poskin M, Stockbauer J, Saffer S. Changing patterns in regionalization of perinatal care and the impact on neonatal mortality. Am J Obstet Gynecol 1998;178:131–135.

29. Day S, McCloskey K, Orr R et al. Pediatric interhospital critical care transport: consensus of a national leadership conference. Pediatrics 1991;4:696–704.
30. Lee SK, Zupancic JAF, Sale J et al. Cost-effectiveness and choice of infant transport systems. Med Care 2002; 40:705–716.
31. Lee SK, Zupancic JAF, Pendray MR et al. Transport risk index of physiologic stability: a practical system for assessing infant transport care. J Pediatr 2001;139:220–226.
32. King BR, King TM, Foster RL, McCans KM. Pediatric and neonatal transport teams with and without a physician: a comparison of outcomes and interventions. Pediatr Emerg Care. 2007 Feb;23(2):77-82.
33. Shenai JP, Johnson GE, Varney RV. Mechanical vibration in neonatal transport. Pediatrics 1981;68:55
34. BS EN 1789:2007. Medical vehicles and their equipment. Road ambulances. British Standards Institute London: 2007.
35. BS EN 13976-1:2003. Rescue systems. Transportation of incubators. Interface conditions. British Standards Institute London:2004.
36. Carmichael A, McCullough S, Kempley ST. Critical dependence of acetate thermal mattress on gel activation temperature. Arch Dis Child 2007;92:F44–F55.
37. Karlsen K. The STABLE Program. STABLE Program, Utah. 2001.
38. Transporting newborns the SAFER way. National Neonatology Forum of India, PENN India Health Group, University of Pennsylvania, WHO Perinatal Collaborating Center, Illinois, 1999.
39. Mathur NB, Arora D. Role of TOPS (a simplified assessment of neonatal acute physiology) in predicting mortality in transported neonates. Acta Pædiatrica 2007:96;172–175.
40. Sehgal A, Roy MS, Dubey NK, Jyothi MC. Factors contributing to outcome in newborn delivered out of hospital and referred to a teaching institution. Indian Pediatr 2001; 38:1289–1294.
41. Daga SR, Daga AS, Dighole RV, Patil RP, Dhinde HL. Rural neonatal care: Dahanu experience. Indian Pediatrics 1992;29(2):189-194.
42. McCall EM, Alderdice F, Halliday HL, Jenkins JG, Vohra S. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD004210. DOI: 10.1002/14651858.CD004210.pub3.
43. Neonatal transferal and transportation: NNF Training module. Eds. Saluja S, Mathur NB .National Neonatology Forum, New Delhi2005.
44. Conde-Agudelo A, Diaz Rossello JL, Belizan JM. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev 2003:CD002771.
45. Teitel D, Rudolph AM. Perinatal oxygen delivery and cardiac function. Adv Pediatr 1985;32:321–347.
46. Fenton AC, Leslie A, Skeoch CH. Optimising neonatal transfer. Arch Dis Child Fetal Neonatal Ed 2004;89:F215–219.
47. Bowman E, Doyle LW, Murton LJ, et al. Increased mortality of preterm infants transferred between tertiary perinatal centres. BMJ 1988;297:1098–1100.
48. Gajendragadkar G, Boyd JA, Potter DW, et al. Mechanical vibration in neonatal transport: a randomized study of different mattresses. J Perinatol 2000;20:307–310.
49. Buckland L, Austin N, Jackson A, et al. Excessive exposure of sick neonates to sound during transport. Arch Dis Child Fetal Neonatal Ed 2003;88:F513–16.
50. Campbell AN, Lightstone AD, Smith JM, et al. Mechanical vibration and sound levels experienced in neonatal transport. Am J Dis Child 1984;138:967–970.
51. Bomont RK, Cheema IU. Use of nasal continuous positive airway pressure during neonatal transfers. Arch Dis Child Fetal Neonatal Ed 2006;91:F85–F89. doi: 10.1136/adc.2005.078022
52. Johannigman JA, Branson RD, Johnson DJ, Davis K Jr, Hurst JM. Out-of-hospital Ventilation: Bag-Valve Device vs Transport Ventilator. Acad Emerg Med. 1995 Aug;2(8):719-724.
53. Costakos D, Allen D, Krauss A, et al. Surfactant therapy prior to interhospital transport of preterm infants. Am J Perinatol.1996;13:309-16.
54. Mildenhall LF, Pavuluri NN, Bowman ED. Safety of synthetic surfactant use before preterm newborn transport. J Paediatr Child Health 1999;35:530-535.
55. The OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant – the judgment of OSIRIS.Lancet 1992;340:1363-9.

