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CONTENTS

EDITORIAL

Newborn care in India is steadily but surely improving. There is lot of excitement whenever we are able to save a smaller and sicker newborn infant. Lot of young pediatricians are showing a keen interest in undergoing fellowship training in Neonatology.

In this issue of bulleting we bring you diverse topics in the field of Neonatology. Perinatal CMV infections are currently under-diagnosed and under-reported. Dr Amrit Jeevan and Dr Hari Balasubramanian have covered topic of perinatal CMV with extensive and exhaustive review of literature.

When a premature infant survives all odds and later develops cerebral palsy it is disturbing. Antenatally magnesium sulphate should be administered to pregnant women < 32 weeks of gestation at risk of preterm labor. Dr Garg and Dr Dash in their article have provided the practical details of role of Magnesium Sulphate in neuro-protection.

NEC is a devastating complication that occurs in preterm infants. Prophylactic uses of probiotics in preterm infants have been shown to decrease incidence of NEC. Dr Garg and Dr Ahmed have written practical guidelines for use of probiotics in preterm infants.

Few landmark therapies that have improved outcomes of newborn infants include use of antenatal steroids, better physiological ventilators, surfactant replacement therapy and inhaled nitric oxide (iNO) therapy. The discovery of iNO as an endogenous biological mediator and its biological roles has been one of the most significant developments in medicine. Many units in India now have capability to administer nitric oxide. In their article, Dr Kabra and Dr Jasani have reviewed systematic reviews of inhaled nitric oxide. A summary of indications and contraindications has been provided.

Research is an integral part of medical practice. A working knowledge of statistics is required to understand and conduct research. We have tried to summarize it in the article: Everything a clinician needs to know about Statistics and Clinical Epidemiology in a nutshell.

With greetings for upcoming festive season of Vijayadashmi and Deepvali.

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Cytomegalovirus Infection in Newborns

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Introduction

Congenital and perinatal cytomegalovirus (CMV) infection can lead to serious morbidities in newborns. Despite its frequency and disabling consequences there is very little awareness about it. This lack in public knowledge is a major barrier towards disease control. Fortunately, fetal infection is preventable through careful hygienic practices like hand washing. This article will highlight important aspects of congenital and perinatally acquired CMV infection.

Incidence

Cytomegalovirus is a ubiquitous virus infecting human beings. The prevalence in adults increases with increasing age in the population. In one study 90 percent of the US population was infected by the eighth decade of life [1]. In a cohort of pregnant women in London sero-positivity rate was 58% indicating previous exposure [2]. This rate was as high as 98 % in African countries [3]. Once acquired the virus remains latent in the cells of myeloid lineage, primarily the monocytes and lymphocytes lifelong [4,5]. The incidence of congenital CMV, worldwide is estimated to be 0.6 -0.7 % making it most commonly acquired congenital viral infection [6]. In immuno-competent individuals, including infants, CMV infection usually goes unnoticed as it is usually asymptomatic or the symptoms may be mild and nonspecific. However, in newborns it can result in more long term neurodevelopmental morbidity than any other perinatally acquired infection. Most commonly observed neurological sequela is sensorineural hearing loss (SNHL), indeed CMV infection is estimated to be the leading non hereditary cause of SNHL [7,8].

Transmission

Vertical transmission of CMV infection can occur through three routes: intrauterine, intrapartum and postnatal. Intrauterine transmission is through placental route. Risk of transmission is more when mother acquires primary infection during pregnancy. Mothers of children who are shedding CMV are ten times more likely to seroconvert during pregnancy. Children in day-care centres represent an important reservoir of CMV. Approximately 1-4% of pregnant mothers acquire primary infection and 30-40% transmit it to the fetus whereas 10-30% of pregnant women have reactivation of primary infection or get infected with a new strain. Risk of transmission to the fetus is however only 1-3% in these seropositive pregnant women [3,9,10,11,12]. Symptoms occur approximately in 12.7% of newborns at birth [6]. Of these symptomatic babies 40-58% go on to develop sequelae [6] which include SNHL, visual deficits, seizure disorder, mental retardation, cerebral palsy and neurodevelopmental delay [13,14,15]. Approximately 13.5% of asymptomatic newborns may also go on to develop neurodevelopmental injury which frequently manifests as hearing loss [6]. Hearing loss may not be detectable at birth only to be later detected in childhood, is often progressive and may be unilateral or bilateral [16,17,18,19,20]. Audiological follow up in childhood until six years of age is therefore recommended. Its progression is amenable to treatment.

Perinatally or postnatally CMV infection can be acquired from the birth canal, breast milk, blood products transfusion or direct contact with person with infected body fluids (e.g. Saliva, Urine). By swabbing babies at birth or

taking vaginal swabs from mother shortly after vaginal delivery to exclude perinatally acquired infection it has been shown that post natal infection is mostly transmitted through breast milk [21,22]. Universal use of leukocyte depleted blood or blood from sero-negative donors virtually eliminates transmission through this route[23]. This still may be a problem in developing world where leukocyte depletion is not being practised due to cost constraints as getting sero-negative donors is not always feasible given the high prevalence rate in general population. One way is to reserve multiple bags from a single donor if a neonate is expected to receive multiple transfusions.

The risk of transmission of virus through breast milk was known as early as 1960's but as the infection was mostly asymptomatic in term babies, no further research was undertaken. Breast milk has a cellular component and cell free component. Virus is present in cell free component, the whey portion, before it is detectable in the cell- containing fraction indicating that free virus is important in transmitting infection via breast milk [24,25]. For reasons unknown reactivation of virus in mammary glands seems to be through different mechanisms in contrast to other organs as virus is not detectable in other body fluids (urine, saliva) of mothers secreting virus in breast milk [26].

Post natal transmission through breast milk was found to be 37% in one study with 48% of infants becoming symptomatic[21] in contrast to 10% in an another other Japanese study[27]. This may be due to different feeding practices. No difference was found between transmitters and non- transmitters with respect to age, race, duration of lactation and duration of CMV excretion in milk in one study [28] although proportion of breast milk given as fresh breast milk in first 4 weeks of life was shown to be related to early appearance of virus in milk and acquisition of infection [21,29,30].

Of note there was a very significant correlation between birth weight and symptomatic transmission with a 100 grams decrease in birth weight being associated with an odds ratio for symptomatic infection of 1.39 (95% CI 1.02 to 1.9) in a study by Maschmann et.al.[30].

Nosocomial transmission and risk to female staffs in nursery

As transmission of CMV is by direct contact with infected body fluids (urine, saliva) and is preventable by practising hand washing in NICU, risk of transmission from one infant to other is virtually negligible if standard hygiene precautions are being followed in NICU's. Therefore there is no need to isolate the infected infant. Also, among the premature infants who had a stay of more than a month in NICU, 13% were found to be silent excretors of CMV [31]. Additionally female staffs working in pediatric clinics and day care nurseries do not seem to be at increased risk of contracting CMV infection as the sero-positivity rate were comparable to women whose occupation did not involve direct care of infants in one epidemiological study [31,32]. Nurses did not over represent when occupations of mothers were compared among 36 congenital CMV cases [32].

Prevention of transmission

Transmission through blood products transfusion is virtually eliminated by having sero-negative donors. If not feasible then leukocyte depleted blood product is recommended. Freeze thawing decreases CMV titres and infectivity by 90-100% which depends primarily on duration of freezing [33].Holder's pasteurization being used for processing during donor human milk banking efficiently eliminates CMV but at the cost of immunological properties of breast milk [34].

Diagnosis

Diagnosis of CMV infection depends on 1) isolation of virus, 2) detection of CMV IgM, 3) Detection of CMV antigen, 4) Identification of CMV DNA-PCR from body fluids.

