Future directions with daptomycin

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Daptomycin is the first new natural-product antibiotic launched in a generation. It was licensed first for skin and soft tissue infections (SSTIs) and, more recently, for staphylococcal bacteraemia and endocarditis. Further clinical trials are in progress, some investigating performance in subsets of SSTIs while others, more interestingly, are evaluating efficacy in enterococcal endocarditis and neutropenic fevers—settings where the compound’s bactericidal activity is potentially advantageous. There is a need for further trials in bone and joint infections. On the negative side, there are several reports of mutational resistance emerging during the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections, mostly in settings with a heavy bacterial load, and there is a need to determine whether higher dosages or combination regimens will reduce this risk. A few patients have already been treated with doses of up to 12 mg/kg. Lastly, daptomycin is entering a market increasingly crowded with new anti-Gram-positive agents. More work is required to establish those settings where daptomycin and other new compounds offer real advantages over established glycopeptides and over each other. There is presently a paradox whereby vancomycin is agreed to be less than ideal, with outcomes impaired against MRSA with modestly raised MICs, but where new agents have yet to demonstrate unequivocal superiority.

Keywords: Gram-positive infections, MRSA, enterococci, *Staphylococcus aureus*

Introduction

Daptomycin is the first natural-product antibiotic launched in a generation. It was investigated by Eli Lilly and Co. in the mid-1980s, but their twice-daily dosing regimen was associated with muscle weakness, resulting in development being abandoned. Daptomycin was then out-licensed to Cubist, who re-evaluated it in a 4 mg/kg once-daily regimen for skin and soft tissue infections (SSTIs). These trials showed equivalence to isoxazolyl penicillins and vancomycin, without significant toxicity, supporting US and EU product licenses in 2003 and 2006, respectively. A subsequent trial, at 6 mg/kg, showed equivalence to vancomycin or isoxazolyl penicillins plus gentamicin for staphylococcal bacteraemia and endocarditis, again without toxicity. The FDA granted a general license for these indications, whereas the European Medicines Evaluation Agency licensed specifically for staphylococcal bacteraemia arising from SSTIs and for right-sided staphylococcal endocarditis. Pneumonia trials found inferiority to ceftiraxone, apparently owing to the inactivation of daptomycin by lung surfactant. Daptomycin entered use with consistent MICs of 0.25–1 mg/L for *Staphylococcus aureus*, 0.12–1 mg/L for coagulase-negative staphylococci, 0.06–1 mg/L for α-haemolytic streptococci, 0.06–0.5 mg/L for β-haemolytic streptococci, 0.25–1 mg/L for *Enterococcus faecalis* and 0.5–4 mg/L for *Enterococcus faecium*. Selection of resistance is difficult in vitro, but was seen in 6/120 daptomycin-treated patients in the bacteraemia and endocarditis trial, in which MICs rose from 0.25 or 0.5 to 4 mg/L.

This experience forms the background for assessing daptomycin’s future. Predictions (always with Bohr’s proviso that ‘Prediction is very difficult, especially when it concerns the future’) must also take account of the increasingly crowded market for anti-Gram-positive antibiotics.

Future targets for daptomycin

Several clinical trials are ongoing or planned with daptomycin (http://www.clinicaltrials.gov) (Table 1). Among the most interesting are those examining enterococcal endocarditis and neutropenic patients; both settings where daptomycin’s rapid bactericidal activity is potentially advantageous. Enterococcal endocarditis is as frequent as its staphylococcal counterpart, and the resistance-driven need for new therapies is even greater, as large proportions of *E. faecalis* and *E. faecium* isolates from endocarditis have high-level resistance to both gentamicin and streptomycin, precluding the synergy upon which standard therapy depends. In these cases, BSAC guidelines suggest

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<table>
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<td>historical controls receiving vancomycin</td>
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<td>proportion of patients receiving antimicrobial prophylaxis within appropriate time-frame before surgical incision; infection rate</td>
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<tr>
<td>Catheter-related Gram-positive bloodstream infections</td>
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<td>—</td>
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high-dose ampicillin, noting vancomycin as an alternative if the organism is susceptible. Some American and continental European authorities suggest ampicillin combined with ceftriaxone.11 None of these regimens is ideal: over 80% of \( E. \) faecium require ampicillin MICs of 32–64 mg/L; the basis of any ampicillin/ceftriaxone synergy is unclear and vancomycin is compromised by frequent resistance in \( E. \) faecium, is poorly cidal and has unproven efficacy as monotherapy in endocarditis.

