*Original Research*

# Antimicrobial Salvage Therapy for Persistent Staphylococcal Bacteremia Using Daptomycin Plus Ceftaroline

George Sakoulas, MD[1]; Pamela A. Moise, PharmD[2]; Anthony M. Casapao, PharmD[3]; Poochit Nonejuie, PhD[1]; Joshua Olson, BS[1]; Cheryl Y.M. Okumura, PhD[1]; Michael J. Rybak, PharmD[3]; Ravina Kullar, PharmD[4,*]; Abhay Dhand, MD[5]; Warren E. Rose, PharmD[6]; Debra A. Goff, PharmD[7]; Adam M. Bressler, MD[8]; Yuman Lee, PharmD[9]; Joseph Pogliano, PharmD[1]; Scott Johns, PharmD[10]; Glenn W. Kaatz, MD[11]; John R. Ebright, MD[11]; and Victor Nizet, MD[1]

*[1]University of California San Diego School of Medicine, La Jolla, California; [2]Cubist Pharmaceuticals, Lexington, Massachusetts; [3]Eugene Applebaum College of Pharmacy and Health Sciences, School of Medicine, Wayne State University, Detroit, Michigan; [4]Oregon State University/Oregon Health & Science University, Portland, Oregon; [5]New York Medical College, Valhalla, New York; [6]University of Wisconsin Madison School of Pharmacy, Madison, Wisconsin; [7]The Ohio State University Wexner Medical Center, Columbus, Ohio; [8]Dekalb Medical Center, Decatur, Georgia; [9]Maimonides Medical Center, Brooklyn, New York; [10]VA San Diego Healthcare System, San Diego, California; and [11]John D. Dingell VA Medical Center, Wayne State University School of Medicine, Detroit, Michigan*

## ABSTRACT

**Purpose:** Guidelines recommend daptomycin combination therapy as an option for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia after vancomycin failure. Recent data suggest that combining daptomycin with a β-lactam may have unique benefits; however, there are very limited clinical data regarding the use of ceftaroline with daptomycin.

**Methods:** All 26 cases from the 10 medical centers in which ceftaroline plus daptomycin was used for treatment of documented refractory staphylococcal bacteremia from March 2011 to November 2012 were included. In vitro (synergy studies, binding assays, cathelicidin LL-37 killing assays), and in vivo (virulence assays using a murine subcutaneous infection model) studies examining the effects of ceftaroline with daptomycin were also performed.

**Findings:** Daptomycin plus ceftaroline was used in 26 cases of staphylococcal bacteremia (20 MRSA, 2 vancomycin-intermediate *S aureus*, 2 methicillin-susceptible *S aureus* [MSSA], 2 methicillin-resistant S *epidermidis*). Bacteremia persisted for a median of 10 days (range, 3–23 days) on previous antimicrobial therapy. After daptomycin plus ceftaroline was started, the median time to bacteremia clearance was 2 days (range, 1–6 days). In vitro studies showed ceftaroline synergy against MRSA and enhanced MRSA killing by cathelicidin LL-37 and neutrophils. Ceftaroline also induced daptomycin binding in MSSA and MRSA to a comparable degree as nafcillin. MRSA grown in sub-inhibitory concentrations of ceftaroline showed attenuated virulence in a murine subcutaneous infection model.

**Implications:** Ceftaroline plus daptomycin may be an option to hasten clearance of refractory staphylococcal bacteremia. Ceftaroline offers dual benefit via synergy with both daptomycin and sensitization to

*Current affiliation: Cubist Pharmaceuticals, Lexington, Massachusetts.

