Clinical Infectious Diseases

SUPPLEMENT ARTICLE

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 *Staphylococcus 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 enterococcus (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 [$MIC_{50/90}$] 0.06/0.06 mg/L for both) and against coagulase-negative staphylococci (CoNS; $MIC_{50/90}$ ≤0.03/0.06 mg/L

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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	–	0.008	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)[a]	–	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 (3563)	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)[a]	–	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]

Table 1. Continued

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)	98.6 (US)/98.4 (EU)[a]	–	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)[a]	–	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)[a]	–	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)[a]	–	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)[a]	–	≤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)[a]	–	0.06 (US)/ 0.015 (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*; MIC, minimum inhibitory concentration; MSSA, methicillin-susceptible *Staphylococcus aureus*.

[a]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 ($MIC_{50/90}$ ≤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 ($MIC_{50/90}$ 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 ($MIC_{50/90}$, 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 $MIC_{50/90}$ values of 0.06/0.06 mg/L against *S. aureus* isolates and ≤0.03/≤0.03 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* ($MIC_{50/90}$ 0.25/0.5 mg/L), regardless of methicillin resistance, as well as against β-hemolytic streptococci, VGS, *S. pyogenes* ($MIC_{50/90}$ 0.12/0.25 mg/L for all), and *Enterococcus faecalis* ($MIC_{50/90}$ 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_{90} 0.5 mg/L versus 2 mg/L), with tedizolid being equally active against both MSSA and MRSA (MIC_{90} 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* ($MIC_{50/90}$ 0.03/0.06 mg/L, with 98.8% of all isolates being susceptible) and CoNS (MIC_{50} 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 ($MIC_{50/90}$ 0.25/0.5 mg/L) than vancomycin-susceptible isolates ($MIC_{50/90}$ 0.015/0.03 mg/L; 99.2–99.8% susceptible). Higher MICs ($MIC_{50/90}$ 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 ($MIC_{50/90}$ 0.004/0.008 mg/L). Strong activity was also seen against *S. pyogenes* ($MIC_{50/90}$ 0.03/0.12 mg/L; 98.4%-98.6% susceptible), while activity was slightly lower against *S. dysgalactiae* ($MIC_{50/90}$ 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* ($MIC_{50/90}$ ≤0.004/0.25 mg/L), *Enterococcus faecalis* ($MIC_{50/90}$ 0.06/1 mg/L), *S. pyogenes* ($MIC_{50/90}$ 0.008/0.015 mg/L), *Streptococcus agalactiae* ($MIC_{50/90}$ 0.008/0.015 mg/L), and *S. dysgalactiae* ($MIC_{50/90}$ 0.008/0.015 mg/L), has been demonstrated (Table 1) [17]. Delafloxacin's activity against gram-negative pathogens, including *E. coli* ($MIC_{50/90}$ 0.03/4 mg/L; against extended-spectrum β-lactamase [ESBL]-positive isolates: $MIC_{50/90}$ 2/>4 mg/L), *Klebsiella pneumoniae* ($MIC_{50/90}$ 0.06/>4 mg/L; against ESBL-positive isolates: $MIC_{50/90}$ 4/>4 mg/L), *Enterobacter* spp. ($MIC_{50/90}$ 0.06/1 mg/L), and *P. aeruginosa* ($MIC_{50/90}$ 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),

Table 2. Activity of Delafloxacin Against Gram-negative Pathogens Causing Skin and Skin Structure Infections

Organism Group Location (Year[s] of Isolation)	Number of Isolates	% of Isolates Susceptible by the Following Criteria:		MIC (μg/mL)			Author (Year) [Reference]
		CLSI	EUCAST	50%	90%	Range	
Pseudomonas aeruginosa							
United States and Europe (2014)	200	–	–	0.25	>4	0.015 to >4	Pfaller et al (2017) [17]
Europe and Surrounding Areas (2014–2016)	275	–	–	0.5	>4	0.03 to >4	Huband et al (2017) [18]
United States (2014–2016)	224	–	–	0.5	4	–	Shortridge et al (2017) [19]
United States and Europe (2014–2016)	2181	63.6	–	0.5	>4	–	Flamm et al (2017) [20]
Enterobacteriaceae							
United States (2014–2016)	1325	–	–	0.12	2	–	Shortridge et al (2017) [19]
United States and Europe (2014–2016)	12468	66.7	–	0.12	4	–	Flamm et al (2017) [20]
***Enterobacter* spp.**							
United States and Europe (2014)	384	–	–	0.06	1	≤0.004 to >4	Pfaller et al (2017) [17]
Escherichia coli							
United States and Europe (2014)	500	–	–	0.03	4	≤0.004 to >4	Pfaller et al (2017) [17]
Europe and Surrounding Areas (2014–2016)	262	–	–	0.06	4	0.015 to >4	Huband et al (2017) [18]
United States and Europe (2014–2016)	4436	64.8	–	0.06	4	–	Flamm et al (2017) [20]
ESBL-positive *Escherichia coli*							
United States and Europe (2014)	92	–	–	2	>4	0.008 to >4	Pfaller et al (2017) [17]
Klebsiella pneumoniae							
United States and Europe (2014)	389	–	–	0.06	>4	0.015 to >4	Pfaller et al (2017) [17]
United States and Europe (2014–2016)	2417	64.8	–	0.12	>4	–	Flamm et al (2017) [20]
ESBL-positive *Klebsiella pneumoniae*							
United States and Europe (2014)	102	–	–	4	>4	0.06 to >4	Pfaller et al (2017) [17]

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum β-lactamase; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration.

