

Emerging Treatment Options for Acute Bacterial Skin and Skin Structure Infections and Bloodstream Infections Caused by *Staphylococcus aureus*: A Comprehensive Review of the Evidence

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Abstract: *Staphylococcus aureus* remains an important human pathogen of concern, with mortality rates surpassing 30% in the case of severe systemic infections. Distinguishing methicillin-susceptible *S. aureus* from methicillin-resistant *S. aureus* (MRSA) is fundamental for therapeutic choices. A crucial emerging concept in the treatment of acute bacterial skin and skin structure infections is the availability of various approved agents with anti-MRSA activity, which allow a personalized approach based on the characteristics of any given patient while at the same time remaining in line with high certainty efficacy evidence from large randomized controlled trials. Regarding the treatment of *S. aureus* bloodstream infections (BSI), interesting aspects that may become relevant in the near future are the presence of both old and novel agents in phase-2 or phase-3 of clinical development for this indication, and the pressing need for high certainty evidence to guide the possible use of combination therapy in specific categories or phenotypes of patients with complicated MRSA BSI.

Keywords: *Staphylococcus aureus*, MSSA, MRSA, ABSSSI, BSI, bacteremia

Introduction

Staphylococcus aureus remains an important human pathogen of concern, with mortality rates surpassing 30% in the case of severe systemic infections.^{1–5}

Distinguishing methicillin-susceptible *S. aureus* (MSSA) from methicillin-resistant *S. aureus* (MRSA) is fundamental for therapeutic choices, since, among β -lactam antibiotics, only fifth-generation cephalosporins currently remain active against MRSA (whereas some other anti-staphylococcal β -lactams can be used for treating MSSA infections).^{6,7} This crucial difference has important clinical implications. Indeed, it implies different treatment algorithms (in terms of potential antibiotic choices besides source control whenever necessary) for MSSA and MRSA infections.^{8–10} Regarding the type of staphylococcal infections, acute bacterial skin and skin structure infections (ABSSSI) and bloodstream infections (BSI) are two common conditions that can be caused by MSSA and MRSA.^{11–14}

In this narrative review, we discuss both current and emerging therapies for the treatment of ABSSSI and BSI caused by MSSA and MRSA.

Methods

In December 2021, we performed different PubMed searches using various combinations of the following keywords: ABSSSI*; antimicrobials, BSI; bacteremia; *Staphylococcus aureus*. Subsequently, the full texts of papers pertinent to the

topic were screened, and eventually selected for inclusion and discussion based on authors' judgement of their relevance for the present narrative review. The final manuscript was then structured as follows: (i) current treatment options for *S. aureus* ABSSSI and BSI; (ii) emerging treatment options for *S. aureus* ABSSSI and BSI (drugs in phase-2 or phase-3 of clinical development); (iii) conclusion.

Current Treatment Options for *S. aureus* ABSSSI and BSI

ABSSSI

ABSSSI are a heterogeneous group of diseases, with severity ranging from mild presentation to life-threatening disease.^{15,16} They encompass erysipelas/cellulitis, skin abscesses, and wound infections, and are described as a bacterial skin infection with an area of ≥ 75 cm² in size, considering the area of redness, induration, or oedema.⁹ ABSSSI may be divided into nonpurulent (eg, erysipela, cellulitis) or purulent (eg, skin abscesses).¹⁷ Although *S. aureus* may cause both nonpurulent and purulent ABSSSI, it is of note that it has been reported as the most common cause of purulent ABSSSI in the last decades.^{15,17–20} This has been accompanied by increased rates of complications and recurrences in the case of MRSA skin infection, with a parallel increase in the need for hospitalization and in healthcare costs.^{15,17–20} It is also noteworthy that strains of community-acquired MRSA (CA-MRSA) encoding the virulent factor Panton-Valentine leukocidin have been associated with severe, necrotizing ABSSSI, also in young people.^{21–23}

The choice of the optimal antibiotic treatment of *S. aureus* ABSSSI for any given patient depends on several parameters related to the microorganism, the disease, the patient, and the drug: (i) methicillin resistance; (ii) severity of clinical presentation; (iii) baseline comorbidities; (iv) possible allergies; (v) adherence to treatment; (vi) need for hospitalization; (vii) possibility of outpatient treatment.^{17,24,25} In the case of mild ABSSSI, physicians can consider empirical therapy with amoxicillin-clavulanic acid.^{9,15,26} In the case of severe, proven MSSA ABSSSI requiring hospitalization and intravenous therapy, an antistaphylococcal penicillin should be administered.^{9,16,27} The role of cefazolin as an alternative to antistaphylococcal penicillins for severe MSSA infections is much debated, with some authors suggesting it as a first-line alternative and others as a second-line option (in this latter case as an alternative to clindamycin for patients allergic to penicillins, supported by a lower than previously thought risk of allergic reactions to cefazolin in patients with self-reported penicillin allergy, although administration should be avoided in patients with previous systemic and/or severe reactions to penicillins).^{9,15–17,27,28} For purulent *S. aureus* ABSSSI, such as abscesses, drainage remains the first therapeutic measure whenever feasible, and MRSA coverage (see below) should be considered for empiric therapy in severe cases while waiting for drug susceptibility test or molecular tests for *mecA*.¹⁶

With regard to crucial clinical concepts regarding the treatment of MRSA ABSSSI, it should be highlighted that a large amount of high-level evidence from large randomized controlled trials (RCT) is available about the use of approved antibiotics showing anti-MRSA activity for the treatment of ABSSSI. Although it is true that most of these large RCT were not focused on MRSA (the study populations were usually patients with ABSSSI and not with MRSA ABSSSI), the high certainty evidence for efficacy in ABSSSI treatment can be generalized (usually non-inferiority to vancomycin, which also has anti-MRSA activity), and should support their use for the treatment of MRSA ABSSSI, also considering that results of subgroup analyses of patients with MRSA ABSSSI were frequently in line with results registered in the entire study populations (see Table 1).^{29–62} Concerning patients with uncomplicated skin abscesses, trimethoprim /sulfamethoxazole (TMP/SMX) or clindamycin, in addition to drainage whenever indicated, may be sufficient for outpatient treatment. Indeed, TMP/SMX and clindamycin showed comparable cure rates in RCTs, and both showed improvement compared with placebo (for more details see Table 1, which also shows that the proportion of patients with MRSA infection was 32–53% in RCTs assessing the efficacy of TMP/SMX or clindamycin in outpatients with uncomplicated skin abscesses or mild, uncomplicated skin infections).^{29–33} Against this background, it is worth noting that the local epidemiology of TMP/SMX resistance and clindamycin resistance may also have a relevant role in eventual treatment choices.

