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ORIGINAL ARTICLE

High Reported Rates of Antimicrobial Resistance in Indian Neonatal and Pediatric Blood Stream Infections

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Background. There is real shortage of national data on antimicrobial resistance rates in Indian neonates and children. A descriptive review was conducted to determine the patterns of antimicrobial resistance in isolates of blood stream infection among hospitalized children in India.

Methods. Published and gray literature on antibiotic resistance in children was searched using "Google Scholar", "Scopus", and "PubMed" databases between January 2000 and July 2015. Studies were included if they were original articles that reported a minimum of 10 pathogenic bacterial isolates from the bloodstream within a pediatric population in India, and studies were excluded if they reported studies done during an outbreak or epidemic.

Results. A total of 1179 studies were screened, and 82 papers were identified as eligible for inclusion. Most studies (78.7%) were reported from neonatal intensive care units. Among a total of 50 545 reported blood cultures, 14 704 (29.1%) were positive. *Staphylococcus aureus* (median, 14.7%; IQR, 7.4%–25.6%) and *Klebsiella pneumoniae* (median, 26%; IQR, 16.7%–35.4%) were the commonest reported Gram-positive and Gram-negative pathogens, respectively. Approximately half of all *S aureus* isolates were reported as methicillin-resistant *S aureus* (median, 50%; IQR, 31.4%–65.1%). After age stratification, the median rate of resistance of common Gram-negative pathogens to ampicillin and gentamicin/amikacin were extremely high (*K pneumoniae*/ampicillin 95.9%; *K pneumoniae*/gentamicin 75%; *Escherichia coli*/ampicillin 92.9%; *E coli*/gentamicin 55.6%). Likewise, the median resistance of common Gram-negative blood stream isolates to cephalosporins were also high (*K pneumoniae*/cefotaxime 62.6%; *E coli*/cefotaxime 47.5%).

Conclusions. High rates of resistance to World Health Organization-recommended first-line treatment options for neonates and children have been identified in blood stream infections across India. There is an urgent need to both enhance antibiotic stewardship and infection prevention and control measures and consider urgently how to repurpose older antibiotics back into routine care in India.

Keywords. antimicrobial resistance; cephalosporins; children; India; MRSA.

There has been a relentless rise in antimicrobial resistance (AMR) globally. Concerns about this serious threat have been raised since the late 1990s as evident by the Global Strategy for Containment of Antimicrobial Resistance of the World Health Organization (WHO) in 2001 [1]. The WHO in its recent global surveillance report states that this reality of AMR is "far from an apocalyptic fantasy", is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country [2].

Due to lack of a national robust surveillance system for AMR in India, there is currently no centrally reported AMR national database. Earlier initiatives to generate AMR data include those carried out by the India Clinical Epidemiological Network (INCLEN) and Indian Network for Surveillance of Antimicrobial Resistance (INSAR) [3, 4]. In 2011, the Indian Council of Medical Research (ICMR) launched the National Policy for Containment of Antimicrobial Resistance, which includes sentinel surveillance of AMR in a phase wise manner across the country [5]. This surveillance has not defined any age stratification. The Jaipur Declaration in 2011 [6] and Chennai Declaration [7] in the subsequent year framed consensus roadmaps to tackle AMR.

Antimicrobial resistance patterns can significantly differ in adult and children [8]. It is estimated that India has the highest neonatal mortality due to neonatal sepsis caused by bacteria resistant to first-line antibiotics [9]. Approximately one fifth of neonates with sepsis die in the hospital, and the mortality rises to 50% for those with culture-proven sepsis [10]. In the absence of any recent national data of AMR rates in blood stream infections (BSIs) in the Indian neonatal or pediatric population, this study aimed to review the published and unpublished data on AMR during 2000–2015 from India.

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METHODS

The published and gray literature on antibiotic resistance in children in English literature was searched using the databases "Google Scholar" and "Scopus", and PubMed was searched using keywords "India" AND "children" OR "pediatrics" OR "neonates" OR "infants" AND "antimicrobial resistance" OR "antibiotic resistance" OR "antibiotic susceptibility" OR "antibiotic sensitivity" AND "blood culture" (see Supplementary Material 1). Gray literature sources such as pediatric conference proceedings and national reports were examined individually. The period between January 1, 2000 and July 1, 2015 was chosen to access maximal information of published abstracts and full-text articles. A single reviewer assessed the study quality and performed data extraction.

