Comparative In Vitro Activities of New Antibiotics for the Treatment of Skin Infections

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Bacterial skin infections result in significant morbidity and have contributed to enhanced health-care resource utilization. The problem is heightened by emerging antimicrobial resistance. Multiple novel agents active against resistant pathogens that cause skin infections—including dalbavancin, tedizolid phosphate, oritavancin, and delafloxacin—have been approved over the past 5 years. Common features of these agents include gram-positive activity and favorable safety. Of these agents, delafloxacin is unique in being active against both gram-positive and gram-negative pathogens that cause skin infections, including those resistant to other antimicrobial agents. It is, therefore, an effective option for the treatment of skin infections.

Keywords. skin infections; antimicrobial susceptibility; delafloxacin; surveillance.

Bacterial skin and skin structure infections—also referred to as skin and soft tissue infections, skin and skin structure infections (SSSI), and (since 2013) acute bacterial skin and skin structure infections (ABSSSI)—impose a significant clinical and economic burden, estimated on the basis of health-care resource utilization. Rates of visits to health-care facilities in the United States for treatment of ABSSSIs increased significantly between 1997 and 2005, from 32.1 to 48.1 visits per 1000 people in the population, representing an increase of 50% and translating into 14.2 million visits in 2005 [1]. Another study reported significant increases in ABSSSI-related hospital admissions, from 1.6% of all hospital admissions in 2005 to 2.0% in 2011 [2]. The current epidemiology and burden of skin infections is discussed in greater detail by Kaye et al in this supplement [X].

The predominant bacterial species associated with skin infections is *S. aureus*, with other gram-positive (eg, *Streptococcus pyogenes*, other Beta hemolytic streptococci, and enterococci) as well as gram-negative species (eg, *Pseudomonas aeruginosa* and *Escherichia coli*) also implicated as causative organisms [3–5].

Of concern is the emergence of resistance to antimicrobial agents over time, particularly among isolates of *S. aureus*, which have shown increasing frequencies of resistance to methicillin (methicillin-resistant *S. aureus* [MRSA]) and other antimicrobial agents globally [5–7]. Moreover, MRSA isolates causing skin infections are often also resistant to macrolides and fluoroquinolones [8, 9]. Increased resistance translates into higher morbidity and costs [10, 11]. An additional concern is the emergence of vancomycin-resistant entercocci (VRE), which can cause wound infections [12]. These concerns prompted efforts to develop new antimicrobial agents that are effective against resistant pathogens, with multiple agents having been approved in the United States within the past decade and additional agents under development for the treatment of ABSSSI [13, 14]. Agents approved in the last 10 years include telavancin, ceftaroline, dalbavancin, tedizolid phosphate, oritavancin, and delafloxacin.

This review provides clinicians with a comparative overview of the antimicrobial activity of antibiotics approved for the treatment of ABSSSI in adults in the United States and Europe over the past 5 years (dalbavancin, tedizolid phosphate, oritavancin, and delafloxacin). Included are studies evaluating the in vitro activity of these agents against both gram-positive and gram-negative pathogens causing ABSSSIs. The antimicrobial activity of these agents is discussed below, with data on activity against gram-positive and gram-negative pathogens being summarized in Tables 1 and 2, respectively.

**Dalbavancin**

Dalbavancin, a second-generation lipoglycopeptide, was approved in the United States and Europe for the treatment of ABSSSIs in adults on the basis of non-inferiority against vancomycin and linezolid [22]. Its activity against gram-positive clinical isolates that cause ABSSSIs has been extensively documented [15, 23–25]. The first study, which evaluated its activity against 81 673 global gram-positive isolates collected between 2002 and 2007, revealed its activity against oxacillin-susceptible and -resistant strains of *S. aureus* (minimum inhibitory concentration [MIC] 0.06/0.06 mg/L for both) and against coagulase-negative staphylococci (CoNS; MIC ≤0.03/0.06 mg/L...
Table 1. Activity of Antimicrobial Agents Approved During the Past 5 Years Against Gram-positive Pathogens Causing Skin and Skin Structure Infections