Daptomycin—with its rapid cidality and proven efficacy in staphylococcal endocarditis—appears attractive in comparison, at least against \( E. \) faecalis, for which its MICs are little higher than for \( S. \) aureus.6 Its potential is less certain against \( E. \) faecium, where MICs commonly range up to 4 mg/L, coinciding with values for ‘resistant’ \( S. \) aureus mutants selected in treatment failures.

Case reports of daptomycin therapy of enterococcal endocarditis present a mixed picture and are subject to publication bias. Segreti et al.12 treated 11 patients with endocarditis and/or bacteraemia due to vancomycin-resistant enterococci (VRE), using daptomycin at 6 mg/kg and recorded five full resolutions and six deaths. This 45% resolution rate compared with full resolution in all of 11 patients similarly treated for methicillin-resistant \( S. \) aureus (MRSA) bacteraemia and endocarditis. A registry analysis13 recorded success with daptomycin at 4–7 mg/kg in 9/12 patients with left-sided and 1/2 with right-sided enterococcal endocarditis, compared with 9/15 and 5/8 for left- and right-sided staphylococcal endocarditis, respectively. These are impressive results, allowing the difficulty of treating left-sided endocarditis. On the other hand—and again with all the issues of publication bias—the recent literature includes several case reports of failure in enterococcal endocarditis, some with selection of resistance.14–16

A key issue in context is whether daptomycin should be given as monotherapy, as in the staphylococcal endocarditis trial, or together with standard anti-enterococcal agents, as in the Cornell University enterococcal trial (Table 1). While there is little evidence of synergy between daptomycin and other compounds, there is no evidence of antagonism. The most obvious combination agent is ampicillin, and we are aware of one cure of \( E. \) faecalis endocarditis with this combination (HPA, data on file). There is also a case report describing successful use of tigecycline plus daptomycin for \( E. \) faecium endocarditis.17 These possibilities deserve full study, as does the critical issue of whether the daptomycin dosage can safely be increased. The Cornell trial is using daptomycin at 8 mg/kg, whereas a trial in SSTIs (Table 1) is using 10 mg/kg. A volunteer study found daptomycin to be well tolerated at up to 12 mg/kg for 14 days.16 If these regimens prove safe, without muscle weakness or other side effects, then they should do much to bring even \( E. \) faecium endocarditis into range and may mitigate against selection of resistant mutants (discussed subsequently). Registry data and conference posters also detail a few patients who have received daptomycin at over 6 mg/kg and up to 12 mg/kg for the treatment of infections,19,20 without toxicity, but the numbers are small.

Two of the trials listed in Table 1 examine activity in neutropenic fevers. Here, again, there are reasons to be optimistic about daptomycin, based on its cidality and on the fact that the most important Gram-positive pathogens in this setting are staphylococci and viridans group streptococci, all of which are susceptible at \( \leq 1 \) mg/L. Depending on the unit, vancomycin-susceptible and
-resistant enterococci may be important, and here, as in endocarditis, much depends on whether it is possible to increase the dosage to cover *E. faecium*. The licensing trial in *S. aureus* bacteremia and endocarditis excluded ‘severely’ leucopenic patients. A small emergency-use programme treated nine neutropenic patients with bacteremia caused by VRE using daptomycin at 4 or 6 mg/kg, recording four cures and five failures, including two deaths early in treatment, before any clinical response could be expected.21

Several trials listed in Table 1 are Phase IV studies seeking to further inform use in SSTIs. Patient groups under study include those with cellulitis or erysipelas, necrotizing infections and renal insufficiency. One straightforward trial, relevant to European practice, has teicoplanin, a drug not licensed in the USA, as the comparator rather than vancomycin; another, perhaps more interesting and less predictable, is examining whether 4 days of high-dose (10 mg/kg) daptomycin is as effective as 7–14 days of vancomycin, while avoiding toxicity. If successful, this would point to a potential for earlier patient discharge and, as discussed later, should ensure drug levels above the MICs for first-step mutants. Even with a standard 4 mg/kg regimen, daptomycin allowed for earlier patient discharge than vancomycin in one study of SSTIs, reducing infection costs from $7552 per patient to $5027.22