Inclusion criteria included original articles describing studies performed in well described health centers in India, published between January 2000 and July 2015, and described blood culture-derived bacterial isolates from children from birth to 18 years, with determination of antimicrobial susceptibility patterns. Excluded studies were those that described less than 10 pathogenic isolates, or those that did not distinguish bloodstream and nonbloodstream sources, and those performed in adult populations. Studies performed during outbreaks or epidemics were also excluded. Bacterial isolates of interest reviewed here included Gram-positive bacteria (*Staphylococcus aureus*, coagulase-negative *Staphylococcus* (CONS), *Enterococcus fecalis*) and Gram-negative bacteria (*Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter* species, *Citrobacter* species, *Acinetobacter baumannii*, *Proteus* species, and *Salmonella typhi*).

Statistical Analysis

The proportions (percentage) and ranges of individual blood-borne pathogens in infants and children resistant to various drugs (mentioned in Tables 1, 2 and 3) were calculated. Because the total number of reported blood cultures varied markedly between studies, proportions and ranges for pathogens were weighted by total sample size of blood cultures and given as weighted median of proportions (percentage) and interquartile ranges (IQRs). Likewise, median and IQRs of resistance rates attributable to a pathogen to recommended antibiotics were reported [11].

RESULTS

Search Analysis

An electronic search on July 9, 2015 identified 298 articles in PubMed, 4980 articles in the database of Google Scholar, and 243 articles in Scopus. Of the 4980 articles, the Google Scholar engine displays only the first 1000. An individual search of abstracts from national conferences of Indian Academy of Pediatrics identified 8 abstracts. Seventy-two articles were common in both search engines. So, in total, 1179 abstracts were reviewed. Most of the articles were excluded because the studies were done in children living outside India or in the adult population (Figure 1). Among the remaining 484 articles, those that met the exclusion criteria were excluded.

Thus, 82 papers (see Supplementary Material 2) were included for analysis. Among these 82 papers, some papers had multiple data sets covering multiple years. Because the data set belonging to a particular year was considered as a separate study, the total number of studies obtained was 89. The positive

Table 1. Median and IQR of Percentage Resistance of Gram-Positive Bacteria: *Staphylococci aureus*, CONS, and *Enterococcus faecalis*

Antibiotic	*Staphylococcus aureus* 14.7% (7.4%–25.6%) [n = 70]	CONS 10.4% (4.2%–15.9%) [n = 68]	*Enterococcus faecalis* 0.9% (0%–4.4%) [n = 44]
Penicillin	NS	NS	88.5% (41.7%–100.0%) [n = 9]
Ampicillin	NS	NS	100.0% (77.5%–100.0%) [n = 4]
Erythromycin	53.0% (39.5%–65.9%) [n = 31]	43.3% (30.5%–67.1%) [n = 26]	53.2% (44.6%–61.9%) [n = 8]
Cloxacillin	50.0% (31.4%–65.1%) [n = 33]	42.5% (19.1%–66.7%) [n = 24]	NS
Amikacin	25.8% (14.2%–48.7%) [n = 40]	28.6% (0.0%–41.0%) [n = 35]	NS
Gentamicin	44.9% (24.9%–69.7%) [n = 42]	50.0% (29.2%–66.7%) [n = 36]	68.5% (41.7%–77.5%) [n = 13]
Cephelexin	34.3% (27.3%–66.6%) [n = 11]	27.3% (0.0%–51.5%) [n = 10]	NS
Cefotaxime	57.1% (25.0%–66.0%) [n = 23]	35.4% (18.4%–64.1%) [n = 22]	NS
Ceftriaxone	40.0% (21.4%–60.0%) [n = 11]	33.0% (9.0%–47.9%) [n = 9]	NS
Cotrimoxazole	57.7% (30.0%–72.7%) [n = 19]	69.9% (60.6%–87.3%) [n = 16]	75.0% (12.5%–100.0%) [n = 4]
Ciprofloxacin	40.0% (25.0%–59.0%) [n = 39]	38.9% (16.7%–53.6%) [n = 31]	50.0% (0.0%–64.4%) [n = 10]
Amoxiclav	25.0% (16.0%–53.6%) [n = 9]	11.1% (0.0%–40.3%) [n = 11]	20.0% (0.0%–40.0%) [n = 2]
Clindamycin	29.3% (15.9%–40.2%) [n = 14]	27.5% (6.1%–37.1%) [n = 14]	NS
Vancomycin	0.0% (0.0%–0.0%) [n = 37]	0.0% (0.0%–0.0%) [n = 35]	0.0% (0.0%–13.7%) [n = 12]
Linezolid	0.0% (0.0%–12.5%) [n = 19]	0.0% (0.0%–0.0%) [n = 17]	0.0% (0.0%–5.0%) [n = 6]
Teicoplanin	0.0% (0.0%–10.5%) [n = 5]	0.0% (0.0%–0.0%) [n = 5]	0.0% (0.0%–16.6%) [n = 3]
Doxycycline	-NS	-NS	40.0% (40.0%–40.0%) [n = 1]