| Organism Group and Antimicrobial Agent (Number of Isolates) | Location (Year[s] of Isolation) | % of Isolates Susceptible by the Following Criteria: | MIC (µg/mL) | Author (Year) [Reference] |
|----------------------------------------------------------|---------------------------------|---------------------------------------------------|-------------|---------------------------|
|                                                          |                                 | CLSI EUCAST                                        | 50%         | 90%          | Range                |
| **Staphylococcus aureus**                                  |                                 |                                                   |             |             |                      |
| Dalbavancin; oxacillin-susceptible (27,052)                | Global (2002–2007)              | – –                                               | 0.06        | 0.06        | ≤0.03 to 0.25        | Biedenbach et al (2009) [15] |
| Dalbavancin; oxacillin-resistant (19,721)                  | Global (2002–2007)              | – –                                               | 0.06        | 0.06        | ≤0.03 to 0.5         | Biedenbach et al (2009) [15] |
| Tedizolid (7813)                                          | United States and Europe (2009–2013) | 99.8 99.8                                           | 0.25        | 0.5         | ≤0.015 to 2          | Bensaci & Sahm (2017) [16] |
| Delafloxacin (1350)                                       | United States and Europe (2014) | – –                                               | ≤0.004      | 0.25        | ≤0.004 to 4          | Pfaller et al (2017) [17] |
| Delafloxacin (903)                                        | Europe and Surrounding Areas (2014–2016) | – –                                               | ≤0.004      | 0.25        | ≤0.004 to >2         | Huband et al (2017) [18] |
| Delafloxacin (3163)                                       | United States (2014–2016)       | – –                                               | 0.008       | 0.25        | –                    | Shortridge et al (2017) [19] |
| Delafloxacin (9355)                                       | United States and Europe (2014–2016) | 88.9 –                                               | –           | 0.5         | –                    | Flamm et al (2017) [20] |
| **MRSA**                                                  |                                 |                                                   |             |             |                      |
| Tedizolid (3234)                                          | United States and Europe (2009–2013) | 99.6 99.6                                           | 0.25        | 0.5         | ≤0.015 to 2          | Bensaci & Sahm (2017) [16] |
| Oritavancin (not reported)                                | United States and Europe (2010–2013) | 98.4 (US)/98.9 (EU)*                                | –           | 0.03 (US)/0.03 (EU) | 0.06 (US)/0.06 (EU) | Mendes et al (2015) [21] |
| Delafloxacin (573)                                        | United States and Europe (2014) | – –                                               | 0.06        | 0.5         | ≤0.004 to 4          | Pfaller et al (2017) [17] |
| Delafloxacin (177)                                        | Europe and Surrounding Areas (2014–2016) | – –                                               | 0.25        | 1           | ≤0.004 to >2         | Huband et al (2017) [18] |
| Delafloxacin (1437)                                       | United States (2014–2016)       | – –                                               | 0.12        | 0.5         | –                    | Shortridge et al (2017) [19] |
| Delafloxacin (3583)                                       | United States and Europe (2014–2016) | 74.4 –                                               | 0.12        | 1           | –                    | Flamm et al (2017) [20] |
| **MSSA**                                                  |                                 |                                                   |             |             |                      |
| Tedizolid (4579)                                          | United States and Europe (2009–2013) | 99.9 99.9                                           | 0.25        | 0.5         | ≤0.015 to 1          | Bensaci & Sahm (2017) [16] |
| Delafloxacin (777)                                        | United States and Europe (2014) | – –                                               | ≤0.004      | 0.008       | ≤0.004 to 4          | Pfaller et al (2017) [17] |
| Delafloxacin (1726)                                       | United States (2014–2016)       | – –                                               | 0.008       | 0.25        | –                    | Shortridge et al (2017) [19] |
| **Coagulase-negative Staphylococci**                      |                                 |                                                   |             |             |                      |
| Dalbavancin; oxacillin-susceptible (2836)                 | Global (2002–2007)              | – –                                               | ≤0.03       | 0.06        | ≤0.03 to 1           | Biedenbach et al (2009) [15] |
| Dalbavancin; oxacillin-resistant (9472)                   | Global (2002–2007)              | – –                                               | ≤0.03       | 0.12        | ≤0.03 to 2           | Biedenbach et al (2009) [15] |
| Tedizolid (623)                                           | United States and Europe (2009–2013) | – 99.0                                             | 0.12        | 0.25        | ≤0.008 to 4          | Bensaci & Sahm (2017) [16] |
| Oritavancin (not reported)                                | United States and Europe (2010–2013) | – (US)/– (EU)*                                     | –           | 0.015 (US)/0.03 (EU) | 0.06 (US)/0.06 (EU) | Mendes et al (2015) [21] |
| Delafloxacin (165)                                        | Europe and Surrounding Areas (2014–2016) | – –                                               | 0.15        | 0.5         | ≤0.004 to >2         | Huband et al (2017) [18] |
| Delafloxacin (228)                                        | United States (2014–2016)       | – –                                               | 0.015       | 0.5         | –                    | Shortridge et al (2017) [19] |
| Delafloxacin (1575)                                       | United States and Europe (2014–2016) | – –                                               | 0.015       | 0.5         | –                    | Flamm et al (2017) [20] |
| **β-hemolytic streptococci**                              |                                 |                                                   |             |             |                      |
| Tedizolid (70)                                            | United States and Europe (2009–2013) | – 100.0                                             | 0.12        | 0.25        | ≤0.008 to 0.25       | Bensaci & Sahm (2017) [16] |
| Dalbavancin (5316)                                        | Global (2002–2007)              | – –                                               | ≤0.03       | ≤0.03       | ≤0.03 to 0.25        | Biedenbach et al (2009) [15] |
| **Viridans Group Streptococci**                           |                                 |                                                   |             |             |                      |
| Dalbavancin (2148)                                        | Global (2002–2007)              | – –                                               | ≤0.03       | ≤0.03       | ≤0.03 to 0.12        | Biedenbach et al (2009) [15] |
