



The Study of in Vitro Sensitivity and Resistance Pattern of Antibiotics in Neonatal Septicemia in Tertiary Care Hospital

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Abstract

Aims and objectives

1. To study in vitro sensitivity and resistance pattern of antibiotics in neonatal septicemia.
2. To find out the incidence of blood culture positive neonatal septicemia in tertiary care hospital

Study Design: This was a Prospective observational cohort study which was conducted in a tertiary care center in a metropolitan city.

Materials and methods: All symptomatic neonates upto 28 days old admitted in NICU of our institute with history and clinical symptoms suggestive of neonatal septicemia were enrolled in this study. The blood culture of all the suspected cases having clinical signs and symptoms of neonatal septicemia were analyzed and studied for culture sensitivity and resistance pattern. Incidence of blood culture positive neonatal septicemia amongst all neonates admitted in neonatal intensive care unit over the study period was also calculated.

Results: Over the study period a total of 2035 neonates were admitted in our NICU. Out of these 2035 Neonates 197 neonates were diagnosed to be having sepsis depending upon clinical criteria. All these 197 cases were studied in this study. Blood samples were drawn from all these neoates and CBC, CRP and blood culture tests were done. On clinical examination the most common signs in these children were Retraction, Flaring, grunting (36.55%), oliguria (26.4%), lethargy (27.41%), vomiting (19.29%) and poor feeding (17.26%). High pitched cry, hyporeflexia, petechial, purpura and hypotonia were least common signs which were seen in 0.51 % cases. Irregular respiration and splenomegaly was not seen in any patient. Blood culture was positive in 53 cases. Out of these 53 blood culture positive cases 28 (52.8%) cases were having lateonset sepsis and 25 (47.2%) cases were having early onset sepsis. An analysis of culture and sensitivity pattern of the blood culture positive cases revealed that overall most common organisms involved in cases of neonatal sepsis were methicillin-susceptible coagulase-negative staphylococci [MSCoNS] (22.64%) followed by enterobacter (16.98%), Methicillin-resistant staphylococcus aureus (13.2%) and klebsiella pneumonia (13.2%) . The most common gram positive organisms involved in neonatal sepsis were MSCoNS (22.64%) while the gram negative organisms most commonly involved were enterobacter (16.98%). 3(5.66%) had fungal septicemia caused by candida. Patients The least common organisms involved in neonatal sepsis were found to be due to *E.tarda*, *C.Frundi* and of polymicrobial etiology which was seen in 1.88% cases each. The

study of sensitivity pattern of organisms revealed that 100% of MRSA were susceptible to ciprofloxacin, ofloxacin, amikacin and gentamicin. E-coli was sensitive to ciprofloxacin, meropenam and amikacin. Klebsiella isolated were found to be relatively resistant to ofloxacin and imipenem while acitenobacter were found to be susceptible to colistin in only 60% cases.

Conclusion: Neonatal sepsis is one of the major cause of morbidity and mortality. Its incidence is increasing as more premature and low birth weight babies are resuscitated and are being managed in neonatal intensive care units. Prematurity, low birth weight babies and male gender are associated with increased risk of developing sepsis. In view of the changing spectrum of the causative agents of neonatal septicemia and their antibiotic sensitivity and resistance patterns from time to time and from one hospital to another, a positive blood culture and the antibiotic sensitivity and resistance pattern testing of the isolates are the best guide to the antimicrobial therapy and which would be beneficial for the best outcome of the disease. Early diagnosis and prompt antibiotic therapy is the key to management of neonatal sepsis.

Keywords: neonatal sepsis, Early onset Sepsis, Late onset sepsis, Blood culture and sensitivity, Antibiotic therapy.

INTRODUCTION

The term "septicemia" indicates the presence of actively multiplying bacteria and their toxins circulating in the blood stream. Neonatal septicemia is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia in the first month of life. Neonatal septicemia is a major cause of morbidity and mortality^[1]. The etiology of septicemia is usually multifactorial. The laboratory diagnosis that is the culture reports may take 48-72hrs and culture positivity may be as low as 20-82%. Therapy cannot wait in a critically sick neonate. On one hand withholding antibiotics can endanger the life of a neonate while on the other hand indiscriminate overuse of antibiotics on the basis of clinical suspicion alone may be a major cause of emergence of resistant organisms^[2].

