Bacteremia due to Methicillin-Resistant *Staphylococcus aureus*

New Therapeutic Approaches

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KEYWORDS

• Methicillin • *Staphylococcus aureus* • MRSA • Bacteremia • Vancomycin • Daptomycin • Ceftaroline • Endocarditis

KEY POINTS

- Vancomycin, optimally dosed, remains the initial antibiotic of choice for the treatment of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and endocarditis due to isolates with vancomycin minimum inhibitory concentration $\leq$2 mg/mL. Daptomycin is an effective, although more costly alternative, and ceftaroline appears promising.
- Treatment options for persistent MRSA bacteremia or bacteremia due to vancomycin-intermediate or vancomycin-resistant strains include daptomycin, ceftaroline, and combination therapies.
- There is a critical need for high-level evidence from clinical trials to allow optimally informed decisions in the treatment of MRSA bacteremia and endocarditis.

INTRODUCTION

Resistance of *Staphylococcus aureus* to the first semisynthetic penicillin, methicillin, was reported within a year of its introduction into clinical medicine, mirroring the rapid identification of penicillin resistance less than a decade earlier. Methicillin-resistant *S aureus* (MRSA) subsequently increased in prevalence, but was largely confined to hospital settings until its emergence in the community in the last decade of the 20th century.

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The progressive emergence of MRSA led to the widespread use of vancomycin and, inevitably, reports of reduced susceptibility emerged, beginning with strain MU80 (vancomycin minimum inhibitory concentration [MIC] of 8 μg/mL) isolated in 1996 from the wound infection of a Japanese child receiving prolonged therapy with this glycopeptide antibiotic. This emergence represented the first identified vancomycin-intermediate *S aureus* (VISA; MIC 4–8 μg/mL) and was followed by the recognition of the emergence of heterogeneous intermediate reduced susceptibility (hVISA) strains, each resulting from cell wall alterations with sequestration of the glycopeptide. The first fully vancomycin-resistant (VRSA) strain (MIC >32 μg/mL) was identified in 2002, an occurrence that has fortunately remained rare.

This evolutionary history, together with the recognition of the frequent failure of vancomycin treatment of MRSA infections regardless of the MIC of the isolate, provides unequivocal evidence of the need for newer more effective therapies and therapeutic approaches (Tables 1 and 2).

GLYCOPEPTIDES AND SEMISYNTHETIC LIPOGLYCOPEPTIDES

Vancomycin

Optimization of vancomycin administration is a critical factor in improving outcomes of patients with MRSA infection, and recent information provides insight into this issue.

Table 1
Pharmacokinetic/pharmacodynamics profile of anti-infective agents for methicillin-resistant *Staphylococcus aureus*

Agent	MIC Breakpoint for *S aureus* (μg/mL)	PK-PD Indices Associated with Efficacy	Activity Against *S aureus*	% Protein Bound	Half-Life (h)	Excretion
Vancomycin	≤2	AUC/MIC	Bactericidal	50	5–11	80%–90% renal
Daptomycin	≤1	AUC/MIC	Bactericidal	90	8–9	89% renal, 6% feces
Ceftaroline	≤1	T > MIC	Bactericidal	20	2.7	88% renal, 6% feces
Dalbavancin	≤0.12	AUC/MIC	Bactericidal	93	346	33% renal, 20% feces
Oritavancin	≤0.12	AUC/MIC	Bactericidal	85	245	<5% renal, <1% feces
Telavancin	≤0.12	AUC/MIC	Bactericidal	90	6.6–9.6	76% renal, <1% feces
Tedizolid	≤0.5	AUC/MIC	Bacteriostatic	70–90	12	20% renal, 80% feces
Linezolid	≤4	AUC/MIC	Bacteriostatic	31	4–5	30% renal, 9% feces
Tigecycline	≤0.25	AUC/MIC	Bacteriostatic	71–89	42	33% renal, 59% feces

Abbreviations: AUC, area under the plasma concentration curve; T > MIC, time of drug concentration above MIC.

Data from Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, OH: Lexi-Comp, Inc; 2015; July 20, 2015; Micromedex Healthcare Series (Internet database). Greenwood Village, CO: Thomson Micromedex.

Although several studies have suggested that a vancomycin MIC = 2 μg/mL is associated with an increased risk of failure of treatment of these infections, a recent meta-analysis contradicted this conclusion.[1] Further confounding the understanding is the observation that a vancomycin MIC = 2 μg/mL is associated with an increased risk of failure of antibiotic therapy for methicillin-sensitive *S aureus* (MSSA) as well as MRSA infections, regardless of the administered antibiotic.[2] Finally, evidence is accumulating that the straightforward use of vancomycin trough concentration (Cmin) is an inaccurate means of achieving optimal dosing.

Although it has been generally accepted that the efficacy of vancomycin in bacteremia due to *S aureus* requires achievement of area under the plasma concentration-time curve (AUC) values greater than or equal to 400 times the MIC (AUC/MIC $\geq$400) and that this can be predicted by measured Cmin alone, recent evidence suggests these assumptions may be incorrect. Modeling studies have demonstrated that unadjusted extrapolation of AUC from serum trough concentrations underestimate AUC by up to 25% and that AUCs varied between patients with similar trough results by up to 30-fold.[3] Furthermore, the threshold for increased concentration-related nephrotoxicity was an AUC $\geq$700 mg h/L, and additional data indicate that a substantial increase in this risk occurs only at AUC $\geq$900 mg·h/L, thus bringing the effective treatment of infections due to isolates with MIC = 2 μg/mL more safely in line with the necessary vancomycin exposure. The increased accuracy of AUC estimations from serum vancomycin concentrations by the addition of Bayesian analysis may allow more precise individualized dosing, especially for targeting treatment of infections due to MRSA with an MIC = 2 μg/mL.[3]

The use of a loading dose and ongoing weight-based dosing are critical to rapid achievement of adequate serum concentrations, the importance of which has been demonstrated by the finding in patients with MRSA-associated septic shock that the highest survival rates were associated with an AUC_{24}/MIC well in excess of 400.[4]

Semisynthetic Lipoglycopeptides

Dalbavancin, oritavancin, and telavancin are semisynthetic lipoglycopeptides that are active in vitro against VISA. Telavancin and oritavancin are also active against VRSA and daptomycin nonsusceptible *S aureus*, while dalbavancin is not active against VRSA.[5]

The heptapeptide core common to all glycopeptides is responsible for impaired bacterial cell wall synthesis, inhibiting transglycosylation and transpeptidation by binding to C-terminal D-Ala-D-Ala. The addition of a lipophilic side chain anchors the molecule to the cell membrane and, in the cases of oritavancin and telavancin (but not dalbavancin), also alters cell membrane permeability by disrupting the bacterial membrane potential.