Abbreviations: CONS, coagulase-negative *Staphylococcus*; IQR, interquartile range; n, number of samples; NS, not studied.
*Data are presented in the following form: median (IQR, Q1–Q3) [number of studies].

Table 2. Median and IQR of Percentage Resistance of Gram-Negative Bacteria: *Klebsiella pneumoniae, Enterobacter* spp, *Escherichia coli, Acinetobacter baumannii, Citrobacter* spp, and *Pseudomonas aeruginosa*

Antibiotic	*Klebsiella pneumoniae* 26% (16.7%–35.4%) [n = 74]	*Enterobacter* spp 3.2% (0%–8.4%) [n = 43]	*Escherichia coli* 9.3% (4.7%–14.5%) [n = 72]	*Acinetobacter baumannii* 5.9% (2.1%–10.8%) [n = 62]	*Citrobacter* spp (0%–3%) [n = 44]	*Pseudomonas aeruginosa* 4.8% (2.5%–9.4%) [n = 65]
Ampicillin	95.2% (74.0%–100.0%) [n = 47]	100.0% (94.7%–100.0%) [n = 19]	92.3% (67.7%–100.0%) [n = 32]	42.9% (7.0%–63.2%) [n = 35]	99.0% (79.2%–100.0%) [n = 10]	NS
Cephalexin	73.7% (49.5%–95.2%) [n = 4]	100.0% (95.2%–100.0%) [n = 3]	58.4% (58.3%–100.0%) [n = 3]	NS	NS	NS
Cefazolin	76.5% (53.8%–100.0%) [n = 3]	NS		NS	NS	NS
Cefotaxime	63.7% (40.9%–80.5%) [n = 52]	70.4% (55.2%–90.3%) [n = 22]	50.0% (40.0%–66.0%) [n = 37]	60.0% (42.2%–90.6%) [n = 29]	60.0% (0.0%–69.1%) [n = 13]	NS
Ceftriaxone	65.0% (28.7%–90.4%) [n = 31]	100.0% (58.8%–100.0%) [n = 11]	50.0% (33.3%–66.7%) [n = 19]	68.9% (49.6%–97.1%) [n = 14]	50.0% (0.0%–62.5%) [n = 11]	NS
Ceftazidime	64.3% (44.4%–88.6%) [n = 34]	67.0% (51.9%–97.6%) [n = 13]	NS	77.8% (50.0%–100.0%) [n = 19]	NS	58.7% (33.3%–73.7%) [n = 26]
Amikacin	41.0% (18.8%–50.5%) [n = 65]	37.9% (20.6%–66.2%) [n = 26]	22.4% (0.0%–40.0%) [n = 43]	NS	50.0% (18.6%–63.5%) [n = 16]	40.0% (25.0%–50.0%) [n = 39]
Gentamicin	75.7% (54.8%–86.8%) [n = 64]	83.3% (65.8%–93.6%) [n = 25]	55.6% (33.3%–83.3%) [n = 43]	64.0% (45.0%–79.6%) [n = 37]	50.0% (33.4%–83.3%) [n = 15]	65.8% (50.0%–75.0%) [n = 36]
Ciprofloxacin	46.2% (28.4%–62.0%) [n = 57]	39.0% (8.3%–62.1%) [n = 23]	40.0% (22.9%–67.0%) [n = 37]	52.8% (32.5%–63.2%) [n = 34]	33.4% (0.0%–64.8%) [n = 16]	50.0% (32.5%–62.6%) [n = 38]
Chloramphenicol	59.2% (9.8%–77.3%) [n = 14]	91.1% (51.7%–100.0%) [n = 6]	63.9% (28.8%–84.9%) [n = 8]	88.9% (65.3%–100.0%) [n = 9]	71.9% (37.5%–93.8%) [n = 4]	NS
Amoxiclav	64.7% (33.0%–90.0%) [n = 19]	NS	74.5% (34.4%–87.8%) [n = 12]	NS	52.3% (12.5%–88.6%) [n = 4]	NS
Piperacillin-tazobactam	42.0% (1.6%–61.4%) [n = 22]	16.7% (0.0%–68.8%) [n = 8]	16.7% (0.0%–40.0%) [n = 11]	22.3% (0.0%–53.2%) [n = 17]	0.0% (0.0%–37.5%) [n = 4]	21.0% (1.2%–33.3%) [n = 17]
Cefoperazone-sulbactam	23.6% (9.5%–53.9%) [n = 12]	23.8% (1.5%–85.4%) [n = 4]	NS	20.0% (9.4%–23.2%) [n = 5]	1.0% (0.0%–1.9%) [n = 2]	NS
Cotrimoxazole	62.5% (50.1%–80.7%) [n = 25]	NS	63.2% (50.0%–78.3%) [n = 17]	NS	33.4% (0.0%–50.0%) [n = 7]	NS
Aztreonam	71.9% (19.0%–84.1%) [n = 9]	100.0% (50.0%–100.0%) [n = 3]	30.9% (2.9%–57.5%) [n = 4]	22.2% (0.0%–86.1%) [n = 4]	0.0% (0.0%–100.0%) [n = 3]	45.0% (6.3%–83.3%) [n = 5]
Meropenem	1.0% (0.0%–17.4%) [n = 17]	16.7% (0.0%–83.4%) [n = 4]	9.0% (0.0%–27.0%) [n = 11]	11.5% (0.0%–47.5%) [n = 12]	0.0% (0.0%–0.0%) [n = 3]	16.7% (0.0%–30.0%) [n = 11]
Colistin	3.8% (0.0%–21.4%) [n = 3]	NS	8.8% (0.0%–17.6%) [n = 2]	NS	NS	0.0% (0.0%–0.0%) [n = 2]
Tigecycline	8.2% (1.0%–18.9%) [n = 4]	NS	0.0% (0.0%–0.0%) [n = 1]	NS	NS	NS

