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Limitations of antibiotic options for invasive infections caused by methicillin-resistant *Staphylococcus aureus*: is combination therapy the answer?

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Invasive infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), particularly those involving persistent bacteraemia, necrotizing pneumonia, osteomyelitis and other deep-seated sites of infections, are associated with high mortality and are often difficult to treat. The response to treatment of severe MRSA infection with currently available antibiotics active against MRSA is often unsatisfactory, leading some physicians to resort to combination antibiotic therapy. Now, with the emergence of community-associated MRSA (CA-MRSA) clones that display enhanced virulence potentially related to up-regulated toxin production, the use of adjuvant protein synthesis-inhibiting antibiotics to reduce toxin production also has been advocated by some experts. In this review, we discuss the limitations of antibiotics currently available for the treatment of serious invasive MRSA infections and review the existing literature that examines the potential role of combination therapy in these infections.

Keywords: MRSA, combination treatment, bactericidal agents, community-acquired infections

Introduction: scope of the problem

Over the past two decades, the proportion of *Staphylococcus aureus* bacteraemia and other invasive infections due to methicillin-resistant isolates has increased relative to those caused by methicillin-susceptible *S. aureus* (MSSA).[1,2] In addition, community-associated methicillin-resistant *S. aureus* (CA-MRSA) clones have recently emerged as frequent causes of bacteraemia and other invasive infections.[3–5] MRSA bacteraemia has been associated with higher mortality than MSSA, even after correcting for confounding variables such as endocarditis, line infections and outbreaks.[6] Clinical failures in the treatment of invasive MRSA infections are common. In the landmark randomized trial comparing daptomycin with standard therapy in the treatment of *S. aureus* bacteraemia and endocarditis, overall clinical success in treating patients infected with MRSA was well under 50%, regardless of the agent received.[7] Similarly, clinical cure rates in the randomized trials comparing linezolid with vancomycin for the treatment of healthcare-associated pneumonia were also low (59% in the linezolid group and 36% in the vancomycin group).[8] The high proportion of clinical failures in the treatment of invasive MRSA infections has prompted a re-evaluation of how these infections are managed. Below, we discuss the limitations of currently available antibiotics used to treat invasive MRSA infections as monotherapy and critically evaluate the *in vitro*, animal model and human clinical data for and against commonly considered antibiotic combinations in the treatment of invasive MRSA disease.

Goals of antibiotic therapy for severe MRSA infections

The ideal antibiotic for MRSA does not yet exist, but such an agent should have the following properties: rapid bactericidal killing; excellent tissue penetration; consistent pharmacokinetics and pharmacodynamics that allow for predictable dosing; low potential for the development of resistance while on therapy; low side effect profile; and demonstrated clinical and microbiological efficacy. As such an agent is not currently available, some have advocated combination therapy to fill in the gaps where each individual agent fails. Until recently, goals of combination antibiotic therapy have included maximizing bacterial clearance, preventing emergence of resistance and ensuring delivery of adequate drug to sites of infection. However, with recent studies suggesting there may be increased toxin release and subsequent host inflammation in infections caused by CA-MRSA clones,[9,10] an additional benefit of combination therapy against CA-MRSA may be attenuation of toxin production.[11]

Limitations of vancomycin as monotherapy

Vancomycin has been the traditional workhorse against serious MRSA infections; however, there is a growing perception among physicians that vancomycin may not be as reliable against MRSA as previously believed.[12] Vancomycin has several major limitations that may potentially contribute to persistent MRSA bacteraemia and other recalcitrant infections. First, while vancomycin is generally considered to be a bactericidal drug versus MRSA, its bactericidal activity may be variable depending on a number of strain-specific factors, including the MBC:MIC ratio and polymorphisms and loss of function in the accessory gene regulator (*agr*) pathway that typically regulates quorum sensing and exotoxin production.[13,14] A recent analysis of 900 bloodstream MRSA isolates from nine medical centres in the USA demonstrated 'tolerance' to vancomycin, defined as an MBC:MIC ratio ≥32, in 181 isolates (20.1%).[15] While loss of *agr* function has been demonstrated to be associated with clinical and microbiological failure of vancomycin therapy,[16] the exact contribution of loss of *agr* function to this failure is unclear, but may be related to enhancement of survival in endovascular and intracellular settings in the face of vancomycin therapy.[17,18] Secondly, while frank resistance to vancomycin in *S. aureus* is extremely rare, several centres have reported slow increases in the MIC of MRSA isolates over time ('MIC creep') associated with an increasing number of clinical failures of vancomycin therapy, even though MICs remain within the 'susceptible' range of ≤2 mg/L.[19] In addition to the 'MIC creep' phenomenon, there have also been increasing reports of *S. aureus* heteroresistant to vancomycin (hVISA), in which subpopulations of a recovered *S. aureus* isolate demonstrate intermediate resistance to vancomycin, although the population as a whole remains vancomycin susceptible.[20] The molecular mechanisms underlying the development of hVISA and development of overt intermediate vancomycin susceptibility (VISA) remain unclear, but are thought to involve a thickened cell wall that prevents vancomycin from reaching its target[21,22] and/or alterations in the *agr* system mentioned above.[22,23] Heteroresistance to vancomycin may be more common than previously recognized, particularly in isolates with vancomycin tolerance or moderate elevation in MIC; 36 of 268 (13.4%) MRSA bloodstream isolates from 9 US hospitals with either a vancomycin MBC:MIC ≥32 or an MIC >1 mg/L were characterized as hVISA in a recent study.[15] Thirdly, because it is highly protein bound, vancomycin exhibits variable tissue penetration, particularly in the skin in patients with diabetes mellitus,[24] the lungs,[25] cortical bone[26] and the meninges.[27]

