Bacterial meningitis in Malawian infants

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Background: Neonatal meningitis is an important cause of morbidity in sub-Saharan Africa and requires urgent empiric treatment with parenteral administered antibiotics. Here we describe the etiology, antimicrobial susceptibility and suitability of the World Health Organization first-line recommended antibiotics (penicillin and gentamicin) for bacterial meningitis in young infants in Malawi.

Methods: We reviewed all cerebrospinal fluid samples received from infants ≤2 months of age with clinically suspected meningitis between January 1, 2002, and December 31, 2008, at the Queen Elizabeth Central Hospital in Blantyre, Malawi.

Results: We identified 259 culture-positive isolates from 259 infants ≤2 months of age. Sixty isolates were from neonates ≤7 days old, in whom the most common pathogens were Group B Streptococcus (27/60; 45.0%), Streptococcus pneumoniae (13/60; 21.7%) and nontyphoidal Salmonella enterica (7/60; 11.7%). One hundred and ninety one isolates were from young infants who were >7 days and ≤2 months of age. In this group, the most common isolates were S. pneumoniae (80/191; 41.9%), Group B Streptococcus (38/191; 19.9%) and nontyphoidal Salmonella enterica (34/191; 17.8%). More isolates were susceptible to ceftriaxone than to the combination of penicillin and gentamicin (218/220; 99.1% vs. 202/220; 91.8%, Fisher’s exact test \( P < 0.006 \)). In particular, Gram-negative isolates were significantly more susceptible to ceftriaxone than to gentamicin (72/74; 97.3% vs. 63/74; 85.1%, Fisher’s exact test \( P = 0.020 \)). Penicillin and gentamicin provided less coverage for Gram-negative than Gram-positive isolates (74/86; 86.0% vs. 155/163; 95.1%, \( \chi^2 = 6.24, P = 0.012 \)).

Conclusions: In view of these results, the World Health Organization recommendations for empiric penicillin and gentamicin for suspected neonatal meningitis should be reevaluated.

Key Words: newborn, infant, meningitis, drug resistance, microbial, Africa

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Original Studies

Bacterial Meningitis in Malawian Infants <2 Months of Age

Etiology and Susceptibility to World Health Organization First-Line Antibiotics

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560 | www.pidj.com

AN estimated 3.6 million neonatal deaths occurred worldwide in 2008, one-third of which were in Africa.1 Of these deaths, 17% were associated with sepsis.1 Although the exact burden of neonatal bacterial meningitis in Africa remains unknown, it represents an important cause of morbidity and mortality. A recent Kenyan study reported that 3–6% of all hospital admissions <59 days old were due to meningitis, with case fatality ratios of 26% in the first week of life and 18% between 7 and 59 days of age.2

Studies into neonatal meningitis in sub-Saharan Africa have reported a wide range of pathogens that vary both between and within countries. Streptococcus pneumoniae, Group B Streptococcus (GBS), Escherichia coli and nontyphoidal Salmonella species appear to predominate in East Africa.3–10 In West Africa, S. pneumoniae, E. coli and Salmonella species remain common, but a greater role is also seen for Staphylococcus aureus.11–13 In Southern Africa, GBS, E. coli and Salmonella species predominate, with a lesser role for S. pneumoniae.14–20

The range of pathogens within sub-Saharan Africa provides a major challenge to global antibiotic guidelines, particularly as treatment is required urgently. The World Health Organization (WHO) has outlined recommendations for empirical antimicrobial treatment for meningitis in neonates and young infants <2 months of age (summarized in Supplemental Digital Content 1, http://links.lww.com/INF/B777).21–28

The WHO Pocket Book of Hospital Care for Children provides the most comprehensive guidance and is intended for use in secondary level health care. It recommends either benzylpenicillin/ampicillin with gentamicin or ceftriaxone/cefotaxime if available as first-line treatment of meningitis in infants <2 months of age.22 Other WHO guidance suggests a third generation cephalosporin if there is no improvement after 48 hours.22 The country-specific appropriateness for these guidelines can only be judged with knowledge of local etiologic organisms and their antimicrobial susceptibility patterns.