Neonatal sepsis may be divided into early-onset or late-onset depending upon onset of signs and symptoms of sepsis. Onset of sepsis within initial 3 days of birth is called early onset sepsis. Majority of babies having early onset sepsis will present within 24 hours after birth and only very small number of patient presents between 48-72 hours^[3]. The usual causative organisms involved in early onset sepsis are derived from maternal flora. Transplacental infections or ascending infections from maternal genital tract are usually transmitted to neonate during late intrauterine life or during the time of delivery as it passes through the vaginal canal. The common organisms

associated with early onset neonatal sepsis are Group B streptococcus, E coli, Staphylococcus epidermidis, H influenza and Listeria monocytogenes^[4].

Late onset sepsis by definition occurs after 3 days (72 hours) after birth. Usually it is seen in babies who were resuscitated. Preterm, low birth weight babies with h/o resuscitation like endotracheal intubation, neonates requiring mechanical ventilation and those in whom venisection or vascular access or catheterization was done are also predisposed for late onset sepsis^[5].

Irrespective of the etiological agent the sepsis in neonates usually present with similar features like lethargy, refusal to feed, Respiratory distress in the form of tachypnea and intercostal and subcostal retractions, convulsions and renal failure^[6]. Most of the times the features of sepsis in neonates are subtle and a high index of suspicion is required as any delay in instituting treatment can prove fatal.

The investigations done to evaluate a neonate with sepsis include complete blood count, Serum C-Reactive protein levels, Urine microscopy and culture sensitivity, Cerebrospinal fluid chemistry and gram staining of CSF and culture and sensitivity^[7]. In cases of severe sepsis the complete blood count may show thrombocytopenia, neutropenia and anemia (secondary to bone marrow suppression). Blood culture and sensitivity is the gold standard test for the diagnosis of neonatal sepsis. Nonetheless it is

a time consuming test and the treatment should not be withheld till culture and sensitivity reports come. Other investigation like micro ESR, Immature to total neutrophil ratio etc can also be used as marker of neonatal sepsis. In cases of severe sepsis disseminated intravascular coagulopathy may develop which may be heralded by prolonged PT, aPTT and thrombocytopenia.

Imaging in neonates with sepsis has a limited role but may help aid in diagnosis. X-ray chest may show pulmonary infiltrate while neurosonography may show changes of ventriculitis and altered echogenicity of brain parenchyma. There can be evidence of intracranial hemorrhage secondary to DIC caused by sepsis.

The management consist of immediate supportive care. In cases of sepsis baby may develop acidosis, hypoglycemia, hypocalcaemia, gastro-intestinal bleeding, convulsions, pneumonia and renal failure. Each of this condition needs highly specialized care like correction of hypoglycemia or hypocalcaemia should be done. Baby should be started on oxygen. Septic shock should be treated in accordance with standard protocols. Anticonvulsants if indicated should be judiciously used. Empirical treatment with the common antibiotics to which the bacterial flora is susceptible should be started. The antibiotics treatment can be changes depending upon the culture and sensitivity report. If nosocomial infections are suspected then cephalosporin and aminoglycoside combination should be empirically started. Pneumonia, pyelonephritis and meningitis must be appropriately treated [8].

MATERIALS AND METHODS

This is a Prospective observational cohort study. All symptomatic neonates upto 28 days old admitted in NICU of tertiary care hospital during November 2011 to November 2013, with history and clinical symptoms suggestive of neonatal septicemia. During this study the blood culture of all the suspected cases having clinical signs and symptoms of neonatal septicemia were analyzed

and studied for culture sensitivity and resistance pattern. Incidence of blood culture positive neonatal septicemia amongst all 2035 neonates admitted in neonatal intensive care unit over a period of two years was also calculated.

At least 3 ml, of blood was collected from any peripheral vein after proper cleaning of the venipuncture site (area of 5cm) with spirit and povidone iodine from where the sample was to be collected, blood sample was collected on the day of appearance of signs of sepsis.

Inclusion criteria: All neonates with clinical history, signs and symptoms of sepsis delivered in tertiary care hospital and admitted in NICU.

Exclusion criteria: 1. Babies more than 28 days of life. 2. Neonates not admitted in NICU.

