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Investigational agents for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia: Progress in clinical trials

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Abstract

Introduction: Bacteremia caused by *Staphylococcus aureus* is common, with cases caused by methicillin-resistant *S. aureus* (MRSA) especially formidable and often lethal. The mortality associated with MRSA bacteremia has not significantly decreased over the past couple of decades, and concerns about the efficacy and toxicity of standard therapy highlight the need for novel agents and therapeutic approaches to emerge.

Areas covered: This review paper will explore clinical trials that investigate novel therapeutic approaches to treat *S. aureus* bacteremia, focusing on MRSA bacteremia. Specifically, this paper discusses monotherapy and combination therapy approaches, while also reviewing novel antimicrobials and adjunctive therapies that are only recently being established for therapeutic use.

Expert opinion: The unfavorable safety profile of combination antimicrobial therapy in clinical trials has outweighed its benefits. Therefore, future investigation should focus on optimizing duration and de-escalation protocols. Antibody and bacteriophage lysin-based candidates have mostly been limited to safety trials, but progress with these agents is demonstrated through a lysin-based agent receiving a phase III trial. Antibiotics indicated for use in treating MRSA skin infections see continued investigation as treatments for MRSA bacteremia despite the difficulty of completing trials in this patient population. Overall, promising agents include dalbavancin, ceftobiprole, ceftaroline, and exebacase.

Keywords

Bacteremia; clinical trials; investigational agent; MRSA; *Staphylococcus aureus*

1. Introduction

Staphylococcus aureus is an important human pathogen that causes a wide variety of infections such as osteomyelitis, pneumonia, skin and soft tissue infections (SSTIs), endocarditis, and bacteremia. *S. aureus* is a leading cause of bacteremia in industrialized nations[1], which is associated with significant mortality[2]. Although methicillin-sensitive *S.*

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aureus (MSSA) accounts for most cases of bacteremia[3, 4], bacteremia caused by methicillin-resistant *S. aureus* (MRSA) is associated with worse clinical outcomes for patients[5, 6]. While the incidence of hospital-onset MRSA bacteremia decreased annually by 17.1% in hospitals in the United States from 2005 to 2012, the decline slowed between 2013 and 2016[7]. The 30-day all-cause mortality of *S. aureus* bacteremia (SAB) is between 18% and 30%[5,7,8, 9], and mortality due to MRSA bacteremia has not changed significantly over time[10].

As antibiotic resistance continues to be a significant problem for therapeutic efficacy, there is a need to identify novel therapeutic agents and strategies to treat SAB. Therefore, this review will discuss novel therapeutic approaches in clinical trials, both completed and in progress, to discuss therapeutic compounds and approaches that may show promise as treatments for SAB, with a focus on MRSA bacteremia. This review will highlight the use of monotherapies as alternatives to standard of care (SOC), combination therapy, and novel antimicrobials and adjunctive therapies.

2. Treatment guidelines for SAB

The development of SAB is frequently associated with other primary infection sites, such as SSTIs, infective endocarditis, pneumonia, or infected indwelling medical devices. SAB can also lead to metastatic infections such as infective endocarditis, septic arthritis, and osteomyelitis[11], underscoring the importance of resolving the infection in a timely manner. Current treatment guidelines for SAB are based on the antibiotic resistance of the isolate as well as the classification of the bacteremia as complicated or uncomplicated (Figure 1). Uncomplicated bacteremia is defined as a positive blood culture plus the following[12]: 1) exclusion of endocarditis; 2) no implanted prostheses; 3) blood cultures obtained after 2–4 days after the first set of blood cultures that do not contain MRSA; 4) defervescence within 72 hours of the beginning of therapy; 5) no evidence of metastatic infection. Complicated bacteremia is defined as a positive blood culture and failure to meet the criteria of uncomplicated bacteremia. Vancomycin and daptomycin are the standard therapies to treat MRSA bacteremia and are the only treatments that are approved by the US Food and Drug Administration (FDA) for this purpose.

3. Standard of care

3.1. Vancomycin

Vancomycin is a glycopeptide antibiotic that exerts antimicrobial activity by binding to D-alanyl D-alanine, which results in the inhibition of peptidoglycan polymerization by preventing the incorporation of *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) into the growing peptidoglycan layer[13]. The dosage and route of administration for vancomycin as a treatment for MRSA bacteremia are outlined in Figure 1. Trough levels of 15–20 mg/L should be maintained for the treatment of MRSA infections; however, such trough levels come with an increased risk of nephrotoxicity, and therefore must be monitored to assess patient risk[14].Vancomycin is inferior to β-lactams for the treatment of patients with MSSA bacteremia and should not be administered in these cases, as its usage is associated with poor patient outcomes[15]. Vancomycin efficacy is also limited by its poor tissue penetration and slow bactericidal activity[16]. There is also the concern of

a rise in bacterial resistance to vancomycin, mostly in the form of an 'MIC (minimum inhibitory concentration) creep,' which refers to an increase in the MIC of an antibiotic against a particular organism over time. While some studies have found an increase in the MIC of vancomycin against *S. aureus* clinical isolates in specific hospitals and regions over time[17, 18], a meta-analysis found no such evidence that the phenomenon exists on a worldwide scale[19]. It is thought that differences in the laboratory methods used to determine MIC values[20, 21] as well as differences in clonal dissemination[22] may impact findings regarding the MIC creep. *S. aureus* isolates with some degree of vancomycin resistance are classified by their MICs in three groups[23]: 1) vancomycin-resistant *S. aureus* (VRSA), MIC ≥ 16 μg/mL 2) vancomycin-intermediate *S. aureus* (VISA), MIC between 4–8 μg/mL 3) heterogeneous VISA (hVISA), sub-population of cells (< 1 per 100,000 colony-forming units (CFU)) with an MIC between 4–8 μg/mL. Resistance mechanisms encountered in VISA strains include the thickening of the cell wall, which limits the localization of vancomycin to the division septum, as well as decreased autolysis[24]. High levels of vancomycin resistance seen in VRSA stains is conferred by the *vanA* operon, which is responsible for the production of D-alanyl D-lactate which has a poor affinity for vancomycin and other glycopeptides (teicoplanin, dalbavancin, telavancin)[25, 26]. The global prevalence of all three vancomycin-resistance groups has increased from pre-2010 to 2019, with VRSA increasing 2.0-fold (1.2% to 2.4%), VISA 3.6-fold (1.2% to 4.3%), and hVISA 1.3-fold (4.0% to 5.3%)[27]. There is no definitive link between the MIC of vancomycin and MRSA bacteremia patient outcomes. One meta-analysis found an association between a high vancomycin MIC value (≥ 1.5 μg/mL) and increased mortality[28], while a meta-analysis and two retrospective cohort studies reported a correlation between increasing vancomycin MIC values and an increased risk of treatment failure[28–30]. However, other retrospective, single-center studies have found no relationship between vancomycin MIC and patient mortality[31, 32]. Nevertheless, the prevalence of VISA and hVISA has been increasing since 2006[33], and with vancomycin continuing to see significant use, it is plausible that isolates with decreased susceptibility to vancomycin may continue to emerge and threaten patient outcomes.

3.2. Daptomycin

Daptomycin is a lipopeptide antibiotic with a controversial mechanism of action, although it is generally accepted that daptomycin penetrates into the bacterial cell membrane, which disrupts membrane integrity and leads to cell death and membrane depolarization[34]. However, more recent studies have demonstrated that daptomycin's mechanism of action might be more specific than previously thought, as it was shown that daptomycin can also bind to lipid II and disrupt cell wall biosynthesis[35].While the dosage recommendation for daptomycin is 6 mg/kg/dose[12], physicians often prescribe higher dosages in the range of 8–10 mg/kg/dose[36, 37]. Like vancomycin, the development of antibiotic resistance is also a concern with the use of daptomycin. Resistance mechanisms include the modification of membrane composition to decrease daptomycin binding. Mutations in *mprF* lead to increased conversion of phosphatidylglycerol (PG) to lysine-PG, which is positively charged and disrupts daptomycin binding, while overexpression of the *dlt* operon leads to an increase in biosynthesis of the machinery that attaches alanine to wall teichoic acid (WTA), which disrupts daptomycin binding by positively increasing the cell-surface charge[34]. In a clinical

trial comparing the efficacy of daptomycin versus SOC to treat bacteremia and endocarditis caused by *S. aureus*, isolates retrieved during or after treatment from the daptomycin-treated group became less susceptible to daptomycin in 6 of 19 patients that experienced microbiological failure[38]. Daptomycin MIC values can also be correlated with those of vancomycin[39], and up to 15% of hVISA isolates have a daptomycin-nonsusceptibility phenotype[40]. The use of daptomycin is inappropriate in patients with MRSA bacteremia secondary to pneumonia, as daptomycin is inactivated by the PG content of pulmonary surfactant[41].

