Pediatric Bloodstream Infections in Cambodia, 2007 to 2011

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Background: Pediatric bacterial bloodstream infections (BSIs) are a major cause of morbidity and mortality worldwide. Epidemiological data from resource-limited settings in southeast Asia, such as Cambodia, are sparse but have important implications for treatment and public health strategies.

Methods: We retrospectively investigated BSI in children at a pediatric hospital and its satellite clinic in Siem Reap, Cambodia, from January 1, 2007, to July 31, 2011. The range of bacterial pathogens and their antimicrobial susceptibility patterns were analyzed in conjunction with demographic, clinical and outcome data.

Results: Of 7682 blood cultures with results (99.9% of cultures taken), 606 (7.9%) episodes of BSI were identified in 588 children. The incidence of BSI increased from 14 to 50/1000 admissions (P < 0.001); this was associated with an increased sampling rate. Most BSI were community acquired (89.1%). Common pathogens included Salmonella Typhi (22.8% of all isolates), Staphylococcus aureus (12.2%), Streptococcus pneumoniae (10.0%), Klebsiella pneumoniae (6.4%) and Escherichia coli (6.3%). 21.5% of BSI were caused by a diverse group of uncommon organisms, the majority of which were environmental Gram-negative species. No Listeria monocytogenses or Group B streptococcal BSI were identified. Antimicrobial resistance, particularly among the Enterobacteriaceae, was common. Overall mortality was substantial (19.0%), higher in neonates (36.9%) and independently associated with meningitis/meningoencephalitis and K pneumoniae infection.

Conclusions: BSI is a common problem in Cambodian children attending hospital and associated with significant mortality. Further studies are needed to clarify the epidemiology of neonatal sepsis, the contribution of atypical organisms and the epidemiology of pneumococcal disease before the introduction of vaccine.

Key Words: bacteremia, epidemiology, Cambodia

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Invasive bacterial infections, including bloodstream infections (BSIs), are a major global cause of pediatric morbidity and mortality, particularly in children <1 year of age. The epidemiology of pediatric BSI is influenced by numerous factors, including age, geographical location, nutritional status and vaccine coverage. Outcomes reflect the capacity of the host to combat infection, pathogen virulence and access to medical treatment, including effective antimicrobials.

Prospective studies of BSI in patients in South and southeast Asia in the last 10 years have been summarized in a recent systematic review. However, there have been relatively few studies investigating pediatric BSI, and these have frequently focused on specific age groups, pathogens or clinical syndromes. In particular, comprehensive, recent data are lacking from Cambodia, which has some of the poorest regional healthcare indicators, widespread malnutrition and limited vaccine coverage against encapsulated bacterial pathogens such as Haemophilus influenzae. Diagnostic microbiology facilities are scarce, and antimicrobial resistance thought to be a major problem. We analyzed the epidemiology, clinical features and outcome of BSI in Cambodian children presenting to a Cambodian pediatric hospital during a 4-and-a-half-year period from 2007 to 2011.

MATERIALS AND METHODS

Study Setting

This was a retrospective study of children with positive blood cultures admitted to Angkor Hospital for Children (AHC) in Siem Reap, northwestern Cambodia, and its satellite clinic (AHC-SC) located 30 km away, between January 1, 2007, and July 31, 2011. AHC is a 50-bedded, charitably-funded pediatric hospital, providing free intensive, surgical and general medical care to children <16 years of age from Siem Reap and surrounding provinces. It has approximately 125,000 attendances and 4000 admissions/year. The ward and outpatient clinic at AHC-SC, which was established in February 2010, has 20 inpatient beds, approximately 12,500 attendances and 1200 admissions/year. Patients requiring intensive care are transferred to AHC. The 2 hospitals manage children from both urban and rural settings. A microbiology laboratory has been undertaking routine work on samples from AHC since late 2006 and from AHC-SC since February 2010.

