ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2011, p. 2495–2497 Vol. 55, No. 5
0066-4804/11/$12.00 doi:10.1128/AAC.00224-11

Striking "Seesaw Effect" between Daptomycin Nonsusceptibility and β-Lactam Susceptibility in *Staphylococcus haemolyticus*

The expression "seesaw effect" was originally used by Sieradzki and Tomasz (7), and subsequently by others, to denote a frequently observed inverse relationship between evolving glycopeptide and β-lactam MICs in *Staphylococcus aureus*. The same expression has recently been revived in two interesting studies by Yang et al. (9) and Lee et al. (4) to signify a similar phenomenon, again seen in *S. aureus*, involving daptomycin instead of glycopeptides. On the other hand, it is well known that *S. aureus* strains progressively acquiring daptomycin nonsusceptibility during daptomycin exposure also exhibit progressively increasing vancomycin MICs (3, 6).

Among coagulase-negative staphylococci, *Staphylococcus haemolyticus*, second only to *Staphylococcus epidermidis* in the frequency of its association with human infections (1), is unique in being predisposed to developing glycopeptide resistance and was the first Gram-positive pathogen to acquire such resistance in the 1980s (2).

After exposure to increasing daptomycin concentrations, by a procedure successfully used with glycopeptides in previous studies in our laboratory (8), a stable clone with a daptomycin MIC of 4 μg/ml was obtained from a daptomycin-susceptible (MIC, 0.5 μg/ml) clinical isolate of *S. haemolyticus*. Vancomycin and teicoplanin MICs also increased from 4 and 8 μg/ml in the parent to 8 and 32 μg/ml in the laboratory derivative, respectively. The parent strain was both penicillin and methicillin resistant: penicillin and cefoxitin MICs were >256 μg/ml; molecular analysis disclosed a type I SCC*mec* cassette and regular *mec* and *bla* operons; β-lactamase production was confirmed by the nitrocefin test. The seesaw effect was striking (Fig. 1): in the daptomycin-nonsusceptible derivative, the penicillin MIC dropped to 0.125 μg/ml, in spite of persistent detection of the *bla* operon and of β-lactamase activity, and the cefoxitin MIC dropped to 2 μg/ml, despite persistent detection of the *mecA* gene and the *mec* operon in a type I SCC*mec*.

Although a number of theories have been advanced to account for the vancomycin/β-lactam and the daptomycin/β-lactam seesaw effect (7, 9), the underlying mechanisms remain poorly understood. Moreover, while previous hypotheses were essentially aimed at explaining a fall in methicillin resistance, thus largely pointing to some modulation of *mecA* expression, this case also involves a plunge in penicillin resistance, despite apparently normal—phenotypically and genotypically—β-lactamase production in the laboratory derivative. In other words, here the seesaw effect needs to be explained in light not only of the *mec* operon/PBP2a-mediated β-lactam resistance system but also of the *bla* operon/β-lactamase-mediated one. It is worth noting that, in a reported case of decreased susceptibility to daptomycin and vancomycin in *S. aureus* during prolonged therapy, a decreased penicillin MIC was found to be associated with the apparent loss of β-lactamase activity (5).

