Bacterial Etiology and Antibacterial Susceptibility Patterns of Pediatric Bloodstream Infections: A Two Year Study From Nemazee Hospital, Shiraz, Iran

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Abstract

Background: Sepsis refers to an illness resulting from a systemic inflammatory response to infection, mainly caused by bacterial agents. Any delay in sepsis treatment can lead to high morbidity and mortality.

Objectives: The aims of this study were to identify the common bacterial agents responsible for pediatric septicemia and determine their antimicrobial susceptibility patterns in Nemazee Hospital, Shiraz, Iran.

Patients and Methods: This cross-sectional study was conducted within a two year period (2011 - 2013) for all patients with clinical manifestations of septicemia. Blood specimens were collected aseptically in BACTEC™ blood bottles, and conventional bacteriological methods were followed for isolation and identification of the bacteria. Antimicrobial susceptibility tests were performed by using the disk diffusion method in accordance with CLSI recommendations.

Results: From a total of 491 blood cultures, 74 (15.1%) samples were detected as positive. The most common isolates were Gram positive cocci, and *Staphylococcus epidermidis* (48.6%) was found to be the most common Gram positive cocci. Among recovered Gram negative isolates, *Acinetobacter* spp. (8.1%) were the predominant isolates. Overall, the most effective antibiotics against Gram positive cocci were vancomycin (98%) and chloramphenicol (72.5%). In addition, the highest sensitivities to the agents tested against Gram negative isolates were to ciprofloxacin (47.8%) and chloramphenicol (30.4%).

Conclusions: Due to the variable nature of antibiotic susceptibility patterns and etiological agents of septicemia, continual assessment of the most frequent pathogens associated with bloodstream infections and detection of their sensitivity patterns to locally available antibiotics seem to be reasonable measures.

Keywords: Sepsis, Microbial Sensitivity Tests, Anti-Bacterial Agents, Child, Hospitalized

1. Background

Sepsis refers to an illness resulting from a systemic inflammatory response to infection, mainly caused by bacterial agents (1). Sepsis has remained an important cause of mortality in developing countries (2). Neonates and young children are especially at risk of nosocomial infections because of their intrinsic vulnerability (3). Previously, a sepsis mortality rate of 14.2% was reported by Najib et al. among hospitalized children in Shiraz, Iran (4).

Any delay in treatment of this life threatening condition is unacceptable; rapid treatment with antimicrobials is essential (5). However, because bacteriological cultures and antibiotic susceptibility tests take days, empirical antibiotic therapy should begin immediately (5).

However, one serious problem associated with empirical treatment is the emergence of antibiotic resistance (6). Antibiotic resistance is a growing problem in developing countries; many studies have reported increasing antibiotic resistance from Iran (7-9). Knowledge of the common causative agents of septicemia and susceptibility patterns to locally available antibiotics has improved the chance for appropriate empirical therapy

and has subsequently reduced the risk of antibiotic resistance (10).

Various bacterial pathogens can cause septicemia; isolation of an organism from the blood culture of suspected patients with clinical symptoms is a standard procedure for sepsis diagnosis (11). The epidemiology of pathogens most often associated with sepsis and the emergence of resistant isolates is constantly changing; therefore, continuous surveillance is necessary in each region (10).

2. Objectives

The aims of present study were to identify the common bacterial agents responsible for pediatric septicemia and determine their antimicrobial susceptibility patterns at Nemazee Teaching Hospital in Shiraz, in the south-west of Iran.

3. Patients and Methods

3.1. Study Area and Subjects

This retrospective cross-sectional study was conducted within two years, from March 2011 to February 2013. All patients with suspected septicemia (according to physician clinical judgment and the diagnosis criteria of "sepsis" as defined by the International consensus conference on pediatric sepsis (12)) who were referred to the Nemazee Teaching Hospital affiliated with the Shiraz university of medical science were included. The exclusion criteria were incomplete medical records and unsuitable age. Nemazee Hospital is a major tertiary care hospital in south-western Iran with 1,000 beds. The patients included in the present study ranged from 11 days to two years old.

