Letters to the Editor

Heteroresistant and Nonheteroresistant Methicillin-Resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* strains have posed many problems to diagnostic laboratories since they were first isolated in the early 1960s. Such problems mostly arise from their heteroresistance, which means that, within a given methicillin-resistant strain, only a certain (usually small) proportion of cells are able to express the resistance trait under normal conditions. Although "over identification" of methicillin-susceptible isolates as methicillin resistant is more common than usually believed (1), the lack of special precautions aimed at favoring an increased expression of the resistance (such as salt addition to the test medium, the use of a larger inoculum, or plate incubation at a lower temperature or for a longer time) may lead to "under identification" of methicillin-resistant *S. aureus* isolates.

S. aureus resistance to methicillin has generally been regarded as a typical example of intrinsic resistance and was recently shown to be related to an extra low-affinity target (2, 6). The terms intrinsic resistance, heteroresistance, and methicillin resistance are often used interchangeably.

Thus, a significant step forward in the understanding of the many problems relating to methicillin resistance is the evidence recently provided by McDougal and Thornsberry (5) that, in those strains which manifest borderline resistance, the resistance trait is mostly mediated by the production of large amounts of β-lactamase which slowly inactivate methicillin. In other words, these methicillin-resistant *S. aureus* isolates are neither intrinsically resistant nor heteroresistant.

These findings can also be of help in understanding some previous results indicating that a minority of staphylococci resistant to methicillin under normal conditions and susceptible in salt-supplemented medium can occasionally be encountered (7). In fact, we have found that these strains are not heteroresistant, produce large amounts of β-lactamase, and in MIC assays exhibit borderline resistance to methicillin which turns into susceptibility in the presence of clavulanic acid. In addition, their ability to produce β-lactamase does not appear to be significantly influenced by the salt concentration of the medium, although with other staphylococci a high salt concentration has been reported to favor the synthesis and release of β-lactamase (4).

However, in assays using agar media with and without methicillin, we have noted that heteroresistance did not necessarily appear to be the rule even within real intrinsically high-level-methicillin-resistant *S. aureus* strains. This is in agreement with the fact that *S. aureus* strains intrinsically and homogeneously resistant to methicillin have been described elsewhere (3). Furthermore, it is significant that, in McDougal and Thornsberry's report, the difficulty with which "heteroresistance" could be detected was expressed by whether or not extra salt needed to be added to the test medium.

In conclusion, it could be more appropriate to recognize at least three groups of methicillin-resistant *S. aureus* on the basis of the occurrence of intrinsic resistance and heteroresistance (even though various degrees of heteroresistance may be exhibited): (i) intrinsically resistant heteroresistant strains, (ii) intrinsically resistant nonheteroresistant strains, and (iii) extrinsically resistant nonheteroresistant strains.

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Author's Reply

We thank Drs. Varaldo, Biavasco, and Montanari for their letter concerning methicillin-resistant *Staphylococcus aureus* and their reference to our recent report on β-lactamase-mediated methicillin resistance (2). They have reviewed some of the problems of identifying these organisms in the clinical microbiology laboratory, and we essentially agree with most of their conclusions. We do, however, offer the following comments.

In reference to their previous report in this journal (3), we have not seen the "reverse pattern" they describe, i.e., strains that were resistant in unsupplemented Mueller-Hinton agar but susceptible when 5% NaCl was added to the same medium. We are not surprised to learn that they have shown these strains to be hyperproducers of β-lactamase and borderline resistant. Although we have thought that an increased concentration of salt(s) in the medium would probably enhance β-lactamase production, we do not have data to support that conclusion. Their finding that increasing the salt concentration did not influence β-lactamase production in these reverse pattern strains does not disagree with any experimental data that we have obtained to date, but, as they indicate, it does disagree with the data of others (1).

