REVIEW

Key considerations in the treatment of complicated staphylococcal infections

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ABSTRACT

Substantial increases in antimicrobial resistance among Gram-positive pathogens, particularly *Staphylococcus aureus*, are compromising traditional therapies for serious bacterial infections. There has been an alarming increase in the rates of methicillin-resistant *S. aureus* (MRSA) over the past two decades, and the more recent emergence of heterogenous vancomycin-intermediate (hVISA), vancomycin-intermediate (VISA) and vancomycin-resistant *S. aureus* (VRSA) strains limits the use of vancomycin, the current standard of care for MRSA infections. Tolerance to vancomycin, which represents a lack of bactericidal activity of vancomycin, is another troublesome property of some *S. aureus* strains that can adversely affect the outcome of antimicrobial therapy. Increasing MICs of vancomycin for staphylococci, poor tissue penetration by the drug and a slow rate of bactericidal action of the drug have also raised concerns about its efficacy in the contemporary treatment of MRSA infections. There is an increasingly apparent need for new agents for the treatment of staphylococcal infections, ideally with potent bactericidal activity against MRSA, hVISA, VISA and VRSA and with superior susceptibility profiles as compared with glycopeptides.

Keywords Bactericidal, Gram-positive infections, MRSA, review, *Staphylococcus aureus*, vancomycin resistance, vancomycin tolerance

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INTRODUCTION

Over the past two decades, there has been a shift in the epidemiology of serious bacterial infections, with an increasing proportion being attributable to Gram-positive bacteria [1–3], which have become the predominant cause of many infections [4,5]. This trend is especially apparent for bloodstream infections, where Gram-positive pathogens can account for up to 70% of infections, and for surgical site infections, where the predominant cause has shifted from Gram-negative bacteria to Gram-positive bacteria over the past 20 years [4]. Consistent with these findings, coagulase-negative staphylococci, *Staphylococcus aureus* and enterococci were the most frequently isolated species from monomicrobial nosocomial bloodstream infections in US hospitals from 1995 to 2002, with incidences of 31.3%, 20.2% and 9.4%, respectively [6]. The increasing association of *S. aureus* with serious infections is of particular concern. In data from the US National Nosocomial Infections Surveillance System, the percentage of *S. aureus* isolates from urinary tract infections and pneumonia cases approximately doubled between 1975 and 2003 [4]. In addition, the SENTRY Antimicrobial Surveillance Program ranks *S. aureus* as the primary cause of skin and soft tissue infections (SSTIs) in Europe, North America and Latin America, with the highest occurrence being in North America (51.6% in 2004) [7].

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THE SHIFTING EPIDEMIOLOGY OF STAPHYLOCOCCAL ANTIMICROBIAL RESISTANCE

There has been a substantial increase in resistance to antimicrobial agents among bacterial pathogens, particularly in Gram-positive bacteria, which is compromising traditional therapies [8]. The prevalence of methicillin-resistant *S. aureus* (MRSA) is increasing significantly in many parts of the world [6,9], with resistance rates being higher than 50% in the USA [6] and some European countries [9]. Over the past decade, MRSA rates doubled in SENTRY program medical centres in the USA, from 27% in 1997 to 54% in 2006. In US intensive care units specifically, a doubling of MRSA rates was also observed over the period 1989–2003, with the most recent resistance rates being in excess of 60% (National Nosocomial Infections Surveillance System; http://www.cdc.gov/ncidod/dhqp/nnis.html; accessed 31 January 2007). Methicillin resistance in coagulase-negative staphylococci has also been increasing, from just over 70% resistance in isolates between 1995 and 1997 to over 80% between 2000 and 2002 in the USA [6].

Vancomycin is currently the drug of choice for the treatment of MRSA, but its use is being compromised by the recent emergence of vancomycin-intermediate or -resistant *S. aureus* (VISA and VRSA) strains [10]. The clinical significance of MRSA infection in *S. aureus* bacteraemia is highlighted by the elevated rates of associated mortality as compared with those seen in infection with methicillin-susceptible *S. aureus* (MSSA). Two separate meta-analyses have demonstrated that infection with MRSA is associated with a higher mortality rate than infection with MSSA (29% vs 12%, $p < 0.001$ [11]; 36% vs 23%, $p < 0.001$ [12]).