Pregnant mothers can be diagnosed by sero-

conversion from immunoglobin G (IgG) - negative to IgG-positive status or by positive immunoglobin M (IgM) if confirmed with low-avidity IgG as IgM may remain positive for 6–9 months after the end of acute phase infection[35]. Diagnosis in fetal life can be made by positive viral culture or polymerase chain reaction from amniotic fluid. Diagnosis of congenital CMV is made by viral detection in body fluids (blood, urine or saliva) via PCR, culture, or antigen testing (pp65 antigen) within the first 3 weeks of life [36] as this is the minimum time taken for CMV to be detectable in urine after peripartum transmission. However, recent prospective studies using sequential testing of samples from various sites have shown that blood CMV DNA is positive 2 weeks before virus is detectable in the urine. If blood is being used for diagnosis, this 21-day cut-off should therefore be revised to 10 days [21]. CMV antibodies or viral DNA identified beyond this point makes congenital versus postnatally acquired infection difficult to distinguish. Antibody titers cannot reliably make the diagnosis as maternal CMV IgG crosses the placenta, and neonates mount weak IgM responses. The preferred specimens are saliva and urine as newborns shed high levels of the virus from these fluids. Saliva samples may be more easily obtained and have been shown to be as reliable as urine samples in diagnosing CMV, so some propose that saliva PCR should be considered the investigation of choice [37,38,39]. Real time PCR assays of both liquid and dried saliva samples had sensitivities of >97% and 99.9% respectively compared with saliva rapid culture. False positive results of both liquid and dried saliva are less than 0.03%. Saliva has been shown to be more sensitive in diagnosing congenital CMV than the use of dried Blood Spots. Obtaining saliva samples is easy, practical and they can be readily stored and transported to the laboratory. The high sensitivity and specificity of dried saliva PCR make this method of testing a readily applicable approach to accurately diagnose congenital CMV. Saliva specimens are also potentially a simple method to use in any future newborn screening programmes [40]. Therefore saliva PCR is highly sensitive and specific and should now be considered as the investigation of choice to detect congenital CMV.

In a large prospective study usefulness of dried blood spot (DBS) PCR as a universal screening tool for diagnosing congenital CMV was assessed [41]. It was seen that approximately two thirds of infections were missed. Hence although a positive DBS CMV PCR taken in the first 3 weeks of life confirms the diagnosis of congenital CMV, but a negative result cannot reliably exclude congenital CMV. DBS PCR now looks a poor screening test for the diagnosis of congenital CMV.

Once the diagnosis is confirmed, further laboratory tests, imaging, vision and hearing assessments are indicated.

Cranial ultrasound is a good screening tool, with subsequent MRI being recommended for definitive evaluation, particularly for infants with abnormal ultrasound examination, microcephaly, or neurological findings. A recent review elegantly summarized the pattern of neurodevelopmental injury as a function of timing of acquisition of brain infection in utero [42]. This review noted that lesions occurring prior to 18 weeks gestational age commonly include lissencephaly with thin cerebral cortex, cerebellar hypoplasia, ventriculomegaly, periventricular calcification, and delay in myelination. At 18 to 24 weeks, migrational abnormalities may occur, including polymicrogyria, schizencephaly, and periventricular cysts. Third trimester infections may be associated with central nervous system (CNS) lesions that may include delayed myelination, dysmyelination, calcification, and white matter disease.

Ophthalmologic assessment should be performed on all infants with congenital CMV infection. Ophthalmologic signs are seen in a large percentage of symptomatic infants and include chorioretinitis, optic atrophy, and cortical visual impairment [43]. Strabismus is

also a common long-term ophthalmologic complication [44].

Audiologic assessment should be performed on all infants with congenital CMV infection; as noted, SNHL may be absent at birth, and progressive in nature, and frequent evaluations are required throughout childhood to evaluate for the possibility of hearing deterioration [45]. At a minimum, audiologic assessment should be performed every 6 months for the first 3 years of life and annually thereafter. For children with severe-to-profound hearing loss caused by congenital CMV, cochlear implantation is a successful intervention [46, 47].

Clinical features

Clinical findings in congenital CMV include intrauterine growth restriction, hydrops, generalized petechiae, purpura, thrombocytopenia, jaundice, hepatosplenomegaly, pneumonitis, microcephaly, periventricular calcifications, seizures, chorioretinitis, sensorineural hearing loss, bone abnormalities, abnormal dentition, and hypocalcified enamel. In a review of 106 infants with symptomatic congenital CMV infection petechiae, jaundice and hepatosplenomegaly were each noted in 70% or more patients. Microcephaly was noted in 53% at birth. Elevated alanine aminotransferase, conjugated hyperbilirubinemia and thrombocytopenia were seen in 83, 81 and 77%, respectively. Eighty-six percent had at least two of the manifestations highly suggestive of congenital infection. Platelet count fell to its nadir during the second week of life whereas elevated alanine aminotransferase and direct bilirubin persisted past the first month. In spite of the difficulty in assessing central nervous system function in the newborn, evidence of damage was present in the majority. Seventy-two had microcephaly, poor suck, lethargy/hypotonia or seizures. Abnormal computerized tomographic scan was present in 16 of 20 (80%) and decreased hearing in 20 of 39 (56%). Cerebrospinal fluid protein was greater than 120 mg/dl in 24 of 52 (46%) and this elevation was associated with neurologic abnormalities as well as hearing loss [48]

CMV diagnostic studies should also be considered in infants with more subtle potential manifestations of illness, such as mild growth retardation, or a failed newborn hearing screen.

Management

It is important to differentiate between symptomatic and asymptomatic disease once a diagnosis of congenital CMV is made. This will require full clinical, radiological, audiology and ophthalmology assessment with blood investigations. Symptomatic disease can then be defined as either mild/moderately symptomatic disease, or severe focal symptomatic organ disease, or symptomatic CNS disease. The evidence base for these definitions is as yet limited. At present pragmatic definitions with a limited evidence base could include: CNS symptomatic disease – microcephaly, radiological abnormalities on MRI or Cranial USG, abnormal CSF parameters or a positive CMV CSF PCR, chorioretinitis, or a sensorineural hearing loss diagnosed by brain stem evoked responses (BSER). Severe Focal Organ Disease includes severe hepatitis, severe bone marrow suppression (anaemia, neutropenia, thrombocytopenia), colitis or pneumonitis. This decision influences treatment and follow up decisions because at present treatment for symptomatic CNS disease or severe focal organ disease is only recommended. For treatment of postnatal CMV evidences are few and case report based. Although ganciclovir has been shown to be of benefit in neonatal hepatitis and cholestasis [49,50]and gastrointestinal manifestations [51]. Whereas one RCT has shown faster resolution of liver enzymes with ganciclovir treatment in congenitally infected infants, all infants eventually normalised their liver enzymes [52]. Others have shown no obvious benefit of ganciclovir (GCV) treatment [53].

Although GCV has been used to treat congenital

CMV for over two decades only one phase III randomised trial by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG 102 study) has been conducted to assess the outcome of GCV treatment in symptomatic congenitally affected infants [54]. 100 newborns with symptomatic congenital CMV were followed over a 10 year period. The treatment group received 6 weeks of intravenous (i.v.) GCV at 6 mg/kg/dose every 12 hours as compared to no treatment in the other group. Treatment was started within the first month of life and was shown to prevent hearing deterioration at 6 months and ⩾ 1 year of life. There was also a short term improvements in weight gain, head circumference and resolution of liver abnormalities. Follow up of these babies was shown to reduce developmental delays at 6 and 12 months compared to untreated infants [55]. Infants treated with GCV have been shown to have more normal neurological outcomes but were still developmentally behind at 6 weeks, 6 months and 12 months.

However data are still very limited for adverse effects of GCV especially in preterm infants. Neutropenia and i.v. line insertion for 6 weeks are two genuine concerns. Currently 6 weeks of i.v. GCV is the only recommended treatment and published in British National Formulary [54,56]. The oral prodrug Valganciclovir (VGCV) is an attractive alternative with comparable effects. As it obviated the need of i.v. line and possibly central line in most cases it is suggested that one can switch over to oral VGCV after 2-3 weeks of i.v. therapy. VGCV pharmacokinetic profile when given in the dosage of 16 mg/kg/dose twice daily is comparable to i.v. GCV [57]. While the oral syrup formulation, available in Europe, initially approved by FDA for prevention of CMV infection at high risk of heart and kidney transplant children between 4 months to 16 years of age, the off label use is still common in symptomatic congenital CMV infection. Crushing the tablet is not at all advisable due to marked variation in pharmacokinetics.

Results of CASG 112 , A RCT comparing 6 weeks versus 6 months of VGC treatment for symptomatic congenital CMV have shown modestly improved hearing and developmental outcomes with longer course at 1 year of age which was maintained at 2 years as well. Longer course although did not show improved hearing at 6 months of age [58].

As GCV is not without side effects it is currently recommended to give GCV for 6 weeks. Blood CMV viral loads usually drop between 1 and 2 logs during treatment, while urine and saliva viral load are usually significantly higher at baseline and fall around 3–4 logs. Viral loads then rise again sharply usually once treatment has stopped. In the absence of any clinical disease progression, a rise in viral load in urine is not a reason for continuing treatment over 6 weeks.

