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Theme : "Neonatal Infection- what next"

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IX National Conference of IAP Neonatology Chapter

IAP NEOCON 2016

Ranchi, Jharkhand

FIRST ANNOUNCEMENT

Dates : 20, 21, 22 & 23 October, 2016

Venue: Indian Institute of Coal Management (IICM), Ranchi

Hosts: IAP Neonatology Chapter,
Indian Academy of Pediatrics Ranchi, Central Coalfields Limited Ranchi

Central Coalfields Limited
A Miniratna Company

IAP Ranchi Branch

Scientific Highlights

Main attractions:

- Dr B B Jha Oration
- Guest Lectures
- Plenary Sessions and Symposia
- Presentation of Gold Medal and Award Papers
- Poster Presentations and Free Papers

Pre-conference workshops:

Invasive Ventilation: 2 days (20th and 21st oct) Ventilation – Basics and settings Surfactant therapy Pulmonary Graphics Patient Triggered Ventilation High Frequency Ventilation Nitric Oxide Therapy Workstations & Hands-on	**Non-invasive ventilation: 1 day (21st oct)** Physiological Basis, Art and Science of Non-Invasive Ventilation Nasal IMV CPAP HHHFNC Case Scenarios Workstations & Hands-on
Point of care USG and functional Echocardiography: 1 day (21st oct) ECHO –PDA, PPHN, Structure Brain USG – Intracerebral Bleeding & RI Chest USG – Pneumothorax, Pleural Effusion Abdominal USG – Ascities, Portal Vein Gas, NEC, Hydronephrosis, Bladder Assessment , Workstations & Hands-on	**Procedures in Neonatology: 1 day (21st oct)** Vascular Access-I –PICC, Managing Difficult Access, Use of Infrared Vein Viewer, Vascular Access-II – UVC, UAC, Central lines Therapeutic Hypothermia – Total Body Cooling (Tecotherm) and Mira Cradle Renal Replacement Therapy with emphasis on Peritoneal Dialysis

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EDITORIAL

I would like to thank the IAP NeoChap for inviting me as Guest editor for this bulletin on

Neonatal infection: What next?

Neonatal infections continue to cause morbidity and mortality in infants. Suspected sepsis, presumed infection, and ruling out sepsis remain the most common diagnoses in the nursery intensive care unit (NICU). Newborn infants are at increased risk for infections because they have relative immunodeficiency. This may be due to decreased passage of maternal antibodies in preterm infants and to immaturity of the immune system in general.

Dr Amit and Piyush have very nicely discussed the epidemiology of neonatal sepsis, in which they have highlighted the microbiological and epidemiological aspects in neonatal infections. They have discussed the differences in sepsis between early and late onset presentation. In Developing countries we have predominantly gram negative infection, which are multi-drug resistant and are associated with very high mortality.

Dr Aparna has highlighted the issues pertaining to intrauterine infections in mother and its impact on the fetus and neonate. Perinatal infections pose a clinical challenge to the Obstetrician as well as Pediatrician and in this article we learn the algorithm on the management of neonate born to mothers with TORCH infections.

Dr Sonali and Sanjay have emphasized the most important concept that Prevention is better than cure. They have highlighted various aspects of infection control in the NICU. House keeping, bundled approach, equipment cleaning, Hand hygiene, skin care, cord care and nutrition are some of the principles which are very important in preventing infections. Surveillance of infections is very important and Audit keeping would help everyone in order to initiate quality improvement initiatives in the NICU.

Antimicrobial stewardship is very important aspect of newborn care. We are all aware of the antibiotic menace and the fact that multi-drug resistance is a major killer. Dr Hemasree and Srinivas have discussed the important aspects of Antibiotic stewardship, which include preventing infections, preventing spread, tracking resistance patterns, improving use of antibiotics and developing new antibiotics and diagnostic tests. It is important to develop a culture of sending blood culture in babies with suspected infections and have a written policy for anti-microbials. Also one needs to have a policy regarding stopping of antibiotics and discussing with the microbiologist.

Developmental outcomes of babies treated with neonatal infections are extremely important as we aim in having intact survival and not mere survival. Sepsis in neonates is associated with adverse neurodevelopmental outcomes and cerebral palsy. Dr Archana has discussed various developmental issues associated with neonatal infections. She has emphasized the need for follow-up and early intervention in babies who are treated with sepsis, meningitis and this would go a long way forward in achieving normal neurological outcomes in these fragile babies treated for infections.

I am sure all these aspects related to neonatal sepsis would enable us to care our small preterm neonates who are vulnerable for infections in a better manner and optimize care so as to prevent infections rather than treat them!!

I hope you all would enjoy reading this bulletin on **"Neonatal Infection- what next".**

Best Wishes.

Guest Editor
Sandeep Kadam

Neonatal Sepsis- Basics

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Introduction:

Neonatal Sepsis (NS) is a global problem with significant mortality & morbidity. It is responsible for total 1.6 million neonatal deaths annually with nearly 40% from developing countries. As per NNPD data (2002-3), the incidence of neonatal sepsis is 30:1000 live births; with nearly 40 % of outborn admissions and responsible for 38 % (amongst outborn) and 19 % (amongst inborn) neonatal deaths. Gram negative infection with increasing menace of antibiotic resistance is culminating as new challenge in the managing newborn sepsis.

Definitions:
NS is a systemic infection occurring in newborn at ⩽ 28 days of life. It is caused predominantly by bacteria, but virus & fungus are also responsible. Based on the age of onset infection, NS is further classified as Early-onset neonatal sepsis (EOS) and Late- onset neonatal sepsis (LOS).

EOS has been variably defined as bacteraemia occurring at ⩽ 72 hours in infants hospitalized in the neonatal intensive care unit (NICU), versus <7 days in term infants. In preterm [PT, gestation age (GA) ⩽ 37 weeks at birth] infants, EOS is most consistently defined as occurring in the first 3 days of life. EOS is caused as vertical transmission of organism from mother to newborn in intrauterine life or at time of birth.

LOS is sepsis occurring after 72 hours in NICU infants and after 7 days of life in term infants. It has been variably defined as occurring up to the age of 28 to <90 or 120 days. With extreme preterm (EP, GA ⩽ 28 weeks) and very preterm (VP,GA ⩽ 32 weeks), Late LOS is increasingly used as a synonym for LOS beyond 28 days up to corrected GA 40 weeks. LOS is usually caused by horizontal transmission of pathogens from environment (nosocomial or community).

Isolation of the organism on culture media is the gold standard evidence for Sepsis. Blood is the most common body fluid used for sepsis work up in NS. Depending on the isolation of the organism, NS is classified as Proven (culture positive) or Suspected (culture negative) sepsis. Suspected sepsis is when there are biochemical markers, but no microbial evidence for sepsis. Proven sepsis with antimicrobial sensitivity guides on the use of antibiotics.

Epidemiology & Pathogenesis:
As per National Neonatal & Perinatal Data (NNPD, India, 2002-3), the incidence of neonatal sepsis in India is 30:1000 live births. Though, the incidence of systemic infection amongst intramural births was only 3% that amongst extramural births was alarmingly high standing as 39.7%. Neonatal Deaths secondary to systemic infection was responsible for nearly 38% amongst extramural births, and 18.6 % amongst intramural births. The common organism responsible is Klebsiella pneumoniae and Staphylococcus aureus, with increasing menace of antibiotic resistant gram negative organism.

EOS is caused by vertical transmission of pathogens. The amniotic fluid surrounding the foetus in intrauterine life gets infected by an ascending infection of bacteria colonization of the maternal perineum. Also, during labor the newborn comes in direct contact with vaginal microbes while passing through the birth canal. Maternal hematogenous transmission and chorioamnionitis are occasional possible

conditions able to induce EOS. Rarely, procedures like cervical cerclage and amniocentesis infect the amniotic fluid, causing likelihood for EOS. Aspiration and digestion of the infected amniotic fluid in utero or infected secretion in the birth canal can effectively produce pneumonia and/or sepsis. Thus, premature birth (< 37 weeks), premature and prolonged time (>18 hours) of membranes rupture, maternal peripartum infection, and low socioeconomic status are strongly associated with EOS. Increase coverage of intrapartum antibiotics and corticosteroids in mothers has decrease the risk of EOS.

LOS sepsis is a horizontal transmission of infection. With advances in neonatal management & increased survival of EP and VP, with increased hospital stay, increase use of invasive lines, ventilation, maternal separation, delayed feeds etc., thus an increased risk of cross infection and LOS. A review study from the NICHD Neonatal Research Network showed the likelihood of neonate developing LOS was inversely related to GA and birth weight. Other factors for LOS are use of parenteral nutrition, indwelling central venous or umbilical catheter, and ventilator treatment. Also prolonged use of empirical antibiotics has shown increased trend to LOS and a significant association to Necrotising Enterocolitis and/or death.

In most developed countries, there is a marked distinction in organism causing EOS & LOS. Group B Streptococci, Escherichia Coli are commonest pathogen for EOS, whereas Coagulase Negative Staphylococcus (CONS) is responsible for most LOS around the world.

In India, both EOS & LOS are generally caused by same organisms with no much distinction in their antibiogram. The commonest organisms responsible are Escherichia coli, Klebsiella sp., and Staphylococcus aureus. Most infections are by gram negative both in EOS & LOS. Thus in India, NS is complicated with predominant gram negative organism with increasing ESBL, Carbapenems resistant strains.

Why neonates are susceptible for infections?

The newborn has predominantly three defence systems, namely- intact epithelial skin surface and secretory mucous membrane, nonspecific humoral immunity & cell mediated immunity. The defence is inversely proportional to GA and post birth age after birth. After birth, newborn immunity improves over the period of 3 months. The net effect of these deficits leaves the neonate extremely susceptible to microbial invasion.

Neonates have fragile skin (preterm newborns; inversely proportionate to GA at birth), decreased circulating complement components (limiting opsonization/killing of pathogens), diminished expression of antimicrobial proteins and peptides (APP), decreased production of type I interferons and T_H1 polarizing cytokines, and quantitative and/or qualitative impairments in neutrophil, monocyte, macrophage, and dendritic cell function.

Neonatal leukocytes, particular under stress conditions, demonstrate diminished cellular functions necessary for bacterial clearance, including diminished responses to most TLR agonists (constituents of microbes), reduced production of cytokines/chemokines and APP, diapedesis, chemotaxis, phagocytosis, and antigen presentation. Neonates are also deficient in functional splenic follicles that filter blood and remove pathogens, further limiting bacterial clearance, and increasing the risk of fulminant infection. The net effect- increased susceptibility to microbial invasion in newborn.

Diagnosis of Neonatal Sepsis:

- **Blood Culture:** Isolation of organism from blood culture is the gold standard of diagnosing Neonatal Sepsis. Conventionally, at least 0.5 ml of blood collected from a peripheral blood vessel in paediatric blood

culture bottle is recommended. Though, larger volume of blood up to 1ml is likely to increase the sensitivity, but may not practically be possible in EP and ELBW neonates. The success of blood culture positivity depends on numerous factors- bacterial blood load, blood volume collected, aseptic precaution avoiding contamination, antibiotic administered before collection, etc. Automated BacT/Alert systems are increasingly used with equal efficacy in correctly identifying a bacterial growth and they do so in a significantly shorter time.

Septic Screen (Complete Blood Count, CRP): The success of blood culture positivity depends on numerous factors- bacterial blood load, blood volume collected, aseptic precaution avoiding contamination, antibiotic administered before collection, etc. Given the factors, the likelihood of positive blood culture is low in literature. Thus surrogate markers viz. - WBC, Immature to total Neutrophil Ratio (ITR), Absolute Neutrophil Counts (ANC), inflammatory markers (CRP) are used in combination for diagnosing NS.

- CRP: Quantitative CRP- ⩾10mg/L.
- Absolute Neutrophil Count: It must be read off on Manroe's charts (Term baby) or Mouzinho's chart (Preterm baby)
- ITR: For term baby ⩾ 0.27 and for preterm ⩾ 0.20 is considered positive for NS.

Two of the above screen markers in background of risk factors for LOS, is taken as evidence for Culture negative sepsis. The screen may be repeated after 12-24 hours. Two consecutive completely negative screens 24-48 hours apart help in ruling out infections in neonates.

- **Cerebrospinal Fluid Study:** CSF study should be part of every LOS workup. Both microscopy and chemistry can guide to meningeal inflammation. Isolation of microbes on culture & ZN staining is diagnostic for meningitis. Also this will be a definite guide for antibiotic therapy, viz. – choice of antibiotic & duration. The treatment of LOS with no CSF study may lead to partially treated meningitis causing morbidity.