Finally, the pharmacodynamics of vancomycin raise important clinical problems. The AUC/MIC ratio is believed to be the best pharmacodynamic predictor of vancomycin efficacy. An AUC/MIC ≥400 has been advocated as a target to achieve clinical effectiveness,[28] though clinical data supporting this notion are limited.[29–31] In order to increase the probability of achieving an AUC/MIC ≥400, the American Society of Health System Pharmacists, the Infectious Diseases Society of America and the Society of Infectious Diseases Pharmacists recently released a joint statement recommending dosing vancomycin to achieve target trough levels of 15–20 mg/L for MRSA pneumonia, endocarditis and other invasive diseases.[32,33] A Monte Carlo simulation reveals that for *S. aureus* isolates with a vancomycin MIC of 1 mg/L, a vancomycin dose of 3–4 g/day is needed in order to ensure a 90% probability of achieving an AUC/MIC ≥400,[34] but for isolates with a vancomycin MIC of 2 mg/L, there is 0% probability of achieving an AUC/MIC ≥400, even with higher dosing of vancomycin.[35] This more aggressive approach to vancomycin dosing may not be without consequence, as several clinical studies have implicated high vancomycin trough levels in the development of nephrotoxicity, though it is not clear if the relationship is causal.[32]

Taken together, the strain-to-strain variability in susceptibility to its bactericidal activity, the link between rising MICs and the development of heterogeneous intermediate susceptibility to clinical failures of therapy, and pharmacokinetic and pharmacodynamic issues that can impair effective delivery of drug to the site of infection have led to the consideration of alternatives to vancomycin monotherapy in the treatment of invasive MRSA disease.

Limitations of other anti-MRSA antibiotics as monotherapy

The currently available alternatives to vancomycin for the treatment of invasive MRSA infection have a number of notable disadvantages, which are summarized in Table 1. Daptomycin is a lipophilic glycopeptide that has shown clinical efficacy similar to that of vancomycin in the treatment of MRSA bacteraemia and endocarditis[7] and complicated skin and soft tissue infections (SSTIs),[36] but is ineffective for pneumonia, as it is inactivated by lung surfactant.[37] In addition, rising daptomycin MICs, 1–2 mg/L, have been seen in association with hVISA and VISA.[38,39] Whether this observation is clinically relevant is not known, but it raises concerns for cross-resistance between daptomycin and vancomycin in hVISA and VISA. In an *in vitro* endocarditis model, it appears that high-dose daptomycin (10 mg/kg/day), rather than the standard dose of 6 mg/kg/day for *S. aureus* bacteraemia, can eradicate *S. aureus* with a daptomycin MIC of 2 mg/L and prevent the further development of resistance.[40] Clinical studies of 10 mg/kg/day dosing of daptomycin are currently underway.

Linezolid is a synthetic antibiotic belonging to the oxazolidinone class; its notable side effects include marrow suppression, lactic acidosis, peripheral and optic neuropathy, and serotonin syndrome.[41,42] Some of these side effects may occur just within a few days, but most are more common with prolonged use; in the USA, linezolid is not approved for use for longer than 28 days because of its side effect profile.[43] While linezolid has shown efficacy in the treatment of MRSA pneumonia[8] and complicated SSTIs,[44] it has generally been avoided as a front-line treatment for MRSA bacteraemia and endocarditis because of its bacteriostatic nature. The data that support a potential role for linezolid in MRSA bacteraemia are extremely limited, as the studies that attempt to demonstrate non-inferiority of linezolid to vancomycin specifically for *S. aureus* bacteraemia have small sample sizes.[45–47] However, a recent report does describe clearance of bacteraemia in 14 of 16 cases in which patients with ≥7 days of MRSA bacteraemia on vancomycin were switched to linezolid-based therapy (linezolid alone in 7 cases and linezolid plus a carbapenem in 9 cases).[48] Thus, linezolid should only be considered for MRSA bacteraemias with caution in salvage situations.

