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# Antimicrobial Resistance in Pediatric Sepsis: A Study from a Tertiary Care Hospital in North India

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## Abstract

Sepsis is a leading cause of mortality in children. However, there is limited data on the pathogens associated with sepsis in children in developing countries. 250 patients aged between 2 months to 5 years clinically suspected of sepsis were recruited in the study. Blood samples were collected from all patients at the time of admission for performing blood culture. Antimicrobial susceptibility pattern was studied using Vitek 2 system. Gram negative bacteria are more commonly associated with sepsis (66.7%) than Gram positive bacteria (33.3%). A higher degree of resistance was seen to fluoroquinolones (71.4%), amoxicillin + clavulanic acid (61.9%), cephalosporins (58.8%) and gentamicin (57.1%), among Gram negative bacteria and to penicillin (100%), gentamicin (57.1%), cephalosporins (57.1) and fluoroquinolones (50%) among Gram positive bacteria. Gram negative bacteria are the predominant agents of pediatric sepsis in developing countries. Antimicrobial resistance to gram negative isolates is rising.

## Article Info

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## Keywords

Antimicrobial resistance, Gram negative infection, Pediatric sepsis.

## Introduction

Sepsis is an important cause of mortality in children in developing countries. Of the approximately 156 million new cases of pneumonia per year worldwide, 151 million are estimated to be in the developing world where a combination of contaminated water, poor sanitation, indoor air pollution, crowding, low birth weight, and insufficient immunization and nutrition allow pathogens to invade and multiply relatively unchecked in the body [1].

Children with sepsis present with fever, difficulty in breathing, lethargy or tachycardia [2]. These signs and symptoms of sepsis are non specific. Moreover, the delay in starting timely treatment may result in complications like shock, disseminated intravascular coagulation or organ failure. Therefore, there is a need to start timely treatment in suspected cases soon. Blood culture remains the mainstay of diagnosis of sepsis. The initiation of early treatment can reduce the morbidity and mortality associated with sepsis. Moreover, the rationale empirical treatment will reduce the emergence of antimicrobial resistance. Various organisms have been associated with sepsis in children including various Gram negative and Gram positive bacteria. A review of 15 studies of neonatal sepsis in developing countries, performed in the late 1990s found that the most commonly encountered species in blood culture-positive cases were *Klebsiella spp*, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas spp* [3]. The antimicrobial susceptibility pattern of the commonly isolated organisms in blood culture in an area is required to form an antibiotic policy. We report the pattern of antimicrobial susceptibility in children with clinical diagnosis of sepsis from a tertiary care hospital in North India.

## Materials and Methods

250 patients between 2 months to 5 years of age presenting with clinical signs of sepsis, to pediatric emergency room of a tertiary care hospital in North India from December 2014 to January 2016 were taken up for study. The study was carried out after taking an informed consent from the parent/ guardian of the patients. Prior ethical clearance was taken from the Institutional ethical committee. The clinical diagnosis of sepsis was made according two or more age dependent signs of sepsis as per the International Pediatric Sepsis Consensus Conference criteria. [2] (Table 1).

A detailed history and clinical examination was taken according to the pre-designed proforma based on the clinical criteria for sepsis.

Approximately 2 ml blood collected in blood culture bottle containing brain-heart infusion broth such that the blood:broth ratio is 1:5 for culture and sensitivity. After blood sample was transferred to blood culture bottle, the bottle was incubated at 37°C for 24 hrs and then subcultured onto 5% sheep blood agar and MacConkey's agar, incubated at 37°C for 18-24 hrs and read the following day.

Culture negative broths were re-incubated and subcultured daily for 5 days. Bacterial growth was identified on the basis of colony characteristics and biochemical reactions and agglutination with specific antisera wherever required.

The bacterial colonies that appeared on the culture plates were subjected to preliminary tests like gram staining, hanging drop for motility, catalase and oxidase tests. Their identity was established by a battery of biochemical tests like fermentation of sugars, indole test, citrate utilization test, urease production test and production of $H_2S$ on TSI as per standard protocol. Final identification was done by agglutination specific antisera wherever applicable. All aerobic isolates obtained were subjected to antimicrobial susceptibility testing using the VITEK-2 system. The MICs were interpreted as per standard Clinical and Laboratory Standards Institute (CLSI) guidelines.

