ORIGINAL ARTICLE

Sepsis in Neonates: Prevalence of Micro-Organisms and Their Susceptibility Pattern in Neonatal Intensive Care Unit of a Tertiary Care Hospital – A Retrospective Study

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ABSTRACT

The main aim of doing this study was to analyze the existing resistance pattern and change the empirical regimen that is currently employed in our unit. Retrospective observational study was carried out at Neonatal Intensive Care Unit (NICU), in a tertiary care private hospital to observe the prevalence of organisms and their resistance. Incidence of suspected neonatal sepsis among admitted neonates in our unit during study period was 58% (1942). Among the 1942 neonates with suspected sepsis only 90 (4.6%) had documented microbial infections. Pathogenic organisms were isolated in 71 cases and the rest of the growth was considered as contaminants. In the 71 documented cases 85.91% (61 neonates) were bacteremia and 14.08% (10 neonates) were yeasts. Among the 61 neonates with bacteremia, gram negative bacilli was the most common accounting for 75.4% (46) of cases and gram positive cocci contributed to 24.5% (15) of cases. *Klebsiella pneumoniae* 48.9%, *Pseudomonas aeruginosa* 14.89% and *Escherichia coli* 10.6% were the common gram negative isolates. In the gram positive group, most common isolated bacteria were *Staphylococcus* sps 11.4% (7 cases), *Enterococcus* sps 8.1% (5 cases) and *Streptococcus agalacticae* 4.9% (3 cases). Out of 23 *Klebsiella pneumoniae*, 39.1% were producing Carbapenamase, 30.4% were Multi Drug Sensitive (MDS), 26% were Extended Spectrum Beta-Lactamase (ESBL) and 4.3% were AmPC beta lactamase producer. In the gram-positive bacteremia, 46.6% were *Staphylococcus* sps, 33.3% were *Enterococcus* species and 20% were *Streptococcus agalactiae*. There were 10 proven fungal sepsis during the study, 30% were *Candida albicans* which had 100% sensitivity to fluconazole. *Candida non albicans* like *C. glabrata*, *C. parapsilosis* and *C. krusei* were isolated in 2 cases each and they had varying resistance to fluconazole.

Keywords: Neonatal sepsis; Antimicrobial Stewardship; Bacterial resistance; Antifungal.

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INTRODUCTION

Antibiotics are one of the commonly used drugs in Neonatal Intensive Care Unit (NICU). Neonatal sepsis is a systemic infection occurring in neonates less than 28 days of life. Isolating a pathogen from sterile body fluids as blood or Cerebrospinal Fluid (CSF) along with clinical features and elevated C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and pro-inflammatory cytokines define sepsis [1]. The source of infection may be in-utero, pertaining to any maternal risk factors or may be acquired from community or hospital [2,3]. Neonatal sepsis is classified as Early onset or Late onset based on the age and timing of sepsis occurrence. It is Early Onset Sepsis (EOS) if infection occurs in first 72 hours of life and Late Onset Sepsis (LOS) if it occurs beyond 72 hours of life [4]. With increase in prevalence of resistant organisms, it becomes difficult to treat the infection which increases the mortality rate [1,5].

An estimated 15 million babies are born preterm every year and Africa and South Asia contributes about more than 60% of preterm deliveries worldwide. In India, about 3.51 million preterm births as per World Health Organization (WHO) were reported in 2016. Globally about 15% neonatal mortality was due to sepsis and meningitis in 2016 [6]. Risk factor for sepsis include prematurity, neonates who require prolonged intravenous access, endotracheal intubation or other invasive procedures that impair the normal protective barrier providing a portal of entry for pathogen [7]. Certain other maternal predisposing factors as prolonged rupture of membrane, fever, foul smelling liquor and chorioamnionitis also contribute for infection in neonates [8]. Most preterm and certain term babies in intensive care units receive antibiotics based on the maternal risk factor for suspected infection. Various factors play an important role in progression of the disease, including the time of exposure, microbial load and their virulence, immunological status of the neonate determine the clinical progress [9]. About 80% of suspected sepsis infants never grew anything in their blood culture and the treatment was initiated earlier once they started showing signs and symptoms of infection [10]. Neonatal sepsis also imparts risk in neuro developmental impairment, alters the gut microbiota and increases the hospital stay independent of the pathogen that caused sepsis [11]. There are proven reports of Ampicillin use being associated with Beta lactamase producing gram negative bacteria and certain Enterobacteriaceae that colonize as well invade the NICU babies [12].