Table 1. Mechanisms of action and limitations of currently available anti-MRSA antibiotics

Antibiotic	Mechanism of action	Limitations
Vancomycin	• inhibits cell wall (peptidoglycan) synthesis • bactericidal activity (variable)	• MIC creep, hVISA development • variable tissue penetration • potential for nephrotoxicity at higher concentrations and in combination with other nephrotoxic agents
Daptomycin	• disrupts cell membrane potential through rapid depolarization • bactericidal activity.	• inactivated by pulmonary surfactant, not effective treatment of MRSA pneumonia • potential for decreased susceptibility with increased vancomycin MIC and hVISA
Linezolid	• inhibits protein synthesis through binding of 50S ribosomal subunit • bacteriostatic activity	• multiple potentially serious side effects (marrow suppression, lactic acidosis, peripheral and optic neuropathy, serotonin syndrome), especially with prolonged use
Trimethoprim/ sulfamethoxazole	• inhibits multiple stages in bacterial folate and thymidine synthesis • bactericidal activity	• may be ineffective in infections involving undrained pus due to thymidine scavenging • limited data supporting use in bacteraemia and endocarditis
Clindamycin	• inhibits protein synthesis through binding of 50S ribosomal subunit • bacteriostatic activity	• largely unproven for treatment of invasive infections in adults • inducible resistance can be missed if D-testing not performed on clinical isolates • association with antibiotic-associated diarrhoea and *Clostridium difficile* colitis
Tetracyclines	• inhibit protein synthesis through binding of 30S ribosomal subunit • bacteriostatic activity	• unproven for treatment of invasive infections
Tigecycline	• inhibits protein synthesis through binding of 30S ribosomal subunit • bacteriostatic activity	• low serum levels • probably not effective in treatment of hospital-acquired MRSA pneumonia
Quinupristin/ dalfopristin	• synergistic combination of two streptogramin compounds that inhibit protein synthesis • bactericidal activity in the absence of MLS_B resistance	• frequent side effects (arthralgias, myalgias, venous intolerance) • multiple drug–drug interactions • limited data supporting use in invasive disease
Rifampicin	• inhibits bacterial transcription • bactericidal activity	• rapid development of resistance; cannot be used as monotherapy • multiple drug–drug interactions • potential hepatotoxicity

Trimethoprim/sulfamethoxazole, clindamycin and the tetracycline antibiotics are used primarily to treat CA-MRSA SSTIs in outpatient settings,[49] but are seldom used to treat serious *S. aureus* infections.[50,51] In the only randomized, prospective study to date to evaluate the use of trimethoprim/sulfamethoxazole in serious *S. aureus* infections that compared intravenous trimethoprim/sulfamethoxazole with vancomycin in 101 injection drug users with *S. aureus* infections requiring hospitalization (65% of which were bacteraemic), vancomycin was found to be superior with regard to duration of bacteraemia, sterilization of wound culture, duration of fever and clinical failure rates; the differences in efficacy were largely seen among patients infected with MSSA.[50] From at least a theoretical standpoint, trimethoprim/sulfamethoxazole may be less effective in clinical settings where there is undrained pus, as *S. aureus* may be able to scavenge thymidine from dead inflammatory cells and injured tissues and thus bypass the thymidine biosynthesis pathway ordinarily blocked by trimethoprim/sulfamethoxazole.[52]

Clindamycin is limited by its bacteriostatic nature and high rate of resistance (both inducible and constitutive) among MRSA clones typically encountered in the hospital setting (HA-MRSA), as well as its ability to predispose to *Clostridium difficile*-associated colitis. However, the emergence of CA-MRSA clones that are mostly clindamycin susceptible has allowed for consideration of its use in infections caused by CA-MRSA. Data supporting the use of clindamycin in severe *S. aureus* infection are mostly limited to the paediatric population[53] and older reports describing its efficacy in bone and joint infections.[54]

Tetracyclines are also bacteriostatic against *S. aureus*; experience in their use in severe *S. aureus* infections is largely anecdotal,[55] though tigecycline, a new glycylcycline structurally similar to minocycline, has shown promise in the treatment of complicated SSTIs and intra-abdominal infections caused by MRSA.[56–58] However, tigecycline is highly protein bound, resulting in low serum levels that limit its effectiveness when bacteraemia is present.[59,60]

Quinupristin/dalfopristin, a streptogramin combination, is bactericidal against MRSA isolates that do not express streptogramin resistance mediated by the macrolide–lincosamide–streptogramin (MLS_B) resistance complex, but is only bacteriostatic against MRSA that do have constitutive MLS_B resistance,[61] a phenomenon that is relatively common among HA-MRSA isolates,[62] but also is starting to emerge in CA-MRSA isolates as well.[63] Quinupristin/dalfopristin has demonstrated limited efficacy in salvage treatment of invasive MRSA infections;[64] however, its propensity to cause severe arthralgias/myalgias and phlebitis and its multiple drug–drug interactions[65] have markedly limited its use.

