

Management of methicillin-resistant *Staphylococcus aureus* infections

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Abstract

This review addresses selected aspects of the management of severe healthcare-associated infections due to methicillin-resistant *Staphylococcus aureus* (MRSA), including the limitations of current therapy, potential alternative agents, new therapeutic options, clinical approaches to MRSA bacteraemia/endocarditis and ventilator-associated pneumonia, and strategies to improve outcomes in patients with severe MRSA infections.

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Introduction

In this decade, there has been a continuous increase in the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) in Europe and the USA, and the latter has witnessed the emergence and dissemination of community-acquired infections due to MRSA. However, an unprecedented decline in MRSA infection rates in several European countries has recently been observed (UK, France, Belgium, Denmark, Finland, Turkey, Cyprus, Slovenia and Austria), whereas other large countries, such as Germany and Spain, have managed to stabilize the incidence of MRSA [1,2]. This good news indicates that, for the first time, a diverse group of European countries with varying baseline prevalences of MRSA was capable of reversing the worrisome trend of inexorably increasing rates of MRSA. The reasons for the observed decline are numerous and beyond the scope of the current review. Clearly, these recent findings suggest that the spread of MRSA can be curbed in hospitals, provided that active control programmes are implemented. For instance, following the introduction of specific programmes for limiting cross-transmission, first at regional levels and subsequently at national levels, MRSA infection rates decreased by almost 50% between 1993 and 2006 in hospitals of the Paris region (Assistance Publique-Hôpitaux de Paris)

and by 20% since 2001 in more than 50 hospitals across France.

The proportion of *S. aureus* infections due to MRSA is increasing, and *S. aureus* infections are increasingly being acquired in the community. In addition, there is growing evidence that patients with MRSA bacteraemia have a worse outcome than similar patients with infections due to methicillin-susceptible *S. aureus* (MSSA) [3]. New antimicrobial agents and new management methods are thus needed.

This review addresses selected aspects of the management of severe healthcare-associated MRSA infections, including the limitations of the current therapy, potential alternative agents, new therapeutic options, clinical approaches to MRSA bacteraemia/endocarditis and ventilator-associated pneumonia (VAP), and strategies to improve outcomes in patients with severe MRSA infections. Community-acquired MRSA infections in Europe are, at the moment of writing, still rare, and therefore will not be addressed; selected aspects of infection prevention and MRSA control are dealt with in the companion articles of this theme section. Although a number of important citations are included, they are by no means exhaustive, and the reader is referred to other sources for further evidence.

Limitations of Current Therapy

Glycopeptides have been the mainstay of treatment for MRSA infections and staphylococcal infections in patients with true penicillin allergy. Glycopeptides are less bactericidal than β -lactam agents, and penetration into tissues is poor. Vancomycin has been reported to clear bacteraemia

in patients with endocarditis more slowly than β -lactams, i.e. 7 days vs. 3.4 days in nafcillin-treated patients [4], and has been found to be associated with higher infection-related mortality than β -lactams in treatment of endocarditis caused by MSSA [5]. For these and other reasons, a number of recent reports have called into question the efficacy of this class of antimicrobials in the treatment of severe MRSA infections. Higher rates of relapse, complications, treatment failure and mortality in cases of MRSA bacteraemia and endocarditis have been associated with vancomycin therapy. Increasing the dose of vancomycin may not safely overcome its limited bactericidal activity, and its combination with a second antistaphylococcal agent does not improve its therapeutic efficacy (mortality being the outcome measure). MRSA strains with lower vancomycin MIC values have been associated with increased rates of treatment success with vancomycin as compared with strains that have higher vancomycin MIC values, whereas increased MICs of vancomycin for *S. aureus* may be predictive of increased treatment failure (30-day mortality) and longer duration of bacteraemia in patients receiving vancomycin therapy [6,7].

Decreasing activity of glycopeptide antimicrobials

Despite more than 50 years of treatment with vancomycin, fully vancomycin-resistant strains (vancomycin-resistant *S. aureus* (VRSA)) are still an anecdotal phenomenon, with fewer than ten strains having been described, mainly in the USA, but also abroad [8,9]. These strains have been associated with only limited clinical consequences, because they have not been associated with invasive disease.

VRSA and vancomycin-intermediate *S. aureus* (VISA) are usually cross-resistant to teicoplanin [10]. VISA and hetero-resistant VISA strains of *S. aureus* that contain subpopulations of daughter cells displaying intermediate sensitivity to vancomycin, but for which the MICs of vancomycin fall within the susceptible range, can be difficult to detect in the microbiology laboratory, because the phenotypes are unstable and can be lost on subsequent passages.

The role of tolerance to vancomycin in *S. aureus* has not been well clarified. It is more frequently associated with MRSA than with MSSA and in isolates from patients with endocarditis [11]. Whether tolerance is a prerequisite for attenuated vancomycin efficacy and the development of glycopeptide resistance warrants further study. Part of the intermediate glycopeptide resistance seen in VISA may be due to tolerance [12]. Several small series and case studies have reported poor clinical response to vancomycin in the treatment of bacteraemia/endocarditis caused by vancomycin-tolerant *S. aureus* and the need for additional agents for a bactericidal effect [13–15].