In suspected septicemia cases, empirical antibiotics are started as early as the neonate show symptoms of infection [10]. Certain signs of sepsis include the presence of one or more suspected clinical features as fever/hypothermia, poor feeding, reduced activity, respiratory distress, apnoeic spells, abdominal distension, vomiting, diarrhea, seizures, abnormal neonatal reflexes, sclerema and signs of respiratory and circulatory dysfunction that is evidenced by tachycardia/bradycardia or Capillary Refilling Time (CRT)>3 seconds and tachypnoea, grunting. Laboratory parameters include reduced total leukocyte count, elevated CRP and positive blood/CSF culture analysis [12,13]. Antibiotic are chosen based on local microbiological data, escalation and de-escalation of antibiotics can be done once the microbiological data confirms the growth of organism. Antibiotic resistance and the emergence of antibiotic resistant organisms have increased dramatically over the past few years. Continuous surveillance for the antibiotic susceptibility

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and rational use of antibiotic according to the local microbiological data is essential [14]. Judicious use of antibiotic is important to prevent the microbial resistance [15,16]. The need for antibiotic therapy should be decided by the clinician based on the culture results, maternal and intrapartum risk factors, CSF cultures, Complete blood cell count and differentials, CRP trends, radio graphs and Clinical progress [7].

Antibiotic use

In neonates, the dosing schedule of a drug is mostly based on their gestational age, post natal age, and weight of the neonate. Prolonged use of antibiotic in neonatal population has increased risk of nephrotoxicity, hepatotoxicity, hematological abnormalities, incidence of Necrotizing Enterocolitis and sometimes death [11]. For diagnosing septicemia blood culture is considered gold standard that should be done prior initiating antibiotic therapy. In a 5 ml to 10 ml culture media, 1 ml of blood is adequate for a blood culture. Usually blood culture should be observed for 72 hours before it is flagged sterile. In case of gram-negative sepsis, culturing CSF is always advised as it imparts a change in choice of drug, duration of therapy and dosing of chosen antibiotic [11,17]. The appropriateness of antimicrobial prescribing was divided into three categories [3,18].

(i) **Prophylactic therapy:** - Antibiotics given in the absence of microbiological documentation with a suspected infection based on clinical presentation of the neonate is prophylactic therapy. This can be done based on clinician decision with minimal or short-term symptoms of infection.

(ii) **Empirical therapy:** - Empirical therapy includes antibiotics course that were initiated pragmatically but were subsequently associated with microbiological documentation. Empirical therapy can be initiated when there is presumed infection with changes in laboratory parameters of infections such as elevated or reduced White Blood Cell counts, elevated CRP, radiographic features suggestive of infection. Antibiotics started empirically based on the suspected organism can be escalated or de-escalated with availability of documented microbiological data.

(iii) **Definitive therapy:** - Antibiotic course initiation with full microbiological documentation of infection and identification of pathogen in definitive therapy. Antibiotics are initiated with proven infection for positive culture from blood such as Central Line Associated Blood Stream Infections and blood stream infections secondary to exposure with pathogenic bacteria. It also involves infection in sterile fluids as CSF and other non-sterile culture positive infections as Urinary Tract Infection or other local infections as cellulitis and thrombophlebitis.

OBJECTIVES

The main aim of conducting this study is to evaluate the existing bacterial resistance pattern among neonates with sepsis for optimizing the antibiotic usage and improve awareness on resistance pattern. These will in-turn help in avoiding unnecessary usage and optimizing empirical therapy of antibiotics in future.

MATERIALS AND METHODS

Study setting and population

A hospital population based retrospective observational study was conducted from January 2015 to December 2018 in an 850 bedded tertiary care private corporate hospital with ethical committee approval.

Inclusion criteria

- All neonates admitted in NICU with suspected early or late onset sepsis.
- Neonates with documented blood culture positive septicemia during their course of stay in the intensive care unit.

Exclusion criteria

- Neonates in whom blood culture was negative.
- Neonates whose blood cultures grew possible contaminants.
- Culture positive from different sites as urine, throat swab, eye and ear swab and E.T. secretions other than blood were also excluded from the study.

