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Incidence of neonatal sepsis and its causative agents

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Abstract

Neonatal sepsis is a clinical syndrome of bacteremia characterized by systemic signs and symptoms of infection in the first month of life. While most infection-related deaths in the neonatal period occur in low- and middle-income countries, there precise data have been lacking. The aim of the study was to determine the incidence and causative organisms for neonatal sepsis among infants and evaluate antibiotic resistance pattern of the organisms isolated. Total 228 clinically suspected cases were studied. Samples collected for culture were Blood, Umbilical swab and Skin swab. Identification and antimicrobial susceptibility testing of microorganisms was carried out by standard procedure. The male to female ratio in the study was not statistical significant. It was observed that babies died in low birth weight had maximum percentage of septicemia followed by very low birth weight, high risk low birth weight and normal birth weight. Male to female ratio showed significant difference with gestation age. Present study reported 39.9% cases to be blood culture positive. *Klebsiella pneumoniae* was found to be predominant organism followed by *CoNS*, *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*. Out of 189 cases, 67 infants showed bacterial growth in skin culture. The percentage of CoNS was maximum followed by *Klebsiella pneumoniae*, *E. coli* and *Pseudomonas*. The predominantly isolated pathogens in the study were CoNS, *Klebsiella* species, *Escherichia coli*, coagulase-positive *staphylococci* and least was *Pseudomonas aeruginosa* and *Proteus vulgaris*. Antibiotic susceptibility studies revealed the resistance pattern of pathogens isolated. *Klebsiella pneumoniae* isolates were resistant to chloramphenicol followed by Ceftriaxone, Ciprofloxacin and sensitive to Amoxyclav followed by Amikacin. *E. coli* isolates were mostly resistant to Chloramphenicol and Ciprofloxacin and sensitive to Amoxyclav and Amikacin. Isolates of *S. aureus* were resistant to Penicillin, and Oxacilline and most sensitive to Amoxyclav and Vancomycin. *C. albicans* isolated from blood culture were sensitive for Amphotericin B and Fluconazole. *CoNS* isolates were resistant to Penicillin and Oxacillin and most sensitive to Vancomycin and Amoxyclav. Most of the isolates of *Pseudomonas aeruginosa* were resistant to Ceftazidime, Cefoperazone and Tobramycin and sensitive to Amikacin, Ciprofloxacin and Ticarcillin. There cannot be single recommendations for the antibiotic regimen for neonatal sepsis in all settings. The choices of antibiotics depend on the prevailing flora responsible for sepsis in the given unit and their antimicrobial sensitivity. Determination of the neonatal sepsis incidence, its' bacterial pathogens, and the patterns and rates of antibiotic resistance among all the neonate and infant populations are necessary.

Keywords: neonatal sepsis, neonates, nicu, umbilical swab, antibiotic resistance pattern, cephalosporin

1. Introduction

The neonatal period, the first 28 days of life, carries the highest risk of mortality per day than any other period during the childhood. According to the study, sepsis is most common cause of neonatal deaths globally. Neonatal sepsis (NS) is a clinical syndrome of bacteremia characterized by systemic signs and symptoms of infection in the first month of life. It encompasses systemic infections of the newborn including septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection. It has been explained that neonates are at the highest risk for bacterial sepsis, with the prevalence at 1 to 10 per 1000 live births worldwide^[1, 2]. NS is a worldwide problem that presents a management challenge to care groups for neonates and infants. Sepsis occurs when the body has an immediate, systemic, and overwhelming reaction to an infection. Advances in diagnosis and management of sepsis can considerably decrease the sepsis complications and improve its outcome, especially in preterm infants^[3]. NS incidence increased during the recent years, it may be due to the more common use of invasive procedures and the development of resistant organisms.

Neonatologists who supervise neonatal intensive care unit (NICU) always face a challenge in managing the neonatal infections due to the changing patterns of the microbial flora and their antibiotic sensitivity^[4, 5].