RESULTS

The study was undertaken at tertiary care hospital in metropolitan city .Cases which were clinically diagnosed as septicemia admitted in Neonatal Intensive Care Unit were studied. They were subjected for laboratory tests like CBC, CRP and blood culture. Observations of these 197 cases were analyzed for following objectives.

As depicted below the most common signs and symptoms associated with neonatal sepsis were respiratory distress in the form of retractions, grunting and nasal flaring accounting for 36.55% of cases of neonatal sepsis. One of the important thing about respiratory distress as a sign of sepsis is that unlike subtle signs and symptoms of neonatal sepsis like lethargy and refusal to feed etc. respiratory signs and symptoms like tachypnea, retractions, grunting and flaring can be objectively assessed and when present always points towards a sinister pathology in a neonate. Irregular respiration which is quite often seen in neonates should not be confused with respiratory distress. Lethargy was the second most common symptom found in 27.4% of cases, oliguria was seen in 26.4% of cases, vomiting in 19.29% of cases and poor feeding in 17.26% of cases (Table 1).

TABLE 1: SIGNS AND SYMPTOMS OF SEPSIS.

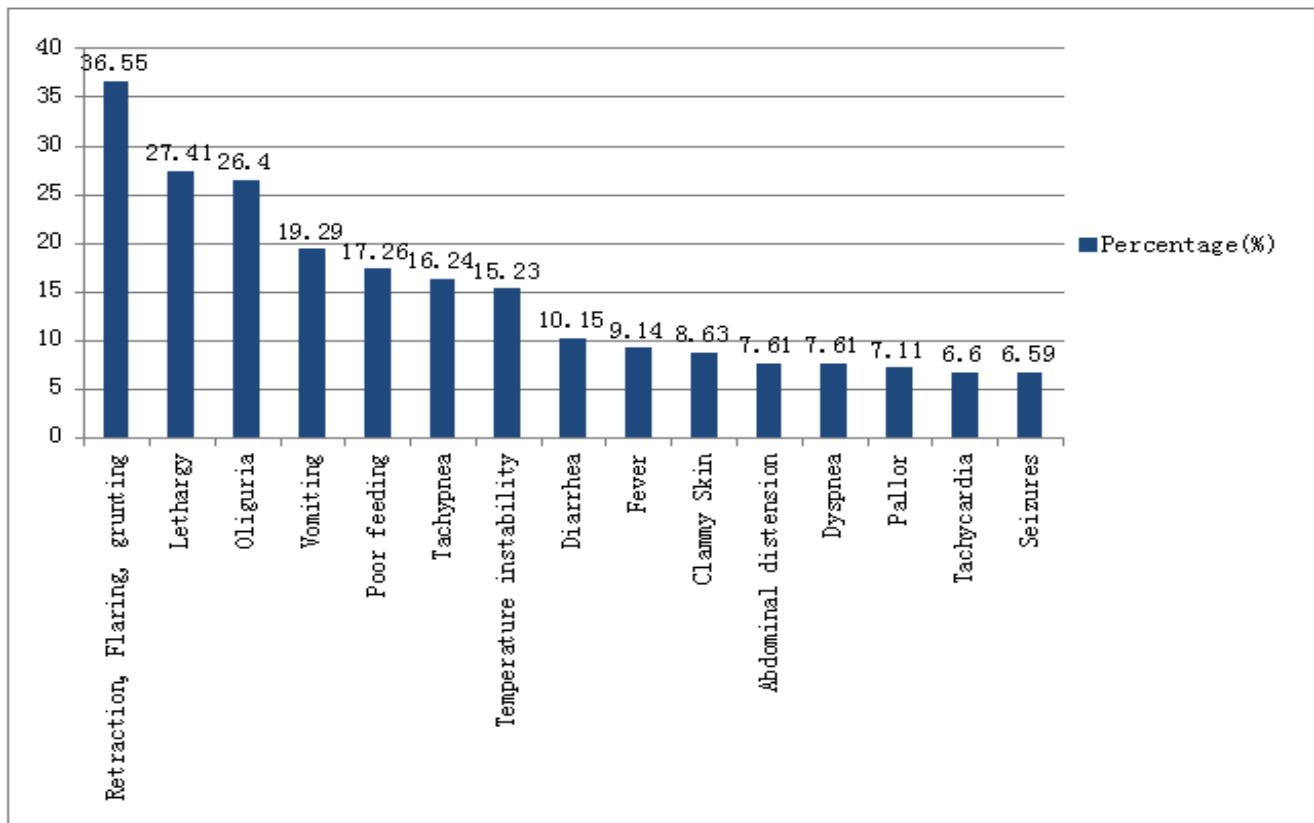
Signs and symptoms	No.(out of 197)	Percentage(%)
Fever	18	9.14
Temperature instability	30	15.23
Not doing well	10	5.08
Poor feeding	34	17.26
Oedema	10	5.08
Irritability	6	3.05
Lethargy	54	27.41
Seizures	13	6.59
Hyporeflexia	1	0.51
Hypotonia	1	0.51
Abnormal Moro's Reflex	5	2.54
Irregular Respiration	0	0
Full fontanelle	2	1.02
High pitched cry	1	0.51
Abdominal distension	15	7.61
Vomiting	38	19.29
Diarrhea	20	10.15
Hepatomegaly	2	1.02
Cyanosis	5	2.54
Apnea	4	2.04
Dyspnea	15	7.61
Tachypnea	32	16.24
Retraction, Flaring, grunting	72	36.55
Oliguria	52	26.4
Pallor	14	7.11
Mottling	11	5.58
Clammy Skin	17	8.63
Tachycardia	13	6.6
Bradycardia	11	5.58
Hypotension	2	1.02
Splenomegaly	0	0
Petechiae, purpura	1	0.51
Bleeding	2	1.02

