Susceptibility to amoxycillin–clavulanate among clinical isolates of *Escherichia coli* resistant to cefoxitin

In a previous article published recently in CMI [1], it was shown that all clinical isolates of *Escherichia coli* resistant to cefoxitin were also resistant to amoxycillin–clavulanate. In contrast, preliminary results from a study performed in Seville (Spain) indicated that 34.4% of cefoxitin-resistant clinical isolates of *E. coli* remained susceptible to amoxycillin–clavulanate (43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, abstract C2-97). Resistance to cefoxitin in clinical isolates of *E. coli* has been associated with hyperproduction of chromosomal or plasmid-borne AmpC-type β-lactamases [1–3]. Clavulanic acid is not a good substrate for these enzymes, so it might be expected that strains of *E. coli* overproducing AmpC β-lactamase would be resistant to cefoxitin and amoxycillin–clavulanate. We would like to report on the frequency of these resistance phenotypes among isolates of *E. coli* from hospitals located in Europe, Asia and America that are included in the Sentry Antimicrobial Surveillance Program.

MICs of cefoxitin and amoxycillin–clavulanate for 23,719 clinical isolates of *E. coli* (Europe, *n* = 8,259; Asia–West Pacific, *n* = 3,655; Latin America, *n* = 3,194; North America, *n* = 8,611) were obtained from the database of the SENTRY Program (1997–2002). MICs were determined by the broth microdilution reference method according to NCCLS guidelines [4]. Isolates were grouped as susceptible or resistant (which included both resistant and intermediate-resistant isolates). Overall resistance to cefoxitin and amoxycillin–clavulanate, respectively, was 4.8% and 20.5% in Europe, 5.9% and 16.1% in North America, 8.9% and 22.8% in Latin America, and 10.5% and 22.1% in Asia–West Pacific. Table 1 shows the frequencies of the four possible phenotypic combinations of susceptibility–resistance to cefoxitin and amoxycillin–clavulanate. The frequencies of the four phenotypes in Europe were similar to those for isolates from North America, Latin America and the Asia-Pacific regions. As has been observed in previous studies [5,6], susceptibility to amoxycillin–clavulanate was more common among cefoxitin-resistant isolates than among cefoxitin-resistant isolates of *E. coli*. Resistance to amoxycillin–clavulanate was common among cefoxitin-resistant isolates (67.4–70.8%). A high percentage of cefoxitin-resistant isolates remained susceptible to amoxycillin–clavulanate, suggesting that a new phenotype of resistance to cefoxitin is emerging worldwide. Although the mechanisms of resistance to cefoxitin (possibly involving changes in outer-membrane proteins or altered penicillin-binding proteins) in *E. coli* isolates with this phenotype is currently under investigation, it cannot be explained simply by the hyperproduction of AmpC, since this enzyme, when overproduced, confers resistance or decreased susceptibility to amoxycillin–clavulanate.

**Table 1.** Distribution of phenotypes of susceptibility–resistance to cefoxitin and amoxycillin–clavulanate

<table>
<thead>
<tr>
<th>Area</th>
<th>FOX-R</th>
<th>FOX-S</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>AMC-S</td>
<td>AMC-R</td>
</tr>
<tr>
<td>Europe</td>
<td>116 (29.2)</td>
<td>30 (7.3)</td>
</tr>
<tr>
<td>Asia–West Pacific</td>
<td>125 (32.6)</td>
<td>258 (67.4)</td>
</tr>
<tr>
<td>Latin America</td>
<td>91 (32.0)</td>
<td>193 (68.0)</td>
</tr>
<tr>
<td>North America</td>
<td>165 (32.4)</td>
<td>345 (67.6)</td>
</tr>
</tbody>
</table>

FOX-R, resistance to cefoxitin; FOX-S, susceptibility to cefoxitin; AMC-R, resistance to amoxycillin–clavulanate; AMC-S, susceptibility to amoxycillin–clavulanate.

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