WJCID World Journal of Clinical Infectious Diseases

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DOI: 10.5495/wjcid.v5.i2.14

World J Clin Infect Dis 2015 May 25; 5(2): 14-29
ISSN 2220-3176 (online)

REVIEW

Treatment of methicillin-resistant *Staphylococcus aureus* infections: Importance of high vancomycin minumum inhibitory concentrations

Alejandra Morales-Cartagena, Antonio Lalueza, Francisco López-Medrano, Rafael San Juan, José María Aguado

Alejandra Morales-Cartagena, Antonio Lalueza, Francisco López-Medrano, Rafael San juan, José María Aguado, Infectious Diseases Unit, Department of Medicine, University Hospital 12 de Octubre, 28041 Madrid, Spain

Author contributions: Morales-Cartagena A and Lalueza A were the main authors in writing the draft version; López-Medrano F and Aguado JM principal physicians involved in the critical revision of the manuscript; all the authors approved the final version of the manuscript.

Conflict-of-interest: The authors declare no conflicts of interest.

Correspondence to: Dr. Alejandra Morales-Cartagena, Infectious Diseases Unit, Department of Medicine, University Hospital 12 de Octubre, Av. Córdoba km 5.400, 28041 Madrid, Spain. a.morales.cartagena@gmail.com
Telephone: +34-91-3908247
Fax: +34-91-3908112

Received: July 3, 2014
Peer-review started: July 4, 2014
First decision: July 29, 2014
Revised: February 26, 2015
Accepted: March 5, 2015
Article in press: March 9, 2015
Published online: May 25, 2015

Abstract

Staphylococcus aureus (SA) infections remain a major cause of morbidity and mortality despite the availability of numerous effective anti-staphylococcal antibiotics. This organism is responsible for both nosocomial and community-acquired infections ranging from relatively minor skin and soft tissue infections to life-threatening systemic infections. The increasing incidence of methicillin-resistant strains has granted an increasing use of vancomycin causing a covert progressive increase of its minimum inhibitory concentration (MIC) (dubbed the MIC "creep"). In this way, the emergence of vancomycin-intermediate SA (VISA) strains and heteroresistant-VISA has raised concern for the scarcity of alternative treatment options. Equally alarming, though fortunately less frequent, is the emergence of vancomycin-resistant SA. These strains show different mechanisms of resistance but have similar problems in terms of therapeutic approach. Ultimately, various debate issues have arisen regarding the emergence of SA strains with a minimum inhibitory concentration sitting on the superior limit of the sensitivity range (*i.e.*, MIC = 2 μg/mL). These strains have shown certain resilience to vancomycin and a different clinical behaviour regardless of vancomycin use, both in methicillin-resistant SA and in methicillin-sensitive SA. The aim of this text is to revise the clinical impact and consequences of the emergence of reduced vancomycin susceptibility SA strains, and the different optimal treatment options known.

Key words: *Staphylococcus aureus*; Minimum inhibitory concentration; Methicillin-resistant *Staphylococcus aureus*; Vancomycin-intermediate *Staphylococcus aureus*; Heteroresistant-vancomycin-intermediate *Staphylococcus aureus*; Vancomycin resistant *Staphylococcus aureus*

Core tip: The emergence of increasing vancomycin-resistance in *Staphylococcus aureus* (SA) isolates, has stirred up the basis of therapeutic approach in staphylococcal infections. Complete vancomycin-resistance is acquired through plasmid transmission of enterococcal gene *vanA*. However, the development of strains with gradual loss of vancomycin-susceptibility seems to be related to conformational bacterial changes and affects its pathogenicity and even its susceptibility to other antimicrobials (other than vancomycin). It has been observed that the impact of diminished vancomycin susceptibility could not only affect methicillin-resistant SA but has also been related to worse prognosis in methicillin-sensitive SA infections. There is yet much to explore to better define the impact of higher vancomycin minimum inhibitory concentration in staphylococcal infections.

Morales-Cartagena A, Lalueza A, López-Medrano F, Juan RS, Aguado JM. Treatment of methicillin-resistant *Staphylococcus aureus* infections: Importance of high vancomycin minumum inhibitory concentrations. *World J Clin Infect Dis* 2015; 5(2): 14-29 Available from: URL: http://www.wjgnet.com/2220-3176/full/v5/i2/14.htm DOI: http://dx.doi.org/10.5495/wjcid.v5.i2.14

STAPHYLOCOCCUS AUREUS, AN EVOLVING AGENT

Little after the beginning of the antibiotic era came the arrival of antibiotic resistance. The first *Staphylococcus aureus* (SA) strains resistant to penicillin appeared in 1942 due to an inducible beta-lactamase, and since then it has been evolving, developing resistance to most other antibiotics used for staphylococcal infections[1]. In 1959 methicillin became the best option to surpass penicillin resistance, however, resistance appeared only 2 years later [methicillin-resistant *Staphylococcus aureus (*MRSA)][2]. It took some years to spread, and not until the mid 1980's did MRSA reach alarming figures[3-5].

The mechanisms leading to methicillin resistance involve the expression a chromosomal gene *mecA*, which is found in the staphylococcal cassette chromosome (SCC), a mobile genomic element. This gene encodes penicillin binding protein 2a (PBP2a) that has a low affinity for certain betalactams, including penicillin and methicillin. The origin of methicillin resistance is uncertain, however, studies up to now suggest that it first appeared in coagulase-negative staphylococci, and then was transferred to methicillin-susceptible *Staphylococcus aureus* (MSSA) through horizontal gene transfer. Genes encoded in SCC*mec* have proved to be decisive in antibiotic resistance, however, it is not clear whether the play any relevant role in *S. aureus* virulence[6].

Whereas methillin-resistance developed in the years following its discovery, *S. aureus* strains showing reduced susceptibility to vancomycin were not described until 1997. However, many reports of similar findings started to appear shortly after[7]. Even if vancomycin resistance expansion has taken a different form than other patterns of antibiotic resistance and perchance less aggressive, it is a growing problematic in staphylococcal infections and deciding the optimal treatment approach is an on-going challenge.

