Management of Neonatal Sepsis with Intravenous Immunoglobulin as an Adjunctive Therapy in Preterm Newborn

Kripanath Mishra[1], Prashant Gaurav[2], Pankaj Kumar[3]

[1, 2, 3] Department of Paediatrics, Darbhanga Medical College & Hospital, Laheriasarai, Darghanga, Bihar, India.

ABSTRACT

BACKGROUND

Neonatal sepsis refers to systemic infections affecting infants within 28 days of life,[1] characterised by invasion of bloodstream by pathogens and possible involvement of multiple organ systems. Neonatal sepsis can present as bloodstream infections (BSI) or septicaemia, pneumonia, meningitis, urinary tract, and bone / joint infections but does not as superficial infections. We wanted to evaluate the rationale of administering intravenous immune globulin (IVIG) with antimicrobials to improve the therapeutic significance of sepsis in preterm neonates.

METHODS

One hundred preterm neonates with sepsis were randomly assigned into study and control categories at SNCU, Department of Paediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. Study-category was given IVIG in addition to standard treatment.

RESULTS

Total 100 sick new-borns were registered, 50 in study, and 50 in control categories. There were no differences in sex ratio (male 50 %, female 50 %) of sick new-borns who were registered. This was also apparent in the study (males 47.7 %, females 52.3 %) and control category (males 52.3 %, females 47.7 %).

CONCLUSIONS

The cause of increased morbidity and mortality in severe infection of preterm neonates was the low level of immunity. IVIG use in conjunction with the antimicrobials and other sympathetic therapy can change the end result.

KEY WORDS

IVIG, Neonatal Sepsis, Preterm Babies

Corresponding Author:
Dr. Prashant Gaurav,
Department of Paediatrics,
Darbhanga Medical College & Hospital,
Laheriasarai, Darghanga, Bihar, India.
E-mail: prashant.gauravs@gmail.com

DOI: 10.14260/jemds/2021/193

How to Cite This Article:
Mishra K, Gaurav P, Kumar P. Management of neonatal sepsis with intravenous immunoglobulin as an adjunctive therapy in preterm newborn. J Evolution Med Dent Sci 2021;10(12):899-904, DOI: 10.14260/jemds/2021/193

Submission 22-05-2020,
Peer Review 23-01-2021,
Acceptance 02-02-2021,
Published 22-03-2021.

BACKGROUND

Neonatal sepsis refers to systemic infections affecting infants within 28 days of life,[1] invasion of bloodstream by pathogens and it can involve multiple organ systems. Neonatal sepsis has many terms like bloodstream infections (BSI) or septicaemia, pneumonia, meningitis, urinary tract, and bone / joint (osteomyelitis / arthritis) infections but does not cover superficial infections. The classification of neonatal sepsis have two different ways:

1. On the basis of culture positivity:
   - Confirmed or culture positive sepsis - when the sepsis is due to micro-organism isolated from the clinical samples in the laboratory.
   - Clinical or culture negative sepsis - when the sepsis is labelled on the basis of clinical and / or laboratory parameters if the culture was negative.
2. On the basis of age of onset:
   - Early onset sepsis (EOS) – sepsis onset at or before 72 hours of age.
   - Late onset sepsis (LOS) - sepsis onset beyond 72 hours of life.

Neonatal sepsis is a major public health problem globally having higher incidence and mortality in developing countries. Globally, sepsis has still been one of the major causes of morbidity and mortality in neonates, in spite of recent advances in healthcare. 2202 per 100000 live births was the estimated global burden of neonatal sepsis, with deaths between 11 % and 19 %[2,3] More than 40 % of under five deaths occur in the neonatal period, which is 3.1 million new-born deaths per year.[4] The range of neonatal sepsis varies from 6.5 - 38 per 1000 live hospital-born babies in developing countries, which is 3 - 20 times higher than developed countries (1 - 5 per 1000 live births).