Abbreviations: IQR, interquartile range; n, number of samples; NS, not studied.
*Data are presented in the following form: median (IQR, Q1–Q3) [number of studies].

Table 3. Median and IQR of Percentage Resistance of *Salmonella typhi*

Antibiotic	*Salmonella typhi* 0% (0%–6.8%) [n = 37]
Ampicillin	50.0% (16.6%–87.1%) [n = 9]
Cefotaxime	0.0% (0.0%–13.6%) [n = 7]
Ceftriaxone	6.3% (0.0%–14.2%) [n = 7]
Ceftazidime	0.0% (0.0%–0.0%) [n = 2]
Ciprofloxacin	14.3% (0.0%–21.4%) [n = 11]
Chloramphenicol	17.9% (0.9%–62.1%) [n = 8]
Amoxiclav	0.0% (0.0%–14.3%) [n = 3]
Cotrimoxazole	12.2% (0.0%–45.1%) [n = 8]
Azithromycin	16.0% (0.0%–31.2%) [n = 3]
Nalidixic acid	35.5% (0.0%–81.3%) [n = 5]

Abbreviations: IQR, interquartile range; n, number of samples.
*Data are presented in the following form: median (IQR, Q1–Q3) [number of samples].

blood culture rate was calculated using 78 of the 89 studies, because the total number of blood cultures analyzed were not available in the remaining 11 studies.