EPIDEMIOLOGY OF AS INFECTION

Incidence of methicillin resistant SA

MRSA has spread like an epidemic, becoming 41.2% of the strains isolated in Europe at the present time[8]. More than 25% of *S. aureus* strains isolated in Spanish hospitals are methicillin resistant[9]. Prevalence of MRSA in Asian hospitals are globally very high, reaching 60% of the SA isolates in countries like Southern Korea, Vietnam or Taiwan[10,11]. In the United States, studies in the last decade declared that more than 94000 MRSA-associated infections occur every year, with an estimation of 18650 MRSA-infections attributable deaths[12]. One of the most important risk factors in developing MRSA infection has been observed to be MRSA colonization, detected through positive nasal-carriage. In a recent meta-analysis evaluating the prevalence of MRSA colonization and infection in patients admitted to the intensive care unit (ICU) (studies included from Europe, North and South America, Asia and Australia) they observed a prevalence of MRSA colonization ranging from 5.8% to 8.3%, which was higher in North American studies, with and upward trend. MRSA colonization was found to be associated with an important increased risk for MRSA infections [relative risk (RR) of 8.33][13].

Lately however, decreasing trends in hospital-onset MRSA infections have been observed in several surveillance studies. In an observational study of all Department of Defence TRICARE beneficiaries from January 2005 to December 2010, they found that annual rates of both community-onset and hospital-onset MRSA bacteraemia decreased (from 0.7 per 100000 person-years in 2005 to 0.4 per 100000 person-years in 2010)[14]. In addition, MRSA central line-associated bloodstream infections have been decreasing in United States intensive care units[15]. Decline in healthcare-associated invasive MRSA infections have also been recently reported[16]. The emergence of community-associated MRSA (CA-MRSA) and its introduction into healthcare settings has changed the epidemiology of *S. aureus* infection in the American continent and worldwide. These isolates are chiefly associated with a wide range of soft tissue infections and are sometimes implicated in severe pneumonias. They are rarely encountered in patients with bacteraemia. In an observational study to analyse the impact of CA-MRSA emergence on *S. aureus* bacteraemia (SAB), they describe a steadily decreasing rate of SAB both for community-associated (especially MSSA bacteraemia) and hospital-onset cases, whereas the rate of community-onset healthcare-associated cases did not change[17]. These results emerge in the context of multiple strategies adopted with the objective of reducing device-related and surgical-site infections in hospital settings. Most of these studies and revisions are based on retrospective data and observational evidence, and must therefore be weighed in this context.

The vast majority of published epidemiological studies about the prevalence and clinical impact of SA infections refer to the American and European continents. There is scarce information about *S. aureus* epidemiology in non-Western parts of the world (Africa, Middle East, Asia and Oceania) as highlighted in Rasigade's review[18].

Morbidity and mortality associated to MRSA infections

MRSA bacteraemia is associated with a considerable mortality. In a recent study that took place in nine different areas of the United States where they analysed almost 9000 MRSA invasive infections, bacteraemia (75%) was the clinical syndrome most frequently associated with invasive MRSA infection. Standardized mortality rate in this study was 6.3 per 100000 (interval estimate 3.3-7.5)[12].

Given that MRSA infections have been historically mainly healthcare-associated, bacteraemia by these pathogens have been found more frequently in patients who are severely ill or with a great number of comorbidities. Thereby there has been a continuing perception that this organism is particularly virulent. However, its virulence compared to that of MSSA remains controversial[19]. Earlier studies and meta-analysis described an almost two-fold increase in mortality in patients with MRSA bloodstream infections than those due to MSSA[19]. However, other studies analysing healthcare-associated MRSA bacteraemia in that same period and in the following years found no differences[20-22]. In a meta-analysis that evaluated the results of 9 international studies comparing MRSA *vs* MSSA risk factors and mortality, they observed that the risk of death was higher in patients with MRSA bacteraemia than those with MSSA bacteraemia in all but one of the studies, with a RR of death of 2, ranging from 0.89 to 4.94. They described potential risk factors associated to MRSA bacteraemia, such as: prior antibiotic therapy, longer previous hospital stay, older age, male sex, past history of MRSA infection and admittance or treatment in an ICU[23]. However once again, this almost two-fold higher mortality risk, seemed to be interfered by the base-line comorbid and nosocomial situation of those patients[19,23].

ROLE OF VANCOMYCIN IN METHICILLIN-RESISTANT *S. AUREUS* INFECTIONS AND CONSEQUENCES OF ITS USE

The use of vancomycin, a glycopeptide discovered in 1952 and approved shortly after, didn't spread until years later with the emergence of pseudomembranous enterocolitis and the spread of MRSA infections[24]. Its mechanism of action consists on the inhibition of the bacterial wall synthesis, with a slow bactericidal effect compared to beta-lactams[24]. Nephrotoxicity is its main toxicity concern, needing caution for patients with renal impairment. In these cases, if treatment with vancomycin is unavoidable, the best possible approach would be to confirm serologic levels stay within optimal concentration for bactericidal activity (see section "Risk of nephrotoxicity with elevated vancomycin doses")[25].

Clinical guidelines still recommend intravenous vancomycin as one of the first choice antibiotic therapies for the treatment of MRSA infections including bacteraemia, infective endocarditis, meningitis, central-line associated infection, septic thrombosis, osteomyelitis, and septic arthritis (in the latter, the addition of rifampin is sometimes considered). In specific severe complications such as severe septic shock, toxic syndrome, or necrotizing pneumonia, some experts consider adding adjunctive therapy with clindamycin or linezolid, which are protein synthesis inhibitors. Intravenous immunoglobulin have also shown good results in these situations[26].

Unlike with other antibiotics, *S. aureus* did not start to show resistance to vancomycin until 40 years after its discovery. In 1996 in Japan, the first vancomycin-intermediate *Staphylococcus aureus* (VISA) isolate was reported[27,28], and subsequently heteroresistant VISA (hVISA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) isolates were described (see section "Minimum inhibitory concentration value for vancomycin and mechanisms of resistance"). Thereafter, vancomycin failure and apparently worse clinical outcome in these staphylococcal infections started to be described[29]. In the Asian continent VISA has never disseminated widely and has only been sporadically reported. VRSA, on the other hand, with greater MIC than 16 μg/mL (harbouring gene *vanA*), have been increasingly reported from northern India and West Bengal, both in clinical and colonization isolates[11].

