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International Journal of Current Research
Vol. 7, Issue, 05, pp.16544-16547, May, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

ANTIMICROBIAL SENSITIVITY PATTERN AND CLINICAL OUTCOME OF NEONATAL SESPSIS: A STUDY AT TERTIARY CARE HOSPITAL IN KASHMIR, J & K, INDIA

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ARTICLE INFO

Article History:
Received 04th February, 2015
Received in revised form
02nd March, 2015
Accepted 28th April, 2015
Published online 31st May, 2015

Key words:

Bacteriemia,
Hypothermia,
Septecemia..

ABSTRACT

Background: Neonatal sepsis contributes significantly to morbidity and mortality among young infants. Neonatal mortality in developing countries is usually due to an infectious cause. The gold standard of investigation in developing countries is a positive blood culture. It is important to know the aetiology of neonatal bloodstream infections so that empirical treatment can be effective.
Methods: We conducted a retrospective clinical study over one year between April 2014 until March 2015, looking at the aetiology of both early and late onset neonatal sepsis. We analysed data from 362 (26.6%) culture proven sepsis patient isolates out of 1360 suspected cases of neonatal sepsis. Blood samples were cultured on MacConkey, blood and chocolate agars and bacteria were identified based on characteristic morphology, gram stain appearance and standard commercially prepared biochemical tests. Antimicrobial sensitivity testing was performed for ampicillin, cloxacillin, gentamicin, amikacin, cefuroxime and ceftriaxone.
Results: Culture proven sepsis was noted in 26.6% (362/1360) of the study participants. Isolated bacterial pathogens were predominantly Cogulase Negative *Staphylococcus aureus(26.79%)*,followed by *Klebsiellaspp(12.98%)* and *Acinitobactor species(11.87%)*. Resistance of blood culture isolates was high to ampicillin 77.7% (280/362) and cloxacillin 70.1% (254/362)), moderate to ceftriaxone 14.91% (54/362) and cefuroxime 19.88% (72/362), and low to amikacin 2.2% (8/362). The overall neonatal mortality was 13.97% (190/1360), being higher in neonates with sepsis 90/362 (24%) as compared to those without 100/998 (10%).
Conclusions: *Cogulase Negative Staphylococcus aureus* was predominant isolate followed by *Klebsiella* and *Acinitobactor species*. There was high resistance to ampicillin and cloxacillin. Mortality rate due to neonatal sepsis was high in our setting. Routine antimicrobial surveillance should guide the choice of antibiotics for empirical treatment of neonatal sepsis.

***Citation*:** KhurshidWani, Imran Gattoo, KaiserAhmed and WaseemQadir, 2015. "Antimicrobial sensitivity pattern and clinical outcome of Neonatal sepsis: A study at tertiary care hospital in Kashmir, J & K, India", *International Journal of Current Research,* 7, (5), 16544-16547.

INTRODUCTION

Neonatal mortality contribute significantly to the infant mortality rates in developing countries, various conditions are responsible for neonatal mortality among which is neonatal sepsis, which account for about 26% of neonatal mortality (Lawn *et al.,* 2005). Neonatal sepsis which is defined as sepsis occurring in the first 28 days of life can be divided into early onset and late onset. Differentiation into early and late onset neonatal sepsis is important in prevention and treatment because of aetiological differences. Clinical presentation of neonatal sepsis varies and there are no pathognomonic features (Vergnano *et al.,* 2005), however some clinical features have been reported to predict sepsis. Kayange et al. in a study which was conducted in Bugando, Tanzania reported inability to breast feed, lethargy, convulsion, chest wall in drawing, jaundice and umbilical redness to be strongly associated with neonatal sepsis (Kayange *et al.,* 2010). Non-specific presentation of neonatal sepsis and poor or delayed laboratory services have resulted in empirical treatment of sepsis in resource limited set up. In the management of neonatal sepsis, clinicians in many resource limited settings make tentative diagnosis and empirical treatment of neonatal sepsis based on the new neonatal WHO Integrated Management of Childhood Illnesses (n-IMCI) guidelines (Edmund and Zaidi, 2010). However aetiology of neonatal sepsis as well as response to antimicrobial agents may vary significantly from time to time and geographically which may affect the success of empirical management (Kayange *et al.,* 2010; Edmund and Zaidi, 2010; Blomberg *et al.,* 2007).Correct and timely identification of infectious agents of neonatal sepsis as well as their antibiotic sensitivity patterns are essential as they guide both empiric and definitive