Study Characteristics

Among the 89 eligible studies that had provided data about positive blood cultures, 78.7% of data were from neonates, 14.6% were from children older than 1 month, and 6.7% studies were done in both neonate and pediatric ages. Studies were spread across India, with 36% reports from North India, 31.5% from South India, 16.9% from Western India, 12.4% from the East, and 3.4% from Central India. Of the 89 studies, 98.9% had been conducted at a tertiary-level healthcare center, and only 1 study (ie, 1.1%) had been reported from a secondary-level healthcare center. The great majority of studies (78.7%) had been reported from neonatal intensive care units (NICUs), and a small percentage (<5%) had been reported from pediatric intensive care unit ward, inpatient department, or their combinations. One study had screened enteric cases using blood cultures from the outpatient department [12].

Blood Culture Positivity

Data were available from a total of 16 777 positive blood cultures from 89 studies, which were used to examine the drug resistance of the isolates. The number of total blood cultures reported was available only in 78 of the 89 studies, which summed to a total 50 545 blood cultures. The positive blood culture rate was calculated from the 78 studies, which varied from 7.2% to 88.5% with a median of 35.4% (IQR, 21.2%–46.6%).

Pathogens Identified

Among 72 studies that reported Gram-positive bacteria, the median percentage of Gram-positive bacteria was 29.2%

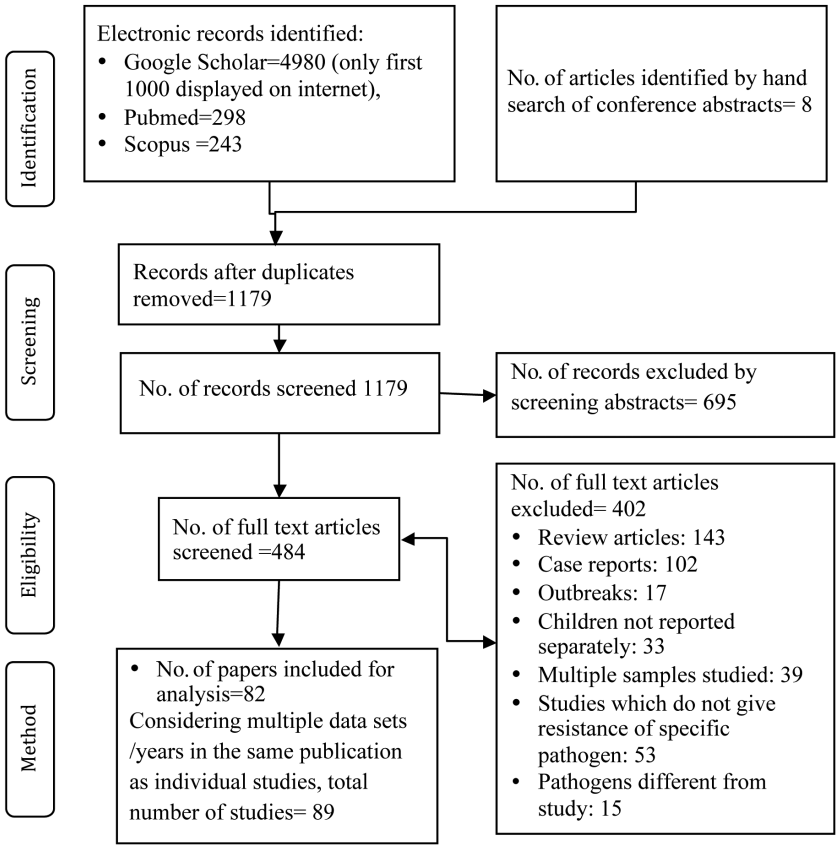

Figure 1. Flow chart of selection of studies based on PRISMA 2009 flow chart.

(IQR, 15.8%–36.8%). Among Gram-positive bacteria, *S aureus* was found to be the most common isolate (median, 14.7%; IQR, 7.4%–25.6%) followed by CONS (median, 10.4%; IQR, 4.2%–15.9%) and *E faecalis* (median, 0.9%; IQR, 0%–4.4%) (Table 1). It was not possible to distinguish true pathogens of CONS from contaminants in this review.

Gram-negative bacteria were reported in 81 studies. The median percentage of Gram-negative bacteria identified among all reported positive cultures was 61.0% (IQR, 34.6%–67.9%). Among Gram-negative bacteria, *K pneumoniae* was found to be the most common isolate (median, 26%; IQR, 16.7%–35.4%) followed by *E coli* (median, 9.3%; IQR, 4.7%–14.5%), *A baumanii* (median, 5.9%; IQR, 2.1%–10.8%), and *P aeruginosa* (median, 4.8%; IQR, 2.4%–9.4%).