3.2. Specimens and Bacterial Identification

Using aseptic conditions, 2 - 5 mL venous blood samples were obtained from patients by the attending nurses and inoculated in BACTEC™ culture bottles. All blood bottles were incubated aerobically at 37°C in the BACTEC™ system (Model: 9050 and 9120) for seven consecutive days. During the incubation periods in the Nemazee Hospital microbiology laboratory, any bottles detected as positive by the BACTEC™ system were removed, and 3 - 5 drops of the positive sample blood were inoculated to blood agar containing 5% blood. Conventional bacteriological methods were followed for the isolation and identification of the bacteria from subcultured samples.

3.3. Antimicrobial Susceptibility Testing

Antimicrobial susceptibility tests were performed by examining the effectiveness of locally available antibiotics using the disk diffusion method in accordance with CLSI recommendations (13). The antimicrobial disks (HiMedia, India) used for Gram positive isolates were the following: ampicillin (10 μg), vancomycin (30 μg), erythromycin (15 μg), co-trimoxazole (25 μg), chloramphenicol (30 μg), gentamycin (10μg), lincomycin (2 ug), ciprofloxacin (5 μg), cephalexin (30 μg), cloxacillin (1 μg), ofloxacin (5 ug), and azithromycin (15 ug). In addition, for the Gram negative isolates, amikacin (30 μg), ceftizoxime (30 ug), cefixime (5 ug), and imipenem (10 μg) disks (HiMedia, India) were also considered. The test was performed on Mueller-Hinton agar (Merck, Germany).

Statistical analyses were performed using SPSS software™, version 19 (IBM Corp., USA). Chi–square or Fisher's exact tests were conducted to analyze the results. A P value of < 0.05 was regarded as statistically significant.

4. Results

Out of the total 491 blood samples in BACTEC™ bottles received and processed during a two year period, the frequency of culture positive specimens was 15.1% (n = 74). The number of specimens and frequency of cultures found to be positive during the years 2011 - 2013 are presented in Table 1. Although the majority of the positive samples were from males (78.4 %), no statically significant gender differences were detected.

The overall frequency of positive cultures between the periodic seasons of years 2011 - 2012 was more than that of a year later, but the only significant differences were seen in summer (P < 0.05) (Table 2). Gram positive cocci, with an incidence of 68.9%, were the predominant isolates recovered from positive cultures. *Staphylococcus epidermidis* was found to be the most frequent Gram positive cocci. It accounted for 48.6% of recovered isolates, followed by coagulase-negative staphylococci (CoNS) (other than *S. epidermidis*), which had an isolation rate of 14.7%. The most frequent Gram negative isolates identified were *Acinetobacter* spp., with an isolation rate of 8.1%. *Escherichia coli* and *Enterobacter* spp. both had a frequency of 6.8%. Moreover, although Gram positive cocci isolation rates between the years 2011 - 2012 (74.5%) were more than those found a year after (56.5%), no statistical differences were observed. The recovered isolates distribution patterns are summarized in Table 3.

Table 1. Number of Studied Specimens and Positive Cultures During 2011 - 2013[a]

Years	Total Samples	Positive Cultures
2011 - 2012	302	51 (16.9)
2012 - 2013	189	23 (12.2)
Total	491	74 (15.1)

[a]Significance Level: 0.25.

Table 2. The Distribution of Recovered Bacterial Isolates From Positive Blood Cultures in the Study[a,b,c]

Isolates	2011 - 2012	2012 - 2013	Total
G+			
S. epidermidis	23 (45.1)	13 (56.5)	36 (48.6)
CoNS (other than *S. epidermidis*)	11 (21.5)	0	11 (14.7)
S. aureus	1 (2)	0	1 (1.4)
Enterococcus spp	1 (2)	0	1 (1.4)
Streptococcus spp	2 (3.9)	0	2 (2.7)
Total G+	38 (74.5)	13 (56.5)	51 (68.9)
G-			
Pseudomonas spp	1 (2)	3 (13)	4 (5.4)
Enterobacter spp	3 (5.9)	2 (8.7)	5 (6.8)
Klebsiella spp	3 (5.9)	0	3 (4.1)
E. coli	4 (7.8)	1 (4.4)	5 (6.8)
Acinetobacter spp	2 (3.9)	4 (17.4)	6 (8.1)
Total G-	13 (25.5)	10 (43.5)	23 (31.1)
Total	51 (68.9)	23 (31.1)	74 (100)

[a]Data are presented as No. (%).
[b]P = 0.174, for differences between overall Gram positive and negative isolates (2011-2013).
[c]G+, overall Gram positive isolates; G-, overall Gram negative isolates.