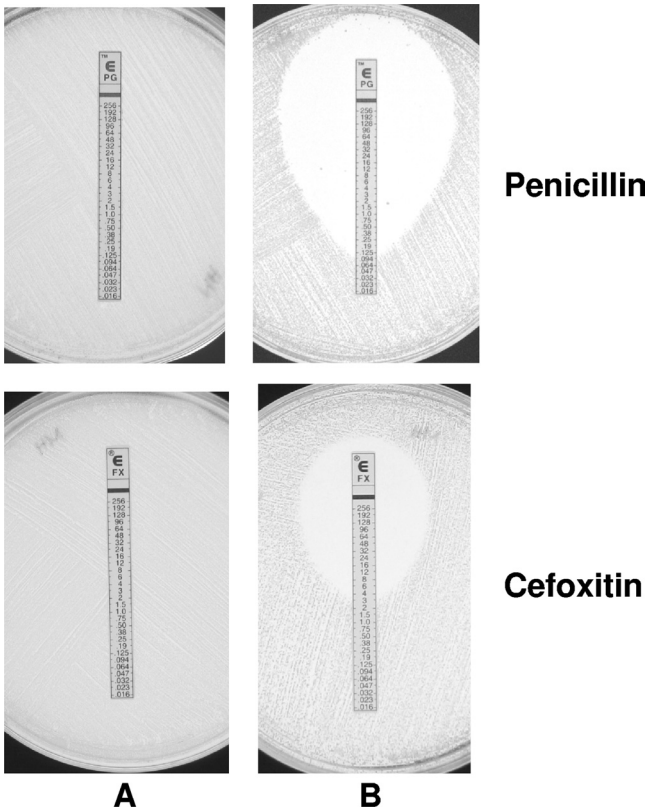

FIG. 1. Diffusion tests using Etest strips (penicillin and cefoxitin). (A) Clinical isolate of daptomycin-susceptible *S. haemolyticus* (parent strain). (B) Daptomycin-nonsusceptible laboratory derivative.

REFERENCES

1. **Bannerman, T. L., and S. J. Peacock.** 2007. *Staphylococcus*, *Micrococcus*, and other catalase-positive cocci, p. 390–411. *In* P. R. Murray, E. J. Baron, J. H. Jorgensen, M. L. Landry, and M. A. Pfaller (ed.), Manual of clinical microbiology, 9th ed. ASM Press, Washington, DC.
2. **Biavasco, F., C. Vignaroli, and P. E. Varaldo.** 2000. Glycopeptide resistance in coagulase-negative staphylococci. Eur. J. Clin. Microbiol. Infect. Dis. **19:**403–417.
3. **Camargo, I. L., H. M. Neoh, L. Cui, and K. Hiramatsu.** 2008. Serial daptomycin selection generates daptomycin-nonsusceptible *Staphylococcus aureus* strains with a heterogeneous vancomycin-intermediate phenotype. Antimicrob. Agents Chemother. **52:**4289–4299.
4. **Lee, C. H., M. C. Wang, I. W. Huang, F. J. Chen, and T. L. Lauderdale.** 2010. Development of daptomycin nonsusceptibility with heterogeneous vancomycin-intermediate resistance and oxacillin susceptibility in methicillin-resistant *Staphylococcus aureus* during high-dose daptomycin treatment. Antimicrob. Agents Chemother. **54:**4038–4040.
5. **Mariani, P. G., H. S. Sader, and R. N. Jones.** 2006. Development of decreased susceptibility to daptomycin and vancomycin in a *Staphylococcus aureus* strain during prolonged therapy. J. Antimicrob. Chemother. **58:**481–483.
6. **Mishra, N. N., et al.** 2009. Analysis of cell membrane characteristics of in vitro-selected daptomycin-resistant strains of methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **53:**2312–2318.
7. **Sieradzki, K., and A. Tomasz.** 1997. Inhibition of cell wall turnover and autolysis by vancomycin in a highly vancomycin-resistant mutant of *Staphylococcus aureus*. J. Bacteriol. **179:**2557–2566.
8. **Vignaroli, C., F. Biavasco, and P. E. Varaldo.** 2006. Interactions between glycopeptides and β-lactams against isogenic pairs of teicoplanin-susceptible