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treatment. Early onset neonatal sepsis occurs within seven days after delivery while late onset sepsis occurs from the eighth day to the end of the neonatal period, which is considered to be 28 days (World Health Organisation, 2010). In developed countries, bacterial infections in neonates are commonly due to Escherichia coli, other Enterobacteriaceae, Listeria monocytogenes, coagulase negative Staphylococci and group B Streptococcus (Stoll *et al.,* 1996; WHO, 1999). Reports of dynamic nature of the aetiological agents and their response to antimicrobial agents in different geographical areas calls for availability of local data in guiding choices of antibiotics. This study was carried out to determine aetiology, antimicrobial resistance of isolated bacteria and outcome of neonatal sepsis.

METHODS

This was a hospital based retrospective study carried out at a neonatal unit in a tertiary care hospital. Both term and preterm neonates admitted with clinical diagnosis of neonatal septicaemia, presenting with any one of the following features were eligible; presence of fever (≥ 38.0°C) or hypothermia (≤36.5°C), convulsions, lethargy, inability to feed, hypoglycaemia, vomiting, bulging fontanels, respiratory distress, jaundice and signs of infection on the skin (pus spots) and umbilical pus discharge or hyperaemia. During the study period 1360 were admitted in the neonatal ward as suspected sepsis out of which 362 came out to be culture proven sepsis. Standardized questionnaires were used to obtain demographic and clinical information which included details of thorough physical examination.

Two millilitres of venous blood was aseptically drawn from anterior cubital fossa of each neonate and inoculated into paediatric blood culture bottles. Blood culture bottles were incubated at 37°C for 24 h after which aliquots were sub-cultured on solid agar plates; MacConkey, blood and chocolate agars for up 96 h before being regarded as no growth. Colonies on solid agar plates were identified based on characteristic morphology, gram stain appearance and standard commercially prepared biochemical tests (Barrow, 2003). Antimicrobial sensitivity testing was performed for antimicrobials which included first and second line antibiotics for treating neonatal sepsis at our cetre first line antibiotics are ampicillin, cloxacillin and gentamicin and second line is ceftriaxone. Ampicillin 10µg, cloxacillin 5µg gentamicin 10µg, amikacin 30µg, cefuroxime 30µg, and ceftriaxone 30µg sensitivity testing were performed by Kirby Bauer diffusion method using Mueller Hinton agar with incubation of 24 h at 37°C. Sensitivity was determined according to Clinical Laboratory Standard Institute standards (Clinical and Laboratory Standard Institute, 2006). Results were recorded as resistant, intermediate and sensitive, however, during data analysis intermediate were categorized as resistant.

RESULTS

Demographic and clinical characteristics of participants

Three hundred and sixty two neonates with a median age of 4 days (range 0–26) were recruited. Two hundred and four (56.35%) were males and hundred and fifty eight (43.6%) were female Table 1 shows demographic characteristics of participants. Most frequently reported clinical features was fever (91.5%). Other included inability to breastfeed, lower chest wall in-drawing, difficulty in breathing, jaundice, bulging fontanelle, skin pustules, convulsion and hypothermia (Table 1).

