



Review

Insights and clinical perspectives of daptomycin resistance in *Staphylococcus aureus*: A review of the available evidence

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ABSTRACT

The emergence of glycopeptide reduced susceptibility and resistance in *Staphylococcus aureus* strains is a growing clinical problem that poses significant clinical challenges in treatment. Its development is a complex and novel process involving many subtle physiological changes in the micro-organism. Daptomycin is the first cyclic lipopeptide approved for clinical use. Unlike most other antimicrobials, a trend towards increased daptomycin resistance has not been reported, although several cases of daptomycin non-susceptibility have been reported. The present review will present the available evidence on daptomycin resistance of *S. aureus*, with particular attention to its development. In addition to a literature overview, we have compiled the reported cases of daptomycin non-susceptibility to shed light on possible clinical mechanisms of resistance. In the 36 reports describing 62 clinical cases, infections caused by meticillin-resistant *S. aureus* (MRSA) strains with a vancomycin minimum inhibitory concentration (MIC) between 1 mg/L and 2 mg/L often led to vancomycin treatment failure, which may be associated with the development of non-susceptibility to daptomycin. Additional evidence suggests that underdosage of daptomycin is an important clinical aspect that merits further study. The current analysis highlights the importance of determining the MIC when using vancomycin to treat patients with severe *S. aureus* infections and that when failure is suspected, testing for heterogeneous vancomycin-intermediate *S. aureus* (hVISA) may also be necessary. Whilst further investigation is needed, it can be hypothesised that MRSA strains become hVISA during prolonged bacteraemia, which may predispose to the development of daptomycin resistance.

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1. Introduction

Staphylococcus aureus continues to be one of the most common bacterial pathogens and causes a broad spectrum of diseases worldwide, including nosocomial infections [1]. Its prevalence in Italy, as demonstrated in a recent epidemiological survey, is 11.6% among all nosocomial pathogens, ranking third after *Escherichia coli* and coagulase-negative staphylococci [2]. These data are in agreement with studies on prevalence performed in other countries, such as in Europe [3] and the USA [4]. In recent decades, treatment of *S. aureus* infections has become more challenging for a number of reasons: (i) the rising frequency of multidrug-resistant isolates, above all in the subset of meticillin-resistant *S. aureus* (MRSA) strains; (ii) the emergence of highly virulent community-associated MRSA

clones; and (iii) the appearance of reduced susceptibility to glycopeptides, which is especially prominent with vancomycin [5]. Moreover, there is also a distinct lack of clinical data supporting the use of antimicrobials other than vancomycin in the treatment of severe *S. aureus* infections.

The present review will summarise the available evidence on resistance of *S. aureus*, with a particular focus on daptomycin. We also review the available clinical evidence on resistance of *S. aureus* to daptomycin in order to provide additional insights into this phenomenon.

2. Resistance in *S. aureus*

2.1. The unique evolution towards resistance in *S. aureus*

The extreme versatility of *S. aureus* lies at the core of its success as a human pathogen [6]. As part of its adaptation in the antibiotic era, *S. aureus* has been able to evolve, acquiring resistance to nearly

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all antibiotics used to eliminate it. The history of the development of antimicrobial resistance in *S. aureus* has been well described in many reviews [7–9], beginning as soon as penicillin was introduced into the market in 1945. The first MRSA strain appeared in 1961 [10], identified by British scientists only 2 years after the introduction of meticillin. Acquisition of the *mecA* gene, which codes for an additional penicillin-binding protein that renders *S. aureus* refractory to all available β-lactam antibiotics, was the first real acquisition in its physiology [11]. Subsequently, new strains of bacteria developed, and the term MRSA actually refers to resistance to an entire class of penicillin-like antibiotics that includes penicillin, amoxicillin, oxacillin, meticillin and others. In addition, *S. aureus*, above all MRSA, was also able to develop resistance to other available antibiotics such as erythromycin, streptomycin and the tetracyclines [12]. In all these cases, the interval between the first introduction of a new antibiotic and the development of resistance was generally very short, ranging between 1 year and 3 years [7]. This is true for all of the above-described antibiotics, but also for some newer agents such as linezolid [13] and daptomycin [14].