For more severe ABSSSI in which MRSA infections is suspected or proven, the scenario is rather unique, since there are currently many options that over the years showed noninferiority (usually to glycopeptides) in RCTs for the treatment of complicated skin and soft tissue infections (cSSTI) or ABSSSI (ie, ceftaroline, dalbavancin, daptomycin, delafloxacin, linezolid, omadacycline, oritavancin, tedizolid, telavancin, tigecycline).^{34–64} Furthermore, favorable results from phase-3

Table I Large RCT Evaluating Agents with Anti-MRSA Activity for the Treatment of ABSSSI or SSTI*

Study, Year [Ref]	Primary Endpoint and Study Population	Intervention Comparator	Results Regarding Primary Endpoint/s in the Primary Study Population/s	Difference (95% CI)	Information on MRSA Subgroups
Boucher et al., 2014 ³⁴ (Pooled results from 2 RCT)	Early clinical response in the intention-to-treat population	<i>Study arms</i> Dalbavancin Vancomycin (with possible switch to oral linezolid)	<i>Early clinical response</i> 525/659 (79.7%) 521/653 (79.8%)	<i>Early clinical response</i> -0.1% (-4.5 to 4.2) (ref)	Investigator-assessed clinical response in patients with MRSA infection was 97.3% (72/74) in the dalbavancin arm and 98.0% (49/50) in the vancomycin arm
Breedt et al., 2005 ³⁵	Clinical success in the clinically evaluable and in the clinically modified intention-to-treat populations	<i>Study arms (CE)</i> Tigecycline Vancomycin plus aztreonam <i>Study arms (c-mITT)</i> Tigecycline Vancomycin plus aztreonam	<i>Clinical success (CE)</i> 200/223 (89.7%) 201/213 (94.4%) <i>Clinical success (c-mITT)</i> 220/261 (84.3%) 225/259 (86.9%)	<i>Clinical success (CE)</i> -4.7% (-10.2 to 0.8) (ref) <i>Clinical success (c-mITT)</i> -2.6% (-9.0 to 3.8) (ref)	Microbiological response in patients with MRSA infection was 83.3% (5/6) in the tigecycline arm and 83.3% (5/6) in the vancomycin plus aztreonam arm
Corey et al., 2010 ³⁸	Clinical cure in the clinically evaluable and the modified intention-to-treat populations	<i>Study arms (CE)</i> Ceftaroline Vancomycin plus aztreonam <i>Study arms (MITT)</i> Ceftaroline Vancomycin plus aztreonam	<i>Clinical cure (CE)</i> 288/316 (91.1%) 280/300 (93.3%) <i>Clinical cure (MITT)</i> 304/351 (86.6%) 297/347 (85.6%)	<i>Clinical cure (CE)</i> -2.2% (-6.6 to 2.1) (ref) <i>Clinical cure (MITT)</i> 1.0% (-4.2 to 6.2) (ref)	Clinical cure in patients with MRSA infection was 95.1% (78/82) in the ceftaroline arm and 95.2% (59/62) in the vancomycin plus aztreonam arm
Corey et al. 2014 ³⁷	Early clinical response in the modified intention-to-treat population	<i>Study arms</i> Oritavancin Vancomycin	<i>Early clinical response</i> 391/475 (82.3%) 378/479 (78.9%)	<i>Early clinical response</i> 3.4% (-1.6 to 8.4) (ref)	Early clinical response in patients with MRSA infection was 80.8% (84/104) in the oritavancin arm and 80.0% (80/100) in the vancomycin arm
Corey et al., 2015 ³⁶	Early clinical response in the modified intention-to-treat population	<i>Study arms</i> Oritavancin Vancomycin	<i>Early clinical response</i> 403/503 (80.1%) 416/502 (82.9%)	<i>Early clinical response</i> -2.7% (-7.5 to 2.0) (ref)	Early clinical response in patients with MRSA infection was 82.0% (82/100) in the oritavancin arm and 81.2% (82/101) in the vancomycin arm
Daum et al., 2017 ²⁹	Clinical cure in the intention-to-treat populations (patients with skin abscesses after incision and drainage of the abscess)	<i>Study arms (ITT)</i> Clindamycin TMP-SMX Placebo	<i>Clinical cure (ITT)</i> 221/266 (83.1%) 215/263 (81.7%) 177/257 (68.9%)	<i>Clinical cure (ITT)</i> 14.2% (6.4 to 22.0) 12.9% (5.0 to 20.8) (ref)	Clinical cure in patients with MRSA infection in the intention-to-treat population was 81.7% (116/142) in the clindamycin arm, 84.6% (110/130) in the TMP/SMX arm, and 62.9% (73/116) in the placebo arm.

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Table I (Continued).

Study, Year [Ref]	Primary Endpoint and Study Population	Intervention Comparator	Results Regarding Primary Endpoint/s in the Primary Study Population/s	Difference (95% CI)	Information on MRSA Subgroups
Dryden et al., 2016 ³⁹	Clinical cure in the clinically evaluable and the modified intention-to-treat populations	<i>Study arms (CE)</i> Ceftaroline Vancomycin plus aztreonam <i>Study arms (MITT)</i> Ceftaroline Vancomycin plus aztreonam	<i>Clinical cure (CE)</i> 342/395 (86.6%) 180/211 (85.3%) <i>Clinical cure (MITT)</i> 396/506 (78.3%) 202/255 (79.2%)	<i>Clinical cure (CE)</i> 1.3% (-4.3 to 7.5) (ref) <i>Clinical cure (MITT)</i> -0.9% (-6.9 to 5.4) (ref)	Favorable clinical response in patients with MRSA infection was 84.0% (21/25) in the ceftaroline arm and 80.0% (12/15) in the vancomycin plus aztreonam arm
Itani et al., 2010 ⁴²	Clinical outcome in the per protocol population	<i>Study arms</i> Linezolid Vancomycin	<i>Clinical success</i> 191/227 (84.1%) 167/209 (79.9%)	<i>Clinical success</i> 4.2% (-3 to 11.5) (ref)	All enrolled patients had MRSA infection
Jauregui et al., 2005 ⁴³	Clinical success in the intention-to-treat population	<i>Study arms</i> Dalbavancin Linezolid	<i>Clinical success</i> NA (88.9%) NA (91.2%)	<i>Clinical success</i> -2.3% (-7.3 to NA) (ref)	MRSA was isolated from 51% (181/358) of cultures in the dalbavancin arm and from 51% (97/192) of cultures in the linezolid arm MRSA eradication was registered in 91% of patients with MRSA infection in the dalbavancin arm and in 89% of patients with MRSA infection in the linezolid arm
Kauf et al., 2015 ⁴⁴	Infection-related length of stay	<i>Study arms</i> Daptomycin Vancomycin	<i>Infection-related LOS</i> 91.5 hours (SD 57.8) 93.2 hours (SD 60.8)	<i>Infection-related LOS</i> Rate ratio 1.0 (0.8–1.2) (ref)	Infection-related length of stay in patients with MRSA infection was 98.5 h (SD 67.0) in the daptomycin arm and 85.9 h (SD 51.8) in the vancomycin arm
Lv et al., 2019 ⁴⁵	Early clinical response in the intention-to-treat population	<i>Study arms</i> Tedizolid Linezolid	<i>Early clinical response</i> 226/300 (75.3%) 238/298 (79.9%)	<i>Early clinical response</i> -4.6% (-11.2 to 2.2) (ref)	Clinical success in patients with MRSA infection was 72.4% (21/29) in the tedizolid arm and 62.5% (20/32) in the linezolid arm
Miller et al., 2015 ³⁰	Clinical cure in the clinically evaluable and intention-to-treat populations of patients with uncomplicated skin infections	<i>Study arms (CE)</i> Clindamycin TMP-SMX <i>Study arms (ITT)</i> Clindamycin TMP-SMX	<i>Clinical cure (CE)</i> 212/237 (89.5%) 202/229 (88.2%) <i>Clinical cure (ITT)</i> 212/264 (80.3%) 202/260 (77.7%)	<i>Clinical cure (CE)</i> (ref) -1.2 (-7.6 to 5.1) <i>Clinical cure (ITT)</i> (ref) -2.6 (-10.2 to 4.9)	MRSA was isolated from 31.8% (84/264) of cultures in the clindamycin arm and from 31.9% (83/260) of cultures in the TMP-SMX arm