During the study period, there was no comprehensive, written antimicrobial policy, but prescribing guidelines existed as part of syndrome-specific treatment protocols. Antimicrobial prescriptions were modified according to the microbiology result where this was thought to be clinically appropriate. AHC followed the National Immunization Program, which recommended the following vaccinations from 2007 to 2011: Bacille Calmette–Guérin and hepatitis B virus vaccines at birth; diphtheria–polio–tetanus, oral polio and booster hepatitis B virus vaccines at 6 weeks, 10 weeks and 14 weeks; and measles vaccine at 9 months. Vaccinations against pneumococcal/meningococcal disease and Salmonella Typhi were however not widely available; H. influenzae B (Hib) vaccine was introduced nationally in early 2010. In a previous study during the same time period, approximately 75% of patients reviewed had received age-appropriate vaccinations.
Data Collection

Medical and laboratory records were retrieved, where possible, and information in the electronic hospital database examined, for all children who had a relevant positive blood culture during the study period. Standardized collection of epidemiological data included: age, demographic and admission details, prehospital treatment, clinical features, past medical history/comorbidities, nutritional status, laboratory investigations (hematology, biochemistry and microbiology), antimicrobial treatment, complications and final outcome. Weight-for-age Z scores were calculated for children <5 years.12

BSI episodes were defined as a clinical presentation consistent with sepsis (as determined by the physician requesting the blood culture) in conjunction with a significant positive blood culture result. Coagulase-negative staphylococci, Micrococcus spp. and some Gram-positive bacilli (Corynebacterium spp., Bacillus spp. and Propionibacterium spp.) were regarded as contaminants unless they were isolated from 2 or more separate blood cultures within a 48-hour period,13 or as part of a polymicrobial BSI with a significant organism. All significant (ie, noncontaminant) organisms cultured were stratified on the basis of likelihood that they were causative into 2 groups: “clear” and “possible pathogens.” Persistent BSI was defined as ≥2 positive blood cultures obtained on different days during the same BSI episode, despite 24 hours of appropriate antimicrobial cover.14 Repeat BSI was defined as a sequential BSI in an individual following complete clinical recovery. Polymicrobial BSI was defined as an episode in which 2 organisms were cultured concomitantly from the same blood culture, or in blood cultures taken within 24 hours of each other. Community-acquired BSI (CA-BSI) and healthcare-associated BSI (HA-BSI) were defined as positive blood cultures taken within and after 48 hours of admission, respectively. The medical case notes were used to refine this distinction where patients had been admitted with symptoms consistent with a continuous septic episode but blood cultures had been taken between 48 and 96 hours after admission; these cases were included as CA-BSI. For patients transferred from other healthcare facilities, details on the preceding duration of admission, where known, were also incorporated into this calculation.

Clinical syndromes and appropriateness of empirical therapy were defined on the basis of a consensus by the authors and, for the latter, included results of susceptibility testing (details available from the corresponding author on request).

Laboratory Methods

Vented blood culture bottles were incubated in air at 37°C for 7 days, with daily inspection and subculture to chocolate and blood agar plates if the culture medium was turbid. Routine subculture was undertaken at 24 hours, 48 hours and 7 days. Organisms were identified using Gram-staining/microscopy, in-house biochemical testing and commercial biochemical analytical profile index kits (bioMérieux, France). Antimicrobial susceptibility testing was undertaken using the disk diffusion method and/or Etest (AB Biodisk, Sweden) in accordance with Clinical and Laboratory Standards Institute guidelines.15

Data Analysis

Data were analyzed in Stata 11.1 (StataCorp, TX). Fisher’s Exact and Kruskal–Wallis tests were used for between-group comparisons of categorical and continuous variables, respectively. Logistic regression was used to determine associations for binary outcomes; the χ²-squared test for trend was used to determine trends over time for proportions. A P value of <0.05 was deemed significant.

Ethical Approval

Ethical approval for the study was granted by the AHC Institutional Review Board and the Oxford Tropical Research Ethics Committee, United Kingdom.

RESULTS

Baseline Characteristics

7689 blood cultures were taken during the study period. Of the 7682 results available (missing results for 7 [0.09%] cases), 464 (6.0%) isolates were designated contaminants (291 coagulase-negative staphylococci, 117 nonpathogenic Gram-positive bacilli, 8 Micrococcus spp., 8 mixed contaminants and 40 recorded only as “contaminants”) and 606 (7.9%) as representative of BSI. The 606 episodes of BSI occurred in 588 children, of which 476 episodes (78.5%) were characterized as BSI with clear pathogens and 130 (21.5%) with possible pathogens. Eight (1.4%) children had repeat BSI, 4 (0.7%) persistent BSI and 14 (2.4%) a polymicrobial infection. The sampling rate increased during the study period from 17% to 66% of admissions (P < 0.001), and this was reflected in the incidence of noncontaminant positive blood cultures, which increased from 14 to 50 positives/1000 admissions and was significantly associated with the increased sampling rate (P = 0.005). The proportion of contaminant blood cultures among positives remained stable over the study period (mean 43%; P = 0.37). The proportion of BSI attributable to possible pathogens increased over the study period from 9.0% to 30.3% (P < 0.001).