2.2. Resistance or reduced susceptibility to glycopeptides has changed *S. aureus*

The development of resistance to glycopeptides has been markedly different to that of other antibiotics. Vancomycin was introduced in 1958 and the first intermediate and resistant strains were isolated after ca. 40 years [7]. This discrepancy compared with other antibiotics can be explained by a variety of reasons, although a mechanism of resistance linked to complex physiological changes related to adaptation, often reversible, of the micro-organism to a selective pressure of the drug is has been widely invoked [6,7,15]. In this respect, the multimodality of reduced susceptibility to glycopeptides and, to some extent lipopeptides, is associated with physiological changes to *S. aureus*: vancomycin-intermediate *S. aureus* (VISA) and heteroresistant VISA (hVISA) isolates are different organisms compared with their susceptible counterparts. A similar event took place with *mecA* acquisition by *S. aureus*, rendering it meticillin-resistant and very different from susceptible clones. In 2002, the first *vanA*-mediated vancomycin-resistant strain was described [16]; since that time only 13 isolates have been reported in the USA [16,17], with a few in India [18] and Iran [19]. Furthermore, a new case of *vanA* transfer was recently described in Brazil [20].

3. The role of glycopeptides in maintaining the glycopeptide-resistant phenotype

Reduced susceptibility to glycopeptides, due to the involvement of complex regulatory systems [6], is to be considered a novel mode of resistance. Optimisation of the dosing regimen of the available antimicrobials is an established strategy for decreasing resistance. A study by Asín et al. compared the pharmacokinetic/pharmacodynamic (PK/PD) breakpoints for several antimicrobial classes against Gram-positive cocci with those defined by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) and found large divergences for some antibiotics [21]. In particular, substantial differences were seen for low doses of vancomycin, linezolid and daptomycin, which had PK/PD breakpoints lower than those defined by the CLSI and EUCAST [21]. Accordingly, any particular isolate would be considered susceptible based on CLSI and EUCAST definitions even if the PK/PD analysis would predict failure. Such discrepancies may explain many reported treatment failures [21–25] and further support the idea that not only antimicrobial activity but also the dosing regimen can increase

the probability of clinical success of antimicrobial treatment. Whilst some studies have indicated that there may be an upward creep of vancomycin minimum inhibitory concentrations (MICs) for MRSA isolates towards the clinical breakpoint [26–28], a 5-year survey of clinical MRSA isolates from a few centres in Northeast Italy reported the absence of upward creep of glycopeptide MICs for MRSA clinical blood isolates [29]. Upward creep was originally reported in 2009 from an analysis of clinical isolates obtained over a 17-year period [12]. In that investigation, a temporal shift in the susceptibility levels to glycopeptides was observed where strains with a vancomycin MIC of ≥ 2 mg/L increased from 19.4% to 35.5% between 1990 and 2007.

The vancomycin CLSI MIC breakpoints for *S. aureus* were lowered in 2006 to improve the correlation of in vitro susceptibility and clinical response. At present, the EUCAST clinical MIC breakpoint for resistance to vancomycin in *S. aureus* is > 2 mg/L. However, considering the important differences in the mechanism of resistance in different strains, it is recommended that the MIC and heteroresistance always be determined when using vancomycin to treat a patient with severe *S. aureus* infection in order to detect hVISA strains [30,31].

Whilst prior to this VISA strains were relatively uncommon in the clinical setting, the new breakpoints may be associated with an increased number of VISA isolates [5,31]. At present, the available data would suggest that the overall prevalence of strains with reduced resistance to vancomycin, at least in the USA, is low (0.3%). However, large variability in the reported prevalence exists: hVISA isolates represent 10.5% of isolates with vancomycin MICs of 2 mg/L and 0.1% of isolates with vancomycin MICs of 1 mg/L [31,32]. Such large variability may be due to differences in methodology used to detect heteroresistance, but also to differences in the distribution of hVISA clones [33]. Strains with altered susceptibility to vancomycin still constitute a substantial public health threat, especially in resource-poor countries [34], even if a recent systematic review found no association of MIC creep with increased mortality [35]. This was also confirmed by a report that high vancomycin MIC was not associated with increased 12-week mortality [33].

hVISA strains can be considered as precursors to VISA strains, which have been found to have several phenotypic changes compared with vancomycin-susceptible *S. aureus* [31,36]. The most conspicuous involves increased cell wall thickness with prominent activation of cell wall synthesis. In addition, reduced autolysis, decreased activity of the staphylococcal global regulator Agr, and reduced susceptibility to lysostaphin have been observed along with changes in teichoic acids of the cell wall. Such changes in VISA strains have the net effect of entrapping glycopeptide so that they are prevented from reaching their target [37]. All of these alterations are associated with multiple genetic changes involving cell wall metabolism in the presence of glycopeptides.