While most infection-related deaths in the neonatal period occur in low- and middle-income countries, until now there precise data have been lacking. This lack of data has prevented public health officials from recognizing neonatal sepsis as an area of serious concern and implementing measures to prevent it^[6]. The aim of the present study was to determine the incidence and causative organisms for neonatal sepsis among infants, who were cared for, in NICUs in Mumbai, India and to evaluate the antibiotic resistance pattern of the organisms isolated.

2. Material and methods

This study was conducted over a period of 24 months between March 2001 and February 2003, at NICU of TN Medical College and Nair Charitable Hospital, Mumbai, India. During the study period, all admitted neonates with clinical signs and symptoms of sepsis at the time of admission or who developed sepsis during their hospital stay were assessed using sepsis screening tool and included in the study. The study protocol was approved by the Institutional Ethics Committee of Nair Hospital where in Inclusion and exclusion criteria were defined. Parents of cases signed informed consent, after explaining the study protocol.

A standard structured data collection form was designed to obtain social demographic, clinical, and laboratory data that were recorded by qualified medical staff. All neonates were subjected to full clinical examination stressing on gestational age, birth weight, mode of delivery, and risk factors for sepsis: premature rupture of membranes (PROM), maternal fever, insertion of an umbilical catheter, and so forth.

Sepsis is defined as presence of at least 3 out of the following four criteria^[1] (i) presence of risk factors of sepsis (e.g., prematurity, chorioamnionitis), (ii) presence of two or more clinical signs of sepsis (poor reflexes, lethargy, respiratory distress, bradycardia, apnea, convulsions, abdominal distension, and bleeding), (iii) abnormal hemogram and positive CRP and positive culture

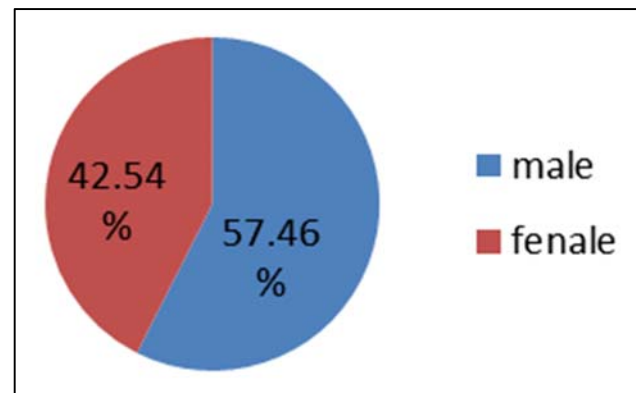
Total 228 clinically suspected cases were studied in the present study. Detailed clinical history and examination findings of these cases were recorded. Samples collected for the culture were Blood, Umbilical swab and skin swab. All these samples were collected as clinically indicated and at the discretion of the Neonatologist. Samples were collected, transported, cultured and identification of microorganisms was carried out by standard procedures^[8].

Antimicrobial susceptibility testing of all bacterial isolates was performed by the Kirby-Bauer disc diffusion method on Mueller-Hinton agar. The antibiotics tested for gram positive bacteria were Penicillin (10 units), oxacillin (1 µg), amoxicillin-clavulanic acid (30 µg), Cefazolin (30 µg), erythromycin (15 µg) and vancomycin (30 µg). The antibiotics tested for gram negative bacteria were amoxicillin-clavulanic acid (30 µg), cefotaxime (30 µg), ceftriaxone (30 µg), Chloramphenicol (30 µg), amikacin (30 µg), ciprofloxacin (30 µg). The antibiotics tested for Pseudomonas species were Ticarcillin (75 µg), ceftazidime (30 µg), Cefoperazone (75µg), Tobramycin (10 µg), Amikacin (30 µg) and ciprofloxacin (5 µg).

Along with isolates tested, known standard cultures were also tested for antibiotic sensitivity. The standard cultures used were *Staphylococcus aureus* ATCC 25923, *Pseudomonas* ATCC 27853, and *E.coli* ATCC 25922

Summary of measures was reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. The differences in distribution were evaluated using the chi-square test for categorical variables. Value ≤ 0.05 was considered statistically significant.