Resistance of Gram-Positive Bacteria

Fifty percent of the *S aureus* isolates were methicillin-resistant *S aureus* (MRSA). High resistance was also noted for *S aureus* to erythromycin (53%), cefotaxime (57%), and cotrimoxazole (57.7%) (Table 1). Lower resistance pattern was shown by CONS except to cotrimoxazole (69.9%). However, *E faecalis* showed very high resistance to antibiotics including penicillins (88.5%), gentamicin (68.5%), and ciprofloxacin (50%). No resistance was found to vancomycin, linezolid, and teicoplanin in all the Gram-positive bacteria reported.

Resistance of Gram-Negative Bacteria

Details of the Gram-negative resistance rates are provided in Table 2. High levels of resistance was reported in *K pneumoniae* to ampicillin (95.2%) and cephalosporins (over 60%). The rates of reported resistance to tigecycline were 8.2%, colistin 3.8%, and meropenem 1%. Reported resistance in *Enterobacter* spp was 100% to ceftriaxone and aztreonam. Resistance to piperacillin-tazobactam was 16.7%, ciprofloxacin 39%, and meropenem 16.7%. There were very high resistance rates identified in *E coli* (Table 2) to ampicillin (92.3%), chloramphenicol (63.9%), and ciprofloxacin (40%) and relatively lower resistance to amikacin (22.4%) and piperacillin-tazobactam (16.7%). Resistance to meropenem of 9.0% and colistin of 8.8% was noted. As seen in Table 2, high resistance of *P aeruginosa* was noted to ceftazidime (58.7%), which is often used empirically for *P aeruginosa* infections. High resistance (16.7%) of *P aeruginosa* to meropenem was noted.

In case of resistance of *A baumanii* and *Citrobacter* spp (Table 2), although the resistance to cephalosporins are high, there was relatively less resistance to ciprofloxacin and β-lactam antibiotics including piperacillin-tazobactam and cefoperazone-sulbactam. *Acinetobacter baumanii* infections were reported to have 11.5% resistance to meropenem.

Salmonella typhi (Table 3) displayed a median resistance of 50% to ampicillin, 35% to nalidixic acid, and 17.9% to chloramphenicol. However, 6.3% resistance to ceftriaxone and 16% to second-line antibiotics such as azithromycin were also noted.

Age-Based Stratification for Commonly Used Pathogen-Drug Combinations

Using age as criterion, the data were then split by age into neonatal (less than 1 month) and pediatric populations (age greater than 1 month) for commonly used pathogen-drug combinations (Table 4). (1) In Gram-positive resistance in neonates versus pediatric population, the overall resistance was found to be greater in neonatal age than pediatric age; however, this difference was not statistically significant. There was no resistance noted of isolates of *S aureus* and CONS to vancomycin and linezolid, in both age groups. (2) In Gram-negative resistance in neonates versus pediatric population, the median resistance of common Gram-negative pathogens to the WHO-recommended combination of ampicillin and gentamicin for the empiric treatment of neonatal sepsis was extremely high (*K pneumoniae*/ampicillin 95.9%; *K pneumoniae*/gentamicin 75%; *E coli*/ampicillin 92.9%; *E coli*/gentamicin 55.6%), and median resistance to cephalosporins were also high (*K pneumoniae*/cefotaxime 62.6%; *E coli*/cefotaxime 47.5%).

DISCUSSION

Main Findings

This literature review provides a comprehensive analysis on the AMR pattern of bacterial BSI in the pediatric population of India over the past 15 years. This study found higher reports of bacteremia caused by Gram-negative bacteria (53.3%) compared with Gram-positive bacteria (30.9%).

The majority of the BSI identified in this study (78.7%) were reported from tertiary NICU's. These NICUs reported very high rates of MRSA BSI (53.6%). The WHO recommends ampicillin plus an aminoglycoside (gentamicin or amikacin) as empirical treatment for community-acquired neonatal sepsis [13]. Very high levels of resistance of more than 90% to ampicillin was noted among the majority of the Gram-negative isolates, and the median resistance to amikacin ranged from 22.4% to 50%. Cephalosporins contribute to over 50% of prescribed antibiotics in pediatrics in India [14, 15]. Cephalosporins are recommended as first-line antibiotics in various community-acquired infections such as enteric fever, meningitis, and severe pneumonia. The high rates of resistance to cephalosporins in Gram-negative BSI isolates of both the neonatal and pediatric population is concerning (*K pneumoniae*/cefotaxime 62.6% in neonates and 70% in children; *E coli*/cefotaxime 47.5% in neonates and 50% in children). In addition, this study noted an emerging resistance to carbapenems.