Weekly blood counts for neutropenia and thrombocytopenia should be done and medication withheld if neutrophil count is less than 0.5×109/L until the neutrophil count rises to 0.75×109/L. Likewise platelet counts below 50×109/L is an indication for stopping antiviral treatment.

Liver function tests need to be monitored weekly during the treatment as congenital CMV can cause hepatitis. Creatinine clearance should also be monitored weekly as GCV is renally excreted. Creatinine clearance recorded between 10 and 19 l/min/1.73 m^2 should lead to once daily dosing of GCV or VGCV until creatinine clearance returns to above 20 ml/min/1.73 m^2.

Long term follow up

Hearing assessment for infants with congenital CMV should be performed every 3–6 months in the first year until age 3 and then yearly until 6 years old. Neurodevelopmental follow up should be performed at 6 months and at least one year in general paediatric clinics. All CNS symptomatic infants should have a neurodevelopmental assessment at one year. Initial ophthalmology assessment is required at

diagnosis to evaluate the presence of retinal scarring. Asymptomatic newborns do not require further examinations. However, symptomatic newborns should undergo annual ophthalmology assessment until the age of 5 to detect the presence of delayed or progressive chorioretinitis.

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Neuroprotective Role of Antenatal Magnesium Sulphate in Preterms

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Introduction:

Cerebral Palsy (CP) is a motor and or postural dysfunction which is not progressive and may be associated with cognitive impairment. CP has a prevalence of 2:1000 live births and the principal obstetric risk factors for CP are preterm birth (before 34 weeks) and low birth weight. Magnesium sulphate (MgSO4) administration to the preterm fetus has been linked with the prevention of CP since 1995. From 2002 to 2008, 5 randomized controlled trials (6145 babies) studied magnesium sulphate for fetal neuroprotection[1-5]. In 2009, a milestone was reached with the publication of 3 meta-analyses, all of which concluded that magnesium sulphate for fetal neuro-protection decreases the risk of childhood CP[6-8].

Pathophysiology:

The exact mechanism for potential neuroprotection is not known but the following pathways have been postulated.

- Vasoactive properties of MgSO4 may improve cerebral blood flow.
- MgSO4 had been shown to prevent neuronal injury from pro inflammatory cytokines which may be involved in the genesis of preterm birth.
- Magnesium may have an anti apoptotic (programmed cell death) effect reducing neuronal loss.
- MgSO4 down regulates excitatory stimuli, by blocking NMDA receptors in the brain.
- Inhibition of calcium influx into cells and free radicle generation.

SOGC clinical practice guidelines[9] (Evidence based recommendation):

1. For women with imminent preterm birth ($\leqslant 31^{+6}$ weeks), antenatal magnesium sulphate administration should be considered for fetal neuroprotection (I-A)
2. Although there is controversy about upper gestational age, antenatal magnesium sulphate for fetal neuroprotection should be considered from viability to $\leqslant 31^{+6}$ weeks (II-1B)
3. If antenatal magnesium sulphate has been started for fetal neuroprotection, tocolysis should be discontinued (III-A)
4. Magnesium sulphate should be discontinued if delivery is no longer imminent or a maximum of 24 hours of therapy has been administered (II-2B)
5. For women with imminent preterm birth, antenatal magnesium sulphate for fetal neuroprotection should be administered as
6. 4g IV loading dose, over 30 minutes, followed by a 1g/hr maintenance infusion until birth (II-2B)
7. For planned preterm birth for fetal or maternal indications, magnesium sulphate should be started, ideally within 4 hours before birth, as a 4g IV loading dose, over 30 minutes, followed by a 1g/hr maintenance infusion until birth (II-2B)
8. There is insufficient evidence that a repeat course of antenatal magnesium sulphate for fetal neuroprotection should be administered (III-L)
9. Delivery should not be delayed in order to administer antenatal magnesium sulphate for fetal neuroprotection if there are maternal and/or fetal indications for emergency delivery (III-E)
10. When magnesium sulphate is given for fetal neuroprotection, maternity care providers should use existing protocols to monitor women who are receiving magnesium sulphate for preeclampsia/eclampsia (III-

A)

11. Indications for fetal heart rate monitoring in women receiving antenatal magnesium sulphate for neuroprotection should follow the fetal surveillance recommendations of the SOGC 2007 Fetal Health Surveillance: Antepartum and Intrapartum Consensus Guideline (III-A)
12. Since magnesium sulphate has the potential to alter the neonate's neurological evaluation, causing hypotonia or apnea, health care providers caring for the neonate should have an increased awareness of this effect (III-C)

Australian National Clinical Practice Guidelines[10] (2010):

Antenatal MgSO4 was recommended for fetal neuroprotection in the same dosage as recommended in SOGC guidelines However, MgSO4 was recommended only at < 30 weeks' gestation, based on 2 considerations :

1) No one gestational age subgroup was considered to show a clear benefit
2) In the face of uncertainty, the committee felt it was prudent to limit the impact of their clinical practice guidelines on resource allocation.

American College of Obstetricians and Gynecologists[11] (2010):

Based on evidence suggests that magnesium sulphate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. No gestational age cut off was given by ACOG.

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Role of probiotics in preterm neonates

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Introduction:
Necrotizing enterocolitis (NEC) is one of the most serious gastrointestinal emergencies in very low birth weight (VLBW) preterm infants, affecting 7% to 14% of these infants (1). NEC is a leading cause of death and morbidity in NICUs and the incidence of NEC has not changed in the past 20 years (2,3).

In neonatal intensive care units, the immaturity of intestinal function, frequent use of broad-spectrum antibiotics, delay in initiating enteral feeding, invasive procedures, delay in reaching full feed, prolonged hospital stay limit the exposure of preterm infants to normal commensal microorganisms. As a consequence, very-low-birth weight (<1500 g) preterm infants experience a delayed and abnormal pattern of gut colonization, particularly with regard to bifidobacteria and lactobacilli, normally dominant in healthy full term infants. This impaired intestinal colonization may predispose preterm infants to necrotizing enterocolitis and increase the risk of bacterial translocation.

Probiotics:
Probiotics are defined as "living organisms which, when included in the diet in adequate amounts, can bring health benefits to the host"(4). As microorganisms able to colonize the digestive tract by adhering to the intestinal epithelium, producing antimicrobial substances, and modulating the immune response and host metabolism, probiotics have been discussed regarding their usefulness for preterm infants. Bifidobacteria and lactobacilli are commonly found in the gut of breastfed infants and most cases of NEC in VLBW infants occur before 6 weeks of age.

Previous systematic reviews of randomised controlled trials (RCTs) showed that probiotic supplementation significantly reduces the risk of definite NEC, all-cause mortality and the time to reach full enteral feeds (~120 to 150 ml/kg/day of milk) in preterm neonates (5,6,7). Based on these results, reports have indicated that routine probiotics supplementation is justified, except for ELBW neonates, given the lack of specific data on this high-risk cohort.

Specific recommendations: (Evidence Based- 8, 9)

- **Strain:**
  Combination containing Lactobacillus and at least one Bifidobacterium species is preferable. Lactobacillus GG alone may not be effective. (LOE 1) & (LOE 2)
- **Dose**:
  3×10^9 organisms per day, preferably in a single dose. (LOE 1) & (LOE 2)
- **When to start?**
  When the neonate is ready for enteral feeds, preferably within first 7 days of life.
  (LOE 1) & (LOE 2)
- **How long to continue?**
  At least until 35 weeks corrected age, or discharge.(LOE 2)
- **Supplementation during acute illness:**
  Stopping the supplementation during an acute illness such as sepsis, NEC or perinatal asphyxia may be safe. (LOE 4)

Guidelines for other clinical and non-clinical use:

- Starting dose for ELBW neonates: 1.5×10^9 cfu/day until reaching 50-60 ml/kg/day feeds.
- Osmotic load: solution should be diluted to

keep the osmolality below 600 mOsm/L.

- Diluent: sterile water or breast milk.
- Volume for administration: 1 to 1.5 ml per dose.
- Clinical monitoring: patients should be monitored for intolerance (abdominal distension, diarrhoea, vomiting), probiotic sepsis, and adverse effects (flatulence, loose stools) of additives such as prebiotic oligosaccharides.