## Statistical analysis

The data was analyzed by using SPSS, ver. 21.0. The association between the qualitative variables was analyzed by using the Chi-square test and the independent sample 't' test. A two-tailed $P < 0.05$ was considered significant.

## Results and Discussions

Out of 250 patients, 156 (62.4%) were males and 94 (37.6%) were females as shown in Table 2. Maximum patients were in the age group 2 months to 6 months (48%).

During the study period, total 250 samples of blood were processed. Out of these, 59 blood samples (23.6%) were positive on culture. The culture positive and culture negative groups did not differ statistically in terms of age in months (p=0.18).

Gram negative bacteria were the predominant isolates, being found in 39/59 (66.1%) samples, and Gram positive bacteria were found in 20/59 (34.6%) samples. The most common organism isolated in blood culture was *Escherichia coli* (22%), followed by *Staphylococcus aureus* (18.6%) and *Klebsiella spp* (16.9%). *Pseudomonas spp* and *Acinetobacter spp* were isolated in 12.7% blood samples each.

Gram negative bacteria were predominantly isolated from children aged 2months to 6 months and from 1 year to 5 years, while Gram positive bacteria predominated in age group of more than 6 months to 1 year.

## Antimicrobial susceptibility of bacteria isolated

The bacterial isolates were tested for antimicrobial susceptibility to wide range of antimicrobial agents as per CLSI guidelines.

All the Gram positive bacterial isolates were sensitive to linezolid (100%), tigecycline (100%) and vancomycin (100%) while all were resistant to penicillin. Gentamicin resistance was seen in 57.1% Gram positive isolates. Sensitivity to other antibiotics varied from 27.3% to 63.6%.(Table 3) Among the 12 isolates of *Staphylococcus aureus*, 41.7% (5/12) were methicillin resistant (MRSA) and among the 9 isolates of Coagulase negative Staphylococcus species, 3 were methicillin resistant (MRCONS) as confirmed by Oxacillin MICs (Table 4 and Fig. 1).

All the Gram negative bacterial isolates were found to be sensitive to colistin (100%). None of the Gram negative bacterial isolates were sensitive to cotrimoxazole. Sensitivity to other isolates varied from 25% to 87.5%.Resistance to Ciprofloxacin was seen in 71.4%, Amoxyclav in 61.9% and Cefepime in 61.5% Gram negative isolates (Table 3). Among the Gram negative bacteria, *Acinetobacter spp* was found to be the most resistant organism (Table 5).

**Table.1** Age dependent signs of sepsis

| Age | Temperatu | Heart Rate | Respiratory | TLC | SBP |
|---|---|---|---|---|---|
| 1month- | >38$^0$C or | >180 or | >35 | >17.5 or | <75 |
| 2yr-5yr | >38$^0$C or | >140 | >30 | >15.5 or | <75 |

**Table.2** Age and sex distribution of subjects

| Age Group | Number of Males | Number of Females | Total (%) |
|---|---|---|---|
| 2months- 6months | 78 (31.2) | 42 (16.8) | 120 (48.0) |
| 6months-1year | 22 (8.8) | 12 (4.8) | 34 (13.6) |
| 1year-2year | 22 (8.8) | 6 (2.4) | 28 (11.2) |
| 2year- 5year | 34 (13.6) | 34 (13.6) | 68 (27.2) |
| Total (n=250) | 156 (62.4) | 94 (37.6) | 250 (100) |