Although we recognize the validity of the three groupings these authors propose, we do not believe that they have clinical utility. The intrinsically resistant strains contain two

subpopulations (methicillin susceptible and resistant), but the number of each will vary over a wide continuum; a culture that is mostly resistant is often called homogeneous, and a culture that has a smaller resistant subpopulation is called heteroresistant or heterogeneous. Methicillin (oxacillin) resistance is generally easy to detect by in vitro tests in homogeneous cultures but more difficult to detect in heteroresistant strains, with the degree of difficulty being proportional to the size of the resistant subpopulation: the smaller the resistant subpopulation, the more difficult it is to detect methicillin resistance. Separation of these intrinsically methicillin-resistant strains has no therapeutic significance, since therapy would be the same for infections caused by either group.

From the clinical point of view, therefore, we do not see the usefulness of subgrouping the intrinsically methicillin-resistant strains as long as the therapy is the same. However, the clinical and epidemiological usefulness of separating the borderline or β-lactamase-mediated methicillin-resistant strains from intrinsically resistant strains cannot be fully assessed until data from clinical therapy trials are developed. For clinical, epidemiological, and laboratory usefulness, we suggest that only two groups be considered, intrinsic (chromosomally mediated) and acquired (β-lactamase mediated). We also suggest, however, that the acquired resistance should not at present be a part of a laboratory report, since it is not clear whether the treatment would be different. It is likely that a laboratory report of acquired resistance would be more confusing to clinicians than helpful. The presence of these strains with acquired resistance should, however, be discussed with infectious disease and infection control personnel.

We have no objections to the development of various names and groupings for academic reasons as long as it does not interfere with appropriate therapy. We also recognize that the use of terms such as β-lactamase-mediated methicillin resistance, thermosensitive heterogeneous, etc., are very useful in describing certain peculiar characteristics associated with these bacteria. We think, however, it may be getting out of hand, since at least 21 terms have been used (C. Thornsberry and L. K. McDougal, Antimicrob. Newsl. **3**:60–62, 1986).

Finally, we have one other bias. We generally prefer the use of oxacillin instead of methicillin in testing for resistance to these antimicrobial agents and for that reason prefer to use oxacillin rather than methicillin in referring to the resistance.

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Bacteriologic Surveillance of Long-Term-Catheterized Patients

Damron and associates have made an important observation in reporting the failure of commercial laboratories to isolate and demonstrate the relatively greater antimicrobial resistance of certain uncommon pathogens in the urine specimens of patients with long-term indwelling catheters (D. J. Damron, J. W. Warren, G. R. Chippendale, and J. H., Tenney, J. Clin. Microbiol. **24**:400–404, 1986). The authors correctly observe that more complete and accurate bacteriologic examination of these specimens will be more expensive and that policies must be established to prevent unnecessary increases in cost.

Existing pressures to contain rising health care costs no longer accommodate justification for performance of additional work purely on the basis of "a desire for accuracy," as was stated by the authors as the first reason for conducting more extensive processing of these specimens. The authors did not provide a cost-benefit analysis to prove that the cost of identification of unusual and resistant strains and the use of this information to guide empiric treatment of infection would provide at least an equal or a greater reduction in the cost of the morbidity and mortality that would occur if this information were not available. The more inclusive reporting that the authors have suggested be applied in all extended-care facilities to lead to a better understanding of infection in these types of patients will not be fruitful if these institutions do not possess the resources or the leadership to evaluate and use the data. I have observed sequential laboratory reports for patients with long-term indwelling catheters that display mixtures of organisms which evolve from one species to another in the "dynamic" sense that the authors describe, yielding a perpetually changing array of antimicrobial susceptibilities. This practice is widespread, costly, and wasteful.

It might have been a more cost-effective suggestion if the authors had proposed that samples be randomly selected on a periodic basis to undergo a complete bacteriologic profile to establish the strains present within the institution. The antimicrobial susceptibility profiles of these isolates could be used to recommend empiric therapy of patients who become bacteremic.

My concern is that their observations may contribute to performance of unnecessarily expensive bacteriology on every specimen submitted from patients with long-term indwelling catheters. Clinical laboratories receive more