Other use of probiotics:

- Current evidence indicates that probiotic supplementation is safe, and effective in reducing the risk of LOS in preterm neonates in NICUs (10,11).
- Probiotics and probiotic-derived therapies represent an exciting avenue to replete the population of commensal microbes and to prevent the immune-mediated sequelae of dysbiosis like allergic disease (12).

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Inhaled Nitric Oxide Therapy in Neonates

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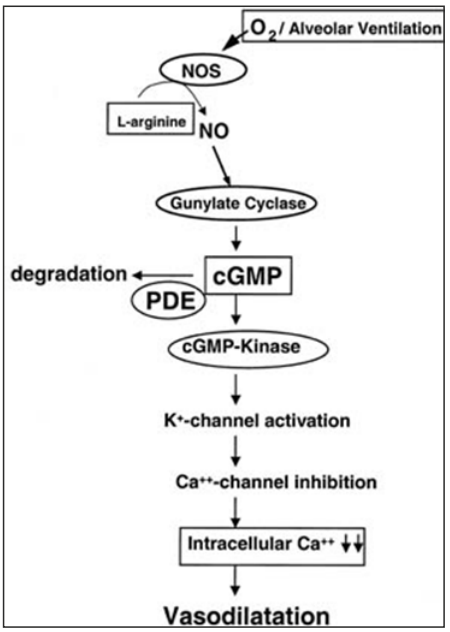
Introduction:

Few landmark therapies that have improved outcomes of newborn infants include use of antenatal steroids, better physiological ventilators, surfactant replacement therapy and inhaled nitric oxide (iNO) therapy. The discovery of iNO as an endogenous biological mediator and its biological roles has been one of the most significant developments in medicine. Inhaled nitric oxide is a naturally occurring vasodilator which is present in the vascular endothelium of all the tissues of the body. At a cellular level it works (see figure 1) by activating guanylate cyclase leading to an increase in the production of cyclic GMP which in turn relaxes vascular smooth muscle. It is rapidly inactivated in the blood stream with production of methaemoglobin and inorganic nitrates and nitrites. Due to these properties, when it is given by inhalation it dilates the pulmonary blood vessels in ventilated lung, reducing pulmonary vascular resistance, increasing pulmonary blood flow and improving ventilation perfusion mismatch without having any significant effect on the systemic vasculature. Its use is well established in term babies with persistent pulmonary hypertension but must still be regarded as experimental in preterm babies.

Figure 1 :



Main Results of Cochrane Reviews:

Term or near-term babies:
Fourteen eligible randomized controlled studies were found in term and near term infants with hypoxia. Seven of the trials compared iNO to control (placebo or standard care without iNO) in infants with moderate or severe severity of illness scores. Four of the trials compared iNO to control, but allowed back up treatment with iNO if the infants continued to satisfy the same criteria for severity of illness after a defined period of time. Two trials enrolled infants with moderate severity of illness score (OI or $AaDO_2$) and randomized to immediate iNO treatment or iNO treatment only if they deteriorated to more severe criteria. One trial studied only infants with congenital diaphragmatic hernia (Ninos 1997), and one trial enrolled both preterm and term infants (Mercier 1998), but reported the majority of the results separately for the two groups.

iNo appears to improve outcome in hypoxaemic term and near term infants by reducing the incidence of the combined endpoint of death or need for ECMO. The reduction seems to be entirely a reduction in need for ECMO; mortality is not reduced. Oxygenation improves in approximately 50% of infants receiving nitric oxide. The Oxygenation Index decreases by a (weighted) mean of 15.1 within 30 to 60 minutes after commencing therapy and PaO2 increases by a mean of 53 mmHg. Whether infants have clear echocardiographic evidence of persistent pulmonary hypertension of the newborn (PPHN) or not does not appear to affect outcome. The outcome of infants with diaphragmatic hernia was not improved; indeed there is a suggestion that outcome was slightly worsened. The incidence of disability, incidence of deafness and infant development scores are all similar between tested survivors who received nitric oxide or not.

Authors of this review conclude that on the basis of presently available evidence, it appears reasonable to use inhaled nitric oxide in an initial concentration of 20 ppm for term and near term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia.

Preterm babies:

Fourteen randomized controlled trials of inhaled nitric oxide therapy in preterm infants were found. The trials have been grouped *post hoc* into three categories depending on entry criteria; entry in the first three days of life based on oxygenation criteria, routine use in preterm babies with pulmonary disease, and later enrolment based on an increased risk of BPD. No overall analyses were performed. Nine trials of early rescue treatment of infants based on oxygenation criteria demonstrated no significant effect of iNO on mortality or BPD. Three studies with routine use of iNO in infants with pulmonary disease also demonstrated no significant reduction in death or BPD [typical RR 0.93 (95% CI 0.86 to 1.01)] although this small effect approached significance. Later treatment with iNO based on the risk of BPD (two trials) demonstrated no significant benefit for this outcome in analyses which are possible using summary data. There is no clear effect of iNO on the frequency of all grades of IVH or of severe IVH. Early rescue treatment was associated with a non-significant 20% increase in severe IVH. No effect on the incidence of neuro-developmental impairment was found.

Authors conclude that iNO as rescue therapy for the very ill preterm infant does not appear to be effective. Early routine use of iNO in preterm infants with respiratory disease does not affect serious brain injury or improve survival without BPD. Later use of iNO to prevent BPD might be effective, but requires further study.

Advantages:
- Selective pulmonary vasodilator without systemic hypotension
- Improves ventilation perfusion matching
- Rapid onset of action

Disadvantages:
- Expensive equipment and costly iNO gas
- Considerable expertise needed to administer therapy
- Potential toxicity to medical and nursing staff

Indications in term & near-term (⩾ 34 weeks) babies:
Nitric oxide should be considered in term or near term infant with PPHN (causes : primary or secondary to MAS, Aspiration, pneumonia, RDS) and ventilation perfusion mismatch with/without PPHN.
- Any baby with severe hypoxic respiratory failure – PaO2 cannot be maintained above 50 mmHg or O2 saturation >90% despite optimal ventilation with FiO2 greater than 80%.
- Any ventilated baby with a significant (>50%) oxygen requirement and echocardiographic evidence of pulmonary artery pressures close to or above systemic pressure and / or evidence of poor cardiac output (RVO <150mls/kg/min) or low mean left pulmonary artery blood flow velocity (<0.2 m/sec)

Indications in preterm babies (⩽ 33 weeks):
low cardiac output or low lung perfusion (as defined above).
- Although there are only observational studies, infants with respiratory failure born after a prolonged period of oligo-hydramnios appear to benefit from the early use of nitric oxide as these infants may have severe pulmonary hypertension and frequently have excellent responses.

Relative contraindications:
- Preterm babies who have not yet received surfactant.
- Cautious consideration should be applied to the use of NO in babies who are born before 26 weeks.
- Any evidence of a coagulopathy.

Considerations:
- In general, ventilation should be optimized and surfactant given prior to consideration of use of iNO, particularly in babies with radiological opacification of the lungs suggesting a primarily parenchymal lung problem.
- Echocardiography may assist in directing appropriate use of iNO. The best response is often seen in babies with relatively normal chest x-rays but echocardiographic evidence of marked pulmonary hypertension. Suggesting so called primary or idiopathic PPHN.
- Infants should receive optimal cardio-vascular management prior to starting iNO.

Dosages:
- Term babies: start at 5-10 ppm increasing up to 20 ppm depending on response (higher doses are unlikely to be of benefit and doses >40 ppm are associatedwith methaemoglobinaemia).
- Preterm babies: Start at 5 ppm increasing to a maximum of 10 ppm depending on response.
- iNO lack of dose response: There is no consistent evidence of a dose response effect with iNO. Therefore:
- Attempts should be made to reduce iNO dose to the minimal effective dose assessed by response to changes in nitric oxide delivery.
- If a trial of increased nitric dose did not have any benefit in oxygenation or haemodynamics, then reduce the dose back to the original dose.
-

Methaemoglobin monitoring:
iNO can theoretically cause methaemoglobinaemia although none of the RCTs using doses of 20ppm or less have

reported any increase in the incidence of methaemoglobinaemia. Preterm infants are more susceptible because of relatively low levels of the enzyme methaemoglobin reductase. Methaemoglobin levels should be checked every 24 hrs if an infant is on less than 20 ppm (every 12 hrs if higher dosing used). If possible, all infants should be. If levels rise above 5%, iNO should be reduced or stopped.