4. Daptomycin in the treatment of *S. aureus* infections

4.1. Mechanism of action of daptomycin

Daptomycin is the first cyclic lipopeptide approved for clinical use and has been clinically available since 2003 [38]. It consists of a cyclic peptide moiety with 10 amino acids, from which 3 amino acids protrude from the N-terminal, which further harbours a decanoyl fatty acyl side chain. The antibiotic is extraribosomally synthesised by *Streptomyces roseosporus* and contains several non-standard amino acids, such as kynurenone and ornithine [39]. The native molecule is anionic, although to bind to the bacterial membrane and exploit the bactericidal activity that is typical of daptomycin there is an absolute requirement for calcium. Thus,

calcium/daptomycin becomes a de facto cationic peptide agent in terms of both charge and mechanism of action.

When calcium is added to the molecule in a 1:1 ratio, a multistep process appears to be initiated (monomer binding, oligomerisation and conversion of the oligomer to a functional pore) that brings about the formation of oligomeric transmembrane pores, as recently demonstrated [39], which are necessary for its antibacterial action. Insertion of this complex into the cell membrane is due mainly to the interaction with the negatively charged phospholipid heads of phosphatidylglycerol and cardiolipin. These interactions are at the basis of the only effect that has been consistently reported in studies from different laboratories [40,41], along with the recent demonstration that membrane depolarisation, mainly due to sodium influx, takes place [42]. Concomitantly with membrane depolarisation, bacterial cells lose the ability to accumulate amino acid substrates, whilst leaving glucose uptake intact, indicating the selective nature of the defect in membrane permeability. In addition, no membrane discontinuities have been observed by electron microscopy, supporting the notion that the functional membrane lesion is discrete and small [43].

Other experiments by Pogliano et al. [44] have shown that insertion of daptomycin into the membrane results in the formation of membrane patches that redirect the localisation of proteins involved in cell division and cell wall synthesis, thereby confirming previous observations on the mode of action of the drug that involve both membrane depolarisation and inhibition of cell wall synthesis. Even if there has been much recent progress in our understanding of the mechanism of action of daptomycin, the complete mechanism by which it causes cell death is not fully elucidated.

4.2. Reduction of susceptibility to daptomycin in *S. aureus*

The prevalence of de novo resistance to daptomycin among *S. aureus* strains without prior exposure has been reported to be extremely rare, with a large survey finding that only 0.4% of clinical isolates of *S. aureus* had an MIC of 2 mg/L [45]. The mechanisms by which *S. aureus* develops resistance to the microbicidal effects of daptomycin are likely multifactorial [15,31,46–49] and related to the species: in fact, daptomycin resistance in *S. aureus* differs substantially from that defined for enterococci [47,49–54]. Moreover, although the principal mechanism of resistance appears to be perturbation of the bacterial cell membrane, it would appear that changes in the process of cell wall turnover may also play a critical role [55–57].

Initial studies indicated that daptomycin-resistant isolates of *S. aureus* demonstrated changes in membrane structure and function as well as alterations in binding and membrane permeabilisation of daptomycin [51]. More recent studies have confirmed those mechanisms, and in addition revealed that overexpression and dysregulation of *dltA* transcription are present in some strains showing daptomycin resistance which may correlate with increased D-alanylation of teichoic acid in the cell wall, although the subsequent phenotypic consequences identified do not appear to be sufficient to completely explain the resistance to daptomycin [58]. In summary, the factors identified to be involved in resistance to daptomycin include: (i) altered expression of net positive surface charge; (ii) gain-in-function of *DltA*, resulting in an increase in the D-alanylated wall teichoic acid content; (iii) *MprF* gain-in-function, leading to altered metabolism of lysylated phosphatidylglycerol; (iv) increased fluidity of the cell membrane; and (v) reduced susceptibility to prototypic cationic host defence peptides [49,58]. Thus, as previously mentioned, resistance of *S. aureus* to daptomycin is complex and appears to involve both multifactorial and strain-specific adaptive mechanisms. A very recent analysis has suggested that *dltA* overexpression represents the common pathway of resistance among genotypically different series of isolates

[15]. As such, it may represent the keystone of resistance to daptomycin in MRSA, leading to electrostatic repulsion and a reduction of autolysin activity. In addition, *mprF* mutations related to increased transcription may also play a role in this complex phenomenon [15,59,60].

Lastly, unlike what has been observed for most other antimicrobials, there has been no trend towards increased daptomycin resistance over a period of 8 years of a worldwide surveillance programme (2005–2012) [61]. In fact, daptomycin has remained highly active against *S. aureus* species worldwide, with no significant yearly or regional variations in daptomycin activity.