Teicoplanin is used in several European countries as the main glycopeptide. The MIC₉₀ of teicoplanin is greater than that of vancomycin. The protein-binding ability of teicoplanin is approximately 92%; however, bactericidal activity depends on the total drug level of teicoplanin rather than on the concentration of the free drug. Teicoplanin is usually seriously underdosed, and a loading dose is needed. Trough concentrations should be maintained at c. 20 mg/L. Teicoplanin-intermediate *S. aureus* may now be more common than VISA, but its clinical impact has not been studied systematically.

There is growing evidence of a vancomycin MIC creep in various MRSA isolates. For example, a study from UCLA Medical Center showed that, among the 6002 clinically relevant MRSA isolates tested, there was a shift in vancomycin MICs from ≤ 0.5 to 1.0 mg/L during the 5-year study period. The percentage of *S. aureus* isolates with a vancomycin MIC of >1 mg/L in 2004 was significantly higher than the percentage of isolates in 2000 (70.4% vs. 19.9%; $p < 0.01$). This shift in vancomycin MIC value was more notable in MSSA [16]. In another recent study from the south of the USA, 90% of the strains demonstrated vancomycin MICs of >2.0 mg/L according to Etest, and 12% demonstrated a vancomycin MIC of 3.0 mg/L [17].

Most unfortunately, there is a poor correlation between MICs obtained by Etest and those obtained by microdilution procedures, and MICs may vary significantly between two different determinations. It is important to realize the important limitations of the clinical laboratory in detecting reduced susceptibility and resistance to vancomycin, and the reader is referred to the review in this issue by Struelens *et al.* for further discussion. On the other hand, it should be realized that vancomycin creep is not a universal phenomenon, and that vancomycin MICs have been found to be stable over time by other investigators [18,19].

There is some evidence for the clinical impact of increased vancomycin MICs. The vancomycin success rate in treating MRSA bacteraemia was found to be much higher for isolates with MICs of ≤ 0.5 mg/L (56%) than for isolates with MIC values of 1.0–2.0 mg/L (10%) [7,20]. Also, in a recent study from Spain, mortality associated with MRSA bacteraemia was significantly higher when vancomycin was used empirically for treatment of infection with strains with a high vancomycin MIC (>1 mg/L) [21]. Other recent reports have linked clinical failure with vancomycin treatment of infections involving strains with MICs of 2–4 mg/L or heteroresistant VISA strains [6,7,20–23]. The CLSI therefore lowered the vancomycin breakpoint for *S. aureus* susceptibility from 4 to 2 mg/L in 2006.

Clinical MRSA strains with high vancomycin MIC values (2 mg/L) require aggressive empirical therapy to achieve trough concentrations ≥ 15 mg/L.

This can be achieved with continuous perfusion of vancomycin, a concept that has become popular in many European countries, in particular in the intensive-care unit (ICU) setting. However, not all studies were able to show that achieving a vancomycin trough in excess of 15 mg/L improved success rates [6].

In summary, vancomycin is recommended for empirical therapy in healthcare settings with an increased incidence of methicillin-resistant staphylococci or when risk factors for MRSA infections are present, such as MRSA-positive surveillance cultures. Although high-level resistance remains rare, data from some centres suggest an evolutionary change in *S. aureus*, as evidenced by reduced susceptibility to vancomycin. This, together with the problem of heteroresistance to vancomycin, as well as poor tissue penetration after systemic administration, presents potential obstacles to the successful treatment of *S. aureus* infections with this glycopeptide. Although it has been suggested that these problems may be overcome by administration of vancomycin in much higher doses by continuous perfusion, the efficacy and safety of this approach remain to be determined.

The subgroup of patients with infections due to strains with vancomycin MIC values of >1 mg/L can be managed by alternative therapy, with the combination of vancomycin and other drugs, or by providing doses of vancomycin high enough to achieve trough levels >15 mg/L. However, the risk with higher dosages is an increase in nephrotoxicity.

Classic Alternatives to Standard Therapy

Trimethoprim–sulphamethoxazole

Trimethoprim–sulphamethoxazole is inexpensive and suitable for sequential therapy. A high proportion of *in vitro* MRSA isolates susceptible to trimethoprim–sulphamethoxazole have been reported recently [24]. In the animal model, folate antagonist treatment fails when delayed, consistent with the possibility that *in vivo* thymidine release inhibits folate antagonists.

Trimethoprim–sulphamethoxazole can be regarded as a second-line agent for the treatment of severe MRSA infections in patients unable to tolerate other more active drugs, such as glycopeptides or linezolid. In a randomized, prospective trial comparing trimethoprim–sulphamethoxazole with vancomycin [25] in intravenous drug abusers with endovascular infections caused by MSSA and MRSA (47% MRSA), trimethoprim–sulphamethoxazole was inferior to vancomycin in terms of duration of bacteraemia (6.7 vs. 4.3 days), sterilization of wound cultures (5.8 vs. 3.8 days), duration of fever, and failure rates (six of 43 patients treated with trimetho-

prim–sulphamethoxazole vs. one of 58 patients treated with vancomycin). If trimethoprim–sulphamethoxazole is selected, intravascular infections and infections with abscesses or a high degree of necrotic tissue must not be considered for treatment, because the availability of exogenous thymidine may inactivate trimethoprim–sulphamethoxazole as it bypasses the double biosynthetic blockade. Trimethoprim–sulphamethoxazole may be better suited for infections with a low bacterial burden, as is the case for chronic osteomyelitis and clinical situations with no risk of death in case of clinical failure.

