Prosthetic hip joint infection with a Streptococcus agalactiae isolate not susceptible to penicillin G and ceftriaxone

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Sir,

Streptococcus agalactiae [group B Streptococcus (GBS)] colonize and cause various infections in neonates and adults. GBS are reported to be universally susceptible to penicillin G.1 Four recent studies documented amino acid substitutions in penicillin-binding protein (PBP) in GBS clinical isolates with increased penicillin MICs.2-5 Here we report a case of invasive penicillin G-non-susceptible GBS infection.

In 2002, a 55-year-old woman with a history of treated ovarian carcinoma had a right hip prosthesis for a fractured femoral neck. In 2004, the culture of the articular fluid from the right hip was positive for GBS. The patient was treated intravenously with 12×106 units of penicillin G Na daily for 6 weeks followed by prolonged oral therapy with 300 mg of penicillin V every 24 h. In 2007, the culture of the pus, from a para-articular collection near the right hip, grew GBS, and penicillin V was increased to 600 mg every 8 h. In 2008, the abscess was drained without surgical debridement, the culture of the pus was negative and the patient was treated with 500 mg of cefadroxil every 12 h for 14 days. Two months later, the technetium and gallium scans were negative for infection, the sedimentation rate and protein electrophoresis were normal and the patient had a normal right hip exam.

Identification of the two GBS isolates was confirmed at the provincial reference laboratory LSPQ/INSPQ. The susceptibility of GBS isolated in 2004 (GBS 2004) and 2007 (GBS 2007) was tested at Hôpital Saint-Luc (Montréal) by Etest (oxacillin, ampicillin and meropenem), by the CLSI disc diffusion method with linezolid 30 μg discs and at LSPQ/INSPQ by the CLSI microdilution method with penicillin G, ceftriaxone, erythromycin, clindamycin, levofloxacin, chloramphenicol and vancomycin.1,6 MICs of 11 antimicrobial agents for the two GBS isolates are reported in Table 1. The GBS 2007 was not susceptible to ceftriaxone with increased MICs of three dilutions and to penicillin G, ampicillin and oxacillin with increased MICs of two dilutions. MICs of meropenem, even if still susceptible, increased from 0.03 mg/L for GBS 2004 to 0.25 mg/L for GBS 2007. The two GBS isolates were susceptible to erythromycin, clindamycin, vancomycin, levofloxacin, chloramphenicol and linezolid, but were resistant to tetracycline. β-Lactamase was negative for both GBS isolates with nitrocefin discs (BD DBL Cefinase discs). PFGE showed that the two GBS isolates were identical.

Table 1. MICs (mg/L) of antimicrobial agents for GBS isolated in 2004 and 2007

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>GBS 2004</th>
<th>GBS 2007</th>
<th>CLSI S</th>
<th>CLSI R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>0.06</td>
<td>0.25</td>
<td>≤0.12</td>
<td>NA</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.12</td>
<td>1</td>
<td>≤0.5</td>
<td>NA</td>
</tr>
<tr>
<td>Oxacillin6</td>
<td>1</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.12</td>
<td>0.5</td>
<td>≤0.25</td>
<td>NA</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.03</td>
<td>0.25</td>
<td>≤0.5</td>
<td>NA</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.06</td>
<td>0.06</td>
<td>≤0.25</td>
<td>≥1</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.06</td>
<td>0.12</td>
<td>≤0.25</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>32</td>
<td>32</td>
<td>≤2</td>
<td>≥8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.25</td>
<td>0.5</td>
<td>≤1</td>
<td>NA</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.5</td>
<td>0.5</td>
<td>≤2</td>
<td>≥8</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>4</td>
<td>4</td>
<td>≤4</td>
<td>≥16</td>
</tr>
</tbody>
</table>

GBS, group B Streptococcus; CLSI S and CLSI R, MIC breakpoints for susceptibility (S) and resistance (R); 6NA, not available.