Weaning:

There is little evidence to guide the best method for weaning iNO, although some authors have anecdotally noted rebound deterioration on stopping iNO in some babies. The aim should be to deliver the minimum dose compatible with normal oxygenation and haemodynamics. As noted above there is little evidence of a dose response relationship with iNO and so if the dose is increased and no effect is observed, then the dose should be reduced as early as possible.

In term babies there may be an advantage in maintaining a low dose of iNO (2-5 ppm) while oxygen and ventilator pressures are weaned, particularly if there is echocardiographic evidence of persistently raised pulmonary artery pressures. In preterm babies the aim should be to wean off iNO as soon as possible.

Indian Scenario:

iNo therapy has become available in selected centers in a few cities in India. Reliable delivery systems have become available. Medical grade iNO gas cylinders are not easily available in India and still remain a major concern.

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Everything a clinician needs to know about Statistics and Clinical Epidemiology in a nutshell

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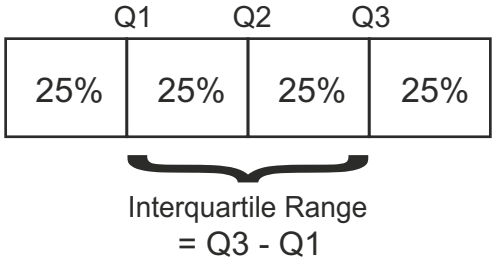
Useful Terms -

1. Mean: arithmetic mean -The "**mean**" is the "average", where we add up all the numbers and then divide by the number of observations.
2. Median: data arranged in ascending or descending order of magnitude, and then the value in middle observation
3. Mode: most commonly occurring value
4. The Mean Deviation: Average of deviations from arithmetic mean
5. The Standard Deviation SD, (**σ**) is a measure of how spread out numbers/data are. Deviation just means how far from the normal. It is "Root - Means –Square – Deviation ". The formula is easy: it is the square root of the

Variance

6. Standard Error/ Standard Error of Mean : The It is the standard deviation of the means, it is measure of the sample error and is given by the formula SD/n
7. Skew is symmetry of distribution
8. Kurtosis is flatness or peakedness of distribution
9. Range – lowest to highest
10. The **interquartile range** (**IQR**) is a measure of variability, based on dividing a data set into quartiles from Q1 to Q3.



Quartiles divide a rank-ordered data set into four equal parts. The values that divide each part are called the first, second, and third quartiles; and they are denoted by Q1(25th Percentile) , Q2 (50th Percentile), and Q3 (75th Percentile), respectively.

11. *P* value: The probability that a particular result would have happened by chance.

Probability of obtaining as or more extreme results provided that the null hypothesis is true.

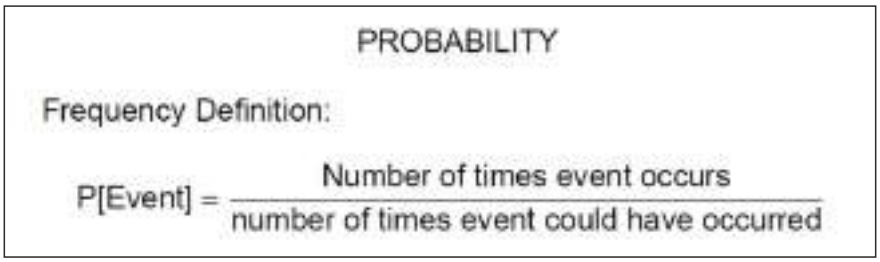
- The p <0.05 is wholly arbitrary
- Statistical significance does not translate in to clinical importance

12. Confidence interval (CI)- A CI gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of sample data.

a. A **confidence interval (CI)** is an interval estimate of a parameter of interest
b. Instead of estimating the parameter by a single value, an interval of likely estimates is given
c. CI are used to indicate the reliability of an estimate

13. Definition of 95% CI: *"The interval computed from the sample data which, were the study repeated multiple times, would contain the true effect 95% of the time"*
14. Type I Error: false positive - *rejecting the null hypothesis when it is true*, false alarm.
15. Type II Error: false negative - *accepting te null hypothesis when it is false, failed alarm.*

16. Type III Error: *correctly rejecting the null hypothesis for the wrong reason (right answer for wrong hypothesis)*
17. Type IV Error: *incorrect interpretation of a correctly rejected hypothesis (wrong answer obtained with the wrong test, overestimation of risks that leads to rejection of an efficacious therapy)*
18. Type V: *made-up, fabricated, fraudulent results*
19. Type O error- From the point of view of confidence intervals, getting it wrong is simply a matter of the population value being outside the confidence interval
20. Probability (P)



21. Odds (O): Odds are alternative way of describing the chance of an event Odds = Event/ No event = P / (1-P) For Calculating probability from odds, P = O/ (1+O)

22. Risk Difference (RD) – this measure of effect tells us what proportion of patients are spared the adverse outcome if they receive the experimental therapy
23. Relative Risk (RR) – this measure tells us the proportion of the original risk of outcome that is still present when patients receive experimental therapy
24. Relative Risk Reduction (RRR) – an estimate of the proportion of baseline that is removed by the therapy. RRR = 1-RR
25. Correlation examines the strength of the relation between two variables, neither of which is necessarily considered the target variable
26. Regression examines the strength of the relation between one or more predictor variables and a target variable
27. Univariate analysis deals with one predictor variable
28. Multivariate analysis deals with multiple predictor variables
29. ***Superiority trials*** are designed to demonstrate that one treatment is more effective than another. Purpose: is to detect difference between two drugs
30. ***Non-inferiority trials*** are designed to demonstrate that a treatment is at least not appreciably worse than another. Purpose: to demonstrate that a new drug is not worse than an active comparator by more than pre-specified amount, non-inferiority margin Δ or δ. Non-inferiority trials are designed to ensure that new therapeutic is not unacceptably worse than the standard therapy
31. ***Equivalence trials*** are designed to demonstrate that one treatment is as effective as another. Purpose - to confirm absence of meaningful difference between treatments). Equivalence is inferred when entire confidence interval falls exclusively within equivalence margins (between – Δ and +Δ).
32. Power of a study – ability of study to find difference if it exists.
33. Blinding in a study can be attempted at following levels in a RCT – Participants, Health Care Providers, Data Collectors, Judicial Assessors of Outcome, Data Analysts, Data Safety and Monitoring Committee, Manuscript Writers
34. Bias- Systematic deviation from the truth…

a. **S**election bias (incomplete randomization) - How patients enter the study?

b. **P**erformance bias (care provided to groups) –additional or co-interventions?

c. **E**xclusion bias (Withdrawal from trial)
d. **D**etection bias (Outcome assessment)- How outcomes are measured?

35. Stratification is the process of grouping members of the population into relatively homogeneous subgroups before sampling

36. Block Randomization- Random allocation can be made in blocks in order to keep the sizes of treatment groups similar at every step in study.

37. In Clinical Epidemiology, an **intention to treat (ITT) analysis** (sometimes also called Intent to treat) is an analysis based on the initial treatment intent, not on the treatment eventually administered. Use every subject who was randomized according to randomized treatment assignment. Ignore noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. ***As randomized, so analyzed***

38. Per-protocol (PP) analysis is in contrast to the **Intention to treat analysis-** It is a strategy of analysis in which only patients who complete the entire clinical trial or other procedure analyzed, not like the ITT analysis which also includes the patients who dropped out. Per-protocol analysis is also called "On treatment analysis"

39. Treatment received analysis - Another approach is to analyze all participants according to the treatment they actually received, regardless of what treatment they were originally allocated

40. Validity - The degree to which the results of a study are likely to be true, believable and free of bias

a. The **internal validity** of a study refers to the integrity of the experimental design
b. The **external validity** of a study refers to the appropriateness by which its results can be applied to non-study patients or populations

41. Sensitivity –

a. The proportion of people with the target disorder who have a positive test result
b. A proportion of truly diseased persons, as measured by the 'gold standard', who are identified as diseased by the test under study
c. Positive in disease rate (PiD Rate)
d. True Positive Rate

42. SnNout - When a test has a high Sensitivity, a Negative test result can help to rule out the diagnosis

43. Specificity –

a. The proportion of patients without the target disorder (healthy people) who have a negative test result
b. Negative in health (NiH) rate
c. True Negative Rate

44. SpPin - When a test has a high Specificity, a Positive test result rules in the diagnosis

45. Positive predictive value –

a. How often the disorder is present if test is positive?
b. Predictive value of a positive test
c. Post-test probability of a positive test
d. Proportion of people with a positive test who have the target disorder

46. Negative predictive value –

a. How often the disorder is absent if test is negative?
b. Predictive value of a negative test
c. Proportion of people with a negative test who are free from target disorder

47. Likelihood Ratio (LR) -The ratio of the probability of a test result among patient with the target disorder (diseased) to the probability of that same result among patients who are free of the target disorder (non-diseased). "Likelihood ratios are odds, odds are not the same as probability"

48. The LRs indicate by how much a given diagnostic test result will raise or lower the pre-test probability of the target disorder

a. LR = 1, no difference
b. LR > 1 indicates that finding/ test makes the disease more likely
c. LR < 1 indicates that finding/test makes disease less likely

49. LR of a Positive Test –

a. Ratio of the probability of a true positive result if the disease is present to a false positive result if the disease is absent.
b. How much more likely is positive test to be found in a person with, as opposed to

without, the condition/disease?