Minimum inhibitory concentration value for vancomycin and mechanisms of resistance

More than 20 years ago, the Clinical and Laboratory Standards Institute (CLSI) first set broad minimum inhibitory concentration (MIC) cut-off point and disk diffusion testing of vancomycin in *S. aureus* isolates (resistance set at ≥ 34 μg/mL). In 1998, after the appearance of the first *S. aureus* strains with reduced vancomycin susceptibility, they lowered the disk diffusion breakpoints, in order to detect these strains to ≤ 4 μg/mL. However, clinical failures with vancomycin in patients with MRSA infections resulted in a re-evaluation of its MIC breakpoints in 2004. Finally in 2006 the CLSI established vancomycin MIC susceptibility cut-off point in ≤ 2 μg/mL, 4-8 μg/mL for VISA and finally ≥ 16 μg/mL for VRSA. MIC for VRSA was lowered to 16 μg/mL because MICs above that limit had shown high probability of adverse clinical outcome[30]. Even with these changes, concerns about the declining susceptibility to glycopeptides in MRSA infections persisted[31].

S. aureus cell wall is composed of layers of murein monomers (peptidoglycan) with D-alanine-D-alanine

(D-ala-D-ala) residues. From the cytoplasm, where these monomers are synthesized, a lipidic transporter (lipid II) transfers them through the membrane. It is then built into the peptidoglycan chain by enzymes situated within the membrane. Vancomycin binds to these D-ala-D-ala residues and blocks the assembly of peptidoglycan monomers, stopping bacterial growth[32]. VISA and VRSA have shown to have different mechanisms of resistance. In the case of VISA, it has been observed that they form a thickened cell wall, with added peptidoglycan layers, and therefore vancomycin isn't able to saturate its target nor reach to the surface of the cell wall, and becomes entrapped within it, never attaining its disruption[33,34]. The term glycopeptide-intermediate SA is sometime used in these strains, given that they frequently show similar patterns of resistance for teicoplanin. Though most VISA strains are also methicillin-resistant, a minority do show susceptibility to methicillin[6]. Intermediate vancomycin resistance has been associated to previous exposure to vancomycin and it seems these isolates can regain vancomycin susceptibility when the antibiotic pressure is withdrawn[35].

VRSA, with MIC breakpoint ≥ 16 μg/mL considering current standards (CLSI) was first detected in 2002. Fortunately it is yet extremely uncommon[36]. VRSA acquire their mechanism of resistance from a gene transferred from vancomycin-resistant enterococci, gene *vanA* (usually transferred by transposon plasmids-Tn*1546*). The resistance mechanism relays on the change of a peptidoglycan residue (D-ala-D-ala by D-ala-D-lactate), so that vancomycin is not able to bind to exert its blockage of the wall synthesis. VISA strains do not carry *vanA*, *vanB*, or *vanC* genes[7,37].

Little after the description of VISA, arose the observation of subpopulations of MRSA apparently vancomycin-susceptible, showing atypical glicopeptide-resistance patterns, referred to as hVISA. These isolates would fall one step before VISA, in vancomycin resistance. Patients with hVISA were found to have been usually exposed to vancomycin in lower levels than desired therapeutic objectives (*i.e.*, < 10 μg/mL). The population analysis profile-area under the curve (AUC) calculation is the reference method to identify hVISA strains, which is an arduous process and is not always available in all laboratories. Measuring vancomycin-MIC values of these subpopulations, most of them will show a MIC ≥ 2 μg/mL, but some yet show MICs < 2 μg/mL. This increases the difficulties involved in their correct identification. There is evidence of prevalence increase of hVISA strains in selected locations. It has been observed that patients with complicated MRSA infections might be at a greater risk of hVISA. In this context, in a recent international study they found that 29% of the patients with MRSA infective endocarditis had isolates with hVISA subpopulations[24,36]. Vancomycin heteroresistant *S. aureus* have been classified with a MIC ranging from 2 to 8 μg/mL.

Table 1 *Staphylococcus aureus* glycopeptide minimum inhibitory concentration cut-off values (μg/mL) as defined by Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing (determined by broth microdilution)

Antibiotic	CLSI (2011)			EUCAST (2011)	
	S	VISA	R	S	R
Vancomycin	≤ 2	4-8	≥ 16	≤ 2	> 2
Teicoplanin	≤ 8	-	≥ 32	≤ 2	> 2

CLSI: Clinical and Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing; S: Sensitive; VISA: Vancomycin-intermediate *Staphylococcus aureus*; R: Resistant.

It has also been recently observed that there are emerging *S. aureus* strains with a MIC sitting on the superior limit of the sensitivity range (*i.e.*, MIC > 1.5 μg/mL), that could show certain resilience to vancomycin and a different clinical behaviour[31,38,39].

This resistance or loss of sensitivity to glycopeptides has given rise to plenty of debates regarding its clinical and epidemiologic relevance. As previously mentioned, partly due to the concerns of reduced vancomycin efficacy, in 2006 the CLSI lowered the *S. aureus* vancomycin-susceptible MIC cut-off point from 4 μg/mL to 2 μg/mL[30]. This cut-off point value is shared by the European Committee on Antimicrobial Susceptibility Testing, yet they do not hold the same MIC classification for VISA strains (which CLSI classify with MIC from 2-4 to 8 μg/mL) and VRSA (MIC ≥ 16 μg/mL), and consider all *S. aureus* strains with MIC higher than 2 μg/mL, as "clinically" resistant to vancomycin (Table 1).

Different microbiologic methods to calculate vancomycin MIC

Detection of VISA strains can be difficult, and they may take more than two days of incubation to grow on culture plate[7]. Quantitative antimicrobial susceptibility methods are the optimum techniques to correctly identify *S. aureus* isolates with VISA subpopulations. Valid quantitative antibiotic sensitivity test are: broth dilution, agar dilution, and agar gradient diffusion (Etest; AB-Biodisk). To correctly measure vancomycin susceptibility, CLSI recommend broth microdilution test done in cation-fixed Mueller-Hinton broth using a bacterial inoculum of 0.5 in McFarland scale, and incubating the dilution at 35 ℃ for 24 h[40]. In laboratories that use automated systems or disk diffusion testing, they recommend using a commercial set prepared with brain-heart infusion agar plate with a vancomycin concentration of 6 μg/mL. By these standards, when a *S. aureus* isolate shows a MIC of ≥ 2 μg/mL (according to the latest MIC classification) it should be confirmed with retesting. If confirmed, this information should be reported as possible VISA (or VRSA if it were ≥ 16 μg/mL), and depending on the country and institution policies, should be communicated to the hospital's infectious diseases department, and established health authorities[7].