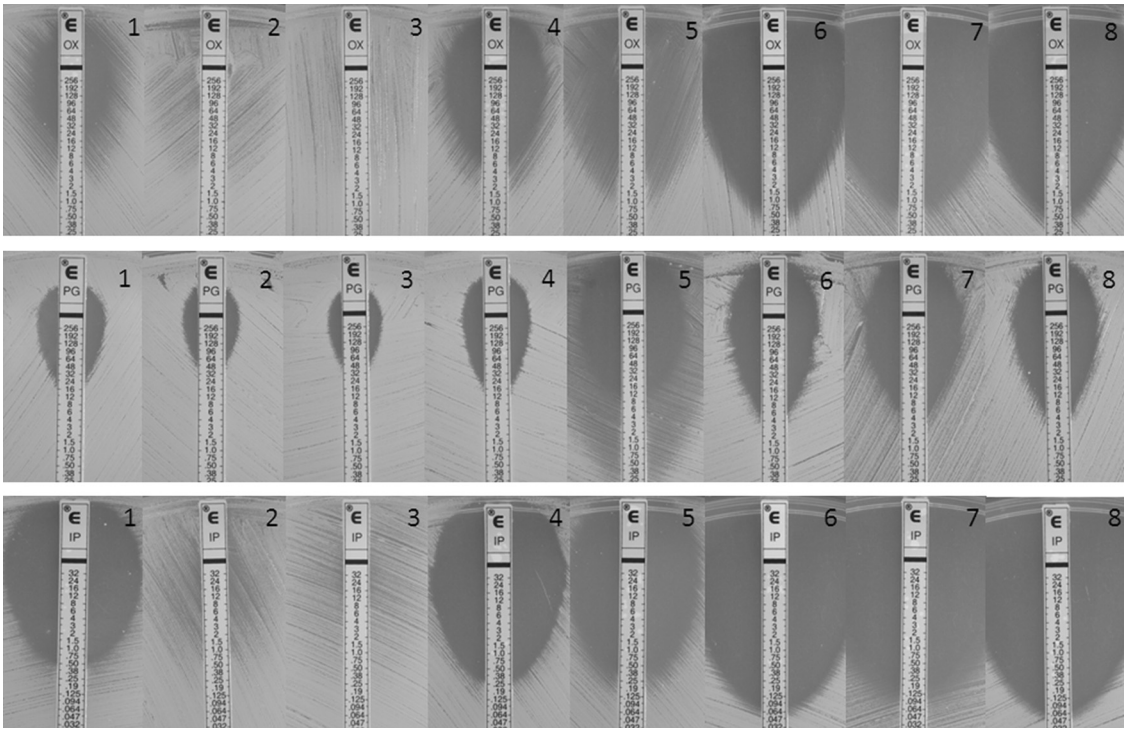

FIG. 1. MICs of oxacillin (OX), penicillin (PG), and imipenem (IP) in eight consecutive *S. aureus* isolates recovered from blood cultures of a patient who was on daptomycin therapy. Isolates 1 to 5 were daptomycin susceptible, and isolates 6 to 8 were daptomycin nonsusceptible.

and -resistant strains of *Staphylococcus haemolyticus*. Antimicrob. Agents Chemother. **50:**2577–2582.

9. **Yang, S. J., et al.** 2010. Daptomycin-oxacillin combinations in treatment of experimental endocarditis caused by daptomycin-nonsusceptible strains of methicillin-resistant *Staphylococcus aureus* with evolving oxacillin susceptibility (the "seesaw effect"). Antimicrob. Agents Chemother. **54:**3161–3169.

Carla Vignaroli
Caterina Rinaldi
Pietro E. Varaldo*
Department of Biomedical Sciences
Section of Microbiology
Marche Polytechnic University
60126 Ancona, Italy

*Phone: 39 071 2206294
Fax: 39 071 2206293
E-mail: pe.varaldo@univpm.it

Authors' Reply

Vignaroli et al. (see foregoing letter) recently reported the "seesaw effect" between daptomycin nonsusceptibility and β-lactam susceptibility in a *Staphylococcus haemolyticus* strain carrying SCC*mec* type 1. In their study, the cefoxitin and penicillin MICs were both >256 μg/ml in the parental daptomycin-susceptible strain but decreased to 2 and 0.125 μg/ml, respectively, in the daptomycin-nonsusceptible derivative. We previously reported a similar "seesaw effect" between daptomycin and oxacillin susceptibility in a series of eight *S. aureus* blood isolates from a patient who was on high-dose daptomycin therapy (1). Genotyping indicated that the eight isolates shared an identical genetic profile and carried SCC*mec* type IV. The oxacillin MICs of the first five daptomycin-susceptible (MIC, ≥0.75 μg/ml) isolates ranged from 16 to >256 μg/ml but dropped to 1 to 3 μg/ml in isolates 6 to 8, which were daptomycin nonsusceptible (MIC, 4 μg/ml) (1).