3. Results



Difference between gender is statistically significant (P=0.004)

Graph I: Gender Distribution n= 228

Table I: Gender distribution with respect to gestation age n= 228

Gender	Less than 34 weeks (%)	More than 34 weeks (%)	Term (%)	Total (%)
Male	19.10	20.60	60.30	100
Female	38.10	19.60	42.30	100
Total	27.20	20.20	52.60	100

Difference between gestation age related to gender is statistically significant (P=0.004)

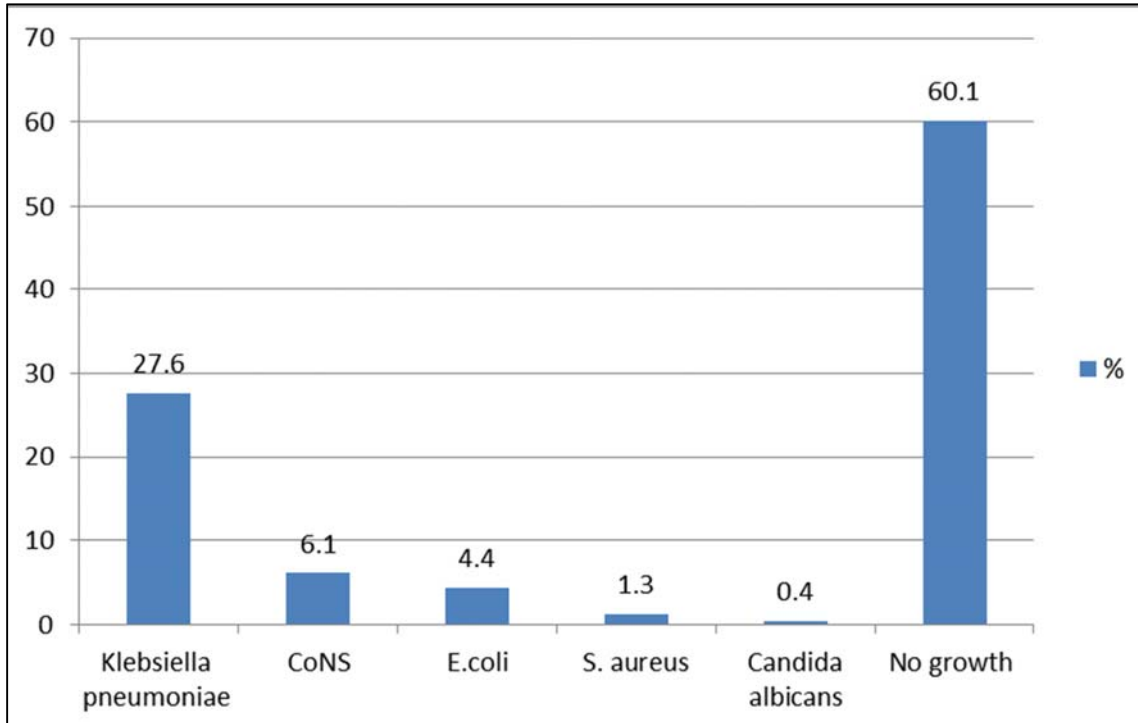
Table II: Birth weight (Kg) and septicemia correlation. n= 228

Birth weight (Kg)	Admissions (%)	Septicemia cases (%) (Out of each admission)
Less than 1.5	24.56	42.90
1.5- 2	22.81	42.30
2- 2.5	22.37	43.10
More than / equal to 2.5	30.26	33.30
Total	100	40.10