4. Investigational agents for the treatment of MRSA bacteremia (Table 1)

4.1. Monotherapy

In an effort to identify antibiotics that may be viable alternatives to SOC for SAB, several antibiotics have been used off-label and compared to either vancomycin or daptomycin in clinical trials to assess evaluate their safety and efficacy for use as a monotherapy.

4.1.1. Ceftobiprole—Ceftobiprole is a fifth-generation cephalosporin antibiotic that was granted fast-track approval status by the FDA in 2003 to treat complicated skin and soft tissue infections (cSSTIs) and hospital-acquired bacterial pneumonia (HABP). Ceftobiprole been investigated as a treatment for cSSTIs in clinical trials[42, 43], but full FDA approval for ceftobiprole for any indication has not yet been granted. While there is currently no data from randomized clinical trials pertaining to ceftobiprole's efficacy and safety for use as a treatment for SAB, there is a phase III, double-blind, randomized clinical trial (NCT03138733) that will compare ceftobiprole to daptomycin (with or without aztreonam) in patients with SAB, with the primary endpoint being overall success rate[44]. Ceftobiprole shows promise in that it has bactericidal activity against both MSSA and MRSA[45, 46], indicating it could see use as a general therapy for the treatment of SAB.

4.1.2. Ceftaroline—Like ceftobiprole, ceftaroline is a fifth-generation cephalosporin with bactericidal activity against MSSA and MRSA[47]. It is currently FDA-approved to treat ABSSSI and community-acquired bacterial pneumonia (CABP). Ceftaroline has shown promise in retrospective analyses and cohort studies – in a retrospective analysis of patients with SAB, 101 of 129 (78%) clinically evaluable patients had clinical success with ceftaroline, with 92.5% of SAB cases in the initial population caused by MRSA[47]. Ceftaroline has not yet been evaluated as a monotherapy for MRSA bacteremia in a randomized clinical trial, but there is evidence that it may useful, particularly as a salvage therapy. In a retrospective comparative study, 132 MRSA bacteremia patients were identified, and the outcomes of 30 patients given ceftaroline were compared to the matched control groups of 46 patients given daptomycin and 56 given vancomycin[48]. Out of the 30 patients given ceftaroline, 17 (57%) had failed initial treatment and therefore were switched to ceftaroline. Clinical outcomes were similar in all groups, including 30-day mortality, 42-day relapse, and 30-day readmission. In a review of the available studies investigating ceftaroline as a salvage therapy for MRSA bacteremia, it was found to be useful[49]. As ceftaroline usage has not been established in the treatment of MRSA bacteremia, its optimal dosage, particularly when used as a salvage monotherapy, has not yet been demonstrated in

any clinical trial. Comparative studies will be needed to assess its standing as a monotherapy for MRSA bacteremia.

4.1.3. Dalbavancin—Dalbavancin is a semisynthetic lipoglycopeptide with activity against Gram-positive pathogens that is currently FDA-approved to treat acute bacterial skin and skin structure infections (ABSSSI). A phase II, randomized, controlled, open-label trial with results published in 2005 showed that dalbavancin may be a viable alternative to vancomycin in patients with catheter-related bloodstream infections caused by Gram-positive pathogens, as 20 of 23 (87%) patients given dalbavancin had treatment success (resolution of signs and symptoms and microbiological clearance of infection) compared to 14 of 28 (50%) patients given vancomycin[50]. However, it is important to note that only 14 patients had MRSA and that most infections in both treatment groups were caused by coagulase-negative staphylococci (CoNS). More recently, there is a phase II, multicenter, open-label, randomized clinical trial (NCT04775953) currently recruiting that will compare dalbavancin to SOC in patients with complicated bacteremia or right-sided endocarditis caused by *S. aureus*. For patients with MRSA, patients randomized to receive dalbavancin will receive a 1500 mg dose intravenously (IV) on day 1 and 1500 mg IV on day 8, while those randomized to receive SOC will receive either vancomycin or daptomycin. The primary outcome measure assesses the resolution of clinical signs of SAB, clinical failure, incidence of metastatic infections, and relapse of infection. It is anticipated that the study will be completed in August of 2023. Dalbavancin is a promising agent given its success in a clinical trial focused on treating Gram-positive bacteremia, while also having an acceptable safety profile. Dalbavancin is also notable for its long plasma-half life, and therefore can be administered once weekly, potentially in an outpatient setting when appropriate[51]. Future trials should hopefully help to clarify its usefulness against MRSA bacteremia. Large clinical trials with glycopeptides would also prove helpful in providing information about the potential for the development of resistance to emerge and affect treatment, as a dalbavancin non-susceptibility phenotype was observed after one patient was treated with both vancomycin and dalbavancin[52] In vitro, the exposure of MRSA to dalbavancin led to a 64–128 fold increase in the MIC of dalbavancin and a 4–16 fold increase in the MIC of vancomycin[53].

4.1.4. Telavancin—Telavancin is another semisynthetic lipoglycopeptide that is FDA-approved to treat cSSTIs, HABP, and ventilator-associated bacterial pneumonia (VABP) caused by susceptible isolates of *S. aureus* when alternative treatments are not available. Telavancin was evaluated to treat MRSA bacteremia in a randomized phase II clinical trial (NCT00062647) in which a total of 60 patients with uncomplicated SAB were randomized to receive either telavancin (10 mg/kg/day IV every 24 hours up to 14 days) or SOC to treat either MRSA or MSSA depending on the methicillin-resistance status of the patient isolate. Approximately 50% of patients in both the telavancin-treated group and the SOC-group had MRSA (15 of 31 patients in the all-treated target population)[54]. At the test-of-cure (TOC) visit, seven of eight (88%) patients given telavancin were cured of infection compared to eight of nine (89%) patients given SOC. All patients with MRSA bacteremia were cured. Serious adverse events (SAEs) were more common in patients given telavancin, with 38% of telavancin-treated patients experiencing an SAE compared to 21% of patients

receiving SOC. There was also an increase in serum creatinine levels in patients given telavancin, with 5 of 25 (20%) patients having serum creatinine ≥ 1.5 mg/dl and at least 50% greater than baseline compared to 2 of 25 (8%) patients given SOC. This study utilized a proof-of-concept design to demonstrate that telavancin could be used to treat SAB but the study population was restricted to patients with uncomplicated bacteremia, which is uncommon and therefore limited the target population[55]. Another trial that evaluated telavancin as a treatment for SAB is a phase III, randomized, open-label, noninferiority trial (NCT02208063) that was terminated due to a lack of statistical power[56]. In this trial, patients with SAB or infective endocarditis caused by *S. aureus* were randomized to receive either telavancin or SOC, with the primary endpoint being the number of participants that were cured at TOC. Out of 47 patients given telavancin, 22 (47%) were determined to be cured of infection compared to 27 of 52 (52%) patients given SOC. SAEs were more common in patients given telavancin, but there were no significant differences between groups in occurrence of acute kidney injury. Larger trials are needed with telavancin before conclusions can be made about its efficacy, as both trials have been too small to draw meaningful conclusions. Future trials with telavancin should also focus on including patients with complicated bacteremia in the study population.