4.3. Clinical cases of daptomycin resistance

A literature search for reports of daptomycin resistance was carried out that identified 36 case reports and case series describing a total of 62 clinical cases (Table 1). Bacteraemia was the most common infection, reported in 36 cases, and was associated with endocarditis in 10 patients. Osteomyelitis was reported in 14 cases, whilst the remaining were due to a variety of conditions, including skin and soft-tissue infection in 4 cases, prosthetic joint infection in 2 cases, leg ulcer in 1 case and thrombophlebitis in 1 case. Endocarditis alone was documented in 6 cases, whilst co-morbidities were present in 25 cases. The reported time until development of daptomycin non-susceptibility varied widely, from 2 days to 14 months. Previous antibiotic use was reported in 60 of the 62 patients. Of these, previous vancomycin use was reported in 38 cases, whilst previous use of vancomycin or daptomycin was referred to in 15 cases. Previous teicoplanin administration was documented in two cases. Thus, the vast majority of cases of daptomycin resistance had been previously treated with a glycopeptide antimicrobial agent. Of the 30 cases with available information, 18 had received an initial dose of daptomycin that was ≤ 6 mg/kg/day, although in a few cases the dose had been increased subsequently. The majority of strains resistant to daptomycin were hVISA with an MIC for vancomycin between 1 mg/L and 2 mg/L (29 of the 39 for which information was available). Three cases had an MIC for vancomycin of 0.75–1.5 mg/L, whilst another seven cases, all from the same report, had a MIC for vancomycin of 0.5–4 mg/L. The vast majority of publications did not report on the mechanism of daptomycin resistance. In the four cases for which the mechanism of resistance was investigated, mutations were found in three cases and alterations in membrane integrity and fluidity was reported in another case. At least eight deaths were documented. Salvage treatment was reported in 22 cases; linezolid was most commonly employed and was used in 10 cases.

4.4. The role of daptomycin underdosage

Guidelines by the Infectious Diseases Society of America (IDSA) for the treatment of MRSA recommend consideration of high-dose (10 mg/kg) daptomycin in patients with persistent MRSA bacteraemia associated with vancomycin failure [97]. However, some studies have demonstrated that there is marked variability in the pharmacokinetics of daptomycin in acutely ill patients despite the use of current recommended doses [98,99]. A recent investigation found high augmented clearance of daptomycin in a subset of critically ill patients and significantly lower drug exposures with the use of standard doses [100]. In light of these results, these authors suggested that higher doses are likely necessary at the onset of therapy in critically ill patients, and that daptomycin dosing merits further study. Others have commented that the presence of sepsis may cause a reduction in the probability of target attainment and cumulative fraction of response that could favour the use of weight-based dosing [101]. At any rate, dosing of daptomycin, during the first days of administration, may require careful revision of dosing

Table 1
Clinical reports of daptomycin (DAP) resistance.

Reference/location	Case description (n)	Age (years) and co-morbidities	Previous treatment with glycopeptides	Dosage of DAP	Time until development of non-susceptibility after usage (days)	DAP MIC shift	Strain characteristics	Salvage treatment	Resistance mechanism
Rezai et al., USA [62]	Bacteraemia and osteomyelitis (2)	NA	NA	6 mg/kg	NA	NA	NA	NA	ND
Mangili et al., USA [63]	Septic thrombophlebitis (1)	54/cirrhosis	VAN	4 mg/kg initial and after 4 days 6 mg/kg	28	Susceptible by KB to 2 mg/L	MRSA	LNZ and then VAN + GEN Death	ND
Hayden et al., USA [64]	Osteomyelitis (2)	86/total knee replacement; 61/IHD	VAN	6 mg/kg	35; 42	0.25–4 mg/L; 0.5–4 mg/L	MRSA (27 strains in the two cases, unrelated by PFGE, hDAP by PAP; one strain hVISA)	NS; DAP	ND
Vikram et al., USA [65]	Bacteraemia, vertebral osteomyelitis (1)	52/DM, micronodular cirrhosis of the liver, pulmonary fibrosis	VAN	6 mg/kg	28	0.5–4 mg/L	MRSA (5 isolates). VAN MIC 2–4 mg/L	LNZ, Q/D, RIF. Death	ND
Hirschwerk et al., USA [66]	Bacteraemia (1)	92/permanent pacemaker	VAN	7 mg/kg	42	0.75–2 mg/L	MRSA (5 serial isolates). VAN MIC of 2 mg/L; all related isolates	NA. Death	ND
Marty et al., USA [67]	Bacteraemia and probable vertebral osteomyelitis, immunocompromised (1)	61/bone marrow transplant	LNZ first, after VAN and GEN	6 mg/kg	20	0.25–4 mg/L	MRSA (4), all equal by PFGE	LNZ and then VAN + RIF	ND; lower bactericidal activity by time-to-kill experiments
Skiest, USA [68]	Septic arthritis and bacteraemia (1)	64/DM, obesity, breast cancer in remission	VAN	Initial dose 8 mg/kg followed by 6 mg/kg	28 weeks over the course of 2 years	? to 4 mg/L	Initial MRSA infection; after amputation the patient developed an MRSA infection. Another MRSA MRSA isolates	LNZ	ND
Tsukimori et al., Japan [69]	Aortic prosthesis infection (1)	45/aortic aneurysm	VAN	6 mg/kg/day	10	? to >1 mg/L	MRSA isolates	LNZ and CLI	ND
Mariani et al., USA [70]	Bacteraemia and prosthetic joint infection (1)	64/total hip replacement	VAN	1 g i.v. q12h	46	0.5–8 mg/L	MRSA. VAN MIC 4 mg/L	NA	ND