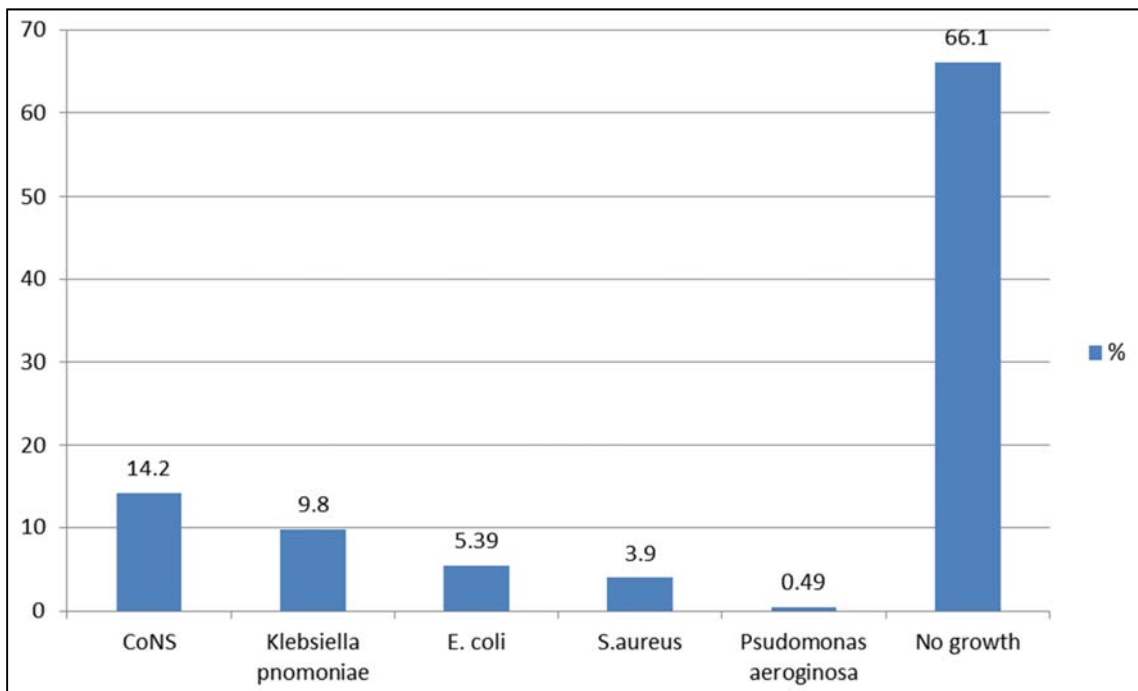
Table III: predominant organisms in preterm and full term infants. n= 228

Blood culture	Preterm infants		Full term infants (%)
	Less than 34 weeks (%)	More than 34 weeks (%)	
<i>Klebsiella pneumoniae</i>	32.25	21.74	27.50
<i>CoNS</i>	4.48	2.17	8.33
<i>E.coli</i>	8.06	00.00	4.17
<i>S. Aureus</i>	00.00	00.00	2.50
<i>Candida albicans</i>	1.61	00.00	00.00
No growth	53.23	76.09	57.50
Total	100	100	100

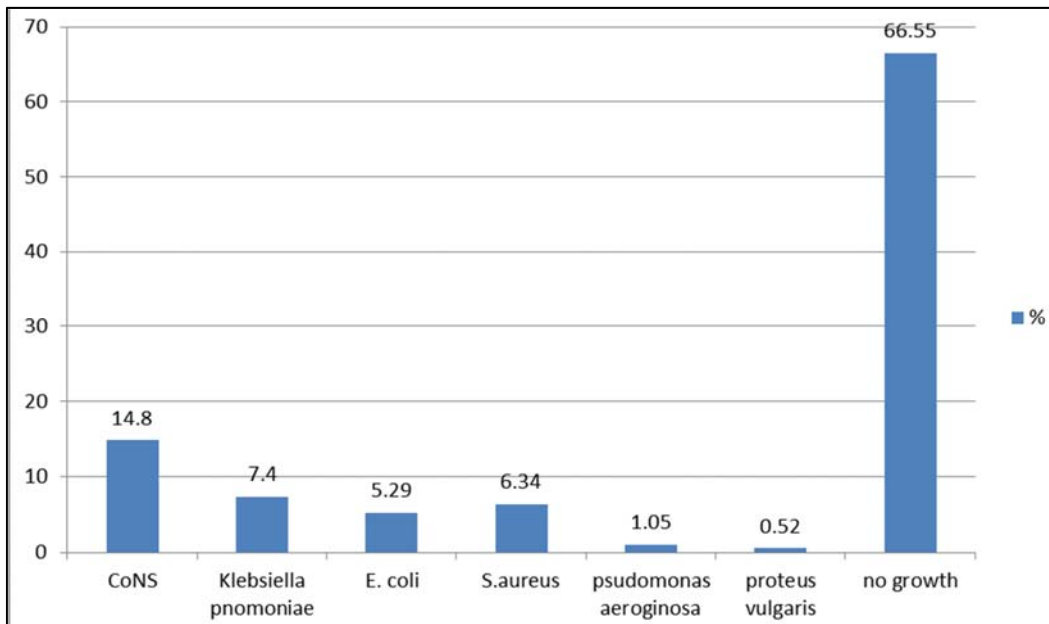
CoNS: Coagulase negative *Staphylococci*