4.1.5. Linezolid—Linezolid is a synthetic antibiotic belonging to the class of oxazolidinone antibiotics that inhibits protein synthesis by binding to both the 30S and 50S subunits of rRNA[57]. It is currently FDA approved for the treatment of HABP and cSSTIs caused by either MRSA or MSSA. The efficacy of linezolid as a treatment for catheter-related bloodstream infections was investigated in an open-label, multicenter trial in which patients with a suspected catheter-related infection were randomized to receive either linezolid 600 mg IV or vancomycin 1 g IV every 12 hours for 7–28 days[58]. Out of 363 patients that received linezolid, 49 (13%) had MRSA, compared to 40 of 363 (11%) patients that received vancomycin. Out of 24 patients with a MRSA bloodstream infection that received linezolid, 19 (79%) achieved clinical success at TOC compared to 16 of 21 (76%) patients with a MRSA bloodstream infection that received vancomycin (95% CI: −21.4 – 27.4). Patients with bacteremia caused by a Gram-negative pathogen were recommended to be given aztreonam or amikacin, although specific information about therapies given to these patients was not made available. An independent review of the treatments given to these patients by two academic physicians found that treatment was adequate in 22 of 59 (37%) patients given linezolid and 19 of 47 (40%) patients in the control group. In patients with Gram-negative bacteremia, negative blood cultures at baseline, or an infection with both Gram-positive and Gram-negative pathogens, a Kaplan-Meier survival curve analysis showed increased incidence of mortality in patients that received linezolid compared to the control group (patients with a negative culture at baseline: hazard ratio (HR) = 2.20, 95% CI: 1.07 – 4.50; patients with Gram-negative bacteremia: HR = 1.94, 95% CI: 0.78 – 4.81). This suggests that linezolid should not be given as an empirical therapy for the treatment of bacteremia and should only be given to patients with a microbiologically confirmed Gram-positive infection. The results of this study led to an FDA warning in 2007 advising against the use of linezolid in patients with bacteremia caused by a Gram-negative or an unknown organism[59].

4.1.6. Trimethoprim-sulfamethoxazole—Trimethoprim-sulfamethoxazole (TMP/SMX) is a fixed antibiotic combination that is currently FDA-approved to treat otitis media in pediatric patients, urinary tract infections, and acute infective exacerbation of chronic bronchitis. It is also used off-label to treat skin infections caused by *S. aureus*. Sulfamethoxazole competes directly with 4-aminobenzoic acid to inhibit the synthesis of dihydrofolate, while trimethoprim inhibits dihydrofolate reductase, leading to an overall interruption in purine biosynthesis[60]. The potential of TMP/SMX to treat SAB was evaluated in a randomized clinical trial in 1992[61], which randomized intravenous drug users hospitalized with suspected SAB to receive vancomycin 1 g or TMP/SMX (320 mg:1600 mg) every 12 hours. Of 43 patients given TMP/SMX, 27 (63%) had bacteremia compared to 38 of 58 (66%) patients given vancomycin. 47% of all infections were caused by MRSA. TMP/SMX was inferior to vancomycin, as 37 of 43 (86%) patients given TMP/SMX were cured of infection compared to 57 of 58 (98%) patients given vancomycin ($P = 0.014$). In a more recent clinical trial, TMP/SMX was again compared to vancomycin to treat MRSA infections (NCT00427076)[62]. Of 252 patients in the trial, 91 (36%) had bacteremia. Treatment failure was observed in 51 of 135 (38%) patients given TMP/SMX compared to 32 of 117 (27%) given vancomycin, and TMP/SMX failed to meet the non-inferiority criterion (defined by a difference of less than 15% for treatment failure). For patients with bacteremia, mortality (30-day all-cause) was observed in 14 of 41 (34%) patients given TMP/SMX compared to 9 of 50 patients (18%) given vancomycin, which led to the authors of the study advising against the use of TMP/SMX to treat severe MRSA infections. Given that TMP/SMX has failed to be non-inferior to vancomycin in two large clinical trials, TMP/SMX is not a viable alternative to SOC for MRSA bacteremia.

4.2. Combination therapy

There has been an abundance of data in the form of in-vitro experiments, animal models, and observational studies to suggest that the use of combination antimicrobial therapy may benefit patients with SAB. Two of the largest clinical trials to date investigating novel therapeutic strategies to treat MRSA bacteremia have evaluated the efficacy and safety of combination therapy.

4.2.1. Rifampicin—Rifampicin is an antibiotic that specifically inhibits bacterial RNA polymerase with increased antimicrobial activity against Gram-positives, as it has difficulty penetrating through the outer membrane in Gram-negatives[63]. When used clinically, rifampicin is used in combination with other antibiotics to suppress the rapid emergence of resistance, which arises from mutations in the *rpoB* gene that encodes the β-subunit of RNA polymerase[64]. The use of rifampicin combination therapy has been established in patients with orthopedic device-related infections, which are particularly difficult to treat because of the recalcitrant nature of the colonizing biofilm[65]. Antibiotic combinations that contained rifampicin were more effective at reducing bacterial load than those without it in a mouse osteomyelitis model[66], and rifampicin has also been implicated for use in combination therapy due to in-vitro evidence that it penetrates eukaryotic cells more effectively than glycopeptides and β-lactams[67], indicating it may help to target intracellular bacteria that are shielded from antibiotics. In a rabbit endocarditis model, the use of rifampicin in

combination with vancomycin led to decreased vegetation titers of MRSA compared to use of either antibiotic alone[68].

In the largest clinical trial investigating a therapeutic strategy to treat SAB to date, 758 patients with SAB were randomized to receive rifampicin (600 mg or 900 mg per day) or a placebo in addition to SOC for 2 weeks[69]. The primary endpoints were the duration of time before treatment failure, recurrence, or death. Of the 758 patients, only 47 (6%) had MRSA bacteremia. Out of MRSA patients, 9 of 26 (35%) given rifampicin reached a primary endpoint by week 12 compared to 3 of 21 (14%) given a placebo. Overall, by week 12, 71 of 388 (18%) patients given rifampicin reached the primary endpoint compared to 62 of 370 (17%) patients given a placebo ($P = 0.81$). This trial showed no added benefit for the addition of rifampicin to standard antibiotic therapy, and instead there was evidence that the use of rifampicin in this manner may further complicate treatment, as 17% of patients given rifampicin had an antibiotic-modifying adverse event compared to 10% of patients given a placebo ($P = 0.004$).

4.2.2. β-lactam antibiotics—β-lactams, the most widely-used class of antibiotics[70], exert antimicrobial activity by binding to penicillin-binding proteins (PBPs) and interrupting the transpeptidation process which results in the termination of peptidoglycan cross-linking[71]. Bacterial resistance to β-lactams is of serious concern, as numerous resistance mechanisms have been described, including drug efflux, production of β-lactamases, overproduction of PBPs, and the reduced affinity of β-lactams for PBPs[72]. This reduced affinity is a defining feature of MRSA, which contains the *mecA* gene that codes for a PBP, called PBP2A, that has reduced affinity for β-lactams[73].

The “see-saw” effect refers to an observed increase in the susceptibility of MRSA to beta-lactams when susceptibility to glycopeptide and lipopeptide antibiotics such as vancomycin and daptomycin decrease[74], suggesting that the addition of β-lactams to SOC may improve clinical outcomes for patients with MRSA bacteremia. In a multicenter, open-label, randomized clinical trial (NCT02365493), patients with MRSA bacteremia were randomized to receive either SOC or a β-lactam (flucloxacillin, 2 g IV every 6 hours; cloxacillin, 2 g IV every 6 hours) in addition to SOC for the first 7 days following randomization[75]. Cefazolin was used in patients with non-type 1 hypersensitivity allergies to penicillin (2 g every 8 hours) and in patients undergoing hemodialysis (2 g 3 times per week after hemodialysis). The primary endpoints of the study were mortality, persistent bacteremia at day 5, microbiological relapse, and microbiological treatment failure. Out of 170 patients, 59 (35%) in the combination therapy group reached a primary endpoint compared to 68 of 175 patients (39%) in the standard therapy group. Despite no difference between groups in the primary endpoint, persistence of bacteremia was observed in 19 of 166 (11%) patients in the combination therapy group compared to 35 of 172 (20%) patients at day 5 ($P = 0.02$). However, 34 of 145 (23%) patients given combination therapy had acute kidney injury compared to 9 of 145 (6%) patients given standard therapy ($P < 0.001$), which led to early termination of the trial. While the safety profile of combination therapy outweighed its clinical impact in this study, the study authors acknowledge that regional differences in vancomycin MICs may have impacted treatment response. This study was also overwhelmingly reliant on vancomycin with flucloxacillin or cloxacillin

with only a few daptomycin and cefazolin treatments (349 out of 352 patients in the trial received vancomycin). Such reliance may have had an impact on the nephrotoxicity results, as cefazolin has been associated with a better safety profile than other anti-staphylococcal penicillins in patients with MSSA bacteremia[76]. Of the 27 patients who received cefazolin in addition to vancomycin, only one developed acute kidney injury.