Finally, rifampicin is often considered in the treatment of MRSA infections in combination with other agents (its low resistance barrier makes it inappropriate for use as monotherapy);[66] evidence for its use in invasive *S. aureus* infections will be discussed below.

The case for antibiotic combination therapies directed against MRSA

In general, the clinical evidence that supports the routine use of antibiotic combination therapy in the treatment of MRSA infection is limited. Evidence supporting combination strategies has come largely from *in vitro* and *in vivo* studies, the majority of which are quite difficult to interpret because of heterogeneity in study designs and evaluations of outcomes—time–kill, chequerboard, Etest, etc.[67] Despite the lack of consistent clinical data, combination therapy is popular. In a survey posed to members of the Emerging Infections Network in 2005, a hypothetical scenario was presented of a case of persistent MRSA bacteraemia treated with vancomycin in which the MRSA isolate vancomycin MIC was 2 mg/L.[68] Only 9% of respondents opted to continue vancomycin alone, while 72% opted to combine vancomycin with one or more additional agents: rifampicin (in 76% of those opting for combination therapy), gentamicin (48%), daptomycin (5%), linezolid (5%) or quinupristin/dalfopristin (2%). Even in cases of 'uncomplicated' catheter-associated *S. aureus* bacteraemia that clears rapidly, combination therapy is often considered despite the absence of clear clinical evidence of its benefit. At a Clinical Consensus Conference on Gram-Positive Bloodstream Infections in June 2007, 49 of 168 physician participants (29%) preferred combination therapy (mostly involving aminoglycosides) for the treatment of uncomplicated *S. aureus* bacteraemia.[69] Below, we examine what evidence exists regarding the clinical benefit of antibiotic combinations commonly considered in the treatment of MRSA infections (Table 2). Combinations involving vancomycin for the treatment of serious MRSA infections are also well summarized in a recent review.[70]

Combination of vancomycin and rifampicin

A recent systematic review of >100 *in vitro*, animal and human studies examining the role of adjunctive rifampicin in the treatment of *S. aureus* infections demonstrated inconsistent correlation between *in vitro* and *in vivo* studies such that no general conclusion could be reached regarding its efficacy.[71] The vast majority of *in vivo* studies that focused on the combination of vancomycin plus rifampicin were in animals; several demonstrated a benefit of combination therapy compared with vancomycin alone, particularly in osteomyelitis[72,73] and device-related infections.[74–76] Of note, the effectiveness of combination vancomycin and rifampicin in animal models of endocarditis was mixed, with one model of left-sided endocarditis in rabbits demonstrating decreased MRSA vegetation titres, increased sterilization of vegetations and overall cure,[77] but with other rat and rabbit models not demonstrating a significant effect.[78,79] To date, only one randomized controlled trial in humans directly compares vancomycin against vancomycin plus rifampicin specifically for the treatment of MRSA infection.[80] In this particular study of mostly patients with right-sided MRSA endocarditis, Levine *et al.*[80] showed a slight increase (9 versus 7 days) in median duration of bacteraemia in patients receiving vancomycin plus rifampicin (600 mg/day) versus vancomycin alone, though clinical outcomes were similar. In both groups, median vancomycin troughs were ~10–11 mg/L, but only 27 of 42 patients had vancomycin levels checked. Only one randomized trial of stable orthopaedic device infections has demonstrated evidence of an improved cure rate with adjuvant rifampicin.[81] In this study (which did not include patients infected with MRSA), patients with device-related infection (26 with MSSA, 2 with methicillin-resistant *S. epidermidis* and 5 with methicillin-susceptible *S. epidermidis*) were treated with 2 weeks of intravenous flucloxacillin (26 patients) or vancomycin (7 patients) plus rifampicin or placebo followed by 3–6 months of oral ciprofloxacin plus rifampicin or placebo. All 18 patients in the rifampicin arm experienced clinical cure, compared with 7 of 12 in the placebo arm ($P=0.02$). The rationale for using rifampicin in foreign device infections and osteomyelitis is based on the observation that rifampicin appears to have particular bactericidal activity against *S. aureus* in the sessile phase in biofilms.[82] Furthermore, *S. aureus* often evades the innate immune system by surviving intracellularly in neutrophils after phagocytosis.[83] In an *in vitro* study, the addition of rifampicin to vancomycin increased killing of phagocytized MRSA >30-fold compared with vancomycin alone.[84]