Increasing rates of MRSA infection have been accompanied by the emergence of MRSA isolates among healthy individuals in the community without apparent traditional risk-factors [13]. Community-acquired MRSA (CA-MRSA) infections have been reported worldwide [14], and are now regarded as a serious public health problem [15]. CA-MRSA strains are distinct from hospital-acquired strains and are characteristically more virulent, but also more susceptible to non-β-lactam antimicrobials, such as clindamycin, trimethoprim–sulfamethoxazole and tetracyclines such as doxycycline [16]. CA-MRSA strains frequently contain the staphylococcal chromosome cassette (SCC) *mec* type IV, which contains *mecA*, the resistance gene against β-lactam agents [16]. SCC *mec* type IV is smaller than the cassettes usually found in hospital strains of MRSA, primarily due to the absence of non-β-lactam resistance genes, which may make it particularly efficient in transferring resistance among bacteria [16]. CA-MRSA strains are also associated with greater toxin production; most strains carry the Panton–Valentine leukocidin genes [16], which encode cytotoxins that can cause tissue necrosis and leukocyte destruction [17]. Panton–Valentine leukocidin is mainly associated with severe community-acquired primary skin infections and necrotising pneumonia [17].

SSTIs are by far the most common clinical manifestations in CA-MRSA cases, and have been reported to represent 75–77% of such cases in US patient cohorts [15,18]. Other types of infections caused by CA-MRSA, occurring at much lower frequencies, include: wound infections (10%) [15], otitis media (7%) [18], respiratory tract infections (2–6%) [15,18], bacteraemia (3–4%) [15,18], sinus infections (4%) [15] and urinary tract infections (1–4%) [15,18]. Almost half of the patients with CA-MRSA infection are found to have at least one risk-factor for healthcare-associated MRSA infection [15,19]. These risk-factors have been identified as: recent hospitalisation, outpatient status, nursing home admission, antibiotic exposure, chronic illness, injection drug use and close contact with a person with risk-factors [19]. For these reasons, it has been proposed to classify community-onset MRSA as either truly community-acquired or healthcare-associated [20].

CA-MRSA outbreaks have been documented in several population groups and settings: correctional facility inmates (associated with sharing of personal items such as linens, and improper diagnosis and medical care) [21,22]; sports participants (associated with equipment- and sport-related abrasions and lacerations, physical contact and sharing of equipment) [23–25]; military personnel (associated with the significant risk of soft-tissue infection for an extended period of time) [26,27]; and population groups with lower socioeconomic status (associated with crowded housing conditions and limited access to healthcare, e.g., Native Americans) [28]. CA-MRSA infection has also been associated with post-partum

women, children in day-care programmes, injection drug users, men who have sex with men, and homeless persons [16,29].

ANTIMICROBIAL TREATMENT OPTIONS FOR STAPHYLOCOCCAL INFECTIONS

β-Lactams are the preferred agents for the treatment of infections caused by MSSA or suspected MSSA, for reasons of overall patient safety, convenience (oral availability) and cost [30]. Penicillinase-resistant, semi-synthetic penicillins, such as flucloxacillin, cloxacillin or dicloxacillin, are the drugs of choice for definitive treatment of MSSA in the UK and for use in empirical therapy (except when MRSA is highly prevalent) [30]. In the USA, the penicillinase-resistant penicillins nafcillin and oxacillin are the parenteral drugs of choice for infections caused by MSSA, whereas dicloxacillin is the oral drug of choice [31]. First-generation cephalosporins, such as cephalexin and cefazolin, are also commonly used, especially in penicillin-allergic patients [31].

Glycopeptides are currently the standard-of-care antimicrobials for treatment of MRSA infections, particularly bacteraemia, complicated SSTIs and bone infections [30]. These drugs have significant in-vitro activity against Gram-positive pathogens, and vancomycin specifically is widely used in the treatment of staphylococcal and enterococcal infections [8]. However, in a large prospective observational study, Chang *et al.* showed that patients with MSSA bacteraemia who received vancomycin therapy had a higher rate of relapse and microbiological failure than those who received nafcillin [32]. Therefore, the use of glycopeptides in the treatment of infections caused by MSSA is only recommended as an option for penicillin-allergic patients [31].

The extensive use of glycopeptides in the past has led to the discovery of glycopeptide-resistant organisms and, consequently, recommendations to restrict the use of these agents in the absence of strong indications [33,34]. Vancomycin-resistant enterococci (VRE) have emerged as important clinical pathogens, particularly in the USA [8], and many VRE isolates show resistance to teicoplanin, aminoglycosides (high-level) and β-lactams, thus limiting the therapeutic options for VRE infections [8]. In a global study, 75.2% of *Enterococcus faecium* isolates in 2003 were resistant to vancomycin (65.8% to teicoplanin), an increase of almost 40% as compared with resistance rates in 1997 [10].