Oritavancin

A study of greater than 9000 MRSA isolates in the United States and Europe from 2008 to 2012 found that 94.6% were inhibited by oritavancin (MIC_{90} = 0.06 μg/mL).[5] Oritavancin is able to bind to D-Ala-D-Lac residues, and as a consequence, remains active against VRSA. The drug achieves very high concentrations within macrophages, a characteristic that may be of importance given the frequent intracellular residence of *S aureus*. Oritavancin therapy was associated with microbiological success in 47 (85%) of 55 patients with uncomplicated *S aureus* bacteremia, 47% of which were intravenous (IV) catheter associated.[5] The proportion due to MRSA (if any) was, however, not stated and, further complicating the analysis, the drug was administered in

Table 2
Dosing, pricing, and drug characteristics of anti-infective agents for methicillin-resistant *Staphylococcus aureus*

Agent	Dosing Regimens	Dose Adjustment	Advantages	Disadvantages, Adverse Effects	Average Daily Cost[a]
Vancomycin	25–30 mg/kg IV load, then 15 mg/kg IV every 8–12 h	Renal	Extensive clinical experience, inexpensive	Red man syndrome, nephrotoxicity (increased risk with higher doses, concurrent aminoglycosides, or pre-existing renal failure)	$15–$55
Daptomycin	6–10 mg/kg IV every 24 h	Renal	Strong evidence for wide range of MRSA infections	May be used in septic pulmonary emboli but not pneumonia; elevated CPK <1%: myopathy (increased risk in those on statins), eosinophilic pneumonia (onset 2–4 wk), peripheral neuropathy	$450–$750
Ceftaroline	600 mg IV every 8-12 h	Renal	Active against VISA, VRSA; exhibits a "see-saw" effect: inverse correlation between the MICs of ceftaroline and vancomycin	Positive Coombs test (without hemolysis ~11%)	$370–$550
Dalbavancin	1500 mg IV as a single dose	Renal	Activity against VISA, VRSA; rapidly bactericidal	Red man syndrome, ALT elevations	$5400 (1500 mg single dose)
Oritavancin	ABSSSI: 1200 mg IV as a single dose	Renal	Activity against VISA, some VRSA, and daptomycin nonsusceptible *S aureus*; in vitro bactericidal biofilm activity in both stationary and growth phases in *S aureus*	Artificially prolongs coagulation tests (INR, PT, aPTT) for ~48 h after administration: use is contraindicated with heparin IV	$3480 (1200 mg single dose)

Telavancin	cSSSI, HAP: 10 mg/kg IV every 24 h	Renal	Activity against VISA, VRSA, and MRSA strains that are resistant to vancomycin, linezolid, and daptomycin	Nephrotoxicity (boxed warning), red man syndrome, QTc prolongation; interferes with coagulation tests (INR, PT, aPTT, ACT) for ~18 h after administration: use is contraindicated with heparin IV. In those with CrCl ≤50 mL/min, decreased clinical response in cSSSI, increased mortality in HAP/VAP (boxed warning)	$430
Tedizolid	200 mg IV/PO daily	None	Excellent tissue penetration, 91% oral bioavailability	Animal and early clinical studies show potentially low to no MAO-mediated drug interactions, minimal myelosuppression or neuropathy (<21 d tedizolid treatment duration)	$300 (IV) $370 (PO)
Linezolid	600 mg IV/PO every 12 h	None	Excellent bone and tissue penetration, >99% oral bioavailability	Peripheral and optic neuropathy, reversible myelosuppression (after 14 d, increased risk in those with underlying hematologic abnormalities or renal insufficiency), serotonin syndrome due to MAO-mediated drug interactions	$190 (IV) $370 (PO)
Tigecycline	100 mg IV load, then 50 mg IV every 12 h	Hepatic	Widely distributed in tissues (Vd 500–700 L)	Controversial use in bacteremia due to low serum concentrations with standard dosing; nausea/vomiting, pancreatitis, hepatotoxicity, treatment-related mortality (US boxed warning)	$340

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; ACT, activated clotting time; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; CPK, creatine phosphokinase; CrCl, creatinine clearance; cSSSI, complicated skin and skin structure infection; HAP, hospital-acquired pneumonia; INR, international normalized ratio; MAO, monoamine oxidase; PO, oral; PT, prothrombin time; VAP, ventilator associated pneumonia; Vd, volume of distribution.

[a] Average daily cost assumes patient is 70 kg.

Data from Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, OH: Lexi-Comp, Inc; 2015; July 20, 2015; Micromedex Healthcare Series (Internet database). Greenwood Village, CO: Thomson Micromedex.

doses ranging from 3 to 10 mg/kg daily (in contrast to recommended practice of a single 1200-mg dose.)

Dalbavancin

In a global surveillance program, 99.6% of 26,975 MRSA isolates were inhibited by dalbavancin at concentrations less than or equal to 0.12 μg/mL.[6] This teicoplanin analogue is not active against VRSA. In an examination of randomized clinical trials of patients with complicated skin and soft tissue infections (SSTI), an analysis of the subset with *S aureus* bacteremia found that bloodstream clearance occurred in 24 of 24 dalbavancin recipients and in 19 of 20 recipients of comparator agents.[7]

Telavancin

A study of almost 5000 MRSA isolates in the United States found that 100% were susceptible to 0.12 μg/mL or less of telavancin, as were isolates with vancomycin MICs of 2 to 4 μg/mL and daptomycin nonsusceptible strains. All 26 VISA strains collected between 2007 and 2008, 12 of which were also daptomycin nonsusceptible, were inhibited by telavancin (MIC $\leq$1 μg/mL). Separately, telavancin MICs of 13 VRSA isolates (MIC range, 2–8 μg/mL) were above the susceptibility breakpoint.[8]

In a retrospective analysis, all 9 clinically evaluable patients receiving telavancin for uncomplicated MRSA bacteremia were cured.[8] Fourteen patients, 11 of whom had endocarditis, received salvage therapy with telavancin after a median duration of persistent bacteremia of 13 days.[9] All 10 with follow-up cultures had clearance of MRSA of the bloodstream a median of 1 day (range, 1–3 days) after the therapeutic switch, although only 8 patients survived. A phase 3, multicenter, randomized, open-label, noninferiority trial of telavancin versus standard IV therapy in the treatment of patients with *S aureus* bacteremia and right-sided infective endocarditis is ongoing.[10]

DAPTOMYCIN

Daptomycin, a cyclic lipopeptide, is a large (1620-Da) molecule that inserts itself into the bacterial cell membrane in a calcium-dependent manner, disrupting cell membrane integrity and function.

