Prediction of Enterococcal Imipenem Susceptibility Using Ampicillin or Penicillin MICs: More Evidence for a Class Concept

Recently Weinstein (12) presented evidence that the susceptibility of enterococci to the carbapenem imipenem could be predicted using the MICs of either ampicillin or penicillin. The current susceptibility testing interpretive tables (9, 10) of the National Committee for Clinical Laboratory Standards (NCCLS) do not list imipenem among the agents (amoxicillin with or without clavulanic acid, ampicillin or sulbactam, and piperacillin with or without tazobactam) whose activities can be determined from ampicillin or penicillin test results. The data presented from bloodstream infection isolates of *Enterococcus faecalis* (201 strains, 24 of which were vancomycin resistant) and *Enterococcus faecium* (24 strains, 19 of which were vancomycin resistant) clearly demonstrated near-complete susceptibility categorical agreement (99.1%) between ampicillin or penicillin MICs and the imipenem MIC using a concentration of \(4 \mu g/ml\) as the susceptibility breakpoint (12). In this short report, expanded data from the SENTRY Antimicrobial Surveillance Program (1997-2000) were used to support the information initially derived from a single medical center in New Jersey.

A total of 6,538 enterococci were tested by reference broth microdilution methods (10) at SENTRY monitoring centers in Europe, the Americas (Iowa City, Iowa), and Australia. The MICs of ampicillin and penicillin were compared to those of imipenem by scattergram and analysis of regression statistics. The correlation coefficient \((r)\) was 0.87 and the regression equation was \(y = 1.8x + 0.72\). Table 1 summarizes the potential of using penicillin to predict imipenem susceptibility. The error rates were as follows: false susceptible (very major errors), 0.4%; false resistant (major errors), 0.9%; and minor errors, 2.0%. The absolute categorical agreement between the test results for both drugs was 96.7%. Similar statistics (96.7% absolute categorical agreement; \(r = 0.87\)) were documented when ampicillin results were used to predict imipenem susceptibility (Table 1). As noted by Weinstein (12) and numerous early investigations (4, 7), imipenem was relatively inactive against *E. faecium* strains (data not shown).

These analyses used the U.S. Food and Drug Administration product package insert interpretive criteria for imipenem.

FIG. 1. Scattergram comparing penicillin and imipenem MICs determined during testing of 6,538 strains of enterococci (SENTRY Antimicrobial Surveillance Program [1997-2000]).
TABLE 1. Interpretive error rates obtained by comparing imipenem MICs to those of ampicillin and penicillin to predict susceptibility for 6,538 strains (SENTRY Antimicrobial Surveillance Program [1997-2000])

<table>
<thead>
<tr>
<th>Surrogate penicillin Category (MIC)</th>
<th>% of isolates that were:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Ampicillin Susceptible (≤8)</td>
<td>78.8(^c)</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Penicillin Susceptible (≤8)</td>
<td>78.2(^d)</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
</tr>
</tbody>
</table>

\(^a\) Values are in micrograms per milliliter.
\(^b\) The MICs at the different breakpoints were as follows: susceptible, ≤4 μg/ml; intermediate, 8 μg/ml; resistant, ≥16 μg/ml.
\(^c\) Absolute categorical agreement (96.7%).
\(^d\) Absolute categorical agreement (96.7%).

tested against enterococci (a MIC of ≤4 μg/ml was considered to indicate susceptibility MIC of ≥16 μg/ml was considered to indicate resistance). These criteria are identical to those published for imipenem by Barry et al. (1) and the manufacturer (11). The use of these breakpoint MICs for imipenem would result in E. faecalis strains (consensus MIC at which 90% of the isolates tested are inhibited [MIC\(_{90}\)], 1 μg/ml) being characterized as susceptible, and E. faecium strains (consensus MIC\(_{90}\), 64 μg/ml) being characterized as resistant (7), validating the results of Weinstein (12).

Numerous clinical trial reports document the clinical efficacy of imipenem in the eradication (clinical success) of enterococci from various types of infection. For example, the clinical success rates for the indicated infection sites were as follows: for bacteremia, 100% (five cases) (5); for endocarditis, 100% (two cases) (3); for endomyocarditis, 57% (seven cases) (2); for intra-abdominal abscess, 80% (five cases) (2); for pelvic infections, 80% (five cases) (2); for peritonitis, 91% (11 cases) (2), and for skin and soft tissue infections, 91% to 100% (53 cases) (2, 6). The overall rate of clinical success using imipenem was 89% (2, 3, 5, 6).

The NCCLS document tables (see Table 2D of reference 9 and Table 2D of reference 10) should be modified as suggested earlier in this journal (12) to allow the testing of penicillin or ampicillin to predict the susceptibility to imipenem. The comments in the above-mentioned Tables 2D should be modified to read as follows: “1) Ampicillin is the class representative for ampicillin and amoxicillin. Ampicillin results may be used to determine susceptibility to amoxicillin/clavulanic acid, ampicillin/subactam, imipenem, piperacillin, and piperacillin/tazobactam among non-β-lactamase-producing enterococci; 2) Penicillin susceptibility may be used to predict the susceptibility to ampicillin, amoxicillin, ampicillin/subactam, amoxicillin/clavulanic acid, imipenem, piperacillin, and piperacillin/tazobactam for non-β-lactamase-producing enterococci.” With the analyses of these more than 6,000 enterococci of diverse species and geographic isolation, the Weinstein (12) recommendations should be finalized. Total susceptibility testing error rates would be minimized to the range of 0.9 (12) to 3.4% (this study), and serious false-susceptible errors remained at very acceptable levels (0.4 to 1.0%).

REFERENCES

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