CSF study may not be of much significance in investigation of EOS; but will be needed in culture proven EOS.

Preterm infants:

Treat: CSF WBC counts≥10/mm^3 or Glucose <24 mg% or protein >170 mg%.

No treatment: CSF WBC count <25/mm^3 AND glucose ≥25mg% AND protein <170 mg%.
If seizures, alteredsensorium, fullness of fontanelles, **then** low threshold for diagnosis

Term infants:
Treat: CSF WBC count >8/mm^3 or Glucose <20mg% or protein >120 mg%. There is no safe cut-ofat which one can recommend "do not treat.

- **Urine – Microscopy & Culture:** Neonates with the nonspecific clinical signs of sepsis, suspected LOS, known with urinary tract anomalies, urinary bladder catheterization or visibly turbid urine should be investigated for Urinary tract infection. It is unlike at investigation for EOS. The sample collected should be either from suprapubic tap or sterile catherisation. Urine specimen from urine bag or indwelling catheters is not ideal. The microscopic analysis of uncentrifuged urine with ⩾ 10 WBC per high power field is highly suggestive of UTI. Urinary nitrites and leucocyte esterase activity may further assist in gram negative UTI. Isolation of organism from urine though a gold standard may have to correlated clinically as high possibility of contaminant.

Challenges in managing NS:

1. Lack of Ideal Biomarker:
The diagnosis of NS is difficult due to nonspecific symptomatology, high false positive rate and delay in positive blood culture. Absence of an ideal biomarker in the detection of definite infection at early stages is a problem. Early phase reactants (Cytokines – IL6, IL8, TNF-alpha & Cell surface markers – nCD64, CD11beta), mid phase (Procalcitonin) and late phase (CRP) are increasingly studied, with some success. Genomics, Proteomics and molecular techniques have been studied. Inter alpha inhibitor proteins (IAIP); serine protease inhibitor is under research. Heart rate characteristics index and Core-peripheral temperature difference (Noninvasive Biomarkers) holds promise.

2. Management of multi-drug resistant infections:
Because of emergence of antibiotic resistant strains of bacteria, many clinicians find difficult to treat neonatal infections. There is proven causal link between antimicrobial exposure and the development of resistance. Neonatal ICU's have been identified as high-risk areas for development and transmission of antibiotic resistance because use of empirical antibiotics. Judicious use of antibiotics is necessary to maintain usefulness of new antimicrobials. Several infection surveillance programs have been established worldwide but only some of them can be implemented successfully into clinical practice.

3. Preventing infection:
Intra-partum prophylaxis, antenatal steroids have prevented EOS. Although, hand hygiene, the safe use and early removal of intravascular catheters are mainstay approaches to prevent nosocomial infection. Other potentially promising strategies like concept of bundles, early enteral feedings, nutritional supplements and maternal vaccination are being studied.

4. Antibiotic stewardship:
The need of limiting use of broad spectrum antibiotics in increasingly felt with rising menace of multidrug resistant organisms. Increasing awareness and sensitizing the medical team to abuse of antibiotics is a growing challenge.

Conclusion: NS is a global problem with high incidence in India, with increasing burden of gram negative and antibiotic resistant strains. Newborn are prone to sepsis due to deficiencies in both innate & acquired immunity. Future research is needed to help in curbing NS.

Table 1: Comparing EOS & LOS

Early Onset of Sepsis (EOS)	**Late onset Of Sepsis (LOS)**
Definition: ⩽ 72 hrs of life. It is vertical transmission of organism, from infected amniotic fluid and vaginal secretion.	**Definition :**> 72 hrs – 28 days of life. It is horizontal transmission of organism. In community, NS is due to aseptic practices whereas in NICU, it is often cross infection.
Organism: - Group B Streptococci, E.coli (Developed countries) -E.coli, Klebsiella sp., Staphylococcus aureus (Developing countries)	**Organism:** - Coagulase Negative Staph. aureus (Developed counties) -E.coli, Klebsiella sp., Staphylococcus aureus (Developing countries)

Risk Factors- **Maternal Factors:** • premature birth (< 37 wk), • premature/ prolonged time (> 18 h) of membranes rupture, • maternal peripartum infection, • low socioeconomic status • maternal age < 20 y &> 35y, • Obstetric practices. **Neonatal factors:** • Preterm (⩽37 weeks) • Very Low birth weight (⩽ 1500 gram) • male sex, • neonatal Apgar scoring, foetal distress, • wet lung, • anaemia, intraventricular hemorrhage, • hypothermia, • metabolic disorders	**Risk Factors-** • Inversely related to gestation age & birth weight. • Maternal intake of antenatal corticosteroids, • Prolonged hospitalization, • mechanical ventilation, • Invasive procedures & devices implantation. • Delayed feeding • Use of empirical, prolonged, broad spectrum antibiotics • Parenteral nutrition
Investigations: Blood Culture. Septic screen- No use. CSF study- Not routine. Only if suspicion of meningitis for Culture positive EOS.	**Investigations:** Blood Culture. Septic screen. CSF study with culture Urine microscopy & culture- in case of EP & VLBW babies.

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Antibiotic Policy in NICU

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The judicious use of antibiotics is an important means to limit the emergence of antibiotic resistant organisms. Antibiotic policy is one of the core elements of the antibiotic stewardship program, which includes accurately identifying patients who need antibiotic therapy, using local epidemiology to guide the selection of empiric therapy, avoiding agents with overlapping activity, upscaling and down scaling, adjusting antibiotics when cultures results become available, monitoring for toxicity, and optimizing the dose, route and limiting the duration of therapy.

The signs and symptoms of sepsis in neonates are non specific and may represent the presentations of a non infectious process, hence identifying the infants who need antibiotics is crucial.

Conditions **where antibiotics are not indicated** are:

- Asymptomatic preterm needing admission
- Asphyxiated infants
- Severe jaundice
- Meconium aspiration syndrome
- Surgical newborn especially if it is a clean surgery such as Congenital diaphragmatic hernia

Conditions **where antibiotics are indicated** are:

Within first 48 hours of life

- Symptomatic infants with respiratory distress with no clear history
- Asymptomatic infants with Preterm PPROM (premature prolonged rupture of membranes)
- Presence of risk factors for infection in case of preterm infants
- Presence of risk factors along with positive septic screen in case of term infants

After 48 hours of life

- Clinical suspicion of sepsis (presence of impaired perfusion, off color, cold peripheries, fever, multi organ involvement, sick neonate with no evident cause etc)

a. Evidence of pneumonia on chest x ray
b. Culture positive sepsis.

Note: In neonates with gestation less than 34 weeks, antibiotics should be started, with any duration of PPROM. In infants between 34 to 36 weeks, a septic screen can be done after six hours of life and if positive, then antibiotics should be started.

The risk factors for early onset sepsis include: preterm PROM, PROM >18 hours, foul smelling liquor, maternal tachycardia, uterine tenderness, maternal UTI and mother on antibiotics prior to delivery

Selection of empiric antibiotic therapy

a. Depends on the local cumulative antibiograms over last 3 to 6 months duration or at-least 30 to 40 culture reports
b. Unit specific antibiograms are most useful as the common organisms prevalent, the common drugs to which they are sensitive and antibiotic resistant organisms (ARO) are different at each of the units.
c. The first line antibiotics chosen may have 70 to 80% sensitivity, the second line 80 to 90% and the third line with more than 90% sensitivity.
d. When choice is available, always choose a narrow spectrum antibiotics for empiric therapy
e. The tissue affected would also decide the empiric choice (meningitis, skin infection)
f. Knowledge of outbreaks can inform the

temporary modification in the empiric regimens

g. Agents with overlapping spectrum of activity should be avoided

To choose the antibiotic for empiric therapy, understanding of the different organisms causing EOS or LOS, and their sensitivity to different antibiotics is necessary. The organisms and the antibiotics can be grouped into the following:

1) Gram negative organisms
- Aminoglycosides (Amikacin or Gentamycin), Cephalosporins, Ampicillin, Piperacillin, Ciprofloxacin, Meropenem, Colistin.

2) Gram positive organisms
- Cloxacillin, Vancomycin, Teicoplanin, Teigocycline

3) Fungus
- Fluconazole, Amphotericin

4) Anaerobic organisms
- Penicillin, Metronidazole

Note: The EOS in our country is usually caused by Gram negative organisms compared to the west, where the GBS is more prevalent. Hence a monotherapy with any one of the above antibiotics would be sufficient instead of a combination therapy like Ampicillin and Gentamycin.

Depending on the time and mode of presentation of the infection the appropriate empiric therapy can be initiated. For instance

Mode and time of suspicion of infection	Appropriate empiric antibiotic
Within 24 hours of life (EOS), overwhelming signs of sepsis	Gram negative cover
LOS, prolonged hospital stay, fever, evidence of abscess or pustules	Gram positive cover
ELBW infants, Multiple antibiotic usage, multiple invasive lines and procedures	Fungal cover

Note:
- Cephalosporins should be avoided as the first line therapy, as there is an emergence of multidrug resistant bacteria (especially ESBL) with their extensive usage.
- Anaerobic infections are rare in neonates

Reevaluating the antibiotic regime

The microbiology report with the antibiotic sensitivity testing is an invaluable tool to determine if antibiotics should be continued, modified, or discontinued.
- The body site from which the positive culture was isolated should be reviewed. Growth from non sterile body sites (such as tracheal aspirates) may be colonizing flora, particularly when the clinical course is not suggestive of infection.
- Susceptibility results provide the opportunity to treat with a narrow spectrum, less toxic, and more efficacious antibiotic.
- The minimum inhibitory concentration (MIC) can guide treatment for infections at sequestrated sites, such as lung or the central nervous system. At these sites, decreased antibiotic penetration is expected. Thus the use of agents with MIC's near the clinical breakpoint (the transition from susceptible to intermediate or resistant) would not be recommended, as the adequate tissue levels may not be achieved.
- The date and time of the microbiology report, provide an opportunity for timely discontinuation of therapy when infection is

not suspected. Nearly all blood cultures with clinically meaningful bacterial growth will be positive within 48 hours.
- Cultures with growth after 48 hours are more likely to be contaminants or colonizing organisms as these microbes are generally present at a lower inoculum.

How to upgrade or downgrade antibiotics:

Depending on the clinical improvement or based on the blood culture and sensitivity pattern, either we upgrade or downgrade the antibiotics. It is always better not to upgrade the antibiotics at-least for 48 to 72 hours of starting if there is improvement. Our focus should also be on the supportive care, which would improve the outcome. It includes

- Maintaining the temperature
- Proper adjustment of the fluid balance
- Correction of the electrolyte disturbances (Na, K and Ca)
- Acid base balance
- Use of inotropes for hypotension
- Ventilation or CPAP if needed
- Blood and blood products to correct anemia or the bleeding tendency

There should be a unit policy for the hierarchy of the antibiotics to be used i.e. from 1st line to 2nd line. To modify from 2nd to 3rd line of antibiotics, the sensitivity report has to be considered or can be done when the infant is very sick, or when there is not much clinical improvement even after 72 to 96 hours of 1st line of antibiotics and the supportive care.

How to downgrade the antibiotics:

- The antibiotics should be downgraded, when there is clinical improvement.
- If on clinical suspicion if multiple antibiotics (e.g. gram negative and antifungal cover) have been started for a sick infant; after the susceptibility report, the antibiotics specific to the organism isolated has to be continued and the rest should be stopped.
- The antibiotic with narrow spectrum should be chosen; for instance, for gram negative organism better to choose one among Aminoglycosides, Pipericillin or Ampicillin. For gram positive organism choose Cloxacillin over Vancomycin and for fungal cover prefer to use Fluconazole over Amphotericin.
- If the neonate has clinically improved, the same empirical antibiotics can be continued, even if there is in-vitro resistance.
- If the organism isolated is Staphylococcus or Pseudomonas, it is always better to follow the susceptible antibiotic on the antibiograms.
- If meningitis is suspected, a drug which penetrates CSF has to be chosen (Cephalosporins and penicillin would be preferable over Aminoglycosides or Quinolones for meningeal penetration)

Modification of antibiotic after the availability of Antibiogram:

- Continue any one of the sensitive antibiotic.
- Any one of the narrowest spectrum should be chosen. For instance choose
  - Ampicillin over Meropenem
  - Pipericillin Tazobactum over Levofloxacin
  - Fluconazole over Amphotericin
  - Cloxacillin over Vancomycin
- If the susceptible antibiotics are of intermediate sensitivity, two of them can be combined.
- If only Aminoglycosides have to be used, its usage has to be restricted to one week duration, because of the nephrotoxicity and ototoxicity.