According to Delhi Neonatal Infection Study (DeNIS) collaboration recently reported that an incidence of 14.3 % of total neonatal sepsis and 6.2 % culture positive neonatal sepsis among the inborn cohort of three academic tertiary hospitals. Nearly two thirds of total incidence occurred at or before 72 hr of life. Two-thirds of the isolates in this study were gram-negative including, acinetobacter spp (22 %), klebsiella spp (17 %), and *Escherichia coli* (14 %) with high rates of multi-drug resistance among these isolates. The predominant gram-positive pathogens had been coagulase negative staphylococcus (15 %), *Staphylococcus aureus* (12 %), and enterococcus spp (6 %).[5]

Neonatal sepsis is more common in infants with lesser birth weight and gestational age. It is the most important factor in neonates which predispose them to infection. It is 10 times higher in those born preterm or with weight less than 1500 grams compared to infants born at full term or with birth weight greater than or equal to 1500 grams. Due to possible following reasons: (a) infection in the genital tract of mother leads to an increased risk of vertical transmission of infection to newborn, is one of the important cause of preterm labour; (b) there is an inverse relationship between the risk of intra-amniotic infection and gestational age; (c) there is an immune dysfunction documented in premature infants and (d) long term intravenous access, endo-tracheal intubation, or other invasive procedures required by premature neonates leading to a portal of entry for infections.[6] The level of immunoglobulin IgG in a full term infant equal to or greater than levels in mother because of active transportation across placenta which is both acquired and neonatally produced IgG in the third trimester. The levels of IgG in cord is directly proportional to the age of gestation, which is about < 100 mg / dl at 18 - 20 weeks of gestation while the level of IgG is up to 400 mg / dl at age of 30 - 32 weeks of gestation in premature infants. "Physiologic hypogammaglobulinemia" is term given to a process in which the levels of maternally derived IgG fall rapidly after birth, which is quiet an important factor in the premature and small–for–gestational-age neonates in comparison with term and appropriate–for–gestational-age neonates, whose IgG levels are often normal.[7] The incidence of neonatal sepsis has been inversely proportional to prematurity and birth weight, which is about double in moderately premature infants in comparison with term infants and it is varies from 10 - 15 cases / 1000 live births among VLBW (< 1500 g) infants in recent reports which is highest.[8] Furthermore, polymorphonuclear chemotaxis is a supplement components, which is deficient in preterm new-borns.[9] The use of IVIG has been stated in the counter active action and treatment of sepsis on neonates from the above reason.

Some studies have demonstrated that the use of anti-microbial agents and IVIG lower the risk of death in septic neonates as compared to the use of anti-microbial only.[10-13] And some neonates who are septic and showing no response to standard anti-microbial therapy, use of IVIG in those neonates showed beneficial results.[14] In the present study deliberated to discern the result of administering IVIG in conjunction with anti-microbial increases the outcome of sepsis in preterm neonates in our settings.

Objectives

To know the improvements in the therapeutic results of sepsis in preterm neonates by concentrating on giving IVIG in addition to antibiotics. To know

- Role of IVIG in the management of neonatal sepsis.
- Effect of hospital stay.
- Effect on the mortality and morbidity.

METHODS

This prospective, randomised controlled study was conducted from November 2018 to October 2019 at SNCU, Department of Paediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. Approval of the institutional ethical committee was taken prior to conduct of this study.

Study Population

Total 100 preterm new-borns having signs and symptoms of neonatal sepsis were selected for this study. Since duration of study was less, purposive sampling technique was done. Selection within the strata has been done for convenience. For this study, ethical committee clearance was obtained from DMCH ethical committee. Preterm neonates < 33 weeks of gestation with suspicion of septicaemia were selected for enlistment. By maternal dates (time from the principal day of

the last menstrual period) gestational age was determined and after admission into the hospital premises, Ballard scoring was done to confirm the gestational age.[15] A standard questionnaire was made on the basis of careful history and appropriate physical examination. On the basis of clinical features including signs and symptoms of neonatal sepsis septicaemia was doubted which presents with nonspecific and subtle features including alteration in feeding pattern. One of the most common findings is manifesting as lethargy / poor activity, refusal to suck or unresponsiveness in a neonate who fed well before. Hypothermia is a common manifestation, especially in preterm infants. Autonomic features including tachycardia or bradycardia, poor perfusion or delayed capillary refill time, hypotonia or absent neonatal reflexes and apnoea or gasping respiration. Neonatal sepsis may involve one or more of the following organ systems:

- Central nervous system (CNS) - irritability, excessive cry, high pitched cry, seizures, and bulging fontanel.
- Respiratory system – tachypnoea, retraction, grunting, apnoea, cyanosis or increased ventilator requirements
- Gastrointestinal system feed intolerance, abdominal distension, paralytic ileus, necrotising enterocolitis, vomiting, diarrhoea, jaundice and hepatomegaly.

Shock, sclerema adiposum in the presence or absence of synergistic risk factors, like; perinatal asphyxia, maternal intra amniotic infections and slowdown in rupture of layers, disseminated intravascular coagulation and pulmonary haemorrhage and metabolic abnormalities like hypo or hyperglycaemia, metabolic acidosis and hypocalcaemia are late features. Meningitis presented with a history of abnormal movements or tightening of body, abnormal or high-pitched cry, depressed sensorium and bulged and / or pulsatile anterior fontanel alongside signs and symptoms of septicaemia. The neonates with respiratory distress syndrome (RDS), inherent malformations and previous history of treatment with antitoxin were avoided.

Laboratory Investigations

Complete blood count (CBC), blood culture and C-reactive protein (CRP) level, sepsis screen was done following admission of suspected new-borns. In sick new-borns with suspected meningitis lumbar puncture was done.

Diagnosis

- Blood culture: it remains the gold standard from where causative pathogens were isolated.
- Sepsis screen: has 5 components out of which 2 or more components if present it is considered to be positive
  - i) Total leukocyte counts < 5000 / cmm
  - ii) Absolute neutrophil count (ANC): cut off for this is gestational age and 2 charts were given, Manroe's and Mouzinho's for term and preterm, respectively, roughly less than 1800 / cmm in term new-borns
  - iii) Immature to total neutrophil ratio (I: T ratio): 0.2 or more
  - iv) Micro ESR: fall in mm in first hour; 3 + age in days in the first week of life or more than 15 mm, if older
  - v) C-reactive protein (CRP) - cut off of more than 10 mg / l or 1 mg / dl. Sepsis screen has been associated with 93 – 100 % sensitivity, 83 % specificity, positive and negative predictive values of 27 % and 100 % respectively in detecting sepsis.
- Lumbar puncture (LP) -indications are
  - i) In early onset sepsis-infant is symptomatic or if blood culture is positive
  - ii) In late onset sepsis-perform LP in all cases along with sepsis work up.

Procedures

Taking consent from the guardians after explaining the advantages and possible reactions of IVIG to them, in the study and control categories, individually the neonates were assigned arbitrarily. Then neonates in study category were treated with standard treatment protocol for neonatal sepsis in conjunction with IVIG, while in control category, infants were treated with the standard treatment protocol for neonatal sepsis without IVIG. For 3 consecutive days once a day IVIG was given at a dose of 400 - 500 mg / kg. The IVIG available in our hospital came with concentration of immunoglobulin 50 mg / ml infusion solution provided in 5g / 100 ml single vial. In both categories' neonates got a similar general care. We had tested the level of immunoglobulin in the neonates before giving IVIG and level of IVIG after 2 days. The levels of immunoglobulin were estimated by enzyme linked immunosorbent assay (ELISA) technique. According to the directions given in the ELISA pack with an expandable syringe, two millilitres of blood was drawn from a vein and the prepared serum was held on - 200 degree centigrade until levels for immunoglobulin concentration by utilising immune-diffusion system.

Outcomes

The number of days of hospital stay of the neonates required and mortality rate in the two categories was recorded on the basis of treatment given.