Table 1 (Continued)

Reference/location	Case description (n)	Age (years) and co-morbidities	Previous treatment with glycopeptides	Dosage of DAP	Time until development of non-susceptibility after usage (days)	DAP MIC shift	Strain characteristics	Salvage treatment	Resistance mechanism
Julian et al., USA [71]	Prosthetic aortic valve, bacteraemic pacemaker and endocardial abscess (1)		VAN (trough levels were low)	NR		1–4–8 mg/L	MRSA (29 isolates) all related by PFGE hVISA/VISA		MprF I420N mutation in three of six strains sequenced
Huang et al., Taiwan [72]	Bacteraemia and endocarditis (1)		VAN (25 mg/kg) and TEIC (300 mg every 3 days)	6 mg/kg	2	1–4 mg/L	MRSA (11 related isolates). VAN MIC 1–4 mg/L	LNZ	ND
Murthy et al., USA [73]	Endocarditis (1)	40/IVDA with chronic HCV	VAN	6 mg/kg	10	1–3–4 mg/L	MRSA (4 related isolates by PFGE). USA300, PVL-positive clone	VAN + GEN + RIF	MprF T345A mutation found
Bennett et al., USA [74]	Bacteraemia and suspected UTI (1)		LVX (500 mg daily). VAN 1 g OD or b.i.d. with monitoring of serum concentration	6 mg/kg	21	0.5–4 mg/L	MRSA (5 related isolates by PFGE); USA100 clone; VAN MIC 0.75–1.5 mg/L, all strains were tolerant	DAP (8 mg/kg) + GEN	ND
Sakoulas et al., USA [75]	Bacteraemia and mitral valve endocarditis (1)	NS	LVX; VAN + GEN	NA	15	0.125–2 mg/L	MSSA (4 isolates). VAN MIC 2 mg/L	NAF + GEN	ND
Kuo et al., Taiwan [76]	Heart transplantation and suspicious post-operative sternum osteomyelitis (1)		VAN (750 mg twice a week); long-term treatment OD TEIC (200 mg daily). LNZ 600 mg daily	250 mg daily	ca. 5 months	0.5–2 mg/L	MRSA (12 related strains); 8 of 12 VISA	Died	ND
Sharma et al., USA [77]	Bacteraemia and IE (4) and osteomyelitis (2)	NS/DM, valvular heart disease	VAN alone and in combination	NA	5–21	0.125–0.5–2–4 mg/L	MRSA. VAN MIC 1–2 mg/L	VAN, RIF, GEN, SXT. Death	ND
Tenover et al., USA [78]	Bacteraemia and endocarditis (1)	60/IHD, DM	VAN (1 g/12 h)	6 mg/kg q48h	10 weeks	NR	MRSA (4 related isolates). VAN MIC 2–8 mg/L	SXT + Q/D and LNZ	ND
Cunha and Pherez, USA [79]	Bacteraemia and mitral valve endocarditis (1)		VAN (1 g/12 h, followed by 500 mg q24h for 4 days)	6 mg/kg for 7 days after high-dose 12 mg/kg q48h	NS	0.5–2 mg/L	MRSA (2 strains). VAN MIC between 1 and 2 mg/L	DAP + RIF. Death	ND