Antibiotic stewardship program

To rationalize the antibiotic usage and prevention of resistant bacteria, antibiotic stewardship program has to be followed. The core components include:

- Formulary restriction or Optimal use of antibiotics
  - Restricting the use of antibiotics
  - Restricting the use of broad spectrum antibiotics
  - Monitoring the drug toxicity
  - Prospective Surveillance and auditing of cultures
- Protocol for antibiotic prescription
- Improving the infection control practices
- Education of the staff

Formulary restriction

- There no role for prophylactic antibiotics
- The blood culture has to be considered to guide the continuation of antibiotics rater than the septic screen
- Minimize the duration of antibiotics
  - Suspect sepsis – 3 days or less
  - Culture positive sepsis – 7 to 10 days for gram negative and 10 to 14 days for gram positive
- Pneumonia or screen positive sepsis- 5 to 7 day
- sThere should be unit policy for upgrading of antibiotics and it should be strictly followed.
- The members of the antibiotic stewardship team should be involved in the use of restricted or broad spectrum or newer antibiotics.

Restricting the use of Broad spectrum antibiotics

- Avoid Cephalosporins as the first line of antibiotics as their use will increase the incidence of drug resistant bacteria (ESBLs)
- Aminoglycosides or Pipericillin are better choices as first line empiric antibiotics
- Re-evaluate the antibiotics after the culture and stop the broad spectrum antibiotics, choose narrow spectrum.
- Rotation of antibiotics is not recommended.
- Audit of the Antibiogram has to be done every 3 to 6 months.

Surveillance of the cultures

- Periodic cultures from the unit (surveillance swabs) should be taken, to understand the prevalence of organisms in the NICU environment.
- The Process measures should be audited, like
  - The procedure of hand washing
  - Availability and usage of disinfectants in the baby care area.
  - Audit of insertion and maintenance of central lines or PICC lines (CLASBI bundle)
  - Use of enteral nutrition
  - Compliance of VAP bundle
- Audit of the cultures is needed to know the type of organisms causing early onset or late onset sepsis, the sensitivity pattern and to formulate the empiric use of first line or second line antibiotics

Antibiotic prescription protocol

- Every unit should have a written antibiotic policy/protocol. Unit protocol should strictly adhere to.
- Restrict the use to 4 to 5 antibiotics in the unit
- Always document the initiation and change of antibiotic
- Upgrading of antibiotics, especially from the second line to third line, must be done under the supervision of the consultant or senior physician
- A blood culture has to be taken before any change in the antibiotic

Protocol for use of commonly used drugs

The dose of the antibiotics would depend on the age, weight and the renal function of the infant; also on the site of infection and simultaneous use of other interfering drugs.

Amikacin

- Dose – 15mg/kg once daily
- Always given as infusion over 30 minutes
- Preferable as single daily dose and duration less than 5 days
- Nephrotoxicity may increase when used with Frusemide, Vancomycin or Cefotaxime
- The serum drugs levels > 10 mcg/L are Nephrotoxic and >35 mcg/L are Ototoxic

Ampicillin

- The dosage depends on the gestational age and the postnatal day of life.

Postmenstrual age	Postnatal age	Dosing
<30 wk PMA	1-28 d of age	100 mg/kg/dose q12h
	>28 d	100 mg/kg/dose q8h
30 – 37 wk PMA	1-14 d of age	100 mg/kg/dose q12h
	>14 d	100 mg/kg/dose 8h
>37 wk PMA	1-7 d of age	100 mg/kg/dose q8h
	>7 d	75 mg/kg/dose q6h

- Dosage adjustment should be done for renal impairment.
- Always be infused over 15 – 20 minutes.
- Reconstituted solution must be used within 1 hour after mixing, due to loss of potency.
- Not compatible with parenteral nutrition, avoid mixing.
- Blunting of the peak Aminoglycoside level if administered simultaneously, so always separate by a saline flush.
- May cause thrombocytopenia, rash or seizures with large doses

Meropenem

- The use of Meropenem is not well established in the neonates. The dose used for the infants more than 3 months of age was found to be effective.
- Dose- 10 to 20 mg/kg/dose q 8 – 12 hours. (In case of meningitis can increase to 40 mg/kg q 8 hourly)
- Always given as infusion over 15 – 30 minutes. Can be reconstituted with Dextrose or saline. The drug reconstituted with sterile water maintains its potency at room temperature (up to 25°C) up to 8 hours and under refrigeration for 48 hours.
- Can be used in resistant and difficult to treat gram negative infections.
- It penetrates well into CSF.
- Most common adverse effects are diarrhea, nausea/vomiting and rash. May cause thrombocytopenia, leucopenia and anemia.

Pipericillin Tazobactum

- Dose – 50 to 100 mg/kg per dose q 8 -12 hourly.
- The dosing depends on the postmenstrual age (PMA) and the postnatal age

PMA (weeks)	Postnatal age (days)	Interval (hours)
⩽ 29	0 to 28 days >28	12 8
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7	12 8
⩾45	All	8

- The reconstituted solution is stable for 24 hours at room temperature and 48 hours if refrigerated.
- Not to be used for meningitis due to poor CSF penetration.
- May cause thrombocytopenia, azotemia, liver dysfunction, cholestasis and hypokalemia.

Vancomycin

- Dose- 10 mg/kg per dose–Bacteremia; 15 mg/kg/dose – Meningitis

PMA (weeks)	Postnatal age (days)	Interval (hours)
⩽ 29	0 to 14 >14	18 12
30 to 36	0 to 14 >14	12 8
37 to 44	0 to 7	12 8
⩾45	All	6

- Reconstituted solution is stable for 4 days if refrigerated.
- Always given as infusion over 1 to 2 hours.
- Rapid infusion can cause hypotension, red man syndrome and thrombophlebitis. Lengthening the infusion time will eliminate the risk of hypotension for subsequent doses.
- Never give rapidly and no IM route.
- Monitor the trough levels as it can cause ototoxicity and Nephrotoxicity.
- Has interaction with Amikacin, Amphotericin, Frusemide, Indomethacin.

Amphotericin B

- Dosage**:** 1-1.5 mg/kg IV q24 hour infusion over 2 to 6 hours.
- Incompatible with saline, hence always dilute with dextrose
- First dose to be given over six hours and the subsequent doses over 4 hours
- Reconstituted solution is stable for 24 hours at room temperature or 7 days in refrigerator.
- Conventional is preferred
- Liposomal can be used if there is intolerance to the conventional
- Nephrotoxic and can cause hypokalemia, bone marrow suppression, thrombophlebitis and fever. Cardiac arrest can occur if 10 times the recommended dose is given.

Fluconazole

- Invasive Candidiasis: 12 to 25 mg/kg loading dose, then 6 to 12 mg/kg per dose as IV infusion over 30 minutes.
- Prophylaxis (only in VLBW at high risk of invasive fungal disease): 3 mg/kg per dose via infusion twice weekly, or orally. A dose of 6 mg/kg per dose can be considered if targeting Candida strains with higher MICs (4 to 8 mcg/ml).
- Thrush: 6 mg/kg on Day 1, then 3 mg/kg per dose every 2 hours orally.
- Invasive Candidiasis dosing interval chart is as follows

Gestational age (weeks)	Postnatal age (days)	Interval (hours)
⩽29	0 to 14 >14	48 24
30 and older	0 to 7 >7	48 24

- Store at room temperature. Do not freeze.

Cefotaxime

- Dose – 50 mg/kg per dose as IV infusion over 30 minutes.
- Restricted use is recommended, to decrease the incidence of ESBLs.

Further Reading:

https://www.youtube.com/watch?v=PWoO6hhjhs8·

- Principles and strategies of Antibiotic stewardship in Neonatal intensive care unit, Sameer J.patel, Semin Perinatol. 2012 December ; 36(6): 431–436.
- Antibiotic use and misuse in Neonatal intensive care unit, Nidhi Tripati, BS, Clin Perinatol. 2012 March ; 39(1): 61–68.
- Centers for Disease Control and Prevention's (CDC) Get Smart Campaign, www.cdc.gov/getsmart/healthcare/

Infection Control Practices in NICU

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Introduction:
Healthcare-associated infection (HAI) is a common complication in critically ill patients in neonatal intensive care units (NICUs) not only in developing but also developed countries. The Centres for Disease Control and Prevention (CDC) defines *HAIs* as infections acquired while in the health care setting, with a lack of evidence that the infection was present or incubating at the time of entry into the health care setting. As Per WHO fact sheet, for every 100 hospitalized patients at any given time, 7 in developed and 10 in developing countries will acquire at least one health care-associated infection.

Newborns are at higher risk of acquiring HAI in developing countries, with infection rates 3 to 20 times higher than in high-income countries. Infants in NICUs are at high risk for hospital infections owing to low birth weight (LBW), Prematurity, Congenital malformations, Prolonged hospital stay, frequent invasive procedures, parenteral nutrition & higher risk of developing infections due to suboptimal immunity.

In this article we have discussed the evidence based strategies for prevention of these infections and its proper implementation, as these can go a long way in providing a safe and intact survival for the patients, as well as reducing the burden on existing healthcare.

A. Physical Designing of the NICU:
Each Infant is a potential source and recipient of microorganisms. CDC has given guidelines for NICU setup, specifically designed for prevention and control of Nosocomial infections.

Annexure 1 :

Components	Specifications	Comments
Space	Minimum 120sq. ft. excluding sinks and aisles, with a 3 ft. aisle adjacent.	Avoid traffic from other services.
Ventilation	90% filtered air. Minimum 6 air changes/hour.	Exhaust vent positioning away from infant bed.
Scrub areas	• 1 hands-free sink for every 4 beds. • Minimum sink dimensions 24in. ×16in. ×10in.	Pictorial hand washing instructions above all sinks. Everyday sink cleaning with a detergent.
Isolation Room	• Every NICU needs isolation room. • Isolate every baby with septicaemia. • Minimum space 150 sq. ft. excluding the work area. • Negative air pressure ventilation with 100% exhaust to outside. • Provision of hands-free two way communication system to connect to the outside.	Area for gowning, hand washing & storage of cleaned and soiled material near the room. Designed so as to promote easy cleaning.
Staff	• Nursing ratio of 1:2 or 3 per patient. • Critical patient : Ratio of 1:1 • Vaccinated with Hep B, Rubella, measles, chicken-pox, influenza (yearly). • Periodic staff training and surveillance.	No direct contact of individuals with respiratory, cutaneous, gastrointestinal infections with the neonates. Dedicated assistance from the staff members to the mothers for infant care.

Dress code and **Personnel protective equipment** **(PPE)**	• Dress code for regular personnel. • Sterile long sleeved gowns to be worn during surgical and invasive procedures in the unit. • PPE includes Gloves, Protective eye wear, mask, gown, Shoe covers, cap /hair cover and should be chosen as per the risk of exposure	1. During Handling of neonate outside the bassinet by the nursing or other personnel, a gown should be worn over the regular clothing and should be either discarded after use or has to be maintained exclusively in the care of that neonate. 2. It is very important to use personal protective equipment effectively, correctly and at all times where contact with patient's blood, body fluids, excretions and secretions may occur

A. Hand Hygiene Practices:

Hand hygiene is *defined* as any method that removes or destroys microorganisms on *hands*. It refers to cleaning of visibly soiled hands as well as removal or killing of the transient microorganisms while maintaining good skin integrity.

Proper Hand hygiene plays a critical central role in any infection control programme. In neonatal intensive care unit (NICU, setting, improved adherence to hand hygiene practices has been shown to reduce infection rates. American academy of Paediatrics and the American college of Obstetricians and Gynaecologists recommend that Personnel should scrub their hands and arms to a point above the elbow with antiseptic soap.

Annexure 2:

TO DO
• Strict Hand hygiene - Before touching patients, Before clean/ aseptic procedure, After body fluid exposure, After touching the patient and after touching the patient surroundings. • Meticulous hand-wash before entering the NICU premises. • Scrubbing hands and arms up to a point above the elbow. • Alcohol Based Hand Rub (ABHR) is preferred method of hand washing between patients, when no visible soiling of hands. • ABHR available at point-of-contact. • Allow ABHR Contact time for action. • Surgical hand scrubbing before every invasive procedure. • Adequate sinks with soap and water to allow hand washing in every unit at the maximum convenience. • Use of disposable paper towels to dry hands and plastic lined functional pedal bin. • No long nails, nail polish, artificial nails or nail enhancements in personnel handling neonates. • No bracelets, wrist-watch or rings in NICU. • Regular teaching activities and proper surveillance and feedback to promote better compliance from staff members. • Counselling parents and caregivers about the importance of hand hygiene.