Statistical Analysis

With a standard procedure data was subjected to statistical analysis. Analysis was done with help of Microsoft Word, Microsoft Excel and Epi Info 7. This study was prospective randomised controlled, in which proportion, mean, standard deviation, chi-square test variables were used.

RESULTS

Total 100 sick new-borns were registered, 50 in study and 50 in control category. There was no differences in sex ratio (male 50 %, female 50 %) of sick new-borns who were registered. This was also apparent in the study (males 47.7 %, females 52.3 %) and control category (males 52.3 %, females 47.7 %). In the study category mean birth weight was 1.450 kg with a standard deviation of 0.290 kg and in the control category newborns were 1.560 kg with a standard deviation of 0.300 kg. In the study category 31.83 ± 1.86 weeks and in the control category 31.82 ± 1.70 weeks was the mean gestational age. In the study and control categories 12.88 ± 4.13 days and 13.32 ± 3.86 days was the mean age on admission respectively. 3 days and 19 days was the minimum and maximum age of neonates.

In respect to birth weight, gestational age, admission age or socio-demographic characteristics there was no significant differences between the study and control categories (P > .05) (Table 1). The most common clinical presentations were refusal to feeds (85 %), lethargy (90 %), temperature instability (58 %), recurrent apnoea (68.0 %), abdominal distension (58.0 %), bleeding tendency (53 %), jaundice (37.0 %) and respiratory distress (12.0 %). Both the categories were similar in respect to clinical presentation as shown by statistical data (Table 2). Blood culture was positive in 72.8 % of cases while 27.2 % were negative in study category. Among the control category 70.8 % of cases were positive and 29.2 % were negative. CRP was found high among 72.9 % of cases in study category and 73.3 % in control category.

Variables	Baseline Characteristics Mean ± SD (%)	Study Category (N = 50) Mean ± SD (%)	Control Category (N = 50) Mean ± SD (%)	P Value
Birth weight	(In Kg)	1.40 ± 0.27	1.51 ± 0.28	0.0483
Gestational age	(In weeks)	31.83 ± 1.86	31.82 ± 1.70	0.9777
Age	(In days)	12.88 ± 4.13	13.32 ± 3.86	0.5833
Sex	Male	24 (47.7)	26 (52.3)	0.6891
	Female	26 (52.3)	14 (47.7)	0.6891
Blood culture	Positive	36 (72.8)	35 (70.8)	0.8255
	Negative	14 (27.2)	15 (29.2)	0.8255
CRP level	High	36 (72.9)	37 (73.3)	0.8217
	Normal	14 (27.1)	13 (26.7)	0.8217

Table 1. Baseline Characteristics of Enrolled Neonates (N = 100)

Clinical Signs and Symptoms	Study Category (N = 50) Mean (%)	Control Category (N = 50) Mean (%)	P-Value
Refusal to feed	42 (84.3)	43 (85.0)	0.7794
Lethargy	46 (93.0)	44 (88.0)	0.5049
Temperature instability	26 (52.0)	32 (63.0)	0.2241
Recurrent apnoea	36 (72.0)	32 (64.0)	0.3911
Abdominal distension	32 (65.0)	26 (52.3)	0.9215
Bleeding tendency	27 (54.0)	26 (51.3)	0.8130
Jaundice	22 (43.6)	15 (30.0)	0.1473
Dyspnea	08 (16.5)	04 (8.0)	0.2183
Vomiting	07 (13.3)	05 (10.0)	0.5382
Convulsion	07 (13.3)	05 (10.0)	0.5382
Fever	08 (16.5)	03 (6.9)	0.1100

Table 2 Clinical Profile of Neonates with Neonatal Sepsis (N = 100)

Baseline Characteristics (%)	Study Category (N = 37) (%)	Control Category (N = 35) (%)
Klebsiella	19 (51.8)	20 (59.2)
Pseudomonas	07 (17.1)	04 (12.9)
Acinetobacter	08 (22.2)	09 (27.0)
Salmonella	03 (8.6)	01 (4.0)
Staphylococci	00	01 (4.0)
Total	37	35

