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Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant cause of health care-associated infections. Vancomycin remains an acceptable treatment option. There has been a welcome increase in the number of agents available for the treatment of MRSA infection. These drugs have certain differentiating attributes and may offer some advantages over vancomycin, but they also have significant limitations. These agents provide some alternative when no other options are available.

Key Words: Methicillin-resistant *Staphylcoccus aureus*; Vancomycin; Treatment

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of serious nosocomial infections.

Vancomycin, a glycopeptide in clinical use for more than 50 years, still serves as the cornerstone of the treatment of drug-resistant Gram-positive infections. However, there are significant concerns owing to decreasing susceptibility to this agent among *S. aureus*. Furthermore, vancomycin is slowly bactericidal, which may be partly responsible for reported clinical failures in treatment of bacteremia and endocarditis. The growing awareness of the limitations of vancomycin has served as an impetus for development of newer agents. Emergence of non-susceptible MRSA strains and recognition of the frequent failure of vancomycin treatment of MRSA infection regardless of the minimum inhibitory concentration (MIC) of the isolate, provides evidence of the need for more effective therapies and therapeutic approaches.

Linezolid, daptomycin, telavancin and ceftaroline are drugs that have received regulatory approval in the last decade for the treatment of infections caused by drug-resistant Gram-positive pathogens. Although these drugs do have certain differentiating attributes and may offer some advantages over vancomycin, they also have significant limitations. More importantly, data from randomized clinical trials to support greater therapeutic efficacy of the newer agents compared with vancomycin in the treatment of serious MRSA infections are limited.

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Vancomycin or daptomycin are the agents of choice for treatment of invasive MRSA infections [1]. Alternative agents that may be used for second-line or salvage therapy include telavancin, ceftaroline, and linezolid. Recent studies of treatment of MRSA bacteremia are reviewed.

Vancomycin

Vancomycin is the agent for which there is the greatest cumulative clinical experience for the treatment of MRSA bacteremia. Although vancomycin has been used for over 50 years, controversies still exist about best to use it. Outcomes may be improved when vancomycin is dosed to achieve to a pharmacokinetics/pharmacodynamics (PK/PD) target, which requires serum concentration monitoring, particularly in the setting of renal dysfunction. Although several studies have suggested that vancomycin MIC = 2 μg/mL is associated with an increased risk of failure of treatment of these infections, a recent meta-analysis did not support this conclusion [2].

The pharmacokinetic driver of efficacy of vancomycin in bacteremia due to *S. aureus* is area under the plasma concentration time curve (AUC) values and an $AUC_{0\text{-}24h}$ to MIC ratio of ≥400 μg·h/mL has been suggested as the target value. The measured trough concentration of 15-20 mg/L alone as been used as a surrogate as it was thought to be predictive of AUC/MIC; recent evidence suggests this 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]. 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.

The use of 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 $AUC_{0\text{-}24h}$/MIC well in excess of 400 [4]. Individualized dosing should be explored in selected patients populations like the critically ill or in intensive care.

In general, if there is a poor clinical response to vancomycin regardless of MIC, but especially if vancomycin MIC approaches the upper limit of the susceptible ranges (2 μg/mL), it should discontinued and therapy switched to an alternative agent, typically daptomycin.

Teicoplanin

Teicoplanin is a glycopeptides with slow bactericidal activity and a spectrum of activity and efficacy camparable to vancomycin. Some use it as the drug of choice for initial therapy of MRSA bacteremia, although good evidence to support this practice is lacking, while others favor its use for patients with intolerance to vancomycin [5]. Much debate has surrounded this antibiotic, however due to data showing inferior efficacy compared with vancomycin. These results can be explained by inadequate dosing of teicoplanin secondary to greater protein binding compared with vancomycin. Recent data and meta-analysis suggest that teicoplanin may not be inferior to vancomycin [6]. One meta-analysis noted a lower risk of nephrotoxicity with teicoplanin than with vancomycin [5].

Telavancin

Telavancin is a semisynthetic lipoglycopeptide that inhibits cell wall synthesis and disrupts cell membrane permeability [7]. The lipophilic side chain of telavancin confers enhanced potency, with approximately 10-fold more potency than vancomycin. It is bactericidal against MRSA, vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA). It has a half-life of seven to nine hours, permitting once daily dosing. Telavancin should be avoided in patients at risk for nephrotoxicity.

Telavancin was approved in November 2009 in the United States for the treatment of acute bacterial skin and skin structure infections (ABSSSI), and in June 2013 in US for hospital-acquired pneumonia (HAP) caused by gram-positive pathogens including MRSA where alternative treatments are not suitable.