Comparison to Other Studies

Despite concern about the high resistance reported from India, it is surprising to note the lack of published data from India. In a study from a mixed population of adults and children across 15 centers in India, the prevalence of MRSA was 42% in 2008 and

Table 4. Age-Based Pathogen Resistance in Common Drug Combinations

Pathogen-Antibiotic Combination	Neonate	Pediatric	$P^{\dagger}$
Staphylococcus aureus-cloxacillin	53.6% (39.8%–66.2%) [n = 22]	33.3% (29.3%–64.3%) [n = 11]	.08
S aureus-clindamycin	33.0% (20.0%–45.7%) [n = 11]	27.7% (0.0%–30.0%) [n = 3]	ns
S aureus-vancomycin	0.0% (0.0%–0.0%) [n = 30]	0.0% (0.0%–0.0%) [n = 7]	ns
S aureus-linezolid	0.0% (0.0%–12.5%) [n = 14]	0.0% (0.0%–13.2%) [n = 5]	ns
Klebsiella pneumoniae-ampicillin	95.9% (76.2%–100.0%) [n = 42]	93.9% (44.6%–100.0%) [n = 5]	ns
Klebsiella-gentamicin	75.0% (54.8%–86.2%) [n = 56]	83.6% (31.3%–98.5%) [n = 8]	ns
K pneumoniae-cefotaxime	62.6% (42.8%–80.2%) [n = 46]	70.0% (14.3%–89.0%) [n = 7]	ns
K pneumoniae-piperacillin-tazobactam	42.0% (5.1%–62.1%) [n = 20]	25.0% (0.0%–50.0%) [n = 2]	ns
K pneumoniae-imipenem	0.0% (0.0%–8.0%) [n = 27]	0.0% (0.0%–0.0%) [n = 5]	ns
Escherichia coli-ampicillin	92.9% (66.7%–100.0%) [n = 27]	83.3% (62.0%–100.0%) [n = 5]	ns
E coli-gentamicin	55.6% (33.3%–83.3%) [n = 38]	50.0% (0.0%–79.4%) [n = 5]	ns
E coli-amikacin	22.3% (2.3%–40.0%) [n = 38]	38.8% (0.0%–50.0%) [n = 5]	ns
E coli-cefotaxime	47.5% (40.0%–66.3%) [n = 32]	50.0% (45.0%–74.3%) [n = 5]	ns
Pseudomonas-amikacin	39.4% (23.5%–50.0%) [n = 32]	40.0% (25.0%–66.3%) [n = 7]	ns
Pseudomonas-ceftazidime	50.0% (33.3%–73.3%) [n = 19]	67.0% (33.3%–75.0%) [n = 7]	ns
Pseudomonas aeruginosa-ciprofloxacin	43.0% (30.0%–60.0%) [n = 31]	63.0% (40.0%–80.0%) [n = 7]	ns
Enterobacter spp-ampicillin	100.0% (97.4%–100.0%) [n = 17]	97.1% (94.2%–0.0%) [n = 2]	ns
Enterobacter spp-gentamicin	88.0% (61.7%–97.4%) [n = 21]	76.5% (67.6%–83.0%) [n = 4]	ns
Citrobacter spp-ampicillin	95.3% (62.5%–100.0%) [n = 6]	99.0% (87.0%–100.0%) [n = 4]	ns
Citrobacter spp-gentamicin	52.8% (39.8%–80.3%) [n = 12]	0.0% (0.0%–0.0%) [n = 3]	ns
Acinetobacter baumannii-gentamicin	63.6% (45.0%–78.9%) [n = 33]	77.1% (18.8%–94.8%) [n = 4]	ns

Abbreviations: IQR, interquartile range; n, number of samples; ns, not significant.
*Data are presented in the following form: median (IQR, Q1–Q3) [number of samples].
†Significance levels using Mann-Whitney *U* test.