Discussed earlier as a monotherapy, ceftaroline has also been investigated for use in combination antimicrobial therapy. The use of ceftaroline in combination with daptomycin as salvage therapy for complicated MRSA bacteremia was demonstrated in a retrospective cohort study, as none of the 30 patients given ceftaroline experienced recurrence of bacteremia within 60 days compared to 9 of 30 patients given SOC ($P < 0.01$)[77]. Further evidence for the use of the daptomycin-ceftaroline combination as a salvage therapy was provided in a case series. In this study, bacteremia persisted for a median of 10 days on previous antibiotic treatment, with infection clearance achieved in a median of 2 days after the start of combination therapy in 23 out of 26 cases (20 were MRSA)[78]. Evidence supporting the efficacy of ceftaroline in combination with daptomycin in the form of data from randomized clinical trials is limited, with only one small phase IV trial with published data and another completed phase IV trial with data not yet available. In a phase IV, randomized, open-label trial (NCT02660346) with 40 participants, patients with MRSA bacteremia were randomized to receive either monotherapy (vancomycin or daptomycin) or 6 to 8 mg/kg/day of daptomycin and 600 mg of ceftaroline every 8 hours[79]. There was a significantly increased risk of mortality in the SOC group compared to patients in the combination therapy group (Kaplan-Meier 60-day survival analysis, $P = 0.028$). As a disproportionate number of deaths occurred in the group receiving monotherapy, the trial was halted early. Of note, two patients with stage IV lung cancer were randomized to the monotherapy group, suggesting random variability between the two groups could have impacted the study's results. The other phase IV trial is a non-randomized, open-label trial evaluating the efficacy and safety of ceftaroline fosamil 600 mg IV given every 8 hours in patients with SAB that persists at least 72 hours after vancomycin and/or daptomycin treatment (NCT01701219). This study was completed in 2014, but the results have not yet been made available. The use of ceftaroline combination therapy is promising, especially with respect to its safety profile, but the only clinical trial with published results was underpowered to make conclusions about efficacy. Larger trials powered to show efficacy in comparison to SOC will prove useful. While we are awaiting full results on the study completed in 2014, this study is non-comparative in nature which limits conclusions about efficacy.

4.2.3. Fosfomycin—Fosfomycin is a phosphonic acid antibiotic first discovered in 1969 that is primarily used to treat lower urinary tract infections. Fosfomycin inhibits the MurA enzyme, which catalyzes the first committed step in peptidoglycan synthesis[80]. The efficacy and safety of fosfomycin in combination with imipenem (a carbapenem) was evaluated for use as a salvage therapy in patients with complicated bacteremia and endocarditis due to MRSA in a study conducted from 2001 to 2010[81]. In total, 16 patients received primarily vancomycin or daptomycin (with some patients also receiving gentamicin, teicoplanin, or linezolid) as the initial therapy, with fosfomycin (2 g IV every

6 hours) in combination with imipenem (1 g IV every 6 hours) added as the salvage therapy. All patients had a negative blood culture 72 hours after the first dose, and 11 patients were cured and 5 had died at TOC. Adverse effects attributed to combination therapy were observed in five patients, and included leukopenia, fungal bloodstream infection, and liver cirrhosis. A follow-up study was completed in 2018 in the form of a randomized, open-label, multicenter clinical trial (NCT00871104)[82]. Among 15 patients with complicated bacteremia or infective endocarditis due to MRSA, 8 were randomized to receive fosfomycin and imipenem, and 7 to receive vancomycin. Four patients (50%) were cured of infection in the combination therapy group, while three patients (43%) that received vancomycin were cured. Hypernatremia was reported in one patient undergoing combination therapy.

In-vitro results and animal studies have shown synergistic activity between fosfomycin and daptomycin, specifically as a means to treat MRSA endocarditis in a rabbit model[83]. A recent, randomized, open-label trial sought to explore this relationship clinically (NCT01898338), in which patients with MRSA bacteremia were randomized to receive 10 mg/kg IV of daptomycin daily with or without 2 g IV of fosfomycin every 6 hours[84]. The primary endpoint was treatment success at TOC (6 weeks after the end of therapy), defined as the resolution of clinical manifestations and a negative blood culture. Out of 74 patients, 40 (54%) given combination therapy had treatment success, compared to 34 of 81 (42%) patients given monotherapy ($P = 0.135$). In the combination therapy group, 12 patients (16%) had complicated bacteremia at TOC compared to 26 (32%) in the SOC group. Adverse events were more common in the combination therapy group and included cardiac failure and electrolyte disorders, including hypokalemia and hypocalcemia. Notably, fosfomycin-related adverse events occurred after a median of 10 days post-treatment, while microbiological efficacy was achieved at 3 and 7 days, suggesting fosfomycin should be administered early during the first week of treatment to minimize the risk of side effects. Fosfomycin may have a role in aggressive treatment regimens, but the risk of side effects relative to monotherapy suggest treatment should be de-escalated to monotherapy when determined to be appropriate. Clinical trials investigating fosfomycin have also been limited in the enrollment of patients with complicated bacteremia. Future trials may look to increase the enrollment of patients with complicated SAB.

4.3. Novel antimicrobials and adjunctive therapies

Several novel antimicrobials, mostly in the form of anti-*S. aureus* antibodies and recombinant lysins, have been evaluated for their potential to treat SAB as adjunctive therapies to SOC.

4.3.1. Altastaph (*S. aureus* capsular polysaccharide immune globulin)—

Altastaph (Nabi Biopharmaceuticals, Rockville, MD) is a *S. aureus* polyclonal immunoglobulin preparation that contains antibodies against capsular polysaccharide (CPS) types 5 and 8, which are produced by about 70% of *S. aureus* clinical isolates[85]. It should be noted however that CPS are not produced[86] by the most abundant clonal lineage of MRSA in the United States, USA300[87], which represents a drawback of therapeutics targeting capsular polysaccharides. Nonetheless, antibodies against CPS types 5 and 8 have been

shown to have high opsonizing activity in vitro[88] and to offer passive immunity against staphylococcal endocarditis and sepsis in several animal models[88, 89]. Previously, a phase II clinical trial evaluating the safety and ability of Altastaph to prevent nosocomial *S. aureus* infections in very low birth weight infants indicated that it was well-tolerated[90]. A randomized phase II clinical trial (NCT00063089) sought to determine the safety and pharmacokinetics of Altastaph in 40 patients with SAB and persistent fever, with patients receiving SOC plus either two infusions of Altastaph (200 mg/kg) 24 hours apart or placebo[91]. Out of the 40 patients, 17 had MRSA bacteremia. In the Altastaph group, high levels of antibodies (> 100 μg/mL) were maintained for four weeks post-treatment. Compared to the placebo group, patients receiving Altastaph had a significantly shorter median time to fever resolution (2 days versus 7 days, $P = 0.09$) and a shorter duration of hospital stay (9 days versus 14 days, $P = 0.03$). Among patients with MRSA bacteremia, the median time to resolution of bacteremia was 0 days in the Altastaph group compared to 2 days in the placebo group ($P = 0.3$), suggesting that Altastaph did not aid in the resolution of SAB. Adverse events determined to be drug and infusion related included fevers, rigors, dyspnea, and chest discomfort. The development of Altastaph was halted in 2005, after Nabi Biopharmaceuticals' StaphVAX® vaccine, which is based on the same technology as Altastaph, failed to meet its primary endpoint in a phase III clinical trial[92].

4.3.2. Tefibazumab (Aurexis®)—Tefibazumab (Aurexis®) is a humanized monoclonal antibody (immunoglobin G1 kappa) that binds to clumping factor A (ClfA), an MSCRAMM (microbial surface components recognizing adhesive matrix molecules) protein in *S. aureus* that promotes the binding of fibrin and fibrinogen to the bacterial cell surface. ClfA is found in nearly all *S. aureus* clinical isolates[93] and is involved in staphylococcal colonization[94–96]. In a sepsis model, mice given a murine monoclonal antibody (MAb 12–9) that targets ClfA prior to bacterial challenge survived longer compared to the control group[97], and in an infective endocarditis model, rabbits given tefibazumab prophylactically did not become bacteremic after bacterial challenge[98]. The safety and pharmacokinetics of tefibazumab in humans was evaluated in a randomized, double-blind, multi-center phase II trial (NCT00198302) that randomized 63 patients with SAB to receive either tefibazumab (20 mg/kg single infusion) or a placebo in addition to SOC[99]. At baseline, MRSA was identified in 37% of the blood culture isolates in the tefibazumab group and in 57% of the placebo group (n = 30 in each group). The biological activity of tefibazumab was defined by at least one of the following endpoints: 1) development of an SAB-related complication that was not present at baseline; 2) microbiologically confirmed relapse of SAB; 3) death. Out of 30 patients given tefibazumab, 2 (7%) reached an endpoint compared to 4 of 30 (13%) patients in the placebo group ($P = 0.455$). Only 2 of 28 (7%) patients with MRSA reached an endpoint. Adverse events were more common in the tefibazumab group, and a hypersensitivity reaction occurred in one patient given tefibazumab. Clinical development of tefibazumab was suspended in 2006, pending the outcome of licensing negotiations[100].