Adjunctive rifampicin treatment should be considered with caution, as it can have significant side effects. In a retrospective review of *S. aureus* endocarditis cases in which rifampicin was given as adjunctive therapy, 9 of 42 patients, all of whom had hepatitis C, had marked elevations (≥5 times baseline level) in hepatic transaminases while on rifampicin treatment.[85] Drug–drug interactions that were not recognized by clinical providers occurred in over half of the patients assessed, including interactions with methadone, warfarin, HIV protease inhibitors, antifungal azoles and phenytoin. Resistance to rifampicin also developed in >50% of cases in which it was added before bacteraemia cleared.[85] Resistance to rifampicin is also commonly encountered in *S. aureus* with intermediate susceptibility to vancomycin (hVISA), as a case–control study of 27 patients with hVISA bacteraemia, many of whom had prosthetic implants, found a significantly higher rate of rifampicin resistance among hVISA than non-hVISA MRSA bacteraemia isolates (44% versus 9%), often in patients who did not receive rifampicin.[86] Data regarding the role of combination vancomycin and rifampicin

Table 2. Summary of *in vitro*, animal model and human clinical data that evaluate commonly considered combination regimens for invasive MRSA infection

Antibiotic combination	*In vitro* data	Animal model data	Human clinical data
Vancomycin *plus*			
rifampicin	inconsistent findings: synergy, indifference and antagonism all observed[71]	increased efficacy compared with monotherapy in osteomyelitis[72,73] and device-related infections;[74–76] mixed results in endocarditis[77–79]	no difference in median duration of bacteraemia in randomized trial of patients with MRSA infection (mostly right-sided endocarditis);[80] hepatotoxicity and drug–drug interactions frequent[85]
gentamicin	synergy;[96, 97] increased bacterial clearance[94,95]	not specifically evaluated	increased nephrotoxicity;[98–100] clinical benefit not specifically demonstrated
quinupristin/dalfopristin	increased bactericidal activity compared with either agent alone;[101–103] antagonism in isolates with MLS_B resistance[104]	additive effect in endocarditis, with or without MLS_B resistance[105]	case reports describing success after glycopeptide monotherapy failed[106–108]
β-lactams	synergy versus hVISA with oxacillin,[139] nafcillin[140] and imipenem[138]	synergy versus hVISA with nafcillin in endocarditis;[141] indifference with cloxacillin in peritonitis[142]	not specifically evaluated
linezolid	antagonism[124,125]	antagonism[157]	not specifically evaluated
clindamycin	antagonism to indifference[158,160]	not specifically evaluated	clinical benefit in case report of patients with persistent bacteraemia on vancomycin[160]
Daptomycin *plus*			
rifampicin	mostly additive effect;[118] enhanced killing of *S. aureus*[111,112] intracellularly and in biofilm[113]	enhanced bacterial killing in endocarditis[110]	case reports describing treatment success in bone and joint infections[114–117]
gentamicin	moderate synergy[118] or indifference;[120] potentiation of bactericidal activity[110,119]	attenuation of gentamicin-induced nephrotoxicity[121]	not specifically evaluated
β-lactams	synergy with oxacillin, ampicillin/sulbactam, ticarcillin/clavulanate and piperacillin/tazobactam[144]	synergy versus MRSA with reduced daptomycin susceptibility with oxacillin in endocarditis[145]	rapid clearance of bacteraemia due to MRSA with reduced vancomycin and daptomycin susceptibility in three patients with oxacillin plus high-dose daptomycin[146]
Linezolid *plus*			
rifampicin	moderate additive effect[124] or indifference[125,126]	moderate additive effect[127] or indifference[123] in endocarditis	not specifically evaluated
gentamicin	mostly indifference[125,126,130] or antagonism[124]	bactericidal effect in endocarditis[131]	not specifically evaluated
carbapenem	synergy, bactericidal activity[147,148]	bactericidal effect in endocarditis[147,148]	outcomes similar to linezolid alone in patients with persistent bacteraemia switched from vancomycin[48]
Trimethoprim/sulfamethoxazole *plus* rifampicin	indifference[134] or antagonism[135]	not specifically evaluated	case reports describing effectiveness in osteomyelitis and device-associated infections[132,133]

specific to the treatment of CA-MRSA are limited, though one *in vitro* study showed antagonism in bacterial killing.[87]