Sometimes microbiology laboratories will only inform of the MIC cut-off point, and some automated antimicrobial sensitivity tests will not detect *S. aureus* isolates with a MIC of 2 μg/mL or less, therefore complicating the detection of VISA and hVISA strains[40]. Within VSSA isolates, a higher MIC (2 μg/mL) increases the likelihood of detecting the hVISA phenotype[41]. In a recent meta-analysis, prevalence of hVISA was observed to be of 1.67% (14 studies published in different countries between 1997 and 2001). They found a much higher incidence of hVISA within MRSA, and even though some studies were biased because they only included MRSA. They hypothesise MRSA could be more likely to harbour hVISA or VISA, given that MRSA is usually health-care related and hVISA/VISA represent strains that emerge under heavy antibiotic pressure[42,43].

MIC elevation has important consequences for the effectiveness of this antibiotic and therefore has an impact on MRSA bacteraemia mortality. Consequently, it would be reasonable to consider vancomycin as a suboptimal treatment for strains with a vancomycin MIC > 1 μg/mL. The majority of the hospitals and health centres routinely use automated tests to estimate vancomycin MIC. However, these methods aren't always comparable to standardized methods (Etest, broth microdilution), on which the outcome data of most of the studies are based. Automated systems are able to detect only 10% of MRSA isolates with a vancomycin MIC of 2 μg/mL. Given these disparities the reference method (usually broth micro-dilution) must always be used as confirmation[44]. Unfortunately, these results may take days to become available, which could delay adequate specific therapy[45].

MIC "creep"

MIC "creep" is the concept of a surreptitious constant vancomycin MIC elevation in *S. aureus* isolates resulting from various factors such as antibiotic exposure and changes in the *S. aureus* clonal population. The clinical impact of MIC "creep" is yet to be determined, however, a feared consequence could be increased mortality and treatment failure in high vancomycin-MIC *S. aureus* infections, treated with vancomycin[29].

Evidence of this concept is reflected in various studies and epidemiologic analysis that have been carried out in the last ten to fifteen years. For instance, an analysis of 6003 *S. aureus* isolates in Los Angeles-California in 2004, found a trend of increasing vancomycin MIC; the prevalence of *S. aureus* with vancomycin-MIC of 1.0 μg/mL increased from 19.9% in 2000 to 70.4% in 2004, when previously most stood at < 1.0 μg/mL[39]. Similarly, in 241605 *S. aureus* isolates tested by the Surveillance Network Database in the United States of America in 2007, they found 16.2% of them had a MIC of 2 μg/mL[30]. In an evaluation of more than 35000 strains of *S. aureus* isolated during 1998-2003, 4.7% to 7.8% of *S. aureus* isolates had a MIC of 2 μg/mL[46]. Moreover, despite the tapering in CLSI's vancomycin breakpoint to 2 μg/mL, one study demonstrated that 80% of the organisms with MICs of 2 μg/mL were demonstrated to have hVISA phenotypes[47]. Thus, we are witnessing a gradual decrement in vancomycin susceptibility which seems to be greater in settings where the drug is most used[48].

Risk factors for vancomycin MIC elevation

In Lubin's prospective study they analysed predictive factors for an elevated vancomycin MIC in *S. aureus* bacteraemia. In the univariate analysis, various variables were associated with high vancomycin MIC; age > 50 years, the presence of sepsis or shock at the time of culture, a known history of MRSA bacteraemia, recent exposure to vancomycin or daptomycin, and the presence of a prosthetic heart valve or non-tunnelled central line. However, in the final predictive model, only age > 50 years, history of chronic liver disease, recent vancomycin exposure (> 48 h during the previous 7 d), presence of a non-tunnelled central venous catheter at the time of culture, and a history of MRSA bacteraemia were included[45].

A recent study carried out in the United States identified several risk factors for reduced vancomycin susceptibility *S. aureus* infection. A previous history of vancomycin exposure, in the month prior to *S. aureus* isolation (OR = 13) or in the previous 3-6 mo (OR = 2.8), and having any positive culture for MRSA in the previous 2-3 mo were independently related to reduced vancomycin-susceptibility *S. aureus* infections[49].

In a study analysing bacteraemia due to MRSA isolates comparing those manifesting hVISA to those fully vancomycin susceptible, they found association between hVISA and infections with high bacterial load, (*i.e.*, endocarditis), resulting statistically significant. These strains were also associated to longer duration of fever, longer time to clearance of the bacteraemia, length of hospital stay, and failure of vancomycin treatment. Furthermore, they found these strains had frequently been under initial low serum vancomycin levels[50].

Other risk factors observed in previous studies have been admittance to an intensive care unit, female sex, elevated body mass index, recent surgery, and cardiovascular disease[51-53].

Fortunately, VRSA infection continues to be a rare occurrence. In the analysis of the few cases observed, some predisposing risk factors for VRSA infections have been identified. These are; previous enterococcal or MRSA colonization or infection, comorbidities such as diabetes or chronic skin sores and ulcers, and vancomycin exposure. Infection control and antibiotic stewardship are crucial to avoid the emergence of VRSA. However, more studies are needed to better define the specific microbiological and clinical characteristics of these strains[54].

Recently, the first VRSA was detected in Europe, in a Portuguese hospital. In the epidemiological study, the patient and 53 contacts were screened for *S. aureus* colonization. All strains recovered were characterized by molecular typing methods, by which they observed that VRSA remained confined to the infected foot of the patient and was not detected in any of the close contacts. Only one of the MRSA isolates detected in the screened population was closely related to the VRSA. The VRSA isolated in Portugal belonged to clonal complex (CC) 5, like most of the characterized VRSA strains from other countries. A recent increase in the incidence of lineages belonging to CC5 has been observed in some European countries. This may result in more frequent opportunities for the emergence of VRSA[55].

CLINICAL RELEVANCE OF VANCOMYCIN MIC ELEVATION

Adjusting vancomycin dose to improve AUC/MIC

Vancomycin exhibits concentration-independent and time-dependent killing. Vancomycin efficacy is best measured using the ratio of the 24-h area under the concentration-time curve (AUC_{0-24}) to the MIC ratio (AUC_{0-24}/MIC), in pharmacodynamic parameters. These findings are based on neutropenic murine thigh-infection models[56]. In patients with *S. aureus* pneumonia, treated with vancomycin, it has been observed that attaining an AUC_{0-24}/MIC $\geqslant$ 350 (MIC determined by broth microdilution) is associated with seven times better odds of clinical success. They found shorter time to bacterial elimination when the AUC_{0-24}/MIC attained was $\geqslant$ 400[57,58]. The AUC_{0-24}/MIC concentration obtained with the usual doses administered (1 g/12 h) and with a trough vancomycin concentration of 10 μg/mL, is approximately 400 mg/h per litre. From these results we could assume that the commonly recommended dose is adequate to treat *S. aureus* infections with a vancomycin MIC $\leqslant$ 1 μg/mL but suboptimal when it is > 1 μg/mL.