| Tedizolid (51)                                            | United States and Europe (2009–2013) | – –                                               | 0.12        | 0.25        | ≤0.015 to 0.25       | Bensaci & Sahm (2017) [16] |
| Delafloxacin (294)                                        | United States and Europe (2014) | – –                                               | 0.015       | 0.03        | ≤0.004 to 2          | Pfaller et al (2017) [17] |
| Organism Group and Antimicrobial Agent (Number of Isolates) | Location (Year[s] of Isolation) | % of Isolates Susceptible by the Following Criteria: | MIC (µg/mL) | Author (Year) [Reference] |
|----------------------------------------------------------|--------------------------------|-------------------------------------------------|-------------|--------------------------|
|                                                          |                                | CLSI                        | EUCAST                        | 50% | 90% | Range |                                  |
| **Streptococcus pyogenes**                               |                                 |                              |                              |     |     |       |                                  |
| Tedizolid (684)                                          | United States and Europe (2009–2013) | 100.0                     | 100.0                        | 0.12 | 0.25 | ≤0.015 to 0.25 | Bensaci & Sahm (2017) [16] |
| Oritavancin (not reported)                               | United States and Europe (2010–2013) | 98.8 (US)/98.4 (EU)*        | –                            | 0.03 (US)/0.03 (EU) | 0.12 (US)/0.12 (EU) | – | Mendes et al (2015) [21] |
| Delafloxacin (433)                                       | United States and Europe (2014)     | –                            | –                            | 0.008 | 0.015 | ≤0.004 to 0.03 | Pfaller et al (2017) [17] |
| Delafloxacin (1699)                                      | United States and Europe (2014–2016) | >99.9                       | –                            | 0.015 | 0.03  | –       | Flamm et al (2017) [20] |
| **Streptococcus agalactiae**                             |                                 |                              |                              |     |     |       |                                  |
| Tedizolid (715)                                          | United States and Europe (2009–2013) | 100.0                     | 100.0                        | 0.25 | 0.25 | ≤0.015 to 0.5 | Bensaci & Sahm (2017) [16] |
| Oritavancin (not reported)                               | United States and Europe (2010–2013) | 97.9 (US)/98.0 (EU)*        | –                            | 0.03 (US)/0.03 (EU) | 0.12 (US)/0.12 (EU) | – | Mendes et al (2015) [21] |
| Delafloxacin (225)                                       | United States and Europe (2014)     | –                            | –                            | 0.008 | 0.015 | ≤0.004 to 0.5 | Pfaller et al (2017) [17] |
| Delafloxacin (827)                                       | United States and Europe (2014–2016) | 98.7                       | –                            | 0.015 | 0.03  | –       | Flamm et al (2017) [20] |
| **Streptococcus dysgalactiae**                           |                                 |                              |                              |     |     |       |                                  |
| Oritavancin (not reported)                               | United States and Europe (2010–2013) | 100.0 (US)/98.3 (EU)*       | –                            | 0.06 (US)/0.06 (EU) | 0.25 (US)/0.5 (EU) | – | Mendes et al (2015) [21] |
| Delafloxacin (132)                                       | United States and Europe (2014)     | –                            | –                            | 0.008 | 0.015 | ≤0.004 to 0.03 | Pfaller et al (2017) [17] |
| **Enterococcus faecalis**                                |                                 |                              |                              |     |     |       |                                  |
| Tedizolid (868)                                          | United States and Europe (2009–2013) | 99.4                       | –                            | 0.25 | 0.5   | ≤0.015 to 1 | Bensaci & Sahm (2017) [16] |
| Oritavancin (not reported)                               | United States and Europe (2010–2013) | 95.6 (US)/99.3 (EU)*        | –                            | 0.015 (US)/0.015 (EU) | 0.06 (US)/0.06 (EU) | – | Mendes et al (2015) [21] |
| Delafloxacin (450)                                       | United States and Europe (2014)     | –                            | –                            | 0.06  | 1     | ≤0.004 to 2 | Pfaller et al (2017) [17] |
| Delafloxacin (173)                                       | Europe and Surrounding Areas (2014–2016) | –                          | –                            | 0.12  | >4    | 0.015 to >4 | Huband et al (2017) [18] |
| Delafloxacin (235)                                       | United States (2014–2016)           | –                            | –                            | 0.12  | 1     | –       | Shortridge et al (2017) [19] |
| **Vancomycin-susceptible Enterococcus faecalis**         |                                 |                              |                              |     |     |       |                                  |
| Tedizolid (829)                                          | United States and Europe (2009–2013) | 99.4                       | –                            | 0.25 | 0.5   | ≤0.015 to 1 | Bensaci & Sahm (2017) [16] |
| **Enterococcus faecium**                                 |                                 |                              |                              |     |     |       |                                  |
| Tedizolid (372)                                          | United States and Europe (2009–2013) | –                            | –                            | 0.25 | 0.5   | 0.03 to 4 | Bensaci & Sahm (2017) [16] |
| Delafloxacin (295)                                       | United States and Europe (2014)     | –                            | –                            | >4    | >4    | 0.008 to >4 | Pfaller et al (2017) [17] |
| **Vancomycin-susceptible Enterococcus faecium**          |                                 |                              |                              |     |     |       |                                  |
| Tedizolid (168)                                          | United States and Europe (2009–2013) | –                            | –                            | 0.25 | 0.5   | 0.03 to 1 | Bensaci & Sahm (2017) [16] |
| Oritavancin (not reported)                               | United States and Europe (2010–2013) | – (US)/– (EU)*               | –                            | ≤0.008 (US)/≤0.008 (EU) | ≤0.008 (US)/≤0.008 (EU) | – | Mendes et al (2015) [21] |
| **Vancomycin-resistant Enterococcus faecium**            |                                 |                              |                              |     |     |       |                                  |
| Tedizolid (202)                                          | United States and Europe (2009–2013) | –                            | –                            | 0.25 | 0.5   | 0.12 to 4 | Bensaci & Sahm (2017) [16] |
| Oritavancin (not reported)                               | United States and Europe (2010–2013) | – (US)/– (EU)*               | –                            | 0.06 (US)/0.15 (EU) | 0.12 (US)/0.06 (EU) | – | Mendes et al (2015) [21] |