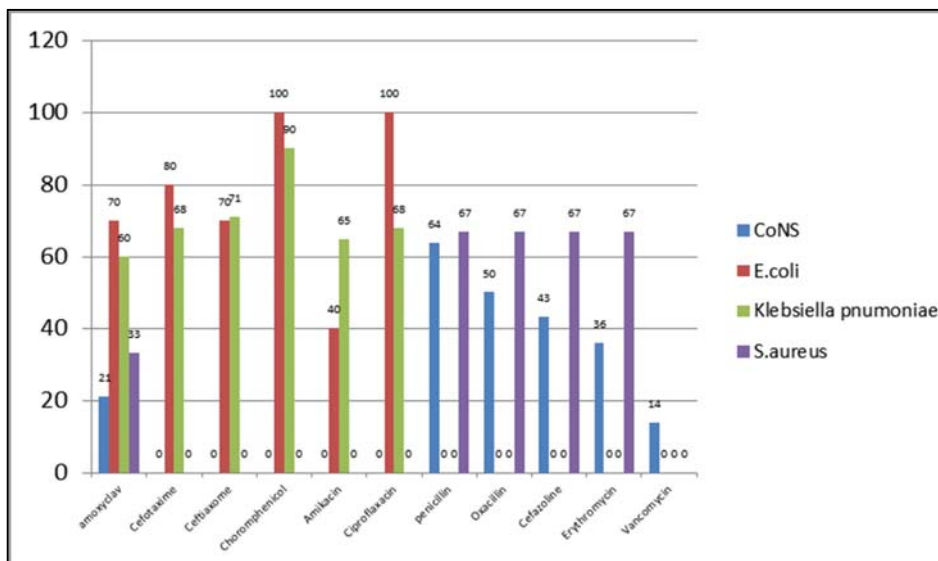
Graph III: Organisms isolated from blood n= 228



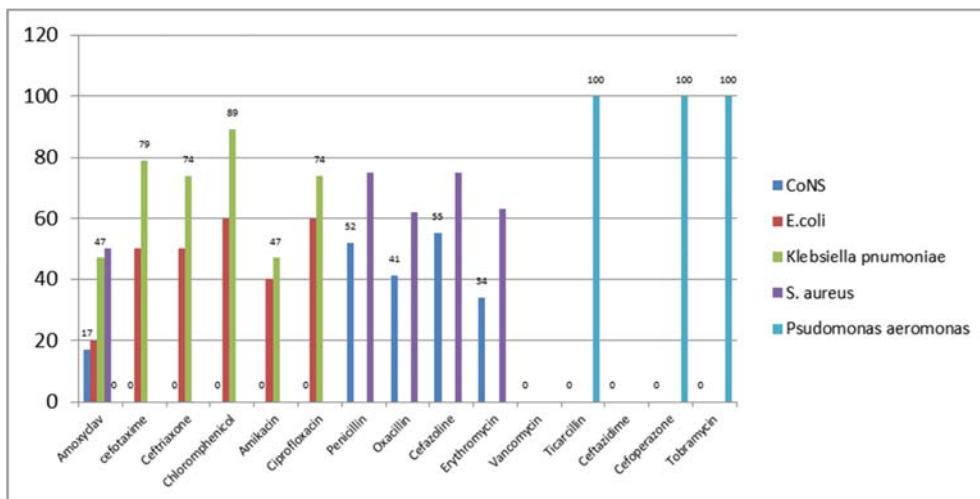
Graph III: Organisms isolated from umbilical cord n= 204