Thus, based on available data, adjuvant rifampicin for *S. aureus* infections should be considered in foreign device infections[88] or osteomyelitis[89] with close clinical monitoring, but not for bacteraemia or native-valve endocarditis. This conclusion is consistent with the current American Heart Association (AHA) guidelines on infective endocarditis, which recommend adjuvant rifampicin (also in combination with gentamicin) with vancomycin for MRSA only when there is prosthetic valvular endocarditis.[90]

Combination of vancomycin and gentamicin

No prospective trial has examined the use of combination vancomycin and gentamicin versus vancomycin for the treatment of MRSA bacteraemia or endocarditis. The AHA guidelines on the management of infective endocarditis currently recommend an optional short course of low-dose gentamicin (1 mg/kg every 8 h) in addition to nafcillin or oxacillin for native MSSA endocarditis; this recommendation was based on one prospective human trial of MSSA endocarditis involving nafcillin and gentamicin[91] and models of endovascular infection that showed more rapid bacterial clearance against both MSSA and MRSA isolates with gentamicin in combination with either an antistaphylococcal penicillin[92,93] or vancomycin.[92–95] In the MSSA endocarditis trial conducted by Korzeniowski and Sande,[91] 6 weeks of nafcillin plus 2 weeks of gentamicin reduced the duration of bacteraemia in left-sided endocarditis by an average of 1 day (with no other clinical benefit observed), but this regimen caused significant renal impairment. *In vitro* data have shown synergy between vancomycin and gentamicin in time–kill assays,[96,97] though this synergy was not observed in MRSA isolates with high level gentamicin resistance (HLGR), MIC > 500 mg/L; non-HLGR strains (0.5 to >128 mg/L) showed either synergy or indifference that could not be predicted based on the MIC.[97] In a meta-analysis of eight studies that measured nephrotoxicity associated with vancomycin and aminoglycoside use from 1983 to 1993, the incidence of nephrotoxicity was estimated to be 13% greater with vancomycin and aminoglycoside combination (range 6%–35% amongst all the studies) compared with vancomycin alone (range 0%–19%).[98] In a recent safety data analysis of a randomized trial comparing daptomycin with standard therapy (an antistaphylococcal penicillin or vancomycin combined with initial low-dose gentamicin, typically for 4–5 days),[7] 27 of 122 (22%) patients receiving initial low-dose gentamicin experienced clinically significant nephrotoxicity, including 15 (44%) of 34 patients with a baseline creatinine clearance of 50–80 mL/min.[99] Although the overall incidence of nephrotoxicity was similar among patients receiving gentamicin in combination with an antistaphylococcal penicillin or vancomycin, increases in serum creatinine peaked at day 7 in patients receiving antistaphylococcal penicillins, while serum creatinine continued to increase over the 28 day study course in patients receiving vancomycin.[99] A study of an observational cohort of 373 patients with infective endocarditis caused by a variety of organisms (18% of which were *S. aureus*) who were treated with gentamicin adjunctive therapy estimated a 0.5% decrease in endogenous creatinine clearance per day of gentamicin received, though this change was not associated with post-discharge mortality.[100] Thus, given marginal clinical benefit and significantly increased risk for renal impairment, the routine use of combination vancomycin and gentamicin for the treatment of *S. aureus* infections is called into question.

Combination of vancomycin and quinupristin/dalfopristin

The combination of vancomycin with quinupristin/dalfopristin against MRSA has been evaluated in a number of *in vitro* studies, with an infected fibrin clot model,[101] time–kill studies[102] and pharmacodynamic models[103] all demonstrating evidence of increased bactericidal activity compared with either agent alone. When *S. aureus* isolates with constitutive MLS_B resistance were exposed to the combination of vancomycin and quinupristin/dalfopristin, antagonism was largely observed in one time–kill study,[104] but a model of rabbit endocarditis showed evidence of an additive effect.[105] Limited case reports exist regarding apparent clinical benefit of the combination of glycopeptides (vancomycin or teicoplanin) with quinupristin/dalfopristin in MRSA infection, often in the setting of deep-seated disease and prior failure of glycopeptide monotherapy.[106–108]

Combination of daptomycin and rifampicin or gentamicin

The impact of combination therapies involving daptomycin in the treatment of severe *S. aureus* infections remains largely unexplored in the clinical setting, but *in vitro* and *in vivo* studies suggest that combination therapy with daptomycin and another agent may have some merits in instances where the infectious inoculum or risk for development of decreased daptomycin susceptibility is high, which can occur after prolonged monotherapy at the standard dosing of 6 mg/kg/day.[40,109] The addition of rifampicin to daptomycin enhanced bacterial killing in an *in vivo* animal model of MRSA endocarditis,[110] among intracellular *S. aureus* in a human macrophage model[111,112] and in MRSA embedded in biofilm.[113] Limited clinical case reports describe treatment success in difficult-to-eradicate bone and joint infections when rifampicin is combined with daptomycin.[114–117]