Medical case records and/or hospital electronic database information was available for all children, although details were missing for some cases. 54.3% of patients were male, but only 16.8% came from the urban center surrounding the hospital. The median total admission duration for patients surviving to discharge was 7 days (interquartile range: 4–13 days); for the 200 of the 535 (37.4%) patients who were admitted to intensive care unit (ICU), the median ICU admission duration was 2 days.16 One hundred ninety three of the 535 (36.1%) patients had a documented comorbidity, including 143 of the 317 (45.1%) of under 5s with moderate/severe malnutrition, and in all age groups, those with congenital heart disease (22 patients; 4.1%), HIV (19; 3.6%) or nephrotic syndrome (9; 1.7%). Malaria films were undertaken in 212 (35.0%) BSI episodes, of which 4 (1.9%) were positive (2 Plasmodium vivax and 2 Plasmodium falciparum).

Neonates were significantly more likely than non-neonates to: require admission to ICU (37/58 cases; 64%, P < 0.001); receive inadequate empirical antibiotic therapy in the first 24 hours after culture (16/29; 55%, P = 0.02); require mechanical ventilation (21/58; 36.2%, P < 0.001) or inotropic support (15/58; 26%, P = 0.002); and die (24/62; 38.7%, P < 0.001). Repeat, persistent and polymicrobial BSI are discussed separately.

Organisms Isolated

Monomicrobial BSI

Of 582 first episodes of monomicrobial BSI, 503 (90.5%) individuals had CA-BSI and 53 (9.5%) HA-BSI (details unavailable for 26 cases). The proportion of HA-BSI increased from 2.5% to 12.7% during the study period (P = 0.03). A summary of cultured organisms are displayed in Table 1, stratified by age group, Gram-stain and pathogen status. Among BSI caused by clear pathogens, Salmonella enterica serovar Typhi (137/459 cases; 29.8%), Staphylococcus aureus (73/459 cases; 15.9%), Streptococcus pneumoniae (59/459; 12.9%), Klebsiella pneumoniae (37/459; 8.1%), Escherichia coli (35/459; 7.6%) and H. influenzae (28/459; 6.1%) were the commonest isolates. A diverse range of organisms was
TABLE 1. Frequency of Organisms Isolated From All First Episodes of Monomicrobial BSI (n = 582) by Age Group

<table>
<thead>
<tr>
<th>Neonates*</th>
<th>Infants*</th>
<th>1–5 yr</th>
<th>&gt;5 yr</th>
<th>Total</th>
<th>P‡</th>
<th>HA-BSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 65)</td>
<td>(n = 139)</td>
<td>(n = 154)</td>
<td>(n = 207)</td>
<td>(n = 582)</td>
<td></td>
<td>(n = 53)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram positive, n (%)§</th>
<th>49 (75.4)</th>
<th>105 (75.5)</th>
<th>110 (71.4)</th>
<th>150 (72.5)</th>
<th>425 (73.0)</th>
<th>0.85</th>
<th>44 (83.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear pathogens, n (%)</td>
<td>29 (59.2)</td>
<td>70 (66.7)</td>
<td>76 (69.1)</td>
<td>132 (88.0)</td>
<td>313 (73.8)</td>
<td>&lt;0.001</td>
<td>30 (68.2)</td>
</tr>
</tbody>
</table>

Other Enterobacteriaceae, n (%)§ | 26 (40) | 41 (29.5) | 51 (33.1) | 121 (58.5) | 242 (41.2) | <0.001 | 29 (54.7) |

Salmonella enterica, total | 2 (3.1) | 5 (3.6) | 36 (23.4) | 108 (52.2) | 154 (26.5) | <0.001 | 0 |

S. enterica Typhí/Paratyphi | 1 (1.5) | 1 (0.7) | 34 (22.1) | 101 (48.8) | 140 (24.1) | <0.001 | 0 |

Nontypoidal salmonella | 1 (1.5) | 4 (2.9) | 2 (1.3) | 7 (3.4) | 14 (2.4) | 0.68 | 0 |