In the last years, there have been several publications regarding diminished efficacy of vancomycin in those cases with *S. aureus* infection with high vancomycin MIC but within the sensitivity range[38,59,60]. Based on these findings, some studies suggest the ideal aimed vancomycin-dose for best clinical results should be an AUC_{0-24}/MIC ratio $\geqslant$ 400, and therefore targeted trough concentrations should be increased to 15–20 mg/L[61]. However, in a recent study with patients with severe MRSA infections treated with vancomycin in which they adjusted daily dose to reach trough concentrations $\geqslant$ 15 mg/mL, they observed that the cure rate for the cases with vancomycin MIC = 2 μg/mL was still inferior to those with MIC $\leqslant$ 1 μg/mL (62% *vs* 85%; P = 0.02)[62].

On the other hand, aggressive dosing strategy could possibly enable targeted vancomycin concentrations in most cases of vancomycin-susceptible *S. aureus* infection. However, this could possibly be unachievable in other clinical settings, such as higher MIC or when limited by vancomycin toxicity. In a recent study, Patel showed that creatinine clearance and vancomycin MIC were inversely related to the probability of achieving adequate AUC_{0-24}/MIC values. He used Monte Carlo simulations to carry out this study. As an example, when administering 1500 mg of intravenous vancomycin every 12 h, target AUC_{0-24}/MIC values were attained in 97% of the cases of vancomycin MIC $\leqslant$ 0.5 mg/L, but they weren't able to reach this target in 38% of the cases with a vancomycin MIC of 2 mg/L[63]. When evaluating vancomycin-susceptible *S. aureus*, VISA, and hVISA in this model, the AUC_{0-24}/MIC ratio required for a static effect was similar for all these organisms. However, the dose required for a 2 $\log^{10}$ kill was 2.5-fold higher for hVISA, compared with VISA. Therefore, the authors concluded that a AUC_{0-24}/MIC ratio of at least 500 was needed to optimize vancomycin pharmacodynamics for hVISA. To attain this AUC_{0-24}/MIC ratio, the needed doses to administer would be extremely high and would involve unacceptable toxicity[64].

In Ghosh's recently published study, they evaluated the utility of previously validated AUC predictions (based on creatinine clearance estimation) and explored the optimal AUC_{0-24}/MIC targets for vancomycin in patients with MRSA bacteraemia. They also investigated whether observed targets are influenced by the sources of the bacteraemia. Treatment failure (persistent bacteraemia, microbiological failure and 30-d all-cause mortality) in their study occurred more frequently in those cases where the AUC_{0-24}/MIC (by broth microdilution) was less than 398 (54% *vs* 23.4%, P < 0.01). Other variables associated with treatment failure were chronic lung disease, on-going immunosuppressive treatment, and high-risk sources of bacteraemia (endovascular, pneumonia, complicated intra-abdominal and central nervous system foci). In their study they also observed significant differences between MIC calculated by Etest or microdilution, as previously described. Etest generally yielded MIC results approximately 1-2 dilutions higher than broth microdilution, which could be circumvented by aiming appropriate MIC-method specific AUC_{0-24}/MIC targets. They also observed that bacteraemic source specific AUC_{0-24}/MIC thresholds may offer better outcome in high risk bacteraemia, with lower doses required for low risk source of infection. However, no further studies have yet been carried out to include these findings in current guidelines for their implementation. The controversy of this study relies also in the fact that they found no significant differences in clinical outcome in those cases with high vancomycin MIC (both measured by Etest or broth microdilution). Finally, they conclude that vancomycin trough concentrations are unlikely to accurately reflect AUC_{0-24}/MIC targets and may result in suboptimal outcomes. They suggest AUC estimation based on validated formulas, may allow for individual patient-dose optimisation resulting in increased treatment success when a vancomycin AUC_{0-24}/MIC of ⩾ 398 is achieved[25].

Risk of nephrotoxicity with elevated vancomycin doses

There is limited data suggesting a direct causal relationship between toxicity and specific serum vancomycin concentrations[61]. However, targeting vancomycin dosing for trough concentrations of 15-20 mg/L leads to a greater risk of nephrotoxicity[65], especially in those patients who also receive other nephrotoxic drugs[66]. In fact, a vancomycin trough concentration > 15 mg/L has shown to be an independent predictor of nephrotoxicity[67]. In one the studies proving this association, they compared nephrotoxicity (defined in their study as a 25% decrease in creatinine-clearance rate) developed in 59% of the patients treated with vancomycin that achieved trough serum concentrations of 15 mg/L, whereas in only 30% of those achieving lower trough concentrations (P = 0.0006)[68]. Nephrotoxicity is frequently a limiting factor for patients to receive the optimal doses in MRSA infections, even when adjusted by AUC_{0-24}/MIC, and often forces rotation to other less validated antibiotic schemes.

CONSEQUENCES OF AN ELEVATED VANCOMYCIN MIC IN INFECTIONS BY MRSA AND MSSA

As it has been previously mentioned, glycopeptides, mainly vancomycin has traditionally been the treatment of choice for MRSA infections. However, because of the numerous studies declaring worse outcome in MRSA infections with vancomycin MIC > 1.5 μg/mL, even after adjusting trough concentration to higher thresholds (15-20 mg/L)[63,69], confidence in this treatment option has somewhat declined. This is similarly observed in hetero-resistant strains, observing a loss of bactericidal activity (tolerance) to glycopeptides and more frequent treatment failure in hVISA[70]. Infections where hVISA are isolated have been associated with high-inoculum infections, persistent bacteraemia and metastatic complications, however, up to now, there are controversial results regarding the impact on mortality in these patients[71].