Chloramphenicol

A very high proportion of MRSA isolates in different areas of the world remain susceptible to chloramphenicol, including community-acquired isolates. In a SENTRY study, 82% of the MRSA isolates from cases of pneumonia were chloramphenicol-susceptible [26]. In six sequential multicentre national studies of *Staphylococcus* performed in Spain from 1986 to 2006, the rates of chloramphenicol susceptibility rose from 92% to 98% [27]. Treatment with chloramphenicol in association with vancomycin has shown an antagonistic effect *in vitro* [28]. Unfortunately, both the potential myelotoxicity of chloramphenicol and the absence of reported recent clinical experience with its use in the treatment of MRSA infections make it a possibility only as a last resort in situations where no better alternatives are available.

Tetracyclines

The long-acting tetracyclines doxycycline and minocycline are well absorbed by the gastrointestinal tract, have very good tissue penetration, and have better antistaphylococcal activity than tetracycline. *In vitro* data suggest that minocycline has better antistaphylococcal activity than doxycycline [29], but clinical superiority has not been demonstrated. The data available are insufficient to support their use in serious infections such as bacteraemia or endocarditis.

Synercid

The streptogramin combination quinupristin–dalfopristin (Synercid) has synergistic antibacterial activity *in vitro* against a wide array of Gram-positive organisms, including a high proportion of MRSA strains. It has proven effective in animal models of infection (bacteraemia and endocarditis) caused by MRSA. Its clinical use is limited, because administration is via slow infusion of a large volume, and it inhibits P450 3A4 and can inhibit agents metabolized through this pathway. Arthralgia and myalgia are among the main adverse events associated with Synercid. Pain and inflammation at the infusion site occur in up to 75% of patients. The drug can also cause

hyperbilirubinaemia and liver toxicity and, by interfering with the metabolism of other drugs, may induce QTc prolongation. Synercid has been found to be equivalent to other agents for the treatment of skin and soft tissue infections, but it was inferior to comparators for the treatment of pneumonia and infective endocarditis [30]. The present status of synercid is that it did not acquire regulatory approval by the FDA for the treatment of MRSA infections. The wide spectrum of adverse effects makes synercid an inferior choice for the treatment of MRSA infections. An in-depth review of the role of antistaphylococcal agents, including fusidic acid, fosfomicin, and others, by Bouza [31] will be available in an upcoming supplement to CMI.

Antibiotic combinations

The combination of vancomycin and aminoglycosides is synergistic against most infections due to MRSA. The synergism of vancomycin and gentamicin is not predictable for MRSA strains with gentamicin MIC values of 0.5 to >128 mg/L [32]. Combination therapy might confer a small advantage in cases of staphylococcal prosthetic valve endocarditis, in accordance with most animal model data, because, after adjustment for duration of treatment by logistic regression analysis, valves from patients with staphylococcal endocarditis receiving any kind of combination therapy were six times more likely to be culture-negative than those receiving monotherapy [33]. Combination regimens involving aminoglycosides have demonstrated a more rapid clinical response and a reduced duration of bacteraemia. Current guidelines for the treatment of *S. aureus* endocarditis recommend the use of a 4–6-week course of vancomycin or an antistaphylococcal β -lactam, with the optional addition of gentamicin (three times daily). The addition of a single high dose of gentamicin at the start of therapy may help to overcome the inoculum effect associated with vancomycin, as bacterial densities approach $6 \log_{10}$ CFU/mL within 24 h. A single high dose of gentamicin in combination with vancomycin may be useful in maximizing synergistic and bactericidal activity and in minimizing toxicity. There have been no studies in humans with *S. aureus* infective endocarditis (IE) demonstrating that early bactericidal activity improves reduction in metastatic complications or mitigation of valvular damage. Therefore, further *in vivo* studies must be performed in order to determine its appropriateness for clinical practice. In any case, the association of vancomycin and gentamicin should be used with caution in patients with MRSA infections, and should be undertaken for a very short period of time, to avoid nephrotoxicity.

The combination of vancomycin with rifampin should also be considered in the treatment of MRSA endocarditis.

Studies of *in vitro* and *in vivo* bactericidal interactions of vancomycin plus rifampin in treating *S. aureus* infections have yielded conflicting results. *In vitro* results concerning interactions between rifampin and other antibiotics are method-dependent, and often do not correlate with *in vivo* findings. In the rabbit model of left-sided endocarditis due to MRSA, vancomycin alone and vancomycin plus rifampin were equally effective in reducing mortality and in sterilizing renal abscesses [34]. In the only prospective trial of rifampin as an adjunct to traditional therapy for *S. aureus* endocarditis, rifampin in combination with vancomycin for treatment of MRSA endocarditis was not beneficial, either in increasing survival or in decreasing the duration of bacteraemia, although the study sample was too small to endorse one regimen over the other [35]. Some results even suggest that the potential for hepatotoxicity, drug–drug interactions and the emergence of resistant *S. aureus* isolates warrants a careful risk–benefit assessment before rifampin is added to standard antibiotics for the treatment of severe *S. aureus* infections [36]. Given the prevalence of staphylococcal infections and the limited number of treatment options, further adequately powered studies of rifampin as adjunctive therapy are needed.