Bleeding manifestation though uncommon in neonatal sepsis must always be looked for. Petechiae, purpura and gastrointestinal bleeding points towards advance stages of neonatal sepsis and may herald onset of disseminated intravascular coagulopathy.

Sepsis when complicated by meningitis may present as convulsions. It may also cause other systemic involvement like acute renal failure or pneumonia. Or oliguria or even anuria if there is involvement of renal system. In our study oliguria was seen in 52 (26.4%). Seizures occurred in 13

(6.59%). There was bleeding diathesis in the form of petechiae, purpura and other bleeding manifestations (Figure 1).

FIGURE 1: SIGNS AND SYMPTOMS OF SEPSIS.



The distribution of the cases depending upon the age at onset of signs and symptoms of sepsis was divided into early onset and late onset sepsis. While 105 (53.3%) cases were that of early onset

sepsis and 92 (46.7%) were that of late onset sepsis if clinical or blood culture criteria was employed (Table 2).

TABLE.2: AGEWISE DISTRIBUTION

Age (in days)	Blood Culture		Total(%)
	Positive (%)	Negative (%)	
3 or less(early onset sepsis)	25 (47.2)	80 (55.6)	105 (53.3)
More than 3 (late onset sepsis)	28 (52.8)	64 (44.4)	92 (46.7)
Total	53 (100)	144 (100)	197 (100)

The percentage of early onset and late onset sepsis was 47.2% and 52.8% in blood culture positive cases. While in overall cases early onset sepsis was more common (53.3%), late onset sepsis was more common (52.8%) in blood culture positive cases (Figure 2)

