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ORIGINAL RESEARCH

To compare clinical profile and outcome of pediatric patients with sepsis admitted in pediatric and neonatal intensive care unit in a tertiary care hospital of central India

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ABSTRACT

Background: Sepsis and septic shock cases in the Neonatal intensive care unit (NICU) and Pediatric intensive care unit (PICU) remain one of the most significant causes of morbidity and mortality in pediatric patients. Therefore, studying and comparing the clinical features and outcomes of pediatric patients with sepsis in ICUs are important, especially in developing countries.

Methods: From 1st July 2021 to 31st December 2021, we have collected data from both of our pediatric ICU and neonatal ICU of Shyam Shah Medical College using a preformed proforma. Complete blood count, C - reactive protein and culture sensitivity reports were used to diagnose or screen sepsis. We compared clinical features, laboratory data, microbiologic results, and final outcome for patients with sepsis in both NICU and PICU.

Results: A total 1509 and 236 cases with sepsis from both NICU and PICU respectively are included in the study (mean duration of stay in NICU 8.9 days±4.3; in PICU 12.5 days±5.3). Among these cases, culture positive cases with sepsis were 66% and 28% in NICU and PICU respectively. Common pathogens isolated from blood cultures were E. coli and pseudomonas in NICU and E.coli and S. aureus in PICU. Mortality, discharges, refers and Left against medical advice cases were compared as outcomes in our study. Comparing with NICU (n=24, 10.1%), mortality due to sepsis in PICU (n=111, 7.3%) was less.

Conclusion: Sepsis in children both in NICU and PICU is associated with high mortality despite aggressive treatment strategies, but more in NICU. Early recognition and prompt treatment is the key to improve outcome of sepsis.

Key words: Blood culture, Sepsis, Septic shock, NICU, PICU, Outcomes

INTRODUCTION

Sepsis is described by an emergency condition in which an immunological defense system activated against infectious process that can results in organ dysfunction.[1,2] It is the leading cause of mortality and morbidity worldwide.[3] According to Watson et al. reported frequency of pediatric severe sepsis to be more than 42000 cases annually and associated mortality rate to be 10% in the United States.[4] Recently published report from the United Kingdom showed that 17% of children die from with severe sepsis and septic shock in pediatric intensive care

unit (PICU).[5] In the developing country like India mortality rate of sepsis in children from PICU is higher than 50%.[6,7] In NICU setup after prematurity second most common cause of mortality is sepsis and it is divided into early (which is from birth to first three days of life) and late (which is after three days of life). Early onset sepsis is mostly due to organism of maternal genital tract in intrapartum period (group B streptococcus and enteric gram negative organism, principally Escherichia coli [E. coli] and Klebsiella pneumoniae)[8-10] and among late onset sepsis organism include coagulase-negative staphylococcus (CoNS), Staphylococcus aureus, enterococcus species, and enterobacteriaceae.[9-11]According to WHO stats around 80% of death in pediatric patient (age <4 years) can be sepsis related death.[12] For reducing this stats World Federation of Pediatric Intensive Critical Care (WFPICC) accentuate the importance of early diagnosis and rapid treatment like early fluid resuscitation, antibiotics, oxygen supplementation, and judicious use of inotropes.[13]In this prospective study we tried to compare clinical profile and outcomes of pediatric patients with sepsis in NICU and PICU at our setting