Table 1. Demographic and clinical characteristics of participants

Variables	N=362	%
Age (Days)		
0 – 6	294	81.21
7 – 28	68	18.74
Sex		
Male	204	56.35
Female	158	43.64
Weight (gm)		
≤ 2500	110	30.38
> 2500	252	69.6
Maturity		
Preterm	102	28.17
Term	260	71.82
Clinical features (signs & symptoms)		
Fever	302	83.42
Hypothermia	8	2.2
Inability to feed	206	56.9
Bulging fontanelle	33	9.1
Difficulty in breathing	73	20.1
Lower chest wall in drawing	89	24.58
Convulsions	10	3.62
Umbilical pus discharge with hyperaemia	317	87.56
Skin rash with pus spots	31	8.5
Jaundice	44	12.15

Three hundred and sixty two participants 26.6 % (362/1360) had blood culture proven bacterial infection . Isolated bacterial pathogens were predominantly Cogulase Negative *Staphylococcus aureus (26.79%)*, followed by *Klebsiellaspp (12.98%)* and *Acinitobactor species (11.87%).* These three organisms accounted for approximately 51.64% of all isolates in blood culture.

Table 2. Bacterial isolation from blood culture of the patients

Organism	Early and late infection (days) (N=74)		
	0 – 6 n(%)	7 – 28 n(%)	Total
Cogulase Negative	81 (25.96)	16 (17.39)	97 (26.79)
Staphylococcus aureus			
Acinitobactor	37(11.85)	6(6.5)	43(11.87)
Enterococcus	14(4.4)	12(13.04)	26(7.1)
Klebsiella species	38(12.17)	9(9.7)	47 (12.98)
Escherichia coli	15(4.8)	0 (0)	15(4.1)
MSSA	18(5.7)	10(10.86)	28(7.7)
Enterobactor	16(5.12)	3(3.2)	19(5.24)
Salmonella	6(1.9)	6(6.5)	6(3.3)
Streptococcipneumonie	6(1.9)	5 (5.4)	6 (3.03)
Pseudomonas spp	12 (3.84)	5 (5.4)	12 (4.6)
MRSA	21(6.7)	15(6.73)	36(9.9)
Yeast	2(.7)	6(6.5)	8(2.2)

Antimicrobial susceptibility of isolated bacteria

Antimicrobial susceptibility pattern was performed for all bacterial isolates. Isolates from blood had highest resistance against ampicillin and cloxacillin. Table 4 shows antimicrobial resistance pattern of organisms isolated form blood culture.

Overall resistance of blood culture isolates was high to ampicillin 77.7% (280/362) and cloxacillin 70.1% (254/362), moderate to ceftriaxone 14.91% (54/362) and cefuroxime 19.88% (72/362), and low to amikacin 2.2% (8/362).

Table 4. Antimicrobial resistance pattern of isolated bacteria from blood (N=362)

Organism	Antibacterial agent					
	Amp R n (%)	Clox R n (%)	Gent R n (%)	Amik R n (%)	Cefur R n (%)	Ceft R n(%)
Cog negative Staphy. aureus	81 (83.50)	79 (81.4)	48(49.48)	0 (0)	14(14.43)	13 (13.40)
Klebsiella species	47 (100)	42 (89.3)	35 (74.46)	3 (6.3)	18 (38.29)	10(21.27)
Acinitobactor	38 (88.37)	43 (100)	22 (51.16)	0 (0)	5 (11.62)	4 (9.3)
MRSA	0 (0)	36(100)	36 (100)	0 (0)	0 (0)	0 (0)

Immediate outcome of sepsis

The overall neonatal mortality was 13.97% (190/1360), being higher in neonates with sepsis 90/362 (24%) as compared to those without 100/998 (10%).