The combination of fosfomicin and imipenem has been found to be highly synergistic and bactericidal against MRSA. In the humanized model of left-sided endocarditis due to MRSA, the combination is consistently more effective in sterilizing the vegetations and in reducing the log of CFU/g of vegetation than either drug used alone or vancomycin. These data indicate that this combination deserves consideration for clinical application (García de la María C, Marco F, Miró JM, et al. Program and abstracts of the 43rd Annual Inter-science Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2003. Abstract B-1091).

New Therapeutic Options

As stated above, low-dose vancomycin may be inferior to some new comparator agents in the treatment of serious MRSA infections, especially in the presence of increased MIC values. Novel agents with activity against MRSA have become available in Europe in recent years, and others are in the advanced stage of clinical development. In some instances, although most comparative trials with these new agents have important limitations in their design, some indirect evidence of their possible superiority over vancomycin is emerging.

Daptomycin

Daptomycin, a new lipopeptide already present in nature 30 million years ago, has a unique mechanism of action,

and is only active against Gram-positive bacteria. It acts at the cytoplasmic membrane, binding but not penetrating the membrane via a calcium-dependent insertion of its lipid tail. Cell death occurs in association with widespread inhibition of the synthesis of DNA, RNA, and protein, but cell lysis and the release of large molecules from the cytoplasm does not occur. Daptomycin susceptibility is defined as an MIC of <1 mg/L (CSLI 2006). Among *S. aureus* strains fully susceptible to vancomycin, 97% are susceptible to daptomycin. With the emergence of an increasing number of strains of *S. aureus* with vancomycin-intermediate susceptibility, a correlation has been noted between acquisition of vancomycin-intermediate susceptibility and non-susceptibility to daptomycin. Among strains with a vancomycin MIC value of 4 mg/L, only 20% are susceptible to daptomycin, and among strains with a vancomycin MIC value of 8–16 mg/L, only 7% are susceptible to daptomycin [37]. Among the first seven VRSA isolates (vancomycin MIC \geq 32 mg/L), all but one remain susceptible to daptomycin [8].

Daptomycin heteroresistance is also found among strains that develop vancomycin heteroresistance during treatment with vancomycin, even when the MIC for the organisms remains within the susceptible range. *In vitro* killing assays demonstrate less rapid killing of these heteroresistant isolates [38]. A strong correlation ($R = 0.814$, $p < 0.0001$) has been found between reduced susceptibility to daptomycin and vancomycin resistance among VISA strains, and this loss of susceptibility correlates with the degree of cell wall thickening ($R = 0.883$, $p < 0.0001$) [39]. It has been postulated that the mechanism of the loss of daptomycin susceptibility is due to the inability of daptomycin to pass through the physical barrier of the enlarged cell wall [39]. In clinical isolates, prior patient exposure to vancomycin is associated with isolates with a small but statistically significant rise in daptomycin MIC values (mean 0.599 vs. 0.726 mg/L, $p < 0.019$), even among strains that remain within the susceptible range (Moise-Broder P, El-Fawal N, Forrest A, et al. 2006. Program and abstracts of the 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington DC: ASM. Abstract C2-1151)[40].

The daptomycin half-life is approximately 8 h, with a volume of distribution of 100 mL/kg, and protein binding of 90–93%, which is independent of dose. Protein binding is reduced to 84–88% among patients with a creatinine clearance of <20 mL/min. Approximately 78% of daptomycin is excreted via the kidney, two-thirds as intact drug. It is not extensively metabolized. In *in vitro* time-kill studies using exponential growth phase MRSA, there is more than a 3 log₁₀ fall in CFU/mL within only 2 h at a 20 mg/L concen-

tration of daptomycin, as compared to a less than 1 log₁₀ fall with 20 mg/L vancomycin. It has concentration-dependent killing activity *in vitro* and in pharmacodynamic studies in mice. It produces a post-antibiotic effect of over 6 h at 16 mg/L, which is concentration-dependent, as compared with a 1.3–1.8 h post-antibiotic effect of vancomycin, which is non-dose-dependent [41]. Unlike vancomycin, it maintains a high level of bactericidal activity when tested against a high inoculum of 9.5 log₁₀ CFU/g of MRSA in an *in vitro* simulated endocardial vegetation model, and has activity against stationary-phase organisms [42,43].

