Increasing Chloramphenicol Resistance in \textit{Streptococcus pneumoniae} Isolates from Papua New Guinean Children with Acute Bacterial Meningitis\textsuperscript{V}

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In Papua New Guinean (PNG) children with acute bacterial meningitis (ABM), all \textit{Haemophilus influenzae} isolates were resistant to chloramphenicol. Although \textit{Streptococcus pneumoniae} isolates had a median chloramphenicol MIC of 3 \(\mu\)g/ml, it was \(\geq 4\) \(\mu\)g/ml in 42.8\%, and the likelihood of an area under the 24-hour concentration-time curve/MIC ratio of \(>100\) h at a MIC of \(\geq 4\) \(\mu\)g/ml was approximately 50\%. All isolates were ceftriaxone sensitive. These data support ceftriaxone rather than conventional chloramphenicol for all PNG children with suspected ABM.

In Papua New Guinea (PNG), \textit{Haemophilus influenzae} type b (Hib) and \textit{Streptococcus pneumoniae} are the major causes of acute bacterial meningitis (ABM) in children (6). Chloramphenicol has been used widely in PNG since the 1980s as empirical therapy for severe bacterial infections, including ABM, but increasing resistance of Hib isolates has prompted progressive changes to national treatment guidelines. The latest version recommends ceftriaxone for all children with suspected ABM (8). Hib vaccine was implemented as part of the PNG vaccine schedule in 2008. Its increasing coverage may see \textit{S. pneumoniae} emerge as the dominant local pathogen in pediatric ABM, especially as pneumococcal vaccination is not currently part of the schedule.

The antibiotic susceptibility of \textit{S. pneumoniae} in PNG is unknown, but if most strains are sensitive, the expected reduction in invasive Hib disease might allow chloramphenicol to be reconsidered as an inexpensive component of the ABM treatment algorithm. To assess this, we characterized the antimicrobial susceptibility of Hib and \textit{S. pneumoniae} isolated from children age 2 months to 10 years who were admitted to Mordor Hospital, the sole referral hospital in Madang Province, between October 2006 and December 2009 with proven ABM isolates. Thirteen of 15 \textit{H. influenzae} isolates were Hib, and the \textit{S. pneumoniae} isolates tested, chloramphenicol and ceftriaxone, were determined using the Kirby-Bauer disc diffusion method (1). The MICs of Hib and \textit{S. pneumoniae} to penicillin antibiotics, chloramphenicol, and tetracycline were determined using Etest strips (AB Biodisk, Solna, Sweden).

We estimated the likelihood of attaining a target chloramphenicol pharmacokinetic/pharmacodynamic (PK/PD) ratio at each \textit{S. pneumoniae} MIC. After an initial intramuscular or intravenous dose of 25 mg/kg of body weight in Melanesian children, the mean \pm standard deviation (SD) area under the concentration-time curve from 0 to 6 h (AUC\textsubscript{0–6}) was 101 \pm 26 or 108 \pm 51 \(\mu\)g \cdot h/ml, respectively, and 134 \pm 63 or 110 \pm 41 \(\mu\)g \cdot h/ml, respectively, after subsequent doses (11). The AUC\textsubscript{0–24} was estimated assuming that children received four doses, one every six hours, of chloramphenicol. We considered an AUC\textsubscript{0–24}/MIC ratio of \(>100\) h to be the target PK/PD parameter. In the absence of definitive data for chloramphenicol from animal and human studies, this cut point was derived from published time-kill curves, a rabbit model of pneumococcal meningitis, and clinical observational data for linezolid (2, 10), an antibiotic with a structure, pharmacodynamic properties, and a toxicity similar to those of chloramphenicol.

Hib and \textit{S. pneumoniae} were isolated from 21 and 22 children, respectively. Difficulties keeping cultures viable until processing in a reference bacteriology laboratory limited susceptibility testing to 17 \textit{S. pneumoniae} and 15 \textit{H. influenzae} isolates. Thirteen of 15 \textit{H. influenzae} isolates were Hib, and the remaining two were serotype A. The antibiotic susceptibilities of Hib and \textit{S. pneumoniae} using disc diffusion and Etest methods are summarized in Table 1. All 14 \textit{H. influenzae} isolates with available antimicrobial susceptibility data were resistant to chloramphenicol. Of the 14 \textit{S. pneumoniae} isolates tested, the chloramphenicol MIC ranged from 0.75 to 24 \(\mu\)g/ml. The median chloramphenicol MIC was 3 \(\mu\)g/ml, and six (42.8\%) had a MIC of \(\geq 4\) \(\mu\)g/ml. All \textit{S. pneumoniae} isolates were fully susceptible to ceftriaxone. The likelihood of attaining an AUC\textsubscript{0–24}/MIC ratio of \(>100\) h for \textit{S. pneumoniae} isolates at different chloramphenicol MICs is shown in Fig. 1. This is close...
TABLE 1. Antibiotic susceptibility testing for Haemophilus influenzae and Streptococcus pneumoniae isolates

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Haemophilus influenzae (n = 15 isolates)</th>
<th>Streptococcus pneumoniae (n = 17 isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of isolates S/I/R by disc diffusion</td>
<td>Median (IQR) Etest MIC (µg/ml)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1/0/14</td>
<td>29 (12–256)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0/0/14</td>
<td>16 (12–32)</td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim</td>
<td>0/0/15</td>
<td>6/7/3</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1/0/14</td>
<td>&gt;32 (≥32–32)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>10/0/0</td>
<td></td>
</tr>
</tbody>
</table>

* Ampicillin disc diffusion and Etest were performed on H. influenzae isolates, while oxacillin and penicillin were used for disc diffusion and Etest, respectively, in S. pneumoniae isolates. S, sensitive; I, intermediate; R, resistant; IQR, interquartile range.

FIG. 1. The likelihood of attaining an AUC/MIC ratio of ≥100 h by Streptococcus pneumoniae MIC. Individual plots by route and timing of chloramphenicol administration are shown.

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REFERENCES