WHO multimodal Hand hygiene improvement strategy has been devised to manage this problem. It consists of: 1.System change 2. Training and education 3. Evaluation and feedback 4. Reminders in the workplace 5. Institutional safety climate.

Invasive Procedure Care: This includes care to be taken during peripheral and central venous catheter insertion, Ventilator care, IV fluid care, Urinary catheter insertion, wound care.

A. Prevention of Ventilator associated pneumonia: Advances in Mechanical ventilation have enabled the provision of respiratory support to extremely preterm infants within the limits of viability. Ventilator associated Pneumonia (VAP) is defined as pneumonia which has developed when the patient was intubated and ventilated or within 48 hours of ventilation.

Annexure 3:

TO DO
• Strict Hand hygiene. • Strict training and supervision of infection control protocols. • Maximum use of Non-invasive ventilation. • Asepsis during intubation. Minimum / No Re-intubation attempts • Optimum Humidification of the ventilato r gases. Closed humidification system use. • Use of disposable ventilator circuits. • Regularly d raining ventilator circuits to minimize fluid accumulation and colonization of circuit tubing with pathologic organisms. • Changing the ventilator circuit as needed, rather than on a fixed schedule • Asepsis during suctioning. Use of closed suctioning. • Least required ventila tor settings. • Early extubation. • Minimizing sedation. • Minimize pooling of secretions. • Frequent position changing of the ventilated infant. • Minimizing antacids use. • Limitation of unnecessary invasive procedures. • Optionally: The endotrach eal aspirate of the patients ventilated for longer duration could be sent for culture & sensitivity, and if the patient develops VAP, antibiotic should be changed as per the report.

A. Prevention of Central line associate blood stream infections (CLABSI):

Although the primary prevention of CLABSI' relies on minimizing the central line use, meticulous attention should be given to aseptic insertion and maintenance of cannula as well as aseptic techniques of fluid administration. When compared to other populations, neonates have among the highest rates of CLABSIs potentially due to intrinsic immunodeficiency, the need for prolonged duration of central line use, and the lack of antibiotic- or antiseptic-impregnated catheters for this population.

Annexure 3:

TO DO
• Meticulous *Hand hygiene*. • Performing daily audits to assess the need for central line. • Aseptic CVC insertion technique. • Optimal use of personal protective attire. • Skin antisepsis with >0.5% chlorhexidine with alcohol. • Selection of the best site for catheter insertion (preferably a peripheral site) • Covering the site with sterile gauze or sterile transparent, semipermeable dressing. • Good hand hygiene compliance during line handling. • Scrubbing the access port or hub immediately prior to use with an appropriate antiseptic like chlorhexidine. • Only sterile devices access to the catheter. • Replacing dressings that are wet soiled or dislodged after surgical hand washing and gl oves. • 'Bundle supplies kit to ensure that all items are readily available for use, checklists for CVC insertion and care. • Newer supplemental strategies that are available include 2% Chlorhexidine bathing, Antimicrobial/ Antiseptic impregnated catheters, Chlorhexidine impregnated dressings. • Recurrent staff education and empowerment. • Surveillance of line handling as well as the other infection control practices and periodic feedback for adherence.

E. Nutrition:

Enteral Feeds*:*

- Encourage Breastfeeding. (Expressed Breastmilk feed whenever breastfeeding not feasible)
- Milk from Breastmilk bank can be kept as option when both the above not possible.
- Early trophic feeds.
- Strict hand hygiene and septic techniques during newborn feeds preparation & handling.
- Whenever disposable syringes are used, they should be discarded after 1 feed.
- Equipment used for feeding the baby need to be cleaned properly with soap and water followed by boiling for 20 minutes for best sterilization.

Parenteral nutrition*:*

- TPN requires greater precautionary handling.
- Parenteral nutrition fluids ordered directly from the supplying company should be used and no decanting should be done at the facility level, to prevent cross infections.
- When done at the pharmacy, strict asepsis and laminar flow needs to be ensured.

F. Skin Care:

- No vigorous attempts for vernix removal.
- Bathing is found to be superior to sponging in a full term normal baby.
- First bath can take place within a few hours after birth. (If the thermal and cardiorespiratory stability is ensured)
- Cleaning with liquid baby cleansers.
- Cleaning of the perineal area with mild soap and warm water.
- Meconium or faeces cleaning from the buttocks with sterile cotton moistened with

sterile water.

- Topical application of emollient ointment or oil such as sunflower oil or olive oil.

G.Umbilical cord care: The WHO currently recommends dry cord care in developing countries and the use of soap and water solution to clean the cord if visibly soiled.

H. Eye Care: Sterile cotton can be used for eyes cleaning.

I. Kangaroo Mother Care: In stabilized LBW infants, KMC was associated with a statistically significant reduction in severe infection/sepsis at latest follow up.

J. Antibiotic Stewardship: Antimicrobial resistance has been identified as a major threat by the WHO. *Antibiotic stewardship* refers to a set of coordinated strategies to improve the use of antimicrobial medications with the goal of enhancing patient health outcomes, reducing resistance to antibiotics, and decreasing unnecessary costs. Two core strategies which are not mutually exclusive, which play a major role in antimicrobial stewardship (IDSA Guidelines 2007) are: Formulary restriction and preauthorization & Prospective audit with intervention and feedback.

The Golden Rules of Antimicrobial Prescribing are: 1. Microbiology guides therapy wherever possible, 2. Indications should be evidence based 3. Narrowest spectrum required, 4. Dosage appropriate to the site and type of infection, 5. Minimise duration of therapy, 6.Ensure monotherapy in most cases. It is an inter-professional effort across the continuum of care, involving timely and optimal selection, dosing, duration of antimicrobial agent, with best clinical outcome and minimal toxicity to the patient and having minimal impact on resistance of organisms.

K. NICU Housekeeping:

The housekeeping routines form an important part for infection prevention in NICU. All practices should be introduced as routine and strictly and consistently followed for best results.

Annexure 1: House Keeping Routines

Name	Disinfection method	Frequency
Floors	Wet mopping with Phenol 3%, Lysol 5%, Sodium Dichloroisocynurate (clean-A-Sept)	No Dry sweeping. Once a shift cleaning. Do not use 2% Glutaraldehyde
Walls	2% Bacillocid, Clean-A-Sept	Once in per shift
Fans	Clean with soap and water	Once a week
Window AC	Surface and filters to be washed with soap and water	Once a week
Refrigerator	Defrosted and cleaned with soap and water	Once a week
Buckets	Soap and water	Daily in morning shift
Sinks	Detergents	
Dustbin	Washed daily with soap and water	Polythene should be changed daily or whenever full
Needles and sharps	Discard in a needle proof container	Daily
Waste and soiled linens	Closed bins should be available; bin must be closed and emptied at regular intervals. Plastic bags should be used in bins, and are discarded as per the waste disposal policy.	

The patient care equipment serves to be a major site of sepsis transmission. It has to be meticulously sterilised and disinfected. Wherever feasible, preferring a disposable option is recommended. However, in a resource limited nation like ours, optimum sterilization of these equipments can help to bring down the sepsis rate to a large extent.

Annexure 2: Patient Care Equipment cleaning & Disinfection

Name	Chemical	Additional information
Incubators and bassinets	Clean with Detergent and water. Disinfect (if needed) with chlorine releasing agents (125ppm)	Should have detachable parts for thorough scrubbing and cleaning.
Incubator fan and air filter	Cleaning as per manufactures instructions.	
Mattresses	Clean with detergent and water, in between patients and as required.	Should be replaced when the surface covering is broken as this can preclude effective sterilization and disinfection.
Baby weighing scales	Clean tray with detergent and water twice daily.	Fresh liner should be used before placing any baby on the scale and discarded thereafter.
Ventilator tubings	Cleaning and drying followed by E thylene oxide treatment. Ventilator tubing used for babies with gram negative organisms have to be discarded.	Disposable preferred
Ambu bag and masks	Clean with detergent and water, dry and thermally disinfect / Ethylene oxide use.	Disposable preferred.
Stethoscopes	Wipe bell and tubing after each use with 70 - 90% alcohol.	Separate stethoscope used for every baby in NICU.
Pulse oximeter probes	Wipe inside and outside with 70 – 90% alcohol or other LLD	Disposable preferred.
Thermometer	Cover with disposa ble sleeve before use and store dry in individual holder (inverted). Clean and wipe with 70 -90% IPA after every use.	Do not mix oral and rectal thermometers.
IV pumps	Clean with detergent and water and dry disinfect with LLD (70 – 90% alcohol or sodium hypochlorite)	After use in isolation, wipe with 2% sodium hypochlorite and dry after cleaning.
IV drip stands	Clean with soap and water	After use in isolation, wipe with 2% sodium hypochlorite and dry after cleaning.
Suction bottles	Clean with sodium hyp ochlorite and dry. Must be heat disinfected or sterilized. Change daily and in between patient use. Store dry when not in use.	Disposable preferred. If disposable, use one bottle patient and discard when 75% full.
Humidifier chambers	Change together with every ventilator circuit and can be thermally disinfected / ETO done	Disposable preferred. Always use closed humidifiers
Nebulizer and nebulizer masks	Clean and heat disinfect & Dry	Masks are not generally used in NICU. If used, separate mask for each patient.
Feeding utensils	Soap and water cleaning	After cleaning, boil the feeding utensils for 20 minutes.
X-Ray Equipment	Damp dust with detergent and water. Switch off. Do not over-wet, allow to dry before use.	Alternative it can be wiped with 70 – 90% alcohol or any other LLD.

Periodic fumigation of the Neonatal nursery and intensive care unit goes a long way in prevention of HAI's.

Annexure 3 : Disinfectants used for fumigation

Formalin (40%)	30ml of Formalin (40%) with 90ml of water per 1000 cubic feet area. Nursery to be sealed properly. Switch off the AC and seal AC duct. Take desired amount of Formalin and water in the fumigation machine and switch on.	Nursery fumigation
ECHOSHIELD (Complex formulation of stabilized hydrogen peroxide 11% w/v with 0.01% w/v silver nitrate solution	Make 20% solution by adding 200ml in 800ml water for 1000cu ft space. Fogging duration may be 20 min at the lowest settings. Fogging machine mount ed at 2 ft height and the angle of fogger being 45°, AC is put on after 1 hr of fogging. Tae 250ml in 5 litre solution and make 5%, mop liberally on all surfaces, walls and floor.	Aerial Disinfection Terminal cleaning (5%)

G. Surveillance :

Surveillance is at the heart of Infection prevention and control. Surveillance in hospital epidemiology and infection control is the process of identifying rates of HAIs, rates of infection or colonization with epidemiologically important organisms (e.g., MRSA, VRE, and *Legionella*), and rates of relevant processes of care such as compliance with hand hygiene. Surveillance can be used to establish baseline infection rates, detect outbreaks, convince clinicians and administrators of potential problems, affect hospital policy, assess the impact of interventions, guide antimicrobial stewardship practices, conduct research, reduce HAI rates, and make comparisons of rates and practices within and between hospitals

Microbiological surveillance of air, water, NICU surfaces can give us a targeted idea of NICU flora and its resistance and guide our antimicrobial policies accordingly. Surveillance of invasive procedures and its consequent courses, antibiotic use, occupational exposures together helps in raising awareness of the problem and thus decreases the infection rates further.

H. Infection control team:

The basic structure of a hospital epidemiology and infection control program includes either a trained infection control professional or a hospital epidemiologist in charge of the program, surveillance personnel, secretarial staff, and computer support personnel for the management and analysis of data. Microbiology laboratory support is crucial to the functioning of an infection control program. Each infection control and prevention program should meet regularly with the infection control committee, and the committee should report to the medical board or medical advisory committee. Roles of the infection control committee include (i) reviewing surveillance data and drafting intervention plans where necessary, (ii) formulating and approving infection control policies, (iii) reviewing outbreaks and formulating a response, (iv) approving the yearly goals and objectives of the infection control program, (v) developing policy regarding public reporting, and (vi) advising the medical and senior administration of the facility. The infection control committee is truly the voice of the infection control and prevention program within the health care facility

Management of Outbreak:

All staff should be vigilant and report to the Infection control team as soon as outbreak is suspected. Having an agreed outbreak plan in place is the best method for ensuring uniformity and effectiveness of response. When a cluster of cases occurs, the hospital Infection control team should conduct an assessment on the risk of possible outbreak and document the findings. If an outbreak is noted, it should assess its extent and implications, activate the hospital outbreak control plan.