Previous etiologic studies of neonatal meningitis have included populations of differing ages. Some have included neonates <30 days,4,10,12,13,15,16,18 young infants <60 days or <90 days3,11 of age and others have described their population simply as neonates.3,4,12 To ensure our results were as relevant as possible to WHO guidance, we elected to include all young infants ≤60 days in an audit of bacterial meningitis in the Queen Elizabeth Central Hospital (QECH) in Blantyre from 2002 to 2008 to determine the etiology and pathogen resistance patterns and therefore evaluate the suitability of WHO recommendations for first-line antibiotic therapy.

Materials and Methods

Setting

QECH in Blantyre, Malawi is a large teaching, referral and district general hospital serving a population of approximately 1 million and admitting around 25,000 children per year. Sick or
premature babies born in hospital are cared for in a separate ward from those born outside the hospital. There is no provision for mechanical ventilation, total parenteral nutrition or central venous lines. During the study, benzyl penicillin (50,000 units or 30 mg/kg 3 or 4 times daily) and gentamicin (6 mg/kg/d) were first-line antibiotic therapy for meningitis in young infants ≤2 months of age in accordance with WHO guidelines. Antibiotic therapy may be changed in light of cerebrospinal fluid sample (CSF) culture and susceptibility results, which typically become available after 48 hours. It should be remembered that QECH is fortunate to benefit from bacterial culture facilities that are not available in many other hospitals in the region.

**Identification of Patients**
All CSF from young infants ≤60 days of age with suspected meningitis received between January 1, 2002, and December 31, 2008, were reviewed. Demographic data were retrieved from laboratory and ward admission books. No infants in the inborn hospital nursery were >60 days of age. Outcome data and HIV status were not available.

**Organism Identification and Speciation**
All diagnostic testing and quality control was performed in the Malawi Liverpool Wellcome Trust Programme laboratories as part of routine clinical surveillance. CSF (1–2 mL) was analyzed by Gram’s stain if the white blood cell count was >10/mm³. All samples were cultured on sheep blood and chocolate agar for ≥60 days of age. Outcome data and HIV status were not available.

**Susceptibility Testing**
Antibiotic susceptibilities of the bacterial isolates were determined on all isolates by disc testing (Oxoid, Hampshire, United Kingdom) and zone size measurement using the British Society for Antimicrobial Chemotherapy sensitivity method for direct cultures.