*****Figures in parenthesis represent percentage of the patients

**Table.3** Resistance of bacterial isolates to different antimicrobials

| Antibiotic | Gram positive cocci | Gram negative |
|---|---|---|
| Penicillin | 21/21(100) | - |
| Gentamicin | 12/21 (57.1) | 24/42 (57.1) |
| Cephalexin | 12/21 (57.1) | - |
| Clindamycin | 8/21 (38.1) | - |
| Erythromycin | 6/21 (28.6) | - |
| Ciprofloxacin | 11/21 (52.4) | 30/42 (71.4) |
| Levofloxacin | 10/21(47.6) | - |
| Oxacillin | 8/21 (38.1) | - |
| Cotrimoxazole | 7/21 (33.3) | 42/42 (100) |
| Teicoplanin | 0/21 (0) | - |
| Tigecycline | 0/21 (0) | - |
| Vancomycin | 0/21 (0) | - |
| Linezolid | 0/21 (0) | - |
| Amoxycyllin/Clavulanic acid | - | 26/42 (61.9) |
| Ceftazidime | - | 24/42 (57.1) |
| Cefepime | - | 16/26 (61.5) |
| Amikacin | - | 16/42 (38.1) |
| Piperacillin+Tazobactam | - | 15/42 (35.7) |
| Imipenem | - | 12/42 (28.6) |
| Meropenem | - | 12/42 (28.6) |
| Colistin | - | 0/42 (0) |

**Table.4** Antimicrobial susceptibility pattern (%) of Gram Positive Cocci

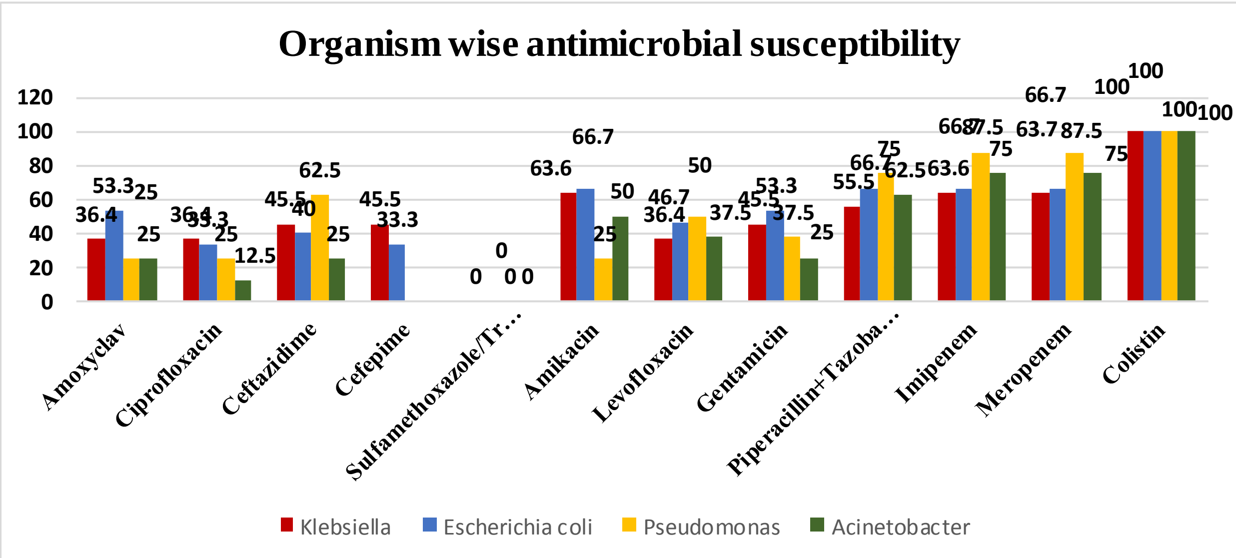
| Organism | P | G | Cf | Cd | E | Cip | Lev | Ox | Te | TGC | SXT | VA | LNZ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Staphylococcus aureus* (n=12) | 0 (0) | 3 (27.3) | 3 (27.3) | 7 (63.6) | 6 (54.5) | 3 (33.3) | 4 (36.7) | 7 (36.7) | 11 (100) | 11 (100) | 6 (53.5) | 11 (100) | 11 (100) |
| CONS (n=9) | 0 (0) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 9 (100) | 7 (77.8) | 7 (77.8) | 6 (66.7) | 9 (100) | 9 (100) | 8 (88.9) | 9 (100) | 9 (100) |