Moran et al., 2014 ⁴⁶	Early clinical response in the intention-to-treat population	<i>Study arms</i> Tedizolid Linezolid	<i>Early clinical response</i> 283/332 (85.2%) 276/334 (82.6%)	<i>Early clinical response</i> 2.6% (-3 to 8.2) (ref)	Early clinical response in patients with MRSA infection was 83% (44/53) in the tedizolid arm and 79% (44/56) in the linezolid arm
Noel et al., 2008 ⁴⁸	Clinical cure in the clinically evaluable and in the intention-to-treat populations	<i>Study arms (CE)</i> Ceftobiprole Vancomycin <i>Study arms (ITT)</i> Ceftobiprole Vancomycin	<i>Clinical cure (CE)</i> 263/282 (93.3%) 259/277 (93.5%) <i>Clinical cure (ITT)</i> 309/397 (77.8%) 300/387 (77.5%)	<i>Clinical cure (CE)</i> -0.2% (-4.4 to 3.9) (ref) <i>Clinical cure (ITT)</i> 0.3% (-5.5 to 6.1) (ref)	Clinical cure in patients with MRSA infection was 91.8% (56/61) in the ceftobiprole arm and 90.0% (54/60) in the vancomycin arm
Noel et al., 2008 ⁴⁷	Clinical cure in the clinically evaluable and in the intention-to-treat populations	<i>Study arms (CE)</i> Ceftobiprole Vancomycin <i>Study arms (ITT)</i> Ceftobiprole Vancomycin	<i>Clinical cure (CE)</i> 439/485 (90.5%) 220/244 (90.2%) <i>Clinical cure (ITT)</i> 448/547 (81.9%) 227/281 (80.8%)	<i>Clinical cure (CE)</i> 0.3% (-4.2 to 4.9) (ref) <i>Clinical cure (ITT)</i> 1.1% (-4.5 to 6.7) (ref)	Clinical cure in patients with MRSA infection was 89.7% (78/87) in the ceftobiprole arm and 86.1% (31/36) in the vancomycin arm
O'Riordan et al., 2018 ⁵¹	Objective response at 48–72 hours, investigator-assessed success, and investigator-assessed cure in the intention-to-treat population	<i>Study arms</i> Delafloxacin Vancomycin plus aztreonam <i>Study arms</i> Delafloxacin Vancomycin plus aztreonam <i>Study arms</i> Delafloxacin Vancomycin plus aztreonam	<i>Objective response</i> 354/423 (83.7%) 344/427 (80.6%) <i>IA success</i> 369/423 (87.2%) 362/427 (84.8%) <i>IA cure</i> 244/423 (57.7%) 255/427 (59.7%)	<i>Objective response</i> 3.1% (-2.0 to 8.3) (ref) <i>IA success</i> 2.5% (-2.2 to 7.2) (ref) <i>IA cure</i> -2.0% (-8.6 to 4.6) (ref)	Objective response at 48–72 hours in patients with MRSA infections was 95.3% (61/64) in the delafloxacin arm and 93.5% (43/46) in the vancomycin plus aztreonam arm Microbiological response in patients with MRSA infections was 96.0% (48/50) in the delafloxacin arm and 97.0% (32/33) in the vancomycin plus aztreonam arm

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Table 1 (Continued).

Study, Year [Ref]	Primary Endpoint and Study Population	Intervention Comparator	Results Regarding Primary Endpoint/s in the Primary Study Population/s	Difference (95% CI)	Information on MRSA Subgroups
Overcash et al., 2021 ⁵²	Early clinical response and investigator-assessed clinical success in the CE and ITT populations	<i>Study arms (CE)</i> Ceftobiprole Vancomycin plus aztreonam <i>Study arms (CE)</i> Ceftobiprole Vancomycin plus aztreonam <i>Study arms (ITT)</i> Ceftobiprole Vancomycin plus aztreonam <i>Study arms (ITT)</i> Ceftobiprole Vancomycin plus aztreonam Ceftobiprole Vancomycin plus aztreonam	<i>Early clinical response</i> 267/283 (94.3%) 262/293 (89.4%) <i>IA clinical success</i> 277/283 (97.9%) 279/293 (95.2%) <i>Early clinical response</i> 306/335 (91.3%) 303/344 (88.1%) <i>IA clinical success</i> 302/335 (90.1%) 306/344 (89.0%)	<i>Early clinical response</i> 5.0% (0.6 to 9.4) (ref) <i>IA clinical success</i> 2.7% (-0.3 to 5.6) (ref) <i>Early clinical response</i> 3.3% (-1.2 to 7.8) (ref) <i>IA clinical success</i> 1.0% (-3.5 to 5.6) (ref)	Early clinical response in patients with MRSA infection in the mITT population was 93.9% (77/82) in the ceftobiprole and 91.8% (67/73) in the vancomycin plus aztreonam arm Investigator-assessed clinical success in patients with MRSA infection in the mITT population was 87.8% (72/82) in the ceftobiprole arm and 90.4% (66/73) in the vancomycin plus aztreonam arm Microbiological response in patients with MRSA infection in the mITT population was 91.5% (75/82) in the ceftobiprole arm and 91.8% (67/73) in the vancomycin plus aztreonam arm Microbiological response in patients with MRSA infection in the ME population was 98.6% (70/71) in the ceftobiprole arm and 100.0% (62/62) in the vancomycin plus aztreonam arm
Prince et al., 2013 ⁵³	Clinical success in the clinically evaluable and modified intention-to-treat populations	<i>Study arms (CE)</i> Lefamulin 100 mg q12 hours Lefamulin 150 mg q12 hours Vancomycin <i>Study arms (MITT)</i> Lefamulin 100 mg q12 hours Lefamulin 150 mg q12 hours Vancomycin	<i>Clinical success (CE)</i> 54/60 (90%) 48/54 (88.9%) 47/51 (92.2%) <i>Clinical success (MITT)</i> 41/50 (82.0%) 42/51 (82.4%) 42/51 (82.4%)	<i>Clinical success (CE)</i> NA NA (ref) <i>Clinical success (MITT)</i> NA NA (ref)	Clinical success in patients with MRSA infection was 85.3% (29/34) in the lefamulin 100 mg arm, 87.5% (28/32) in the lefamulin 150 mg arm, and 82.1% (32/39) in the vancomycin arm
Prokocimer et al., 2013 ⁵⁴	Early clinical response in the intention-to-treat population	<i>Study arms</i> Tedizolid Linezolid	<i>Early clinical response</i> 259/332 (78.0%) 255/335 (76.1%)	<i>Early clinical response</i> 1.9% (-4.5 to 8.3) (ref)	Clinical success in patients with MRSA infection was 85.2% (75/88) in the tedizolid arm and 85.6% (77/90) in the linezolid arm