METHODS

From 1st July 2021 to 31st December 2021, we have collected data from both of our pediatric ICU and neonatal ICU of Shyam Shah Medical College, Madhya Pradesh using a preformed proforma. All pediatric patients admitted in our ICUs were included in our study except those who were admitted under observation or on day care basis. Investigations like complete blood count, C-reactive protein (CRP) and blood culture and sensitivity tests were sent for all patients with suspected sepsis from both ICUs periodically after consulting treating physicians. Positive blood cultures for recognized pathogens (Gram-negative and Gram-positive bacteria) and Candida species were included in the study. We excluded episodes of positive blood cultures for organisms that were considered contaminants by the treating physician, such as diphtheroids, bacillus species, and non-speciated streptococci. Blood and urine cultures of all the cases were sent at the time of admission to the PICU. CSF culture was sent for all sick infants <3 months of age and in older children if signs and symptoms of meningitis were present. Tracheal cultures were sent by tracheal aspiration for all ventilated patients after 48 h of intubation or earlier, if the clinical signs were suggestive of chest infection. A colony count of 105 in tracheal culture was considered significant.[14]Collected data included demographics, gestational age, type of delivery, weight at birth, signs of sepsis at time of blood culture draw, comorbidities, presence of central venous catheter, type of respiratory support, enteral and parenteral nutritional status, laboratory values at time of sepsis, microbiology data (including type of organism and antimicrobial susceptibility), previous antibiotics exposure, type of empiric treatment, and final outcome. Early-onset sepsis was defined as onset of sepsis before the age of 3 days (< 72 hours after birth), and late-onset sepsis was defined as onset of sepsis after the first 3 days of life (>72 hours after birth).[5] CBC parameters like Leucopenia, leukocytosis, thrombocytosis along with CRP positive and/or positive blood cultures for recognized pathogens (Gram-negative and Gram-positive bacteria) and Candida species were included in the study as sepsis proven cases. Culture proven sepsis was defined as 1 or more positive blood collected at the time of admission to the PICU. Diagnosis of coagulase-negative staphylococcal sepsis (CONS) required at least 2 positive blood cultures.[15]The primary outcome was mortality, recorded as alive or death status at the time of discharge from the ICU. We compared clinical features, laboratory data, microbiologic results, and final outcome for patients with sepsis in both NICU and PICU after entering in a Microsoft Excel Spreadsheet, coded appropriately, and analyzed using SPSS version 18.0. Chi square test with or without Yate's correction was applied. A P value of< 0.05 was considered statistically significant.

RESULTS

In our study, clinical profile and outcomes of pediatric patients with sepsis in NICU and PICU were compared (Table 1-4). Total 1667 neonates and 2880 pediatric patients were admitted in our NICU and PICU respectively during our study period. Of these patients, 605 (36%) in NICU and 1141 (39%) were female. 526 (31% of total admitted neonates) were premature, with a median gestational age of 33 weeks and a median birth weight of 1.5 kilograms (range: 0.9–4.2 kg). In NICU (n=236), 43% were early-onset sepsis and 57% were late-onset sepsis, with a mean age of 4.5 days at time of sepsis was diagnosed. 84% of neonates with sepsis were preterm and 153 (65% of neonates with sepsis) were referred from other hospitals i.e. around 19% neonates who were referred from other hospitals were diagnosed with sepsis. The common pathogens isolated from blood cultures in NICU were E. coli (15.3%), Pseudomonas (13.4%), Candida (12.8%) and Methicillin resistant Staphylococcus aureus (12.8%) among total 156 culture positive neonatal cases (Table 2). Group B streptococcus was the most common cause of early-onset sepsis and E.coli was the most common cause of late-onset sepsis. Out of total admissions in NICU (1667) and PICU (2880), 236 and 1509 cases were diagnosed with sepsis respectively and the difference was found to be significant (Table 4).

In PICU, Infants, accounted for 46% of total admissions, followed by school age group (16.5%), pre-school (31%) and adolescents (6.5%) group. The male to female ratio was 1.5:1. A total 1509 (52%) cases were diagnosed with sepsis and around 45% of them went into septic shock eventually. Average duration of stay of a pediatric patient in PICU was longer i.e. 8.3 days (±3.4) compared to NICU (7.3 days ±4.2) (Table 1) and average duration of stay of a pediatric patients with sepsis was longer than others (PICU= 12.5 days ±5.3; NICU= 8.9 days ±4.3). When compared with NICU (n=24, 10.1%), mortality due to sepsis in PICU (n=111, 7.3%) was less. Mean age of pediatric patients with mortality in PICU and NICU were 4.2 years and 5.6 days respectively; whereas mean age of pediatric patients with mortality due to sepsis were 3.1 years and 3.9 days respectively. The culture reports of PICU patients are tabulated in (Table 3). The common pathogens isolated from Blood cultures were E. coli (17.7%) followed by S. aureus (15.8%), from throat cultures was P. aeroginosa (25%), from urine culture was E. coli (75%) and from CSF culture it was S. pneumoniae (Table). S. pneumoniae (25%) was the most common organism isolated from cultures of a pediatric patient with mortality due to sepsis followed by S. aureus, Pseudomonas and E. coli. Mortality of pediatric patients due to culture positive sepsis was 21% in PICU and was 12.1% in NICU; whereas mortality of pediatric patients due to culture negative sepsis was 2% in PICU and 6.2% in NICU. Out of total admissions in NICU (1667) and PICU (2880), 18 and 4 cases were referred to higher centres respectively and the difference was found to be significant. Comparison of outcomes of pediatric patients in PICU and NICU has been tabulated in Table 4.