Just one trial listed in Table 1 addresses osteomyelitis—specifically in prosthetic joint replacements. Bone and joint infections surely warrant wider investigation, given both their numbers and associated morbidity.23 At present, there are *in vitro* studies showing that daptomycin has activity against slow-growing sessile bacteria in stratified biofilms,24,25 as on a contaminated prosthetic device. However, there is a lack of published bone penetration or activity studies, and clarification is urgently needed, not the least because the compound’s activity is affected by the calcium ion concentration.26 A review of daptomycin use in bone and joint infections considered 12 individual case reports and three series, with the latter representing 53 patients.27 Most patients had staphylococcal infections and many had failed on standard therapy, meaning that the sample was non-random. The case series, with daptomycin at 4–6 mg/kg every 24 h or every 48 h, recorded cures in 43/53 cases, with 37.4 days of treatment on average. All 23 patients with osteomyelitis were cured, against 12/20 with joint arthroplasty infection. A caveat was that many patients underwent further surgery, with joint removal or debridement, which may have influenced outcome. Despite prolonged therapy, only two patients in the case series suffered significant side effects, with nausea in one and elevated creatinine phosphokinase in the other. There was no need to discontinue daptomycin therapy in any patient. Resistance emerged in just 1 of the 53 case-series patients, from whom a *Staphylococcus* isolate with an MIC of 4 mg/L was obtained; however, resistance was mentioned as emerging in 5 of the 12 individual case reports, leading the review’s authors to express concern about this risk. Animal studies support efficacy in orthopaedic infections; both daptomycin and vancomycin achieved 100-fold reductions in bacterial load over 21 days, in a rat osteomyelitis model. Nevertheless, neither regimen reliably eradicated infection.28

Owing to its thermostability, daptomycin can be incorporated into polymethylacrylate beads, where it shows similar release kinetics to vancomycin.29 Such beads, containing daptomycin 7.5% by weight, gave local bone concentrations of up to 178 mg/g in a rat osteomyelitis model and maintained levels above 10 mg/g for over 10 days; similarly loaded vancomycin beads achieved a peak of 49 mg/g and maintained levels above 10 mg/g for <8 days.28 Daptomycin-containing beads have yet to be used in human orthopaedic infections, but their successful use was reported in four patients with lower-limb prosthetic vascular graft infections;30 vancomycin- and tobramycin-containing beads were used in other patients, but numbers were too small for meaningful comparison.

Such beads, or daptomycin-containing bone cement, might be used prophylactically in orthopaedic or vascular graft surgery, as currently with gentamicin cement. More controversially, intravenous (iv) daptomycin might be used prophylactically in high-risk surgical patients, particularly MRSA carriers, and one trial detailed in Table 1 examines its performance in coronary bypass patients. Vancomycin is already widely employed in MRSA-risk patients undergoing vascular or orthopaedic surgery,31 even though: (i) there is little evidence of its efficacy in this role; and (ii) as an essentially bacteriostatic agent, it is not a logical choice for single-dose prophylaxis, where the aim is rapidly to reduce the numbers of contaminating bacteria. Daptomycin’s bactericidal activity should offer greater potential, and its relatively long half-life would be advantageous if surgery was delayed or prolonged. Nevertheless, there will be an understandable reluctance to advocate early use of a new-class antibiotic for prophylaxis.

**Resistance risks for daptomycin**

Case reports of emerging resistance to daptomycin have already been reported.3,14–16,32 Most relate to deep-seated infections, particularly endocarditis, where there is a heavy bacterial load. Few concern SSTIs, where daptomycin is most used and where the bacterial load is typically lower.

While no antibiotic launched to date has escaped resistance, the early reports for daptomycin are surprising, allowing that it is extremely difficult to select resistance *in vitro*. This recapitulates a pattern seen with linezolid, where, again, resistance is hard to select on agar but was reported as emerging in a few early clinical cases—mostly in enterococci rather than MRSA.33 Perhaps, the clearest conclusion is the poor predictive power of the mutant selection tests routinely sought by companies and regulators.