Pullman et al., 2017 ⁵⁵	Objective response at 48–72 hours, investigator-assessed success, and investigator-assessed cure in the intention-to-treat population	<i>Study arms</i> Delafloxacin Vancomycin plus aztreonam <i>Study arms</i> Delafloxacin Vancomycin plus aztreonam <i>Study arms</i> Delafloxacin Vancomycin plus aztreonam	<i>Objective response</i> 259/331 (78.2%) 266/329 (80.9%) <i>IA success</i> 270/331 (81.6%) 274/329 (83.3%) <i>IA cure</i> 172/331 (52.0%) 166/329 (50.5%)	<i>Objective response</i> -2.6% (–8.8 to 3.6) (ref) <i>IA success</i> -1.7% (–7.6 to 4.1) (ref) <i>IA cure</i> 1.5% (–6.1 to 9.1) (ref)	Objective response at 48–72 hours in patients with MRSA infections was 81.9% (59/72) in the delafloxacin arm and 90.5% (76/84) in the vancomycin plus aztreonam arm Microbiological response in patients with MRSA infections was 100.0% (58/58) in the delafloxacin arm and 98.5% (65/66) in the vancomycin plus aztreonam arm
Sacchidanand et al., 2005 ⁵⁶	Clinical response in the clinically evaluable and in the clinical modified intention-to-treat populations	<i>Study arms (CE)</i> Tigecycline Vancomycin plus aztreonam <i>Study arms (c-mITT)</i> Tigecycline Vancomycin plus aztreonam	<i>Clinical response (CE)</i> 165/199 (82.9%) 163/198 (82.3%) <i>Clinical response (c-mITT)</i> 209/277 (75.5%) 200/260 (76.9%)	<i>Clinical response (CE)</i> 0.6% (–7.4 to 8.6) (ref) <i>Clinical response (c-mITT)</i> -1.5% (–9.0 to 6.1) (ref)	Microbiological response in patients with MRSA infection was 76.2% (16/21) in the tigecycline arm and 81.0% (17/21) in the vancomycin plus aztreonam arm
Schmitz et al., 2010 ³¹	Treatment failure in patients with uncomplicated skin abscess, after incision and drainage	<i>Study arms</i> TMP-SMX Placebo	<i>Treatment failure</i> 15/88 (17.0%) 27/102 (26.5%)	<i>Treatment failure</i> -9.5% (–21 to 2) (ref)	MRSA was isolated from 60% (50/84) of cultures in the TMP-SMX arm and from 47% (47/100) of cultures in the placebo arm
Stevens et al., 2002	Clinical success in the intention-to-treat population	<i>Study arms</i> Linezolid Vancomycin	<i>Clinical success</i> 109/192 (56.8%) 93/169 (55.0%)	<i>Clinical success</i> 1.8% (–8.5 to 12.0) (ref)	Clinical success in patients with MRSA infection was 58.9% (33/56) in the linezolid arm and 63.2% (36/57) in the vancomycin arm
Stryjewski et al., 2008 ⁵⁸ (Pooled results from 2 RCT)	Clinical cure in the clinically evaluable population	<i>Study arms</i> Telavancin Vancomycin	<i>Clinical cure</i> 658/745 (88.3%) 648/744 (87.1%)	<i>Clinical cure</i> 1.2% (–2.1 to 4.6) (ref)	Clinical cure in patients with MRSA infection was 90.6% (252/278) in the telavancin arm and 86.4% (260/301) in the vancomycin arm
Talan et al., 2016 ³³	Clinical cure in the per protocol and modified intention-to-treat populations of patients with uncomplicated skin abscesses (after incision and drainage)	<i>Study arms (PP)</i> TMP-SMX Placebo <i>Study arms (MITT)</i> TMP-SMX Placebo	<i>Clinical cure (PP)</i> 487/524 (92.9%) 457/533 (85.7%) <i>Clinical cure (MITT)</i> 507/630 (80.5%) 454/617 (73.6%)	<i>Clinical cure (PP)</i> 7.2% (3.2 to 11.2) (ref) <i>Clinical cure (MITT)</i> 6.9% (2.1 to 11.7) (ref)	MRSA was isolated from 43.5% (274/630) of cultures in the TMP-SMX arm and from 47.2% (291/617) of cultures in the placebo arm
Talan et al., 2016 ³²	Wound infection cure in patients with uncomplicated wound infection in the per protocol population	<i>Study arms</i> Clindamycin TMP-SMX	<i>Wound infection cure</i> 187/203 (92.1%) 182/198 (91.9%)	<i>Wound infection cure</i> 0.2% (–5.8 to 6.2) (ref)	MRSA was isolated from 38.4% (78/203) of cultures in the clindamycin arm and from 41.9% (83/198) of cultures in the TMP-SMX arm

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Table I (Continued).

Study, Year [Ref]	Primary Endpoint and Study Population	Intervention Comparator	Results Regarding Primary Endpoint/s in the Primary Study Population/s	Difference (95% CI)	Information on MRSA Subgroups
Weigelt et al, 2005 ⁵⁹	Clinical response in the intention-to-treat population	<i>Study arms</i> Linezolid Vancomycin	<i>Clinical response</i> 439/476 (92.2%) 402/454 (88.5%)	<i>Clinical response</i> 3.7% (-0.1 to 7.5) (ref)	Microbiological success in patients with MRSA infection was 88.6% (124/140) in the linezolid arm and 66.9% (97/145) in the vancomycin arm
Wilcox et al., 2004 ⁶⁰	Clinical response in the intention-to-treat population (mostly SSTI)	<i>Study arms</i> Linezolid Teicoplanin	<i>Clinical response (SSTI)</i> 113/117 (96.6%) 103/111 (92.8%)	<i>Clinical response (SSTI)</i> 3.8% (-2.0 to 9.6) (ref)	MRSA information available for bacteremic patients (see original study for details)
Wilcox et al, 2009	Microbiological success in the modified microbiologically evaluable population	<i>Study arms</i> Linezolid Vancomycin	<i>Microbiological success</i> 146/163 (89.6%) 134/149 (89.9%)	<i>Microbiological success</i> -0.3% (-7.1 to 6.4) (ref)	Microbiological success in patients with MRSA infection was 87.5% (42/48) in the linezolid arm and 87.2% (34/39) in the vancomycin arm
Wilcox et al., 2010 ⁶¹	Clinical cure in the clinically evaluable and the modified intention-to-treat populations	<i>Study arms (CE)</i> Ceftaroline Vancomycin plus aztreonam <i>Study arms (MITT)</i> Ceftaroline Vancomycin plus aztreonam	<i>Clinical cure (CE)</i> 271/294 (92.2%) 269/292 (92.1%) <i>Clinical cure (MITT)</i> 291/342 (85.1%) 289/338 (85.5%)	<i>Clinical cure (CE)</i> 0.1% (-4.4 to 4.5) (ref) <i>Clinical cure (MITT)</i> -0.4% (-5.8 to 5.0) (ref)	Clinical cure in patients with MRSA infection was 91.4% (64/70) in the ceftaroline arm and 93.3% (56/60) in the vancomycin plus aztreonam arm

Note: *With study population > 200 enrolled patients.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CE, clinically evaluable; CI, confidence interval; c-mITT, clinically modified intention-to-treat; IA, investigator-assessed; ITT, intention-to-treat; MITT, modified intention to treat; mITT, microbiological intention-to-treat; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available; PP, per protocol; RCT, randomized controlled trials; SD, standard deviation; SSTI, skin and soft tissue infections; TMP-SMX, trimethoprim-sulfamethoxazole.