In an *in vitro* time–kill study, the combination of daptomycin plus gentamicin exhibited a moderate amount of synergy against *S. aureus* with a wide range of daptomycin MICs (0.25–8 mg/L), while the combination of daptomycin and rifampicin was mostly additive.[118] Other *in vitro* models of *S. aureus* endocardial vegetations suggested that adding gentamicin to daptomycin dosed at either 6 or 10 mg/kg/day potentiated bactericidal activity, generally more so than rifampicin;[110,119] however, a study measuring serum bactericidal titres derived from healthy volunteers given daptomycin 6 mg/kg/day failed to show an increase in bactericidal effect by adding gentamicin.[120] Interestingly, daptomycin has been demonstrated in a rat model to moderately attenuate the nephrotoxicity of gentamicin,[121] possibly due to daptomycin-induced electrostatic cell membrane changes.[122]

Combination of linezolid and rifampicin or gentamicin

In vitro studies and rabbit models of endocarditis that have evaluated the combination of linezolid with rifampicin versus *S. aureus* have demonstrated either indifference or a mild additive effect.[123–127] Rifampicin co-administration with linezolid,

however, has been reported to result in reduced linezolid serum levels.[128,129]

The *in vitro* data for the combination of linezolid and gentamicin have mostly shown indifference or antagonism,[124–126,130] but a rabbit endocarditis model did show a bactericidal effect with combination linezolid and gentamicin.[131]

Combination of daptomycin and linezolid

The combination of daptomycin and linezolid has been advocated by some experts[68] despite a lack of *in vivo*, *in vitro* and clinical data regarding possible antagonism, indifference or synergy. However, this combination may be of at least theoretical benefit in patients with MRSA bacteraemia and pneumonia that are failing vancomycin, as daptomycin is ineffective in the treatment of MRSA pneumonia.

Combination of trimethoprim/sulfamethoxazole and rifampicin

A few case series describe the effectiveness in combining trimethoprim/sulfamethoxazole with rifampicin in the treatment of MRSA osteomyelitis, especially in the presence of foreign bodies,[132,133] though the only *in vitro* studies to evaluate this combination showed indifference[134] and antagonism.[135] Despite these findings and the lack of clinical data, the combination of trimethoprim/sulfamethoxazole and rifampicin is popular in the management of SSTIs caused by MRSA.

β-Lactams in combination therapy in the age of CA-MRSA

Because of their relatively stronger binding affinities for penicillin-binding protein 2a, which can be down-regulated in MRSA with reduced vancomycin susceptibility,[136] certain β-lactams have partial activity against MRSA, including ampicillin/sulbactam, piperacillin/tazobactam and imipenem,[137,138] leading some to consider combining them with vancomycin for the treatment of hVISA. *In vitro* studies have demonstrated synergistic activity against hVISA when vancomycin has been combined with oxacillin,[139] nafcillin[140] and imipenem.[138] A rabbit model of hVISA endocarditis also demonstrated synergy with a combination of vancomycin and nafcillin,[141] though a mouse peritonitis model using MRSA strains with vancomycin MICs ranging from 1 to 8 mg/L did not show *in vivo* evidence of synergy between vancomycin and cloxacillin.[142] Recent work from Japan also indicates that β-lactam exposure may cause reduced susceptibility to vancomycin in some MRSA strains.[143]

A time–kill *in vitro* study demonstrated evidence of synergy versus MRSA when daptomycin was combined with oxacillin, ampicillin/sulbactam, ticarcillin/clavulanate or piperacillin/tazobactam.[144] One recent abstract also demonstrated increased *in vitro* susceptibility to β-lactams in MRSA isolates with reduced susceptibility to daptomycin (compared with isogenic strains fully susceptible to daptomycin) and synergistic reduction in tissue burden of MRSA with combination daptomycin–oxacillin in a rabbit model of endocarditis using a strain with reduced daptomycin susceptibility;[145] another reported rapid (24 h) clearance of bacteraemia when oxacillin was added to high-dose (10 mg/kg/day) daptomycin in three patients with bacteraemia due to MRSA with reduced susceptibility to vancomycin and daptomycin following sequential treatment with vancomycin and daptomycin.[146]

The combination of linezolid with either imipenem or ertapenem has been demonstrated to be synergistic and bactericidal in time–kill and animal endocarditis models.[147,148] The study of 16 patients with persistent MRSA bacteraemia on vancomycin who were switched to linezolid with or without a carbapenem did not show a significant effect of adding a carbapenem (7 of 7 patients switched to linezolid alone had clearance of bacteraemia, compared with 7 of 9 patients switched to linezolid plus a carbapenem).[48]