*P=Penicillin, G=Gentamicin, Cf=Cephalexin, CD=Clindamycin, E=Erythromycin, Cip=Ciprofloxacin, Lev=Levofloxacin, Ox=Oxacillin, Te=Teicoplanin, TGC=Tigecycline, SXT=Sulfmethoxazole/Trimethoprim, Va=Vancomycin, Lnz= Linezolid
**Figures in parentheses represent percentage of the susceptible isolates

**Table.5** Antimicrobial susceptibility of Gram negative bacilli

| Organism | AMC | Cip | Cfzd | Cpm | SXT | AK | Levo | G | PT | Imp | Mrp | Col |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Klebsiella spp* (n=11) | 4 (36.4) | 4 (36.4) | 5 (45.5) | 5 (45.5) | 0 (0) | 7 (63.6) | 4 (36.4) | 5 (45.5) | 6 (55.5) | 7 (63.6) | 7 (63.6) | 11 (100) |
| *Escherichia coli* (n=15) | 8 (53.3) | 5 (33.3) | 6 (40) | 5 (33.3) | 0 (0) | 10 (66.7) | 7 (46.7) | 8 (53.3) | 10 (66.7) | 10 (66.7) | 10 (66.7) | 15 (100) |
| *Pseudomonas spp* (n=8) | 2 (25) | 2 (25) | 5 (62.5) | - | 0 (0) | 2 (25) | 4 (50) | 3 (37.5) | 6 (75) | 7 (87.5) | 7 (87.5) | 8 (100) |
| *Acinetobacter spp* (n=8) | 2 (25) | 1 (12.5) | 2 (25) | - | 0 (0) | 5 (50) | 3 (37.5) | 2 (25) | 5 (62.5) | 6 (75) | 6 (75) | 8 (100) |

**Figure.1** Organism wise antimicrobial susceptibility




Antimicrobial resistance in pediatric population is a cause of concern. Gram negative bacteria are the common cause of bloodstream infections in children in developing countries. We also found various gram negative bacteria to be the common cause of pediatric sepsis in our study, *Escherichia coli* being the most common. Pediatric sepsis can also be caused by viruses, parasites and fungi, explaining the low bacterial culture positivity in most clinical studies.

Another factor responsible for the low culture positivity is administration of antibiotics prior to collection of blood sample, incorrect information regarding antibiotic intake history from referred patients and the time lost in transport of the blood sample from the site of collection to the laboratory. In the present, we found a bacterial blood culture positivity rate of 23.6%. This is similar to most studies in developing countries.

During the study period of one year, 250 samples of blood and 29 samples of CSF were processed, out of which 59 (23.6%) blood samples were positive on culture. This is consistent with the results of Kapoor *et al.*, [4] (20%), Sharma *et al.*, [5] (22.9%), Agnihotri *et al.*, [6] (19.19%), Tsering *et al.*, [7] (22.6%) who had a similar culture positivity rate in paediatric cases. However, Chacko B *et al.*, [8] found a high rate of culture positivity (43.0%) in the paediatric patients of sepsis. Most Indian studies in children had a culture positivity rate similar to our study [4,5,6,7].

Blood cultures yielded maximum positivity in clinically diagnosed pneumonia (28.6%) and diarrhoea (27.5%) cases. In cases which were clinically diagnosed as bloodstream infection, the blood culture was positive in only 12.8% cases. The clinically diagnosed enteric fever cases had 25% blood culture positivity rate.

Gram-negative bacteria were predominantly isolated, found in 42 (66.7%) samples, whereas gram-positive bacteria were isolated in 21 samples (33.3%). Previous Indian studies [4,5,7] also reported gram-negative infections to be predominant in paediatric sepsis.