4.3.3. 514G3 (monoclonal antibody)—514G3 (XBiotech, Austin, TX) is a human anti-SpA monoclonal antibody that binds to staphylococcal protein A (SpA), which promotes immune evasion by interfering with the development of humoral immunity[101]. Anti-SpA monoclonal antibodies have been shown to have protective effects in vivo,

protecting mice against *S. aureus* sepsis, subsequent staphylococcal infections, and nasopharyngeal colonization[102]. Mice given 514G3 in addition to vancomycin had increased survival six days after bacterial challenge compared to vancomycin alone in a bacteremia model[103]. The safety of 514G3 was assessed in patients hospitalized with SAB in a Phase I-II clinical trial (NCT02357966), with subjects randomized to receive either a single dose of 514G3 (2, 10, or 40 mg/kg) or a placebo in addition to SOC[104]. In total, 16 subjects were enrolled in the phase I study, with 6 cases of MRSA (38%). SAEs were reported in 3 of 12 patients (25%) given 514G3 compared to 2 of 4 (50%) patients given a placebo, but the investigators determined these were not treatment-related. In the Phase II trial, patients with SAB were randomized to receive either a single dose of 514G3 at 40 mg/kg or a placebo, both in addition to SOC, with duration of hospitalization and incidence of SAEs the primary clinical endpoints[105]. While the length of hospital stay was decreased by 33% in the 514G3 group compared to the placebo group, the difference was not statistically significant. There was a 56% relative risk reduction for the incidence of *S. aureus*-related SAEs in patients receiving 514G3 compared to the placebo (4 of 36 (11%) versus 4 of 16 (25%), respectively), but no definition of *S. aureus* related SAEs was given and the results were not statistically significant ($P = 0.23$). 514G3 is the lone antibody-only candidate that is still seeing clinical investigation as an adjunctive treatment for MRSA bacteremia. Its phase II trial was designed to provide insight into both safety and efficacy, but the trial was too small to make conclusions regarding efficacy and lacked significant results. It should also be noted that no information was given on the prevalence of MRSA bacteremia or complicated bacteremia in the study population. Therefore, a larger trial – preferably with an emphasis on efficacy endpoints, should be completed to demonstrate its potential.

4.3.4. DSTA4637S (anti-*S. aureus* antibody-antibiotic conjugate)—Long-term colonization with *S. aureus* and associated clinical failures may be linked to the establishment of intracellular reservoirs inside host cells[106], which shield the bacteria from antibiotics[107]. Aiming to target such reservoirs, DSTA4637S (Genentech, San Francisco, CA) is a Thiomab antibody-antibiotic that contains an engineered human immunoglobulin G1 (IgG1) anti-*S. aureus* monoclonal antibody linked to a novel rifamycin class bactericidal antibiotic (dmDNA31) via a protease-cleavable valine-citrulline (VC) linker[108–110]. The antibody targets the β-*N*-acetylglucosamine (β-GlcNAc) sugar modification of WTA. dmDNA31 only becomes active after cathepsins in the phagolysosome cleave the VC linker once bacteria bound to the antibody have been phagocytosed[108]. The in-vivo efficacy of this conjugate was demonstrated in a mouse model where mice pre-treated with the conjugate prior to MRSA challenge had a significantly lower CFU burden in the kidneys four days after infection compared to mice pre-treated with vancomycin[108].

In humans, DSTA4637S was first used in a phase I randomized, placebo-controlled, single-ascending dose study (NCT02596399) that assessed its safety, tolerability, pharmacokinetics, and immunogenicity in healthy volunteers[111]. Treatment-emergent adverse events (TEAEs) were considered mild and included nasal discharge discoloration, headache, and nausea. The plasma pharmacokinetics of DSTA4637S were approximately dose-proportional with a mean half-life ranging from 4.3 to 6.1 days, and no anti-drug antibodies were detected post-baseline. The second phase I trial (NCT03162250) randomized 27 patients with SAB

to receive DSTA4637S at a low, intermediate, or high dosage (infusion within 24 hours of randomization on day 1 and then every 7 days up to 6 doses) or a placebo in addition to SOC. The full results of the trial have not yet been made available but a comparison of the pharmacokinetics of DSTA4637S between healthy volunteers and SAB patients has been published. Peak serum concentrations of DSTA4637S were reduced 26.7% to 51.3% in SAB patients compared to healthy volunteers, potentially due to factors such as disease status, target-mediated clearance and/or non-specific uptake of the antibody-antibiotic conjugant[112]. As clinical trials with DSTA4637S have been focused on characterizing its safety and pharmacokinetics, a larger trial focused on efficacy is necessary to demonstrate its potential as a novel therapeutic agent for SAB. It would also be beneficial if such a trial can investigate if reduced serum concentrations of DSTA4637S has a meaningful effect on treatment efficacy.

4.3.5. SAL200 (N-Rephasin™)—Endolysins are bacteriophage-derived hydrolytic enzymes that target the cell wall and show promise as potential therapeutic agents for infections caused by Gram-positive pathogens. For the treatment of SAB, SAL200 (N-Rephasin™) is an endolysin-based candidate that utilizes SAL-1, a recombinant bacteriophage endolysin derived from SAP-1[113, 114], a *Staphylococcus*-specific bacteriophage. Antibacterial activity of SAL200 and synergism with antibiotics against both MRSA and MSSA has been demonstrated both in vitro and in a mouse model[115]. Preclinical evaluations of the safety of SAL200 in dogs and rats revealed only mild, transient adverse effects after injection[116]. In a placebo-controlled single-dosing and dose-escalating phase I clinical trial (NCT01855048), which was also the first-in-human phase I study to intravenously administer a bacteriophage endolysin-based drug to human patients, the safety profile, pharmacokinetics, and pharmacodynamics of SAL200 were evaluated in 36 healthy male volunteers[117]. SAL200 was well tolerated, with no SAEs and only mild and transient adverse events. Another phase I, multiple-ascending dose trial (NCT03446053) was recently completed[118]. Among patients given SAL200, adverse events included chills, pyrexia, and headache, but no SAEs were reported. To evaluate the safety and efficacy of SAL200 in patients with SAB, a phase II placebo-controlled trial (NCT03089697)[119] was completed, which randomized patients to receive either a placebo or SAL200 in addition to SOC. Incidence of TEAEs were similar in both the placebo and experimental groups. Efficacy endpoints, which included the percentage of patients in each group with treatment failure by day 14, percentage of patients who died of SAB within 14 days of diagnosis, and percentage of patients with a negative first blood culture, were also similar in both groups. This trial was terminated by the study's sponsor, Intron Biotechnology, prior to completion for strategic reasons. There is currently no data to suggest that SAL-200 is effective when used as an adjunctive therapy, although this is because its clinical investigation has focused on characterizing its safety and pharmacokinetics. These studies suggest that it is well-tolerated, but future studies will need to be designed to make conclusions about its efficacy.

4.3.6. Exebacase (CF-301)—Another bacteriophage lysin-based candidate for the treatment of SAB is exebacase (CF-301). In vitro, exebacase has rapid bacteriolytic activity against MRSA and MSSA, anti-biofilm activity, synergy with SOC antibiotics and human blood components (albumin and lysozyme), and a lower resistance profile relative to other

antibiotics[120–123]. Notably, exebacase is bacteriolytic against 120 MRSA isolates and has a lower molar MIC against MRSA compared to vancomycin and daptomycin[120]. The safety of exebacase was first evaluated in a phase I, dose-escalating trial with 20 healthy subjects (NCT02439359), with no reported adverse effects[124]. Since then, a phase II, randomized, double blind trial has been completed, primarily evaluating the safety, efficacy, and pharmacokinetics of exebacase in patients with SAB (NCT03163446)[125].