S. aureus non-susceptibility to daptomycin after vancomycin treatment is a source of considerable concern. Clinical cases showing decreasing susceptibility of *S. aureus* to vancomycin due to antibiotic pressure exerted by daptomycin, or vice versa, and showing treatment failure have been reported. Rose et al. [44] evaluated the resistance of daptomycin after exposure to vancomycin in clinical *S. aureus* isolates (four MRSA isolates and one MSSA isolate), using an *in vitro* pharmacokinetic/pharmacodynamic model. Their results demonstrate that reduced daptomycin susceptibility is an unstable event and is strain-specific. With the exception of vancomycin, reduced susceptibility to daptomycin due to prior treatment with other antibiotics has not been reported.

Minimal skeletal muscle toxicity is rarely seen with the current dosage. It is predicted by elevations in serum creatinine phosphokinase and is reversible upon discontinuation of treatment. No signs of toxicity in cardiac or smooth muscle have been reported. Other side effects related to daptomycin are unusual and have not been associated with significant increases in adverse events as compared to comparator arms in randomized trials. Exceptions are events related to the peripheral nervous system, including paresthesias, dysesthesia and peripheral neuropathy, which were observed in 9.2% of patients receiving daptomycin in the bacteraemia trial, as compared with 1.7% of patients in the comparator arm ($p < 0.02$). These events were transient and resolved during continued treatment [69]. Daptomycin would be a drug of choice for patients with MRSA bacteraemia who are either intolerant to vancomycin or infected with daptomycin-susceptible strains of VRSA.

Daptomycin has been prospectively compared with standard therapy in patients with *S. aureus* bacteraemia and/or right-sided endocarditis. The success rates were similar in patients with MRSA isolates. Daptomycin, however, was associated with a higher rate of microbiological failure than was standard therapy. Some of the isolates of the patients classified as microbiological failures developed reduced susceptibility to daptomycin.

Renal dysfunction occurred more frequently in the patients receiving vancomycin rather than daptomycin (26% vs. 11%) [45].

Daptomycin should not be used for treating patients with pneumonia, because of the lack of efficacy due to inactivation of the drug by lung surfactant. Resistance to daptomycin is uncommon, but can be induced by serial passage in the presence of increasing concentrations of the antibiotic. Clinically, resistance occurs in patients who receive prolonged courses of treatment [46,47].

Daptomycin is approved in the European Union for the treatment of complicated skin and skin structure infections (cSSSIs), right-sided endocarditis due to *S. aureus*, and *S. aureus* bacteraemia associated with right-sided endocarditis or cSSSIs [48].

Linezolid

Linezolid, the first available agent in the new class of oxazolidinone antibiotics, represents a significant advance in the management options available for combating MRSA infections. Linezolid has a unique mechanism of action whereby it selectively binds to the 50S ribosomal unit and prevents formation of the initiation complex. This action is thought to prevent cross-resistance with other antimicrobial agents. Protein binding is low. This agent is bacteriostatic against staphylococci, and has an MIC₉₀ of 2 mg/L against MRSA [49].

The oral bioavailability of linezolid is approximately 100%, thus allowing sequential intravenous-to-oral administration without changing the drug or dosage regimen. In a multinational, randomized, phase III trial, linezolid recipients, as compared with vancomycin recipients, had a median length of hospitalization that was 5–8 days shorter; there were more discharges during the first week of treatment, and fewer days of intravenous therapy [50]. Retrospective pooled analysis and simultaneous meta-analysis of five prospective, randomized, controlled studies demonstrated that linezolid was associated with outcomes that were not inferior to those obtained with treatment with vancomycin in 144 patients with *S. aureus* bacteraemia, including patients with MRSA bacteraemia [51]. Linezolid has been used successfully in the treatment of IE caused by resistant Gram-positive cocci. The studies, however, were retrospective, and represent daily clinical practice; in many cases of IE, the patients were those failing with other drugs or those in whom linezolid was introduced sequentially after other primary therapy. The question of using a bacteriostatic antibiotic for the treatment of IE remains contrary to classic principles. Conversely, in a large randomized study in patients with catheter-related bacteraemia, there was an excess number of deaths in the linezolid arm, mainly due to Gram-negative bacillary infec-

tions [52], and therefore it has not been approved by the FDA for treatment of catheter-related bacteraemia or endocarditis.

Although it is generally well tolerated, adverse effects as a result of treatment with linezolid can be serious. Gastrointestinal adverse effects are relatively common. Bone marrow suppression, especially thrombocytopenia, is the most common serious adverse effect. Both peripheral and optic neuropathy have been reported with prolonged use (more than 28 days). Linezolid has a weak activity as a monoamine oxidase inhibitor and, when it is given to patients with serotonin re-uptake inhibitors, these patients may develop the serotonin syndrome.

Tigecycline

Glycylcyclines comprise a novel group of antimicrobial agents. These agents retain a central four-ring carbocyclic skeleton of the tetracycline class that is crucial for antimicrobial activity. Tigecycline has a 9-*t*-butyl-glycylamido side chain on the central skeleton. Active efflux of drugs from inside the bacterial cell, and ribosomal protection, are the two main mechanisms of bacterial resistance to tetracyclines. Tigecycline most likely overcomes these tetracycline resistance mechanisms through steric hindrance by a large substituent at position 9.

Tigecycline is bacteriostatic against MRSA (MIC₉₀ 0.5 mg/L) and has *in vitro* activity against VISA and VRSA (MIC₉₀ ≤0.5 mg/L) [53].