Daptomycin nonsusceptibility in *S aureus* may emerge under the selective pressure exerted by its administration but may also occur in its absence, possibly as the result of similar pressure exerted by cationic host defense peptides.[11] The most commonly identified mutations associated with resistance occur in the *mprF* gene, which encodes a membrane protein important in phospholipid synthesis causing "gain-of-function" mutations that result in partial neutralization of the negatively charged bacterial cell membrane, thus reducing the binding affinity of the positively charged calcium-complexed daptomycin molecule.[12]

Daptomycin and vancomycin MICs may trend together, and a recent review estimated that between 38% and 83% of VISA isolates and 15% of hVISA isolates were nonsusceptible to daptomycin, although its activity against VRSA is maintained.[13] Although this has raised concern about the use of daptomycin salvage therapy in patients with persistent infection in the face of vancomycin administration, a recent retrospective analysis found that previous vancomycin exposure did not affect the efficacy of daptomycin.[14]

Although national guidelines recommend 6 mg/kg/d daptomycin dosing for uncomplicated MRSA bacteremia, they also indicate that 8 to 10 mg/kg/d dosing may be considered for complicated and/or persistent bacteremia, although the latter

recommendation is not based on high-level evidence.[15] Higher doses, in addition to possibly enhancing the antibacterial effect, may also potentially prevent the emergence of resistance, especially in high burden infections. A recent review of persistent MRSA bacteremia cases, however, found that significant increases in daptomycin MICs occurred during therapy in 7 of 18 patients despite all 7 having received 8 to 10 mg/kg/d. The daptomycin MIC increase was associated with microbiological failure.[16]

Clinical evidence suggesting a benefit of higher doses of daptomycin is limited. A retrospective case series compared standard (mean 5 mg/kg/d) versus high (mean 8 mg/kg/d) dosing regimens in 53 patients with *S aureus* infections (mostly MRSA), including 37 with bacteremia or endocarditis. Although, in the entire cohort, high-dose recipients received therapy for a longer duration (mean of 13.5 days vs 19 days), there was no significant difference in outcomes in those with bacteremia or endocarditis.[17]

Treatment with high-dose daptomycin has been retrospectively compared with standard vancomycin administration in MRSA bacteremia. Kullar and colleagues[18] reviewed 70 patients with endocarditis, 54 due to MRSA, each with a baseline vancomycin MIC = 2 μg/mL, treated with daptomycin (median dose 9.8 mg/kg/d) alone or, in one-third, in combination with daptomycin that was added after a median of 4 days of vancomycin monotherapy. The investigators reported a clinical success rate of ~85%. However, details of the vancomycin dosing were not indicated, a problem with many relevant studies. Separately, Murray and colleagues reported 85 patients with MRSA bacteremia due to isolates with vancomycin MICs $\geq$1.5 μg/mL whose therapy was switched to daptomycin (median dose 8.4 mg/kg/d after median of 1.7 days of vancomycin) and compared their outcomes to 85 matched historical controls treated only with vancomycin (median trough 17.6 μg/mL).[19] Patients treated with daptomycin experienced less frequent clinical failure and had a lower 30-day mortality.[19]

FIFTH-GENERATION CEPHALOSPORINS: CEFTAROLINE

Ceftaroline fosamil received approval by the US Food and Drug Administration (FDA) in 2010. Another cephalosporin with MRSA activity, ceftobiprole medocaril, is not available in the United States, but has received approval in several European countries. The activity of ceftaroline against MRSA is the result of its high affinity for penicillin-binding proteins, but especially to an allosteric site of PBP2a near the transpeptidase domain. Binding to this site causes a conformational change that opens the active site of the molecule, allowing binding of a second ceftaroline molecule with consequent inhibition of its enzymatic activity. Resistance to ceftaroline results from *mecA* mutations that disrupt this allosteric mechanism, although additional mutations may contribute.[20]

A survey of 2013 MRSA bloodstream isolates collected at US medical centers from 2009 to 2013 found that 95.4% were susceptible (MIC $\leq$1 μg/mL), 4.6% had an MIC = 2 μg/mL (intermediate), whereas none were resistant to ceftaroline.[21] Ceftaroline is active in vitro against hVISA and VISA, as well as against at least one VRSA strain, and exhibits a "see-saw" effect, with an inverse correlation between the MICs of ceftaroline and vancomycin observed.[22]

Like other β-lactams, ceftaroline exerts time-dependent killing and has a relatively prolonged post-antibiotic effect against *S aureus*. Pharmacodynamic modeling found that *f*T > MIC of 32.1% was associated with a 2 $\log_{10}$ decrease in CFUs, but if *f*T > MIC is less than 50%, organism regrowth occurred at 96 hours.[23] As a consequence, it has

been suggested that, in order to diminish the risk of resistance selection, the optimal pharmacodynamic target should be *f*T > MIC greater than 50%. This target is readily achieved in healthy volunteers for isolates with an MIC = 2 μg/mL after administration of the recommended dose of 600 mg every 12 hours infused over 1 hour.[24] This conclusion is of note because a dose of 600 mg every 8 hours has been used in several patients with MRSA bacteremia reported in the literature, but the added benefit resulting from this regimen remains to be demonstrated. A recent Monte Carlo analysis in adults with cystic fibrosis, however, found that 600 mg ceftaroline administered 1 hour every 8 hours was required to assure a >90% probability of attainment of ≥60% T>MIC.[25] This is presumably the consequence of the frequent increased renal clearance of drugs observed in cystic fibrosis patients.

In a phase 4 registry study of *S aureus* bacteremia secondary to either acute bacterial SSTIs or to community-acquired bacterial pneumonia, clinical success in those with MRSA infection was reported in 18 of 32.[26] For many patients (the proportion was not reported), however, ceftaroline was administered together with a second antibiotic.