RCTs in patients with ABSSSI were recently reported for ceftobiprole, which may represent an additional important option if eventually approved for this indication by regulatory agencies.⁵² More details and comments (especially with regard to subgroups with MRSA infection) on the results of large RCTs investigating all these agents for the treatment of ABSSSI are reported in Table 1. Overall, considering that the rule in all RCTs was the achievement of noninferiority, it may be reasonable to primarily base the choice of the agent on considerations other than efficacy (assumed to be similar), eg, need for hospitalization or possibility of outpatient treatment, possibility of step-down to oral or long-acting formulations and early discharge, expected patient's adherence to treatment, allergy, risk of toxicity based on the drug profile and the patient's baseline comorbidities, risk of *Clostridioides difficile* infections, and costs. Notably, all these considerations are in line with a personalized medicine approach, and a possible algorithm guiding the empirical use of anti-MRSA agents (based on risk factors for MRSA and on patient-centered considerations) is proposed in Figure 1.

BSI

S. aureus has been reported to cause up to 20% of healthcare-associated BSI, with crude mortality reaching >30% for MRSA BSI.^{11,65,66}

Treatment algorithms are different for MSSA BSI and MRSA BSI. The first-line treatment of MSSA BSI relies on intravenous antistaphylococcal penicillins (eg, oxacillin, nafcillin, cloxacillin, flucloxacillin). As for MSSA ABSSSI, cefazolin has been proposed as a possible first-line alternative to the antistaphylococcal penicillins in the treatment of MSSA BSI. This possibility is supported by a lower risk of nephrotoxicity and the favorable results of many recent observational studies and meta-analyses,^{67–82} although, while waiting for the results of ongoing RCTs that could ultimately resolve the issue (more than one RCT may be necessary for eventually reaching a solid consensus),⁸³ some caution may still remain necessary due to the nonrandomized nature of the currently available comparative evidence and because of a described potential risk of cefazolin treatment failure in the case of high-inoculum infections.^{7,84} For penicillin-susceptible *S. aureus* BSI, some studies also suggest a possible role of penicillin as an alternative to

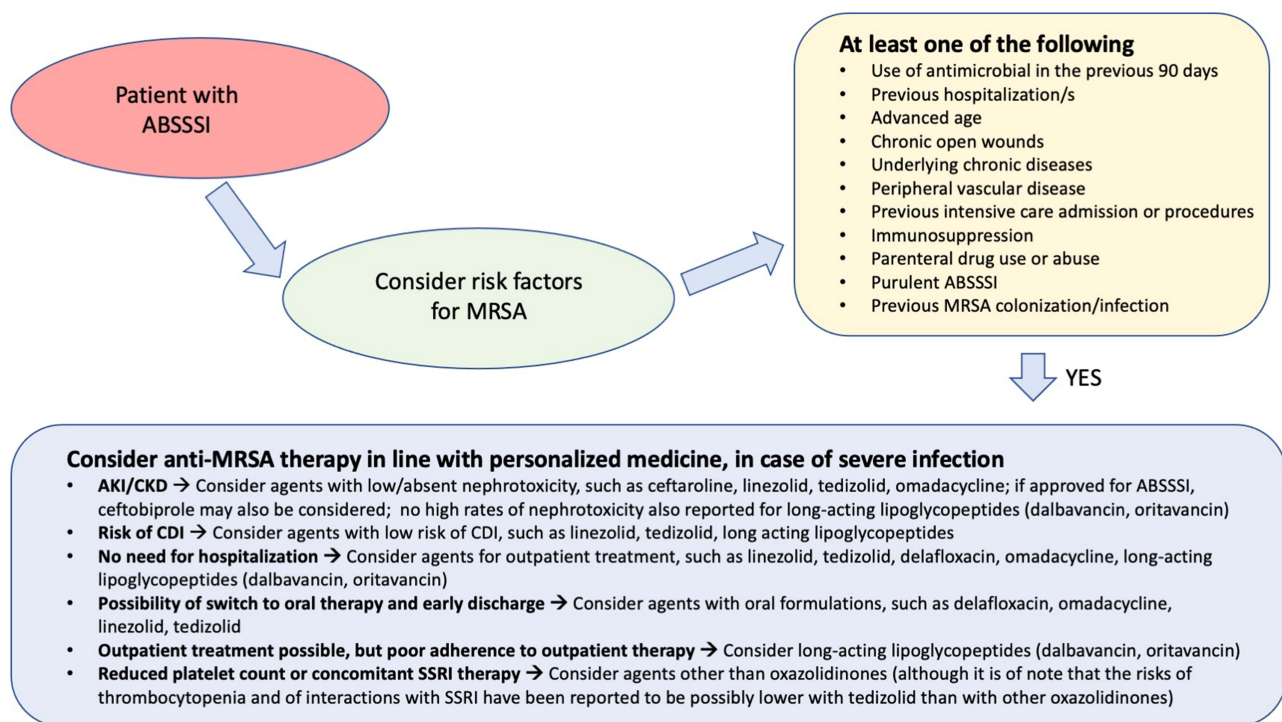


Figure 1 Proposed clinical reasoning for the empirical treatment of MRSA acute bacterial skin and skin structure infections.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AKI, acute kidney injury; CDI, *Clostridioides difficile* infection; CKD, chronic kidney disease; MRSA, methicillin-resistant *Staphylococcus aureus*; SSRI, selective serotonin reuptake inhibitors.

antistaphylococcal penicillins, although based on retrospective evidence.^{85–88} In the case of severe penicillin allergy, an alternative agent should be administered for treating MSSA BSI. Daptomycin is frequently considered in a similar situation, owing to its noninferiority to standard of care (antistaphylococcal penicillins or vancomycin) in the treatment of *S. aureus* BSI, caused either by MSSA or by MRSA in a RCT of 235 patients with *S. aureus* BSI with or without right-sided endocarditis.⁸⁹ This is also in line with the results of a small recent observational study of 89 patients with MSSA BSI, in which clinical outcomes (a composite of clinical failure, MSSA recurrence or MSSA persistence, and in-hospital mortality) were similar between patients receiving daptomycin and those receiving antistaphylococcal beta-lactams.⁹⁰ Conversely, vancomycin has been associated with increased mortality, persistent bacteremia, and nephrotoxicity when compared to antistaphylococcal β -lactams for the treatment of MSSA BSI.^{91–94} Finally, it is worth noting that addition of daptomycin to standard beta-lactam monotherapy did not provide an advantage in efficacy in a double-blind RCT of 104 patients with MSSA BSI.⁹⁵ A lack of advantage in terms of efficacy was also observed for additional rifampin in 758 patients with *S. aureus* BSI, of which 94% were caused by MSSA.⁹⁶