In a rat model of aortic MRSA endocarditis, a reduction of more than 4 log₁₀ CFUs of the MRSA isolate was reported. In this experimental model, tigecycline was more effective than vancomycin in reducing bacterial colony counts at a lower dose [54].

Tigecycline is available only as an injectable antibiotic, and is administered twice daily as a 1-h infusion. Tigecycline has a large and variable volume of distribution, which has been found to range from c. 5 to >10 L/kg; this is significantly greater than what has been determined for currently available tetracyclines.

The most frequently reported adverse events associated with tigecycline are nausea, vomiting, and headache. Although the frequency of these events is high, the severity is low, and the overall rate of treatment discontinuation because of nausea in the phase III studies was <1.5%. Experience with currently marketed tetracyclines may suggest other adverse effects due to tigecycline, e.g. deposition in teeth and bone during calcification, and drug interactions with antacids, anti-coagulants, and other agents.

At the time of writing, only two double-blind trials of tigecycline for the treatment of MRSA infections have been

published; both studies concerned cSSSIs, and vancomycin was used as the comparator.

No published experience is available concerning patients with MRSA bacteraemia/endocarditis or MRSA pneumonia. It appears that the target AUC for tigecycline should be two to four times the MIC. As the MIC₉₀ range for MRSA is 0.25–0.5 mg/L, caution should be exercised when using tigecycline for the treatment of bacteraemia [55]. It is approved in the European Union for the treatment of cSSSIs and complicated intra-abdominal infections.

Tigecycline may be considered as alternative empirical therapy for patients with mild-to-moderate cSSSIs and for complicated intra-abdominal infections. The main issue regarding MRSA infections, however, concerns the role of tigecycline in the treatment of other severe infections caused by MRSA, including nosocomial pneumonia, bacteraemia, catheter-related bloodstream infections, and bone and joint infections. A trial comparing tigecycline with imipenem–cilastatin in the treatment of nosocomial pneumonia ended recently, but full information is not yet available as a published report. Tigecycline failed to achieve the non-inferiority results (Maroko R, Cooper A, Dukart G et al. 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract L-730, Chicago, 2007) [56].

Clinical Approach to MRSA Bacteraemia and Endocarditis

S. aureus bacteraemia and endocarditis are serious infections that require prompt attention and pertinent clinical decisions to improve outcomes. Currently, *S. aureus* is a leading cause of healthcare-associated bloodstream infections and, accordingly, the first cause of IE in most regions of the developed world. A convincing amount of experience indicates an increased risk of death for patients with MRSA bacteraemia, as compared with the risk for similar patients with MSSA bacteraemia [3,57], and reveals high mortality rates among patients with left-sided MRSA endocarditis. Thus, the management of bacteraemia and endocarditis caused by MRSA should be regarded as a growing clinical challenge.

Establishing the source and the extent of the infection, and initiating appropriate empirical antibiotic therapy, are the most important aspects of the clinical approach. Most patients have an identifiable underlying focus of infection at the time of initial evaluation, but the source of infection is uncertain in the remaining patients. The most common sources of MRSA bacteraemia are intravenous catheters and other intravascular devices, skin and soft tissue infections, and VAP [58]. Approximately one-third of patients with

MRSA bacteraemia, either primary or secondary, will develop metastatic complications, including involvement of heart valves, intervertebral discs, intra-abdominal organs, and bones and joints, especially when prosthetic material is present [59]. In the clinical setting, it can be difficult to establish whether an infected organ is the primary source of the secondary bacteraemia or whether an organ was secondarily infected from a primary bacteraemia. Identification of the infected sites is essential, and both a careful patient history and a physical examination, including radiographic imaging studies and echocardiography of the heart, are important. Empirical antibiotic therapy should be established according to the principles outlined in this review, and it should be taken into account that delaying appropriate antibiotic therapy for *S. aureus* bacteraemia beyond 48 h is associated with increased mortality [60].

For the purposes of this review, three different clinical situations are considered:

Catheter-related bacteraemia

Recommendations for catheter management are similar for bacteraemia due to MSSA and that due to MRSA. The catheter should be removed as soon as the diagnosis of catheter-related bacteraemia is considered. Prospective studies have demonstrated that removal of an infected central venous catheter (CVC) is associated with a more rapid clinical response and a lower rate of recurrence than maintenance of the infected CVC [61,62].

Furthermore, failure to remove the CVC or other infected intravascular prosthetic material has been associated with an almost doubled rate of mortality. Management of tunelized catheters without catheter removal, using both systemic and local (antibiotic-lock technique) antimicrobial treatments, should be reserved for very unusual circumstances and selected patients.

Empirical antibiotic treatment should be initiated with vancomycin, i.e. the standard therapy. Teicoplanin is another option, as randomized studies in cancer patients with CVC-related bacteraemia have shown similar clinical and microbiological outcomes with both glycopeptides [63]. A switch to daptomycin therapy may be considered in patients with slow response, persistent bacteraemia, or worsening renal function, or in those infected with VISA strains. It should also be considered in situations in which a significant proportion of MRSA isolates exhibit vancomycin MIC values of >1 mg/L.