Ceftaroline has been used as "salvage" therapy for patients with perceived failure of treatment of MRSA bacteremia with another antibiotic, but the definition of failure has been variable and, in some cases, difficult to discern. In one such study, ceftaroline therapy was reported to achieve clinical success in 101 of the 129 patients with *S aureus* (92.5% MRSA) bacteremia, 92.0% of whom had endocarditis.[27] An unstated proportion, however, received ceftaroline in combination with a second antibiotic.

The relative efficacy of continuing the initial therapy (most with vancomycin) or switching to ceftaroline in patients with ongoing MRSA bacteremia was evaluated in a small case-control study.[28] Microbiological cure was observed in 14 of 16 controls and in 16 of 16 cases, although the time to resolution of bacteremia was shorter after the switch to ceftaroline than it was for the total duration of vancomycin in controls.

Ceftaroline was administered to 31 patients after initial therapy with vancomycin or daptomycin; in 10 patients, it was given in combination with another antibiotic, most frequently daptomycin.[29] Nine of the patients had endocarditis, mostly involving the tricuspid valve. Overall, microbiological cure was achieved in 64.5% (not all patients had test of cure) and clinical success in 74.2%, and the median duration of bacteremia after the switch to ceftaroline monotherapy was 4 days (range, 1–8 days). Finally, after a change to ceftaroline therapy, blood cultures became negative in 1 to 5 days in 5 patients with persistent MRSA bacteremia, 2 of whom had endocarditis.[30] Switching from initial therapy to ceftaroline in 4 patients with endovascular infection was associated with clearance of bacteremia in all within 2 to 7 days.[31] Rapid clearance of bacteremia (day 0 of ceftaroline administration) in 2 of 3 patients occurred after a switch to ceftaroline therapy, while a third patient, who had been bacteremic for 28 days before a change to ceftaroline therapy, was still bacteremic on the day of death 7 days later.[32]

OXAZOLIDINONES

The oxazolidinones inhibit bacterial protein synthesis by binding to the 23S ribosomal RNA of the 50S ribosomal subunit, preventing the formation of the 70S initiation complex. Tedizolid, the second drug of this class to become available, has key structural differences that allow additional target binding site interactions, accounting for its greater potency (with MICs 2- to 8-fold lower than linezolid against staphylococci) and retained activity despite linezolid resistance in some instances.[33]

S aureus resistance to linezolid fortunately remains rare, having been detected in only 2 of 1454 isolates from 60 US centers; both carried *cfr*.[34] Most *cfr*-positive isolates, however, remain susceptible to tedizolid. Thus, 11 (85%) of 13 *S aureus* isolates

were susceptible to tedizolid, whereas none of 17 with 23S rRNA mutations and only 1 (17%) of 6 with L3 or L4 modifications remained susceptible to this antibiotic.[35]

The FDA approved tedizolid in 2014 for use in acute bacterial SSTI caused by susceptible organisms, including MRSA. Published information regarding the use of tedizolid for the treatment of bacteremia is exceedingly limited. Bacteremia was present at enrollment in the ESTABLISH-1 and -2 trials of patients with SSTI in a small proportion of subjects.[35] In the 11 bacteremic patients assigned tedizolid, 4 infections were due to *S aureus* (2 MSSA and 2 MRSA), whereas in the 16 assigned linezolid, 9 were caused by *S aureus* (3 MSSA and 6 MRSA). All 11 tedizolid recipients and 11 of the 16 given linezolid responded to their assigned therapy.

The experience with linezolid may prove instructive in predicting the potential role of tedizolid in the treatment of MRSA bacteremia. A pooled analysis of 5 randomized trials found that clinical cure was achieved in 14 (56%) of 25 linezolid recipients, and in 13 (46%) of 28 of the subset with MRSA infection given vancomycin, a difference was not statistically significant.[36] In a prospective open randomized trial, clinical success at test of cure was achieved in 19 of 24 (79.2%) linezolid recipients and 16 of 21 (76.2%) of those given vancomycin.[37] In patients with persistent ($\geq$7 days) MRSA bacteremia while receiving vancomycin for at least 5 days, a switch to linezolid therapy (half also received a carbapenem) led to similar outcomes as seen in those in whom vancomycin was continued.[38]

Like linezolid, tedizolid is bacteriostatic, making its use in endocarditis problematic. When administered in a dose consistent with human exposure, tedizolid exerted only a modest bactericidal effect that was inferior to both vancomycin and daptomycin in a rabbit model of experimental endocarditis, a result similar to that previously observed with linezolid.[39]

TIGECYCLINE

The first of a new generation of tetracyclines, glycylcyclines, tigecycline inhibits bacterial protein synthesis, specifically by binding the 30S ribosomal subunit and blocking entry of amino-acyl tRNA to the A site of ribosome. Tigecycline is an analogue of minocycline that carries an added bulky side chain that sterically hinders the drug efflux and ribosomal protection mechanisms that cause resistance to the tetracyclines.[40]

The use of tigecycline in bacteremia is controversial because of its low serum levels with standard dosing.[41] In a pooled, retrospective data analysis of phase 3 clinical trials, 91 patients being treated with tigecycline had secondary bacteremia detected.[42] In the subset of patients with *S aureus* infection (n = 10), cure rates were 83.3% and 75% in the tigecycline and comparator arms, respectively.

COMBINATION THERAPY

Combinations with Vancomycin

Synergistic interactions between vancomycin and a wide variety of penicillinase-stable β-lactams, including semisynthetic penicillins, cephalosporins, β-lactam/β-lactamase inhibitor combinations, and carbapenems (but not the monobactam, aztreonam), have been demonstrated in vitro. With at least some β-lactams, this effect extends to isolates of hVISA, VISA and, at least in one case, VRSA. It has been suggested that synergy results from a reduction in cell wall thickness caused by β-lactam exposure with a reduction in sequestration of the glycopeptide, allowing increased access to its functional target.[43]

In a retrospective study of patients with MRSA bacteremia, microbiological eradication was achieved in 48 of 50 (96%) patients who received vancomycin together with a