In 2011, US guidelines recommended daptomycin or vancomycin as a first-line treatment for MRSA BSI.⁹⁷ This was based on the results of an open-label RCT in which daptomycin was compared to standard of care (antistaphylococcal penicillins for MSSA BSI vancomycin for MRSA BSI) for the treatment of *S. aureus* BSI with or without right-sided endocarditis.⁸⁹ The primary endpoint was treatment success at 42 days after the end of treatment in the intention-to-treat population, and it was achieved in 53/120 patients (44%) and in 48/115 patients (42%) treated with daptomycin or standard of care, respectively (absolute difference 2.4%, with 95% confidence interval [CI] from –10.2% to 15.1%), thereby meeting the prespecified criteria for noninferiority.⁸⁹ Notably, in the subgroup of patients with MRSA BSI, the primary endpoint was achieved in 20/45 patients (44%) and 14/44 patients (32%) in the daptomycin arm and in the standard of care arm, with 95% CI for absolute difference from –7.4% to 32.6%.⁸⁹ Despite these results, recent UK guidelines do not recommend daptomycin as an alternative to vancomycin and suggest linezolid as the preferred second choice when vancomycin is contraindicated.⁹⁸ Although it is true that the information on daptomycin efficacy for MRSA BSI is limited to a small subgroup of less than 100 patients and thus the evidence on this matter remains inconclusive, there are, in our opinion, some possible considerations that should support daptomycin as first-line treatment for MRSA BSI: (i) although with the large uncertainty of estimates due to the small population, it is of note that clinical success was numerically higher in the daptomycin arm; (ii) as a possible indirect supporting evidence, daptomycin was not associated with worse clinical outcomes compared to antistaphylococcal beta-lactams for the treatment of MSSA, whereas worse clinical outcomes were observed for targeted treatment of MSSA with vancomycin compared to antistaphylococcal beta-lactams; (iii) the good safety profile of daptomycin and its concentration-dependent bactericidal killing are potential theoretical advantages of daptomycin treatment over vancomycin for MRSA BSI, also considering the results of comparisons between the two drugs in observational studies; (iv) the necessity of therapeutic drug monitoring for vancomycin.^{45,89–91,93,99–101} Of note, teicoplanin has been reported to be less nephrotoxic than vancomycin, although the more limited evidence for the treatment of MRSA BSI available in the literature in comparison to vancomycin should be considered.^{98,102}

Regarding linezolid, a bacteriostatic oxazolidinone approved for the treatment of ABSSSI and pneumonia and usually not considered as first line for MRSA BSI,^{4,16,103} the evidence on its possible noninferiority to vancomycin for MRSA BSI comes from a pooled analysis of RCTs including patients with secondary BSI and from a subgroup analysis in patients with Gram-positive catheter-related BSI.^{62,104} For this reason, in our opinion, its use for MRSA BSI should deserve caution and be primarily reserved as possible salvage treatment in selected situations. Linezolid has also been proposed as a potential step-down oral therapy in selected situations, a possibility deserving further investigation.¹⁰⁵ Other potential agents for the treatment of MRSA BSI when first-line agents are contraindicated are the fifth-generation cephalosporins ceftobiprole and ceftaroline.^{106–110} These two agents are currently not approved for primary MRSA BSI, although it is of note that a phase-3, double-blind RCT (ERADICATE study) comparing ceftobiprole to daptomycin for the treatment of *S. aureus* BSI (by either MSSA or MRSA) with or without right-sided endocarditis is currently ongoing.¹¹¹ The primary endpoint is overall success at the post-treatment evaluation visit and consists of the following: (i) survival; (ii) resolution of symptoms; (iii) microbiological eradication; and (iv) absence of development of new complications or metastatic foci.¹¹¹ If ceftobiprole meet noninferiority, this could lead for the first time to the availability of a beta-lactam as a first-line alternative for the treatment of primary MRSA BSI, expanding the currently still limited therapeutic arsenal for this indication. Results of this RCT are currently awaited.

Ceftobiprole and ceftaroline have also been considered in real-life practice as possible companions to first-line agents (daptomycin or vancomycin) for salvage treatment of MRSA BSI after failure of first-line monotherapy, or as initial combination treatment for complicated MRSA BSI, based on in vitro synergy and preliminary results from observational studies.^{112–121} Similar strategies have also been proposed with other possible companion agents to daptomycin or vancomycin, such as antistaphylococcal penicillins, other beta-lactams, or fosfomycin.^{122–131} While this approach is certainly reasonable from a theoretical standpoint in the case of salvage treatment, the evidence from RCTs about an initial approach with combination therapy for complicated MRSA BSI remains controversial. On the one hand, a RCT in which a combination regimen (daptomycin or vancomycin as the first agent plus an antistaphylococcal penicillin or cefazolin as the companion agent) was compared to monotherapy with daptomycin or vancomycin for the treatment of MRSA BSI was early terminated because of a registered increased cumulative incidence of acute kidney injury in patients receiving the combined regimen.¹²³ On the other hand, another RCT comparing vancomycin plus flucloxacillin to vancomycin monotherapy in patients with MRSA BSI showed an improved mean time to resolution of BSI in the combination arm (being 65% of that in the monotherapy arm, with 95% CI from 41% to 102%).¹²² Furthermore, a recent RCT compared a combined regimen of daptomycin plus fosfomycin to daptomycin alone in patients with MRSA BSI with or without endocarditis, registering a treatment success of 54% in the combination arm and 40% in the monotherapy arm (relative risk 1.25; 95% CI 0.93–1.80), whereas adverse events that led to drug discontinuation occurred in 18% of patients in the combination arm and in 5% of patients in the monotherapy arm.¹²⁴ Regarding fifth-generation cephalosporins, an open-label RCT comparing daptomycin plus ceftaroline to daptomycin alone for the treatment of MRSA BSI was early terminated after the enrollment of only 40 patients due to an imbalance in mortality with an excess in the number of deaths in the monotherapy arm (26% vs 0%).¹³² Unfortunately, no conclusive interpretations can stem from this study since the early termination also implied imbalances due to chance in the distribution of clinical features between arms that could have also affected the prognosis. Furthermore, one additional patient favoring either combination or monotherapy would have impacted results significantly.^{133,134} Regarding the possible addition of rifampin, it is of note that only as few as 47/758 (6%) of patients enrolled in a RCT comparing standard therapy plus rifampin vs standard therapy plus placebo from *S. aureus* BSI had MRSA infection, thereby precluding any conclusion without further investigation.⁹⁶ Overall, further results from large RCTs remain necessary to eventually understand whether combination therapy could be associated with clinically relevant benefit in patients with MRSA BSI, or maybe more relevant, in which categories/phenotypes of patients with complicated MRSA BSI could initial combination therapy truly provide benefits, which, in our opinion, remains the most crucial unresolved question. A possible algorithm for guiding the use of anti-MRSA agents in the treatment of MRSA BSI is proposed in [Figure 2](#).