In this trial, 121 patients with SAB/endocarditis were randomized to receive either a single dose of exebacase (0.25 mg/kg) or a placebo in addition to SOC. Out of 121 patients, 116 had a confirmed *S. aureus* bloodstream infection (BSI), with a total of 37 (32%) BSI patients with MRSA. After 14 days, 50 of 71 (70%) patients given exebacase were clinical responders compared to 27 of 45 patients (60%) given antibiotics-alone ($P = 0.31$). Out of 27 MRSA patients given exebacase, 20 (74%) were clinical responders compared to 5 of 16 (31%) MRSA patients given antibiotics-alone ($P = 0.01$). Among patients with complicated MRSA bacteremia, 13 of 17 (76%) patients were clinical responders compared to 3 of 13 (23%) patients given antibiotics-alone (90% CI: 21.0 – 85.8). There was no statistically significant difference in clinical responder rates between the exebacase-treated group and the antibiotics-alone group in patients with MSSA and the overall cohort. This is potentially due to differences in the in-vivo antibacterial activity of the antibiotics used to treat MSSA compared to MRSA, as well as differences in the distribution of subgroup comorbidities such as left-sided endocarditis (15% of patients given exebacase had left-sided endocarditis compared to 7% of patients given antibiotics-alone). The incidence of TEAEs were similar in the exebacase-treated and antibiotics-alone groups and no hypersensitivity reactions to exebacase were reported, despite 21% of patients in the exebacase-treated group having anti-drug antibodies at baseline. Although the sample size of MRSA patients is small, this study is unique among clinical trials for adjunctive therapies for MRSA bacteremia because it employed a superiority-design that provides proof-of-concept for the use of exebacase as an adjunctive therapy. The efficacy and safety of exebacase for SAB treatment is currently undergoing further evaluation in a phase III, randomized, placebo-controlled study with an estimated enrollment of 348 patients (NCT04160468).

5. Conclusion

With only two FDA-approved antibiotics for the treatment of MRSA bacteremia, there is an urgent need to identify new treatments as mortality remains high and antibiotic resistance continues to increase the risk of treatment failure. While there remains a lack of high-quality evidence supporting the use of specific alternatives to vancomycin or daptomycin, clinical trials have revealed promising agents and therapeutic approaches while providing valuable information that will inform clinical management of MRSA bacteremia and lead to improved patient outcomes.

6. Expert Opinion

Vancomycin has remained the primary treatment for MRSA bacteremia for decades, with daptomycin emerging as another treatment option after it was shown to be non-inferior to vancomycin in 2006[38]. There is an urgent need to identify novel therapeutic agents

and approaches to treat MRSA bacteremia as the mortality rates associated with MRSA bacteremia have remained stable since the 1990s[5], in addition to concerns over both vancomycin's efficacy and toxicity and the emergence of bacterial non-susceptibility to daptomycin. In the pursuit of novel agents and treatments, investigations have focused primarily on three types of approaches: alternative antibiotics to SOC that can be used as monotherapies, combination antimicrobial therapies, and novel antimicrobials that can be used as adjunctive therapies to SOC.

Several different classes of antibiotics have been evaluated for use as a monotherapy to treat MRSA bacteremia, including cephalosporins, lipoglycopeptides, and oxazolidinones. Ceftobiprole and ceftaroline, both cephalosporins, are promising in that they have bactericidal activity against both MRSA and MSSA. This feature gives them the potential to act as a general treatment for SAB, regardless of the methicillin-resistance status of the isolate, but their efficacy as treatments for MRSA bacteremia have not yet been established through randomized clinical trials. There is an active clinical trial that will compare ceftobiprole to daptomycin as a treatment for SAB that seeks to establish its efficacy. Similarly, there is limited data substantiating the usefulness of dalbavancin and telavancin. Dalbavancin had success in treating bacteremia caused by Gram-positive bacteria in a clinical trial, but only a small subset of the study population had MRSA bacteremia. Telavancin did not perform better than SOC in the two clinical trials previously discussed, although it should be noted that one was a proof-of-concept study while another was terminated early. Although not discussed extensively in this review, oritavancin is another lipoglycopeptide that is FDA-approved to treat ABSSSI that has seen some success as a treatment for Gram-positive bacteremia[126], but there is a lack of high quality data in patients with SAB. Notably, oritavancin is a candidate for outpatient parenteral antimicrobial therapy (OPAT) due to its extremely long half-life of 2 weeks[127]. There is a phase IV proof-of-concept trial (NCT03761953) that will evaluate the safety and efficacy of oritavancin as a treatment for bacteremia and endocarditis caused by *S. aureus* in opioid users[128]. This trial may pave the way for a larger, randomized trial with oritavancin in the future.

Linezolid was shown to be non-inferior to vancomycin in patients with Gram-positive infections but concerns about increased mortality in patients without Gram-positive infections make microbiological confirmation of the isolate crucial when considering the use of linezolid. Tedizolid is another oxazolidinone antibiotic, but it has not yet been evaluated as a treatment for MRSA bacteremia in clinical trials. Tedizolid may be a good candidate for future trials as it can be administered once daily, in addition to having a more favorable safety profile and shorter therapy duration than linezolid as a treatment for ABSSSI[129].

Trimethoprim-sulfamethoxazole was shown to be inferior to vancomycin as a treatment for MRSA bacteremia in two clinical trials discussed in this review, arguing against its use as a frontline therapy for MRSA bacteremia. Apart from dalbavancin, ceftaroline, and ceftobiprole, which are currently under investigation, there is no evidence to suggest that any of these monotherapy agents should be considered a frontline alternative to SOC; instead, it seems that their usefulness may lie as salvage therapies when patients do not respond to initial treatment. Future clinical trials investigating the efficacy of these potential salvage therapies may clarify which agents show the most promise.

A combination of in-vitro, animal model, and observational cohort studies have suggested that combination antimicrobial therapy may benefit patients with MRSA bacteremia. In the first large-scale, clinical evaluation of the usefulness of combination therapy, there was no added benefit of the addition of rifampicin to SOC as combination therapy lead to an increase in antibiotic-modifying adverse events. Since then, investigation has largely focused on evaluating the efficacy and safety of the addition of β-lactams to SOC, driven by the observation of the aforementioned "see-saw" effect. This effect is proposed to arise after the disruption of PrsA, a lipoprotein that acts as a post-translocational chaperone, leads to impaired post-translational maturation of PBP2A and a subsequent increase in susceptibility to β-lactams[130]. The clinical efficacy of β-lactams in addition to SOC was explored in the CAMERA-2 trial, which showed no benefit for this type of combination therapy. Despite bacteremia persistence decreasing in patients given combination therapy, the increased risk of acute kidney injury cannot be understated. However, it is important to note that 99% of patients in the trial were given vancomycin – therefore, increased usage of daptomycin may have allowed for a comparison of the safety profiles for both antibiotics when used in conjunction with β-lactams. Future clinical trials may consider exploring this topic. Additionally, future trials may emphasize using β-lactam antibiotics that have more favorable safety profiles, such as cefazolin or ceftaroline, compared to those primarily used in the CAMERA-2 trial. These approaches should help elucidate which combinations are most effective while keeping patient safety in mind. Ceftaroline in combination with daptomycin has been investigated in a clinical trial but the small sample size limited conclusions about its efficacy. Nonetheless, it was well-tolerated and warrants future investigation in a larger trial. The combination of daptomycin and fosfomycin has also shown promise as more patients given the combination therapy compared to SOC reached treatment success at six weeks post-treatment. However, the comparison was not statistically significant, and these results were accompanied by an increased incidence of adverse events in the combination therapy group. Fosfomycin is currently not available for intravenous use in the United States, and larger trials should reveal more about fosfomycin's safety profile and its potential as a treatment for MRSA bacteremia.

