β-lactam Antibiotics Active against Methicillin-Resistant *Staphylococcus aureus*

To the Editor—Chambers and Sachdeva [1] recently suggested that the in vitro susceptibility of two test strains of methicillin-resistant *Staphylococcus aureus* (MRSA) to a series of β-lactam antibiotics correlates well with the avidity of the drugs to bind to penicillin-binding protein (PBP) 2a, the low-β-lactam-affinity PBP produced by these organisms. These findings confirm comparable observations made earlier in our laboratory [2]. Also, recent genetic evidence [3] clearly implies a quantitative contribution of PBP 2a to the MIC values of β-lactams for MRSA: selective transposon inactivation of the PBP 2a gene resulted in a massive drop in MIC values of methicillin, from 1000 to 4 mg/l.

Most clinical isolates of MRSA produce penicillinase, and β-lactam antibiotics of potential clinical use against MRSA must be able to resist enzymatic degradation as well as having good PBP 2a affinity. Alternatively, a penicillinase-susceptible β-lactam with relatively good PBP 2a affinity can be combined with penicillinase inhibitors such as clavulanate or sulbactam. Indeed, in some in vitro experiments by Chambers et al. [4] and in earlier studies by others [2, 5–7], drug combinations such as ampicillin with sulbactam and amoxicillin with clavulanate showed relatively low MIC values for MRSA strains. Surprisingly, however, ampicillin and sulbactam cured only 30% of MRSA infections when tested in vivo in the rabbit model of experimental endocarditis [4]. These disappointing results are also in sharp contrast with the high rate of successful treatment observed in in vivo experiments reported earlier from our laboratory [6, 7] using the rat model and by Washburn et al. [5] using the rabbit model of endocarditis. In both laboratories, amoxicillin with clavulanate or ampicillin with sulbactam successfully treated ≥80% of the animals, a result equal or superior to that obtained with vancomycin in an identical experimental setting in rats.

The discrepancy between in vivo observations of Chambers et al. [4] and the successful in vivo experiments reported earlier [5–7] requires an explanation. On the basis of the poor in vivo performance of ampicillin and sulbactam (and some other β-lactams), Chambers et al. [4] express pessimism concerning the chemoptherapeutic potential of β-lactam antibiotics currently in clinical use. We disagree: We believe an appropriate increase in the concentrations of the antibiotic and penicillinase inhibitor easily achievable under clinical conditions could make this combination therapy a highly relevant and economically feasible alternative treatment for MRSA infections.

While the larger numbers of bacteria on the infected vegetations at the beginning of treatment in rabbits compared with that in rats may have contributed to the different outcome of these experiments [4, 5–7], it seems that the critical difference has to do with the dosage of the drugs. We recently observed (using the rat model) that the therapeutic efficacy of amoxicillin and clavulanate closely correlated with the dosage of the penicillinase inhibitor clavulanate [7]. In a typical experiment, successful treatment of endocarditis caused by penicillinase-producing MRSA increased from 30% to 70% and >90% simply by increasing by two and five times, respectively, the proportion of clavulanate in the antibiotic regimen. When an isogenic penicillinase-negative derivative of the same MRSA strain (i.e., the original strain cured of its penicillinase plasmid in the laboratory) was used in the rat model, amoxicillin given alone successfully treated >90% of endocarditis. Amoxicillin is known to have relatively good PBP 2a affinity [1, 2]. Using the same penicillinase-negative MRSA, we found that cloxacillin at higher concentrations than amoxicillin could not achieve cure. Cloxacillin, in contrast to amoxicillin, has poor binding capacity to PBP 2a.

Even more significant were our tests in which the highly and homogeneously resistant (free of penicillinase) MRSA strain COL [8] was used to produce experimental endocarditis in rats. Amoxicillin given alone resulted in >90% successful treatment even though there were high numbers of bacteria on the infected valves and all were expressing high resistance levels at the beginning of antibiotherapy [7].

Taken together, these data cause us to draw a conclusion opposite to that of Chambers et al. β-lactam antibiotics with relatively good affinity for PBP 2a, when applied at appropriate concentrations, can be quite effective against MRSA strains both in vitro and in vivo. Such β-lactams are available, as are effective penicillinase inhibitors. The combination of these agents may provide an important chemotherapeutic alternative that should not be overlooked when designing curing regimens against MRSA infections.

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