**TABLE 1. Frequency of CSF Isolates by Age Group N (%).**

<table>
<thead>
<tr>
<th>Isolate</th>
<th>≤7 days</th>
<th>&gt;7 days ≤2 months</th>
<th>Age unknown</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive organisms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>13 (21.7)</td>
<td>80 (41.9)</td>
<td>2 (25)</td>
<td>95 (36.7)</td>
</tr>
<tr>
<td>Group B <em>Streptococcus</em></td>
<td>27 (45.0)</td>
<td>38 (19.9)</td>
<td>3 (37.5)</td>
<td>68 (26.3)</td>
</tr>
<tr>
<td>Group D <em>Streptococcus</em></td>
<td>1 (1.7)</td>
<td>0 (0)</td>
<td>1 (12.5)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>0 (0)</td>
<td>3 (1.6)</td>
<td>0 (0)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Group A <em>Streptococcus</em></td>
<td>0 (0)</td>
<td>3 (1.6)</td>
<td>0 (0)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. enterica</em> serovar Typhimurium*</td>
<td>7 (11.7)</td>
<td>28 (14.7)</td>
<td>1 (12.5)</td>
<td>36 (13.9)</td>
</tr>
<tr>
<td><em>S. enterica</em> serovar Enteritidis*</td>
<td>0 (0)</td>
<td>3 (1.6)</td>
<td>0 (0)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
<td>0 (0)</td>
<td>3 (1.6)</td>
<td>0 (0)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td><em>H. influenzae</em> type b</td>
<td>1 (1.7)</td>
<td>14 (7.3)</td>
<td>0 (0)</td>
<td>15 (5.8)</td>
</tr>
<tr>
<td><em>H. influenzae</em>-untyped</td>
<td>0 (0)</td>
<td>3 (1.6)</td>
<td>0 (0)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>3 (5.0)</td>
<td>5 (2.6)</td>
<td>0 (0)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td><em>E. cloacae</em></td>
<td>3 (5.0)</td>
<td>2 (1.1)</td>
<td>0 (0)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td><em>Enterobacter agglomerans</em></td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>3 (5.0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (12.5)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>1 (1.7)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><em>Neisseria meningitides</em></td>
<td>0 (0)</td>
<td>2 (1.1)</td>
<td>0 (0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td><em>Acinetobacter lwoffi</em></td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><em>Serratia odorfera</em></td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>191</td>
<td>8</td>
<td>259</td>
</tr>
</tbody>
</table>
14–30 days) of age. Eight (3.1%) were admitted as “neonates” to the dedicated neonatal ward but their exact ages were not recorded. Isolates from this last group were included in the overall analysis of pathogens and susceptibility patterns, but excluded from age-specific analyses (Table 1).

Across all age groups, 171/259 (66.0%) of isolates were Gram-positive and 88/259 (34.0%) were Gram-negative. Overall, the commonest pathogens were S. pneumoniae in 95/259 (36.7%), GBS in 68/259 (26.3%), nontyphoidal Salmonella enterica (NTS) in 42/259 (16.2%) and Haemophilus influenzae type b (Hib) in 15/259 (5.8%, Table 1).

In neonates ≤7 days, GBS was the most common organism found (27/60; 45.0%), followed by S. pneumoniae (13/60; 21.7%) and NTS (7/60; 11.7%). For young infants >7 days to ≤30 months of age, the most frequent isolate was S. pneumoniae (80/191; 41.9%), followed by GBS (38/191; 19.9%) and NTS in 34 of 191 (17.8%, Table 1).

Antimicrobial Susceptibility

In vitro isolate susceptibility to 9 antibiotics (penicillin, erythromycin, ampicillin, chloramphenicol, gentamicin, cotrimoxazole, tetracycline, ciprofloxacin and ceftriaxone) is summarized in Table 2 (full data in Supplemental Digital Content 2, http://links.lww.com/INF/B778). Not all isolates were tested against all antibiotics, in particular, 10 isolates were not tested against either penicillin or gentamicin and 33 were not tested against ceftriaxone.

Overall, 229/249 (92.0%) of isolates tested showed in vitro susceptibility to the first-line combination of penicillin and gentamicin (Table 2). Gram-positive isolates were significantly more likely to be susceptible than Gram-negative isolates (155/163; 95.1% vs. 74/86; 86.0%, \( \chi^2 = 6.24, P = 0.012 \)). Of the 226 isolates tested against ceftriaxone, 224 (99.1%) were susceptible (Table 2). A subset of 220 isolates from the 226 was tested against both a first-line antibiotic and ceftriaxone. These isolates were significantly more susceptible to ceftriaxone than to the combination of penicillin and gentamicin (n = 218/220; 99.1% vs. n = 202/220; 91.8%, Fisher’s exact test P = 0.006). Gram-positive isolates were all susceptible in vitro to ceftriaxone (n = 151); however, of the 162 tested against penicillin, 153 (94.4%) were susceptible (Table 2). A subset of 145 Gram-positive isolates were tested against both penicillin and ceftriaxone, with 139 of 145 (95.9%) susceptible to penicillin and all 145 (100%) to ceftriaxone.