50. LR of a Negative Test

a. Ratio of the probability of a false negative result if the disease is present to the probability of a true negative result if the disease is absent

b. How much more likely is negative test to be found in a person with, as opposed to without, the condition/disease?

51. Receiver/ Relative operating characteristic (**ROC**), or simply **ROC curve**, is a graphical plot of the true positives (sensitivity) on Y axis versus false positives (1 – specificity) on X axis

52. Overview: a term for any summary of the medical literature

53. Meta-analysis: systematic review that uses quantitative methods (statistical synthesis) to summarize the results. A review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method.

Assessing Normality of Data: Table 1

Table 1. Graphical Methods versus Numerical Methods

	Graphical Methods	Numerical Methods
Descriptive	Stem-and-leaf plot, (skeletal) box plot, dot plot, histogram	Skewness Kurtosis
Theory-driven	P-P plot Q-Q plot	Shapiro-Wilk, Shapiro- Francia test Kolmogorov-Smirnov test (Lillefors test) Anderson-Darling/Cramer-von Mises tests Jarque-Bera test, Skewness-Kurtosis test

Table 2

Relationship between Common Language and Hypothesis Testing

COMMON LANGUAGE	STATISTICAL STATEMENT	CONVENTIONAL TEST THRESHOLD
"Statistically significant" "Unlikely due to chance"	The null hypothesis was rejected.	$P < 0.05$
"Not significant" "Due to chance"	The null hypothesis could not be rejected.	$P > 0.05$

3 Relationship between 95% CI and p values

Table 3
Examples Demonstrating 95% CIs and P Values

EXAMPLE	EFFECT MEASURE	VALUE FOR NO DIFFERENCE	CI INCLUDES NO DIFFERENCE?	STATISTICALLY SIGNIFICANT? (P < 0.05)
The average weight loss was 7 lbs (95% CI, −3 to 17)	Difference in means	0	Yes	No
42% absolute reduction in the need for intubation (95% CI, 7% to 70%)	Difference in proportions	0	No	Yes
The relative risk for cancer was 2.3 for smokers compared with nonsmokers (95% CI, 1.8 to 3.0)	Relative risk	1	No	Yes
The odds ratio for readmission was 0.8 for managed care patients (95% CI, 0.3 to 1.2)	Odds ratio	1	Yes	No

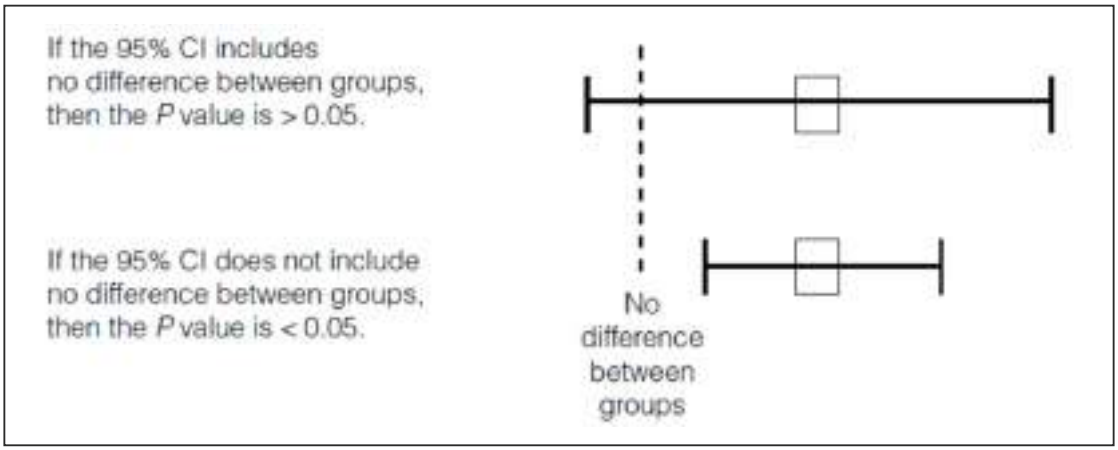


Table 4: Interpretation of *p* values

P>0.1	Little evidence to suggest a real difference
0.05≤P<0.1	A "trend" towards or a "suggestion" of a real difference
0.01≤P<0.05	Evidence to indicate a real difference exists. Data are STATISTICALLY SIGNIFICANT
0.001≤P<0.01	Strong evidence to indicate a real difference Data are HIGHLY SIGNIFICANT
P<0.001	Extremely strong evidence of a real difference Data are EXTREMELY SIGNIFICANT

Table 5: Ideal Study Design according to purpose of study:

Table 5 *Ideal study designs according to purpose of study*

Purpose	*Study design*	
	Observational	*Intervention*
To estimate prevalence	Cross sectional	
To determine natural history	Cohort	
To identify causes or risk factors or people at high risk	Cohort, case-control, or cross sectional	Randomised trial
To prevent disease		Randomised trial
To alter course of disease		Randomised trial

TABLE 6 DETAILS OF REPORTING GUIDELINES FOR DIFFERENT STUDY DESIGNS

Study Design	**Guideline/Statement**	**Source**
Randomized controlled trial	**CON**solidated **S**tandards Of **R**eporting **T**rials (CONSORT) Statement	http://www.consort-statement.org/
Diagnostic accuracy studies	**STA**ndards for **R**eporting of **D**iagnostic accuracy (STARD)	http://www.stard-statement.org/
Observational studies	**ST**rengthening the **R**eporting of **OB**servational studies in **E**pidemiology (STROBE)	http://www.strobe-statement.org/index.php?id=available - checklists
Systematic reviews/ Meta-analyses of RCT	**P**referred **R**eporting **I**tems for **S**ystematicreviews and **M**eta-**A**nalyses (PRISMA)	http://www.prisma-statement.org/
Meta-analyses of observational studies	**M**eta-analysis **O**f **O**bservational **S**tudiesin **E**pidemiology (MOOSE)	www.consort-statement.org/?o=1347
Case reports	**CaRe** guidelines	http://www.care-statement.org/

Table 7: Type of Data and choosing the correct Statistical Test

Type of data	Two treatment groups consisting of different individuals	3 or more treatment groups consisting of different individuals	Before and after a single treatment in the same individuals	Multiple treatment in same individuals	Association between two variables
Nominal (Proportions)	Chi Square, Fisher Exact	Chi Square	McNemar's	Cochrane Q	RR, OR, RD, RRR
Ordinal and Ranked	Mann-Whitney rank-sum test	Kruskal-Wallis	Wilcoxon Signed rank test	Friedman Statistic	Spearman rank correlation
Numerical discrete and continuous (For Normal Distribution)*	Unpaired (Two Sample) t–test	ANOVA	Paired (One sample) t- test	Repeated measures ANOVA	Linear regression, Pearson product moment correlation
Survival Time	Mantel Haenszel chi square	Log rank chi square			

Table 8 : Calculations on an RCT and Cohort Study

Outcome	**Disease +** **(Event)**	**Disease -** **(No Event)**	**Total**
Treatment Group	a	b	a + b
Control Group	c	d	c + d
Total	a + c	b + d	N = a+b+c+d

Absolute risk in Treatment Group = EER = a /(a+b)
Absolute risk in Control Group = CER = c/(c+d)
Risk Difference (ARR/ARD/RD/ERD) = RD = CER- EER = [c/(c+d)]- [a/(a + b)]
Number Needed to Treat = NNT =1/RD ..... when negative called as NNH
Relative Risk (risk ratio) = RR = EER/CER = [a/(a + b)] /[c/(c+d)]
Relative Risk Reduction = RRR = RD/CER = (CER- EER)/ (CER) =1- RR
OR (odds ratio, ratio of odds, cross product ratio) = ad/bc