We also observed changes in penicillin and imipenem MICs in parallel to changes in oxacillin MICs (Fig. 1). However, the "seesaw effect" was less striking, in part likely due to the heterogeneous methicillin resistance displayed by our isolates (Fig. 1). Although the MICs of penicillin decreased in isolates 6 to 8, they remained in the resistance range, at ≥6 μg/ml. The cefoxitin MICs of isolates 6 to 8 also remained in the resistance range, at 24 to >256 μg/ml (data not shown). Of note, only isolates 2 and 3, which had the highest oxacillin MICs, displayed resistance to imipenem; the other six isolates had MICs in the susceptible range, although a drop in MICs occurred in isolates 6 to 8 (Fig. 1).

The clinical significance of such a "seesaw effect" and differential display of β-lactam susceptibility among species of staphylococci carrying different types of SCC*mec* elements is unknown at present. The first report of the "seesaw effect" was observed between glycopeptide and β-lactams (2). Such a phenomenon is now seen with isolates exposed to daptomycin (1, 3; see foregoing letter), and there is a positive correlation between daptomycin and vancomycin nonsusceptibility (1; see foregoing letter). Although it is unknown if changes in vancomycin MICs occurred in the daptomycin-nonsusceptible strains in the study by Yang et al. (3), the authors provided a thoughtful and detailed discussion on the possible mechanisms of the "seesaw effect," indicating that a complex network associated with cell wall synthesis is involved. We concur with Yang et al. and Vignaroli et al. that both *mecA*-dependent and *mecA*-independent mechanisms are implicated (3; see foregoing letter). Further studies on the mechanisms contributing to such a

phenomenon may lead to discovery of therapeutic potentials against multidrug-resistant staphylococci.

REFERENCES

1. **Lee, C. H., M. C. Wang, I. W. Huang, F. J. Chen, and T. L. Lauderdale.** 2010. Development of daptomycin nonsusceptibility with heterogeneous vancomycin-intermediate resistance and oxacillin susceptibility in methicillin-resistant *Staphylococcus aureus* during high-dose daptomycin treatment. Antimicrob. Agents Chemother. **54:**4038–4040.
2. **Sieradzki, K., and A. Tomasz.** 1997. Inhibition of cell wall turnover and autolysis by vancomycin in a highly vancomycin-resistant mutant of *Staphylococcus aureus.* J. Bacteriol. **179:**2557–2566.
3. **Yang, S. J., et al.** 2010. Daptomycin-oxacillin combinations in treatment of experimental endocarditis caused by daptomycin-nonsusceptible strains of methicillin-resistant *Staphylococcus aureus* with evolving oxacillin susceptibility (the "seesaw effect"). Antimicrob. Agents Chemother. **54:**3161–3169.

Chen-Hsiang Lee
Division of Infectious Diseases
Department of Internal Medicine
Chang Gung Memorial Hospital—Kaohsiung Medical Center
Chang Gung University College of Medicine
Kaohsiung, Taiwan

Feng-Jui Chen
Tsai-Ling Lauderdale*
Division of Infectious Diseases
National Health Research Institutes
35 Keyan Road
Zhunan, Taiwan 350

*Phone: 886 37246166
Fax: 886 37586457
E-mail: lauderdale@nhri.org.tw

Ed. Note: *Yang et al. (reference 9 in the comment letter) did not wish to respond.*