Along these lines, previous studies have declared worse clinical outcomes in *S. aureus* infections, especially bacteraemia, with decreased vancomycin susceptibility (within VSSA ranges)[60,62,69,72]. These results have been reproduced for VISA and hVISA infections, finding bloodstream infections by these strains were more frequently associated to persistent bacteraemia than those that did not show this phenotype[50]. In another study yet, they observed that MRSA bacteraemia was associated with higher mortality when vancomycin was used empirically, on those cases where vancomycin MIC was > 2 μg/mL[60]. But not all publications corroborate these results, generating further controversy[73-75].

A recent meta-analysis which included a total of 22 studies[69] studied the impact of a vancomycin MIC ⩾ 1.5 μg/mL on the clinical outcome of *S. aureus* infections. In this meta-analysis they highlighted an association between higher vancomycin MIC in MRSA infections and poorer outcomes (even mortality), regardless of the source of infection or MIC methodology (OR = 1.64; 95%CI: 1.14-2.73, P = 0.01). They described an increased all-cause 30-d mortality in MRSA bloodstream infections with a vancomycin MIC of 2 μg/mL (determined by Etest), however, no mortality differences were detected in isolates with a MIC of 1 μg/mL and 1.5 μg/mL. Treatment failure, defined as persistent bacteraemia, was also more frequently observed in cases of high vancomycin MIC. After these results have been published, other authors have approached this association with discordant conclusions.

Therefore, despite some contradictory findings, it seems the observation of a higher vancomycin MIC has been repeatedly shown to confer a worse prognosis for MRSA bacteraemia[60,62,69]. This association, however, has been scantily investigated for MSSA strains. The present evidence is scarce, however some studies described a similar association between worse clinical outcome and elevated vancomycin MIC in MSSA bacteraemia, regardless of antibiotic treatment administered (anti-staphylococcal penicillin or vancomycin). In a study of 99 patients with MSSA catheter-related bacteraemia, vancomycin MIC (Etest) ⩾ 1.5 μg/mL was the only independent risk factor for the development of complicated bacteraemia (OR = 22.9; 95%CI: 6.7-78.1), regardless of the initial antibiotic administered[76]. Similarly, another study revealed that mortality increased 2.4-fold in patients with a vancomycin MIC > 1.5 μg/mL, and the choice of antibiotic treatment had no statistical significant effect on 30-d mortality in the multivariable model[72].

S. aureus is one of the main causes of infective endocarditis (IE), being MSSA more frequently found to be responsible for native-valve IE (85% *vs* 15%) compared to MRSA, with a very high morbidity and mortality, that sits around 25%[77-79]. In 2009, a study carried out to analyse the effect of vancomycin MIC on the outcome of MRSA endocarditis, revealed persistent bacteraemia, heart failure and mortality were associated to vancomycin MIC > 1.5 μg/mL[80]. More recently described, higher vancomycin MIC left-sided MSSA endocarditis were more frequently associated with systemic emboli and a higher in-hospital and one-year mortality. In this study, patients with endocarditis by a MSSA strains with a vancomycin MIC ⩾ 1.5 μg/mL (determined by E-test) had 3-fold higher mortality (OR = 3.1; 95%CI: 1.2-8.2)[81].

Evidence that the mechanisms underlying worse clinical outcomes in high-MIC VSSA infections go beyond antibiotic failure was given in a recent multi-centre observational cohort study of 532 *S. aureus* bacteraemic patients[72]. In this study, increasing vancomycin MIC was associated with increased mortality in vancomycin-

Table 2 Treatment recommendations in *Staphylococcus aureus* with reduced vancomycin susceptibility infections[1]

General recommendations	
Removal of indwelling hardware (prosthetic devices, surgical material, intravascular catheter, *etc.*)	
Surgical debridement of infected wounds and abscess drainage	
Follow specific guidelines and local protocols, based on infection site, for treatment duration decisions	
Antibiotic treatment considerations	
Vancomycin	If used aim: AUC_{0-24}/MIC ⩾ 400 or trough blood concentrations of 15-20 mg/L
	Careful monitoring of renal function is imperative
Daptomycin	Bactericidal. Good results with VISA and VRSA endovascular infections
	Consider administration of higher doses (*i.e.*, 10 mg/kg per day) in severe infections and if vancomycin MIC > 2 μg/mL (including VISA)[2]
	Consider synergic combinations (*i.e.*, cloxacillin, aminoglycosides, betalactans, fosfomycin) in infections involving high inoculum (as in IE) and prosthetic devises
	It is inhibited by pulmonary surfactant, therefore should be avoided in SA respiratory or lung infections
	Monitor CK and liver function
Linezolid	Bacteriostatic
	Protein synthesis inhibitor. Inhibits bacterial toxin synthesis
	High tissue bioavailability
	Good results in SSTI and pneumonia (including VAP)
	Oral formulation with similar bioavailability
	Myelotoxicity: Monitor CBC
	Severe interactions with SSRIs and MAOIs, must not be given simultaneously
Tigecycline	Low plasma concentrations. Bacteriostatic. Avoid monotherapy

[1]Treatment recomendations for SA with reduced vancomycin susceptibility usually take methicillin resistance for granted. If the strain were methicillin sensitive, the latter would be the treatment of choice; [2]In VISA and SA with MIC > 2 μg/mL, worse results with lower daptomycin doses have been observed, probably related to cell wall thickness changes in these strains. AUC: Area under the curve; MIC: Minimum inhibitory concentration; VISA: Vancomycin-intermediate *Staphylococcus aureus*; VRSA: Vancomycin-resistant *Staphylococcus aureus*; IE: Infective endocarditis; SA: *Staphylococcus aureus*; CK: Creatinine kinase; SSTI: Skin and soft tissue infections; VAP: Ventilator associated pneumonia; CBC: Complete blood count; SSRI: Selective serotonine reuptake inhibitor; MAOI: Monoamine oxidase inhibitor.

treated patients. Moreover, even in patients with MSSA bacteraemia treated with flucloxacillin, mortality was higher if the vancomycin (Etest) MIC of their isolate was > 1.5 μg /mL, compared with those with lower MIC isolates (26.8% *vs* 12.2%; P < 0.001). These results suggest that apart from antibiotic choice, other factors (clinical and microbiological) might be crucial in patient outcome.

Interestingly, despite previous information about poorer prognosis associated to elevated vancomycin MIC, these strains have been found to be associated with a diminished inflammatory response, and therefore less incidence of septic shock. This suggests these strains could have alterations in their pathogenic activity and virulence[60,73]. Peleg studied the pathogenesis of *S. aureus* infections using *Galleria mellonella*. Using both clinical and laboratory strains, they demonstrated that with the evolution of reduced susceptibility to vancomycin, the virulence of *S. aureus* becomes attenuated. The degree to which virulence is attenuated appears to be proportional to the vancomycin MIC[74].