In the present study, *Escherichia coli* (22%) was the predominant isolate in blood, followed by *Staphylocccus aureus* (18.6%) and *Klebsiella spp* (16.9%). Other isolates in blood in this study were coagulase negative staphylococcus species (15.3%), *Pseudomonas spp* (13.6%) and *Acinetobacter spp* (13.6%). This is similar to a previous study [9] where authors found *Escherichia coli* to be the predominant isolate (26%) in children. Other predominant isolate in this study was *Staphylococcus aureus* which was found in 11.9% cases and the other 33% isolates included *Klebsiella spp*, *Enterobacter spp*, *Citrobacter spp* and *Serratia spp*. In contrast, *Klebsiella spp* was the predominant gram-negative isolate in most paediatric studies in India [4,5,7]. Previous researchers [4] found gram-negative bacteria to be the predominant isolates (62%), commonest being *Klebsiella pneumoniae* (34%) followed by *Escherichia coli* (17%), *Acinetobacter spp*

(9%) and *Enterobacter aerogenes* (2%). Gram-positive cocci were isolated in 20% cases, of which coagulase negative staphylococcus was the predominant isolate (11%) followed by *Enterococcus* spp. (5%) and *Staphylococcus aureus* (4%). In another study, [5] authors found gram-negative organisms as the most predominant isolates (88.8%). Commonest was *Klebsiella spp* (47.1%) followed by *Salmonella spp* (16.2%) and *Pseudomonas spp* (8%) whereas in gram-positive, *Staphylococcus aureus* 76 (7.6%) was the most common. Authors in another study [7] reported that gram-negative septicemia was encountered in 61% of the culture-positive cases. *Pseudomonas* and *Enterobacter species* were the predominant pathogens amongst gram-negative organisms. The most common gram-positive organism isolated was *Staphylococcus aureus* (97%).

*Escherichia coli* was the predominant isolate in CSF as well, isolated in 50% of the samples. Other isolates in CSF were *Klebsiella spp* (25%) and *Staphylococcus aureus* (25%). This was similar to the study by Iregbu *et al.*, [10] who found *Staphylococcus aureus* (32.2%), *Klebsiella pneumoniae* (21.5%) and *Escherichia coli* (14.3%) as the predominant isolates. Chong *et al.*, [11] also found gram-negative bacteria such as *Escherichia coli*, *Klebsiella spp* were the predominant isolates in bacterial meningitis. Another study in North India by Bareja *et al.*, [12] reported *Staphylococcus aureus* (37%) as the most common cause of bacterial meningitis in this age group, followed by *Pseudomonas spp* (13%) and *Escherichia coli* (12%).

Among the gram-positive bacterial isolates, high resistance was observed to first line antibiotics like penicillin (100%), gentamicin (57.1%), cephalosporins (57.1%) and fluoroquinolones (50%). However, Kapoor *et al.*, [4] found high sensitivity to Ciprofloxacin in contrast to our study which reported 52.4% sensitivity to ciprofloxacin. Linezolid, Vancomycin, Teicoplanin and Tigecycline were found to be the most sensitive (100%) drugs for gram-positive infection. Rose *et al.*, [13] (100%), Sharma *et al.*, [5] (99%) and Rao *et al.*, [14] also found gram-positive isolates to be most sensitive to Linezolid (93.56%). 41.7% of the Staphylococcus aureus isolates were Methicillin resistant (MRSA). All these were sensitive to Linezolid, Vancomycin, Teicoplanin and Tigecycline. This finding is similar to the study at CMC Vellore by Rose *et al.*, [13] who found 40% MRSA isolates in their study all of which were sensitive to Vancomycin and Linezolid. Rao *et al.*, [14] also found a high sensitivity to vancomycin (97.0%) and Linezolid (93.6%). They reported moderate resistance to ciprofloxacin (39.05%) among the gram-positive isolates.

Among the gram-negative bacterial isolates, high resistance was observed to gentamicin (57.1%), fluoroquinolones (71.4%) and cephalosporins (58.8%) in the present study. This is similar to the results of Rose *et al.*, [13] who found high resistance to 3rd generation Cephalosporins (57.8%), fluoroquinolones (73.5%) and Gentamicin (72.9%) among the gram-negative isolates. High resistance was observed to amoxicillin+clavulanic acid (61.9%) which is similar to the results of Kapoor *et al.*, [4] who reported >80% resistance to amoxicillin+clavulanic acid. A study in Pakistan by Rao *et al.*, [14] found 47% resistance to ciprofloxacin among the gram-negative isolates. Variable degree of resistance to cephalosporins was observed, ranging from 15% to cefoperazone to 85.5% to cefaclor. Amikacin had a moderate degree of resistance (37%) in this study which was similar to our study (38.1%). Another study in Nigeria by Meremikwu *et al.*, [15] found 61.6% sensitivity to gentamicin and 70-80% sensitivity to cephalosporins in gram-negative isolates in paediatric population. Studies in neonatal population in India as well as other developing countries have reported high sensitivity to gentamicin and cephalosporins [16,17,18]. The variation in results could be due to different geographical distribution and age group of the study subjects and different antimicrobial usage policy.