β-lactam (piperacillin-tazobactam in 34 of 50) and in 24 of 30 (80%) ($P = .021$) given vancomycin alone.[44] In the subset of patients with endocarditis, clearance of bacteremia was achieved in 11 of 11 and in 9 of 11 in the 2 groups, respectively. Separately, a hemodialysis patient with septic subclavian thrombophlebitis who failed treatment of relapsed MRSA bacteremia with ceftaroline plus daptomycin experienced clearance of bacteremia within 24 hours of a change to ceftaroline plus vancomycin.[45] In a pilot randomized study involving a total of 60 patients given vancomycin with or without flucloxacillin, combination therapy was associated with a reduction in mean duration of MRSA bacteremia from 3.00 to 2.94 days.[46] Thus, the mean time to resolution of bacteremia in those receiving vancomycin plus flucloxacillin was 65% (95% confidence interval, 41%–102%; $P = .06$) of that observed the patients given vancomycin alone. No differences in clinical endpoints were observed. In contrast to these experiences, there continues to be a lack of evidence of benefit of vancomycin combined with antibiotics other than β-lactams. Seah and colleagues[47] retrospectively reviewed the cases of 76 patients with persistent MRSA bacteremia for greater than 7 days after initiation of vancomycin therapy, 50 of whom continued to receive monotherapy with this glycopeptide, whereas 26 had one or more agents added to their regimen. These added antibiotics included rifampin plus fusidic acid in 12, rifampin alone in 3, rifampin plus trimethoprim-sulfamethoxazole and doxycycline plus trimethoprim-sulfamethoxazole in 2 each with 1 each receiving either rifampin plus gentamicin or rifampin plus ciprofloxacin. There was no evidence of benefit from combination therapy with these diverse agents; the median durations of bacteremia after initiation of combination therapy were 19 days and 14 days in the combination and continued vancomycin groups, respectively.

In a retrospective study, 35 patients with persistent (≥7 days) MRSA bacteremia while receiving vancomycin had their therapy altered.[48] In 12 cases, vancomycin was continued, with an aminoglycoside added in 6, rifampin in 4, and both an aminoglycoside and a rifampin added in 2, but bacteremia cleared within 72 hours in only 2 (17%).

Combinations with Daptomycin

Daptomycin plus β-lactams

In vitro synergy with daptomycin occurs in combination with any of a broad array of β-lactam antibiotics, although it is reported that β-lactams that preferentially bind PBP-1 are more potent in this regard.[49] When complexed with calcium at physiologic concentrations, daptomycin acts as a cation, allowing it to bind to the negatively charged bacterial cell membrane. β-Lactam antibiotic exposure increases membrane charge negativity, thus enhancing daptomycin binding and presumably accounting for synergy. In addition, the combination of daptomycin with a second antibiotic appears to slow the emergence of nonsusceptibility to the lipopeptide antibiotic.[50]

The combination of daptomycin and ceftaroline had superior bactericidal activity in an in vitro hollow fiber model compared with either agent alone against 2 MRSA isolates that were daptomycin nonsusceptible.[43] Examination of different potential clinical strategies of administration found that de-escalation from combination to monotherapy with either agent after 4 or 8 days was equivalent to continued combination therapy and superior to monotherapy from the start. In addition, a simulated daptomycin dose of 6 mg/kg/d was not inferior to a 10-mg/kg/d dose in the combination regimen.

Among patients with MRSA bacteremia enrolled in a daptomycin registry study, most of whom had received prior antibiotic therapy, clinical or microbiological success was observed in 18 of 22 (82%) who received daptomycin in combination with a β-lactam antibiotic and in 27 of 34 (79%) who received this lipopeptide antibiotic without a

β-lactam (many, however, received other antibiotics), a difference that was not significant.[51] The use of daptomycin in combination with rifampin, gentamicin, or vancomycin was not associated with a significant difference in outcome when compared with monotherapy.

The efficacy of salvage therapy with daptomycin and ceftaroline in combination was examined in patients at 10 medical centers with persistent staphylococcal bacteremia.[52] Of the 26 infections, 22 were due to MRSA, including 2 VISA; 4 isolates were daptomycin nonsusceptible. Fourteen patients had endocarditis with 12 of these being left sided. The median duration of bacteremia before initiation of daptomycin plus ceftaroline was 10 days (range, 3–23 days), and this combination was a third- or fourth-line therapy in 69% of patients. Daptomycin monotherapy had failed in 12. The median duration of bacteremia after initiation of this combination therapy was 2 days (range, 1–6 days).

Seven patients with persistent or relapsed MRSA bacteremia who had sequentially failed vancomycin and daptomycin monotherapies cleared their bloodstreams a median of 1 day (range, 1–2 days) after the addition of a semisynthetic penicillin to daptomycin.[53]

Daptomycin plus trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole given alone did not meet the test of noninferiority compared with vancomycin monotherapy in the treatment of patients with severe MRSA infections that included 91 patients with bacteremia,[54] but its role as part of combination regimens suggest possible benefit. The combination of daptomycin and trimethoprim-sulfamethoxazole was bactericidal against both daptomycin-susceptible and nonsusceptible strains of MRSA in an in vitro model of endocarditis using simulated vegetations.[55] In a retrospective review of patients with deep-seated MRSA infections, 75.0% initially received vancomycin before switching to daptomycin after a median of 4 days with the most frequent reason (60.7%) for change in therapy being a vancomycin MIC = 2 μg/mL. Daptomycin was then continued as monotherapy for a median of 5 days until the addition of trimethoprim-sulfamethoxazole. In the 20 patients still bacteremic at the time of addition of trimethoprim-sulfamethoxazole to daptomycin, subsequent bloodstream clearance occurred within a median of 2.5 days. The median time to clearance after the initiation of combination therapy in the 6 patients infected with a daptomycin-nonsusceptible strain was 6.5 days, whereas it was 2 days in those infected with a daptomycin-susceptible MRSA. Hyperkalemia was a frequent occurrence during combination therapy.