Steps involved in Outbreak of Infection:

1. Developing a case definition , identifying the site, pathogen and affected population
2. Notification of the appropriate departments and personnel
3. Search additional cases, microbiological investigations and develop epidemic curve and hypothesis. Hypothesis testing by reviewing other microbiological, epidemiological cases.
4. Specific control measures & monitoring further cases and effectiveness of control measures. Report should be prepared for presentation to the ICC, departments involved in the outbreak, administration.

Conclusion:

As medical care has become more complex, antimicrobial resistance and HAIs have increased, as have their attributable morbidity and mortality and further have an implication on the total duration of hospital stay and finances. Evidence supports proactive strategies to prevent health care–associated infections in the NICU. An infection control programme that includes active surveillance and strict adherence to hand disinfection

policies is found to be effective in controlling NICU-acquired infections and colonisations.

Suggested Reading:

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Impact of Maternal Perinatal Infections on the newborn

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Maternal infections during pregnancy can present with vague and non-specific complaints such as malaise, aches and pains and headache. In pregnant women, they cannot be dismissed as trivial as they may be in others. May times, vertically transmissible infections may be asymptomatic. Asymptomatic women screened for perinatal infections might turn up with an unexpectedly positive result. This often leaves the physician worried not only for the wellbeing of the fetus, but also about potential for litigation if things go wrong.

This article describes the practical approach to a few common perinatal infections – viral (cytomegalovirus, rubella and herpes), parasitic (toxoplasmosis) and spirochetal (syphilis). Cytomegalovirus (CMV)

CMV is the largest and most complex member of human herpesvirus family, and causes characteristic cytopathalogical changes in the infected cells, making them appear enlarged (cytomegalic) with intranuclear and intracytoplasmic inclusion bodies.

Epidemiology of maternal infections

Infections in immunocompetent adults are generally subclinical, while infections in immunocompromised adults such as those with acquired immunodeficiency syndrome (AIDS) can present with end organ disease of varying severity. The seroprevalence of CMV antibodies progressively increases with age rising from 36% in children between 6 and 11 years of age to 89% among 70 to 79 year old adults and is higher in underdeveloped nations. The incidence of congenital CMV closely parallels the seroprevalence of adult CMV.

Infected individuals continue to excrete the virus for as long as 6 months after primary infections and intermittently whenever there is reactivation of latent infection. Transmission occurs continuously in the population. Known sources of infection are urine, oropharyngeal secretions, cervical secretions, semen, milk, tears, blood and organ allografts.

Possible indications for antenatal testing in pregnant mothers include

1. Routine testing: In populations with high seroconversion rates – day care workers, parents with a child in day care centres etc.
2. History of illness suggestive of CMV disease – fever with atypical lymphocytosis which is "Monospot" negative
3. History of exposure to known CMV infected individual or blood product
4. Immunocompromised mother
5. Antenatal ultrasound abnormalities suggestive of CMV.

Maternal diagnosis of CMV infection

IgM for CMV- is 75% sensitive and 75% specific for the diagnosis of CMV infection. False positive results can occur due to herpes infections, automimmune disorders and sometimes, pregnancy itself. A positive IgM, along with IgG seroconversion within the next 2-4 weeks, especially low avidity antibodies indicates probable recent infection.

Management of primary maternal CMV infection

There is no effective maternal treatment to prevent transmission to the fetus. Fetal diagnosis may be attempted by:

1. Serial fetal ultrasounds: Findings such as microcephaly, intracranial calcifications, hydrops, oligo or polyhydramnios, pseudomeconium ileus, intrauterine growth restriction and pleural/ pericardial effusions are helpful although sensitivity is only 30-50%.

2. Invasive tests – Amniocentesis for CMV polymerase chain reaction (PCR) is 45% sensitive if taken before 20 weeks and 80-100% sensitive if done beyond 20 weeks. The sensitivity increases if performed ⩾ 6 weeks of maternal infection. Specificity approaches 100%. Positive results do not indicate the extent of fetal damage, whereas quantitative CMV PCR or viral load may correlate better with severity of fetal infection. Viral culture for CMV performs poorly with sensitivity of around 56% even when performed beyond 20 weeks.

Termination is an option by informed choice and at present, more data is required before active recommendations can evolve.

Neonatal CMV infection

There are 2 possible types of CMV disease differentiated based on the routes of transmission:

1. Congenital infection: CMV is the leading cause of congenital infections with an incidence of 0.3 to 2% of all live births. In contrast to congenital rubella and toxoplasmosis which occur only as a result of primary infection in the mother, CMV infections can result from primary as well as non-primary infections which may be due to reactivation or re-infection. Risk of transmission of congenital CMV from mother to the fetus is summarised in Fig. 1. Risk of transmission remains elevated upto 4 years after primary CMV infection in the mother. Clinical features of congenital CMV are summarised in Panel 1.
2. Perinatal infections: Perinatally acquired CMV infection may occur from (i) intrapartum exposure to the virus within the maternal genital tract, (ii) postnatal exposure to infected breast milk, (iii) infected blood or blood products, or (iv) nosocomially through urine or saliva. Typically, this requires exclusion of congenital CMV infection by demonstrating absence of viral excretion in the first 2 weeks. Almost all term healthy infants who acquire infection perinatally remain asymptomatic, with a negligible risk of neurodevelopmental sequelae, although hearing loss can still occur. Preterm and sick infants with perinatal CMV, especially post transfusion CMV can develop respiratory distress, pallor, purpurae and hepatosplenomegaly. Risk of mortality is 20%.

CMV has been associated with pneumonitis occurring in infants <4 months old presenting with features similar to afebrile/ atypical pneumonia. Diagnosis of CMV infection requires viral isolation by culture of molecular techniques like PCR (Table 1).

Treatment and Prevention

1. Pharmacotherapy: The two drugs currently licensed for use in CMV infection are ganciclovir and foscarnet. Intravenous ganciclovir at a dose of 6 mg/kg/dose has been given twice daily for 6 weeks in the Collaborative Antiviral Study Group (CASG) in neonates with symptomatic congenital CMV involving neurological signs. Treatment resulted in significant improvement in hearing. The only significant adverse effect was neutropenia. Treatment outside this indication remains controversial. Oral valganciclovir has been tried for 6 months in the place of IV ganciclovir.
2. Intravenous immunoglobulin to pregnant women with primary CMV infection to prevent transmission to foetuses has been ineffective.

Prevention:

- The Centers for Disease Control and Prevention recommends that pregnant women practise hand-washing with soap and water after contact with diapers or oral secretions
- In women of extremely premature infants known to be CMV positive, pasteurizing breast milk at 220°C or freezing breast milk, may reduce the titer of CMV although it will not eliminate active virus
- Transfusions in vulnerable neonates should

be performed with blood/blood products from CMV-seronegative donors or filtered, leukoreduced products.

- Rubella (German measles)

Rubella virus is a human-specific RNA virus of the Togavirus family.It causes mild self limiting illness in adults, but effects of fetal infections can be devastating. Fig. 2 describes the approach to rubella infection during pregnancy.

Management of an infected neonate

- No specific management is available
- Breast feeding is not contraindicated
- Ensure ophthalmologic, cardiac and hearing evaluations at birth
- Regular (3-6 monthly) assessments in the first year are recommended to detect hearing impairment, neurological defects, epilepsy, cataract, retinopathy, tooth defects and failure to thrive
- Infected infants are infectious for at least 12 months and due precautions need to be taken by pregnant health care providers
- Infant should be isolated while in hospital

Herpes simplex virus (HSV)

HSV is a double-stranded, enveloped DNA virus with two virologically distinct types: types 1 and 2. By adulthood, nearly 80% of the population is seropositive with HSV type 1, the cause of recurrent orolabial disease, and 40% with HSV-2, the predominant cause of recurrent genital disease, and thereby, neonatal herpes infection.[3] Highest risk of transmission is seen with mothers with *primary HSV-2 disease* during pregnancy in mothers with no prior infection (50%), followed by newly acquired HSV-2 in women already infected with HSV-1or *initial non-primary infection*(33%) and least with recurrent HSV-2 in a woman with prior infection (3%). Importantly, mo*st mothers of neonates with HSV infection are asympto-matic shedders.*

Management of maternal Genital Herpes

Delivery by Caesarean section is recommended

- In confirmed primary HSV infection in a mother who is previously unexposed to HSV and presenting late in pregnancy/ labour (also consider suppressive dose of acyclovir)
- In confirmed primary HSV infection diagnosed in early pregnancy with failure to seroconvert later in pregnancy
- Active genital lesions on per speculum examination even in the presence of prior genital HSV or recurrent disease

Caesarean section adds no benefit if duration of rupture of membranes is more than 6 hours.

Manifestations of neonatal HSV

Morbidity due to HSV can be well correlated with 3 patterns of neonatal disease

1. Skin, eye, and mouth infection: Nearly 50% of neonatal HSV can be localised to skin, conjunctiva and mucocutaneous membranes with vesicles appearing between days 6 to 9. Neurological sequelae may occur in 10% of infants.
2. Neurological disease: Nearly one-third of neonatal HSV presents with neurological symptoms such as lethargy, seizures, temperature instability and hypotonia between days 10 to 14 of life. Nearly 15% of these neonates die and two-thirds may develop neurological sequelae.
3. Disseminated disease: Nearly 22% of neonates with HSV have fulminant disease presenting within the first week with seizures, shock, respiratory distress, disseminated intravascular coagulation (DIC), pneumonitis and multi-organ failure. Mortality is 57%.

Management of neonatal HSV is detailed in Fig. 3. Fig. 4 describes an approach to a neonate with maternal perinatal varicella infection.

Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoan which exists in 3 infective forms-tachyzoites, bradyzoites and cysts.[3] Seroprevalence during pregnancy is variable and ranges from 3% to 40%. Antenatal

screening may be performed (a) routinely as in some countries (eg. Australia) where there should be an appropriate management plan in place, or (b) in the presence of maternal acute toxoplasmosis like illness in the form of malaise, fever and lymphadenopathy (cervical). Diagnosis of recent acute maternal toxoplasmosis is described in Panel 2.

Fetal risk assessment with maternal toxoplasmosis

Management of maternal toxoplasmosis is summarised in Fig. 5. Importantly risk of fetal infection increases from 5-15% in first trimester to nearly 90% at term. The fetal disease severity, however, is inversely proportional to gestational age with most fetuses affected in the first trimester having severe central nervous system (CNS) and ophthalmologic disease while most foetuses infected in the later stages have subclinical disease only.

Maternal treatment

1. Spiramycin, a macrolide antibiotic, at a dose of 1 gram 8th hourly, is recommended for treating maternal infections before 18 weeks' gestation until term if the fetus is uninfected by amniotic fluid PCR performed at 18 weeks. Spiramycin reduces or delays vertical transmision to the fetus through high placental levels (3-5 times maternal serum levels).
2. Pyrimethamine- sulfadiazine can be used if maternal infection was diagnosed beyond 18 weeks upto term gestation as pyrimethamine interferes with organogenesis. Leucovorin 10-20 mg daily is to be continued till 1 week after stopping pyrimethamine.

Diagnosis and management of neonatal toxoplasmosis

Evaluation of a neonate exposed to maternal toxoplasmosis has been detailed in Fig. 6. The classic triad of hydrocephalus, Chorioretinitis, and intracranial calcifications. Yet the disease can present as a clinical spectrum with neurological signs such as microcephaly or bulging fontanelle, increased head circumference, seizures, Opisthotonus, paralysis, swallowing difficulties, encephalitis and deafness or ophthalmic signs such as Chorioretinitis, retinal detachment, optic atrophy, iritis, scleritis, uveitis, and vitreitis.
Toxoplasmosis is known to cause focal necrotizing retinitis, with yellow-white cotton-like patches and extensive exudates which may prevent visualization of the fundus, usually bilateral. Macular lesions are more common than peripheral. Untreated chorioretinitis is associated with 100% risk of scarring.[3] Other manifestations include hepatosplenomegaly, conjugated hyperbilirubinemia, thrombocytopenia, lymphadenopathy and myocarditis. Postnatal management of infant at risk of congenital toxoplasmosis is as follows (Fig. 6)

Treatment of neonatal toxoplasmosis

Therapy is recommended, regardless of symptoms, to prevent the high incidence of sequelae, resolve acute symptoms, and improve outcomes. Drugs used are:

1. Pyrimethamine (1 mg/kg every 12 hours for 2 days, then daily for until 2 to 6 months of age, then 3 times weekly until 1 year of age), and sulfadiazine (50 mg/kg every 12 hours until 1 year of age) act synergistically
2. Alternative medications include clindamycin, azithromycin, and atovaquone. Other less frequent side effects include gastrointestinal distress, convulsions, and tremor.
3. Prednisone (0.5 mg/kg every 12 hours) is recommended for active CNS disease (CSF protein exceeding 1 g/dL) or active chorioretinitis.