Sampling and analysis

Blood samples were collected from the neonates with suspected sepsis. Blood was collected from peripheral vein under sterile aseptic procedure. Approximately 1 ml blood was collected into blood culture medium vials and sent to clinical microbiological laboratory for further analysis.

Statistical analysis

Comparisons between two categorical variables were analysed using Chi Square Test for Independence to analyse the association of sepsis risk among study population. All statistical tests done were two sided at a level of significance $P<0.05$. Analysis was performed using GraphPad Prism Windows version 7.

RESULTS

General characteristics and clinical profile

During the study period, 16089 neonates were born of which 3347 neonates required admission to NICU. In neonates admitted longer than 24 hours in NICU there were 1942 (58%) cases with suspected sepsis episodes that were included for analysis. A total of 90 study infants were found to have blood culture positive sepsis, of which 61 were positive for bacteremia, 19 were considered possible contaminants and 10 for fungal sepsis.

Neonates were admitted with a mean duration of 20.6 days hospitalization. Most neonates presented with symptoms of de-saturation, abdominal distension, reduced activity, tachypnea, tachycardia, seizure, apnea or de-ranged glucose homeostasis suggesting the onset of infection. Gestational age and weight showed statistically significant dependence; all other variables compared were independent, data as provided in Table 1.

Isolated pathogens

Out of 1942 suspected sepsis cases, only 4.63% (90 cases) showed growth of different bacteria and fungi. Among the 71 neonates, 61 had pathogenic bacteremia and 10 had fungemia. Gram negative bacteria accounted for 77.1% (47 cases) and gram-positive organism accounted for 22.9% (14 cases) of sepsis which contributed to 2.3% and 0.8% out of the total suspected sepsis cases respectively. A total of 15 different organisms were isolated (Table 2) from 61 positive blood cultures. We had 37.7% (23 cases) *Klebsiella pneumoniae*, 11.4% (7 cases) *Pseudomonas aeruginosa*, 8.2% (5 cases) each of *Escherichia coli*, *Enterococcus* sps and *Staphylococcus* sps and 4.9% (3 cases) of *Enterobacteraceae*, *Acinetobacter baumannii*, *Streptococcus agalacticae*.

Gram negative organisms

Klebsiella pneumoniae 48.9% (23 cases) was the most commonly isolated gram-negative organism, following which 14.8% (7 cases) was contributed by *P. aeruginosa* and 10.6% by *E. coli* with varying resistance patterns. Out of 23 *Klebsiella pneumoniae* isolated 9/23 (39.1%) were *Klebsiella pneumoniae* Producing Carbapenamase (KPC) sensitive only to Polymyxins, 7/23 (30.4%) were Multi Drug Sensitive (MDS), 6/23 (26%) were producing ESBL sensitive to Carbapenems, Amikacin and

Polymyxins, and 1/23 (4.34%) was AmPC Beta Lactamase producer sensitive to Carbapenems and Polymyxins.

KPC were treated with either colistin alone or in combination with a carbapenem. 85.7% (6/7) *Pseudomonas aeruginosa* were multidrug

Table 1: Demographic description of study population.

Demographics		Early Onset Sepsis (EOS)		Late Onset Sepsis (LOS)		p value
Gender	Male	13		34		0.14
	Female	3		21		
Place of birth	Inborn	7		25		0.9
	Outborn	9		30		
Mode of delivery	LSCS	11		42		0.53
	NVD	5		13		
Gestational age	<33 weeks	3		26		0.1
	33-37 weeks	3		9		
	>37 weeks	10		20		
		1 Kg	1-1.5 Kg	1.5-2.5 Kg	>2.5 Kg	p value
Onset of sepsis	EOS	2	0	5	9	0.22
	LOS	10	9	17	19	
Gestational age	<33 weeks	11	6	11	1	<0.0001
	33-37 weeks	1	2	6	3	
	>37 weeks	0	1	5	24	

Table 2: Prevalence of bacterial pathogens.

