JOURNAL OF CLINICAL MICROBIOLOGY, July 2008, p. 2471–2472 Vol. 46, No. 7
0095-1137/08/$08.00+0 doi:10.1128/JCM.00519-08

Clinical Rationale for Treatment of Endocarditis Caused by Methicillin-Susceptible *Staphylococcus aureus* Developing Nonsusceptibility to Daptomycin

A recent case report by Sakoulas et al. demonstrated acquired daptomycin (lipopeptide) resistance in an immunecompetent adult patient with native valve endocarditis due to methicillin-susceptible *Staphylococcus aureus* (MSSA) (8). Daptomycin resistance developed following exposure to levofloxacin and vancomycin prior to daptomycin treatment. The observation that vancomycin exposure may induce resistance mechanisms in staphylococcal species is consistent with another recent report in which vancomycin exposure was accompanied by decreased expression of *agr*, resulting in resistance to platelet microbicidal proteins (6). It is believed that daptomycin's mechanism of action involves functional disruption of the bacterial plasma membrane (1, 4, 7).

However, what is most striking about the article is the impression that the patient was not managed optimally. Nafcillin/cloxacillin (with/without an aminoglycoside) would be widely accepted as the drug of choice to treat MSSA native valve endocarditis; comparative studies have confirmed cloxacillin/nafcillin to have superior efficacy to vancomycin in patients with MSSA bacteremia (2, 5). Despite confirmation that the offending organism was methicillin sensitive, the patient was first managed on levofloxacin and then switched to vancomycin. Following a poor response to vancomycin, the patient was placed on nafcillin for a very brief period (3 days only), before switching to daptomycin monotherapy. The clinical rationale applied is not explained in the methods section nor taken up in the discussion.

Resistance to daptomycin was documented after 6 to 7 days of treatment. Only after 17 days of antibiotic treatment did the patient receive a prolonged course of nafcillin and gentamicin. Unfortunately, the patient's mitral valve was destroyed by the time infection was brought under control and he underwent successful valve replacement, which remains a suboptimal outcome. It would be interesting to know why first vancomycin and then daptomycin were regarded as the drugs of choice to treat a patient with MSSA bacteremia. According to the clinical trial (3) of daptomycin versus standard therapy of *S. aureus* bacteremia and right-sided endocarditis referred to in the report by Sakoulas et al., success rates favored daptomycin over vancomycin among patients with methicillin-resistant *S. aureus* but were higher for MSSA infection treated with an antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) compared to daptomycin.

Despite the fact that one of the authors is affiliated with the company producing daptomycin, no conflict of interest was declared. We believe it is essential that every publication should include a conflict of interest statement. This article demonstrates the importance of ensuring transparency in order to protect the best interests of our patients.

REFERENCES

1. **Alborn, W. E., Jr., N. E. Allen, and D. A. Preston.** 1991. Daptomycin disrupts membrane potential in growing *Staphylococcus aureus*. Antimicrob. Agents Chemother. **35:**2282–2287.
2. **Chang, F. Y., J. E. Peacock, Jr., D. M. Musher, P. Triplett, B. B. MacDonald, J. M. Mylotte, A. O'Donnell, M. M. Wagener, and V. L. Yu.** 2003. *Staphylococcus aureus* bacteremia recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine **82:**333–339.
3. **Fowler, V. G., Jr., H. W. Boucher, and G. R. Corey.** 2006. Daptomycin versus standard therapy for bacteraemia and endocarditis caused by *Staphylococcus aureus*. N. Engl. J. Med. **355:**653–665.
4. **Hancock, R. E. W.** 2005. Mechanisms of action of newer antibiotics for gram-positive pathogens. Lancet Infect. Dis. **5:**209–218.
5. **Lodise, T. P., Jr., P. S. McKinnon, D. P. Levine, and M. J. Rybak.** 2007. Impact of empirical-therapy selection on outcomes of intravenous drug users with infective endocarditis caused by methicillin-susceptible *Staphylococcus aureus*. Antimicrob. Agents Chemother. **51:**3731–3733.
6. **Moise, P. A., D. S. Smyth, N. El-Fawal, and D. A. Robinson.** 2008. Microbiological effects of prior vancomycin use in patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. J. Antimicrob. Chemother. **61:**85–90.
7. **Thorne, G. M., and J. Alder.** 2002. Daptomycin: a novel lipopeptide antibiotic. Clin. Microbiol. Newsl. **24:**33–40.
8. **Sakoulas, G., W. Rose, M. J. Rybak, S. Pillai, J. Alder, R. C. Moellering, Jr., and G. M. Eliopoulos.** 2008. Evaluation of endocarditis caused by methicillin-susceptible *Staphylococcus aureus* developing nonsusceptibility to daptomycin. J. Clin. Microbiol. **46:**220–224.