Concerns have also emerged about the efficacy of vancomycin in the treatment of MRSA infections, due to increasing MICs for staphylococci, poor tissue penetration and a slower rate of bacterial killing than was recognised previously [8]. Usually, decreased susceptibility of *S. aureus* to vancomycin is accompanied by decreased susceptibility to teicoplanin, further compromising treatment options [35]. VISA isolates have been widely recognised in the past 10 years, although retrospective testing indicates a longer-term presence [10]. In contrast, the first naturally occurring, definitively VRSA isolate was reported in the USA in June 2002 [36].

Vancomycin resistance is thought to be mediated by cell-wall thickening or acquisition of the *vanA* gene [34]. In VISA strains, the production of excessive peptidoglycan with increased numbers of D-alanyl–D-alanine residues can potentially both sequester vancomycin molecules from their bacterial target and impede the progress of further vancomycin molecules through the cell wall [34]. Resistance in VRSA strains has been attributed to the acquisition of the *vanA* gene from a conjugative plasmid in *Enteroccus faecalis* [36–39]. This gene encodes VanA ligase, which is required for the replacement of D-alanyl–D-alanine residues in the peptidoglycan assembly pathway with D-alanyl–D-lactate, a substitution that prevents the binding of vancomycin to cell-wall components [40]. Plasmid transfer of the *vanA* gene from VRE to MRSA has been demonstrated experimentally [41], but there is no evidence yet for the subsequent transmission of emergent VRSA strains [42].

Although VISA and VRSA (high-level resistance to vancomycin) strains are rare among clinical *S. aureus* isolates [43], there is evidence that heterogeneous VISA (hVISA) strains may be more common [44,45]. hVISA strains, the acknowledged precursors of VISA strains, contain sub-populations of *S. aureus* with MICs in the intermediate range, resulting in a 'combined' MIC falling between that of wild-type MRSA (≤ 2 mg/L or susceptible) and VISA (8–16 mg/L) [10]. Data generated using techniques that provide population analysis profiles for suspected hVISA suggest that up to 18% of *S. aureus* strains with vancomycin MICs of 0.5–4.0 mg/L are in fact

heteroresistant [46]. Although the full clinical relevance of hVISA is still under investigation [47], a growing body of microbiological and clinical data indicates that patients with *S. aureus* isolates are less likely to respond to vancomycin therapy when the vancomycin MICs are ≥ 4 mg/L [48].

In 2006, the CLSI reduced the vancomycin MIC breakpoints in order to increase the detection of heterogeneously resistant isolates [48]. The susceptibility breakpoint was lowered from ≤ 4 mg/L to 2 mg/L, the intermediate breakpoint from 8–16 mg/L to 4–8 mg/L and the resistance breakpoint from ≥ 32 mg/L to ≥ 16 mg/L [48]. Lowering of the vancomycin MIC breakpoints for *S. aureus* may improve the correlation between the in-vitro definition of susceptibility and the likelihood of a clinical response to vancomycin, and facilitate the identification of hVISA isolates that may lead to treatment failure [48]. However, it does not directly address the issues of vancomycin tolerance and vancomycin MIC creep, and the technical shortcomings of standard broth microdilution, agar dilution and disk-diffusion assays in the detection of hVISA.

Vancomycin tolerance, defined as a minimum bactericidal concentration (MBC):MIC ratio ≥ 32 or an MBC:MIC ratio ≥ 16 associated with a resistant-level vancomycin MBC of ≥ 32 mg/L, represents a lack of bactericidal activity [10,49–51]. It has been found to occur in *S. aureus*, particularly MRSA, and can adversely affect the outcome of antimicrobial therapy for serious infections [49–51]. A significant subset of *S. aureus* strains is associated with the risk of clinical failure due to vancomycin tolerance, regardless of the reported susceptibility levels (MICs) [10]. In a recent study of 213 *S. aureus* strains, 15% of wild-type MRSA strains, 74% of hVISA strains and 100% of VISA and VRSA strains were tolerant to vancomycin [10]. In contrast, when tested against daptomycin, these strains had MBC:MIC ratios of 1 and 2, respectively, indicating the strong bactericidal activity of daptomycin against all strains [10].

Large-scale surveillance programmes have failed to recognise the phenomenon of vancomycin MIC creep [10], but increasing MICs have been reported by institutional-level surveys. For instance, a survey of *S. aureus* isolates from California, USA reported a shift in vancomycin MIC values from ≤ 0.5 mg/L to 1 mg/L in the 5 years from 2000 to 2004, together with a significantly higher percentage of isolates with an MIC of 1 mg/L in 2004 than in 2000 (70.4% vs 19.9%, $p < 0.01$) [43]. Furthermore, a 1.5-fold increase in vancomycin MIC has also been documented in MRSA blood isolates at the New Hanover Medical Regional Center (Delaware, USA), with a concomitant rise in the percentage of isolates with an MIC of 1 mg/L in 2005 as compared with 2001 (69% vs 16%, $p < 0.0001$) [52].