Isolated micro-organisms	Number of cases (%)	EOS Number (%)	LOS Number (%)
Gram Negative Bacilli			
Klebsiella pneumonia	23 (37.7%)	7 (30.4%)	16 (69.5%)
Pseudomonas aeruginosa	7 (11.4%)	1 (14.2%)	6 (85.7%)
Escherichia coli	5 (8.1%)		5 (100%)
Enterobacter cloacae	3 (4.9%)	1 (33.3%)	2 (66.7%)
Acinetobacter baumannii	3 (4.9%)		3 (100%)
Serratia marcescens	2 (3.2%)		2 (100%)
Pantoea agglomerans	2 (3.2%)	1 (50%)	1 (50%)
Burkholderia cepacia	1 (1.6%)		1 (100%)
Elizabethkingia meningoseptica	1 (1.6%)		1 (100%)
Gram Positive Cocci			
Staphylococcus epidermidis	3 (4.9%)	2 (66.7%)	1 (33.3%)
Enterococcus faecium	3 (4.9%)		3 (100%)
Streptococcus agalacticae	3 (4.9%)	3 (100%)	
Enterococcus faecalis	2 (3.2%)		2 (100%)
Staphylococcus aureus	2 (3.2%)		2 (100%)
Alpha Hemolytic *Streptococci*	1 (1.6%)	1 (100%)	
Total	61	16	45

Table 3: Sensitivity data of antibiotics with the Gram-Negative organisms and their corresponding resistance patterns towards various antibiotics observed in our NICU.

	Klebsiella pneumonia								*Escherichia coli*				*Pseudomonas aeruginosa*	
	ESBL (n=6)		AmPC (n=1)		KPC (n=9)		MDS (n=7)		MDS (n=4)		ESBL (n=1)		(n=7)	
	S	% of cases	S	% of cases	S	% of cases	S	% of cases	S	% of cases	S	% of cases	S	% of cases
Piperacillin Tazobactam	4	66.66	0	0	0	0	6	85.71	4	100	1	100	5	71.4
Ampicillin Sulbactam	1	16.66	0	0	0	0	4	57.14	1	25	0	0	6	85.71
Cefoperazone Sulbactam	5	83.33	0	0	0	0	7	100	4	100	1	100	0	0
Co-trimoxazole	0	0	0	0	1	11.11	0	0	2	50	0	0	0	0
Imipenem	6	100	1	100	0	0	7	100	4	100	1	100	6	85.7
Meropenem	6	100	1	100	0	0	7	100	4	100	1	100	6	85.7
Amikacin	6	100	1	100	1	11.11	7	100	4	100	1	100	4	57.14
Gentamicin	1	16.66	1	100	0	0	7	100	4	100	1	100		
Tigecycline	4	66.66	1	100	4	44.4	7	100			1	100	5	71.42
Colistin	6	100	1	100	9	100	7	100			1	100	7	100

Table 4: Sensitivity data of antibiotics with the Gram-Positive organism.

	S. agalactiae (n = 3)		E. faecalis (n = 3)		E. faecium (n = 2)	
	S	% of cases	S	% of cases	S	% of cases
Ampicillin Sulbactam	3	100	1	33.33	2	100
Piperacillin Tazobactam	3	100	1	33.33	2	100
Cefoperazone Sulbactam	1	33.33				
Co-trimoxazole	2	66.66				
Vancomycin	3	100	3	100	1	50
Linezolid	3	100	3	100	2	100
Clindamycin	3	100				
Teicoplanin	-	-	3	100	1	100
Gentamicin	-	-	0	0	0	0

Table 5: Prevalence of fungal sepsis.

Isolated pathogen	Number of cases (%)	EOS N (%)	LOS N (%)
Candida albicans	3 (30%)		3 (100%)
Candida glabrata	2 (20%)		2 (100%)
Candida parapsilosis	2 (20%)	1 (50%)	1 (50%)
Candida krusei	2 (20%)		2 (100%)
Candida famata	1 (10%)		1 (100%)
Total	10	1	9

sensitive, 1/7 (14.3%) were extensively drug resistant and sensitive only to Colistin. 80% (4/5) *Escherichia coli* were multidrug sensitive and 1/5 (20%) were ESBL producer. Sensitivity data gram negative organisms towards antibiotics are provided in Table 3. *Acinetobacter baumannii* 3/3, *Burkholderia cepacia* 1/1, *Escherichia coli* 5/5, *Enterobacteraceae* 2/3 and *Klebsiella pneumoniae* 16/23 presented as LOS. One baby with *Salmonella enterica* in CSF presented with seizures and elevated CRP was also isolated and treated with Ceftriaxone for about 21 days.