Klebsiella spp. | 14 (21.5) | 11 (7.9) | 7 (4.5) | 6 (2.9) | 38 (6.5) | <0.001 | 22 (41.5) |

Escherichia coli | 3 (4.6) | 19 (13.7) | 7 (4.5) | 5 (2.4) | 35 (6.0) | <0.001 | 3 (5.7) |

Enterobacter spp. | 4 (6.2) | 3 (2.2) | 1 (0.6) | 1 (0.5) | 9 (1.5) | 0.02 | 4 (7.6) |

Other Enterobacteriaceae | 3 (4.6) | 2 (1.4) | 0 | 1 (0.5) | 6 (1.1) | 0.02 | 0 |

Non-Enterobacteriaceae, n (%)§ | 3 (4.6) | 30 (21.6) | 25 (16.2) | 11 (5.3) | 71 (12.2) | <0.001 | 1 (1.9) |

Acinetobacter spp. | 0 | 21 (15.1) | 9 (5.8) | 1 (0.5) | 31 (5.3) | <0.001 | 0 |

Burkholderia pseudomallei | 1 (1.5) | 1 (0.7) | 9 (6.0) | 7 (3.4) | 19 (3.3) | 0.08 | 0 |

Pseudomonas aeruginosa | 1 (1.5) | 4 (2.9) | 5 (3.3) | 2 (1.0) | 12 (2.1) | 0.37 | 1 (1.9) |

Neisseria meningitidis | 0 | 4 (2.9) | 2 (1.3) | 1 (0.5) | 7 (1.2) | 0.27 | 0 |

Other non-Enterobacteriaceae | 1 (1.5) | 0 | 1 (0.6) | 0 | 2 (0.3) | 0.19 | 0 |

Possible pathogens, n (%)†† | 20 (40.8) | 35 (25.2) | 30 (20.0) | 18 (12.0) | 112 (26.3) | <0.001 | 14 (31.8) |

Gramp positive, n (%)§ | 16 (24.6) | 35 (25.2) | 43 (27.9) | 57 (27.5) | 157 (27.0) | 0.93 | 19 (37.3) |

Clear pathogens, n (%)* | 15 (93.8) | 31 (88.6) | 39 (90.7) | 56 (98.3) | 146 (93.0) | 0.25 | 8 (88.9) |

Staphylococcus aureus | 15 (93.9) | 31 (96.9) | 12 (7.8) | 36 (17.4) | 73 (12.5) | 0.03 | 7 (13.5) |

Streptococcus pneumoniae | 1 (1.5) | 18 (11.5) | 22 (14.3) | 18 (8.7) | 59 (10.1) | 0.02 | 1 (1.9) |

Streptococcus pyogenes | 3 (4.6) | 2 (1.4) | 3 (2.5) | 2 (1.0) | 10 (1.7) | 0.28 | 0 |

Other pathogenic streptococci†† | 2 (3.1) | 1 (0.7) | 0 | 4 (0.6) | 0 | 0.05 | 0 |

Possible pathogens, n (%)‡‡‡ | 1 (6.2) | 4 (11.4) | 4 (9.3) | 1 (1.7) | 11 (7.0) | 0.18 | 1 (11.1) |

Organisms identified in healthcare-associated BSI (HA-BSI) are also listed separately in the right-hand column.

*Neonates defined as children <28 days, infants as children >28 days and <1 year of age.

†Details of age not available for 17 cases including BSI with S. Typhi (3), S. aureus (3), one of which methicillin-resistant S. aureus (S). S. pneumoniae (2), E. coli, B. pseudomallei, Rhizobium radiobacter, Ralstonia pickettii, Moraxella catarrhalis, Acinetobacter baumannii–calcoaceticus, Acinetobacter spp., nontyphoidal salmonella and an unspeciated Gram-negative bacillus (1 each).

‡‡Includes 8 cases of S. Typhi.

§Denotes as a percentage of Gram-negative BSI.

¶Denotes as a percentage of Gram-positive BSI.

