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Assessment of neonatal septicemia in government medical college, bettiah and antibiotic susceptibility pattern in them

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Abstract
There is a difference in the causative organisms for neonatal sepsis between the developed and developing countries. In the developing world, Escherichia coli, Staphylococcus aureus and Klebsiella sp. are the most common pathogens of earlyonset sepsis, whereas Staphylococcus aureus, Streptococcus pyogenes, and Streptococcus pnemoniae are the most commonly reported organisms in late-onset sepsis. Hence the present study was planned to assess the bacteriological profile of clinically suspected septicemia cases of neonates from blood sample and to determine the sensitivity pattern and selection of appropriate antibiotics of the same.
The present study was planned in the Department of Pediatrics, Government Medical College Bettiah, West Champaran from Dec 2018 to April 2019. Total 280 cases were studied and out of that 42 cases were found positive for the septicemia.
The spectrum of bacteria associated with neonatal sepsis is constantly changing. The rates of Antibiotic resistance among the bacterial pathogens is high. Hence there is a need to constantly monitor the same in NICU's. Antimicrobial stewardship program should be implemented to make antibiotic policy at local level to deal the current scenario.

Keywords: neonatal septicemia, antibiotic, susceptibility, etc

Introduction
Sepsis remains a leading cause of mortality and morbidity, especially during the first five days of life and in low and middle-income countries (LMIC) [1]. Hospital infection also remains a major cause of mortality in children despite progress encountered in the last decades. WHO recommends ampicillin (or penicillin; cloxacillin if staphylococcal infection is suspected) plus gentamicin for empiric treatment of neonates with suspected clinical sepsis; when referral is not possible, once daily gentamicin plus oral amoxicillin may be used. It is known, however, that in many countries, agents with a broader spectrum, such as third-generation cephalosporins, are commonly used to treat neonatal and infant sepsis [2]. Against this background, concerns are increasing regarding bacterial pathogens with reduced susceptibility to empiric medication with variations both between and within LMIC [3]. The WHO seeks to provide a paediatric perspective on antibiotics to be included on the list of essential medicines, which is currently in the process of being updated. The potential need to revise the existing WHO guidelines based on new antimicrobial resistance (AMR) data or evidence relating to drug safety in neonates and children must be evaluated. For this purpose, a number of reviews have been commissioned to address these aspects.
Neonatal sepsis is a type of neonatal infection and specifically refers to the presence in a new born baby of a bacterial blood stream infection (BSI) (such as meningitis, pneumonia, pyelonephritis, or gastroenteritis) in the setting of fever. Older textbooks may refer to neonatal sepsis as "sepsis neonatorum". Criteria with regards to hemodynamic compromise or respiratory failure are not useful clinically because these symptoms often do not arise in neonates until death is imminent and unpreventable. Neonatal sepsis is divided into two categories: early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS refers to sepsis presenting in the first 7 days of life (although some refer to EOS as within the first 72 hours of life), with LOS referring to presentation of sepsis after 7 days (or 72 hours, depending on the system used). Neonatal sepsis is the single most common cause of neonatal death in hospital as well as community in developing country.
It is difficult to clinically exclude sepsis in new borns less than 90 days old that have fever (defined as a temperature > 38 °C (100.4 °F). Except in the case of obvious acute viral bronchiolitis, the current practice in new borns less than 30 days old is to perform a complete workup including complete blood count with differential, blood culture, urinalysis, urine culture, and cerebrospinal fluid (CSF) studies and CSF culture, admit the newborn to the hospital, and treat empirically for serious bacterial infection for at least 48 hours until cultures are demonstrated to show no growth. Attempts have been made to see whether it is possible to risk stratify newborns in order to decide if a newborn can be safely monitored at home without treatment despite having a fever. One such attempt is the Rochester criteria.
Note that, in neonates, sepsis is difficult to diagnose clinically. They may be relatively asymptomatic until hemodynamic and respiratory collapse is imminent, so, if there is even a remote suspicion of sepsis, they are frequently treated with antibiotics empirically until cultures are sufficiently proven to be negative. In addition to fluid resuscitation and supportive care, a common antibiotic

regimen in infants with suspected sepsis is a beta-lactam antibiotic (usually ampicillin) in combination with an aminoglycoside (usually gentamicin) or a third-generation cephalosporin (usually cefotaxime-ceftriaxone is generally avoided in neonates due to the theoretical risk of kernicterus.) The organisms which are targeted are species that predominate in the female genitourinary tract and to which neonates are especially vulnerable to, specifically Group B Streptococcus, Escherichia coli, and Listeria monocytogenes (This is the main rationale for using ampicillin versus other beta-lactams.) Of course, neonates are also vulnerable to other common pathogens that can cause meningitis and bacteremia such as Streptococcus pneumoniae and Neisseria meningitidis. Although uncommon, if anaerobic species are suspected (such as in cases where necrotizing enterocolitis or intestinal perforation is a concern, clindamycin is often added.