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innate host defense peptide cathelicidin LL37, which could attenuate virulence of the pathogen. (*Clin Ther*. 2014;36:1317–1333) 

**Key Words:** ceftaroline, daptomycin, MRSA, MRSE bacteremia, MSSA, VISA.

## INTRODUCTION

Bacteremia due to methicillin-resistant *Staphylococcus aureus* (MRSA) poses significant surgical and medical challenges to clinicians and the health care system.[1] The most difficult cases are those that persist despite appropriate antimicrobial therapy and without an easily identified and removable focus, or cases in which an infected biomedical device is identified but cannot be removed without extreme risks to the patient.[2] We have previously shown *S aureus* cross-resistance between cationic antimicrobial host defense peptides (HDPs) of the human innate immune system and vancomycin and daptomycin,[3,4] the only antibiotics approved by the US Food and Drug Administration for the treatment of MRSA bacteremia. These data portend a worrisome scenario in clinical cases in which the pathogen resists eradication and resistance to these agents could develop simultaneously under continuous selective pressures, not just by administered antibiotics but also by HDPs. Thus, the sense of clinical urgency in eradicating these infections is just becoming realized.

We have previously described very successful outcomes in patients with refractory MRSA bacteremia using combination therapy with daptomycin and an antistaphylococcal β-lactam.[5] In addition, development of daptomycin resistance by MRSA in vitro was suppressed in the presence of antistaphylococcal β-lactams.[6]

Ceftaroline was approved by the US Food and Drug Administration in 2010, and it became the first β-lactam available in the United States in 2011 with in vitro and in vivo MRSA activity for the treatment of bacterial skin and skin structure infections.[7] We anticipated that the combination of daptomycin plus ceftaroline therapy might exhibit superior activity against MRSA given the following: (1) the demonstrated synergy between daptomycin and β-lactams[5]; (2) the intrinsic activity of ceftaroline against MRSA[7]; (3) the observed decrease in *S aureus* ceftaroline MIC in *S aureus* upon loss of daptomycin susceptibility[8]; and (4) a recent case in which daptomycin plus ceftaroline was used successfully in salvage therapy with supporting in vitro data.[9]

In the present article, we report the use of daptomycin and ceftaroline as a salvage antimicrobial regimen in the treatment of refractory staphylococcal bacteremia at 10 US medical centers. In vitro synergy of ceftaroline plus daptomycin against MRSA is demonstrated and correlated to enhanced daptomycin binding induced by ceftaroline. Finally, we show that antistaphylococcal activity of human cathelicidin HDPs and neutrophils of the innate immune system are significantly increased by ceftaroline.

## MATERIALS AND METHODS

### Clinical Cases

All 26 cases from the 10 medical centers in which ceftaroline plus daptomycin was used for the treatment of documented refractory staphylococcal bacteremia from March 2011 to November 2012 were included (Figures 1 and 2). Additional case details are outlined in Table I. Participating institutions included the following: Sharp Memorial Hospital, San Diego, California; Detroit Medical Center, Detroit, Michigan; Oregon Health & Science University Hospital, Portland, Oregon; Westchester Medical Center, Valhalla, New York; University of Wisconsin Hospital, Madison, Wisconsin; The Ohio State University Wexner Medical Center, Columbus, Ohio; Dekalb Medical Center, Decatur, Georgia; Maimonides Medical Center, Brooklyn, New York; VA San Diego Healthcare System, San Diego, California; and John D. Dingell VA Medical Center, Detroit, Michigan. Approval or waiver from each center's institutional review board was obtained where appropriate based on the number of cases per site.

### Bacterial Isolates

One MRSA isolate (SA1, case 23, isolate 2, daptomycin MIC 1.0–2.0 mg/L; ceftaroline MIC 1 mg/L; nafcillin MIC 8 mg/L) and 1 methicillin-susceptible *S aureus* (MSSA) isolate (LUC77, case 22, daptomycin MIC 1.0 mg/L; ceftaroline MIC 0.25 mg/L; nafcillin MIC 0.5 mg/L) available from the case series were chosen for further in vitro analyses. SA1 was determined to have a daptomycin MIC of 1 mg/L by using broth microdilution testing but an MIC of 2 mg/L by Epsilometer test (Etest, BioMerieux, Durham, NC). In vivo mouse studies described in the following text were performed on previously published strain MRSA