FIGURE 2: AGEWISE DISTRIBUTION

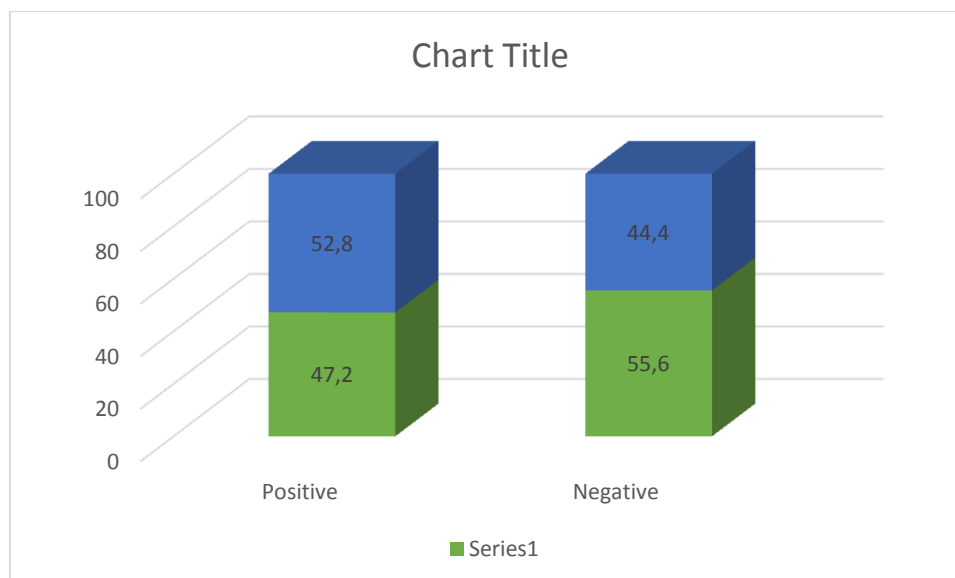


TABLE 3: ORGANISMS ISOLATED IN BLOOD CULTURE.

Organism detected in Culture	Number of cases	Percentage(%)
Gram negative organism		
Enterobacter	9	16.98
Klebsiellapneumoniae	7	13.2
Acinetobacterbaumanni	5	9.43
Escherechia coli	2	3.77
Edwardsiellatarda	1	1.88
Citrobacterfrundi	1	1.88
Gram positive organism		
MSCONS	12	22.64
MRSA	7	13.2
MSSA	5	9.43
Polymicrobial		
MR CONS + Enterococcus	1	1.88
Others		
Candida	3	5.66
Total	53	100

Out of the 53 culture positive maximum i.e 12 (22.64%) of the isolates were of MSCONS cases , enterobacter were 9(16.98 %).Klebsiella 7(13.2%) , MRSA were 7(13.2%), MSSA were 5(9.43%), Acinetobacter were 5(9.43%), Ecoli were 2(3.77%), Edwardsiella was isolated in 1case (1.88%), citrobacter 1(1.88%),polymicrobial like MRCONS and enterococcus was found in 1.88%, and candida in 5.66% of cases (Figure 3)