Therefore the arguments linking vancomycin resistance with both reduced bacterial fitness and increased virulence, are yet to be proved, and more studies are needed to determine their clinical significance[6].

Other virulence and prognostic factors in *S. aureus* infections that have taken a leading role are the expression and function of certain genes. The dysfunction of accessory gene regulator (*agr*), has been found to possibly play a key role in MRSA virulence, and seems related to vancomycin resistance. The *agr* locus is in charge of regulating the expression of certain virulence genes and other constitutive genes, required for the maintenance of basic cellular function. The overexpression of *agr* increases the toxin production and reduces the expression of cell surface adhesins[6]. The *agr* locus dysfunction has been associated with reduced vancomycin susceptibility[82], persistent MRSA bacteraemia[58,83], and increased mortality[84], and has been considered a subrogated marker of health-care associated situations. However more studies and investigations are needed to establish the impact of these findings and the possible consequences derived in daily clinical practice (treatment modifications it could imply, invasive procedures to asses, *etc.*).

Overall, there seems to be numerous studies and data indicating that elevated vancomycin MIC in both methicillin resistant and sensitive VSSA, could be a subrogated virulence marker, however, these results are yet controversial, and have not been universally proven. In this realm of controversy, evidence based clinical decisions seem like an arduous and complicated task.

ALTERNATIVE THERAPIES FOR MRSA AND MSSA INFECTIONS WITH REDUCED VANCOMYCIN SUSCEPTIBILITY (TABLE 2)

Clinical approach to S. aureus with > 1.5 vancomycin MIC infections

Up to now, there is no evidence-based unified clinical approach for patients with *S. aureus* infections that have an elevated vancomycin MIC within the sensitivity thresholds (MIC ⩾ 1.5 μg/mL). If the

Table 3 Infection control recommendations for patients colonized or infected by drug-resistant *Staphylococcus aureus* (vancomycin-intermediate *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus*, and methicillin-resistant *Staphylococcus aureus*, Centers for Disease Control and Prevention recommendations[1])

Spread prevention
Isolate patient in a private room
Facilitate gowns and gloves to enter the room
Facilitate mask protection
If risk of aerosol spread consider mask use
Practice hand hygiene with an antibacterial agent (preferably chlorhexidine-based soaps or solutions)
Avoid sharing equipment among patients
Continue isolation until results of tests of nares and infected sites are negative 3 times over 3 wk (including hospital readmission)
Minimize number of staff caring for patient
Educate staff about appropriate precautions and assess compliance
Infection control in nosocomial spread and evaluation
Perform baseline and weekly cultures of hands and nares of healthcare workers in charge of index patient
Consider baseline and weekly cultures for other healthcare workers and persons with extensive contact
Decolonize index patient and healthcare workers with topical mupirocine
Consider avoiding direct patient-contact of colonized healthcare workers until negative culture

[1]Centers for Disease Control and Prevention Healthcare-associated Infections recommendations and guidelines (http://www.cdc.gov/HAI/prevent/prevent_pubs.html).

decision were to use vancomycin, it seems crucial to beware of the different formulas to attain adequate AUC/MIC targets. More studies are needed to consider the contrasting efficacy of other antibiotic treatments in this situation.

The possibility of it being a surrogated virulence marker possibly implies these cases should be up-scored in the severity scale, and this awareness should be maintained for clinical decision-making. Current recommendations include patient isolation and infection control policies, similar to other cases of multi-drug resistant microorganisms infections or colonization (Table 3)[7]. However there are no present studies that define specific indications or clinical algorithms in these cases.

New drugs for MRSA

Daptomycin: Resistance to daptomycin (MIC ⩾ 1 μg/mL) is infrequent and the strains that have shown elevated MIC have been found to have mutations associated with cell membrane structure and cell wall thickness (mprF, yycFG). This has been more frequently observed in VISA strains with a lower sensitivity to glycopeptides[85].

The main concern with the use of daptomycin is the emergence of resistance in the course of treatment. This problem seems to appears more frequently in cases where daptomycin is introduced as rescue treatment after vancomycin has failed or in cases of hVISA or VISA infections[86]. A study carried out in the United States observed a correlation between *S. aureus* strains with reduced vancomycin-susceptibility and the emergence of intra-treatment daptomycin resistance. This was especially found in cases of MRSA infections with vancomycin MIC of 4 μg/mL or greater[87].

Given that daptomycin's mechanism of action is unique, there doesn't seem to be crossed resistance with other antibiotics. Nevertheless, some studies have observed that *S. aureus* with higher vancomycin-MIC (4-16 μg/mL) also show reduced sensitivity to daptomycin[87]. In those strains with vancomycin MIC 4-16 μg/mL, daptomycin MIC was ⩾ 2 μg/mL, and therefore would fall over the sensitive threshold. However, *vanA* resistance to vancomycin does not affect daptomycin sensitivity[86]. In short, reduced vancomycin MIC is a call for awareness and precaution before using daptomycin in *S. aureus* infections. In these cases it would be important to know precise daptomycin MIC (broth micro-dilution or Etest) before starting this treatment.

In order to overcome these difficulties and to increase the bacterial-killing activity, it has been recommended to use higher doses of daptomycin in high risk infections (8-10 mg/kg per day) and up to now there has not been more toxicity associated to these doses in healthy volunteers treated for 14 d[88]. Another possible option that is lately being considered, especially in infections that involve prosthetic materials is the use of daptomycin in combination with other antibiotics. The combination with aminoglycosides and rifampin, has shown to be synergic[89]. Other synergic combinations in experimental models and in preliminary studies with promising results are, cloxacillin[90,91] other betalactams[92-94] and fosfomycin[95]. These options have been mainly studied for MRSA infections and for prosthetic devices associated infections. Future guidelines may contemplate treatment of MRSA infections with borderline vancomycin susceptibility with any of such combinations.