Even with the new CLSI breakpoints, vancomycin susceptibility testing may fail to accurately differentiate between cases that are potentially responsive and those with a higher likelihood of clinical failure [10]. Vancomycin MIC results of 1.5–2 mg/L have been shown to be an independent predictor of a poor response to vancomycin therapy in MRSA infections, even when sufficient trough levels of vancomycin were achieved [53]. In MRSA bacteraemia specifically, the increasing vancomycin MIC, even within the new susceptibility range, demonstrates a significant risk of vancomycin treatment failure [54]. For example, in a well-conducted study, MRSA isolates with vancomycin MICs of ≤ 0.5 mg/L were associated with 55.6% treatment success with vancomycin, whereas MICs of 1–2 mg/L resulted in 9.5% treatment success with vancomycin [54]. In addition, vancomycin treatment failures associated with modest MICs have been observed in other studies of the treatment of MRSA endocarditis [55] and of serious MRSA infections associated with deep-seated infection [56]. Despite revisions, the CLSI recommendations for testing vancomycin still lack an acceptable degree of predicted accuracy. Tracing the evolution of susceptibility of MRSA to vancomycin may require more accurate susceptibility testing, including the direct assessment of bactericidal activity, or alterations to the standard MIC method that incorporate more precise dilution schedules. Furthermore, local changes in the clonality of endemic MRSA should be assessed along with their effects on vancomycin MIC results.

NEED FOR NEW ANTIBIOTICS

The emergence of serious staphylococcal infections with reduced susceptibility to vancomycin highlights the need for more antimicrobial options with increased potency or enhanced

bactericidal activity against MRSA, hVISA, VISA and VRSA [8,33,57]. Only two new classes have been introduced over the past few decades: the oxazolidinones and the cyclic lipopeptides [58]. Among the antimicrobial agents that have more recently been approved for clinical use, daptomycin (a cyclic lipopeptide), linezolid (an oxazolidinone) and tigecycline (a glycylcycline) have activity against Gram-positive organisms, including MRSA. With further clinical experience, these new agents will be judged against several properties that are considered to be ideal for effective antimicrobials, as well as properties that are desirable in any pharmaceutical agent: low toxicity, a wide therapeutic index, multiple routes of administration, favourable pharmacokinetics, flexible dosing, good combinability, and minimal drug–drug interactions. In the context of complicated staphylococcal infections, considerations such as bactericidal activity and the potential for development of resistance are of particular importance.

Bactericidal activity was considered to be one of the most significant benefits of the penicillin class. However, the subsequent rapid development of penicillin resistance led to an increased use of bacteriostatic agents or drugs with low bactericidal activity, such as vancomycin and linezolid [59]. There remain clinical indications for which bactericidal compounds are considered to be superior, i.e., endocarditis, meningitis and infections in neutropenic patients [59]. In these contexts, the speed of response is considered to be critical and bactericidal antimicrobials should be the first treatment option [59]. Conceptually, the use of bactericidal drugs in other, less serious infections should also result in superior clinical outcomes [59]. Activity in the stationary phase of bacterial population growth is also beneficial in infections such as endocarditis, because the bacteria in cardiac vegetations, which are present at very high densities, become dormant and less susceptible to antimicrobial killing [60].

A low potential for the development of resistance is a key requirement for new antimicrobial agents and is one of the attractions of new classes with novel mechanisms of action, because this lowers the potential for cross-resistance [61]. The unique mechanism of action of the cyclic lipopeptide class also demonstrates that bactericidal drugs do not have to be bacteriolytic. Previously, the lysis produced by bactericidal agents was considered to be a disadvantage, due to the inflammatory reaction that could result from release of intracellular bacterial products, such as lipopolysaccharides (Gram-negative organisms) and peptidoglycans (Gram-positive organisms) [62].

CONCLUSION

The increasing prevalence of Gram-positive infections and antimicrobial-resistant strains in healthcare and community settings, especially MRSA, are serious challenges faced in contemporary medical practice. Use of the current standard treatment for MRSA, vancomycin, has become compromised, not just by the emergence of VISA and VRSA strains, but also by vancomycin tolerance and MIC creep associated with documented treatment failures. Consequently, there is an emergent clinical need for new agents for the treatment of infections caused by resistant strains, and, ideally, new candidate antimicrobials should have potent bactericidal activity and susceptibility profiles superior to those of the currently used glycopeptides (vancomycin and teicoplanin).

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