Table1: Clinical profile of patients in PICU and NICU

PICU	NICU
Characteristics: Admission =2880 Sex (male:female)=1739:1141 Median Age on admission= 3.9 yrs Median weight= 9.3 kg Median height= 75.5 cm Mean length of stay(±SD)= 8.3 days (±3.4)	Characteristics: Admission =1667 Sex (male:female)= 1062: 605 Median age on admission= 2.4 days Term babies=1141 <2.5 KG birth weight=778 Mean length of stay (±SD)= 7.3 days (±4.2)
Sepsis =1509 Culture proven sepsis=423	Sepsis =236 Culture proven sepsis =156

Septic shock=189	Septic shock=39
Sepsis associated Organ dysfunction: CVS=980 Renal=1071 CNS=724 Hepatic=467 Respiratory=906 Hematological=299	Sepsis associated Organ dysfunction: CVS=154 Renal=163 CNS=94 Hepatic=61 Respiratory=115 Hematological=35
Outcomes : Discharged=2621 Death=150 Leave Against medical advice =84 Abscond =2 Refer 4	Outcomes : Discharged=1325 Death=276 Leave against medical advice= 35 Abscond = 0 Refer 18

Table.2: Culture positive cases in NICU

Pathogens	Total culture positive cases (n = 156)	Total deaths among culture positive cases (n= 19)
Acinetobacter	11	0
Klebsiella p.	16	2
Candida species	20	1
CoNS	16	3
E. coli	24	5
Pseudomonas	21	4
MRSA	20	3
Group B streptococcus	10	1
Enterobacter	6	0
Enterococcus faecalis	12	0

Table 3: Culture positive cases in PICU

Culture type (n)	Pathogens	Total culture positive cases (n= 423; overlapped cases)	Total deaths among culture positive cases (n= 89; overlapped cases)
Blood culture (399)	S. epidermidis	51	2
	S. aureus	63	16
	C. albicans	18	2
	C. diphtheriae	2	0
	S. saprophyticus	18	0
	Enterococcus	37	6
	P. aeroginosa	41	15
	S. typhi	4	1
	E. coli	71	14
	Acinetobacter	37	10
	B. species	21	2
	S. pneumonia	36	19
Tracheal culture (16)	S. aureus	2	1
	P. aeroginosa	4	1

	E. coli Acinetobacter S. pneumoniae Enterobacter	2 3 3 2	1 0 2 0
Urine culture (18)	E. coli K. pneumoniae Candida	12 4 2	2 1 0
CSF culture (4)	S. pneumonia	4	1

Table 4: Comparison of outcomes of pediatric patients with sepsis

	PICU (n=2880)	NICU (n=1667)	p-value
Total discharges	2621	1325	0.003
Total LAMAs	84	35	0.10
Total absconded	2	0	0.73
Total refers	4	18	0.00003
Total deaths	150	276	0.000001
Total sepsis	1509	236	0.00001
Discharges after sepsis	1378	212	0.0001
LAMA after sepsis	6	5	0.54
Absconded after sepsis	0	0	1
Refer cases after sepsis	4	1	0.75
Deaths after sepsis	111	24	0.000006

DISCUSSION

Sepsis and septic shock along with associated multi organ dysfunctions are two important causes of mortality and morbidity in PICU and NICU. Sepsis due to gram negative pathogens was significantly associated with higher mortality rate in ICUs even after providing empirical antibiotic therapy. No statistical significance was found when clinical features or routine laboratory values were compared for patients admitted in PICU vs. NICU.