Monitoring during treatment:

Pyrimethamine (a dihydrofolate reductase inhibitor) can induce bone marrow suppression; patients should be monitored by a

complete blood count, differential, and platelet count twice weekly. Neutropenia is more frequent than megaloblastic anemia or thrombocytopenia. Folinic acid (10 mg 3 times weekly) until 1 week after pyrimethamine stopped helps prevent bone marrow suppression.

Syphilis

Syphilis is a sexually transmitted illness causes by Treponema pallidum. The risk of transmission to the fetus correlates largely with the duration of maternal infection—the more recent the maternal infection, the more likely is the transmission to the fetus. The likelihood of transmission from an untreated woman with primary or secondary syphilis is nearly 100%. Pregnant women with a reactive non-treponemal test (positive rapid plasma reagin (RPR) test or the venereal disease research laboratory (VDRL) test) confirmed by a reactive treponemal test such as fluorescent treponemal antibody absorption test (FTA-Abs) or Treponema pallidum particle agglutination (TP-PA) should be treated with benzathine penicillin and followed up to document reducing titres.

Evaluation of a neonate exposed to maternal syphilis

- Complete physical examination- rash, mucosal lesions, nasal discharge (snuffles), bone tenderness, hepato-splenomegaly, hydrops, pseudoparalysis, jaundice, anemia
- Nasal secretions for dark field microscopy.
- Serum quantitative non-treponemal test (VDRL or RPR)
- Placenta or umbilical cord for fluorescent antibody staining and histopathology ± PCR

If any abnormality found in any of the above, then one has to complete evaluation with long bone x-rays and lumbar puncture. Late manifestations (keratitis, deafness, Hutchinson teeth) may be delayed for several years and regular assessment may be warranted.

Table 2 summarises treatment of a neonate born to mother with syphilis.

Perinatal infections in the mother pose a medical as well as ethical challenge to the physician as we still do not have answers to all questions. Knowledge about risk of vertical transmission and severity of perinatal infections, diagnosis and treatment have important implications in preventing neonatal morbidity.

Suggested Reading

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Panel 1: Clinical features of symptomatic congenital CMV

Clinical features of congenital CMV

Neurological: Microcephaly* (35-50%), seizures (10%), chorioretinitis (10-20%), intracranial (periventricular calcification)*, sensorineural hearing loss (25-50%), elevated CSF protein >120 mg/dL (45-50%), risk of neurological sequelae ⩽ 70%

Abdomen: Hepato-splenomegaly (40-60%), jaundice (40-65%), abdominal calcification, ascites, pseudo meconium ileus

Respiratory: Pneumonia (<1%), pleural effusions

Cutaneous: Purpuric rash (50-75%), "blueberry muffin spots" due to extramedullary hematopoiesis

Hematological: Thrombocytopenia (50%), hemolytic anemia (10-50%)

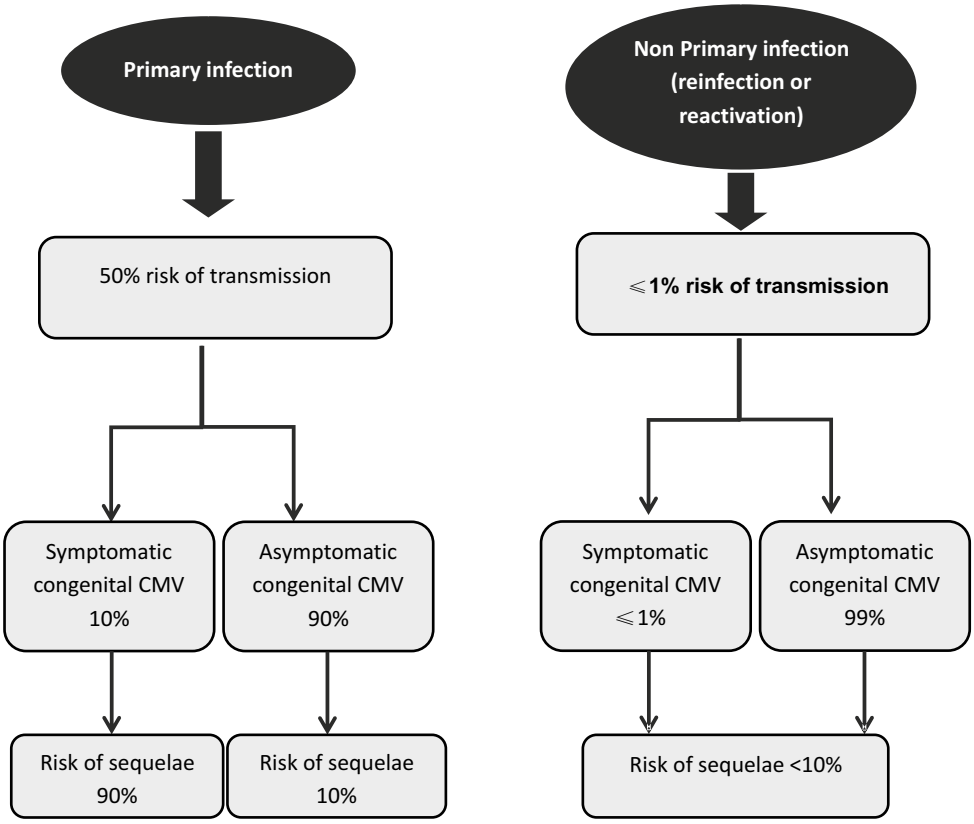
Others: Intrauterine growth retardation /IUGR* (50%), hydrops fetalis, oligo or polyhydramnios, pleural or pericardial effusions, dental abnormalities (30%). Overall risk of mortality is 30%.

Transmission of CMV is distributed equally in all 3 trimesters. Risk of serious neurological sequelae and features highlighted * are more likely with maternal infection in first trimester; Visceral manifestations like hepatitis, pneumonitis and thrombocytopenia are more likely with later infections. Neurological sequelae occur in the form of mental retardation, sensorineural hearing loss and chorioretinitis and more common with symptomatic infections following primary infection

Non Primary infection (reinfection or reactivation)