Table 3. Organisms Causing Sepsis in Culture Positive Neonate (N = 72)

Ig Level	Normal Value (mg / dl)	Pre-Administration (mg / dl)	Post-Administration (mg / dl)	t-Test (P-Value)
Ig G	600 - 1463	621 ± 153.61	785 ± 118.63	18.34 (P < 0.0001)
Ig M	6 - 34.6	7.74 ± 2.138	11.08 ± 2.83	13.53 (P < 0.0001)
Ig A	1.3 - 43	4.34 ± 2.33	8.35 ± 4.64	14.46 (P < 0.0001)

Table 4. Immunoglobulin (Ig) Level in Neonates (Study Category) Pre and Post Treatment with IVIG

In the 72 neonates who were culture-positive, 98.6 % showed gram-negative bacilli, only 1 (1.1 %) showed gram-positive. The most common organism was *Klebsiella pneumoniae* (54.16 %, 39 / 72), followed by acinetobacter (23.6 %, 17 / 72) and pseudomonas (15.27 %, 11 / 72). In both the categories (Table 3) similar patterns of organisms were isolated out of which most of these organisms were reluctant to frequently employed antimicrobials. These isolates were mostly sensitive to third generation cephalosporin, ciprofloxacin and imipenem. Netilmicin and gentamicin were also found sensitive in more than fifty percent of cases. IgM, IgG, and IgA level were done before and after the treatment with IVIG only in study category so that their changes were evaluated at the two stages. Then t-test was applied, and statistically significant changes were found in all three immunoglobulin levels after treatment with IVIG (P < 0.0001) (Table 4). To see the differences in respect of hospital stay and mortality between the two categories' t-test and c2-test was done. The minimum and maximum hospital stay was 7 and 21 days with mean hospital stay of the study category was 14.53 + - 3.88. While on the other hand in control category the minimum and maximum hospital stay were 3 and 35 days with mean hospital stay was 18.30 = - 6.88. There was statistically significant (t = 2, P < 0.05) difference found between two categories. Total 77 neonates out of 100 were discharged from the hospital after being cured. The mortality rate was lesser in study category compared to control category but was not statistically significant (c2 = 3.35, P = 0.06).

DISCUSSION

In this study, birth weight, sex, mean age, gestational age and clinical profile (P > 0.05) were practically identical in both the study and control categories. The clinical features as found in neonates is quite similar to clinical features mentioned in other studies related to neonatal sepsis and in different textbooks of paediatrics is charted in Table 2.[16-20] For early and late neonatal sepsis group B streptococcus and coagulase negative staphylococci were the most common bacteria respectively. While, in developing countries these organisms are rare in comparison to another bacterial range; *Escherichia coli* and klebsiella are the most common bacteria leading to neonatal septicaemia.[21] In the present study, it was observed that klebsiella was the most regular organisms causing sepsis in neonates in study category (51.8 %) & control category (52.9 %), which was followed by pseudomonas in study category (17.1 %) & control category (12.9 %). There was only one case discovered due to staphylococcus & no case of category B streptococcus.[22-23] In 2013, one study was done in similar neonatal intensive care unit (NICU), gram negative bacilli were isolated from blood in neonates in about 3 / 4th (73 %) of the isolated organisms. In which the percentage for isolated organisms were as follows, highest for *Escherichia coli* and least for pseudomonas (10 %) while *Klebsiella pneumoniae* (23 %) was in between them. *Staphylococcus aureus* was present only in 16.7 % of the isolated organism which is gram positive bacteria.[24] These changes occurring in the pattern of isolated organism from the same health facility in an interval of 2 years might be because of changing neonatal septicaemia aetiology inside a troop graphical area with