On the other hand, a switch to oral linezolid therapy may be considered in patients with a rapid response and negative blood cultures after catheter removal. The duration of therapy will depend on the presence of complications. If the response is good and there is no evidence of a complicated

course, patients can be safely discharged to complete 14 days of therapy at home. There are no convincing data to support recommending shorter treatment schedules in cases of MRSA bacteraemia.

Complicated bacteraemia

Complicated bacteraemia is usually defined as the presence of metastatic infection during hospitalization, attributable mortality, or recurrent infection during the follow-up period. The classical predictors of complicated bacteraemia are community origin of the infection, absence of an identifiable portal of entry, and persistence of fever; however, the strongest indicator is persistent bacteraemia, defined as a positive result with blood cultures performed 3–4 days after the initiation of therapy [58]. Persistent bacteraemia (PB), a characteristic feature of *S. aureus* bloodstream infection, appears to be more frequent among MRSA-infected patients. In fact, the recognized risk factors for PB are maintenance of intravascular devices, chronic renal failure, methicillin resistance, and vancomycin therapy. The presence of PB or any other clinical indicator of complicated infection warrants a thorough search for endocarditis or another metastatic focus of infection. In this context, repeating blood cultures every 48–72 h and performing trans-oesophageal echocardiography are mandatory [64]. Patients undergoing glycopeptide therapy with documented PB or lack of clinical response should be treated with daptomycin as the first alternative. Results of *in vitro* susceptibility testing and final diagnosis of the complication (endocarditis, espondilitis, endophthalmitis, etc.) should guide the choice of definite therapy.

Endocarditis

Patients with left-sided MRSA endocarditis are more likely to have chronic conditions (immunosuppressive therapy, maintenance haemodialysis and treatment of diabetes mellitus), have healthcare-associated infections, or have persistent bacteraemia. Mortality rates are higher, and may be as high as 70%. Prosthetic endocarditis and denial of surgery when indicated are associated with a worse prognosis.

Right-sided MRSA endocarditis is less frequent and affects intravenous drug users; it is more often community acquired and caused by community-associated MRSA genotypes. The prognosis is better, with c. 15% mortality rates.

According to the current guidelines, in spite of the limited efficacy of the drug for this infection, vancomycin remains the reference standard for the treatment of both prosthetic and native right-sided and left-sided MRSA endocarditis. Sometimes, gentamicin or rifampin is added to enhance bactericidal activity; this possibility is mentioned in guidelines,

but not recommended specifically. Gentamicin is usually added when MRSA strains are non-susceptible; there is no evidence of increased efficacy in terms of reducing mortality, and the combination is often nephrotoxic. In the case of rifampin, the combination may even be antagonistic, and resistance may develop during therapy [35,36].

The consensus is that right-sided endocarditis can be treated safely with vancomycin, 15 mg/kg/12 h/6 weeks (achieving trough levels of 15–20 mg/L), while paying careful attention to the patient's evolving condition. In cases of renal impairment, sustained bacteraemia for more than 7 days, or infection with a VISA strain, treatment should be with daptomycin, 6 mg/kg/day or a higher daily dose, for 6 weeks.

Recommendations for treating left-sided MRSA endocarditis are more complicated. The occurrence of treatment failure with vancomycin should be regarded as very possible from the beginning of therapy. Blood cultures should be performed on a 2-day basis, early surgery should be considered in every case, and MICs/MBCs of vancomycin, daptomycin and all possible relevant alternatives should be investigated. To date, the results obtained with either vancomycin or daptomycin therapy, using standard doses, have been disappointing [45]. If treatment failure with vancomycin occurs, or the infecting strain shows reduced vancomycin susceptibility, an early switch to high-dose daptomycin therapy (10 mg/Kg/day) is recommended, provided that the strain remains fully susceptible to the drug. Patients who have been heavily exposed to vancomycin may be at increased risk of a sub-optimal response to daptomycin; accordingly, when indicated, such switching should be performed as soon as possible. Patients who fail to respond to these agents must be treated with other antibiotic combinations on a compassionate basis under expert evaluation. In this setting, linezolid or the combination of high-dose fosfomycin and imipenem are alternative choices, as discussed earlier.

Management of MRSA Vap

S. aureus is one of the leading causes of VAP in Europe. VAP due to MRSA is rising in incidence and poses unique challenges for management. Risk factors for the development of MRSA-related VAP include nasal carriage, prior antibiotic therapy, prolonged mechanical ventilation, poor infection control practices, head trauma/coma, and viral infection [65]. Data suggest that a diagnosis of MRSA-related VAP is an important determinant of excess hospitalization and ICU length of stay, as well as attributable costs, as compared with MSSA infection [66].

Current management guidelines recommend glycopeptides as the initial therapy for MRSA-related VAP. However, success rates for vancomycin are low. This may be due to the poor penetration of vancomycin into the lung, in particular when using conventional, low-dose regimens. Antibiotic penetration into tissues and fluids at the specific site of infection, rather than the concentration in serum, has been increasingly recognized as being much more valuable in predicting response to drugs.