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; EU, Europe; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus.

*The interpretive criteria used were those approved by the US Food and Drug Administration.
for oxacillin-susceptible CoNS and ≤0.03/0.12 mg/L for oxacillin-resistant CoNS; Table 1) [15]. Both β-hemolytic and viridans group streptococci (VGS) were highly susceptible (MIC<sub>50/90</sub> ≤0.03/≤0.03 mg/L; Table 1). A subsequent analysis of dalbavancin’s activity against 1555 isolates, collected in 2011 in the United States, revealed its activity against both methicillin-susceptible S. aureus (MSSA) and MRSA (MIC<sub>50/90</sub> 0.06/0.06 mg/L for both) [23]. An evaluation of its activity against 1600 gram-positive isolates, collected in the United States in 2012, documented its stable activity over time since the initial evaluations (MIC<sub>50/90</sub> 0.06/0.06 mg/L against MSSA, MRSA, and CoNS; ≤0.03/≤0.03 mg/L against β-hemolytic streptococci; and ≤0.03/0.06 against VGS) [24]. An analysis of dalbavancin’s activity against 8527 gram-positive isolates responsible for SSSIs in the United States and Europe, collected between 2011 and 2013, revealed MIC<sub>50/90</sub> values of 0.06/0.06 mg/L against S. aureus isolates and ≤0.03/≤0.03 mg/L against VGS and β-hemolytic streptococci isolates from both regions [25].

