

# Delafloxacin in Acute Bacterial Skin and Skin Structure Infections

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Skin and soft tissue infections (SSTIs) are among the most frequent infection-related reasons for visits to primary care, emergency department, and hospital settings. In the current supplement, Kaye et al review the current epidemiologic literature suggesting that SSTI visits in various settings have risen between 125% and 165% over the last 10 years. Kaye et al, [1] describe the economic consequences of SSTI (US\$13.8 billion) and suggest that more efficient use of healthcare resources, including ambulatory management and shorter hospitalization, could abrogate the cost of SSTI in the United States [2].

The main causes of SSTI remain *Staphylococcus aureus* and  $\beta$ -hemolytic streptococci. Indeed, Kaye et al argue that community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has played a key role in the rising burden of SSTI. However, in a departure from the traditional SSTI narratives, Kaye et al review the role of gram-negative and mixed gram-positive and gram-negative infections in SSTI. The authors argue that there is a subset of SSTI—namely, healthcare-associated SSTI, perineal SSTI, and abdominal surgical site infections—where gram-negative pathogens play an important role. Kaye et al describe the clinical implications of inappropriate initial antibiotic therapy, closing the argument that clinicians need to consider the possibility of pathogens other than susceptible gram-positive organisms.

Golan provides a review of SSTI treatment that also breaks from the traditional narrative, by providing optimism for anti-infective drug availability and development [3]. Golan describes the current SSTI guidelines and provides perspective on the clinical data supporting the use of more traditional antimicrobials, recently approved antimicrobials, and novel agents in late-stage clinical development. Golan highlights how novel agents can be used to meet the particular needs of SSTI in the United States—in

particular, how agents with gram-positive and gram-negative activity, such as ceftaroline, delafloxacin, and potentially omadacycline, could provide key options for some patients.

Antimicrobial activity is a critical factor when considering treatment of SSTI. Shortridge and Flamm provide a comprehensive review of published data on how dalbavancin, tedizolid, oritavancin, and delafloxacin perform in susceptibility testing among pathogens that cause SSTI [4]. Although the article does not contain all possible comparative data, the manuscript does provide evidence for microbiologic efficacy of delafloxacin against both gram-positive and gram-negative pathogens.

Tulkens et al review the novel structure of delafloxacin, an anionic or nonzwitterionic fluoroquinolone with its attendant in vitro, pharmacologic, and pharmacodynamic properties [5]. Delafloxacin has shown an appropriate spectrum of activity for SSTI both in vitro and in animal models. MRSA, including fluoroquinolone-resistant strains, is susceptible to delafloxacin in both in vitro and clinical studies. The implications of an anionic fluoroquinolone are described in terms of the consequence of this novel property and intracellular penetration and antibacterial activity at lower pH. The authors argue that the biologic structure of delafloxacin differentiates the drug from other fluoroquinolones and may provide justification for the reintroduction of fluoroquinolones into the SSTI treatment armamentarium.

Giordano et al review the 2 pivotal phase 3 trials that supported the US Food and Drug Administration's (FDA) approval of delafloxacin for SSTI [6]. A total of 1510 patients were enrolled into these studies in which delafloxacin, both intravenous and oral, was compared with vancomycin with or without aztreonam. As per FDA guidance, an objective response at 48–72 hours was evaluated and reported to be noninferior. At various time points and assessments, delafloxacin was shown to be noninferior to the comparator.

Although there are arguments supporting the use of delafloxacin as a unique fluoroquinolone with a potential role in SSTI, the fluoroquinolone class has had a checkered safety history with several preceding members either being withdrawn or markedly restricted on their labels. The Tulkens et al and Bassetti articles provide some evidence that clinicians should potentially think of delafloxacin differently [7]. For example, Tulkens et al describe that delafloxacin did not demonstrate

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Clinical Infectious Diseases® 2019;68(S3):S191–2

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DOI: 10.1093/cid/ciy1089

QTc prolongation or phototoxicity in positively controlled studies [8]. The FDA-approved label for delafloxacin does not include a safety warning related to QTc prolongation or phototoxicity. The lack of QTc prolongation effect may be particularly important for geriatric populations at higher risk for torsades de pointes. The FDA label for delafloxacin still mentions the potential for peripheral neuropathy, tendinopathy, central nervous system effects, hypersensitivity, and *Clostridium difficile*-associated diarrhea, which are considered class effects. The safety data from pooled clinical trials presented by Bassetti demonstrate that these events were not more common than the comparator arm, but we still await larger safety datasets from real-world settings in higher-risk patients to better understand the safety profile of delafloxacin [9].

SSTIs are common and increasingly complex due to population changes and shifting patterns of the underlying microbiology. Inappropriate antibiotic prescribing and its contingent outcomes could be avoided by better understanding of the range of potential treatment options currently available and in development. Delafloxacin is a fluoroquinolone with unique structure, microbiologic activity, and safety profile that may make the drug an option for some patients.

#### Notes

**Supplement sponsorship.** This supplement is sponsored by Melinta Therapeutics, Inc.

**Potential conflicts of interest.** G. R. C. has received consulting fees from Cempra Pharmaceuticals, PRA International, Furiex Pharmaceuticals, Inimex Pharmaceuticals, Dr Reddy's Laboratories, Cubist, Cerexa/Forest Laboratories, AstraZeneca, GlaxoSmithKline,

Merck, Trius Therapeutics, ContraFect, Theravance, and Astellas; has received research grants from Theravance, Innocoll, and The Medicines Company; and has served on advisory boards of Pfizer, Polymedix, Trius Therapeutics, Seachaid Pharmaceuticals, BioCryst Pharmaceuticals, Durata, Achaogen, ContraFect, and Nabriva. J. M. has served as a consultant and on the advisory boards of Accelerate, Achaogen, Allergan, Melinta, Menarini, Cempra, Thermo Scientific, and Science37; has served on the speaker's bureau for Allergan; and is the president of Expert Stewardship. M. R. has received consulting fees from Merck, Theravance, Bayer, Melinta, and Accelerate; has received research grants from Theravance and The Medicines Company; and serves on the advisory board of Achaogen. All authors have 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.

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