Gram positive organisms

Enterococcus sps contributing to 35.7% (5/14), *Staphylococcus epidermidis* 21.4% (3/14), *Streptococcus agalacticae* 21.4% (3/14) were the common gram-positive organism isolated and *Staphylococcus* aureus 14.2% (2/14) contributed the least. Sensitivity pattern of antibiotics were provided in Table 4. All *Streptococcus agalactiae* isolated were sensitive to Ampicillin, Piperacillin and Clindamycin and were treated with higher dose of Ampicillin. *Streptococcus agalactiae* also known as Group B Streptococcus, a gram positive, beta hemolytic pathogen remains as a major cause of bacterial sepsis and meningitis in early neonatal period of term neonates. One of the 2 *Staphylococcus* aureus had resistance pattern of MRSA+MLSB (Methicillin Resistant *Staphylococcus* aureus, Macrolide Lincosamide Streptogramin B) treated with intravenous Linezolid. Penicillin resistance was noted in 2/5 *Enterococcus* species and were treated with Vancomycin. We had one case of Vancomycin resistant Enterococci in a 24 weeker at one month of life, treated with Linezolid.

Antibiotic susceptibility pattern

Overall, among the gram-negative pathogens 22 (47.8%) were Multi Drug Sensitive (MDS), 9 (19.5%) Extended Spectrum Beta Lactamase producers and 15 (32.6%) were Multi Drug Resistant (MDR). In gram positive pathogens 9 (60%) were MDS and 6 (40%) were MDR. We used Beta Lactam antibiotic combined with an aminoglycoside (usually Ampicillin with Amikacin) in 40 (65.5%) cases providing broad spectrum coverage for suspected early onset sepsis. About 11 (18%) out-born neonates were empirically started with Carbapenems or Polymyxin as they were exposed to first line antibiotics in the referral hospital. ESBL producing *Escherichia coli* and *Klebsiella pneumoniae* were treated with Meropenem. The empirical beta-lactam, aminoglycoside combination was escalated to mostly Carbapenem based on the culture reports.

Fungal prevalence

We encountered 10 (14.1%) cases of candida sepsis in our intensive care unit over a period of 4 years. Among them 7 (70%) were delivered at outside hospital and initially treated with multiple antibiotics. Two of the 3 babies who had fungemia delivered in our hospital were Extreme Preterm (<26 weeks). We found 3 cases of *C. albicans*, 2 cases each of *C. krusei*, *C. glabrata* and *C. parapsilosis* and one case of *C. famata* shown in Table 5. All Isolated *C. albicans* were sensitive to Fluconazole and therapy was initiated in the higher dose. A loading dose of 25 mg/kg/day on day 1 followed by 12 mg/kg/day once daily for rest of the regimen with routine monitoring of liver function tests. All these *non albicans* were sensitive to Voriconazole and hence were treated with Voriconazole with a dose of 6 mg/kg/dose every 12 hours with periodic monitoring of hepatic function. Serum electrolytes particularly calcium, magnesium and potassium were monitored prior to initiation and during therapy. Intravenous fluconazole was the empirical anti-fungal used in clinical suspicion of fungal sepsis and in case of resistance to azoles, Amphotericin B or Voriconazole which demonstrated 100% susceptibility was used.

DISCUSSION

Incidence of neonatal sepsis is increasing owing to the surge in antibiotic resistance. As reported from a meta-analysis by Murthy et al. it was found that male gender, outborn neonates, need for artificial ventilation, gestational age <37 weeks and premature rupture of membranes are the most common risk factors for neonatal sepsis [19]. Similarly, in our study we had a higher incidence of sepsis in preterm (57.7%), male (66.2%), outborn neonates (54.9%) and LOS (77.5%) was more common than EOS (22.5%). We also had more incidence of sepsis in neonates delivered by Caesaerean section 74.64% than in Normal vaginal delivery 25.3%. This is similar to a study conducted by Gandhi et al. [20]. There was male predominance with a male to female ratio 1.95:1 which is in accordance with a study conducted by Kaistha et al. [21].