Kuo et al., Taiwan [80]	Bacteraemia (1)		VAN (1 g/12 h); FLZ (400 g/day for 10 days) and then AmB 30 mg/day and later CAS 50 mg/day	350 mg/24 h	17 weeks	0.5–2 mg/L	MRSA (10 related strains by PFGE). VAN MIC 2–4 mg/L (already resistant to DAP before exposure to the drug)	Death	ND
Kirby et al., UK [81]	CVC-associated infections and endocarditis (1)	41/chronic renal failure requiring haemodialysis	VAN + RIF TEIC FA	6 mg/kg	14 months	0.25–4 mg/L	MRSA (6 related strains as determined by PFGE, clone MRSA-15). All strains were hVISA and after VISA (VAN MIC 1–4 mg/L and TEIC MIC 1–16 mg/L)	TMP + RIF	ND
Hsu et al., Singapore [82]	Bacteraemia (6)		VAN	NR	2 weeks	0.19–4 mg/L	MRSA (19 strains; 4 strains of ST5 MRSA II clone; 14 strains of ST239-MRSA III clone, all related by PFGE); hVISA develop during glycopeptide therapies	NR	ND
Lee et al., Taiwan [83]	Bacteraemia, septic arthritis, vertebral osteomyelitis (1)	59/lymphoma	TEIC	12 mg/kg/day	17	0.5–4 mg/L	MRSA. VAN MIC 2 mg/L. hVISA	LNZ and CEF	ND
Mammina et al., Italy [84]	Leg ulcer (1)	30/congenital arteriovenous malformation	GEN SXT TEIC + GEN	Topical	30	8 mg/kg	Multiple MRSA ST398 isolates, all belonging to the same PFGE profile. hVISA	Surgical therapy	ND
Boyle-Vavra et al., USA [85]	Recurrent bacteraemia (1)		VAN and TZP	6 mg/kg	21	<0.25–2 mg/L	MRSA (2 isolates; related by PFGE and identified as USA800; ST5, agrII, SCmec IVa). VAN MIC 1–2 mg/L	VAN + LVX. Death	Point mutation in <i>mprF</i> gene (S337L)
Kelley et al., Australia [86]	In vitro study on hVISA and VISA MRSA isolates								

Table 1 (Continued)

Reference/location	Case description (n)	Age (years) and co-morbidities	Previous treatment with glycopeptides	Dosage of DAP	Time until development of non-susceptibility after usage (days)	DAP MIC shift	Strain characteristics	Salvage treatment	Resistance mechanism
van Hal et al., Australia [87]	Persistent bacteraemia secondary to vertebral osteomyelitis (1)	66/IHD, DM and COPD	VAN, LNZ, Q/D, TIG	No DAP	56	0.25–2 mg/L	MRSA (8 isolates, all related and identified as ST239-MRSA-III)	ND	ND
Chen et al., Taiwan [88]	Bacteraemia and ICD device-related endocarditis (1)	28/paroxysmal ventricular tachycardia	VAN, LNZ TEIC	6 mg/kg after 9 mg/kg and 12 mg/kg in combination with i.v. FOS 6 g/6 h	94	0.25–1 mg/L	MRSA (7 isolates, with the exception of the first and the last isolates, all were related by PFGE)	DAP high-dose plus FOS	ND
Kirby et al., UK [89]	Tricuspid valve endocarditis (1)	35/IVDA	TEIC and RIF	NR	7	0.19–4 mg/L	Group G streptococcus and MRSA (2) with TEIC MIC at 8 mg/L CA-MRSA defined as PVL-positive and CIP-susceptible	CIP + LNZ	ND
Rose et al., USA [108]	Endocarditis (1)	NS/ESRD with haemodialysis, DM and obesity	DAP	6 mg/kg followed by 10 mg/kg	NR	0.75–2 mg/L	MRSA (n = 4, all related by spa typing t002 and ST5). VAN MIC of 4 mg/L VISA	DAP high-dose + ceftaroline	Membrane integrity and fluidity
Sivakumar et al., Australia [90]	Prosthetic joint infection (1)	82/cardiac history and MRSA-positive at admission	VAN VAN + GEN TEIC for the hVISA	NR	42	MIC not reported but under TEIC the hVISA became DAP-resistant	Polymicrobial with MRSA (n = 3, the last was hVISA)	PRI + CIP	ND
Yu et al., Canada [91]	Endocarditis (1)	75/type II DM, obesity, hypertension, aortic valve replacement	VAN	6 mg/kg	37	1–>4 mg/L	MRSA (3 strains). VAN MIC 2–4 mg/L hVISA to VISA	NR	ND
Levy et al., USA [92]	Left ventricular device infection (1)	40/alcoholic-related cardiomyopathy	VAN DOX	8 mg/kg, RIF and GEN	NS	0.25–1.5 and 8 mg/L	MRSA (6 strains all related by PFGE); all strains were hVISA; SCCmec II	LNZ and SXT	ND