Fig. 1: Congenital CMV: Fetal transmission risk assessment

Fig. 1: Congenital CMV: Fetal transmission risk assessment

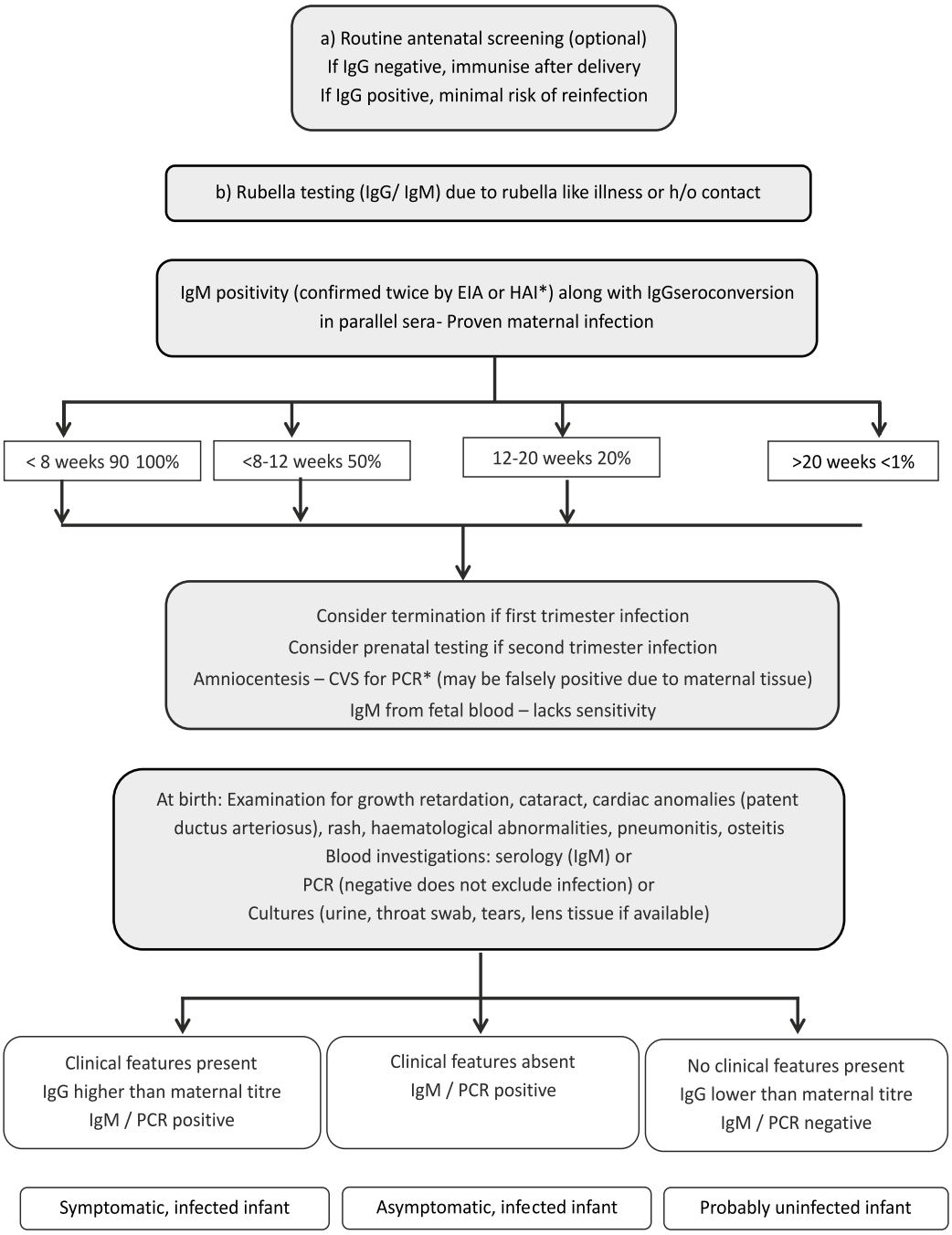


CMV- Cytomegalovirus

Table 1: Laboratory diagnosis of CMV infection in the neonate

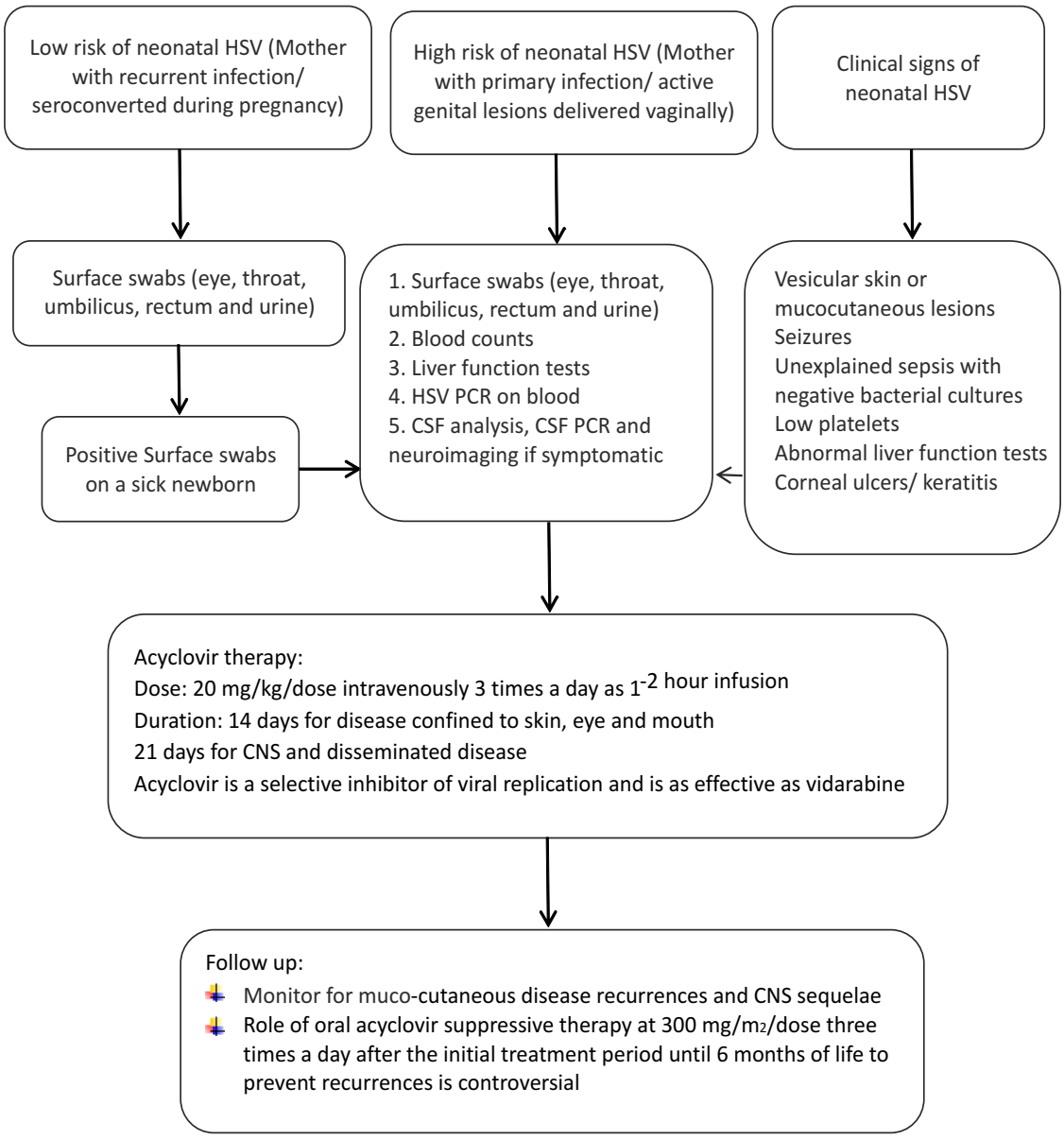
Laboratory Investigations	Advantage	Disadvantage
Detection of Virus or viral antigen		
Standard tube culture	Standard reference method; Can be combined with immune-fluorescence for rapid results	Takes 2-4 weeks for reports to come, not suitable for screening
Shell vial assay	Rapid (24-72 hours), sensitive and commercially available	Expensive
CMV antigenemia	Rapid, assay for pp65 from lysed neutrophils is simple, can be used for follow up	Negative test does not rule out infection
Nucleic acid amplification methods		
Polymerase chain reaction (PCR) amplification	Simple and can be used to screen large numbers; Preferred samples are urine, saliva and blood – buffy coat (White cells); Sensitivity 89% and specificity 95.8%	Has not been sensitive as screening test when dried blood spot is used
DNA hybridization assay	Sensitive	Complicated; Needs radio-labelled probe
Serology		
CMV- IgM assay	Simple and widely used	Low sensitivity, unreliable for screening and diagnosis

Fig. 2: Diagnosis and Management of Rubella infection in mother and neonate



**EIA- Enzyme immunoassay; HAI- Hemagglutination inhibition assay; PCR- Polymerase chain reaction; CVS- Chorionic villus sampling*

Fig. 3: Management of neonatal Herpes simplex virus (HSV) infections



CSF- Cerebrospinal fluid; PCR- Polymerase chain reaction; CNS- Central nervous system

Fig. 4: Management of neonate born to mother with perinatal varicella

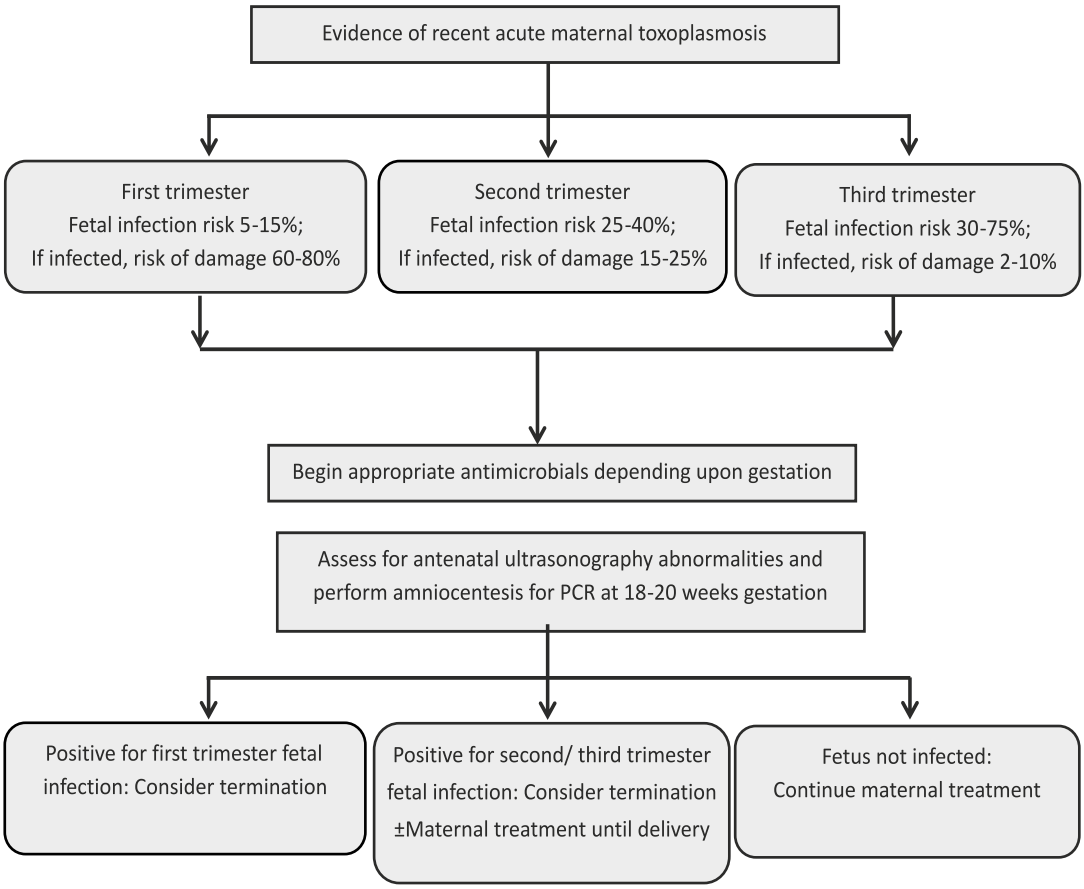
Time with respect to birth of baby (days)														
-8	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7
The infant would have protective antibodies			The infant would not have protective antibodies and likelihood of severe neonatal disease is high (mortality 30%)							The infant would not have protective antibodies but the likelihood of severe neonatal disease is low				
Do not separate baby from mother. Isolate dyad from other infants.			Separate mother and baby until maternal lesions have dried up and crusted. If baby also develops rash then baby to stay with mother. Mother and/or baby with active vesicles should be isolated from other mothers and babies.							Separate mother and baby until maternal lesions have dried up and crusted. If baby also develops rash then baby to stay with mother. Mother and/or baby with active vesicles should be isolated from other mothers and babies.				
Acyclovir60 mg/kg divided every 8 hours only if baby develops rash Continue breastfeeding			VZIG* within 72 hours of exposure Treatment of neonate - acyclovir60 mg/kg divided every 8 hours intravenously for 14 days *(No need of VZIG if mother has zoster)* Give expressed breast milk even if mother infant dyad is separated. Breast fee ding allowed once mother is noninfectious.							Acyclovir (same dose as in the previous category) if the infant develops varicella				

*VZIG(Varicella zoster immunoglobulin) to be given as early as possible to allneonates exposed to varicella in the absence of maternal history of prior varicella infection or neonates <1 kg or <28 weeks even in the presence of maternal history of prior varicella; Dose of VZIG: 125 IUintramuscularly; If VZIG unavailable give IVIG 400 mg/kg

Panel 2: Diagnosis of recent acute maternal toxoplasmosis

Recent acute maternal toxoplasmosis (within 3 months) is suggested by a combination of :
Repeatedly positive IgM (gap of 4 weeks) or highly positive IgM with either
Rising IgG or low IgG avidity or Positive IgA antibodies

Fig. 5: Management of maternal toxoplasmosis



VDRL- Venereal Disease Research Laboratory test; CSF- cerebrospinal fluid, IV- intravenous, IM- intramuscular

Maternal infection with toxoplasma

Perform histopathology of placenta
Evaluate the newborn:

- Physical examination of newborn
- Eye examination for chorioretinitis
- CT brain for calcifications, hydrocephalus and cerebral atrophy
- Serology: IgM, IgG titre (if significantly more than mother's – positive)
- Other tests like CSF examination

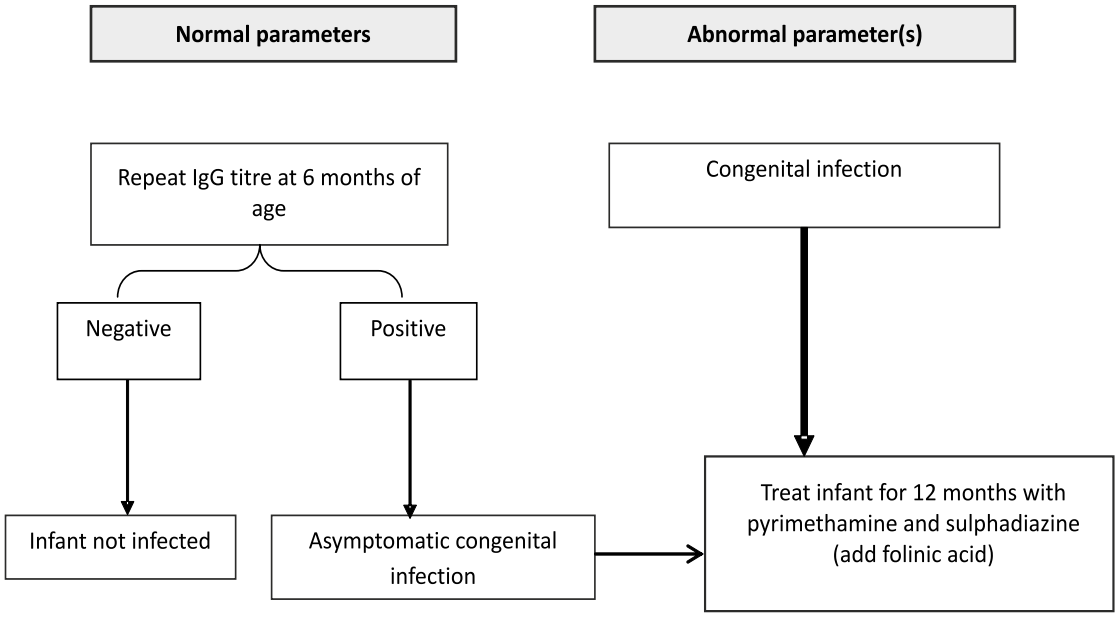


Table 2: Management of a neonate born to a mother with syphilis

1	Proven or highly probable syphilis - Abnormal physical examination - Neonatal non treponemal titre that is fourfold higher than the mother's - Positive dark field or fluorescent antibody test of body fluid	Clinical examination and CSF analysis with CSF VDRL Complete blood counts with platelets Long bone radiographs and chest Radiograph Liver function tests Cranial ultrasound Hearing and eye evaluation **Treatment:** Aqueous crystalline penicillin G 100,000 to 150,000 units/kg/day IV for 10 days OR Procaine penicillin 50000 units/Kg/Dose IM once daily for 10 days
2	Infants who have normal examination and VDRL titre same or less than fourfold the maternal titre and one of the following- - Maternal treatment not given - Maternal treatment with non-penicillin drug - Maternal treatment administered <4 weeks before delivery	Clinical examination and CSF analysis with CSF VDRL Complete blood counts with platelets Long bone radiographs **Treatment:** Aqueous crystalline penicillin G 100,000 to 150,000 units/kg/day IV for 10 days OR Procaine penicillin 50000 units/Kg/Dose IM once daily for 10 days If evaluation is normal and follow up certain, a single dose of benzathine penicillin G 50,000 units/kg IM may be substituted for the full 10-day course
3	Infants with normal clinical examination VDRL titre same or less than fourfold the maternal titre, AND - Maternal treatment with penicillin 4 weeks prior to delivery - No evidence of maternal infection or relapse	No further evaluation Treatment: Single dose of Benzathinepencillin of 50000 units/kg Intramuscularly
4	Infants with normal clinical examination VDRL titre same or less than fourfold the maternal titre, AND - Maternal treatment with penicillin 4 weeks prior to delivery - ***Low maternal VDRL titre at delivery*** - No evidence of maternal infection or relapse	No further evaluation or treatment

VDRL- Venereal Disease Research Laboratory test; CSF- cerebrospinal fluid, IV- intravenous, IM- intramuscular

Neurodevelopmental Outcomes of Neonatal Infections

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Introduction:
Neonatal sepsis is a major cause of morbidity and mortality in neonatal intensive care units. It is most common in the smallest and most premature infants and the incidence is therefore inversely proportional to gestational age and birthweight. While the mortality rate of neonatal sepsis has decreased, the question of the long-term consequences of neonatal sepsis has become more important. In addition; various viral, bacterial and protozoan transplacental infections causes permanent central nervous system (CNS) damage to the fetus.