DISCUSSION

From the findings of this study, neonatal sepsis is common and contributes significantly to mortality among neonates admitted in the neonatal ward at GB Pant hospital, Government Medical College Srinagar. The prevalence of positive blood culture sepsis of 26.1% observed in this study is higher than 15.9% reported by Bloomberg *et al*. 2007. It is also higher than 6.5% which was reported by Klingenberg *et al*. 2003 from a study conducted in another referral hospital. The increase in prevalence of sepsis could be accounted for by the increase in resistance to antimicrobial which may have resulted in inadequate treatment in lower health care facilities. Collectively, our study and that of Bloomberg *et al*. 2007 indicate a high magnitude of neonatal sepsis which may reflect low quality of neonatal care as opposed to developed countries which have lower prevalence rates of neonatal sepsis (Edmund, 2010; World Health Organization, 1995).

Clinical outcome of neonatal sepsis

In this study, the overall neonatal mortality was 13.97% (190/1360), being higher in neonates with sepsis 90/362(24%) as compared to those without 100/998 (10%). Reports from other two referral hospitals in Tanzania by Kayange *et al*. 2010 and Klingenberg *et al*. 2003 found infant mortality due to neonatal sepsis to be 19% and matched closely with the findings of 18% by Mugalu *et al*. 2006 in a Ugandan study. Collectively, these findings reflect the significant contribution of neonatal sepsis in both neonatal and infant mortality.

Aetiology of neonatal sepsis

We found Cogulase Negative *Staphylococcus aureus*, *Klebsiellaspp* and *Acinitobactor* to be the predominant bacterial isolates, which is in keeping with findings from a number of studies conducted in sub-Saharan Africa (Kayange, 2010; Iregbu *et al.,* 2006; Newton, 2007). Cogulase Negative *Staphylococcus aureus*was the main isolate in early as well as late onset sepsis and this is similar to report by Mokuolu *et al*.2002 in a study which was conducted in Nigeria. *Staphylococcus aureus* was the main isolate from swabs which may be attributed to acquisition of bacteria through handling of the neonates by health care providers and family members.

Antimicrobial susceptibility of bacterial isolates

Our findings show that most of the common bacterial isolates showed high resistance to ampicillin, cloxacillin and gentamycin which are first line antimicrobials for treating neonatal sepsis at our centre. More than 80% of *Staphylococcus aureus* and more than 90% of *Klebsiella* sppfrom blood were resistant to ampicillin and cloxacillin, while more than 50% of *Staphylococcus aureus* and more than 60% of *Klebsiella* spp were resistant to gentamycin. High resistance noted may be attributed to excessive and irrational use of these antibiotics at primary health facilities from which neonates are referred to our centre. Notably, the resistance of all isolates to ceftriaxone, cefuroxime and amikacin was significantly low. From our findings and other studies in the region showing high levels of antimicrobial resistance to ampicillin, cloxacillin and gentamycin (Bloomberg *et al*. 2007; Shitaye *et al.,* 2010; Newton, 2007) it is apparent that the current antimicrobial regiment for empirical treatment of neonatal sepsis need to be revisited. Amikacin and cefuroxime may be alternative choice of antimicrobials in empiric treatment of neonatal sepsis however these will be more expensive.

Study limitations

Some of the study participants referred to our hospital might have been inadequately treated resulting in selection bias in our study. Anaerobes which may cause sepsis and other infections with similar presentation to sepsis including malaria (Mwaniki *et al.,* 2010) were not looked for in this study. Extended beta lactamase resistant strains were not determined and resistance to methicillin by *Staphylococcus aureus* isolates were not determined in this study.

Conclusions

Cogulase negative Staphylococcus aureus and *Klebsiellaspp* were the predominant bacterial isolates in this study and showed high resistance to ampicillin and cloxacillin which are WHO recommended to be used as first line drugs for neonatal sepsis. This calls for institutional based antimicrobial surveillance to guide choices of antibiotics for treating neonatal sepsis.

Competing interests

Authors declare that they have no competing interests.

Acknowledgements

Authors are grateful to the nurses in the neonatal ward at GB Pant Hospital for facilitating data collection. Special thanks to

laboratory technicians in the Department of Microbiology Government Medical College Srinagar for carrying out laboratory tests. Authors also want to thank all the parents and guardians who consented for participation of their children in the study.

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