Emerging Treatment Options for *S. aureus* ABSSSI and BSI (Drugs in Phase-2 or Phase-3 of Clinical Development)

Some agents showing anti-MRSA activity have completed phase-3 RCTs for the treatment of ABSSSI. Iclaprim is a novel inhibitor of bacterial dihydrofolate reductase that remains active against some TMP-resistant isolates and that does not need to be combined with a sulfonamide for exerting antibacterial activity.^{25,135,136} In the two phase-3 RCTs REVIVE-1 and REVIVE-2, iclaprim was noninferior to vancomycin for the treatment of ABSSSI in terms of the primary endpoint of early clinical response.^{40,41} More in detail, early clinical response was achieved in 80.9% (241/298) and 81.0% (243/300) of patients in iclaprim and vancomycin arms, respectively, in REVIVE-1 (difference -0.1%, with 95% CI from -6.4% to 6.2%), and in 78.3% (231/295) and 76.7% (234/305) of patients in iclaprim and vancomycin arms, respectively, in REVIVE-2 (difference 1.6%, with 95% CI from -5.1% to 8.3%).^{40,41} In 2019, the US Food and Drug Administration (FDA) approval was not granted due to concerns about possible increased liver toxicity in patients receiving iclaprim, and the conduction of an additional RCT was encouraged.¹³⁷ Another agent that recently completed a phase-3 RCT for the treatment of ABSSSI is ceftobiprole. In the TARGET study, a double-blind RCT comparing ceftobiprole with vancomycin plus aztreonam for the treatment of ABSSSI, the FDA primary endpoint of early clinical response in the intention-to-treat population was achieved in 91.3% (306/355) and in 88.1% (303/344) of patients receiving ceftobiprole and vancomycin plus aztreonam, respectively (difference 3.3%, with 95% CI from -1.2% to

Patient with MRSA bloodstream infection



First-line agents

- Daptomycin (not active in the case of pneumonia; uncommon but possible: eosinophilic pneumonia, rhabdomyolysis, induction of tolerance with use)
- Guidelines also suggest vancomycin (possible disadvantages such as nephrotoxicity, less rapid bactericidal than daptomycin, observational comparisons possibly favoring daptomycin, need for vancomycin TDM)



Complicated MRSA BSI or salvage therapy

- Consider combination therapy of a first-line agent with one of the following (pending high certainty evidence from RCT)
- Ceftobiprole or ceftaroline
 - Other beta-lactams (e.g., antistaphylococcal penicillins)
 - Fosfomycin
 - Consider toxin-inhibiting agents in the case of toxin-producing MRSA

Figure 2 Proposed clinical reasoning for the treatment of MRSA bloodstream infections.

Notes: Ceftobiprole could also become available for the treatment of MRSA bloodstream infections in the future, provided the results of an ongoing phase-3 RCT are favorable and approval for this indication is granted by regulatory agencies.

Abbreviations: BSI, bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus*; RCT, randomized clinical trials; TDM, therapeutic drug monitoring.

7.8%), thereby meeting criteria for noninferiority.⁵² In the next few years, FDA review and possible approval of ceftobiprole is expected for ABSSSI and, possibly, for *S. aureus* BSI according to the results of the ongoing ERADICATE phase-3 study discussed in the previous section. Currently, ceftobiprole is approved in several European and non-European countries for the treatment of pneumonia (community-acquired pneumonia and hospital-acquired pneumonia).^{106,138}

Other agents with anti-MRSA activity in clinical development have completed phase-2 studies for the treatment of ABSSSI. Brilacidin is a non-peptide chemical agent mimicking antimicrobial peptides, that causes the depolarization of the bacterial membranes with an immediate dose-dependent bactericidal activity.^{139,140} Two phase-2 RCTs have been conducted to compare brilacidin to daptomycin in patients with ABSSSI (NCT02052388 and NCT01211470). In the first of these two studies, 215 patients were enrolled, and the primary endpoint of early clinical response was achieved in >90% in both daptomycin and brilacidin arms (overall, there were four arms, since three of them explored different brilacidin dosing schedules).^{141–143} Of note, adverse events were mild in all arms, and there were no serious adverse events or adverse events leading to drug discontinuation.^{141–143} A phase-3 RCT in patients with ABSSSI was initially planned, and later delayed.¹⁴⁰ Another agent that completed phase-2 of clinical development for ABSSSI is lefamulin, an agent belonging to the pleuromutilin class already approved for the treatment of community-acquired pneumonia.¹⁴⁴ Lefamulin acts by binding domain V of 23S rRNA, with inhibition of the bacterial protein synthesis.¹⁴⁵ A phase-2 RCT was conducted in patients with proven or presumed Gram-positive ABSSSI, comparing lefamulin with vancomycin.⁵³ Patients were randomized to receive: (i) lefamulin at 100 mg every 12 hours; (ii) lefamulin at 150 mg every 12 hours; (iii) vancomycin at 1 g every 12 hours. Overall, 186 patients completed the study, and clinical success was observed in 90.0%, 88.9%, and 92.2% in the lefamulin 100 mg, lefamulin 150 mg, and vancomycin arms, respectively.⁵³ No phase-3 studies of lefamulin for the treatment of ABSSSI have been currently registered.

Another novel class of antibiotics with anti-MSSA and anti-MRSA activity in clinical development for the treatment of ABSSSI is that of inhibitors of the enoyl-acyl carrier protein reductase (FabI), an enzyme involved in the bacterial fatty acid

biosynthesis.¹⁴⁶ An agent belonging to this novel class is afabacin (Debio1450, previously AFN-1720), which is a pro-drug of the active moiety afabacin desphosphono (Debio1452, previously AFN-1252).¹⁴⁷ In a phase-2 single-arm study conducted in patients with staphylococcal ABSSSI, the early clinical response was 97.3% in the microbiologically evaluable population (n = 76). It is worth noting that microbiological eradication for *S. aureus* was 91.9% at long-term follow-up, with eradication rates being 89.7% for MSSA and 91.9% for MRSA. Very similar microbiological eradication rates (>90%) were registered at short-term follow-up.¹⁴⁷ In a double-blind, phase-2 RCT, patients with staphylococcal ABSSSI were randomized in three groups to receive two different dosages of afabacin (both intravenous with subsequent oral step-down) or intravenous vancomycin (with subsequent oral stepdown to linezolid). Early clinical response (at 48–72 h) was achieved in 94.6% of patients treated with afabacin at 80/120 mg every 12 hours (87/92), in 90.1% of patients treated with afabacin at 160/240 mg every 12 hours (82/91), and in 91.1% of patients treated with vancomycin/linezolid (92/101).¹⁴⁸ These recent favorable results could support further development of afabacin for the treatment of staphylococcal ABSSSI, although no phase-3 RCT has been currently registered. Another FabI inhibitor, CG-400549, was evaluated in a single-arm, Phase 2 study conducted in patients with complicated ABSSSI caused by MRSA, as an oral agent administered once daily. Results were preliminarily reported in 2013, showing 90.9% response at 48–72 hours and 100% at day 21–28, without drug discontinuation or serious adverse events.¹⁴⁹ However, no further information has been provided subsequently.