56. Mori R, Fujimura M, Shiraishi J, Evans B, Corkett M, Negishi H And Doyle P. Duration of inter-facility neonatal transport and neonatal mortality:Systematic review and cohort study. Pediatr Int 2007;49(4):452–458.
57. Brimball DC. Medical legal issues of patient air transport; current concepts in transport. University of Utah Medical Center, AirMed Transport System, 1982.

Annexure

1. **Sample Referral Note and Documentation Sheet-I (Another version of Referral form is available at the website www.nnfpublication.org)**

Date _____ Time _____

Address _____

_____

Name _____ Mother's Name_____ Father's Name _____

DOB _____ TOB _____ Sex __

Duration of Pregnancy _____ LMP _____ EDD _____

Birth Details

Mode of Delivery _____ Attended by _____

Place of Delivery _____

Time of 1st Cry _____ Apgar 1 min ___ 5 min ___ 10 min ___

Resuscitation details: Tactile stimulation / Free flow oxygen /
Bag & Mask Ventilation / Chest compressions

Duration of: O_2 _____, Bag & Mask Vent. _____, Chest compression _____

Birth weight _____ grams

Clinical course

Feeding well Yes / No, Breast feeds Yes / No, Spoon Feeds Yes / No

Type of feeds EBM / Formula / Any other milk Diluted milk Yes / No

Passage of Urine Yes / No Stool Yes / No

Reason for transfer: LBW / Respiratory distress/ Not feeding well/ Convulsions/ Jaundice/ Malformation/ Any other

Examination Findings

Jaundice Yes / No Any congenital malformations _____

Soles Warm/Cold, Trunk Warm/Cold Temperature _____ ^{o}C

Heart Rate ____ / min Resp Rate ____ / min Chest Retractions Yes / No

Central Cyanosis Yes / No CFT < 3 sec / > 3 sec

Receiving oxygen Yes / No With Nasal canula / Face mask / Oxyhood FiO_2 ___%

SaO_2 ____% Dxtx _____ mg%

Time of Last Feed

Investigations with date

_____

_____

_____

Treatment Given

_____

_____

_____

Place to which being referred _____

Mode of transport _____ Accompanying person _____

Name and Phone number of person at Referral Hospital _____

_____

Signatures, Name, Date and Time

2. **Sample Consent form**

I, Mr./Ms. _____ _____ (relation) of B/O_____ hereby give consent to transport my baby to neonatal unit of _____ Hospital, _____. I have been fully explained by Dr. _____ about my baby's condition. I fully understand the nature of illness of my child and have been informed about risk and untoward incidents which may occur during transport. The likely course of illness, treatment and duration of stay at the referral hospital has been explained to me.

I have been explained about the referral hospital which has facilities to treat my child's illness. I also understand the financial implication of the transport and treatment at the referral hospital.

I also give my consent for any emergency procedures which may be needed during transport. In case baby deteriorates during hospital, the baby will be taken to the nearest available health facility.

Signature	Signature of Doctor
Name	Name
Relation	
Date	Date
Time	Time

Name and Signature of Witness

Information about various currently working emergency transport services models in India is available at www.nnfpublication.org

Feedback and Correspondence

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