92 S. pneumoniae isolates tested against penicillin, 6 (6.5%) had intermediate resistance (detected by disc testing only), whereas all 92 (100%) of the isolates tested against ceftriaxone were susceptible (Table 2).

Gram-negative isolates were also significantly more susceptible to ceftriaxone than to first-line antibiotics. Eighty-six Gram-negative isolates were tested against gentamicin, of which 74 (86.0%) were susceptible, compared with 73 of 75 (97.3%) which were susceptible to ceftriaxone (Table 2). A subset of 74 Gram-negative isolates were tested against both gentamicin and ceftriaxone, and 63 of 74 (85.1%) were susceptible to gentamicin while 72 of 74 (97.3%) were susceptible to ceftriaxone (Fisher’s exact test \( P = 0.020 \)).

All NTS isolates were tested against gentamicin and 37 of 42 (88.1%) were susceptible. Of these isolates, 33 were tested against ceftriaxone and showed universal susceptibility (Table 2). Among those 33 isolates susceptible to ceftriaxone, 5 were resistant to gentamicin.

Only 2 isolates were resistant to ceftriaxone: Klebsiella pneumoniae and Enterobacter cloacae, isolated from 4- and 5-day-old neonates, respectively. These 2 isolates were also resistant to gentamicin, but showed in vitro susceptibility to ciprofloxacin. Both isolates were identified in 2007, towards the end of the study period.

Although numbers were small, no significant trend in annual resistance patterns was found amongst isolates to the combination of penicillin and gentamicin (\( \chi^2 \) for trend, \( P = 0.291 \), Supplemental Digital Content 3, http://links.lww.com/INF/B779).

**DISCUSSION**

**CSF Isolates**

Our findings are similar to those of a previous study of neonatal sepsis ≤30 days of age in the same unit in Blantyre (1996–2001). This earlier study examined neonatal meningitis (n = 202) as a subset of neonatal sepsis (n = 784), but did not analyze CSF isolates further by age group. The authors reported GBS as the most common CSF isolate ≤30 days of age (60/202; 29.7%), followed by S. pneumoniae (47/202; 23.3%) and NTS (33/202; 16.3%) but used a cut off of 30 days (favoring GBS) as opposed to 60 days in our study. Analysis of our data by age group revealed GBS was the commonest pathogen in neonates ≤7 days and S. pneumoniae in those >7 days but ≤2 months of age. Therefore, our results may not represent a true change in isolate frequency, but are more likely due to the inclusion of older infants in our study.
S. pneumoniae was the major CSF pathogen in 36.7% of infants ≤2 months of age in this study, which is consistent with reports from East Africa3,37–39 and West Africa.3,40 S. pneumoniae resistance to penicillin is therefore of particular interest. In a recent review of invasive pneumococcal disease across all age groups (>3 months, n = 4445) penicillin resistance was reported to be stable at ≈10% over a decade.33 In our study, resistance to penicillin was 6.5% (6/92).

S. pneumoniae isolates in our study were universally susceptible to ceftriaxone. No ceftriaxone resistance amongst S. pneumoniae was detected in our study since the antibiotic’s introduction.33 However, a recent study from our setting did report resistance to penicillin is therefore of particular interest. In a recent review of invasive pneumococcal disease across all age groups (>3 months, n = 4445) penicillin resistance was reported to be stable at ≈10% over a decade.33 In our study, resistance to penicillin was 6.5% (6/92).

S. pneumoniae isolates has been reported in this setting since the antibiotic’s introduction.33 However, a recent study from our setting did report resistance to penicillin is therefore of particular interest. In a recent review of invasive pneumococcal disease across all age groups (>3 months, n = 4445) penicillin resistance was reported to be stable at ≈10% over a decade.33 In our study, resistance to penicillin was 6.5% (6/92).