However, as recent research suggests that the virulence of CA-MRSA is at least partially due to overproduction of toxins and abnormal host inflammatory response,[10,149] the strategy of adding β-lactams to traditional anti-MRSA agents in the treatment of invasive CA-MRSA infection could potentially do more harm than good, as there is *in vitro* evidence suggesting that subinhibitory concentrations of nafcillin can cause MRSA and MSSA to overexpress Panton–Valentine leucocidin (PVL), α-toxin and toxic shock syndrome toxin (TSST-1).[11] Similarly, subinhibitory concentrations of oxacillin have been shown to increase PVL production in a laboratory *pvl*+ MSSA strain 3-fold.[150,151] It is not clear, however, whether up-regulation of virulence toxins by oxacillin and nafcillin is a class phenomenon that is seen across all the β-lactam antibiotics, including the cephalosporins and carbapenems.

Is inhibition of protein synthesis important for invasive CA-MRSA infections?

Even before the era of CA-MRSA, it was known that protein synthesis-inhibiting antibiotics suppress staphylococcal virulence factors such as α-toxin and TSST-1.[152] *In vitro* and animal studies support the routine use of clindamycin in the treatment of necrotizing fasciitis and toxic shock syndrome caused by *Streptococcus pyogenes*.[153] The advantage of clindamycin stems from its ability to inhibit bacterial protein synthesis independent of bacterial growth phase.[154] Thus, with the emergence of severe infections caused by CA-MRSA, including necrotizing fasciitis,[155] the role of protein synthesis inhibition in treatment of these infections has been explored. Several agents with antistaphylococcal activity inhibit protein synthesis in addition to clindamycin, including linezolid, tetracyclines, aminoglycosides and rifampicin. Tetracyclines bind the 30S ribosomal subunit, whereas clindamycin and linezolid bind the 50S subunit. Aminoglycosides also bind the 30S subunit, but, unlike the other protein synthesis-inhibiting antibiotics, they exhibit bactericidal activity. Rifampicin is currently the only anti-MRSA agent that exerts its inhibitory effect at the transcriptional level. *In vitro* studies with CA-MRSA isolates similarly demonstrated that subinhibitory concentrations of clindamycin, linezolid and rifampicin block production of PVL, α-toxin and TSST-1.[11,150,151] Clinical data remain anecdotal, as favourable clinical outcomes have been reported in three cases of necrotizing CA-MRSA pneumonia where patients received vancomycin plus clindamycin, linezolid alone or linezolid plus rifampicin, all after apparent failure with vancomycin monotherapy.[156] While the use of adjuvant clindamycin or linezolid seems attractive for severe CA-MRSA infections, this approach remains largely unproven. The

limited data that exist regarding the combination of vancomycin and linezolid in the treatment of MRSA have largely been disappointing, as time–kill curve studies[124,125] and an experimental model of endocarditis[157] have shown evidence of antagonism compared with either agent alone. The combination of vancomycin and clindamycin has also been shown to be antagonistic in *in vitro* time–kill studies,[158,159] though clinical improvement associated with increased serum inhibitory and bactericidal activity was seen in one report (prior to the CA-MRSA epidemic) of seven patients persistently bacteraemic with MRSA on vancomycin when clindamycin was added, despite indifference to mild antagonism of the combination in time–kill studies.[160]

New anti-MRSA agents

Several new antibiotics with anti-MRSA activity may become available in the next few years, including new lipoglycopeptides (telavancin, oritavancin and dalbavancin) and cephalosporins active against MRSA (ceftobiprole and ceftaroline). It is welcome news to know that many of these antibiotics have activities against hVISA and VISA though their clinical efficacy is not known.[161] Furthermore, *in vitro* studies have reported synergy against hVISA and VISA isolates when some of these newer antibiotics are combined with other older antibiotics.[162–164]

Conclusions

Severe infections caused by MRSA are associated with high mortality and are often difficult to treat. Current antibiotic options for the treatment of invasive MRSA infections have limitations when used as monotherapy, so combination therapy is frequently considered. While there does appear to be some good evidence for the use of combination therapies involving rifampicin in the treatment of MRSA osteomyelitis and device-related infections (though patients receiving rifampicin must be closely monitored for hepatotoxicity and drug–drug interactions), evidence supporting the use of rifampicin or other combinations in other settings is much more scant. The role of combination treatment in invasive infections caused by CA-MRSA clearly needs further study, particularly with regard to the effects of different antibiotic classes on toxin production, though it seems appropriate to consider the addition of antibiotics that inhibit protein synthesis in severe infections. The need for combination therapy in the treatment of invasive MRSA infection should be determined on an individual basis and in consultation with an infectious diseases specialist.

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