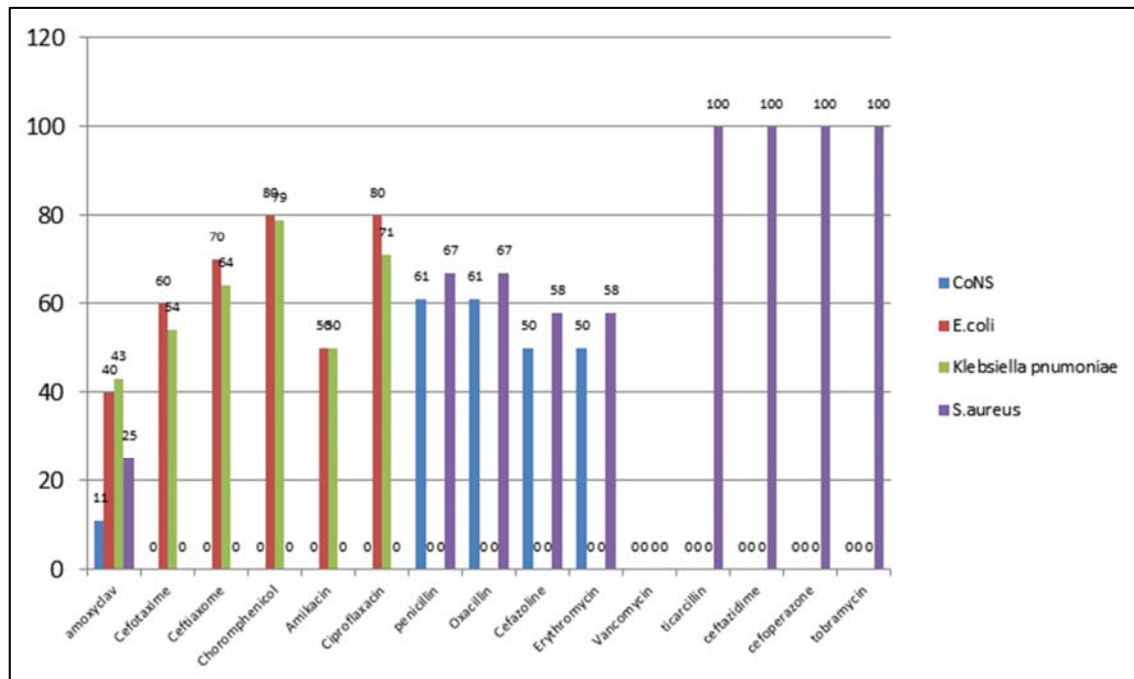
Graph IV: Organisms isolated from skin culture n= 189



Graph V: Antibiotic resistance pattern of organisms isolated from blood culture n= 90



Graph VI: Antibiotic resistance pattern of organisms isolated from Umbilical cord n= 69



Graph VII: Antibiotic resistance pattern of organisms isolated from skin n= 67

4. Discussion

Sepsis is the commonest cause of neonatal mortality and is probably responsible for 30-50% of the total neonatal deaths each year in developing countries [10, 11]. It is estimated that 20% of all neonates develop sepsis and approximately 1% die of sepsis related causes [11]. According to data from National Neonatal Perinatal Database 2000, the incidence of neonatal sepsis has been reported to be 38 per 1000 intramural live births in tertiary care institutions. Septicemia was the commonest clinical category with an incidence of 24 per 1000 live births [12].

In the present study total 228 neonates were studied. The male to female ratio in the study was found to be 1.43: 1, which was not statistical significant and were similar to those of other studies. This increasing susceptibility to infection in males was postulated due to a gene on X chromosomes involved with functioning of thymus and synthesis of immunoglobulin. Females have double the number of genes and therefore greater resistance to infection [13].