passing of years.[25-28] The most common organism of neonatal sepsis isolated in India was gram negative organisms, mentioned in many studies done in India.[17,22] There is more rapid declination of IgG in blood of preterm neonates in comparison to term neonates after birth, lower level during the process of birth. The reason given supporting this low level of immunoglobulin in preterm neonate and immunoglobulin IgG in a full-term infant equal to or greater than levels in mother owing to active transportation across placenta which is both acquired and neonatally produced IgG in the third trimester. The levels of IgG in cord is directly proportional to the age of gestation, which is about < 100 mg / dl at 18 - 20 weeks of gestation while the level of IgG is up to 400 mg / dl at age of 30 - 32 weeks of gestation in premature infants. "Physiologic hypogammaglobulinemia" is term given to a process in which the levels of maternally derived IgG fall rapidly after birth, which is quiet an important factor in the premature and those who are smaller in size than normal for the gestational age (SGA) in comparison to term and those who are born with gestational age findings similar to calendar age (AGA), whose IgG levels are often normal.[7] In intrauterine infection the level of IgA and IgM is elevated in cord blood because IgA, IgM, IgD and IgE did not cross the placenta.[7] There is an inverse relationship between gestational age and mean IgG level which is evidence as 368 mg / dl in an untimely born neonates during childbirth, which came to a level of 104 mg / dl at age of 3 months and increases gradually in the study of Fisher, et al.[14] In another study done by, Weisman, et al. there was significant increase ($P < 0.05$) in the level of serum IgG in patients undergoing treatment with IVIG.[29] In the study done by Kinney, et al. observation was made that the level of mean IgG before each given dosage were higher in neonates having treatment with IVIG than the neonates having placebo treatment.[30] A study done by, Weisman, et al revealed that the level of IgG was increased in untimely born neonates with early onset sepsis having treatment with IVIG in correlation with albumin.[31] Serum IgG level was found to be 621 mg / dl in our study category. To reveal the lesser duration of facility stay, several studies were done, one of these were by Conway, in which neonates in treatment category had a lesser stay in ICU ($P = 0.001$).[32] In a study by Lassiter, neonates treated with IVIG had a decreased hospital stay.[33] Kinney, et al. done a randomised study which demonstrated that there was a lesser mean stay in health facility for neonates having treatment with IVIG than the neonates giving only placebo, which was 43.1 days (36.3 - 49.9) and 46.5 days respectively.[30] While, contrary to this, a randomised study was done on multi-centre in Hyderabad, India, there were almost no difference in the duration of hospital stay between three different subgroups, subgroup having only placebo treatment, subgroup having IVIG treatment and subgroup having regular standard treatment, the duration of hospital stay were: 18.3 ± 2.34 days, 17 ± 2.08 days and 13.3 ± 2.91 days.[13] The category getting treatment with IVIG (13.3 %) had much lower death rate in contrast with the control category getting regular standard treatment (33.3 %). Though, in reality there was not such a big significant ($C^2 = 3.35$, $P = 0.06$) difference in mortality between two categories but the death rate was much lower in the study category demonstrated by inclination. The blended outcomes were coming from different studies done at different health centres at different interval illustrated for decreasing of mortality rate in severely morbid neonates treated with IVIG having neonatal septicaemia. In severely morbid neonates Sidiropoulos documented the adoption of IVIG for the treatment of neonatal sepsis of bacterial origin.[34] In which the death in the control category and the study category undergoing treatment with IVIG were 27 % (4 / 15) and 10 % (2 / 20) ($P = 0.016$). Neonates with sepsis along with low birth weight given treatment with IVIG, got best remarks for IVIG. Commuting all 4 important assessments deliberately directed towards providing adequate information about IVIG exposed that occurrence of death is only 9 % (6 / 67) of IVIG treated category, in contrast to control category which was 30 % (20 / 67).[14] A study exposed that the occurrence of death was 29.41 % (5 / 17) among neonates of control category in comparison to 11.76 % death (2 / 14) in IVIG treated premature born neonates.[31] In another study the death rate was equivalent (17.5 %) in both control and study categories of premature born neonates.[35] In all the three categories the mortality observed was the same (28 %), IVIG treated category as well as in control category in another multi-centre study done in Hyderabad, India.[13] The neonates in IVIG treated categories had basically lower mortality due to sepsis inferred from two studies by Haque, et al. ($P < 0.001$).[36,37]