FIGURE.3: ORGANISMS ISOLATED IN BLOOD CULTURE

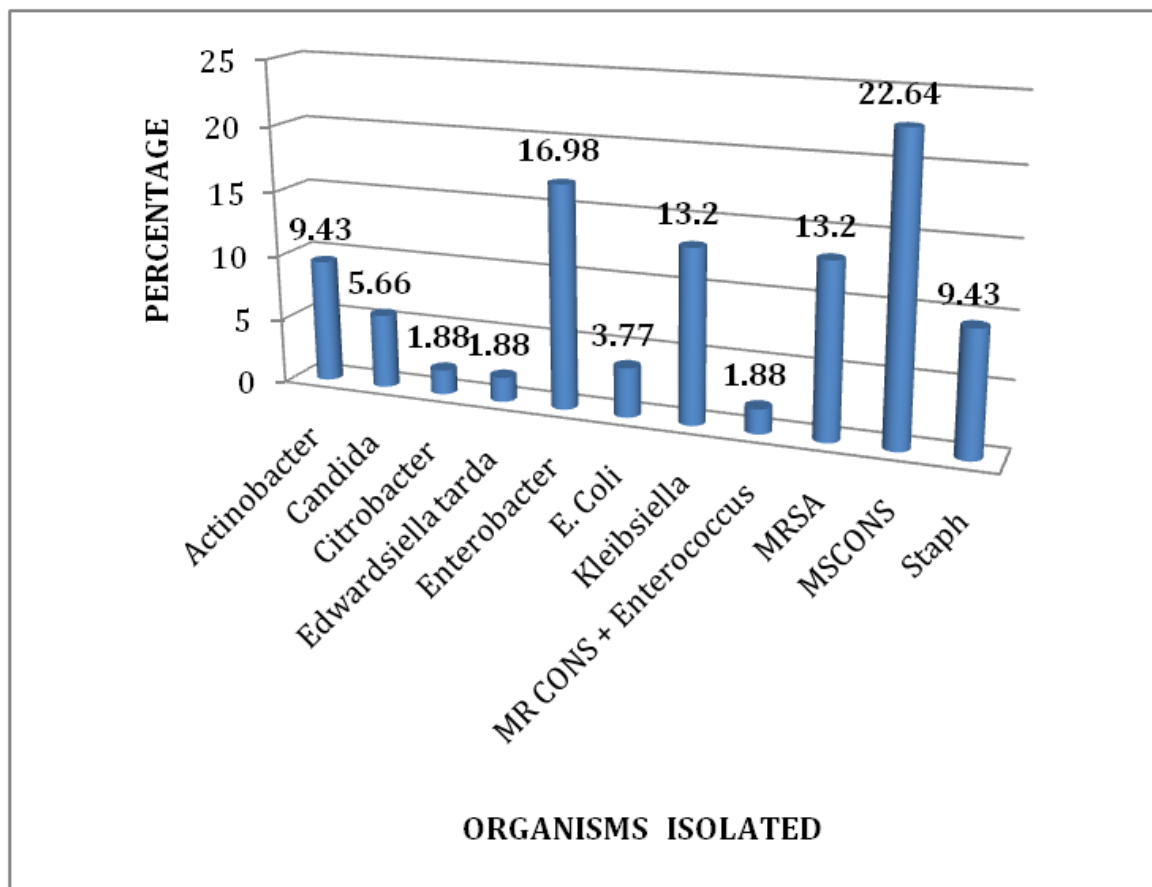
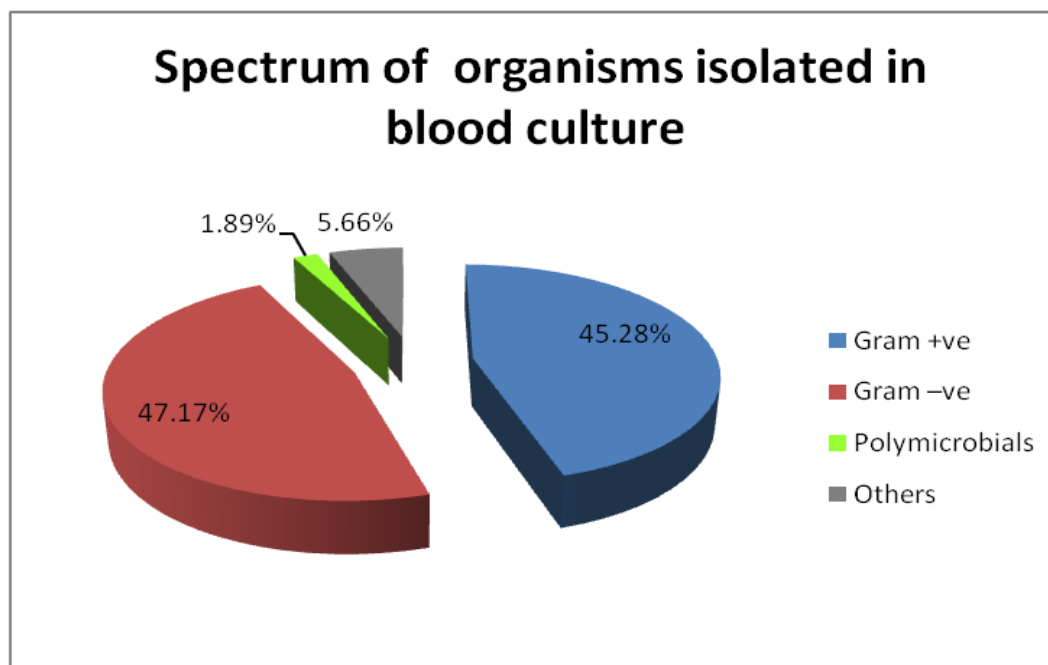


FIGURE 4 : ORGANISMS ISOLATED IN BLOOD CULTURE



The analysis of sensitivity pattern of the organisms revealed that Enterobacter were sensitive to Amikacin i.e.55.55% followed by linezolid i.e.33.33%. About 28.57% of klebsiella

isolates were susceptible to Ofloxacin and Imipenem. While 60% cases of Acinetobacter isolates were susceptible to colistin Edwardsiellatarda had 100% sensitivity to

ciprofloxacin and ofloxacin. E.coli showed 100% sensitivity to ciprofloxacin, amikacin, meropenem, imipenem, piperacillin, tazobactam, cefixime. MRSA isolates were 100% susceptible to Ofloxacin, Ciprofloxacin and Gentamicin, Amikacin. MRSA isolates were 100% susceptible to Ofloxacin, Ciprofloxacin and Gentamicin, Amikacin while only 85% of these were susceptible to linezolid and 70% of the strains were susceptible to vancomycin. MSSA were 100% sensitive to amoxicillin clavulanic acid, 60% were sensitive to vancomycin. In Coagulase negative staphylococcus aureus, 91.66% of cases were sensitive to ciprofloxacin, 83.33% to gentamicin, 75% were sensitive to teicoplanin.