Tedizolid
Tedizolid, available as the prodrug tedizolid phosphate, is an oxazolidinone approved in the United States and Europe for the treatment of ABSSSI following a demonstration of non-inferiority versus linezolid [26, 27]. An evaluation of its activity against 11,231 gram-positive clinical isolates, collected between 2009 and 2013 in the United States and Europe, revealed it to be highly active against S. aureus (MIC<sub>50/90</sub> 0.25/0.5 mg/L), regardless of methicillin resistance, as well as against β-hemolytic streptococci, VGS, S. pyogenes (MIC<sub>50/90</sub> 0.12/0.25 mg/L for all), and Enterococcus faecalis (MIC<sub>50/90</sub> 0.25/0.5 mg/L; Table 1) [16]. A subsequent analysis of 3929 S. aureus isolates, collected from 12 countries between 2014 and 2016, revealed tedizolid to be 4-fold more active compared with linezolid (MIC<sub>50</sub> 0.5 mg/L versus 2 mg/L), with tedizolid being equally active against both MSSA and MRSA (MIC<sub>50</sub> 0.25 mg/L) [28].

Oritavancin
Oritavancin is another lipoglycopeptide available for the treatment of ABSSSI in adults caused by gram-positive pathogens, including MRSA, and was approved based on non-inferiority versus vancomycin [29]. An analysis of activity against 13,262 isolates causing ABSSSIs, collected between 2010 and 2013, demonstrated its activity against S. aureus (MIC<sub>50/90</sub> ≤0.03/0.06 mg/L, with 98.8% of all isolates being susceptible) and CoNS (MIC<sub>50/90</sub> 0.015 mg/L and 0.03 mg/L in isolates from the United States and Europe, respectively; Table 1) [21]. Isolates of E. faecalis were all susceptible at ≤0.5 mg/L, although vancomycin-resistant isolates were 16-fold less susceptible (MIC<sub>50/90</sub> 0.25/0.5 mg/L) than vancomycin-susceptible isolates (MIC<sub>50/90</sub> 0.015/0.03 mg/L; 99.2–99.8% susceptible). Higher MICs (MIC<sub>50/90</sub> 0.03/0.12 mg/L) were exhibited by Van A–containing strains of Enterococcus faecium, while Van B–containing and vancomycin-susceptible strains showed identical MICs (MIC<sub>50/90</sub> 0.004/0.008 mg/L). Strong activity was also seen against S. pyogenes (MIC<sub>50/90</sub> 0.03/0.12 mg/L; 98.4%-98.6% susceptible), while activity was slightly lower against S. dysgalactiae (MIC<sub>50/90</sub> 0.06/0.25 mg/L; ≥98.3% susceptible).