During the study period, maximum number of admissions were seen of normal birth weight with 30.26% followed by low birth weight (2- 2.5 Kg) with 22.37%. very low birth weight (1.5-2 kg) with 24.56 % and high risk low birth weight (less than 1.5 kg) with 22.81%. It was observed that babies died in low birth weight had maximum percentage of septicemia (43.10%) followed by very low birth weight (42.9%), high risk low birth weight (42.30%) and normal birth weight (22.3%). These finding are consistent with those of other investigators [14].

52.60% babies were full term and 47.40 % were pre term. While 27.20% were born before the 34th week of their life and 20.20 % were born after 34th but before 37th week of their life. In present study male to female ratio showed significant difference with gestation age. S.P. Khatua reported similar findings with reference to gestational age and sex distribution [15]. Ledger W.J *et al* had stated in his

study that earlier the pregnancy, poor the fetal survival [16]. The present study had similar observations.

Klebsiella pneumonia was the predominant organism in preterm and full term babies. Followed by *Escherichia coli* and *Staphylococcus aureus*. Savey *et al* reported 81% of *CoNS* in premature babies [17]. Jevon *et al* reported *Bacillus cereus* in his case presentation [18].

Present study reported 39.9% cases to be blood culture positive. *Klebsiella pneumoniae* was found to be predominant organism with 27.6% followed by *CoNS* (6.10%), *E.coli* (4.40%), *S. aureus* (1.30%) and *C. albicans* (0.40%) Abida malik *et al* also found *Klebsiella pneumoniae* as important pathogens [19]. Anita Chandana found 37.5% of *E. coli* as predominant organism in her study [20]. Sue Hall showed *CoNS* as the predominant organism [21]. Sinha *et al* found *Pseudomonas aeruginosa* as predominant organism followed by *Klebsiella* species and *E. coli* [22]. Makhou *et al* reported 49 neonates with acquired fungal sepsis, but in this study only one isolate of *C. albicans* was found [23]. Sharon welbel isolated *C. parapsilosis* from blood stream infection in NICU as a common source of outbreak [24].

69 infants showed bacterial growth in umbilical culture. The organisms isolated were *CoNS* (12.79%), *Klebsiella pneumonia* (8.89%), *E. coli* (4.0%), *S. aureus* (3.50%) and *Pseudomonas aeruginosa* (0.4%). Susan Landers reported 71% of *CoNS* causing umbilical sepsis [25]. Goldmann *et al* found *E.coli* as predominant colonizing organism on umbilical culture followed by *Klebsiella species* and *Pseudomonas species* among gram negative organism and *S. aureus* from gram positive organisms [26].

Out of 189 cases, 67 infants showed bacterial growth in skin culture. The percentage of *CoNS* was maximum with 12.30% followed by *Klebsiella pneumoniae* (6.10%), *E.coli* (4.40%) *Pseudomonas aeruginosa* (0.90%) and *Proteus vulgaris* (0.40%). This study had similar findings as compared to Carl D' Anglo *et al*. Routine culturing of the

surface sites of hospitalized infants is a prediction of the pathogens which subsequently cause invasive infection^[27].

The predominantly isolated pathogens in our study were CoNS, *Klebsiella* species, *Escherichia coli*, coagulase-positive *staphylococci* and least was *Pseudomonas aeruginosa*.

While Rajiv Aggarwal *et al* reported *Klebsiella pneumoniae* was the most frequently isolated pathogen (31.2%), followed by *Staphylococcus aureus* (17.5%) among the intramural live births. Among extramural babies admitted for neonatal problems, *Klebsiella pneumoniae* was the commonest organism (36.4%), followed by *Staphylococcus aureus* (14.3%) and *Pseudomonas* (13.2%)^[28].