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Repeat, Persistent and Polymicrobial BSI

For the cases of repeat BSI, 5 children, of whom 2 died, had multiple episodes of HA-BSI during single hospital admissions, and 3 children had repeat episodes of CA-BSI. In the latter group, 1 HIV-positive child had 2 nontypoidal salmonella BSI within 3 months apart and a subsequent pneumococcal BSI; 1 child with nephrotic syndrome experienced 2 pneumococcal BSI within 11 months apart; and 1 child had 2 S. Typhi BSI 1 month apart. The 4 cases of persistent BSI involved 2 infections with clear pathogens (Burkholderia pseudomallei and Enterobacter cloacae) and 2 with possible pathogens (Burkholderia cepacia and Ralstonia pickettii). Polymicrobial BSI occurred in 14 children, including 10 mixed Gram-negative infections (8 with at least 1 clear pathogen) and 4 mixed Gram-positive/Gram-negative infections (2 with at least 1 clear pathogen). Eleven (78.6%) polymicrobial BSI were in children <1 year of age, but mortality at 23.1% was not statistically different from monomicrobial BSI (P = 0.72).

Antimicrobial Susceptibility Data

The multidrug resistant phenotype predominated among S. Typhi strains (108/130 tested; 83.1%) and 96 of 99 (97.0%) multidrug-resistant S. Typhi demonstrated intermediate susceptibility to ciprofloxacin. 73.2% (52/71) of E. coli/K. pneumoniae strains had a third-generation cephalosporin (3GC)-resistant phenotype. Resistance to other antimicrobial agents was common in these organisms: 68%, 59.5%, 58.3% of K. pneumoniae and 33.3%, 30.8%, 20.7% of E. coli tested demonstrated resistance to a 3GC + gentamicin, a 3GC + ciprofloxacin or a 3GC + co-amoxiclav + gentamicin + ciprofloxacin, respectively. Imipenem resistance was seen in 3 of the 94 (3.2%) isolates tested, all of which were A. baumannii–calcoaceticus, 2 of which were community acquired. 3GC resistance was present in 90.9% of HA-BSI versus 69.2% of CA-BSI K. pneumoniae strains (P = 0.08), and methicillin-resistance in 42.9% of HA-BSI versus 7.9% of CA-BSI S. aureus strains (P = 0.03). Methicillin-resistant S. aureus isolates were more commonly ciprofloxacin and gentamicin resistant than methicillin-susceptible strains (62.5% versus 4.5% and 57.1% versus 4.6%, respectively; P < 0.001, P = 0.001).

Risk Factor Analyses for Monomicrobial BSI With Possible Pathogens, Healthcare-associated BSI and Mortality

First episodes of monomicrobial BSI with possible pathogens were shown by univariable analysis to be significantly associated with age <5 years, a respiratory syndrome, previous...
hospitalization, lower temperature and a longer time to culture positivity compared with clear pathogens. Associations with hematological parameters, duration of symptoms, prior administration of intravenous fluids/antibiotics, other clinical syndromes and setting were nonsignificant. Age <5 years (adjusted odds ratio [AOR]: 2.15; 95% confidence interval [CI]: 1.31–3.52, \( P = 0.002 \)) had a lower culture positivity (AOR: 1.27 per day; 95% CI: 1.10–1.47, \( P = 0.001 \)) and previous hospitalization (AOR: 1.12; 95% CI: 1.08–1.15, \( P < 0.001 \)) and ICU admission (AOR: 2.36; 95% CI: 1.06–5.26, \( P = 0.03 \)) remained independently associated on multivariable analysis.

For HA-BSI, age less than 5 years, total length of stay, presence of malnutrition and ICU admission were identified as risk factors compared with CA-BSI on univariable analysis. Age <5 years (AOR: 7.06; 95% CI: 2.87–17.3, \( P < 0.001 \)), total length of hospital admission (AOR: 1.12; 95% CI: 1.08–1.15, \( P < 0.001 \)) and ICU admission (AOR: 2.36; 95% CI: 1.06–5.26, \( P = 0.03 \)) were independently associated on multivariable analysis.

Overall, 104 (19.0%) children with a first episode of monomicrobial BSI died (includes all patients who died during their admission or patients discharged home to die; mortality data available in 548 cases). Crude mortality was 19.0% for clear pathogens and 18.8% for possible pathogens \((P = 1.0)\). \( K.\ pneumoniae \) infection, duration of admission and meningitis/meningoencephalitis were independently associated with 14-day mortality in a multivariable model \((AOR: 28; 95\% \ CI: 1.85–451.73, P = 0.02\); AOR: 0.75, 95% CI: 0.65–0.87, \( P < 0.001 \); AOR: 4.60, 95% CI: 1.29–16.40, \( P = 0.02 \), respectively; the model included the 5 commonest pathogens, except \( S.\ Typhi \), for which the mortality is low and the pathogenesis different).