Table 3. The Distribution Patterns of Bacterial Isolates According to the Season They Were Recovered

Season	2011 – 2012		2012 - 2013		Significance level
	Total Samples	Positive Samples [a]	Total Samples	Positive Samples[a]	
Spring	90	15 (16.7)	70	9 (12.9)	.5
Summer	63	13 (20.6)	68	5 (7.3)	.027
Fall	71	13 (18.3)	26	7 (26.9)	.35
Winter	75	10 (13.3)	25	2 (8)	.47
Total	302	51 (15.9)	189	23 (12.2)	.25

[a]Data are presented as No. (%).

Antibacterial susceptibility tests revealed that the highest resistance rates for Gram positive isolates were to erythromycin (90.2%), cephalexin (86.3%), and cloxacillin (82.3%). On the other hand, the most effective antibiotics for Gram positive cocci were vancomycin (98%) and chloramphenicol (72.5%). Among the Gram negative isolates, all the screened isolates were resistant to tetracycline and cephalexin. Also, a high resistance rate to cefixime (95.6%) was observed among the Gram negative isolates. Overall, the highest sensitivity rates to the agents tested against Gram negative isolates were to ciprofloxacin (47.8%) and chloramphenicol (30.4%). However, gentamycin (75%) and amikacin (50%) showed the highest effectiveness against Pseudomonas spp. isolates. The susceptibility patterns for Gram positive and negative isolates are displayed in Tables 4 and 5, respectively.

Table 4. Antibiotic Susceptibility Patterns of Gram-Positive Isolates Recovered From Blood Cultures in the Study[a]

Isolates/Antibiotics	*S. aureus* (Total No: 1)	*Enterococcus* spp. (Total No: 1)	*Streptococcus* spp. (Total No: 2)	CoNS (Other Than (*S. epidermidis*) (Total No: 11)	*S. epidermidis* (Total No: 36)
Cloxacillin					
R	0	1 (100)	2 (100)	9 (81.8)	28 (77.7)
I	0	0	0	0	2 (5.6)
S	1 (100)	0	0	2 (18.2)	6 (16.7)
Lincomycin					
R	0	1 (100)	1 (50)	9 (81.8)	30 (83.3)
I	0	0	0	0	0
S	1 (100)	0	1 (50)	2 (18.2)	6 (16.7)
Chloramphenicol					
R	0	0	0	3 (27.3)	9 (25)
I	0	1 (100)	0	0	1 (2.8)
S	1 (100)	0	2 (100)	8 (72.7)	26 (72.2)
Vancomycin					
R	0	1 (100)	0	0	0
I	0	0	0	0	0
S	1 (100)	0	2 (100)	11 (100)	36 (100)
Co-trimoxazole					
R	0	1 (100)	1 (50)	7 (63.6)	31 (86.1)
I	0	0	0	0	0
S	1 (100)	0	1 (50)	4 (36.4)	5 (13.9)
Ciprofloxacin					
R	0	1 (100)	0	10 (90.9)	27 (75)
I	1 (100)	0	0	0	0
S	0	0	2 (100)	1 (9.1)	9 (25)
Erythromycin					
R	1 (100)	1 (100)	0	11 (100)	33 (91.7)
I	0	0	0	0	0
S	0	0	2 (100)	0	3 (8.3)
Gentamycin					
R	0	0	0	9 (81.8)	23 (63.9)
I	0	0	0	0	1 (2.8)
S	1 (100)	1 (100)	2 (100)	2 (18.2)	12 (33.3)
Cephalexin					
R	0	1 (100)	0	9 (81.8)	30 (83.3)
I	0	0	0	2 (18.2)	2 (5.6)
S	1 (100)	0	2 (100)	0	4 (11.1)
Ofloxacin					
R	NA	1 (100)	0	NA	NA
I	NA	0	1 (50)	NA	NA
S	NA	0	1 (50)	NA	NA
Azithromycin					
R	NA	10 (100)	NA	NA	NA
I	NA	0	NA	NA	NA
S	NA	0	NA	NA	NA
Ampicillin					
R	NA	1 (100)	1 (50)	NA	NA
I	NA	0	0	NA	NA
S	NA	0	1 (50)	NA	NA