3 Société de Microbiologie du Québec (SMQ), 2004 5 chemin Sainte-Marie, Sainte-Anne-de-Bellevue, succ. Centre-Ville, Montréal, Québec, Canada, H3C 3J7; 4Medecine interne, CHUM-Hôpital Saint-Luc, 1058 rue Saint Denis, Montréal, Québec, Canada, H2X 3J4; 5Département de microbiologie et immunologie, Université de Montréal, CP 6128 succ. Centre-Ville, Montréal, Québec, Canada, H3C 3J7; 6Laboratoire de santé publique du Québec/Institut national de santé publique du Québec (LSPQ/INSPQ), 20045 chemin Sainte-Marie, Sainte-Anne-de-Bellevue, Québec, Canada, H9X 3RS; 7Microbiologie médicale et infectiologie, CHUM-Hôpital Notre-Dame, 1560 rue Sherbrooke Est, Montréal, Québec, Canada, H2L 4M1.
The coding regions of the transpeptidase domain of the \textit{pbp1a}, \textit{pbp2b} and \textit{pbp2x} genes of the two GBS isolates were amplified and sequenced according to previously outlined methods.\textsuperscript{4} Amino acid sequences were deduced and analyzed using the ClustalW alignment tool included in the Lasergene software (DNASTar, Madison, WI, USA). Nucleotide and deduced amino acid sequences were compared with those of the reference penicillin-susceptible strains 2603V/R (GenBank accession number: NC_004116) and NEM316 (GenBank accession number: NC_004368). DNA analysis revealed that the \textit{pbp} genes of the clinical GBS isolates possessed many amino acid substitutions compared with the corresponding genes of the reference strains 2603V/R and NEM316. Five previously described amino acid substitutions were observed in both the penicillin-susceptible GBS and penicillin G-non-susceptible GBS isolates (S43N and N682D in \textit{PBP1a}, V625I in \textit{PBP2b}, and I377V and G627V in \textit{PBP2x}).\textsuperscript{4} However, there were three novel substitutions (T526A in \textit{PBP1a}, P278L in \textit{PBP2b} and N575D in \textit{PBP2x}) found exclusively in the penicillin G-non-susceptible GBS 2007 isolate.\textsuperscript{5}

In previous studies, the V405A and Q575E substitutions adjacent to the conserved SSN and KSG motifs in \textit{PBP2x}, considered to form the active site of the enzyme, were found in 4 invasive GBS with elevated, but still susceptible, MICs of one or multiple \(\beta\)-lactam antibiotics, in 21 penicillin G-non-susceptible GBS isolated from the respiratory tract and in a penicillin G-non-susceptible GBS recurrently isolated from a sacral decubitus ulcer.\textsuperscript{2–5} Several amino acid substitutions in \textit{PBP1a}, \textit{PBP2a} and \textit{PBP2b} were also found in penicillin G-non-susceptible GBS isolated from the respiratory tract.\textsuperscript{4} However, the \textit{PBP2a} amino acid substitutions were documented in only two GBS with penicillin MICs of 1 mg/L.\textsuperscript{6} In the present study, the penicillin G-non-susceptible GBS 2007 isolate did not harbour the \textit{PBP2x} V405A and Q575E substitutions previously associated with reduced susceptibility to penicillin.\textsuperscript{2–5} Instead, the penicillin G-non-susceptible GBS 2007 isolate possessed three novel substitutions (T526A in \textit{PBP1a}, P278L in \textit{PBP2b} and N575D in \textit{PBP2x}). At this time it is not known whether these substitutions can actually increase resistance to penicillin since they were not found within or in the proximity of the putative conserved motifs, and their significance needs to be assessed in future studies. Moreover, it is possible that the penicillin G-non-susceptible GBS 2007 isolate harboured mutations in other \textit{pbp} or non-\textit{pbp} genes that are responsible for the observed phenotype. To our knowledge, that is the first report of development of invasive GBS not susceptible to penicillin G and ceftriaxone after prolonged low-dose oral penicillin V.

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Transparency declarations
None to declare.

References

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Raltegravir: is a 400 mg once-daily dose enough?

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Keywords: atazanavir, HAART, HIV infection, pharmacokinetics

Sir,
In the STARTMRK trial, 400 mg of raltegravir twice daily + tenofovir/emtricitabine showed non-inferior efficacy versus efavirenz.\textsuperscript{2} The lack of teratogenicity and favourable drug–drug interaction profile of raltegravir supports first-line use, but the current cost prevents widespread use of raltegravir for first-line treatment.

In dose-ranging studies, raltegravir has shown strong efficacy at doses of 100–400 mg twice daily, with no clear correlation