Delafloxacin
Delafloxacin is a non-zwitterionic (anionic) fluoroquinolone approved for the treatment of ABSSSI based on efficacy versus vancomycin and linezolid [30–32]. Its activity against 6485 clinical isolates, collected in 2014 from the United States and Europe, including the gram-positive pathogens S. aureus (MIC<sub>50/90</sub> ≤0.04/0.25 mg/L), Enterococcus faecalis (MIC<sub>50/90</sub> 0.06/1 mg/L), S. pyogenes (MIC<sub>50/90</sub> 0.008/0.015 mg/L), Streptococcus agalac-tiae (MIC<sub>50/90</sub> 0.008/0.015 mg/L), and S. dysgalactiae (MIC<sub>50/90</sub> ≤0.008/0.015 mg/L), has been demonstrated (Table 1) [17]. Delafloxacin’s activity against gram-negative pathogens, including E. coli (MIC<sub>50/90</sub> 0.03/4 mg/L; against extended-spectrum β-lactamase [ESBL]-positive isolates: MIC<sub>50/90</sub> 2/>4 mg/L), Klebsiella pneumoniae (MIC<sub>50/90</sub> ≤0.06/>4 mg/L; against ESBL-positive isolates: MIC<sub>50/90</sub> ≤1/>4 mg/L), Enterobacter spp. (MIC<sub>50/90</sub> 0.06/1 mg/L), and P. aeruginosa (MIC<sub>50/90</sub> 0.25/>4 mg/L), was also demonstrated (Table 2). It has shown high activity even against levofloxacin–non-susceptible isolates of S. aureus (both MRSA and MSSA) that cause ABSSSI [33].

In 2 subsequent studies, delafloxacin’s activity was confirmed against clinical isolates, including fluoroquinolone-resistant isolates, responsible for ABSSSI in Europe and the United States between 2014 and 2016 (Tables 1 and 2) [18, 19]. Together, these studies evaluating activity against ABSSSI isolates, collected over a 3-year period from 2 geographic regions, highlight its continued activity over time.

DISCUSSION AND CONCLUSIONS
Collectively, the reviewed studies highlight the comparative in vitro activity of agents approved over the past 5 years against bacterial pathogens that cause skin infections. An important characteristic of these antibiotics is their broad-spectrum activity against gram-positive pathogens implicated in skin infections, including resistant organisms [34–38]. Moreover, delafloxacin is also active against gram-negative pathogens [17–20]. Notably, delafloxacin has been shown to be significantly more active against S. aureus at a low pH, as compared with moxifloxacin, with this higher activity being attributed to its higher intracellular accumulation at a lower pH, which, in turn, is a function of it being predominantly uncharged at the low pH [39] (see also the review by Tulkens and colleagues in this issue [X]). The broad spectrum of activity of delafloxacin augurs well for addressing an important, unmet need: namely, the emergence of resistance and a consequent reduction in efficacy.

The trend of resistance in S. aureus, particularly MRSA, has been tracked globally by the SENTRY Antimicrobial Surveillance Program [40]. Over the last 20 years (1997–2016),
the rise of MRSA reached its peak 10 years ago and has been decreasing since then in all regions. In addition, the susceptibility of some older agents has increased, and may be associated with the emergence of epidemic clones (eg, USA 300) with fewer resistance determinants. Several of the newer agents discussed in this review have maintained excellent in vitro activity against *S. aureus*. The trend of increasing susceptibility was not the same for enterococci, with the prevalence of VRE increasing in all regions over the same period [41]. However, newer agents have maintained their excellent in vitro activities against VRE.

The choice of antimicrobial agents for the treatment of skin infections depends largely on the agent’s spectrum of activity, including against resistant pathogens. Delafloxacin, with its activity against both gram-positive (including MRSA) and gram-negative pathogens and its heightened activity in the acidic environments characteristic of skin abscesses, presents an effective therapeutic option for the treatment of skin infections.

**Notes**

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