Various cell surface changes and mutations have been associated with daptomycin resistance, including: (i) increased membrane fluidity; (ii) increased translocation of phospholipid lysyl-phosphotidyglycerol to the outer leaflet of the membrane and, perhaps contingent upon this, an increased positive charge to the bacterial surface; (iii) reduced susceptibility to daptomycin binding and to consequent membrane depolarization and permeabilization; and (iv) increased resistance to cationic host defence peptides, including human neutrophil peptide 1 and thrombin-induced platelet microbicidal protein 1.34,35 There is a curious association between intermediate resistance to vancomycin in MRSA (MICs > 4 mg/L) and slightly raised daptomycin MICs (0.5–2 mg/L, rather than the typical 0.25–0.5 mg/L).36,37 It may be that the thickened cell wall of such ‘VISA’ (vancomycin-intermediate *S. aureus*) strains impedes access of daptomycin to the membrane surface, acting as a ‘depth filter’,
or that these uncommon and often unstable bacteria have other unsuspected membrane changes.

In general, MICs for the resistant *S. aureus* mutants selected during daptomycin therapy are 2–4 mg/L, compared with 0.12–0.5 mg/L for their parent strains. There are several ways in which the risk of selection might potentially be minimized, although none has been formally evaluated. First, it should not be assumed that daptomycin (or any other agent) will be effective in conditions in which surgery is warranted. In this context, it is suggested, at least in retrospect, that most or all of the six endocarditis trial patients in whom resistant MRSA mutants were selected should have undergone debridement.3 Secondly, it may be possible to increase the dosage of daptomycin, achieving serum levels inhibitory for first-step mutants. Trials now in progress with daptomycin at 8–12 mg/kg (Table 1) are relevant here, particularly since resistant MRSA mutants were selected under a 6 mg/kg regimen in a rabbit endocarditis model, but not when this was increased to 10 mg/kg.38 One pharmacodynamic model suggested that the risk of selecting resistant mutants should be reduced by a 10 mg/kg dosage—though the caution needed for such prognostications is underscored by another, which, contrary to subsequent experience, asserted that a dose of 6 mg/kg should maintain levels above the ‘mutant selection window’.13

Gene transfer constitutes an unpredictable long-term threat to daptomycin, as shown by the seminal studies of D’Costa et al.,46 who examined soil streptomyces for the ability to degrade antibiotics. To their surprise, they found that 80% of the 80 daptomycin-resistant strains examined could inactivate the compound in culture broths and speculated that there might be more than one destructive pathway. Soil streptomyces may have this ability either in order to compete with daptomycin-producing strains or because they use daptomycin-like molecules as metabolic regulators and need a mechanism to remove the excess regulator. This, though, is academic; what matters is that the resistance genes of streptomyces notoriously migrate to plasmids and transposons, which then spread into human pathogens. Thus, for example, actinomycetes are the source of the *erm* determinants of macrolide resistance41 and of the genes encoding several aminoglycoside-modifying enzymes.42 It is to be feared that the same ‘escape’ will occur with the genes conferring resistance to daptomycin, but there is no certainty of it, and there is no predictable time scale. D’Costa also found that 41% of the 49 rifampicin-resistant streptomyces could inactivate rifampicin and 7% of the 128 macrolide-resistant strains inactivated erythromycin; however, inactivation of rifampicin has not been described in clinical isolates, and macrolide inactivation (in contrast to target modification or efflux) remains unknown in Gram-positive pathogens.

**Putting daptomycin into context**

Lastly, it should be said that daptomycin is not being launched in a vacuum, but into a market increasingly crowded with anti-Gram-positive agents (Table 2), all of them first evaluated in SSTIs, with trials confirming non-inferiority to glycopeptides. None of these compounds has yet shown unequivocal clinical superiority over vancomycin in this setting, though advantages have been shown for secondary outcomes, such as earlier discharge.22 Unless and until one does show superiority, the market agents seem likely to be fragmented between compounds and companies.

Perhaps, the biggest differentiating factor in daptomycin’s favour—already stressed—is its rapid cidality, which should be an advantage in endocarditis and immunosuppressed patients. The only other antistaphylococcal agents with similarly rapid killing are the dual-action glycopeptides, telavancin and oritavancin,34,44 while the anti-MRSA cephaporphins, cefotiboprole and ceftaroline, belong to a chemical class generally agreed to have adequate cidality in any patient type.36 In contrast, dalbavancin has the slow cidality of classical glycopeptides, linezolid and tigecycline are bacteriostatic, and quinupristin/dalfopristin is cidal only if the isolate is not constitutive for MLSB.36