CONCLUSIONS

Neonates, mainly preterm, due to their immaturity of immunity and invasiveness of procedures in neonatal NICU, increases the incidence of morbidity and mortality related to neonatal sepsis. There is a high risk of occurrence of systemic infection, especially in premature neonates due to immaturity of immunity leading to low levels of immunoglobulin. Administration of antimicrobials and IVIG together can improve the outcome and reduces the mortality in preterm neonates. Neonates having septicaemia treated with IVIG along with antibacterial defences have very good results and IVIG can have an adjunctive role for antibacterial defences in neonatal sepsis.

Limitations

Nevertheless, there was no data regarding safety and chronic complications related to administration of IVIG in preterm neonates.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

REFERENCES

[1] Agarwal R, Deodari A, Paul V, et al. AIIMS protocols in Neonatology. Vol. 1. 2nd edn. New Delhi: Noble Vision, Medical Book Publishers 2019: p. 303-15.
[2] Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, et al. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med 2018;6(3):223-30.

[3] Wu JH, Chen CY, Tsao PN, et al. Neonatal sepsis: a 6-year analysis in a neonatal care unit in Taiwan. Pediatr Neonatol 2009;50(3):88-95.
[4] UNICEF, WHO, The World Bank and The United Nations. Levels and trends in child mortality. New York: UNICEF 2011.
[5] Investigators of the Delhi Neonatal Infection Study (DeNIS) Collaboration. Characterisation and antimicrobial resistance of the sepsis pathogens in neonates born in tertiary care centers in Delhi, India: a cohort study. Lancet Glob Health 2016;4(10):e752-e60.
[6] Kliegman RM, St. Geme J. Nelson Textbook of Paediatrics. 21st edn. Philadelphia: Elsevier 2020: p. 996-1005.
[7] Kliegman RM, Stanton, St. Geme J, et al. Nelson Textbook of Paediatrics.. Vol. 1. First South Asia edition. India Private Ltd., Reprinted 2017: p. 909-25.
[8] Eichenwald EC, Hansen AR, Martin CR, et al. Cloherty and Stark's Manual of Neonatal care. 8th edn. South Asian edition. New Delhi: Wolters Kluwer India Pvt Ltd., Second Indian reprint 2018: p. 684-719.
[9] Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Cochrane Database Syst Rev 2001;2:CD000361.
[10] Kim SK. Use of intravenous immunoglobulin in the treatment of neonatal sepsis. American Journal of Diseases of Children 1989;143(11):1257-8.
[11] Lacy JB, Ohlsson A. Administration of intravenous immunoglobulins for prophylaxis or treatment of infection in preterm infants: meta-analyses. Arch Dis Child Fetal Neonatal Ed 1995;72(3):F151-F5.
[12] Whitelaw A. Treatment of sepsis with IgG in very low birthweight infants. Arch Dis Child 1990;65(4 Spec No):347-8.
[13] Shenoi A, Nagesh NK, Maiya PP, et al. Multicenter randomized placebo controlled trial of therapy with intravenous immunoglobulin in decreasing mortality due to neonatal sepsis. Indian Pediatr 1999;36(11):1113-8.
[14] Fischer GW. Use of intravenous immune globulin in newborn infants. Clinical Exp Immunol 1994;97(Suppl 1):73.
[15] Ballard JL, Khoury JC, Wadig A, et al. New Ballard Score, expanded to include extremely premature infants. J Pediatr 1991;119(3):417-23.
[16] Haque MM, Ahmed AS, HAlder SK. Clinical manifestation and bacteriological profile of septicaemia in preterm neonates: experience from a tertiary level pediatric hospital. Bangladesh J Med Sci 2004;10(1):29-33.