DISCUSSION

Neonatal sepsis is one of the leading causes of neonatal morbidity and mortality. The incidence of neonatal sepsis is expected to rise as more and more premature and low birth weight babies are surviving due to improved neonatal care. Neonatal sepsis is divided into early onset and late onset sepsis depending upon whether manifestations of sepsis appeared before or after 72 hours of birth. The etiology, organisms involved and manifestations are usually different in early and late onset sepsis. The common organisms involved in early onset sepsis are Group B streptococcus, E-Coli, Coagulase negative staphylococcus, H. Influenzae and Listeria [9]. Organisms involved in late onset sepsis are Staphylococcus epidermidis, E-Coli, Klebsiella and pseudomonas [10]. Various studies show that the incidence of Staph. Epidermidis sepsis is increasing in cases of late onset neonatal sepsis. The colonization of conjunctiva, umbilicus, GI and respiratory tract by these organisms occurs in neonates after birth and may cause sepsis in susceptible neonates [11].

The common manifestations of sepsis in neonates include lethargy, refusal to feed, dusky appearance, tachypnea, intercostal and subcostal retractions and sometimes seizures. Premature and low birth weight babies are susceptible for

development of sepsis. Moreover the signs and symptoms of sepsis in these babies are more subtle and hence a high index of suspicion is required in these babies as delay in initiation of antibiotics may cause fulminant septic shock which may ultimately prove fatal [12]. The progression of sepsis from entry of bacteria to development of fulminant sepsis can be very rapid. It may cause redistributive shock requiring inotropes [13].

The investigations required in evaluation of neonatal sepsis may include Total blood count including platelet count, Micro ESR, I/E ratio, Blood culture and sensitivity test and C -Reactive protein levels. Total blood count may show thrombocytopenia and neutropenia. Blood culture may show offending organisms and sensitivity test may help towards deciding treatment. Blood culture and sensitivity patterns are important because there are no universal flora and organisms differ from place to place and it is essential that the treatment plan should take into consideration the local flora associated with sepsis [14].

Since sepsis carries a high morbidity and mortality in neonates prevention is one of the important aspects of management of sepsis. Prenatal care provided to pregnant patients is important in prevention of early-onset GBS sepsis with identification of maternal carriage of Group B Streptococcus through screening for all pregnant women [15]. If GBS infection is found in pregnant patients penicillin prophylaxis can be given and in patients allergic to penicillin alternative antibiotic therapy like clindamycin can be considered [16]. During NICU stay avoiding unnecessary catheterization, proper hand washing by NICU personnel, proper care during various invasive procedures and parenteral nutrition can significantly reduce the incidence of neonatal sepsis [17].

Management of neonatal sepsis includes prompt institution of antibiotics. Once there is clinical suspicion of neonatal sepsis the treatment with antibiotics must not be withheld as this may prove fatal due to relative immunosuppression in the

neonate. The antibiotics should be immediately started. The antibiotics can be changed depending upon the report of blood culture and sensitivity [18]. In addition to antibiotics patient may also require supportive treatment in the form of inotropic support, thermoregulation and parenteral nutrition. Risk of bleeding manifestations requires that a close watch should be kept on bleeding time, clotting time and platelet count and if required blood transfusions or blood component therapy should be given. Disseminated intravascular coagulation must be judiciously managed [10]. Any focus of infection like abscess or empyema etc should be immediately drained [19]. Other therapies which may be used for the treatment of neonatal sepsis include IV immunoglobulin, Granulocyte Monocyte transfusion, exchange transfusion and recombinant cytokines but efficacy of these therapies are unproven [20].

CONCLUSION

Neonatal septicemia is still a leading cause of morbidity and mortality in developing countries like India. In view of the changing spectrum of the causative agents of neonatal septicemia and their antibiotic sensitivity and resistance patterns from time to time and from one hospital to another, a positive blood culture and the antibiotic sensitivity and resistance pattern testing of the isolates are the best guide to the antimicrobial therapy and which would be beneficial for the best outcome of the disease.

CONFLICT OF INTEREST: none

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