Linezolid: The main disadvantages of using linezolid for high-risk infections that need antibiotic therapy for an extended period of time (*i.e.*, endocarditis) are that it is a bacteriostatic anti-staphylococcal and its myelotoxicity. On the other hand, it offers the advantage of the possibility of oral administration and has high tissue distribution. In an endocarditis study, linezolid was effective in 4 out of 8 patients (50%) with IE by VISA (MIC 2-4 μg/mL) that had failed with vancomycin[96]. In another retrospective study, 70% (of 22 patients) with MRSA IE that received linezolid because of failure of vancomycin or as sequential oral treatment were cured[97]. Sequential treatment showed 100% cure rate in 8 patients with MRSA IE with early valve surgical replacement (mean 5 d). Linezolid was administered from the fifth day onwards during approximately 3 wk[98]. Therefore, linezolid is an option for selected IE cases, when other treatments fail, or in patients that have intolerance to other treatments.

MRSA resistance to linezolid was first described associated to ribosomal mutations, and recently it has been described related to the appearance of *cfr* (for chloramphenicol-florfenicol resistance gene) gene. This is a plasmid-borne methyltransferase-mediated resistance mechanism that leads to resistance to various antibiotics, as well as linezolid[99,100]. This gene is responsible for the synthesis of a methylase that interferes with 23S rRNA. Hospital outbreaks of linezolid-resistant infections have been associated to these mutations.

Other: There is little clinical experience in the treatment of MRSA severe infections (such as endocarditis or pneumonia) with the "new" glycopeptides such as dalbavancin, oritavancin or telavancin, with tigecycline, or with the new cephalosporins (ceftobiprole or ceftaroline). However the majority of these drugs have shown potential efficacy in experimental models[101-106].

In two recently published trials oritavancin and dalbavancin, showed to be non-inferior to vancomycin and linezolid for the treatment of skin and soft tissue infections (SSTI). These new glycopeptides offer unusual pharmacodynamic and pharmacokinetic properties that allow treating once or twice a week, as has been proved in skin and soft tissue infections, however more studies are needed for other sources of infection[107,108]. Telavancin is approved for the treatment of adult patients with complicated SSTIs and nosocomial pneumonia caused by gram-positive bacteria, including MRSA, when no other options are available. Up to now, the use of telavancin is restricted to MRSA infections with a vancomycin MIC ⩾ 1 μg/mL, hVISA infections, lack of response to vancomycin treatment or patients who do not tolerate other antistaphylococcal antibiotics[109].

Tigecycline is a semisynthetic drug derived of minocycline. Being a broad spectrum antibiotic, it has anti gram-positive and gram-negative activity[110]. Drawbacks to the use of tigecycline in bloodstream infections come from both, intrinsic drug characteristics and clinical experience. It is a bacteriostatic antibiotic and it reaches high tissue concentration but low concentration in plasma. Moreover, in previous studies it has been associated to worse prognosis and higher mortality rates in patients with severe infections. Consequently, tigecycline is not normally recommended as a first line antibiotic for bloodstream or severe MRSA infections[111,112].

Ceftaroline-fosamil is a cephalosporin with anti-MRSA activity[113]. In two clinical trials comparing ceftaroline with vancomycin plus aztreonam for SSTIs, they found treatments were comparable[114]. There is still little experience in the use of ceftaroline in other sources of MRSA infections.

Ceftobiprole is a new cephalosporin, that shows a broad-spectrum and strong bactericidal activity even for MRSA[115]. Ceftobiprole has high affinity for PBP2a (main PBP responsible for methicillin resistance), and is also stable to class A penicillinases, thence its good anti-MRSA activity[115]. In an animal MRSA endocarditis model, ceftobiprole was found superior to vancomycin, daptomycin, and linezolid[116].

Combination therapies

Rifampin and gentamycin are the two antibiotics that have most frequently been associated to vancomycin. The use of rifampin is based on its activity against *S. aureus* in stationary phase. However this synergy has not been proved *in vitro*[117,118] and the clinical benefits of adding rifampin to vancomycin in the treatment of MRSA IE hasn't been proved either[119]. The association of vancomycin and an aminoglycoside has been found synergic[120] and is therefore contemplated in patients with persistent bacteraemia. However this association hasn't proved a lower mortality rate in IE, and it has shown increased nephrotoxicity[121], so it probably shouldn't be held as a first option treatment.

The combination of vancomycin and linezolid, both *in vitro* and *in vivo*, is indifferent or possibly antagonistic[122]. There are experimental studies[123] and a scarce clinical experience[124] that showed that the combination of vancomycin and quinupristin-dalfopristin was synergic, safe and useful for the treatment of 5 patients with severe MRSA infections.

There is scarce evidence about possible antibiotic combinations with linezolid, and results are contradictory. *In vitro* studies have shown decreased antibiotic activity of both gentamycin and vancomycin when associated to linezolid[125]. On the other hand, in animal models of IE they observed advantages in the combination of linezolid and gentamycin *vs* only linezolid[126]. Synergic combinations of linezolid with ertapenem and imipenem have also been communicated, both *in vitro*, and in experimental endocarditis models. However this association only is observed if the carbapenem is given in sub-inhibitory doses, whereas therapeutic doses decreases linezolid's antibiotic activity[127].

Daptomycin at a dose of 10 mg/kg per day (and perhaps higher) may be more effective than the currently approved 6 mg/kg per day dose for severe *S. aureus* infections caused by non-susceptible strains (*i.e.*, those with MICs of > 1 μg/mL)[128]. In an experimental animal aortic valve MRSA endocarditis model, combinations of daptomycin with an aminoglycoside or rifampin didn't show synergy[129].

While fosfomycin is Food and Drug Administration approved only for the treatment of uncomplicated urinary tract infections, it has demonstrated good antimicrobial activity against a broad spectrum of pathogens, including MSSA and MRSA[130]. Fosfomycin, which acts by inhibition of an early step in cell wall synthesis, has been used successfully in combination with beta-lactams to treat severe staphylococcal infections[131]. It also shows *in vitro* synergy when combined with daptomycin[132]. Three cases have been recently published where they observe that the *in vitro* combination of high doses of daptomycin plus fosfomycin can be effective in the treatment of both native- and prosthetic-valve endocarditis caused by MSSA or MRSA[133].

CONCLUSION

MRSA proves to be a persistently lurking microorganism underlying both community and healthcare associated infection. The emergence of increasing vancomycin resistance patterns and the different consequences derived have created a new area of uncertainty in the clinical and therapeutic approach to these infections. More studies and trials are needed in order to better define these issues.

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P- Reviewer: Schwan WR **S- Editor**: Gong XM **L- Editor**: A
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