Table 9: RCT Calculations: Solved Example: TIPP Study

Outcome	**PDA**	**No PDA**	**Total**
Prophylactic Indomethacin	a 142	b 459	a + b 601
Placebo Group	c 301	d 300	c + d 601
Total	a + c 443	b + d 759	N=a+b+c+d 1202

RD = CER- EER = [c/(c+d)]- [a/(a + b)] = 0.50 – 0.24 = 0.26,
NNT = 1/RD = 3.84 = 4
RR = EER/CER = [a/(a + b)]/[c/(c+d)]= 0.24/0.50 =0.48,
RRR = (CER- EER)/ (CER) =1- RR = 1-0.48 = 0.52
OR = ad/bc =(142 x 300)/(459 x 301)= 42600/138159 = 0.308

Table 10: Intepreation of Diagnostic Test

Outcome	Target Disease +ve	Target Disease -ve	Total
Diagnostic Test +ve	TP A	FP b	a + b
Diagnostic Test - ve	FN C	TN d	c + d
Total	a + c	b + d	N = a+b+c+d

Target disease present = a+c
Test positive = a+b
Accuracy = (a+d)/ (a+b+c+d)
Sensitivity (TP Rate) = a/(a+c)
Positive Predictive Value = a/ (a+b)
Negative Predictive Value = d/ (c+d)

Target disease absent = b+d
Test Negative = c+d
Prevalence = (a+c)/ (a+b+c+d)
Specificity (TN Rate) = d/(b+d)

Likelihood Ratio of a Positive Test = (a/[a+c])/(b/[b+d])
Likelihood Ratio of a Negative Test = (c/[a+c])/(d/[b+d])

Sample Size Calculations When?

- Quantitative studies
- Not required for qualitative research (note: this means formal qualitative methods, such as content analysis)
- May not be required for certain preliminary pilot studies
  - However, such studies will often be

performed prior to performing definitive study or applying for funding

Why?

- In studies concerned with estimating some characteristic of a population (e.g. the prevalence of asthmatic children), sample size calculations are important to ensure that estimates are obtained with required precision or confidence
- In studies concerned with detecting an effect (e.g. a difference between two treatments, or relative risk of a diagnosis if a certain risk factor is present versus absent), sample size calculations are important to ensure that if an effect deemed to be clinically or biologically important exists, then there is a high chance of it being
- If the sample is too small, then even if large differences are observed, it will be impossible to show that these are due to anything more than sampling variation

What all is required?

1. Type of outcome Nominal, Ordinal, Rank, Numerical-Discrete, and, Numerical - Continuous
2. Design (2-arm, k-arm, cross-over, factorial, repeated measures, etc.)
3. Statistic (e.g.., *x* sample mean estimates, population mean), one sided or two sided test
4. Type of effect measure (MD, RD, RR, OR, HR)
5. Estimate of variability of control group (^2_c), SD of continuous outcome variables
6. Significance level: Type I Error (alpha,), False Positive
7. Desired Power (1-) or Type II Error ()
8. Minimally clinically important effect ($_0$)
9. Rough idea of cost per patient
10. Software, Statistician
11. Choose the correct formula

INDIAN ACADEMY OF PEDIATRICS NEONATOLOGY CHAPTER

NOTICE

ELECTION FOR THE OFFICE BEARERS 2017-18

Nominations of eligible persons are invited for the election of

- PRESIDENT (One post)
- SECRETARY (One post)
- JOINT SECRETARY (One post)
- TREASURER (One post)
- EXECUTIVE MEMBERS (Two posts per zone)

Applications are invited from the eligible members prescribed in the Rules & Regulations as per election schedule detailed below for one post one person only:-

Sr. No.	Event	Date(s)
1	Filing of nominations	From 1.9.16 to 15.10.16, 4 pm
2.	Withdrawal of nominations	From 16.10.16 to 23.10.16, 4 pm
3.	Display of final list candidates	24.10.16
4.	Election ballot dispatch, if required	8.11.16 onwards
5.	Counting of votes/declaration of result	8.12.16

Elections will be conducted by following Election Commissioners
1. Chief Election Commissioner : Dr Ranjan Pejavar
2. Election Commissioners : Dr Srinivas Murki and Dr Naveen Jain

Complete Nomination forms should be posted to :

Dr Ranjan Pejavar
Tharanga, ≠ 5 Binny Layout,
Behind Athiguppe,
Vijayanagar, Banglore. PIN: 560040

Eligibility for Various Offices:

PRESIDENT

1. Should have been a ratified member of good standing in the Society for a minimum of 5 years.
2. Must have held an organizational position as an office bearer for at least two complete terms for the Chapter
3. Should have attended three annual conferences of IAP Neonatology Chapter in preceding 5 years.
4. Should have published at least 3 papers in the field of Neonatology/Perinatology in the national or international journals or should have been speaker in at leas 3 National or International conferences in the field of Neonatology/Perinatology.
5. Should have age of 40 years or above
6. Should have no dues towards the Society.
7. Should have no prior convections civil or criminal by a court of law.
8. Should have no other professional body organisational sensibility as an office bearer(state or national).
9. Should have at least 1 year gap from being an office bearer for any other professional body.

SECRETARY:

1. Should have been a ratified member of good standing for at least 5 years.
2. Must have held an organizational position as an office bearer for at least one complete term in Chapter
3. Should have actively participated in the annual scientific meeting of the Society at least twice in last 5 years.
4. Should have Published at least 2 papers in the field of Neonatology/Perinatology in the national or international journals or should have been speaker in at least 2 National/International conferences in the field of Neonatology/Perinatology.

TREASURER :

1. Should have 5 years standing as ratified members of the Society
2. Must have held an organizational position as an office bearer for at least one complete term in I Chapter

JOINT SECRETARY:

1. Should have 3 years standing as ratified members of the Society

EXECUTIVE COMMITTEE MEMBERS :

1. Should be ratified member of Society for at least two years.
2. Two members from five Zones, East-west,north, south & Central (total of 10) shall be elected.

3. Should have actively participated in the annual scientific meeting of the Society at least once in last 5 years.

In case of no nominations for elections, the President in consultation with the secretary shall nominate members to the executive board..

Complaints/Grievances

- Any member who has any complaint about the election shall give the same in writing addressed to the President of the Chapter within 21 days of the declaration of the result.
- An Election Tribunal consisting of the President as the Chairperson and two Immediate Past Presidents shall be constituted to go into the complaint and the decision of the Tribunal shall be final. If there is a difference among the members of the election tribunal, the decision shall be by majority.

- Any dispute shall be subject to Aurangabad jurisdiction.

Election Commissioners

1. Dr. Ranjan Pejaver

2. Dr. Srinivas Murki

3. Dr. Naveen Jain

NOMINATION FORM FOR THE OFFICE OF

PRESIDENT/SECRETARY/JOINT SECRETARY/TREASURER/EXECUTIVE MEMBERS

NAME :.....

Date of Birth :.....

Address :.....

Email id…….. Cell No: .....

Chapter Life Membership No: .....

IAP Life Membership No: .....

POST Applied for:.....

Name of the proposer :.....

Address of the proposer .....

.....

Email id..... Cell no .....

Chapter Life Membership No :

IAP Life Membership No :

Signature .....

Seconded by:- a) Name .....

b) Address.....

c) Signature.....

Email id..... Cell no.....

Chapter Life Membership No:

IAP Life Membership No:

I hereby give my consent for the above nomination for the office of President/Secretary/Joint Secretary/Treasurer/Executive Member of Indian Academy of Pediatrics, Neonatology Chapter.

Name :.....

Signature :.....