Abbreviaton: NA, not available.

[a]Data are presented as No. (%).

Table 5. Antibiotic Susceptibility Patterns of Gram-Negative Isolates Recovered From Blood Cultures In The Study[a]

Isolates/ Antibiotics	*Acinetobacter* spp. (Total No: 6)	*E. coli* (Total No: 5)	*Enterobacter* spp. (Total No: 5)	*Klebsiella* spp. (Total No: 3)	*Pseudomonas* spp. (Total No: 4)
Ceftizoxime					
R	6 (100)	2 (40)	5 (100)	3 (100)	4 (100)
I	0	0	0	0	0
S	0	3 (60)	0	0	0
Tetracycline					
R	5 (83.3)	5 (100)	5 (100)	3 (100)	4 (100)
I	1 (16.7)	0	0	0	0
S	0	0	0	0	0
Amikacin					
R	5 (83.3)	2 (40)	5 (100)	2 (66.7)	2 (50)
I	0	0	0	1 (33.3)	0
S	1 (16.7)	3 (60)	0	0	2 (50)
Chloramphenicol					
R	6 (100)	4 (80)	0	2 (66.7)	4 (100)
I	0	0	0	0	0
S	0	1 (20)	5 (100)	1 (33.3)	0
Ciprofloxacin					
R	5 (83.3)	2 (40)	0	1 (33.3)	0
I	0	0	1 (20)	1 (33.3)	1 (25)
S	1 (20)	3 (60)	4 (60)	1 (33.3)	3 (75)
Gentamycin					
R	5 (83.3)	3 (60)	5 (100)	3 (100)	1 (25)
I	0	0	0	0	0
S	1 (16.7)	2 (40)	0	0	3 (75)
Cefixime					
R	6 (100)	4 (80)	5 (100)	3 (100)	4 (100)
I	0	0	0	0	0
S	0	1 (20)	0	0	0
Cephalexin					
R	6 (100)	5 (100)	5 (100)	3 (100)	4 (100)
I	0	0	0	0	0
S	0	0	0	0	0
Co-trimoxazole					
R	5 (83.3)	3 (60)	5 (100)	2 (66.7)	4 (100)
I	1 (16.7)	0	0	0	0
S	0	2 (40)	0	1 (33.3)	0
Imipenem					
R	5 (83.3)	NA	NA	NA	NA
I	0	NA	NA	NA	NA
S	1 (16.7)	NA	NA	NA	NA

Abbreviaton: NA, not available.
[a]Data are presented as No. (%).

5. Discussion

Sepsis can be fatal if adequate attention is not paid in the early stages (14). Interventions to identify and treat sepsis as soon as possible in developing countries have been shown to reduce mortality in children (1, 15). Thus, immediate identification of the etiological agents of septicemia in developing countries will play an important role in any future management strategy (1). Proper antibiotics usage in the early management periods is linked with survival (1). However, the diversity of bacterial pathogens, often even in the tropics, is a potential obstacle against effective empirical therapy. In a previous study by Japoni et al. in Shiraz, Iran, 25 individual pathogens accounted for the etiology of septicemia (16). However, defining the epidemiology of all causative agents of sepsis in developing countries seems indispensable to introducing the most cost-effective interventions in these countries (1).