Zukile Gqada*
Department of Pathology, Division of Medical Microbiology
Faculty of Health Sciences
Stellenbosch University and the NHLS
Tygerberg Hospital
Cape Town, South Africa

Ben Marais
Department of Paediatrics and Child Health
Faculty of Health Sciences
Stellenbosch University
Tygerberg Hospital
Cape Town, South Africa

Elizabeth Wasserman
Colleen Bamford
Heidi Orth
Department of Pathology, Division of Medical Microbiology
Faculty of Health Sciences
Stellenbosch University and the NHLS
Tygerberg Hospital
Cape Town, South Africa

*Phone: 27 21 938 4032
Fax: 27 21 938 4005
E-mail: zgqada@sun.ac.za

Authors' Reply

We appreciate the interest raised in our article "Evaluation of endocarditis caused by methicillin-susceptible *Staphylococcus aureus* developing nonsusceptibility to vancomycin" (1). A discussion of optimal medical management of endocarditis was not the purpose of our paper. Details regarding antibiotic exposure were provided only to describe the exposure background of the sequential isolates studied in vitro, which was the focus of the paper. Nonessential clinical details were omitted because this was not intended as a "case report."

In response to the authors' queries, levofloxacin and vancomycin had been administered empirically prior to knowledge of the patient's diagnosis. Nafcillin was indeed used once MSSA bacteria were identified; this was switched to daptomycin in response to persistently positive blood cultures on nafcillin.

We support not only the principle of author transparency, but also the duty, as exemplified by our paper, to report any limitations or other cautionary observations regarding use of antibiotics to treat serious infections. All authors fully declared to the journal any relevant financial relationship when the paper was submitted. These are as follows. G.S. was a consultant for Cubist Pharmaceuticals and Pfizer; had a research grant from Cubist Pharmaceuticals and Pfizer; and was a member of the Speakers Bureau for Cubist Pharmaceuticals, Pfizer, and Wyeth. W.R. had no relevant financial relationships. M.J.R. was a consultant for Cubist Pharmaceuticals, Pfizer, Johnson & Johnson, Astellas, Cerexia/Forrest, and Wyeth; had research grants from Cubist Pharmaceuticals, Pfizer, Johnson & Johnson, Astellas, and Cerexia/Forrest; and was a member of the Speakers Bureau for Cubist Pharmaceuticals, Pfizer, Ortho-McNeil/Johnson & Johnson, and Wyeth. S.P. had no relevant financial relationships. J.A. was employed by Cubist Pharmaceuticals at the time of study and publication. R.C.M. was a consultant to Cubist Pharmaceuticals and Ortho-McNeil/Johnson & Johnson. G.M.E. was a consultant to Cubist Pharmaceuticals and had a research grant from Cubist Pharmaceuticals.

REFERENCE

1. **Sakoulas, G., W. Rose, M. J. Rybak, S. Pillai, J. Alder, R. C. Moellering, Jr., and G. M. Eliopoulos.** 2008. Evaluation of endocarditis caused by methicillin-susceptible *Staphylococcus aureus* developing nonsusceptibility to daptomycin. J. Clin. Microbiol. **46:**220–224.

George Sakoulas*
Department of Medicine
Division of Infectious Diseases
New York Medical College and Westchester Medical Center
Munger Pavilion, Room 245
Valhalla, New York 10595

Warren Rose
Michael J. Rybak
Anti-Infective Research Laboratory
Eugene Applebaum College of Pharmacy and Health Sciences
Wayne State University
Detroit, Michigan 48201

Satish Pillai
Department of Infectious Disease
Cleveland Clinic Foundation
Cleveland, Ohio 44195

Jeff Alder
Cubist Pharmaceuticals
Lexington, Massachusetts 02421

Robert C. Moellering, Jr.
George M. Eliopoulos
Department of Medicine
Beth Israel Deaconess Medical Center and Harvard Medical School
Boston, Massachusetts 02215

*Phone: (914) 594-4974
Fax: (845) 361-1156
E-mail: george_sakoulas@nymc.edu