While study in Iran reported, predominantly isolated pathogen in all the study groups in their study was *Enterobacter species* and other pathogens such as *Escherichia coli* and coagulase-positive *staphylococci* were less common^[29]. A study by Weston *et al.* reported Group B *Streptococcus* as the most common pathogen, followed by *Escherichia coli*^[30]. Naderi-nasab *et al.* reported gram positive organisms were more frequent than gram negative organisms in nosocomial and acquired infections in NICUs of Mashhad, Iran^[31]. Also, in a study on the Pakistani population, *Escherichia coli* was the most common organism followed by *Klebsiella*, and among the gram positive organisms, *Staphylococcus aureus* was most frequent^[32]. Most of the previous reports have emphasized on the pivotal role of Gram-negative organisms such as *E. Coli*, *Klebsiella* and *Staphylococcus aureus* as main pathogens causing neonatal sepsis^[33]. *Enterobacter* species can cause fatal conditions such as urinary tract infections, hepatobiliary sepsis, endocarditis, surgical wound infection, bacteremia and neonatal sepsis, and also stem the further development of antibiotic resistance^[34]. Hence preventing the spread of this pathogen especially in developing countries such as India could help to reducing the mortality and morbidity.

Antibiotic susceptibility studies revealed the resistance pattern of pathogens isolated. *Klebsiella pneumoniae* isolates were resistant to chloramphenicol followed by Ceftriaxone Ciprofloxacin and sensitive to Amoxycylav followed by Amikacin. Malik *et al*, had reported Amikacin and Ciprofloxacin to be most sensitive and Chloramphenicol as less effective drug. But in our study Amikacin and Ciprofloxacin were to be less effective drug^[35]. *E.coli* isolates were mostly resistant to Chloramphenicol and Ciprofloxacin followed by Cefotaxime, Amoxicillin and sensitive to Amoxycylav and Amikacin. Isolates of *S. aureus* were resistant to Penicillin and Oxacilline and most sensitive to Amoxycylav and Vancomycin. *C. albicans* isolated from blood culture were sensitive for Amphotericin B and Fluconazole. Our results were similar to studies of Johnson *et al*^[36]. CoNS isolates were resistant to Penicillin and Oxacillin while were most sensitive to Vancomycin and Amoxycylav. Most of the isolates of *Pseudomonas aeromonas* were resistant to Ceftazidime, Cefoperazone and Tobramycin and sensitive to Amikacin, Ciprofloxacin and Ticarcillin.

Resistance of sepsis-related pathogens against routine antibiotics has been reported widely. Aftab *et al.* found higher resistance to gentamycin and cephalosporins compared to imipenem, with acceptable sensitivity against sepsis-related pathogens^[32]. Aurangzeb *et al.* reported considerable resistance to commonly used antibiotics such

as ampicillin, amoxicillin, ceftazidime, cefotaxime, and comparatively low resistance to gentamycin, tobramycin, imipenem, amikacin, ofloxacin and ciprofloxacin^[37]. Recently, a high incidence of resistance to aminoglycosides was noted amongst most gram negative organisms, whereas imipenem was effective in most of the cases^[38]. Therefore, the therapeutic role of some antibiotics such as quinolones, may gain considerable importance in the near future, mainly due to the emergence of resistant bacterial strains in the NICUs. Reduction of the susceptibility of the bacteria to imipenem can be attributed to its over-prescription in our population that emphasizes on prescribing antibiotics such as third-generation cephalosporin for these patients.

There cannot be single recommendations for the antibiotic regimen for neonatal sepsis in all settings. The choice of antibiotics depend on the prevailing flora responsible for sepsis in the given unit and their antimicrobial sensitivity. Decision to start antibiotics is based upon clinical features and/ or a positive septic screen. Empirical antibiotic therapy should be unit specific and determined by the prevalent spectrum of etiological agents and their antibiotic sensitivity pattern. Antibiotics once started should be modified according to the culture sensitivity reports. The empirical choice of antibiotics is dependent upon the probable source of origin of infection^[28d].

5. Conclusion

Appropriate identification of the sepsis source, prompt antibiotic prescription, and aggressive management can effectively prevent adverse events following neonatal sepsis. Determination of the neonatal sepsis incidence, its' bacterial pathogens, and the patterns and rates of antibiotic resistance among all the neonate and infant populations are necessary. Our study had few limitations, as the sample size was small. Hence we cannot generalize the results of our study to other hospitals of Mumbai.

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