Clinical trials investigating novel antibodies and bacteriophage endolysins as adjunctive therapeutics for MRSA bacteremia have been mostly limited to small trials that primarily focus on safety evaluations, with SAL200 and exebacase being the most notable candidates in the clinical evaluation stage. These are the only bacteriophage lysin-based candidates that currently show the most promise for therapeutic use; candidates in the pre-clinical stage include LysGH15, P128, and ClyF, which have had success as treatments in MRSA bacteremia mouse models, but have no timetable on future development[131–133]. Encouragingly, SAL200 and exebacase have been well-tolerated, with generally mild adverse events and only a few instances of hypersensitivity reactions. Although anti-drug antibodies have been reported, specifically with SAL200 and exebacase, it remains to be seen how they affect treatment. Nevertheless, it is important to monitor the development of anti-drug antibodies to assess their potential to play a role in hypersensitivity reactions or treatment failure. The most promising agent in this class is exebacase, which is the first of its class to receive a phase III trial. Not only was it shown to be effective as an adjunctive therapy when added to SOC, but it also has an acceptable safety profile and no

hypersensitivity reactions were reported in a phase II trial despite the presence of anti-drug antibodies. Only 8 of 43 patients with MRSA in the trial were given daptomycin; thus, the efficacy of exebacase was mostly established in combination with vancomycin, but the ongoing phase III trial may further establish efficacy with daptomycin. Exebacase was granted Breakthrough Therapy designation by the FDA following the results of the phase II trial[134], and it is anticipated that the phase III trial will be completed in late 2022. In order for antibody and bacteriophage lysin-based candidates to reach their full potential, future trials will need to focus on demonstrating their efficacy. In this regard, SAL200, 514G3, and DSTA4637S should hopefully see larger trials with efficacy endpoints in the future.

The approval of novel agents to treat MRSA bacteremia significantly lags behind the approval of agents for use in treating ABSSSI or cSSTIs caused by MRSA. While there are only two drugs indicated for use as treatments for MRSA bacteremia, several drugs discussed in this review have already been approved for use in treating either ABSSSI or cSSTIs. Contributing to this is the relative difficulty of completing SAB trials compared to trials for ABSSSI/cSSTIs. Compared to these trials, bacteremia trial design for marketing approval lacks guidance from the FDA, which makes these trials difficult to standardize, in addition to being very expensive to run[55]. Bacteremia trials are also challenging because of the inherent difficulty in treating MRSA bacteremia; patients must be given an appropriate empirical therapy, and investigators must distinguish between uncomplicated and complicated bacteremia. The resistance profile of the patient isolate must also be considered in order to compare the efficacy of the investigational agent to SOC for either MRSA or MSSA bacteremia. Such difficulties present challenges to patient enrollment and make it difficult to conduct carefully controlled studies with largely homogeneous patient populations. In summary, investigators have learned through clinical trials that the drawbacks associated with combination therapy argue against widespread usage, but investigation focused on optimizing treatment duration and best practices for de-escalation to monotherapy should provide insight into maximizing patient safety during aggressive treatment regimens[135]. Only a few antibody and lysin-based candidates are seeing active development as adjunctive treatments for bacteremia, with their safety being established first and foremost – but exebacase's upcoming phase III trial demonstrates that progress has been made towards conducting larger trials with these agents that are designed to show efficacy. While several antibiotics investigated as monotherapies have already been studied for treating cSSTIs and ABSSSIs caused by MRSA, they will need to be studied in patients with MRSA bacteremia before conclusions are made. To this end, clinical trials with ceftobiprole and dalbavancin should hopefully be completed within the next five years. Based on this timeline, the near future will reveal more about the standing of novel monotherapies than the other approaches discussed in this review.

While vancomycin and daptomycin will continue to remain the first-line treatments for MRSA bacteremia, clinical trials have identified other agents that may prove to be alternative treatment options in the future such as dalbavancin, ceftobiprole, ceftaroline, and exebacase. Despite the fact that previous clinical trials have failed to support strong alternatives to standard therapy, the future of therapeutics for MRSA bacteremia looks bright, as several ongoing and planned clinical trials indicate the continued motivation of the pharmaceutical industry in this field.

Abbreviations:

ABSSSI	acute bacterial skin and skin structure infections
β-GlcNAc	β-*N*-acetylglucosamine
BSI	bloodstream infection
CABP	community-acquired bacterial pneumonia
CoNS	coagulase-negative staphylococci
CPS	capsular polysaccharide
cSSTIs	complicated skin and soft tissue infections
FDA	U.S. Food and Drug Administration
HABP	hospital-acquired bacterial pneumonia
HR	hazard ratio
hVISA	heterogeneous vancomycin-intermediate *Staphylococcus aureus*
IV	intravenous
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
MSCRAMM	microbial surface components recognizing adhesive matrix molecules
MSSA	methicillin-sensitive *Staphylococcus aureus*
NAG	*N*-acetylglucosamine
NAM	*N*-acetylmuramic acid
PBP	penicillin-binding protein
PG	phosphatidylglycerol
SAB	*Staphylococcus aureus* bacteremia
SAE	serious adverse event
SOC	standard of care
SSTIs	skin and soft tissue infections
TEAE	treatment-emergent adverse event
TMP/SMX	trimethoprim-sulfamethoxazole
TOC	test-of-cure
VC	valine-citrulline

VABP	ventilator-associated bacterial pneumonia
VISA	vancomycin-intermediate *Staphylococcus aureus*
VRSA	vancomycin-resistant *Staphylococcus aureus*
WTA	wall teichoic acid

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Article highlights

- The mortality associated with MRSA bacteremia has remained high and steady for decades, and there are concerns about the toxicity of standard therapy and the potential for antibiotic resistance to affect treatment efficacy.
- In large trials investigating the efficacy of combination therapy, no benefit has been shown for vancomycin plus rifampicin or β-lactam antibiotics. Moreover, safety profiles favor monotherapy over combination therapy.
- Ceftobiprole and ceftaroline are unusual in that they are β-lactam antibiotics that are used to treat MRSA infections. Both are currently under investigation as treatments for MRSA bacteremia and show acceptable safety profiles.
- Trials that are focused on investigating novel antimicrobials and adjunctive therapies, including antibody and bacteriophage lysin-based agents, have mostly been limited to small studies that seek to establish their safety and pharmacokinetics.
- Exebacase, a bacteriophage lysin-based candidate, is a standout among its class with efficacy as an adjunctive therapy to vancomycin for MRSA bacteremia shown in a phase II trial. Exebacase is undergoing further investigation in an upcoming phase III trial.
- There are no clear alternatives to vancomycin or daptomycin for treating MRSA bacteremia, but several agents currently under investigation demonstrate a continued effort to improving patient outcomes.

