Best Alternative to Vancomycin for Serious Methicillin-Resistant Staphylococcus aureus Infections: Let’s Just Say It

To the Editor—The recently published articles by Patel et al [1], Kullar et al [2], and Lubin et al [3] persuasively bolster the growing consensus opinion that the gold-standard antimicrobial agent for treatment of serious infections involving methicillin-resistant Staphylococcus aureus (MRSA), vancomycin, has become tarnished.

Undeniably, these works add to what clearly has become fact: 1) the prevalence of MRSA infections, both inpatient and outpatient, has greatly increased to the point of dominance (inpatient infections); 2) serious infections with MRSA are associated with significantly higher morbidity, mortality, lengths of hospital stay, and total costs, especially when inadequately treated; 3) the rising minimal inhibitory concentration (MIC) of vancomycin against MRSA greatly hinders this drug from achieving the agreed-on required pharmacodynamic parameter (eg, ratio of the area under the concentration–time curve to MIC [AUC/MIC] $\geq 400$) necessary for adequate bactericidal activity; 4) automated susceptibility testing methods do not accurately reflect the higher MICs produced with standardized methods such as microbroth dilution and E test; and 5) targeting higher serum trough vancomycin levels (15–20 mg/L) to attain an AUC/MIC $\geq 400$, as recently recommended in a summary report [4], carries with it a higher probability of drug-induced nephrotoxicity. In light of this information, it is suggested that alternative anti-MRSA agents be considered in treating known or suspected serious MRSA infections, particularly bacteremia. Unfortunately, for the practicing clinician, neither these articles, nor the recently published clinical practice guidelines by the Infectious Diseases Society of America (IDSA) for the treatment of MRSA infections in adults and children [5], offer an opinion as to what actually is, or likely would be, the best alternative anti-MRSA agent.

Acknowledging the absence of evidence from any head-to-head clinical trials among the relatively new antimicrobial agents with approved MRSA treatment indications (eg, quinupristin–dalfopristin, linezolid, daptomycin, tigecycline, telavancin, and ceftaroline), the most we may say is that based on the predetermined primary clinical efficacy endpoint of resolution of signs and symptoms, such that no further antimicrobial therapy was required at the test-of-cure visit, for the treatment of acute bacterial skin and skin-structure infections (ABSSSI, formerly termed complicated skin and skin-structure infections [cSSSI]) involving Gram-positive microorganisms, including MRSA, each of these agents was noninferior to vancomycin. However, a post hoc analysis of treatment duration among patients achieving clinical success with intravenous therapy alone in the phase 3 trials (cSSSI) involving daptomycin revealed that 63% of patients given daptomycin required only 4–7 days of therapy compared with 33% of patients in the comparator arm that included vancomycin ($P < .0001$) [6]. Although the 3 days of comparative analysis now required in ABSSSI trials...
was not a clinical endpoint at the time the trial was conducted, this information would seem to favor daptomycin because twice as many randomized patients not receiving daptomycin required a second week of intravenous therapy to achieve a noninferior end-of-treatment clinical efficacy in the modified intent-to-treat population. Moreover, soft-tissue infection has been identified as the presumed source of infection in 37% of patients with S. aureus bacteremia in a large prospective observational study [7]. In the only clinical trial comparing any new anti-MRSA agent to vancomycin or a semisynthetic penicillin for the treatment of S. aureus bacteremia and endocarditis [8] (a more vigorous test of antimicrobial efficacy), daptomycin was equally effective in the treatment of patients with endocarditis caused by methicillin-sensitive S. aureus (MSSA) or MRSA but had numerically higher success rates than vancomycin (44.4% vs 31.8%, respectively) when MRSA was the pathogen. A cost analysis of treatment derived from this study demonstrated that when all costs of therapy were considered, the cost effectiveness of daptomycin and vancomycin–gentamicin was similar, even if the cost of vancomycin was 0 dollars [9]. Accordingly, the IDSA MRSA guidelines have identified daptomycin as the only alternative to vancomycin for the treatment of MRSA bacteremia or endocarditis (with no specification of right or left sided), and interestingly assigned a strength of recommendation and quality of evidence score of A-I to daptomycin but A-II to vancomycin [5].

We are not without precedent in recommending antimicrobial treatment regimens for pathogen-specific disease states based in large part on pharmacodynamic modeling and in vitro bactericidal activity. For example, the American Heart Association scientific statement concerning the antimicrobial treatment of infective endocarditis is heavily weighted with consensus opinions based on small (if available) numbers of well-controlled, randomized clinical trials.

If the essential role of the antimicrobial agent is to eradicate the causative organism(s), in this instance MRSA, from the site of infection and thereby help to bring about a successful clinical outcome, the impressively superior rapid concentration-dependent bactericidal activity and prolonged postantibiotic effect of this lipopeptide compound [10] that possesses a unique mechanism of action makes for a strong argument in naming daptomycin today’s best alternative, if not the replacement, for vancomycin in treating serious MRSA infections. Perhaps, we should just say it!

Note

Potential conflicts of interest. L. M. B. is a speaker for Cubist Pharmaceuticals.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Larry M. Bush 1,2,3

1Affiliated Professor of Biomedical Science, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, 2Affiliated Associate Professor of Medicine, University of Miami–Miller School of Medicine, and 3Department of Infectious Diseases, JFK Medical Center, Palm Beach County, Florida

References


Correspondence: Larry M. Bush, MD, FACP, Atlantis Medical Center, 5503 South Congress Avenue, Suite 104, Atlantis, FL, 33462 (larry561@aol.com).

Clinical Infectious Diseases 2011;53(9):965–6

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10.1093/cid/cir528

DOI: 10.1093/cid/cir528

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