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Letters to the Editor

Ticarcillin-Clavulanic Acid Dosing Ratio for Treatment of Experimental *Staphylococcus aureus* Endocarditis

I read with interest the recent article "Efficacy of Ticarcillin-Clavulanic Acid for Treatment of Experimental *Staphylococcus aureus* Endocarditis in Rats" by Catherall et al. (1). In their study, the authors showed that ticarcillin-clavulanic acid was as effective as other standard antistaphylococcal agents for the treatment of serious staphylococcal infections. Interestingly, the ratio of ticarcillin to clavulanic acid utilized in this study was 10:1, whereas the ratio of these two components in the preparation commercially available in the United States is 30:1. This difference is not mentioned in the report, and the results could therefore be misleading.

REFERENCE

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Author's Reply

In his letter, Dr. Goodman points out that the dosing ratio of ticarcillin to clavulanic acid was 10:1 in our experimental endocarditis studies, whereas the ratio of the two components is 30:1 in the preparation clinically available in the United States. The reason for this is that ticarcillin and clavulanic acid are cleared much more rapidly from rats than from humans because of differences in serum elimination and metabolism. To adjust for this, and on the basis of previous experience, the doses of ticarcillin and clavulanic acid were selected to give rise to concentrations in rat serum that approximated those in human serum and that were measurable for at least 4 h after dosing, taking into account the practical necessity for dosing every 8 h compared with every 4 to 6 h recommended for humans. The levels in rat serum obtained were depicted in graphic form, and peak concentrations were similar to or slightly higher than those seen in human serum (1, 2). To achieve the required concentrations, it was necessary to dose ticarcillin-clavulanic acid at a ratio of 10:1.

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Detecting Methicillin Resistance in *Staphylococcus aureus* by Polymerase Chain Reaction

We read with interest the article by Tokue et al. concerning the use of the polymerase chain reaction (PCR) to detect the methicillin resistance determinant (*mec*) in *Staphylococcus aureus* (4). The key point of the article was that PCR detected several resistant isolates that conventional testing did not. However, we have two concerns about the conventional methods used in the study. First, although the authors reference standard methods, they did not use the current recommendation of the National Committee for Clinical Laboratory Standards (NCCLS) (2). There are two critical differences. First, the incubation temperature is noted as 37 instead of 35°C. Increased temperature is associated with false-susceptible results with *S. aureus* (3). Second, the inoculum size, although not stated in the article, may have been a factor. An inoculum of less than 5×10^5 CFU/ml has also been associated with false-susceptible results (1). Inoculum size should initially be standardized by colony counts because some automated systems and disposable inoculators are not accurate and necessitate adjustments in the starting inoculum.

Our second concern is that no conventional confirmation method was used in the study. An oxacillin screen plate containing 6 μg of oxacillin and 4% NaCl in Mueller-Hinton agar is recommended by the NCCLS as a backup method for detecting oxacillin resistance, especially for those laboratories that use automated methods. This test has both high sensitivity (it approaches 100% for *S. aureus*) and high specificity (1). The results of such a test may have considerably lowered the false-susceptible results noted in the article.

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2. **National Committee for Clinical Laboratory Standards.** 1990. Methods for dilution antimicrobial susceptibility tests for bacte-

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3. **Thornsberry, C., J. Q. Caruthers, and C. N. Baker.** 1973. Effect of temperature on the in vitro susceptibility of *Staphylococcus aureus* to penicillinase-resistant penicillins. Antimicrob. Agents Chemother. **4**:263–269.
4. **Tokue, Y., S. Shoji, K. Satoh, A. Watanabe, and M. Motomiya.** 1992. Comparison of a polymerase chain reaction assay and a conventional microbiologic method for detection of methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **36**:6–9.

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Author's Reply

In response to the questions raised by Dr. Tenover and Dr. McDougal, we wish to note the following. (i) The six strains which were PCR positive and were classified as methicillin susceptible at 37°C were also incubated at 30°C in the presence of 3% NaCl. It was found that four of the six strains (strains 25, 27, 28, and 29) were susceptible to methicillin at 30°C and that strain 30 was methicillin resistant at 30°C; strain 31 was oxacillin resistant at 37°C.

(ii) The inoculum size in our experiment was 10^6 CFU/ml.

(iii) The agar screen susceptibility test is probably the best test currently available for the identification of methicillin-resistant *S. aureus*. However, the use of NaCl supplementation and a low inoculum in the 24-h agar screen test, as is currently recommended by the NCCLS, is less accurate (1). Although *S. aureus* is classified as being resistant on the basis of results of conventional susceptibility tests, many factors are known to influence the phenotypic expression of methicillin resistance. Detection of the presence or absence of the PBP2′ gene is a simple, rapid, unambiguous test for the identification of methicillin resistance.

REFERENCE

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