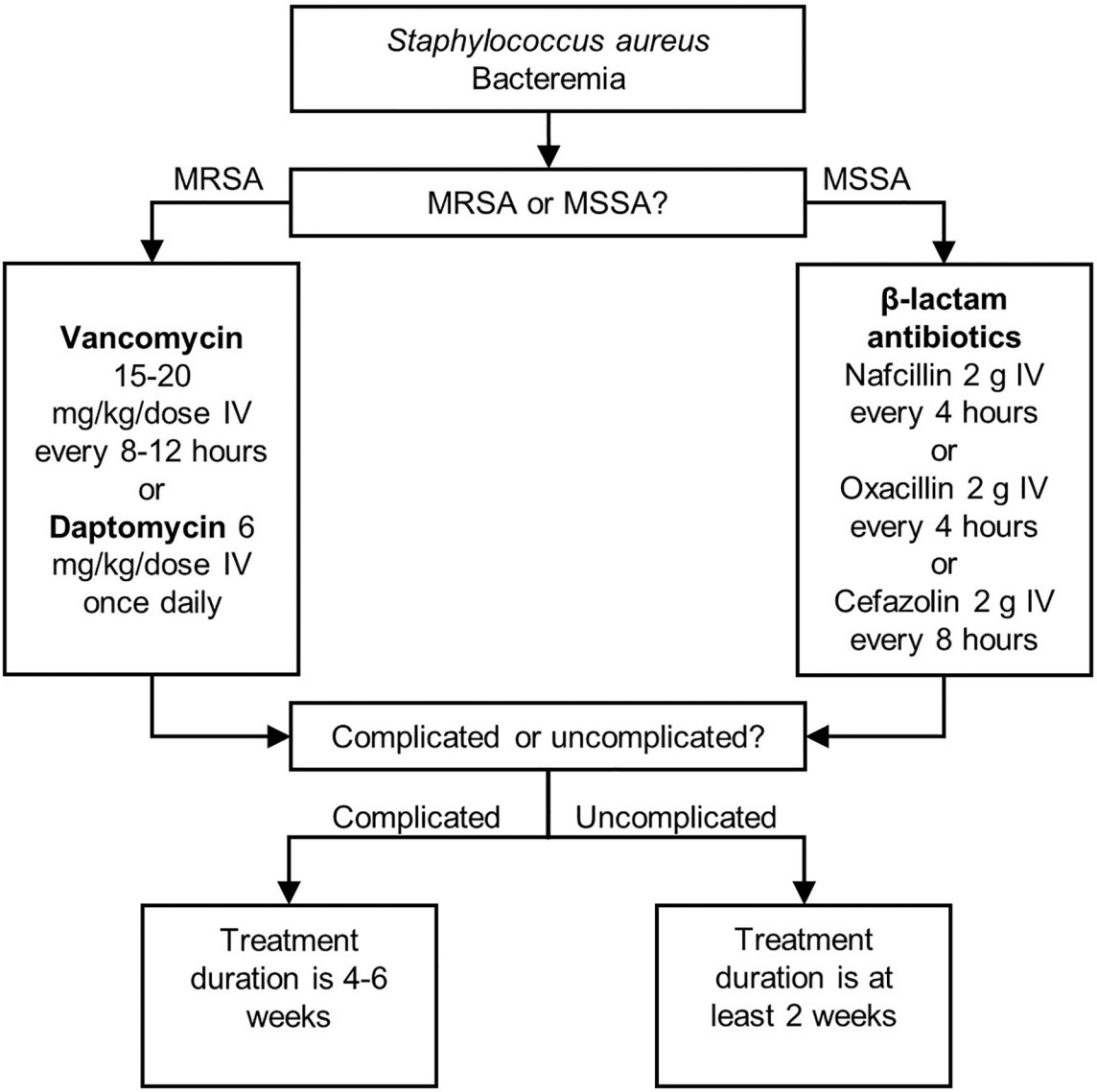

Figure 1.
Treatment guidelines for bacteremia caused by *Staphylococcus aureus*.

Table 1.

Investigational agents for the treatment of staphylococcal bacteremia in clinical trials

Clinicaltrials.gov Identifier	Intervention	Phase	Proposed Sample Size/ Enrollment	Primary Endpoints	Status	Results
Monotherapy						
NCT03138733	Ceftobiprole vs. daptomycin (with or without Aztreonam)	III	390	Overall success at the post-treatment evaluation (around day 70)	Active	N/A
NCT04775953	Dalbavancin vs. SOC	II	200	Resolution of clinical signs and symptoms, clinical failure, infectious complications	Recruiting	N/A
NCT00062647	Telavancin vs. SOC for uncomplicated SAB	II	60 (approximately 50% of patients had MRSA)	Presence or absence of clinical signs and symptoms associated with SAB, metastatic complications, positive culture at TOC evaluation	Completed	7/8 patients (88%) given telavancin were cured of infection compared to 8/9 patients (89%) given SOC.
NCT02208063	Telavancin vs. SOC	III	121	Alive at TOC, resolution of clinical signs and symptoms, no evidence of microbiological persistence or relapse, no new metastatic infections	Completed (terminated early)	22/47 (47%) patients given telavancin were cured of infection compared to 27/52 (52%) given SOC.
NCT00427076	Trimethoprim-sulfamethoxazole (TMP/SMX) vs. vancomycin for invasive MRSA infections	III	252 (91 had bacteremia)	Improved patient condition or cure with or without antibiotic modifications, survival at 7 days, 30-day all-cause mortality	Completed	51/135 (38%) patients given TMP/SMX had treatment failure compared to 32/117 (27%) given vancomycin. Patients with bacteremia given TMP/SMX had increased mortality (14/41, 34%) compared to patients given vancomycin (9/50, 18%).
Combination therapy						
NCT02365493	SOC with a β-lactam antibiotic vs. SOC for patients with MRSA bacteremia	III	358	All-cause mortality, persistent bacteremia at day 5 or later, microbiological relapse, microbiological treatment failure	Completed	59/170 (35%) patients in the combination group reached a primary endpoint compared to 68/175 (39%) patients given SOC. Increased risk of acute-kidney injury in the combination therapy group ($P < 0.001$).
NCT02660346	Daptomycin with ceftaroline vs. SOC for patients with MRSA bacteremia	IV	40	Time to bacteremia clearance	Completed	Significantly increased risk of mortality in the SOC group compared to the combination therapy group ($P = 0.028$). See section 4.2.2.

Clinicaltrials.gov Identifier	Intervention	Phase	Proposed Sample Size/ Enrollment	Primary Endpoints	Status	Results
NCT01701219	Ceftaroline fosamil in patients with SAB or MRSA bacteremia persisting 72 hours after initial treatment	IV	56	Time to bacteremia clearance, time to defervescence, clinical outcome, mortality, readmission	Completed	Results not posted.
NCT00871104	Fosfomycin and imipenem vs. vancomycin for patients with bacteremia or infective endocarditis due to MRSA	IV	50	Negative blood culture at 7 days	Completed	4/8 (50%) patients given combination therapy were cured of infection compared to 3/7 (43%) patients given vancomycin.
NCT01898338	Fosfomycin and daptomycin vs. daptomycin for patients with MRSA bacteremia	III	167	Clinical and microbiological response at week 6	Completed	40/74 (54%) patients given combination therapy had treatment success at TOC compared to 34/81 (42%) patients given daptomycin.
Novel antimicrobials and adjunctive therapies						
NCT00063089	Altastaph (polyclonal immunoglobulin preparation) vs. placebo, both in addition to SOC	I/II	40 (17 with MRSA)	Safety	Completed	Adverse events included fevers, rigors, and dyspnea. Patients given Altastaph had a significantly shorter median time to fever resolution (2 days versus 7 days, $P = 0.09$) and a shorter median duration of hospital stay (9 days versus 14 days, $P = 0.03$).
NCT00198302	Tefibazumab (Aurexis®) (humanized monoclonal antibody) vs. placebo, both in addition to SOC	II	60 (15 with MRSA)	Safety, pharmacokinetics, progression of uncomplicated SAB to complicated SAB, microbiological relapse, mortality	Completed	2/30 (7%) patients given tefibazumab reached a primary endpoint compared to 4/30 (13%) patients given a placebo ($P = 0.455$). 12/30 (40%) patients given tefibazumab had at least one SAE, compared to 9/30 (30%) given a placebo.
NCT02357966	514G3 (human monoclonal antibody) vs. placebo, both in addition to SOC	I/II	16 (Phase I). 52 (Phase II). 6 patients in phase I had MRSA.	Safety, tolerance, maximum tolerated dose (phase I). Duration of hospitalization, incidence of severe-adverse effects (phase II)	Completed	No adverse events attributed to the experimental treatment were reported in phase I. 56% relative risk reduction for the incidence of *S. aureus* related SAEs for patients given 514G3 compared to placebo ($P = 0.23$). Duration of hospitalization was decreased in patients given 51463 compared to placebo (8.6 ± 7 days for patients given 514G3, 12.7 ± 9 days

Clinicaltrials.gov Identifier	Intervention	Phase	Proposed Sample Size/ Enrollment	Primary Endpoints	Status	Results
						for patients given a placebo, (P = 0.092)
NCT03162250	DSTA4637S (antibody-antibiotic conjugate) vs placebo, both in addition to SOC	II	27	Incidence of adverse events	Completed	Full results not yet available. See section 4.3.4.
NCT03089697	SAL-200 (anti-staphylococcal lysin) vs. placebo, both in addition to SOC	II	25	Incidence of adverse events	Completed (terminated early)	10/12 (83%) patients given SAL-200 had a TEAE compared to 12/13 (92%) patients given a placebo.
NCT03163446	Exebacase (CF-301) (anti-staphylococcal lysin) vs. placebo, both in addition to SOC for patients with SAB or infective endocarditis	II	121 (37 with MRSA)	Incidence of adverse events, clinical outcome at day 14, pharmacokinetics	Completed	50/71 (70%) patients given exebacase were clinical responders compared to 27/45 (60%) patients given a placebo (P = 0.31). 20/27 (74%) patients with MRSA given exebacase were clinical responders compared to 5/16 (31%) patients with MRSA given a placebo (P = 0.01).
NCT04160468	Exebacase (CF-301) (antistaphylococcal lysin) vs. placebo, both in addition to SOC for patients with SAB or infective endocarditis	III	348	Clinical response at day 14, treatment-emergent adverse events through day 60	Recruiting	N/A

MRSA – methicillin-resistant *Staphylococcus aureus*; N/A – not applicable; SAB – *Staphylococcus aureus* bacteremia; SAEs – severe adverse events; SOC – standard of care; TEAE – treatment-emergent adverse event; TMP/SMX – trimethoprim/sulfamethoxazole; TOC – test-of-cure