Jongsma et al., USA [93]	Endocarditis and osteomyelitis (1)	50/DM and chronic active HCV; multiple MRSA infections treated with VAN	VAN and TZP	8 mg/kg, plus RIF	22	0.38–3 mg/L	MRSA (3 strains). VAN MIC 1–2 mg/L	Ceftaroline	ND
Velazquez et al., USA [94]	10 cases as follows: 4 SSTIs 2 native valve endocarditis 2 osteomyelitis 1 abdominal abscess 1 respiratory colonisation	8 of 10 had a significant medical history; 2 were healthy	7 of 10 received VAN or DAP previously; 2 never received DAP	NS	NS	2–4 mg/L	MRSA (8 strains; VAN MIC between 1.5 and 2 mg/L). MSSA (2 strains). All MRSA were typed and were USA600, USA300, USA100 and USA500. Almost unrelated	Different	ND
Dortet et al., France [95]	Right-sided IE (1)	55/COPD	AMC and LVX LNZ	7 mg/kg and after 16 mg/kg	68	0.25–2 mg/L	MRSA (3 isolates). VAN MIC 0.75–1.5 mg/L and RIF -resistant	VAN, GEN, LNZ	ND
Gasch et al., Spain [96]	Bacteraemia (7)	65–84/NS	VAN or DAP	8–10 mg/kg	NS	<0.5–2 mg/L	MRSA (7 unrelated isolates). VAN MIC 0.5–2 mg/L	NS	ND

MIC, minimum inhibitory concentration; NA, not available; ND, not determined; NS, not stated; VAN, vancomycin; KB, Kirby–Bauer test; MRSA, meticillin-resistant *Staphylococcus aureus*; LNZ, linezolid; GEN, gentamicin; IHD, ischaemic heart disease; PFGE, pulsed-field gel electrophoresis; hDAP, daptomycin-heteroresistant *S. aureus*; PAP, population analysis profile assay; hVISA, heterogeneous vancomycin-intermediate *S. aureus*; DM, diabetes mellitus; Q/D, quinupristin/dalfopristin; RIF, rifampicin; CLI, clindamycin; i.v., intravenous; q12h, every 12 h; NR, not reported; VISA, vancomycin-intermediate *S. aureus*; TEIC, teicoplanin; IVDA, intravenous drug abuse; HCV, hepatitis C virus; PVL, Panton–Valentine leukocidin; UTI, urinary tract infection; LVX, levofloxacin; OD, once daily; b.i.d., twice daily; MSSA, meticillin-susceptible *S. aureus*; NAF, naftcilin; IE, infective endocarditis; SXT, trimethoprim/sulfamethoxazole; q48 h, every 48 h; q24 h, every 24 h; FLZ, fluconazole; AmB, amphotericin B; CAS, caspofungin; CVC, central venous catheter; FA, fusidic acid; TMP, trimethoprim; CEF, cefpirome; TZP, piperacillin/tazobactam; SCCmec, staphylococcal cassette chromosome *mec*; COPD, chronic obstructive pulmonary disease; TIG, tigecycline; ICD, implantable cardioverter-defibrillator; FOS, fosfomycin; CA-MRSA, community-associated MRSA; CIP, ciprofloxacin; ESRD, end-stage renal disease; PRI, pristinamycin; DOX, doxycycline; SSTI, skin and soft-tissue infection; AMC, amoxicillin/clavulanic acid.

strategies. This is also in consideration that higher fixed doses may be associated with greater toxicity [101]. However, identification of the optimal dosing regimen for daptomycin will require comparative studies that directly examine a fixed-dose regimen with one based on weight.

Considering the potential for daptomycin toxicity at increased doses, a study by Kullar et al. on infective endocarditis, in which 70 patients received high-dose daptomycin (defined as ≥ 8 mg/kg/day), reported that all patients had successful outcomes [102]. Moreover, no patient required discontinuation of high-dose daptomycin due to creatine phosphokinase elevations. Indeed, it has been further reinforced that a dose of daptomycin of ≥ 8 mg/kg/day is needed for treatment of infective endocarditis [103]. None the less, potential underdosing of daptomycin remains a significant clinical problem that warrants further investigation.