40% in 2009. However, 60% of the isolates were from skin and soft tissue infections, whereas the present study reported only on blood culture isolates. No isolate was found to be resistant to vancomycin and linezolid similar to the present study [4].

A high incidence of MRSA BSI in neonates was also reported from a large prospective multisite cohort study by the Delhi Neonatal Infection Study (DeNIS) collaboration (38%) [16]. Although the rate of Gram-negative sepsis and the most common Gram-negative pathogens isolated in this study were similar to ours, the proportion of *Acinetobacter* spp identified (22%) was much higher than ours (5.9%). On comparing our data with a systematic review of Gram-negative AMR in sepsis in resource-limited countries, the figures from Asian studies show a similar resistance pattern for Gram-negative isolates except for a lower resistance to cotrimoxazole and chloramphenicol [11].

Since the 1990s, *S typhi* had acquired resistance to the former first-line drugs recommended by WHO (ampicillin, chloramphenicol, and fluoroquinolones) [17]. In the present study, one third of invasive *Salmonella* isolates (35%) in children had resistance to nalidixic acid similar to the resistance of 37.3% found in the systematic review of Asian studies [10]. Ceftriaxone and azithromycin are currently recommended as first-line and second-line therapy for multidrug-resistant typhoid fever (MDRTF). However, the resistance rates reported here were significant with ceftriaxone (6.3%) and azithromycin (16%). A recent review on MDRTF in India had similarly noted isolated reports of ceftriaxone resistance [18].

Study Limitations

Selection Bias

This study has several biases and limitations. Over 80% of studies were reported from tertiary Intensive Care Units where children have prolonged length of stay and underlying medical conditions. Most of the studies in the data were laboratory based, with very limited clinical information, and it was not possible to determine whether the infections were community or hospital acquired. Despite the exclusion of any study reporting an outbreak, it is probable that some studies had unrecognized outbreaks.

Surveillance Bias

The data were largely contributed by tertiary medical centers. It is noted from the Centers for Disease Control and Prevention's surveillance on AMR [19, 20] that expansion of surveillance to include smaller community hospitals (<200 beds) resulted in reduction in the pooled mean percentage resistance for certain resistance phenotypes such as MRSA.

Reporting Bias

The heterogeneity in data showed the lack of any uniform protocol being followed for reporting key drug-bug combination data in a standardized manner. There were no formal national guidelines on reporting AMR until February 2015 when the Indian Council of Medical Research announced the Standard Operating Procedure [21].

Next Steps

Although there are many limitations and biases, this study clearly highlights the concerning level of AMR in serious infections within the tertiary neonatal and pediatric setting in India. It is important to differentiate between hospital-acquired and community-acquired infections to develop appropriate empirical therapy choices. Guidelines on regional empirical treatment cannot be made on the basis of the present study because it is not representative of the resistance in the community [22]. Improved multicenter, prospective studies using a standardized protocol, such as the DeNIS study, are required, with data on underlying disease, treatment, and clinical outcomes, which are essential to give a more accurate assessment of the true burden of disease, especially in relation to the clinical outcome.

The factors contributing to AMR in India are complex and diverse and range from unregulated use of antibiotics in the community and hospital settings, poor infection control policies, and the unavailability of culture facilities or point of care tests. The stewardship programs recommended by the developed countries require time, personnel, and resources, which are currently completely lacking in the Indian healthcare system. It is very important to develop a simple, easy-to-implement antimicrobial stewardship program adapted to resource-poor settings.

CONCLUSIONS

In 2016, the Government of India launched the National Treatment Guidelines for Antimicrobial Use in Infectious Diseases [23]. Although this is a major step to ensure a uniform rational practice in the country, there is a need to formulate a similar guideline for neonates and children. In addition, participation of pediatricians should be encouraged in active surveillance for antibiotic resistance by bodies such as ICMR, Indian Academy of Pediatrics, and international networks. More importantly, the awareness about the magnitude of antibiotic resistance and the essence of rational antibiotic use needs to be highlighted more urgently among practicing physicians and families. Resistance rates to current antibiotics are now so high that there is an urgent need to consider how to reintroduce older antibiotics back into routine clinical practice and determine how the very few new antibiotics under development can be introduced into high-risk clinical care in a rational and affordable manner.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online.

Notes

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