Daptomycin plus either ceftaroline or trimethoprim-sulfamethoxazole: A comparison

A retrospective analysis of 34 patients with MRSA bacteremia with a median duration of bacteremia while receiving primary or secondary treatment of 7 to 8 days had resolution of bloodstream infection when therapy was changed to daptomycin plus either ceftaroline or trimethoprim-sulfamethoxazole, after a median of 2 days in each case.[56]

Trimethoprim-sulfamethoxazole plus ceftaroline

Twenty-five patients with MRSA bacteremia (65% with endovascular infection) received combination therapy (trimethoprim-sulfamethoxazole in 23, daptomycin in 2) with ceftaroline after initial administration of another antibiotic, mostly vancomycin.[57] In those still bacteremic at the time of the switch, the median subsequent duration of bacteremia was 3 days, whereas it had been 9.5 days before the change. Although microbiologic success was achieved in 90%, only 31% were considered

Table 3
Approximate cost of combination therapy for methicillin-resistant *Staphylococcus aureus*

Weekly Cost (AWP 2016)	Cefazolin 1 g Q8H	Nafcillin 1 g Q4H	Ceftaroline 600 mg Q12H	Ceftaroline 600 mg Q8H	TMP/SMX 10 mg/kg/day
Daptomycin 700 mg Q24H (10 mg/kg)	$5400	$5800	$7800	$9000	$5500
Vancomycin 1g Q12H (15 mg/kg)	$230	$700	$2700	$4000	$350

Abbreviation: TMP/SMX, trimethoprim sulfamethoxazole.

Data from Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, OH: Lexi-Comp, Inc; 2015; July 20, 2015; Micromedex Healthcare Series (Internet database). Greenwood Village, CO: Thomson Micromedex.

Table 4
Investigational drugs with activity against methicillin-resistant *Staphylococcus aureus* in clinical trials

Antibiotic	Class	Status
Debio 1452 (prodrug of Debio 1450)	FabI inhibitor	Phase 1 completed
MRX-1	Oxazolidinone	Phase 1
Radezolid	Oxazolidinone	Phase 2 completed
LCB01-0371	Oxazolidinone	Phase 1
BC-3781	Pleuromutilin	Phase 2 completed
Fusidic acid (CEM-102)	EF-G blocker	Phase 2 completed (SSTI)
Omadacycline	Tetracycline	Phase 2 completed
Eravacycline	Tetracycline	Phase 3 (cIAI and cUTI)
Brilacidin	Mimics CDP	Phase 2
AFN-1252	*Fab*I enoyl-(acyl carrier protein) reductase inhibitor	Phase 2 completed
CG400549	*Fab*I enoyl-(acyl carrier protein) reductase inhibitor	Phase 2a completed
GSK1322322	Peptide deformylase inhibitor	Phase 2a completed
Delafloxacin	Fluoroquinolone	Phase 2 completed
Nemonoxacin	Fluoroquinolone	Phase 3 (CAP)
Finafloxacin	Fluoroquinolone	Phase 2 completed (cUTI)
GSK2140944	Type II topoisomerase inhibitor	Phase 1 completed
Avarofloxacin	Fluoroquinolone	Phase 2 completed
JNJ-32729463	Fluoroquinolone	Phase 2
WCK 2349	Type II topoisomerase inhibitor	Phase 1 completed
WCK 771	Type II topoisomerase inhibitor	Phase 1 completed
TD-1607	Cephalosporin-glycopeptide heterodimer	Phase 3
Iclaprim	Dihydrofolate reductase inhibitor	Phase 3
CBR-2092	Rifamycin-quinolone hybrid	Phase 1
WAP-8294A2	Cyclic lipodepsipeptide	Phase 1

Abbreviations: CAP, community-acquired pneumonia; cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections.

From Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, OH: Lexi-Comp, Inc; 2015; July 20, 2015; Micromedex Healthcare Series (Internet database). Greenwood Village, CO: Thomson Micromedex; with permission. Available at: http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2014/03/12/tracking-the-pipeline-of-antibiotics-in-development. Accessed June 30, 2015.

to be clinical successes, but the way in which this was defined is open to challenge. Thus, only 4 patients were considered by the investigators to be clinical failures, and in 2, this may have been the result of inadequate source control.

Combinations with Fosfomycin

Fosfomycin, which is not available in a parenteral formulation in the United States, has been demonstrated to be synergistic with daptomycin in vitro. Two patients with MRSA left-sided endocarditis were successfully treated with high-dose daptomycin plus fosfomycin after failure of initial therapy.[58] MRSA bloodstream infection cleared in a patient receiving vancomycin with persistent (>10 days) bacteremia 3 days after the addition of fosfomycin to the regimen.[59]

Sixteen patients with persistent (N = 14) or relapsed (N = 2) MRSA bacteremia who had received a median of 9.5 days of antibiotic therapy (mostly vancomycin, but daptomycin in 2 cases) were treated with the combination of imipenem and fosfomycin with bloodstream clearance within 72 hours in each case, and the clinical success rate was 69% (**Tables 3** and **4**).[60]

SUMMARY

The lack of high-level evidence precludes definitive conclusions regarding optimal treatment of MRSA bacteremia. However, based on the available data and experience, the following can be proposed:

- Vancomycin, appropriately dosed, remains the first-line therapy, with daptomycin an effective, although more costly, alternative.
- Laboratory data suggest that the administration of daptomycin in higher than approved doses may be superior to lower doses in terms of efficacy and reducing the risk of selection of resistance, but clinical data to support this hypothesis are largely lacking.
- Ceftaroline may be a promising alternative, but its broad spectrum of activity is an undesirable quality for use as definitive therapy in the absence of polymicrobial infection.
- Combinations of daptomycin or vancomycin with a β-lactam, or daptomycin with trimethoprim-sulfamethoxazole, may eventually prove to be more effective than monotherapy, particularly in "salvage" situations, but a definitive answer will require prospective randomized trials. In vitro modeling with daptomycin and ceftaroline suggests that, although the combination is superior to either agent alone, one or the other may be discontinued after 4 days without loss of efficacy; in addition, a simulated daptomycin dose of 6 mg/kg/d is not inferior to 10 mg/kg/d when used in combination.

REFERENCES

1. Kalil AC, Van Schooneveld TC, Fey PD, et al. Association between vancomycin minimum inhibitory concentration and mortality among patients with Staphylococcus aureus bloodstream infections. JAMA 2014;312(15):1552.
2. Cervera C, Castañeda X, De La Maria CG, et al. Effect of vancomycin minimal inhibitory concentration on the outcome of methicillin-susceptible Staphylococcus aureus endocarditis. Clin Infect Dis 2014;58(12):1668–75.
3. Neely MN, Youn G, Jones B, et al. Are vancomycin trough concentrations adequate for optimal dosing? Antimicrob Agents Chemother 2014;58(1):309–16.