Some novel fluoroquinolones showing anti-MRSA activity were also evaluated for the treatment of ABSSSI. Oral avarofloxacin (JNJ-Q2) at a dosage of 250 mg every 12 hours was compared to oral linezolid at a dosage of 600 mg every 12 hours in a double-blind, phase 2 RCT conducted on 161 patients with ABSSSI.¹⁵⁰ Noninferiority was not met with respect to the primary endpoint of early clinical response. Nonetheless, it is of note that noninferiority for early treatment success was achieved in a post-hoc analysis based on the 2010 FDA guidance.¹⁵⁰ No phase-3 RCT for ABSSSI has been currently registered for avarofloxacin, whereas a phase-3 RCT has been conducted in India for levonadifloxacin (WCK771) and its oral L-alanine prodrug alalevonadifloxacin (WCK2349), which also show anti-MRSA activity.^{151–153} In the phase-3 study conducted in 500 subjects in India, both oral levonadifloxacin and intravenous levonadifloxacin were noninferior to linezolid (clinical cure rates 95.2% vs 93.6% for oral levonadifloxacin vs linezolid, respectively [treatment difference 1.6%, with 95% CI from -4.2 to 7.3], and 91.0% vs 87.8% for intravenous levonadifloxacin vs linezolid, respectively [treatment difference 3.2%, with 95% CI from -4.5 to 10.9]).¹⁵³

With regard to oxazolidinones, radezolid (RX-1714) and contezolid acefosamil (MRX-4) were evaluated in phase-2 studies in patients with ABSSSI. In a phase-2 RCT conducted on 150 patients with ABSSSI, patients were randomized to receive: (i) oral radezolid 450 mg every 24 hours; (ii) oral radezolid 450 every 12 hours; (iii) oral linezolid 600 mg every 12 hours.¹⁵⁴ Clinical response was registered in 97% of patients receiving radezolid every 24 hours (38/39), in 94% of patients receiving radezolid every 12 hours (34/36), and in 97% of patients receiving linezolid (37/38). No phase-3 studies for ABSSSI have currently been announced. Regarding contezolid acefosamil, it is the prodrug of contezolid (MRX-I). In a double-blind, phase-2 RCT, contezolid was compared to linezolid (both administered intravenously with the possibility of switching to oral therapy) for the treatment of ABSSSI. Early clinical response was achieved in 77.9% and 78.5% of patients in contezolid acefosamil and linezolid arms, respectively.¹⁵⁵ Contezolid is approved for ABSSSI in China based on noninferiority of linezolid registered in a phase-3 study conducted in China.¹⁵⁶

Another agent in phase-2 of clinical development is a hybrid rifamycin-quinolone antibiotic, TNP-2092 (CBR-2092).^{157,158} TNP-2092 was compared to vancomycin in a double-blind randomized, phase-2 RCT for the treatment of confirmed or suspected Gram-positive ABSSSI. The study has been completed, and results are awaited.¹⁵⁹ Gepotidacin (GSK2140944) is a topoisomerase type IIA and DNA gyrase inhibitor, belonging to the class of triazaacenaphthylene antibacterials.^{160,161} Gepotidacin was evaluated in a phase 2, randomized study divided into two parts (one open-label and one double-blind), in patients with ABSSSI infection, including MRSA (isolated in 44% of cases). Three different intravenous gepotidacin dosages (750 mg q12h, 1000 mg q12h and 1000 mg q8h) and the primary endpoint (a composite of safety and early clinical response) were met in two dosage groups (750 mg q12h, 1000 mg q8h) but not in the third group.¹⁶² The reasons underlying this result are not completely clear, although the small sample size and the distribution of types of skin lesions and rates of drug discontinuation across arms may have contributed.^{140,162} Further study is needed to characterize the possible role of this novel agent more solidly for the treatment of ABSSSI. Finally (with regard to agents in phase-2 of clinical development for the treatment of ABSSSI), cefilavancin (TD-1792) is a multivalent glycopeptide-cephalosporin agent that was compared to vancomycin for complicated ABSSSI treatment in

a phase-2 RCT, although subsequently no phase-3 studies have been registered. In the phase-2 RCT, the clinical response at the test of cure (7–14 days after the end of treatment) was 91.7% and 90.7% in cefilavancin-treated and vancomycin-treated patients, respectively.¹⁶³

Regarding agents in phase-2 (or with completed phase-2) of clinical development for the treatment of *S. aureus* BSI. Exebacase (CF-301) is a lysin (a bacteriophage-encoded peptidoglycan hydrolase) with potent activity against *S. aureus* in in vitro studies.^{164,165} Exebacase was evaluated in a phase-2 RCT in combination with conventional antibiotics vs conventional antibiotics alone for the treatment of *S. aureus* BSI with or without right-sided endocarditis.¹⁶⁶ Overall, 121 patients were enrolled, and the primary endpoint of clinical response at day 14 was 70.4% and 60.0% in the exebacase plus conventional therapy arm and conventional therapy alone arm, respectively (difference 10.4%, with 90% CI from –6.3 to 27.2). Of note, the difference was more marked in the subgroup of patients with MRSA infection, with clinical response at day 14 being 74.1% and 31.1% in the exebacase plus conventional therapy arm and conventional therapy alone arm, respectively (difference 42.8%, with 90% CI from 14.3 to 71.4).¹⁶⁶ A Phase 3 randomized, double-blind, superiority RCT (DISRUPT) is currently ongoing.¹⁶⁷ Another agent that underwent phase-2 of clinical development for the treatment of *S. aureus* BSI is SAL200, a molecule containing recombinant SAL-1, which is a phage endolysin derived from the bacteriophage SAP-1.¹⁶⁸ A phase-2 RCT was conducted, comparing SAL200 (single intravenous dose administration) to placebo (both in addition to standard antibiotic therapy) in patients with persistent *S. aureus* BSI for more than 48 hours from the beginning of active antibiotics. However, enrolment into this study was early terminated before the achievement of a predefined sample size.¹⁶⁹ Another agent in clinical development is 514G3, a monoclonal antibody targeting *S. aureus* cell wall protein A.¹⁷⁰ In a double-blind RCT, 514G3 was compared to placebo (both in addition to standard antibiotic therapy) for the treatment of *S. aureus* BSI. In a small study population of 52 patients, a higher number of deaths were observed in the 514G3 arm (4 vs 0). On the other hand, results in terms of length of stay and adverse events were apparently more favorable in the 514G3 arm.¹⁷¹ Further investigation would be necessary to better understand these apparently opposite results.

Conclusion

Treatments of *S. aureus* ABSSSI and BSI rely on different therapeutic algorithms based on the methicillin susceptibility or resistance of the suspected/proven causative isolate. A crucial concept is the availability of different agents for the treatment of *S. aureus* ABSSSI, which uniquely allows a personalized approach based on the characteristics of any given patient while at the same time remaining in line with high certainty efficacy evidence from large RCTs. An even more precision-medicine tailored approach could become a reality in the forthcoming future, owing to the presence of several other agents with anti-MSSA and anti-MRSA activity (belonging both to old and novel antibiotic classes) in the late phases of clinical development for the treatment of ABSSSI. Regarding the treatment of *S. aureus* BSI, interesting aspects that may become relevant in the near future are the possible availability of a beta-lactam for the treatment of MRSA BSI (provided results from a dedicated phase-3 study evaluating ceftobiprole for this indication are favorable) and the pressing need for high certainty evidence to guide the possible use of combination therapy in specific categories or phenotypes of patients with complicated MRSA BSI.

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