Telavancin may prove effective for treatment of MRSA bacteremia. In a phase 2 trial of telavancin for treatment of bacteremia including 17 patients, cure rates were comparable for telavancin and standard therapy (88 vs. 89%) [8]. 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 [9]. This agent is an alternative when other options are not available.

Daptomycin

Daptomycin is a lipopeptide class antibiotic that disrupts cell membrane function via calcium-dependent binding, resulting in bactericidal activity in a concentration-dependent fashion. It is active against methicillin- and vancomycin –resistant staphylococci. It is the only new antibiotic that has a licensing indication for the treatment of *S. aureus* bacteremia (SAB) and right-sided endocarditis at 6 mg/kg/day [10]. It has the advantage of being a once-daily dosed, rapidly bactericidal agent. However, it lacks efficacy in pneumonia owing to its inactivation by pulmonary surfactant and it can cause muscle toxicity, so requires serum creatine kinase monitoring [11].

Daptomycin is currently the only antibiotic to have shown noninferiority to vancomycin in the treatment of MRSA bacteremia. A study comparing daptomycin versus initial low-dose gentamicin plus either an anti-staphylococcal penicillin or vancomycin in 124 patients with SAB and endocarditis demonstrated that daptomycin was not inferior to standard therapy [10]. Clinical success was low in the MRSA subset of patients but favored daptomycin (20 out of 45; 44.4%) over standard therapy (14 out of 44; 31.8%). However, five MRSA patients in the daptomycin group, most of whom had deep-seated infections or left-sided endocarditis, had microbiological failure with emergence on therapy of isolates with reduced daptomycin susceptibility (MIC increased from 0.25-0.5 to 2-4 μg/mL).

Daptomycin is an acceptable alternative to vancomycin for treatment of MRSA bacteremia. Historically, daptomycin has been used as salvage therapy in patients failing vancomycin therapy, particularly with high vancomycin MIC infections, but increasingly it is being used as initial therapy in high inoculum MRSA infections. A recent case-control study showed a possible advantage of daptomycin over vancomycin in infections caused by isolates with elevated vancomycin MIC [12]. Murray and colleagues reported 85 patients with MRSA bacteremia due to isolates with vancomycin MICs ≥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). Patients treated with daptomycin experienced less frequent clinical failure and had a lower 30-day mortality. Limitations of this study were use of non-contemporaneous, historical vancomycin "control" group, and a much higher rate of infectious diseases consultation, which has been shown to improve outcomes in the daptomycin group [13].

Prior therapy with vancomycin, intermediate susceptibility to vancomycin (*i.e.* VISA) and retained prosthetic devices have been associated with an increased risk of daptomycin resistance. This is reflected in the Infectious Diseases Society of America guidelines for treatment of MRSA infections, where daptomycin dosing is recommended at 8 to 10 mg/kg for complicated bacteremia and in combination with other agents if there has been prior vancomycin treatment failure [1]. 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. Daptomycin resistance and cross-resistance in the setting of reduced vancomycin susceptibility raises concerns about widespread use of this agent.

Ceftaroline

Ceftaroline is a fifth-generation cephalosporin with bactericidal activity against MRSA and VISA as well as Gram-negative pathogens [14]. Ceftaroline fosamil, the pro-drug of ceftaroline, received approval by the US Food and Drug Administration (FDA) in 2010. 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 changes that opens the active site of the molecule, allowing binding of a second ceftaroline molecule with consequent inhibition of its enzymatic activity [15]. Ceftaroline is active *in vitro* against VISA and heterogeneous VISA (hVISA), as well as VRSA, and exhibits a "see-saw" effect in which there is an inverse correlation between the MICs of ceftaroline and vancomycin [16].

Ceftaroline has been approved for use in the treatment of ABSSSI and community-acquired pneumonia (CAP). In a phase 4 registry study of *S. aureus* bacteremia secondary to either bacterial SSTIs or to community-acquired bacterial pneumonia, clinical success in those with MRSA infection was reported in 18 of 32 [17]. Data for use of ceftaroline for treatment of MRSA bacteremia are limited to small retrospective case series.

In one study, ceftaroline therapy was reported to achieve clinical success in 101 of the 129 patients with SAB, 92% of whom had endocarditis [18]. For many patients, however, ceftaroline was administered together with a second antibiotics. Ceftaroline in combination with a second agent, most com-

monly daptomycin, has been effective as a salvage regimen in patients with persistent MRSA bacteremia.

Oxazolidinones

Linezolid is a bacteriostatic oxazolidinone that inhibits initiation of protein synthesis at the 50S ribosome [19]. This drug class may have enhanced efficacy against strains producing toxins such as Panton-Valentine leukocidin, α-hemolysin, and toxic shock syndrome toxin 1 [20]. Unlike vancomycin, linezolid achieves high levels in the epithelial lining fluid of the lungs, making it a promising candidate for treatment of patients with HAP, including MRSA.