In our study, gram negative organisms (77%) were most commonly isolated, specifically *Klebsiella pneumoniae* 37.7%, 11.4% *Pseudomonas aeruginosa* and 8.1% *Escherichia coli*. A study conducted by Pokhrel et al. and Ahmed et al. at Nepal and Bangladesh respectively showed gram-negative predominance whereas there was gram-positive predominance in a study conducted by El-din et al. and Peterside et al. at Egypt and Nigeria respectively [22-25]. Causative organism for neonatal sepsis varies from region to region and local microbiological data is important in choosing empirical antibiotics. In neonates with

suspected bacterial infection broad spectrum coverage is mandated [26]. The incidence of death due to sepsis as revealed by Chauraisa et al. is two to four fold higher in South Asian Countries and the prevalence of gram negative organisms (60%) were more common with *Klebsiella* sps 23%, *Escherichia coli* (14%) and *Acinetobacter baumannii* (8%) [27].

Klebsiella pneumoniae isolated had 100% susceptibility to colistin, 60.8% to Meropenem, 69.5% to Tigecycline and 43.4% to Piperacillin and Tazobactam in our study. Whereas in a study conducted by Pokhrel et al. had 100% susceptibility to Meropenem and 88.8% to Colistin, 81.8% to *Streptococcus agalacticae* Tigecycline and 40% to Piperacillin and Tazobactam(22). Peterside et al. isolated *Staphylococcus* aureus (51.5%) as the most common organism with 87.5% sensitivity to Vancomycin and among the gram negatives they had predominance of *Escherichia coli* 16 (16.5%) [25]. In contrast we had only 3.27% of *Staphylococcus* aureus isolated during the study with 100% susceptibility to Vancomycin and being the predominant among gram-positive bacteria in our study.

Fungal infections

We had 0.8% incidence of fungal sepsis during our study with 70% *Candida non-albicans* predominance and 30% *Candida albicans*. A study conducted by Mohdyunus et al. about 9.2% admissions in NICU had fungal sepsis, 73% of them were *Candida non-albicans* most commonly *Candida krusei* (63.8%) and 26.5% were *Candida albicans* [28]. In another study by Jajoo et al. reported *Candida albicans* (5%), *Candida parapsilosis* (4.5%), *Candida Krusei* (4%) and *Candida glabrata* (2%) [29]. In our study 30% of fungal sepsis were in extreme preterm (< 26 weeks) and VLBW which agrees with the study conducted by Devleta et al. there was higher incidence (39%) of fungal sepsis in extreme preterm and very low birth weight neonates and *non albicans* like *Candida Krusei*, *Candida parapsilosis* and *Candida glabrata* being more common organisms in neonatal fungal sepsis [30]. *Candida non-albicans* had 57.1% resistance to Fluconazole in our unit which agrees with Chaurasia et al. that revealed more prevalence of *Candida non-albicans* (80%) and their isolates were more sensitive towards Amphotericin B followed by Fluconazole and Itraconazole [27].

CONCLUSION

Antimicrobial resistance is increasing not only in general population but also in neonatal units due to emergence of MDR bacteria that creates a dilemma in therapy. Reserving antibiotics for high risk infants and optimally de-escalating based on the microbiological data is a strategy in improving outcomes and preventing the development of drug resistant organisms. Overall prevalence showed that gram negative organisms are predominating mainly represented by *K. pneumoniae*, *E. coli*, and *P. aeruginosa*. Of the gram-positive Staphylococci and Enterococci remained more prevalent. Resistance in the gram-negative organism is on the rise and in our study nearly 40% of K. pneumonia was Carbapenem resistant and 30% was ESBL producer. Irrational antibiotic use in neonates may be associated with some adverse effects as alteration of gut colonization with commensal and beneficial organisms that could either alter the resistance pattern of existing organism or it may become pathogenic. It also increases the risk of fungal colonization predisposing the neonates to invasive fungal infections. Antibiotic stewardship principles in neonatal intensive care unit includes identifying the neonates who needs antibiotics therapy or cessation of the therapy once the cultures turn out to be negative or the neonate seems to be not septic clinically. A combination of both restricted use and educational measures seems to be essential in improving prudent use of antibiotics.

LIMITATIONS OF THE STUDY

Since this is a retrospective study we could not escalate or de-escalate the antibiotics. Because there were very less cases, we couldn't conclude the final empirical regimen.

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CONFLICT OF INTEREST

The authors had no conflict of interest.

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