SCIENTIFIC PROGRAM

IAP Neocon 2016, Ranchi

Day 1 (22nd October, Saturday)

8.00- 9.00 AM	**Registration**	
Time	**Topic**	**Speaker**
9.00-10.00 AM	**Neonatal Cardiology**	
9.00-9.15 AM	PDA: whom, when and how to treat	Dr Pradeep Suryawanshi (Pune)
9.15-9.30 AM	PPHN management: Sildenafil, non-invasive inhaled NO	Dr Mohit Shahni (Surat)
9.30-9.45 AM	Which inotrops and when in NICU	Dr Ravi Shankar (Hyderabad)
9.45-10.00 AM	Q&A all speakers	
10.00-11.00 AM	**Neonatal Hematology**	
10.00-10.15 AM	Crash cart treatment of severe NNJ	Dr Sandeep Kadam (Pune)
10.15-10.30 AM	Neonatal cholestasis in NICU: a practical approach	Dr Jaykishan Mittal (Jaipur)
10.30-10.45 AM	Thrombocytopenia and platelet transfusion in neonates	DR V C Manoj (Trissur))
10.45-11.00 AM	Q&A all speakers	
11.00-12.00 PM	**Neonatal sepsis**	
11.00-11.15 AM	Which antibiotics work and which don't for neonatal sepsis in India	Dr Ashish Mehta (Ahmedabad)
11.15-11.30 AM	Strategies to prevent bacterial and fungal infection in NICU	Dr Deepak Chawla (Chandigarh)
11.30-11.45 AM	NEC free NICU	Dr Monika Kaushal (Dubai)
11.45-12.00 PM	Q&A all speakers	
12.00-1.00 PM	**Panel discussion:**	**Moderator: Srinivas Murki (Hyderabad)**
	Challenges in diagnosis and management of Neonatal Sepsis in India Panelists: Dr Manas Upadhyay (Cuttak), Dr Neeraj Gupta (Jodhpur), Dr Rajiv Sharan (Jamsedpur), Dr Bijan Shaha (Kolkata), Dr Reeta Bora (Dibrugarh)	
1.00-2.00 PM	**Poster walk**	
1.00-2.00 PM	**LUNCH**	
2.00-3.00 PM	**Panel discussion:**	**Moderator: Dr Kartik Nagesh (Banglore)**
	Care of ELBW babies Panelists: Dr Anu Thakral (Delhi), Dr Tushar Parikh (Pune), Dr Kamal Arora(Ludhiana), Dr Nitin Verma (Bhopal)	
3.00-4.00 PM	**Neonatal neurology**	
3.00-3.15 PM	Neuroprotection for NE – cooling and beyond	Dr Nandkishor Kabra (Mumbai)
3.15-3.30 PM	Levetiracetam for neonatal seizure	Dr Rahul Yadav (Chennai)
3.30-3.45 PM	Predicting long term outcome in NICU	Dr Naveen Jain (Trivendrum)
3.45-4.00 PM	Q&A all speakers	
4.00-5.00 PM	**Respiratory care**	
4.00-4.30 PM	Therapeutic adjuncts in ventilated babies	Dr Sunil Sinha (UK)
4.30-5.00 PM	Nasal Ventilation	Dr Vinnet Bhandari (USA)
5.00-6.00 PM	**The mixed basket**	
5.00-5.15 PM	Strategies that help avoid ventilation whenever possible	Dr Dinesh Chirla (Hyderabad)
5.15-5.30 PM	The Golden hour of Neonatology	Dr Amit Upadhyay (Merut)
5.30-5.45 PM	ROP: Laser or anti VGEF	Dr Arijit Mahapatra (Bhubaneswar)
5.45-6.00 PM	Q&A all speakers	

SCIENTIFIC PROGRAM

IAP Neocon 2016, Ranchi

Day 2 (23rd October, Sunday)

Time	Topic	Speaker
8.00-9.00 AM	Free papers	
9.00-9.20 AM	Management of LBW babies in resource limited setting	Dr Binod Kumar Singh (Patna)
9.20-9.40 AM	The Pediatrician's Role in Caring for Late Preterm and Early Term Neonates	Dr Ashok Kumar (Varanasi)
9.40-10.20 AM	Quality improvement in Healthcare-Paradigm shift in practice of Neonatology	Dr A K Deorari (Delhi)
10.20-11.00 AM	Conference theme address: Innovations in neonatology for affordable care.	Dr Girish Gupta (Deharadun)
11.00-11.40 AM	Dr B. B. Jha Oration	Dr Praveen Kumar (Chandigarh)
11.40- 12.20 PM	Keynote address: HHHFNC	Dr Sunil Sinha (UK)
12.20-01.00 PM	Prevention of BPD	Dr Vineet Bhandari (USA)
01.00-02.00 PM	Gold medal award paper presentation, Free paper award, Poster award	
0.200-2.30 PM	LUNCH	
2.30-4.30 PM	**Jharkhand Neocon**	

IAP Neocon 2016, Ranchi

Pre Conference Workshop (20th and 21st October)

Workshop	National Coordinator	Other Faculties	Venue
Invasive Ventilation (2 days) ***20th and 21st October***	**Dr Deepak Chawla (Chandigarh)**	**Dr Ashish Mehta, Dr Jaykrishan Mittal, Dr Neeraj Gupta, Dr Monika Kaushal, Dr Reeta Bora**	**Rani Hospital**
Non-invasive Ventilation (CPAP, HHHFNC, Nasal ventilation) ***21st October***	**Dr Srinivas Murki (Hyderabad)**	**Dr Sandeep Kadam, Dr Anu Thakral, Dr Bijan Saha, Dr Arjit Mahapatra**	**Gandhinagar Hospital**
Functional Echo and POC USG in Neonatology ***21st October***	**Dr Pradeep Suryawanshi (Pune)**	**Dr Mohit Shahni, Dr Ravishankar, Dr Tushar Parikh, Dr Nitin Verma**	**Rajendra Institute of Medical Sciences**

IX National Conference of IAP Neonatology Chapter

IAP NEOCON 2016

Ranchi, Jharkhand

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 – Ascites, 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

Conference Secretariat and address for correspondence :

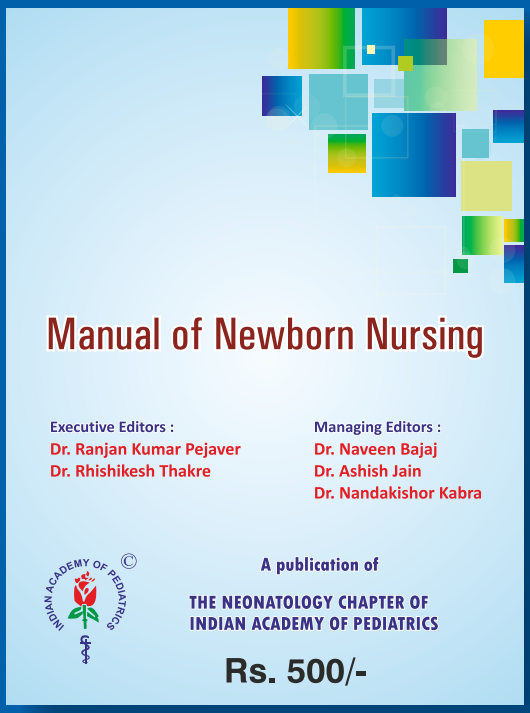
Dr. Rajesh Kumar, Org Secretary

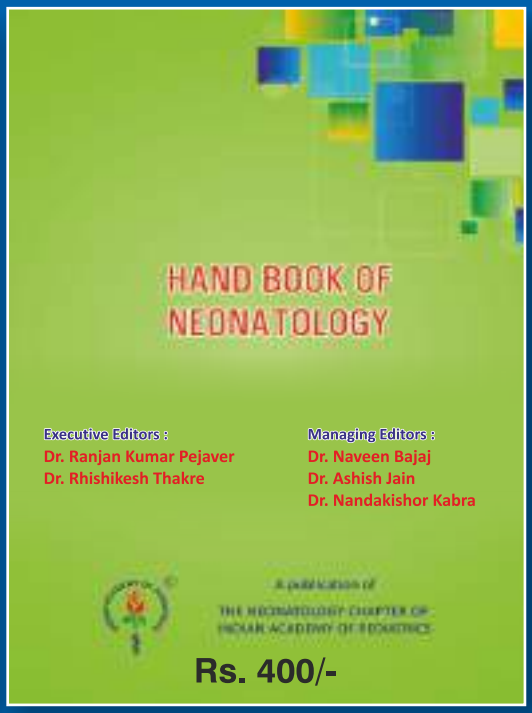
Rani Hospital, Behind Machhail Ghar, Ranchi, Jharkhand - 834001

Landline : +91-65-2360411, +91-651-3197000 Cell : +91-9431346222, +91-9431337737

website : iapneocon2016.org.in **e-mail : iapneocon2016@gmail.com**

THE OFFICIAL PUBLICATIONS OF IAP NEONATOLOGY CHAPTER





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