Linezolid has been compared with vancomycin for SAB in several case series and observational cohorts [21]. 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 [22]. In patients with persistent (≥7 days) MRSA bacteremia while receiving vancomycin for at least 5 days, a switch to linezolid therapy led to similar outcomes as seen in those in whom vancomycin was continued [23]. Linezolid resistance and linezolid failure have been described [24]. Thus, an increasing frequency of resistance may potentially accompany more widespread use of this drug.

Tedizolid, the second drug of oxazolidinones, has key structural differences that allow additional target binding site interactions, accounting for its greater potency (2- to 8-fold lower MICs than linezolid against staphylococci) [25]. 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. 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 [26]. Further study of tedizolid for treatment of MRSA bacteremia is needed.

Tigecycline

The first of a new generation of tetracyclines, glycylcyclines, tigecycline inhibits bacterial protein synthesis. Tigecycline's distinctive feature is that it confers broad antibiotic coverage of drug-resistant Gram-positive bacteria and certain, but not all, species of multidrug-resistant Gram-negative bacteria, although it is a bacteriostatic agent.

There are substantial clinical trial data available on the use of tigecycline for intra-abdominal infections, complicated ABSSSIs, and nosocomial pneumonia, but there are insufficient data available specifically assessing the role of tigecycline in invasive MRSA infections. The use of tigecycline in bacteremia is controversial because of its low serum levels with standard dosing [27]. In a pooled, retrospective data analysis of phase 2 clinical trials, 91 patients being treated with tigecycline had secondary bacteremia detected. 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 [28]. The paradox of higher mortality and lower cure despite excellent in vitro activity is thought to be due to PK/PD considerations including high protein binding, an inadequate AUC/MIC with standard dosing, poor serum concentrations, and penetration into some tissues [29].

Combination Therapy

1. Combination with vancomycin

Synergistic interactions between vancomycin and a wide variety of β-lactams, have been demonstrated *in vitro*. The mechanisms for this synergy are not clear but may include β-lactam induced potentiation of host defense peptide activity against *S. aureus*, and a "see-saw" effect whereby reduced vancomycin susceptibility results in reduced transcription of *mecA* and increased susceptibility to β-lactams. A retrospective study found a higher rate of clearance of MRSA bacteremia in patients receiving empiric vancomycin plus a β-lactam than in patients receiving vancomycin alone [30]. A pilot randomized clinical trial comparing an antistaphylococcal β-lactam in combination with vancomycin to vancomycin alone found that the duration of MRSA bacteremia was shorter by about a day 3.00 days with vancomycin alone versus 1.94 days with the combination [31]. There is a lack of evidence of benefit of vancomycin combined with other antistaphylococcal antibiotics. In a retrospective study, 35 patients with persistent (≥7 days) MRSA bacteremia while receiving vancomycin had their therapy altered. 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%) [21].

2. Combination with daptomycin

The combination of daptomycin and β–lactam enhances killing against daptomycin-susceptible and daptomycin-nonsusceptible MRSA, increases daptomycin binding to the bacterial cell membrane, and prevents the development of daptomycin resistance. Experiments in the rabbit model of endocarditis caused by a daptomycin-nonsusceptible strain of MRSA have shown that the combination of daptomycin of daptomycin with β–lactam reduced bacterial densities in all tissues compared to single agents [32]. Case reports describe the successful clearance of persistent bacteremia caused by MRSA strains, including strains that are nonsusceptible to daptomycin [33].

Summary

Treatment of MRSA bacteremia requires prompt source control and initiation of active antimicrobial therapy. Vancomycin remains the initial antibiotic of choice for the treatment of patients with MRSA bacteremia and endocarditis due to isolates with vancomycin MIC ≤2 μg/mL. Daptomycin is an effective, although more costly alternative, and ceftaroline appears promising. Although often attributed to antibiotic failure, persistent MRSA bacteremia more often is dues to inadequate poor source control of foci of infection. The optimal salvage regimen for persistent MRSA bacteremia is uncertain. Treatment options for persistent MRSA bacteremia or bacteremia due to VISA or VRSA include daptomycin, ceftaroline, and combination therapies.

The need for antibiotics that are more efficacious than vancomycin has never been greater. Fortunately, several agents have become available for the treatment of MRSA. Compelling evidence of the improved efficacy of the newer agents against MRSA infections complicated by bacteremia in prospective, randomized, double-blind studies is lacking and even in observational studies the total number of MRSA is relatively small. The exact role and choice of agent needs to be defined.

Conflicts of Interest

No conflicts of interest.

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