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

Author contributions. Both authors were involved in the drafting, review, and approval of the manuscript for submission.

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References

1. Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. Arch Intern Med **2008**; 168:1585–91.

2. Kaye KS, Patel DA, Stephens JM, Khachatryan A, Patel A, Johnson K. Rising United States hospital admissions for acute bacterial skin and skin structure infections: recent trends and economic impact. PLOS One **2015**; 10:e0143276.
3. Summanen PH, Talan DA, Strong C, et al. Bacteriology of skin and soft-tissue infections: comparison of infections in intravenous drug users and individuals with no history of intravenous drug use. Clin Infect Dis **1995**; 20(Suppl 2):S279–82.
4. Moet GJ, Jones RN, Biedenbach DJ, Stilwell MG, Fritsche TR. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY Antimicrobial Surveillance Program (1998–2004). Diagn Microbiol Infect Dis **2007**; 57:7–13.
5. Ray GT, Suaya JA, Baxter R. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: a retrospective population-based study. BMC Infect Dis **2013**; 13:252.
6. Lee GC, Dallas SD, Wang Y, et al. Emerging multidrug resistance in community-associated *Staphylococcus aureus* involved in skin and soft tissue infections and nasal colonization. J Antimicrob Chemother **2017**; 72:2461–8.
7. Loewen K, Schreiber Y, Kirlew M, Bocking N, Kelly L. Community-associated methicillin-resistant *Staphylococcus aureus* infection: Literature review and clinical update. Can Fam Physician **2017**; 63:512–20.
8. Baek YS, Jeon J, Ahn JW, Song HJ. Antimicrobial resistance of *Staphylococcus aureus* isolated from skin infections and its implications in various clinical conditions in Korea. Int J Dermatol **2016**; 55:e191–7.
9. Maina EK, Kiiyukia C, Wamae CN, Waiyaki PG, Kariuki S. Characterization of methicillin-resistant *Staphylococcus aureus* from skin and soft tissue infections in patients in Nairobi, Kenya. Int J Infect Dis **2013**; 17:e115–9.
10. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, Camargo CA Jr. Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*. Ann Emerg Med **2008**; 51:291–8.
11. Suaya JA, Mera RM, Cassidy A, et al. Incidence and cost of hospitalizations associated with *Staphylococcus aureus* skin and soft tissue infections in the United States from 2001 through 2009. BMC Infect Dis **2014**; 14:296.
12. Rivera AM, Boucher HW. Current concepts in antimicrobial therapy against select gram-positive organisms: methicillin-resistant *Staphylococcus aureus*, penicillin-resistant pneumococci, and vancomycin-resistant enterococci. Mayo Clin Proc **2011**; 86:1230–43.
13. Abbas M, Paul M, Huttner A. New and improved? A review of novel antibiotics for Gram-positive bacteria. Clin Microbiol Infect **2017**; 23:697–703.
14. Russo A, Concia E, Cristini F, et al. Current and future trends in antibiotic therapy of acute bacterial skin and skin-structure infections. Clin Microbiol Infect **2016**; 22(Suppl 2):S27–36.
15. Biedenbach DJ, Bell JM, Sader HS, Turnidge JD, Jones RN. Activities of dalbavancin against a worldwide collection of 81,673 gram-positive bacterial isolates. Antimicrob Agents Chemother **2009**; 53:1260–3.
16. Bensaci M, Sahm D. Surveillance of tedizolid activity and resistance: in vitro susceptibility of Gram-positive pathogens collected over 5 years from the United States and Europe. Diagn Microbiol Infect Dis **2017**; 87:133–8.
17. Pfaller MA, Sader HS, Rhomberg PR, Flamm RK. In vitro activity of delafloxacin against contemporary bacterial pathogens from the United States and Europe, 2014. Antimicrob Agents Chemother **2017**; 61:e02609–16.
18. Huband MD, Streit JM, Shortridge D, Flamm RK. In vitro evaluation of delafloxacin activity when tested against contemporary ABSSSI isolates from Europe and surrounding areas (2014–2016): results from the SENTRY Antimicrobial Surveillance Program [poster # P1351]. In: Program and abstracts of European Congress of Clinical Microbiology and Infectious Diseases 2017 (Vienna, Austria). **2017**.
19. Shortridge D, Streit JM, Huband MD, Rhomberg PR, Flamm R. In vitro evaluation of delafloxacin activity when tested against contemporary ABSSSI isolates from the United States (2014–2016): results from the SENTRY Antimicrobial Surveillance Program [poster Sunday 4]. In: Program and abstracts of American Society of Microbiology (ASM) Microbe 2017 (New Orleans, LA). **2017**.