4. Zelenitsky S, Rubinstein E, Ariano R, et al. Vancomycin pharmacodynamics and survival in patients with methicillin-resistant Staphylococcus aureus-associated septic shock. Int J Antimicrob Agents 2013;41(3):255–60.
5. Zhanel GG, Calic D, Schweizer F, et al. New lipoglycopeptides. Drugs 2010; 70(7):859–86.
6. McCurdy SP, Jones RN, Mendes RE, et al. In vitro activity of dalbavancin against drug resistant *Staphylococcus aureus* from a global surveillance program. Antimicrob Agents Chemother 2015;59(8):5007–9.
7. Dunne M, Puttagunta S. Clearance of Staphylococcus aureus bacteremia in patients treated with dalbavancin. Poster session presented at: IDWeek 2013, October 2–6; San Francisco, CA.
8. Corey GR, Rubinstein E, Stryjewski ME, et al. Potential role for telavancin in bacteremic infections due to gram-positive pathogens: focus on Staphylococcus aureus. Clin Infect Dis 2014;60:787–96.
9. Ruggero MA, Peaper DR, Topal JE. Telavancin for refractory methicillin-resistant Staphylococcus aureus bacteremia and infective endocarditis. Infect Dis (Lond) 2015;47(6):379–84.
10. Theravance Biopharma Antibiotics, Inc. A phase 3 telavancin Staphylococcus aureus bacteremia trial. NCT02208063 [Internet]. Available at: https://clinicaltrials.gov/ct2/show/NCT02208063. Accessed June 30, 2015.
11. Bayer AS, Mishra NN, Sakoulas G, et al. Heterogeneity of mprF sequences in methicillin-resistant Staphylococcus aureus clinical isolates: role in cross-resistance between daptomycin and host defense antimicrobial peptides. Antimicrob Agents Chemother 2014;58(12):7462–7.
12. Bayer AS, Schneider T, Sahl H-G. Mechanisms of daptomycin resistance in Staphylococcus aureus: role of the cell membrane and cell wall. Ann N Y Acad Sci 2013;1277(1):139–58.
13. Humphries RM, Pollett S, Sakoulas G. A current perspective on daptomycin for the clinical microbiologist. Clin Microbiol Rev 2013;26(4):759–80.
14. Culshaw D, Lamp KC, Yoon MJ, et al. Duration of prior vancomycin therapy and subsequent daptomycin treatment outcomes in methicillin-resistant Staphylococcus aureus bacteremia. Diagn Microbiol Infect Dis 2015;83(2):193–7.
15. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52(3): e18–55.
16. Gasch O, Camoez M, Domínguez MA, et al. Emergence of resistance to daptomycin in a cohort of patients with methicillin-resistant Staphylococcus aureus persistent bacteraemia treated with daptomycin. J Antimicrob Chemother 2014; 69(2):568–71.
17. Bassetti M, Nicco E, Ginocchio F, et al. High-dose daptomycin in documented Staphylococcus aureus infections. Int J Antimicrob Agents 2010;36(5):459–61.
18. Kullar R, Casapao AM, Davis SL, et al. A multicentre evaluation of the effectiveness and safety of high-dose daptomycin for the treatment of infective endocarditis. J Antimicrob Chemother 2013;68(12):2921–6.
19. Murray K, Zhao J, Davis S, et al. Early use of daptomycin versus vancomycin for methicillin-resistant staphylococcus aureus bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: A matched cohort study. Clin Infect Dis 2013;56(11):1562–9.

20. Otero LH, Rojas-Altuve A, Llarrull LI, et al. How allosteric control of Staphylococcus aureus penicillin binding protein 2a enables methicillin resistance and physiological function. Proc Natl Acad Sci U S A 2013;110(42):16808–13.
21. Sader HS, Farrell DJ, Flamm RK, et al. Activity of ceftaroline and comparator agents tested against Staphylococcus aureus from patients with bloodstream infections in US medical centres (2009-13). J Antimicrob Chemother 2015;70(7):2053–6.
22. Espedido BA, Jensen SO, van Hal SJ. Ceftaroline fosamil salvage therapy: an option for reduced-vancomycin-susceptible MRSA bacteraemia. J Antimicrob Chemother 2014;70(3):797–801.
23. MacGowan AP, Noel AR, Tomaselli S, et al. Pharmacodynamics of ceftaroline against Staphylococcus aureus studied in an in vitro pharmacokinetic model of infection. Antimicrob Agents Chemother 2013;57(6):2451–6.
24. Drusano GL. Pharmacodynamics of ceftaroline fosamil for complicated skin and skin structure infection: rationale for improved anti-methicillin-resistant Staphylococcus aureus activity. J Antimicrob Chemother 2010;65(Suppl 4):iv33–9.
25. Autry EB, Rybak JM, Leung NR, et al. Pharmacokinetic and pharmacodynamic analyses of ceftaroline in adults with cystic fibrosis. Pharmacotherapy 2016;36(1):13–8.
26. Vazquez JA, Maggiore CR, Cole P, et al. Ceftaroline fosamil for the treatment of Staphylococcus aureus bacteremia secondary to acute bacterial skin and skin structure infections or community-acquired bacterial pneumonia. Infect Dis Clin Pract 2015;23(1):39–43.
27. Casapao AM, Davis SL, Barr VO, et al. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. Antimicrob Agents Chemother 2014;58(5):2541–6.
28. Paladino JA, Jacobs DM, Shields RK, et al. Use of ceftaroline after glycopeptide failure to eradicate meticillin-resistant Staphylococcus aureus bacteraemia with elevated vancomycin minimum inhibitory concentrations. Int J Antimicrob Agents 2014;44(6):557–63.
29. Polenakovik HM, Pleiman CM. Ceftaroline for meticillin-resistant Staphylococcus aureus bacteraemia: case series and review of the literature. Int J Antimicrob Agents 2013;42(5):450–5.
30. Ho TT, Cadena J, Childs LM, et al. Methicillin-resistant Staphylococcus aureus bacteraemia and endocarditis treated with ceftaroline salvage therapy. J Antimicrob Chemother 2012;67(5):1267–70.
31. Lin JC, Aung G, Thomas A, et al. The use of ceftaroline fosamil in methicillin-resistant Staphylococcus aureus endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. J Infect Chemother 2013;19(1):42–9.
32. Tattevin P, Boutoille D, Vitrat V, et al. Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study. J Antimicrob Chemother 2014;69(7):2010–3.
33. Rybak JM, Marx K, Martin CA. Early experience with tedizolid: clinical efficacy, pharmacodynamics, and resistance. Pharmacotherapy 2014;34(11):1198–208.
34. Flamm RK, Mendes RE, Hogan PA, et al. In vitro activity of linezolid as assessed through the 2013 LEADER surveillance program. Diagn Microbiol Infect Dis 2015;81(4):283–9.
35. Burdette S, Trotman R. Tedizolid: the first once daily oxazoidinone class antibiotic. Clin Infect Dis 2015;61(8):1315–21.