Granulocyte-macrophage colony stimulating factor (GM-CSF) is sometimes used in neonatal sepsis. However, a 2009 study found that GM-CSF corrects neutropenia if present but it has no effect on reducing sepsis or improving survival [4].

Trials of probiotics for prevention of neonatal sepsis have generally been too small and statistically underpowered to detect any benefit [5], but a randomized controlled trial that enrolled 4,556 neonates in India reported that probiotics significantly reduced the risk of developing sepsis [6]. The probiotic used in the trial was Lactobacillus plantarum.

A very large meta-analysis investigated the effect of probiotics on preventing late-onset sepsis (LOS) in neonates. Probiotics were found to reduce the risk of LOS, but only in babies who were fed human milk exclusively. It is difficult to distinguish if the prevention was a result of the probiotic supplementation or if it was a result of the properties of human milk. It is also still unclear if probiotic administration reduces LOS risk in extremely low birth weight infants due to the limited number of studies that investigated it. Out of the 37 studies included in this systematic review, none indicated any safety problems related to the probiotics. It would be beneficial to clarify the relationship between probiotic supplementation and human milk for future studies in order to prevent late onset sepsis in neonates [7].

In resource-limited settings with limited and/or intermittent access to laboratory evaluations this definition is not workable. Consequently, a highly specific definition of neonatal sepsis is not available for LMIC settings. Instead it is recommended that initiation of antibiotics should be prompted by clinical signs of Possible Serious Bacterial Infection (PSBI), a highly sensitive definition aiming to reduce the number of false negatives (i.e. missed cases of sepsis). Clinical signs of PSBI, according to the Young Infants Clinical Signs Clinical Study criteria of WHO's Integrated Management of Childhood Illness (IMCI) guidelines, are defined as the presence of any one of a history of difficulty feeding, history of convulsions, movement only when stimulated, respiratory rate of 60 or more breaths per min, severe chest retractions, or a temperature of 37.5 °C or higher or 35.5 °C or lower [8].

There is a difference in the causative organisms for neonatal sepsis between the developed and developing countries [9]. In the developing world, Escherichia coli, Staphylococcus aureus and Klebsiella sp. are the most common pathogens of earlyonset sepsis, whereas Staphylococcus aureus, Streptococcus pyogenes, and Streptococcus pnemoniae are the most commonly reported organisms in late-onset sepsis.

Hence the present study was planned to assess the bacteriological profile of clinically suspected septicemia cases of neonates from blood sample and to determine the sensitivity pattern and selection of appropriate antibiotics of the same.

Methodology

The present study was planned in the Department of Pediatrics, Government Medical College Bettiah, West Champaran from Dec 2018 to April 2019. Total 280 cases were studied and out of that 42 cases were found positive for the septicemia.

Neonatal septicemia was diagnosed as per the clinical criteria given by Vergnano et al. [10]. Blood sample(0.5 to 2 ml) was collected with all aseptic precaution and was inoculated into blood culture bottle BactT/Alert® PF (BIOMERIEUX, INC. Durhams, NC 27704) containing 20 ml of broth.

The blood and broth were mixed gently and bottles were transported to laboratory for incubation in BacT/Alert 3D system and further processing was done as per manufacturer's guideline.

Those blood culture bottles which were indicated positive, query positive and query negative by Bact/ Alert 3D system were sub cultured on Sheep blood agar and MacConkey agar. The blood agar and MacConkey's medium were incubated at 35 ± 20 Celsius for 18 - 24 hours in aerobic atmosphere. Various organisms were identified on the basis of colony morphology and standard biochemical tests. Those blood culture bottles which were indicated as negative by 5 days (as per setting of Bact / Alert 3D system) were reported as "no growth". The isolates were subjected to antimicrobial susceptibility testing by Kirby Bauer disk diffusion method as per CLSI guidelines 2011 [11].

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Results & Discussion

Early diagnosis and therapy are essential for the prevention of morbidity and mortality of neonatal sepsis in the neonatal intensive care unit. Although males have been reported to be have two- to five-fold higher likeliness to develop septicemia than females.