5. Combination therapy with daptomycin and β -lactams

Combination therapy can be used to provide broad-spectrum antimicrobial coverage, to increase the likelihood of clinical success, and to treat infections caused by drug-resistant pathogens. It may also decrease the probability of emergence of resistance. Initial in vitro studies evaluated daptomycin in combination with several β -lactam antibiotics (reviewed in [104]). The majority of studies have focused on the clinically relevant combinations of daptomycin with either rifampicin or gentamicin. In general, it has been found that daptomycin does not adversely affect the activity of other antimicrobial agents when given concomitantly, and either additive or no effects have been seen with daptomycin combinations in vitro and in animal models. For some isolates of vancomycin-resistant enterococci, synergy has been observed when exposed to daptomycin and rifampicin, and unexpected synergy was demonstrated against MRSA by daptomycin in combination with β -lactams that is both strain- and drug-specific. In an in vitro of simulated endocardial vegetations [105], the combination of daptomycin plus trimethoprim/sulfamethoxazole appeared to be the most effective regimen against MRSA isolates, although the combination of daptomycin plus linezolid or cefepime also provided good antimicrobial activity. In that study, it was considered that such combination may provide a clinical option to treat daptomycin-non-susceptible MRSA. Further in vitro and in vitro studies have confirmed the potential utility of the daptomycin/ β -lactam combination in the treatment of MRSA [106].

Berti et al. studied adjunctive antimicrobial combinations with daptomycin in vitro and the emergence of daptomycin resistance over time using clinical isolates of daptomycin-susceptible MRSA [107]. Interestingly, cell wall thickening was observed for all antibiotic combinations regardless of their effect on the daptomycin MIC, whilst changes in cell membrane fluidity were variable and dependent on the combination used. It was further found that the emergence of daptomycin resistance in MRSA strains was strongly influenced by the presence of subinhibitory concentrations of the adjunctive agents used. Further evidence for the potential use of daptomycin plus β -lactam therapy comes from a report in which the addition of ceftaroline to daptomycin after emergence of daptomycin-non-susceptible *S. aureus* during therapy improved the antibacterial activity [108]. In that study, combination therapy with daptomycin and ceftaroline restored daptomycin sensitivity in vivo and resulted in clearance of persistent blood cultures. In vivo- and in vitro-derived daptomycin resistance resulted in *S. aureus* with more fluid cell membranes, although after ceftaroline was added to the model fluidity was restored to the level of the initial isolate.

Clinically, daptomycin in combination with either nafcillin or oxacillin was used to successfully treat seven cases of refractory

MRSA bacteraemia. In that report, it was further seen that there was a definite increase in daptomycin binding to the surface cells co-treated with the β -lactam antibiotic [109]. More recent in vitro studies have confirmed the validity of the daptomycin/nafcillin combination in enhanced killing of MRSA isolates [110,111].

In 2013, Moise et al. carried out a multicentre evaluation of daptomycin with and without concomitant β -lactams in patients with *S. aureus* bacteraemia and mild-to-moderate renal impairment [112]. This is of relevance since patients with underlying renal disease may be vulnerable to vancomycin-mediated nephrotoxicity. In 106 patients, treatment success with daptomycin was 81%, whilst the overall efficacy was somewhat increased by the addition of a β -lactam antibiotic (87% vs. 78%; $P = 0.336$). However, this trend was most noticeable for bacteraemia associated with endocarditis or bone/joint infection or bacteraemia from an unknown source (90% vs. 57%; $P = 0.061$). Accordingly, it was suggested that the efficacy of daptomycin treatment might be improved with β -lactam combination therapy in primary endovascular and bone/joint infections. Whilst promising in combination with β -lactams, it is clear that additional studies are warranted in order to better understand the clinical efficacy of daptomycin combinations.

6. Lessons for the future

As mentioned in Section 4.3, in clinical cases the reported time until development of daptomycin non-susceptibility varied widely, from 2 days to 14 months; however, the most typical scenario for development of non-susceptibility appeared to be ca. 20–45 days following previous treatment with vancomycin, notwithstanding the extremely large variability. Moreover, cases with very short and very long times to development of non-susceptibility all reported previous vancomycin use. However, the exact duration of previous treatment was not clearly indicated in all reported cases and thus it is not possible to reach a more general conclusion in this regard. It would appear that hVISA or VISA strains almost always develop heteroresistance prior to developing resistance to daptomycin. This stresses the importance of determining the MIC when using vancomycin to treat a patient with severe *S. aureus* infection [30]. In addition, in selected cases, e.g. when therapeutic failure is suspected, testing for hVISA may also be necessary. In fact, analysis of the published cases would suggest that the predisposition to developing hVISA and VISA has a definitive negative impact both on therapy and outcomes, despite reports that there is no association between infection with hVISA strains and increased mortality [32]. From this systematic review of published clinical cases, it is possible that some MRSA clones more than others become hVISA during prolonged bacteraemia, which predisposes them to development of resistance to daptomycin. Further evidence may confirm these observations in the future.

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