

## EDITORIAL COMMENTARY

# Ceftobiprole: A New Option for Treatment of Skin and Soft-Tissue Infections due to Methicillin-Resistant *Staphylococcus aureus*

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(See the article by Noel et al. on pages 647–55)

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as an important nosocomial pathogen, accounting for >50% of all bloodstream *S. aureus* isolates recovered from 49 representative US hospitals [1], with similar trends in Europe [2]. MRSA infection has also become common in outpatients [3]. Even more worrisome is the fact that MRSA was identified as the most common pathogen in patients presenting with acute, purulent skin and soft-tissue infections to emergency departments in the United States [4]. Such infections are associated with longer hospital stays, longer durations of antibiotic use, higher costs, and, probably, greater mortality rates, compared with infections caused by methicillin-susceptible *S. aureus* [5, 6]. The emergence of community-onset MRSA infection aggravates control of MRSA infection; a validated guideline for control of community-onset MRSA infection has not yet been pub-

lished, and community-onset MRSA infection adds to the overall burden of MRSA infection [7], even in countries where a “search and destroy” policy is in place [8]. From the United States, the predominant community-onset MRSA clone, USA300 (ST8), can rapidly be spread by travelers and health care workers in different parts of the world [9, 10]. Therefore, new antimicrobial agents are urgently needed [11].

The role of vancomycin as the reference standard for treatment of MRSA infection has been recently challenged [12]. In fact, efficacy data have never been submitted to the US Food and Drug Administration, and breakpoints have recently been lowered by the Clinical and Laboratory Standards Institute to improve the correlation between in vitro susceptibility and clinical outcome. Many new drugs against gram-positive pathogens—recently reviewed in *Clinical Infectious Diseases* [13]—have been developed, and some of them have even been approved by the US Food and Drug Administration (e.g., daptomycin, tigecycline, and linezolid). However, tigecycline and linezolid are bacteriostatic rather than bactericidal. Bactericidal activity is important for therapeutic efficacy in certain infections, such as endocarditis, meningitis, and infections in neutropenic

patients. Although once-daily daptomycin is bactericidal and approved for *S. aureus* bacteremia, including endocarditis, it is not active against *S. aureus* pneumonia [14]. Other not yet approved drugs, such as second-generation glycopeptides, have a smaller spectrum of antimicrobial activity. Iclaprim, a folate inhibitor with bactericidal activity against MRSA and gram-negative pathogens, is still being studied in clinical trials [15].

In infectious diseases, survival is significantly improved when the initial choice of antibiotics is “appropriate,” which is defined as all isolated pathogens being susceptible to >1 of the antimicrobial agents administered [16]. In addition, multiple studies provide strong evidence that rapid therapy improves outcome, including that of MRSA infection [6, 17, 18].

Complicated skin and skin-structure infections and pneumonia are the most frequently observed infections due to community-onset MRSA. Currently, the Infectious Diseases Society of America guidelines recommend vancomycin or linezolid for empirical treatment if MRSA is suspected [19]. Microbiological results require several days, and expensive PCR tests must be performed to rule out MRSA infection. Therefore, empirical coverage for serious complicated skin and skin-

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structure infections requires coverage against MRSA infection in hospitals and in areas where MRSA infection is highly endemic.

The carefully conducted randomized, controlled clinical trial by Noel et al. [20] provides strong evidence for noninferiority of ceftobiprole, compared with the combination of vancomycin and ceftazidime, for treatment of complicated skin and skin-structure infections. A similar trial comparing ceftobiprole with vancomycin alone supports the results of this trial, with similar outcomes in both regimens [21]. Other  $\beta$ -lactam antibiotics with activity against MRSA are under development, but no other agent is as advanced in clinical trial testing as ceftobiprole [22]. Ceftobiprole has an increased binding to penicillin-binding protein 2a from methicillin-resistant staphylococci and to penicillin-binding protein 2x in a penicillin-resistant *Streptococcus pneumoniae* strain, resulting in bactericidal activity against these emerging pathogens. In addition, ceftobiprole demonstrates activity against vancomycin-intermediate and -resistant *S. aureus* [22]. Polymicrobial infections are common in complicated skin and skin-structure infections in patients with diabetes; *S. aureus*, including MRSA, and, less commonly, *Pseudomonas aeruginosa* are most frequently identified as causes of such infections. Culture findings of swab specimens from an ulcer are difficult to interpret, but *S. aureus* and *P. aeruginosa* should be covered for treatment if found on culture of tissue specimens or, preferably, bone biopsy specimens. Ceftobiprole has in vitro activity similar to that of ceftazidime or cefepime against Enterobacteriaceae but is more active towards AmpC-mediated  $\beta$ -lactam resistance than is ceftriaxone or ceftazidime [22]. Therefore, a single agent is now available for treatment that previously required combinations of antibiotics. In such infections, ceftobiprole may become the drug of choice—if currently unknown ad-

verse effects do not limit its use in the future.

Activity against enterococci is another advantage of ceftobiprole. Enterococci are frequent colonizers of foot ulcers in patients with diabetes but rarely require treatment. However, serious infections are encountered in the immunocompromised host, in whom resistance to ampicillin and vancomycin has emerged [23].

Ceftobiprole demonstrated a low potential to select for resistance; the highest MIC found in the presence of prolonged serial passages with ceftobiprole at sub-inhibitory concentrations was 8 mg/mL in 1 of 10 strains after 50 passages [24]. However, resistance will most likely emerge if the drug is not used wisely. The adverse effects associated with ceftobiprole are similar to those associated with comparators, with nausea and taste disturbance (dysgeusia) being the most common.

Ceftobiprole may become an important new antibiotic for complicated skin and skin-structure infections before microbiological results allow streamlining of antimicrobial therapy. MRSA coverage with ceftobiprole may improve outcome by enabling early bactericidal therapy in patients admitted to emergency departments because of complicated skin and skin-structure infections not yet identified as being due to MRSA. In addition, mixed infections involving MRSA could be treated with ceftobiprole, replacing vancomycin-based combination therapy. Available data do not allow clinical statements against anaerobic infections. In vitro activity indicates lower ceftobiprole MICs for *Acinetobacter* and *Alcaligenes* species, compared with ceftriaxone and even cefepime [25], but ceftobiprole is not likely to be suitable for gram-negative pathogens expressing extended-spectrum  $\beta$ -lactamases. Ceftobiprole has shown superiority to vancomycin in a rat model of left-side MRSA endocarditis [26].

This promising new agent may be regarded as the first clinically effective cephalosporin against MRSA for treatment of

complicated skin and skin-structure infections, with 2 randomized clinical trials supporting its efficacy [20, 21]. Its additional activity against ampicillin-susceptible enterococci, penicillin-resistant pneumococci, and most Enterobacteriaceae may allow ceftobiprole to be categorized as a new class of cephalosporins; it may be considered to be a member of the fifth-generation cephalosporins.

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