Types of neonatal infections having neurological sequelae
Bacterial- Sepsis, Meningitis.
Transplacental infections-TORCH (toxoplasmosis, rubella, cytomegalovirus [CMV], herpes simplex, and syphilis), HIV, varicella-zoster virus, and lymphocytic choriomeningitis virus.

Fungal Infections- Candidiasis.

Pathogenesis of Neurological sequelae in various infections

Neonatal Sepsis
Neonatal Sepsis potentially affects long-term neurodevelopmental outcomes, either by directly affecting the central nervous system or by eliciting a sustained systemic inflammatory injury. The mechanisms mediating brain injury in preterm infants with sepsis are postulated to be injury to oligodendroglial precursor cells, the major cellular target in the pathogenesis of white matter injury. White matter is important in neural networking and connectivity. They are particularly vulnerable to free radicals that are generated in response to ischemia-reperfusion.

Candida infection
Candida involvement of the central nervous system is known to include meningitis, diffuse cerebral abscesses and venticulitis with or without obstructive hydrocephalus.

TORCH infections
The pathogenetic mechanisms of these infections are unique. The fetus is especially susceptible to infection during the first trimester and the perinatal period. Early in pregnancy the most complex events in embryogenesis take place, making the CNS and sensory organs such as the eyes and ears vulnerable.

Types of adverse neurodevelopmental outcomes associated with neonatal sepsis

I Motor impairment
II Cognitive delay
III Visual impairment
IV Auditory impairment
V Long-term growth impairment

Sequelae of Neonatal Infections
During follow-up, children who had suffered neonatal sepsis were more likely to develop cerebral palsy, cognitive delay or combined psychomotor delay. The diagnosis of neonatal sepsis either bacterial or fungal in very low birthweight (VLBW) infants; is associated with an increased risk of one or more long-term Neuromotor impairments including higher association with cerebral palsy, lower scores on cognitive scales and deafness.

Candida infection is associated with the

increased incidence of advanced stages of retinopathy of prematurity in extremely low birth weight (ELBW) infants, requiring more surgical interventions.

The incidence of hearing impairment and seizures after neonatal meningitis is high.

The majority of the studies focus on very preterm and, or VLBW infants. Data on the outcome of sepsis in near term infants is sparse.

Infection	Developmental delay	Epilepsy	Eye	Hearing	Behaviour	Growth impairment
Toxoplasmosis	+	+	Chorioretinitis			+ hydrocephalus
Rubella	+	+	Cataract Retinopathy, Microopthalmia, Glaucoma, Severe myopia	Sensorineural hearing loss	Autistic features	+ Microcephaly
CMV	+	+	Chorioretinitis	Sensorineural hearing loss		+ Micro or macrocephaly,
Varicella	+	+	Chorioretinitis Microopthalmia cataract			+ Microcephaly

Follow up of babies with neonatal sepsis

Babies who have suffered neonatal sepsis are classified as moderate risk for adverse neurodevelopmental outcomes whereas babies having meningitis, neonatal shock needing inotropes and vasopressor support are classified as high risk babies. These babies are hence followed up in a high risk clinic.

Clinical Manifestations:

I **Motor impairment**: This could be manifest as

1. Delay in acquisition of motor milestones
2. Abnormal Neurology on Amiel Tison on follow up visits- i.e. abnormal head size, tone, persistent primitive reflexes, delayed acquisition of postural reflexes, brisk jerks or abnormal movements.
3. Motor DQ <70 on the motor scale of the DASII (Developmental Scale for Indian Infants), the gold standard for diagnosing developmental delay.
4. Cerebral palsy - A diagnosis of cerebral palsy is generally evident if the neurological signs persist by 18-24 months.
5. Difficulties with eye hand coordination, Poor oromotor tone causing drooling and issues with speech clarity.

Intervention Babies with tone abnormalities identified are started on intervention, investigated accordingly and followed diligently.

II **Cognitive Delay:** This could manifest as

1. Delayed acquisition of cognitive, language and motor milestones.
2. Child failing developmental screens routinely administered.
3. Mental DQ<70 DASII (Developmental Scale for Indian Infants), the gold standard for diagnosing develop-mental delay.
4. Behaviour issues.

Intervention: On early identification of cognitive delay, an individualized stimulation program with necessary therapies is initiated with parents in the loop.

III Visual Impairment This could clinically manifest as poor visual fixing and following, no social smile, nystagmus, no reaching for objects or holding objects too close.

Intervention Preterm babies are screened for ROP as per protocol. A child with possible cortical visual impairment is investigated by an ophthalmic evaluation, MRI brain and VEP and intervention is planned accordingly.

IV Hearing Impairment: This manifests clinically as no startle to sound, no turn to sound, delayed expressive language or behaviour issues like hyperactivity**.**

Intervention A BERA is done as part of high risk follow up at corrected 3 months of age. In case of sensorineural hearing loss, early intervention with intensive speech stimulation is initiated early.

Hearing loss secondary to congenital CMV is progressive in childhood so a diligent follow up for the same is warranted.

V Growth impairment:
A regular follow up of child's growth parameters would help identify deviations earlier.

Evidence:
Sepsis in VLBW infants was associated with an increased risk of one or more long-term neurodevelopmental impairments (odds ratio (OR) 2.09; 95% confidence interval (CI) 1.65 to 2.65) including cerebral palsy (CP; OR 2.09; 95% CI 1.78 to 2.45). Thus sepsis is associated with a strong two-fold rise in incidence of cerebral palsy in VLBW babies.

Summary

1. Neurodevelopmental impairment after neonatal sepsis reveals a higher association with cerebral palsy, lower scores on cognitive scales and deafness.
2. TORCH infection of the fetus may be seen at birth, soon afterward, or not until years later. The infected newborn infant may display growth retardation, developmental anomalies and neurosensory abnormalities that need active early intervention.
3. Newborns with neonatal infection are followed up in the high risk clinic. The aim is early detection and early intervention.
4. Infection control is another neuroprotective practice that has potential to improve outcomes in vulnerable neonates.
5. Early intervention helps in better functional outcomes.

Further reading

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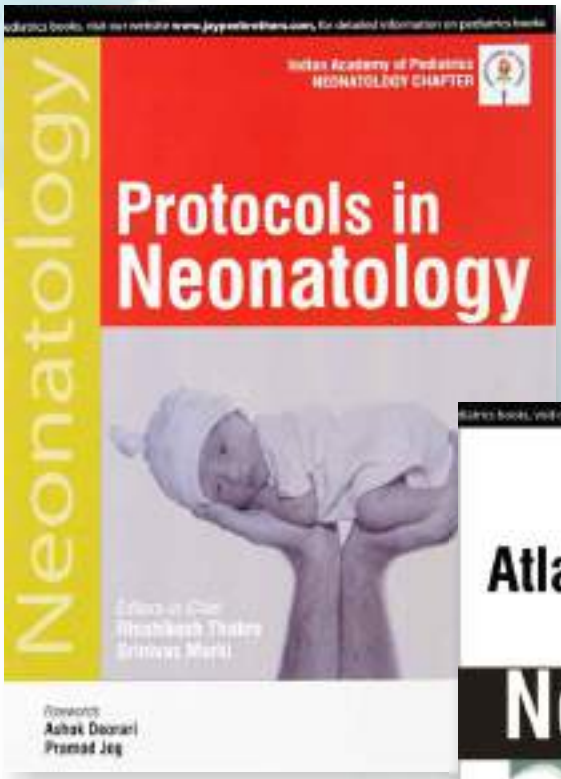

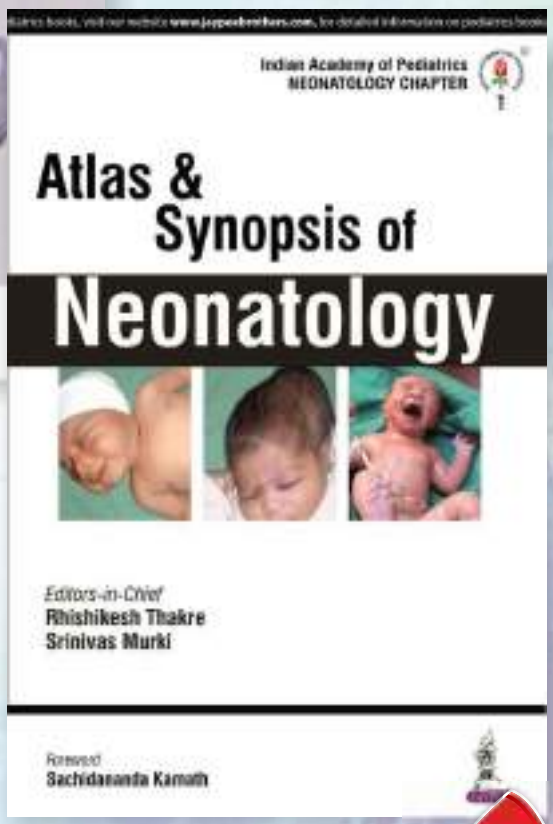

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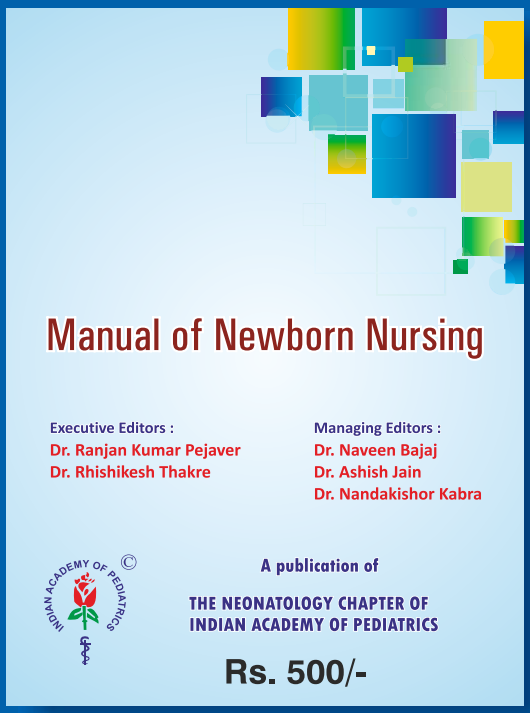

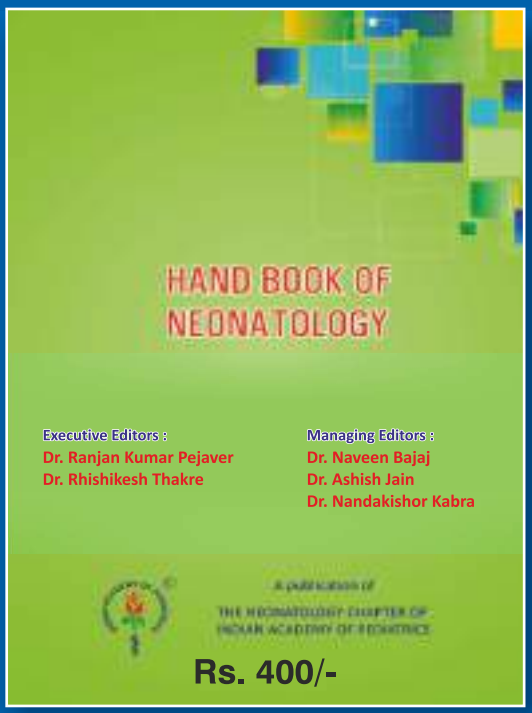

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