Notably, in our study E.coli was the most common cause of overall sepsis in NICU and likewise group B streptococcus was the most common cause of early onset sepsis, as well as sepsis in full-term neonates.[16]In NICU, the general protocol to start empiric antibiotics for presumed sepsis includes ampicillin plus gentamicin for early onset sepsis, and a carbapenem plus vancomycin for late-onset sepsis.[16] Factors that would favor to upgrade antibiotic regimen include leukopenia or leukocytosis, thrombocytopenia, positive CRP, and referral from another hospitals.[17] The epidemiology of the causes of sepsis in the NICU differs from one country to another and from one institution to another. Gram-negative organisms were also the most common causes of sepsis in NICU in other studies; one study showed that 35.4% of sepsis cases were caused by Klebsiella pneumoniae, and 28% of K. pneumoniae and E. coli isolates were ESBL producers.[18] Viswanathan et al. (2014) reported that almost one-third (32.1%) of positive blood cultures in NICU were caused by glucose-non-fermenting Gram-negative bacilli, of which Acinetobacter species was the most common organism and 50% of those isolates were MDR.[19] Another study revealed that among the positive blood cultures (n=115), 84 were Gram negative bacilli, and 32% of the isolates were ESBL producers.[20] By contrast, Sharma et al. (2013) found that Gram-positive bacteria (Staphylococcus aureus) were the most common cause of sepsis (37.2%), followed by Klebsiella pneumoniae (27%) and E. coli (19.7%).[1] Given the considerable variation in the bacteriology of sepsis in the NICU, every medical institution needs to review and study the local epidemiology, and to differentiate between early-onset vs. late-onset sepsis and full-

term vs. preterm neonates when discussing the most common organisms that cause sepsis in the NICU.[16] Fewer studies have attempted to identify risk factors and outcome for infection with multidrug resistant organisms in NICU and PICU in developing countries. Even in our study patients with Gram-negative organisms' bacteremia had higher rates of infection related complications and overall case fatality rate. Singh et al. (2002) identified very low birth weight (<1,000 g) and prolonged exposure to antimicrobial agents as two independent risk factors associated with MDR enterobacteriaceae infection in critically ill neonates.[21]A crucial approach is to continuously evaluate the dose, duration, and the indication to continue patients on these broad-spectrum antibiotics. Another important step is to implicate antimicrobial stewardship programs and infection control polices to achieve judicious use of antibiotics in the NICU. Ongoing surveillance of local epidemiology and antimicrobial susceptibility is essential to ensure appropriate empiric and targeted antimicrobial therapy.[16]
The mortality related to sepsis in pediatric age group has decreased significantly over the past few decades.[22] This is largely due to implementation of standard protocols, guidelines, clinical practice parameters, goal directed therapies and educational programs implemented throughout the world to combat sepsis associated mortality.[23,24] We found that mortality due to sepsis and incidence of septic shock are less in PICU than NICU in our setting. Despite all the improvement in developed world, sepsis is still a significant health care problem and is associated with high morbidity and mortality in PICU settings of developing countries.[10,11]
The hospitalization rate for severe sepsis has almost doubled in the last decade.[25] Infants had the highest frequency of sepsis in the present study. Similar results have been shown by Watson et al. in their study in which 48% of the patients with sepsis were less than 1 year old.[8] There is a male preponderance reported in previous studies (55%–59%) in patients with sepsis which is comparable to the present study.[26] Only (n=423) 28% of pediatric patients with sepsis had a positive blood culture as compared to a high culture yield of about 50%–60% in previous studies.[26,27] This could be due to use of antibiotics prior to presentation as these drugs are readily available over the counter in this part of the world. However, the possibility of contamination during the blood collection from peripheral vessel for the high incidence of coagulase negative staphylococcus bacteremia cannot be ruled out. The frequency of sepsis-related multi organ dysfunction syndrome (MODS) in the some studies was significantly higher.[27] However, the recent studies have shown that there is a significant increase in the incidence of MODS.[26] This could be either due to increasing awareness, better documentation of organ dysfunction or delay in presentation to intensive care setting. The overall mortality in the present study is comparable to figures from United Kingdom and Italy.[9,26] Much higher mortality rates have been observed from PICUs of developing countries like Brazil and India.[10,11] The present low mortality rate could be due to strict adherence to the international guidelines and standardized case management.

CONCLUSION

In this study, sepsis and septic shock in children both in NICU and PICU are associated with high mortality despite aggressive treatment strategies, but more in NICU. Common pathogens isolated from blood cultures were E. coli and pseudomonas in NICU and E.coli and S. aureus in PICU. Early recognition and prompt treatment is the key to improve outcome of sepsis. More prospective studies should be done on the basis of new sepsis definitions and clinical practice guidelines to evaluate the true burden and outcome of sepsis in the developing countries.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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