**Clinical Syndromes**

For patients with a first episode of monomicrobial infection \( (\text{details unavailable for 47 cases}), 247 (46.2\%) \) children had evidence of a clear single clinical focus for their BSI, incorporating respiratory \((n = 130)\), gastrointestinal \((69)\), neurological \((26)\), skin and soft tissue \((18)\), bone/joint \((2)\) and genitourinary \((2)\) sources. One hundred ninety-two \((35.9\%)\) had mixed clinical foci, and 96 \((17.9\%)\) children had no obvious focus.

**Respiratory**

In 69 of the 132 \((52.3\%)\) of children with severe/very severe pneumonia, the concomitant BSI was caused by 5 pathogens, namely \( S.\ aureus \), \( S.\ pneumoniae \), \( E.\ coli \), \( K.\ pneumoniae \) and \( B.\ pseudomallei \). For mild pneumonia, \( S.\ pneumoniae \), \( S.\ typhi \), \( S.\ aureus \) and \( H.\ influenzae \) accounted for 54.3% \((n = 89/164)\) of presentations. \( A.\ baumannii–calcoaceticus \) was also commonly isolated in respiratory cases \((8\%\) of mild, 9 of severe/very severe cases; 9 CA-BSI; all cases <6 years of age).

**Gastrointestinal**

Isolated gastrointestinal symptoms were most commonly associated with \( S.\ Typhi \) infection \((36/69; 52.2\%)\); however, BSI with 45 of the 60 types of organism cultured was found in conjunction with gastrointestinal symptoms, making them relatively nonspecific.

**Meningitis/Meningoencephalitis**

One hundred seven children had evidence of neurological involvement, with seizures, neck stiffness or a bulging fontanelle occurring in 69, 25 and 25 children, respectively. More than 50% \((n = 59)\) of these cases occurred in children <1 year of age. Organisms identified from blood in >5% of cases were \( S.\ pneumoniae \), \( E.\ coli \), \( H.\ influenzae \), \( S.\ aureus \) and \( Neisseria meningitidis \). Of 72 children who had a documented lumbar puncture, cerebrospinal fluid culture results were available in 62 \((S.\ pneumoniae \ [n = 5]\), \( H.\ influenzae \ [4]\), \( N.\ meningitidis \ [2]\), \( E.\ coli \ [1]\) and \( S.\ aureus \ [1]\). For individuals with a positive cerebrospinal fluid culture result, blood culture results were concordant except for 2 cases \((1\) each with \( E.\ coli/S.\ pneumoniae \) [blood/cerebrospinal fluid], \( Stenotrophomonas maltophilia/S.\ aureus \)). Overall mortality was 31%, and 3 survivors suffered neurological sequelae \((S.\ pneumoniae \) and \( H.\ influenzae \) case[s]).

**Skin/Soft Tissue and Bone/Joint Infections**

\( S.\ aureus \) \((n = 33)\) and \( Streptococcus pyogenes \) \((5)\) accounted for 61.2% of the 62 skin/soft tissue infections and were mostly community acquired \((36/38)\) and seen in children >1 year old \((32/38)\). Twelve \( S.\ aureus \) cases were associated with concomitant osteomyelitis. Three cases of septic arthritis \((2\) hip and \(1\) knee) were identified \((1\) each of \( S.\ aureus \), \( H.\ influenzae \) and \( S.\ pyogenes \)).

**No Obvious Focus**

\( S.\ Typhi \) was the dominant BSI in this group, responsible for 64 of the 92 \((66.7\%)\) of episodes.

**DISCUSSION**

Bloodstream infection is a major clinical problem in Cambodian children attending our institution, with an incidence of up to 50 positive blood cultures/1000 admissions. Our increased sampling rate was attributable to a prospective study investigating febrile illness \((2009\) to \(2010)\), and it may be that the incidence is even higher as potentially not all children with suspected sepsis were cultured. Proportions of contaminants and noncontaminants isolated are similar to elsewhere in Asia.\(^4\) Although BSI was dominated by community-acquired infections, the proportion of HA-BSI quadrupled over the study period.