TABLE 3. Frequency of CSF Isolates by Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Gram-positive organisms</th>
<th>Gram-negative organisms</th>
<th>S. pneumoniae</th>
<th>Group B Streptococcus</th>
<th>Nontyphoidal Salmonella</th>
<th>H. influenzae type b</th>
<th>Total isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>22</td>
<td>14</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>2003</td>
<td>31</td>
<td>22</td>
<td>22</td>
<td>11</td>
<td>9</td>
<td>11</td>
<td>66</td>
</tr>
<tr>
<td>2004</td>
<td>24</td>
<td>11</td>
<td>17</td>
<td>17</td>
<td>9</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>2005</td>
<td>35</td>
<td>9</td>
<td>15</td>
<td>15</td>
<td>7</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>2006</td>
<td>20</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>7</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>2007</td>
<td>24</td>
<td>14</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>2008</td>
<td>15</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>7</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>95</td>
<td>95</td>
<td>95</td>
<td>68</td>
<td>42</td>
<td>259</td>
</tr>
</tbody>
</table>

Mean, arithmetic mean; SD, standard deviation.
First-line Antibiotic Susceptibility—Ceftriaxone

Ceftriaxone has been available in the pediatric unit at QECH since 2001, although not for neonatal use. Its use has become more widespread since 2007 and in 2009, it was introduced as the second-line antibiotic for neonatal meningitis. Ceftriaxone has good CSF penetration and is given once daily, reducing pressure on nursing staff. These factors are of particular importance in resource-poor settings.

In vitro susceptibility to ceftriaxone was 99.1% (224/226) and was significantly higher than for penicillin and gentamicin. The difference in susceptibility was particularly marked for Gram-negative isolates. Our data shows only 2 cases of ceftriaxone resistance in neonatal meningitis involving a Klebsiella pneumoniae and an E. cloacae isolate. Emerging resistance to third generation cephalosporins is of particular concern in resource limited settings. For example, only 72% of Gram-negative blood culture isolates showed susceptibility to cefotaxime in Kenyan infants of the same age group. A recent study of Enterobacteriaceae in blood cultures from all age groups in QECH (n = 1191) identified 19 ceftriaxone-resistant isolates, 10 of which showed extended-spectrum β-lactamases (ESBL) phenotypes. These were predominantly isolated from pediatric patients and the authors advised that increased use of ceftriaxone was likely to result in a rapid ESBL expansion. Although ESBL genotyping was not available for our study, the presence of ceftriaxone-resistant Gram-negative organisms in the absence of widely available alternative antibiotics is cause for considerable concern.

Questions remain regarding the safety of ceftriaxone use in neonates, including precipitation with calcium containing compounds, biliary sludging and the displacement of albumin causing kernicterus. In vitro susceptibilities to antibiotics may not translate into good outcomes. A prospective randomized controlled trial to investigate the outcome of neonatal meningitis when treated with penicillin and gentamicin compared with a third generation cephalosporin and the safety of ceftriaxone in neonates is currently underway in Malawi (NCT01247909).

As a single center study, generalization of these results must be made with caution. This study was hospital based and may underrepresent early neonatal meningitis if babies born at home who died before attending the hospital. There was also no reliable way of distinguishing between community-acquired and hospital-acquired infections.

CONCLUSION

Ceftriaxone provides significantly better in vitro coverage than the WHO-recommended combination of penicillin and gentamicin in meningitis in young infants in Blantyre, Malawi where Gram positive isolates predominate. This gap in susceptibility may be even higher in settings where Gram-negative isolates have a larger role. Ceftriaxone's once daily dosing schedule also reduces pressure on nursing staff but resistance is emerging among Gram-negative isolates and the safety profile of ceftriaxone in neonates is yet to be fully confirmed. In view of these results, the WHO recommendations of empirical penicillin and gentamicin for suspected neonatal meningitis should be reevaluated. This is particularly important for those settings where the prevalence of gentamicin resistant Gram-negative meningitis is high.

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REFERENCES