In the current study, 15.1% of blood cultures yielded bacterial growth, a rate higher than that in previous reports from Shiraz, with rates of 12.1% reported by Japoni et al. between the years 2001 and 2004 (16). However, our study was restricted to neonatal and pediatric wards, whereas the study of Japoni et al. included adult wards as well.

Bacterial isolation from blood samples is reported with various frequencies in other parts of the country. Aletayeb et al. from Ahvaz reported the lowest isolation rate (4.1%); also, Karambin et al. from Rasht and Gheibi et al. from Urmia reported isolation rates of 10.6% and 11%, respectively (17-19).

The reports published by two separate studies carried out in Uganda and Nigeria show higher isolation rates compared to ours: 32.5% and 16.5%, respectively. On the other hand, a very low isolation rate (2.3%) was observed in a study conducted in Kuwait by Mokaddas et al. (6, 20, 21).

In agreement with a previous study conducted in Shiraz by Japoni et al., in our study, Gram positive cocci, with an isolation rate of 68.9%, were the predominant organisms of septicemia (16). However, in Japoni et al.'s study, because of the study design and elimination of CoNS results for their potential contamination of adult blood cultures, Staphylococcus aureus was reported as the most frequent Gram positive cocci (25%) (16). In our study, the S. aureus isolation rate reached a maximum of 1.4%, and considering the important role of CoNS in nosocomial infections of the neonatal and pediatric population (22-24), *S. epidermidis* was the most frequent Gram positive cocci, with an isolation rate of 48.6%. In addition, the results from repeated sampling and cultures do not suggest the possibility of contamination of specimens. *E. coli*, with a rate of 12.1%, was introduced as the most common Gram negative isolate by Japoni et al. (16), whereas *Acinetobacter* spp. (8.1%) was isolated as the leading Gram negative pathogen in our study. *Acinetobacter* spp. has become a growing cause of nosocomial infections and has been known to cause different kinds of opportunistic in-fections (25, 26). In recent years, the *Acinetobacter* spp. isolation rate in our region, especially at Nemazee Hospital, has been remarkable (25, 27)

Etiological agents of septicemia have varied in previous reports from Iranian studies. In agreement with our study, Gheibi et al. from Urmia reported Gram positive cocci, especially CoNS, as the most prevalent agents of neonatal septicemia (19). However, Aletayeb et al. from Ahvaz and Karambin et al. from Rasht mentioned Gram negative isolates *Klebsiella pneumonia* and *Enterobacter* spp., respectively as causative agents of septicemia (17, 18).

Some reports from our neighboring countries, Kuwait and India, are similar to ours in that they have shown Gram positive cocci as the most common pathogens isolated from blood cultures (6, 14).

Overall, our Gram positive isolates showed less sensitivity to the tested antibacterial agents when compared to the results of a previous study by Japoni et al. from Shiraz. However, similar to our findings, Japoni et al. found vancomycin (98.4%) and chloramphenicol (86.4%) to be the most effective antibiotics for Gram positive isolates in vitro (16). But in contrast to our study, in which resistance to cephalexin (86.3%) was considerably higher for Gram positive isolates, in Japoni et al.'s study, this resistance rate reached 19.6% (16). Among the Gram negative isolates, this different pattern can still be seen; ciprofloxacin from our study was substituted with imipenem in the study by Japoni et al. as the most effective agent against Gram negative isolates (16).

Aletayeb et al. from Ahvaz reported imipenem as the best in vitro choice for their recovered Gram negative isolates (17), whereas Karambin et al. from Rasht with results closest to ours stated that ciprofloxacin was the most effective agent for Gram negative isolates (18). These differences in antibacterial susceptibility patterns are also observed in other reports from our neighboring countries (6, 14).

The findings of the current survey highlight the variable nature of etiological agents of septicemia and their antibiotic susceptibility patterns both in time and location, not only among different geographical locations and but also within the same region. Therefore, it is reasonable to continually assess the pathogens most frequently associated with blood stream infections and their resistance patterns to locally available antibiotics. The results of our study provide useful information for more effective empirical therapies and optimizing institutional infection control policies.

Acknowledgments

Footnotes

Authors' Contribution: Study concept and design:

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