Compare to adults, infants are having much higher tendencies to develop infections. 3 This is attributed by several factors including an in-properly developed immunological system making sepsis a risk to the newborn, particularly under poor hygienic conditions. In pre antibiotic era, mortality from neonatal sepsis exceeded 90% but now with availability of antibiotics, the mortality rate has been reduced to between 10 and 50% as describe in Rubin et al. [12] and Yalaz et al. [13] In advance centers, blood culture is positive in 80% of genuine sepsis [14].

The higher rate of EOS observed in our study may be due to early horizontal transmission of pathogens from NICU and delivery rooms or vertical transmission of these pathogens colonized in maternal genital tract after unhygienic obstetric practices. LOS is caused by postnatal acquisition of the pathogens, caused by the bacteria which thrive in the external environment of the hospital or home. A possible

explanation for lower incidence of late onset septicemia could be better understanding in the importance of cleanliness, hygiene, and using aseptic techniques in a hospital setting by medical staffs.

Positivity rate depend on many factors like non-bacterial causes of septicemia, anaerobic bacterial infection, ongoing antibiotic therapy, less volume of blood etc [15]. Klebsiella spp. and Coagulase Negative Staphylococci are commonly isolated organism in different studies. [16] May be because of their nature as saprophyte or commensals [17], environmental factors, low birth weight or prematurity which makes them more susceptible to surrounding infectons. Some studies also found E. coli and Staphylococcus aureus as commonly isolate organisms may be because of different geographical area [18].

The majority of isolates causing neonatal septicemia were gram-negative isolates, similar to findings of Roy et al. 2002 [19] and investigators of the Delhi Neonatal Infection Study (DeNIS) Collaboration [20]. Likewise, preponderance of the gram-negative bacilli has been reported in other studies conducted in Nepal and Pakistan [21]. On contrast, other studies from abroad revealed gram-positive cocci including S. aureus, CONS, and group B streptococci as the predominant isolates [22].

Table 2: Type & Causative Microbes

Parameters	No. of Cases
Type of sepsis	
Early Onset Sepsis	20
Late Onset Sepsis	22
Causative bacteria	
Gram Positive	18
Gram Negative	24

Table 2: Positive Cases and Drug Sensitivity

Organisms	Blood culture positive Cases
Gram-positive	
Staphylococcus aureus	9
Methicillin-resistant Staphylococcus aureus	6
Staphylococcus epidermidis	3
Total Cases	18 cases
Gram-negative:	
Klebsiella pneumonae	13
Acinetobacter	6
Citrobacter	3
Pseudomonas	2
Total Cases	24 cases

Table 3: Resistance of Isolates to Antibiotic

Antibiotics	Staphylococcus aureus	Kleibsella spp.	E. Coli	Pseudomonas spp.
Amoxicillin	40	38	36	40
Cotrimoxazole	33	29	22	39
Gentamycin	29	32	29	28
Piperacillin	0	0	1	2
Cefoperazone	2	2	2	1
Cefotaxime	16	15	14	21
Ciprofloxacin	29	30	25	29
Ceftriaxone	12	13	9	8

Antibiotic susceptibility pattern of the isolates varies from region to region. Prior knowledge of the antibiogram of the isolates in the region would help the clinician to choose on the right antibiotic.

Of the risk factors evaluated for neonatal sepsis, the factors which were statistically significant are low birth weight, maternal fever and premature rupture of membranes. Similar studies carried out on neonatal sepsis have reported pre-term and low birth weight babies, gravida less than or equal to two, maternal fever and PROM for more than 16 hours as significant risk factors for developing neonatal sepsis [23]. Prompt antib

iotic therapy has a great influence on the outcome of neonatal sepsis. Thus, the knowledge of the antibiogram and the groups at risk for sepsis will help the clinician to choose the right antibiotic therapy.

The positive blood culture with antibiotic sensitivity of the isolated organism is the best guide to antimicrobial therapy, as resistance to antibiotics is a worldwide problem that causes ineffectiveness of empirical treatment. More so, strict infection control practices combined with judicious use of antibiotic therapy are the main solutions to this problem. However, it will be important to continue the surveillance of neonatal septicaemia in order to closely follow changes in trends and identify risk factors, to obtain information for empiric antibiotic therapy and to act rapidly in case of major changes in susceptibility patterns.

Conclusion

The spectrum of bacteria associated with neonatal sepsis is constantly changing. The rates of Antibiotic resistance among the bacterial pathogens is high. Hence there is a need to constantly monitor the same in NICU's. Antimicrobial stewardship program should be implemented to make antibiotic policy at local level to deal the current scenario.

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