## References

1. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bulletin of the world health organization. 2008 May; 86(5): 408-16B.
2. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatric critical care medicine. 2005 Jan 1; 6(1): 2-8.
3. The WHO Young Infants Study Group. Etiology and clinical signs of serious infections in young infants in developing countries: a WHO collaborative study. Pediatr Infect Dis J 1999; 18: S32–34.
4. Kapoor L, Randhawa VS, Deb M. Microbiological profile of neonatal septicemia in a pediatric care hospital in Delhi. Journal of Commun Dis 2005;37:546–8.

5. Sharma M, Goel N, Chaudhary U, Aggarwal R, Arora DR. Bacteraemia in children. Indian J Pediatr. 2002 Dec; 69(12): 1029–32.
6. Agnihotri N, Kaistha N, Gupta V. Antimicrobial susceptibility of isolates from neonatal septicemia. Jpn J Infect Dis. 2004 Dec 1; 57(6): 273-5.
7. Tsering DC, Chanchal L, Pal R, Kar S. Bacteriological profile of septicemia and the risk factors in neonates and infants in Sikkim. J Glob Infect Dis. 2011 Jan; 3(1): 42-5
8. Chacko B, Sohi I. Early onset neonatal sepsis. Indian J Pediatr. 2005 Jan; 72(1): 23-6.
9. Kumar S, Rizvi M. Serum tumor necrosis factor α and C-reactive protein in pediatric patients with sepsis and its correlation with microbiologic findings. Indian Journal of Pathology and Microbiology. 2010 Jul 1; 53(3):494.
10. Iregbu KC, Abdullahi N. Profiles of acute bacterial meningitis isolates in children in National Hospital, Abuja. Niger Med J. 2015 Jul-Aug; 56(4): 297-300. doi: 10.4103/0300-1652.169749.
11. Chong HT, Tan CT. Epidemiology of central nervous system infections in Asia, recent trends. Neurology Asia. 2005 Jun; 10: 7-11.
12. Bareja R, Pottathil S, Shah RK, Grover PS, Singh VA. Trends in bacterial etiology amongst cases of meningitis. J Acad Indus Res. 2013; 1: 761-5.
13. Rose W, Veeraraghavan B, Pragasam AK, Verghese VP. Antimicrobial susceptibility profile of isolates from pediatric blood stream infections. Indian Pediatr. 2014 Sep; 51(9): 752-3.
14. Rao MH, Khan S, Waseem T, Naeem S, Sabir S. Sepsis in Infants: Analysis of Bacterial Pathogens and their Antibiotic Susceptibility, A Study at Government Tertiary Care Hospital, Karachi. Journal of Dow University of Health Sciences. 2013 Jan 1; 7(1): 35-40
15. Meremikwu MM, Nwachukwu CE, Asuquo AE, *et al.*, Bacterial isolates from blood cultures of children with suspected septicaemia in Calabar, Nigeria. BMC Infect Dis 2005; 5: 110.
16. Milledge J, Calis JC, Graham SM, *et al.*, Aetiology of neonatal sepsis in Blantyre, Malawi: 1996–2001. Ann Trop Paediatr 2005; 25: 101–10.
17. Aurangzeb, B., Hameed, A., 2003. Neonatal sepsis in hospital-born babies: bacterial isolates, antibiotic susceptibility patterns. J.Coll. Physicians Surg. Pak. 13, 629—632
18. Laving, A.M., Musoke, R.N., Wasunna, A.O., Revathi, G., 2003. Neonatal bacterial meningitis at the newborn unit of Kenyatta National Hospital. East Afr. Med. J. 80, 456—462.

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