Two recent systematic reviews of community-acquired pediatric BSI in Africa and Asia have highlighted important epidemiological differences. In African children, in the context of a much greater burden of HIV, \( S.\ pneumoniae \) (23.3%), nontyphoidal salmonella (18.7%) and \( S.\ aureus \) (12.0%) were most common. Malaria coinfection was also frequent (8–69%), unlike in our cohort.\(^1\) In Asian children, \( S.\ Typhi \) was most common (25.1%), followed by \( S.\ pneumoniae \) (12.8%) and \( H.\ influenzae \) (8.4%).\(^4\) In our study, \( S.\ Typhi \) was the predominant isolate (22.8% of all isolates), but was then followed in almost equal proportions by \( S.\ aureus \) (12.2%) and \( S.\ pneumoniae \) (10.0%), with \( H.\ influenzae \) being less common (4.8%). Variation in laboratory methods, the use of prehospital antimicrobials and Hib vaccination may explain some of these differences, but they may also reflect true epidemiological diversity. There are currently no data on the distribution of serotypes among invasive pneumococcal isolates in Cambodia, with implications for vaccination strategies, particularly given the regional variation in serotypes.\(^6\)

Almost half of BSI were caused by Enterobacteriaceae, and compared with other Asian sites, there was a greater role played by \( E.\ coli \) (6.3% versus 1.5%; \( P = 0.03 \)) and \( K.\ pneumoniae \) (6.4% versus 1.1%; \( P < 0.001 \)).\(^4\) Wide-ranging antimicrobial resistance in these organisms is of particular concern. Although an initial association between the use of optimal antimicrobial therapy and survival did not remain in a multivariable model, this was perhaps because the number of subjects by organism type was relatively small. Rapid, horizontal transfer of genes encoding multidrug resistance,\(^17\) in combination with high selection pressures exerted by the largely unregulated use of antibiotics in Cambodia, represent a major threat to clinical management.

A relatively small group of neonates was included in our cohort, but it is interesting that no cases of \( Streptococcus agalactiae \) or \( Listeria monocytogenes \) were seen. Our methods should be
adequate to recover these organisms, and their absence may relate to prehospital antimicrobial administration or death. Of note, AHC does not provide obstetric or intrapartum care. No data on maternal carriage of S. agalactiae/L. monocytogenes are available from Cambodia; it is therefore conceivable that rates of carriage and infection are lower.2,16 A specific study of neonatal sepsis in our region is warranted, particularly given the high rates of mortality in this group. Distinguishing significant from contaminating isolates in blood cultures is difficult when atypical organisms are isolated;19 there is also limited guidance on susceptibility testing and optimal antimicrobial treatment. Environmental Gram-negative glucose nonfermenters can cause BSI in immunocompromised individuals and those with high environmental exposures to soil and water,20–22 and coagulase-negative staphylococci can be neonatal pathogens.23 24 High rates of malnutrition in our population represent a significant burden of relative immunosuppression. To reduce the isolation of contaminants, we have replaced povidone-iodine with alcohol-chlorhexidine25 for skin cleansing prior to sampling, and have encouraged repeat testing if atypical organisms are isolated.

This study is limited by its retrospective observational design, and nonsystematic sampling of hospital attendees may underestimate the true burden of BSI.26 Assessing prehospital treatment was difficult; nevertheless, at least 30% of our study cohort had taken antimicrobials and at least 19% had been given intravenous fluids either at home or in public/private clinics. Substantial community use of antimicrobials may bias culture results in favor of resistant organisms or particular species. Patchy documentation may have limited the power to identify possible associations of relevance, such as the isolation of environmental Gram-negative bacilli and prior use of intravenous fluids.

Despite the limitations, we have determined that BSI represents a major burden of disease among Cambodian children and identified the spectrum of relevant pathogens. We highlight the worrying contribution of antimicrobial-resistant Gram-negative organisms. As a result of this study, an antimicrobial prescribing guideline has been introduced at AHC/AHC-SC, and the association of particular pathogens with specific clinical syndromes has assisted in this process.27 Combining such data from several sites could inform the development of regional and international guidelines and be used to monitor epidemiological trends in response to future public health interventions.

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