20. Flamm RK, Shortridge D, Huband MD, McCurdy S, Pfaller MA. Activity of delafloxacin when tested against bacterial surveillance isolates collected in the US and Europe during 2014–2016 as part of a global surveillance program [poster #1222]. In: Program and abstracts of ID Week 2017 (San Diego, CA). **2017**.
21. Mendes RE, Farrell DJ, Sader HS, Flamm RK, Jones RN. Activity of oritavancin against Gram-positive clinical isolates responsible for documented skin and soft-tissue infections in European and US hospitals (2010-13). J Antimicrob Chemother **2015**; 70:498–504.
22. Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med **2014**; 370:2169–79.
23. Jones RN, Sader HS, Flamm RK. Update of dalbavancin spectrum and potency in the USA: report from the SENTRY Antimicrobial Surveillance Program (2011). Diagn Microbiol Infect Dis **2013**; 75:304–7.
24. Jones RN, Flamm RK, Sader HS. Surveillance of dalbavancin potency and spectrum in the United States (2012). Diagn Microbiol Infect Dis **2013**; 76:122–3.
25. Mendes RE, Castanheira M, Farrell DJ, Flamm RK, Sader HS, Jones RN. Update on dalbavancin activity tested against Gram-positive clinical isolates responsible for documented skin and skin-structure infections in US and European hospitals (2011-13). J Antimicrob Chemother **2016**; 71:276–8.
26. Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis **2014**; 14:696–705.
27. Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA **2013**; 309:559–69.
28. Karlowsky JA, Hackel MA, Bouchillon SK, Alder J, Sahm DF. In vitro activities of Tedizolid and comparator antimicrobial agents against clinical isolates of Staphylococcus aureus collected in 12 countries from 2014 to 2016. Diagn Microbiol Infect Dis **2017**; 89:151–7.
29. Corey GR, Kabler H, Mehra P, et al; SOLO I Investigators. Single-dose oritavancin in the treatment of acute bacterial skin infections. N Engl J Med **2014**; 370:2180–90.
30. Kingsley J, Mehra P, Lawrence LE, et al. A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. J Antimicrob Chemother **2016**; 71:821–9.
31. Melinta Therapeutics I. Baxdela (delafloxacin) prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208610s000,208611s000lbl.pdf. Accessed 21 October 2017.
32. Pullman J, Gardovskis J, Farley B, et al; PROCEED Study Group. Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a Phase 3, double-blind, randomized study. J Antimicrob Chemother **2017**; 72:3471–80.
33. McCurdy S, Lawrence L, Quintas M, et al. In vitro activity of delafloxacin and microbiological response against fluoroquinolone-susceptible and nonsusceptible staphylococcus aureus isolates from two phase 3 studies of acute bacterial skin and skin structure infections. Antimicrob Agents Chemother **2017**; 61:e00772–17.
34. Juul JJ, Mullins CF, Peppard WJ, Huang AM. New developments in the treatment of acute bacterial skin and skin structure infections: considerations for the effective use of dalbavancin. Ther Clin Risk Manag **2016**; 12:225–32.
35. Ferrández O, Urbina O, Grau S. Critical role of tedizolid in the treatment of acute bacterial skin and skin structure infections. Drug Des Devel Ther **2017**; 11:65–82.
36. Brade KD, Rybak JM, Rybak MJ. Oritavancin: a new lipoglycopeptide antibiotic in the treatment of gram-positive infections. Infect Dis Ther **2016**; 5:1–15.
37. Gleghorn K, Grimshaw E, Kelly EK. New antibiotics in the management of acute bacterial skin and skin structure infections. Skin Therapy Lett **2015**; 20:7–9.
38. Van Bambeke F. Delafloxacin, a non-zwitterionic fluoroquinolone in Phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics and clinical efficacy. Future Microbiol **2015**; 10:1111–23.
39. Lemaire S, Tulkens PM, Van Bambeke F. Contrasting effects of acidic pH on the extracellular and intracellular activities of the anti-gram-positive fluoroquinolones moxifloxacin and delafloxacin against *Staphylococcus aureus*. Antimicrob Agents Chemother **2011**; 55:649–58.
40. Diekema DJ, Pfaller MA, Shortridge D, Zervos M, Jones RN. Twenty-year trends in antibiotic susceptibility among *Staphylococcus aureus* from the SENTRY antimicrobial surveillance program [poster Friday-425]. In: Program and abstracts of ASM Microbe 2018 (Atlanta, GA). **2018**.
41. Pfaller MA, Mendes RE, Cormican M, Jones RN, Flamm RK. Temporal and geographic variation in antimicrobial susceptibility and resistance patterns of Enterococci: results from the SENTRY Antimicrobial Surveillance Program, 1997–2016 [poster Friday-450]. In: Program and abstracts of ASM Microbe 2018 (Atlanta, GA). **2018**.