For vancomycin and linezolid, the most important pharmacokinetic/pharmacodynamic parameter seems to be the 24-h AUC, although both antibiotics demonstrate concentration independence [42,43]. However, vancomycin at dosages that achieve such levels may be associated with renal dysfunction, especially when it is given concomitantly with other nephrotoxic drugs [67].

Linezolid is an alternative to vancomycin for the treatment of MRSA-related VAP. A *post hoc* analysis of two double-blind trials of patients with MRSA nosocomial pneumonia found that patients treated with linezolid had significantly higher survival rates than those treated with vancomycin [68]. This analysis has been criticized on methodological grounds, specifically because of a non-prespecified subgroup analysis, the heterogeneity of results in the separate studies, and the small numbers of patients infected with MRSA (7.3% of the combined microbiologically evaluable population). However, linezolid may be preferred if patients have renal insufficiency or are receiving other nephrotoxic agents, or when infection is caused by a strain with a vancomycin MIC value of ≥ 1.5 mg/L.

Strategies to Improve Outcome in MRSA Infection

There is an urgent need to improve early diagnosis and empirical treatment of severe MRSA infection. The recent development of accurate molecular techniques to identify blood culture isolates in a much shorter time frame than that required for traditional phenotypic methods is one more step towards achieving rapid diagnosis of MRSA bacteraemia. Indeed, rapid reporting of identification and susceptibility results for *Staphylococcus* spp. in blood culture is expected to improve treatment and reduce the length of hospitalization. Various types of molecular tests have been considered for the rapid identification and differentiation of 'Gram-positive cocci in clusters' as revealed by direct examination of positive blood cultures. Controlled trials will be necessary to determine whether these techniques are sufficiently reliable to exclude pseudobacteraemia and contamination of the bloodstream by coagulase-negative staphylococci,

and finally, to impact on antibiotic treatment decisions and patient outcomes [69].

Identification of patients at high risk of hospital-acquired MRSA infection is possible on the basis of clinical risk factors. Known risk factors for bacteraemia after MRSA colonization include recent antibiotic therapy, ICU stay, extended length of stay, initial involvement of bones or joints, and intravenous catheterization [70]. Individuals who are known to have harboured MRSA for >1 year are at high risk of subsequent MRSA infection, and this warrants intervention [71]. Although precise thresholds have not been established, it seems prudent to prescribe an agent effective against MRSA to patients with several risk factors for hospital-acquired MRSA infection or to patients who have presumed severe staphylococcal infections in settings where the prevalence of MRSA is known to be $\geq 20\%$.

Patients with recurrent MRSA bloodstream infection, or with a history of extended vancomycin exposure, should be considered to be at high risk of infection with MRSA for which vancomycin MIC values are elevated. Appropriate and aggressive empirical therapy is required for these patients. In some US centres, patients with bloodstream infections due to MRSA with vancomycin MIC values of ≥ 1.5 mg/L have responded poorly to vancomycin, and alternative anti-MRSA therapies should be considered for these patients. Several treatment options are summarized in Table 1.

Whether linezolid has a role in the treatment of staphylococcal bacteraemia remains controversial, although, on the basis of pooled analysis of five studies comparing linezolid with vancomycin in patients with secondary *S. aureus* bacteraemia, it was claimed that linezolid is non-inferior to vancomycin. The incidence of adverse events was similar between treatment groups [51]. Clearly, less expensive bactericidal agents should be considered as valuable alternatives to linezolid for the treatment of MRSA bacteraemia.

The initial therapeutic approach to MRSA infection varies with the circumstances of the diagnosis of suspected *S. aureus*

TABLE 1. Treatment options for severe infections due to methicillin-resistant *Staphylococcus aureus* (MRSA)

Treatment option	Clinical scenario
Glycopeptide (trough level 15–20 mg/L)	Standard option for initial treatment, in particular for sepsis that is not life-threatening, and MIC ≤ 1 mg/L or unknown MIC
Change to daptomycin	Slow response, complicated bacteraemia, relapse or breakthrough MRSA bacteraemia and/or MIC >1.0 mg/L. Check daptomycin MIC if patient has had previous glycopeptide exposure
Initial daptomycin	Sepsis is life-threatening, renal impairment, known MIC >1.0 mg/L of glycopeptide (check daptomycin MIC), and previous, optimally conducted glycopeptide therapy

infection. In any case, rapid measures should be taken to culture the microorganism. A rapid examination of retrieved material with a Gram stain may guide empirical antibiotic therapy. It should also take into account the patient's underlying conditions, the severity of infection, the suspected source of infection, and the response to previous antibiotic therapy. In the presence of an indwelling device or foreign body, it is crucial to consider the need for removal of potentially infected foreign bodies, or surgical debridement and drainage of any necrotic areas or purulent collections.

In contrast to many other bacterial infections, *S. aureus* infections often require a prolonged course of treatment because of the risk of late-onset complications such as abscesses, osteo-articular infection, and other secondary foci due to haematogenous or direct seeding. In cases of documented bacteraemia, the recommended minimum duration of treatment is at least 14 days, as short-course therapy is currently not considered to be safe and effective.

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