36. Shorr AF, Kunkel MJ, Kollef M. Linezolid versus vancomycin for Staphylococcus aureus bacteraemia: pooled analysis of randomized studies. J Antimicrob Chemother 2005;56(5):923–9.
37. Wilcox MH, Tack KJ, Bouza E, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study. Clin Infect Dis 2009;48(2):203–12.
38. Park HJ, Kim S-H, Kim M-J, et al. Efficacy of linezolid-based salvage therapy compared with glycopeptide-based therapy in patients with persistent methicillin-resistant Staphylococcus aureus bacteremia. J Infect 2012;65(6):505–12.
39. Chan LC, Basuino L, Dip EC, et al. Comparative efficacy of tedizolid phosphate (prodrug of tedizolid), vancomycin and daptomycin in a rabbit model of methicillin-resistant Staphylococcus aureus endocarditis. Antimicrob Agents Chemother 2015;59(6):3252–6.
40. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev 2001;65(2):232–60.
41. Stein GE, Babinchak T. Tigecycline: an update. Diagn Microbiol Infect Dis 2013;75(4):331–6.
42. Gardiner D, Dukart G, Cooper A, et al. Safety and efficacy of intravenous tigecycline in subjects with secondary bacteremia: pooled results from 8 phase III clinical trials. Clin Infect Dis 2010;50(2):229–38.
43. Barber KE, Werth BJ, Rybak MJ. The combination of ceftaroline plus daptomycin allows for therapeutic de-escalation and daptomycin sparing against MRSA. J Antimicrob Chemother 2015;70(2):505–9.
44. Dilworth TJ, Ibrahim O, Hall P, et al. β-Lactams enhance vancomycin activity against methicillin-resistant Staphylococcus aureus bacteremia compared to vancomycin alone. Antimicrob Agents Chemother 2014;58(1):102–9.
45. Barber KE, Rybak MJ, Sakoulas G. Vancomycin plus ceftaroline shows potent in vitro synergy and was successfully utilized to clear persistent daptomycin-non-susceptible MRSA bacteraemia. J Antimicrob Chemother 2015;70(1):311–3.
46. Davis JS, Sud A, O'Sullivan MV, et al. Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: A Pilot Multicenter Randomized Controlled Trial. Clin Infect Dis 2016;62(2):173–80.
47. Seah J, Lye DC, Ng T-M, et al. Vancomycin monotherapy vs. combination therapy for the treatment of persistent methicillin-resistant Staphylococcus aureus bacteremia. Virulence 2013;4(8):734–9.
48. Jang H, Kim S, Kim KH, et al. Salvage treatment for persistent methicillin-resistant Staphylococcus aureus bacteremia: efficacy of linezolid with or without carbapenem. Clin Infect Dis 2009;49(3):395–401.
49. Berti AD, Sakoulas G, Nizet V, et al. β-Lactam antibiotics targeting PBP1 selectively enhance daptomycin activity against methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 2013;57(10):5005–12.
50. Berti AD, Wergin JE, Girdaukas GG, et al. Altering the proclivity towards daptomycin resistance in methicillin-resistant Staphylococcus aureus using combinations with other antibiotics. Antimicrob Agents Chemother 2012;56(10):5046–53.
51. Moise PA, Amodio-Groton M, Rashid M, et al. Multicenter evaluation of the clinical outcomes of daptomycin with and without concomitant β-lactams in patients with Staphylococcus aureus bacteremia and mild to moderate renal impairment. Antimicrob Agents Chemother 2013;57(3):1192–200.

52. Sakoulas G, Brown J, Lamp KC, et al. Clinical outcomes of patients receiving daptomycin for the treatment of Staphylococcus aureus infections and assessment of clinical factors for daptomycin failure: a retrospective cohort study utilizing the Cubicin® Outcomes Registry and Experience. Clin Ther 2009;31(9): 1936–45.
53. Dhand A, Sakoulas G. Daptomycin in combination with other antibiotics for the treatment of complicated methicillin-resistant Staphylococcus aureus bacteremia. Clin Ther 2014;36(10):1303–16.
54. Paul M, Bishara J, Yahav D, et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant Staphylococcus aureus: randomised controlled trial. BMJ 2015;350:h2219.
55. Claeys KC, Smith JR, Casapao AM, et al. Impact of the combination of daptomycin and trimethoprim-sulfamethoxazole on clinical outcomes in methicillin-resistant Staphylococcus aureus infections. Antimicrob Agents Chemother 2015;59(4):1969–76.
56. Zasowski E, Claeys K, Roberts K. Retrospective evaluation of daptomycin (DAP) plus ceftaroline fosamil (CPT) versus DAP plus sulfamethoxazole/trimethoprim (SMX/TMP) for methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections (BSI). Presented in poster session at the 25th European Congress of Clincial Microbiology and Infectious Diseases (ECCMID), Copenhagen, Denmark, April 25 – 28, 2015.
57. Fabre V, Ferrada M, Buckel WR, et al. Ceftaroline in combination with trimethoprim-sulfamethoxazole for salvage therapy of methicillin-resistant Staphylococcus aureus bacteremia and endocarditis. Open Forum Infect Dis 2014; 1(2):ofu046.
58. Miŕo JM, Entenza JM, Del Río A, et al. High-dose daptomycin plus fosfomycin is safe and effective in treating methicillin-susceptible and methicillin-resistant Staphylococcus aureus endocarditis. Antimicrob Agents Chemother 2012; 56(8):4511–5.
59. Linasmita P. Successful management of methicillin-resistant Staphylococcus aureus bacteremia unresponsive to Vancomycin by adding fosfomycin: a case report. J Med Assoc Thai 2012;95(7):960–3.
60. Del Rio A, Gasch O, Moreno A, et al. Efficacy and safety of fosfomycin plus imipenem as rescue therapy for complicated bacteremia and endocarditis due to methicillin-resistant Staphylococcus aureus: a multicenter clinical trial. Clin Infect Dis 2014;59(8):1105–12.