[17] Chandna A, Rao MN, Srinivas M, et al. Rapid diagnostic tests in neonatal septicemia. Indian J Pediatr 1988;55(6):947-53.
[18] Mir F, Aman S, Khan SR. Neonatal sepsis: a review with a study of 50 cases. J Trop Pediatr 1987;33(3):131-5.
[19] Haque KN, Remo C, Bahakim H. Comparison of two types of intravenous immunoglobulins in the treatment of neonatal sepsis. Clin Exp Immunol 1995;101(2):328-33.
[20] Gotoff S. Infections of the neonatal infant. Nelson Textbook of Paediatrics. 16th edn. Philadelphia: WB Saunders Company, 2000: p. 538-52.
[21] Kuruvilla KA, Thomas N, Jesudasan MV, et al. Neonatal group B streptococcal bacteraemia in India: ten years' experience. Acta Paediatr 1999;88(9):1031-2.
[22] Rao PS, Baliga M, Shivananda PG. Bacteriology of neonatal septicaemia in a rural referral hospital in South India. J Trop Pediatr 1993;39(4):230-3.
[23] Aurangzeb B, Hameed A. Neonatal sepsis in hospital-born babies: bacterial isolates and antibiotic susceptibility patterns. J Coll Physicians Surg Pak 2003;13(11):629-32.
[24] Ahmed ASMNU, Chowdhry MAKA, Hoque M, et al. Clinical and bacteriological profile of neonatal septicaemia in a tertiary level pediatric hospital in Bangladesh. Indian Pediatr 2002;39(11):1034-8.
[25] Dawodu A, Al Umran K, Twum-Danso K. A case control study of neonatal sepsis: experience from Saudi Arabia. J Trop Pediatr 1997;43(2):84-8.
[26] Moreno MT, Vargas S, Poveda R, et al. Neonatal sepsis and meningitis in a developing Latin American country. Pediatr Infect Dis J 1994;13(6):516-20.
[27] Saha SK, Rikitomi N, Ruhulamin M, et al. The increasing burden of disease in Bangladeshi children due to haemophilus influenzae Type B Meningitis. Ann Trop Paediatr 1997;17(1):5-8.
[28] Gladstone IM, Ehrenkranz RA, Edberg SC, et al. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. Pediatr Infect Dis J 1990;9(11):819-90.
[29] Weisman LE, Stoll BJ, Kueser TJ, et al. Intravenous immune globulin prophylaxis of late-onset sepsis in premature neonates. J Pediatr 1994;125(6 Pt 1):922-30.
[30] Kinney J, Mundorf L, Gleason C, et al. Efficacy and pharmacokinetics of intravenous immune globulin administration to high-risk neonates. Am J Dis Children 1991;145(11):1233-8.
[31] Weisman LE, Stoll BJ, Kueser TJ, et al. Intravenous immune globulin therapy for early-onset sepsis in premature neonates. J Pediatr 1992;121(3):434-43.
[32] Conway SP, Gillies DR, Docherty A. Neonatal infection in premature infants and use of human immunoglobulin. Arch Dis Child 1987;62(12):1252-6.
[33] Lassiter HA. Intravenous immunoglobulin in the prevention and treatment of neonatal bacterial sepsis. Adv Pediatr 1991;39:71-99.
[34] Sidiropoulos D, Bohme U, Von Muralt G, et al. Immunoglobulin substitution in the treatment of neonatal septicemia. Schweiz Med Wochenschr 1981;111(44):1649-55.
[35] Stabile A, Sopo SM, Romanelli V, et al. Intravenous immunoglobulin for prophylaxis of neonatal sepsis in premature infants. Arch Dis Child 1988;63(4):441-3.
[36] Haque KN, Zaidi MH, Haque SK, et al. Intravenous immunoglobulin for prevention of sepsis in preterm and low birth weight infants. Pediatr Infect Dis J 1986;5(6):622-5.
[37] Haque KN, Zaidi MH, Bahakim H. IgM-enriched intravenous immunoglobulin therapy in neonatal sepsis. Am J Dis Child 1988;142(12):1293-6.