There are settings where other compounds have the advantage. Daptomycin is inappropriate in pneumonia, owing to inactivation by lung surfactant,3 while there is evidence, from a subset analysis of two pooled trials, that linezolid is superior to vancomycin in MRSA pneumonia, though not in *S. aureus* pneumonia in general.47 Prospective trials are underway to confirm or refute this analysis, which was subjected to statistical criticism.48 In contrast to linezolid’s success in nosocomial pneumonia, tigecycline proved inferior to imipenem/cilastatin in the setting, specifically owing to poorer performance in the subset of patients with ventilator-associated pneumonia.39 The reasons remain unclear, but it is striking that many of the tigecycline failures were with MRSA and not with those Gram-negative pathogens, such as *Acinetobacter* and *Klebsiella* spp., where MICs are close to the breakpoint. Similarly, cefotiboprole proved inferior to linezolid/ceftazidime in patients with ventilator-associated pneumonia.50 This latter finding remains to be published in a peer-review format, and it is not clear whether it reflected behaviour against Gram-positive or -negative pathogens.

There is a lack of clinical trials for any of the new agents in bone and joint infections, despite their frequency, and despite the importance of MRSA in the setting. The potential of daptomycin was discussed earlier, and the compound deserves full investigation. Among other new agents, quinupristin/dalfopristin was extensively used in orthopaedic infections on a compassionate basis, with positive results.51 Nevertheless, no prospective trial was done and the compound is now little used owing to the need for a central line and its side effect profile, with frequent arthralgia and myalgia. There was early enthusiasm about linezolid in orthopaedic infections,52 with several positive case reports, but optimism has been dimmed by concern about side effects associated with the prolonged treatments typically needed for these infections, including irreversible optic neuropathy as well as reversible thrombocytopenia.53 These side effects make it unlikely that any formal trial will be undertaken. The other new compounds with *prima facie* potential in bone and joint infections are the once-daily, rapidly cidal, glycopeptides telavancin and oritavancin; also dalbavancin which, while not rapidly cidal, does have the major convenience of a once-weekly regimen.

Secondary features such as dosing convenience and the facility for outpatient use may be critical advantages. Daptomycin, like teicoplanin, is a once-daily parenteral drug, suitable for home iv use, whereas injectable compounds that need more frequent administration—e.g. vancomycin, tigecycline and the anti-MRSA cephaporphins—are less suitable. Other competitors may, however, be even more convenient:
linezolid has an established oral formulation; iclaprim has an oral formulation entering Phase II; and dalbavancin has a once-weekly iv regimen.

Perhaps most critical of all is the question of how perceptions of glycopeptide efficacy develop. When the new anti-Gram-positive compounds began to reach the market, their manufacturers saw vancomycin as a ‘soft’ target; poorly bactericidal, requiring expensive monitoring and with significant toxicity. In reality, vancomycin has proved tough to beat because: (i) none of the new agents has shown unequivocal superiority; (ii) many clinicians are innately conservative in a time of concern about resistance; and (iii) the acquisition cost is low, though this is offset by the costs of the serum monitoring needed for vancomycin.

Recently, several American studies have found that the performance of vancomycin diminishes markedly in severe infections as the MIC for MRSA exceeds 0.5 or 1 mg/L, even though CLSI and EUCAST susceptible breakpoints are ≤ 2 and ≤ 4 mg/L, respectively (Table 3). Such observations remain to be confirmed for the EMRSA-15 and -16 clones that dominate in the UK and it remains to be established whether vancomycin’s efficacy diminishes so markedly when it is combined with rifampicin, which may improve outcomes versus EMRSA-15.

Some authors suggest that the MICs of vancomycin for staphylococci are creeping upwards. Table 4 shows the vancomycin MIC distributions for MRSA collected in the BSAC bacteraemia surveillance from 2001 to 2006; further analysis (data not shown) indicates that the geometric mean MICs drifted from 0.78 mg/L in 2001 to 1.28 mg/L in 2006, but we are cautious of giving significance to this trend because: (i) there were

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<th>Vancomycin success (%)</th>
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<td>≤0.5</td>
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<td>56</td>
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<td>21</td>
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in Table 3. Vancomycin and MRSA bacteraemia: clinical outcomes in relation to MIC, from Sakoulas et al.54
similar drifts in the MICs for methicillin-susceptible *S. aureus* on Iso-Sensitest agar; and (ii) there was no equivalent rise in vancomycin MICs determined on DST (‘Diagnostic Sensitivity Test’) agar supplemented with lysed blood. On this basis, we believe that the drift more probably reflects changes in the formulation of Iso-Sensitest agar, as previously associated with rises in aminoglycoside MICs for *Pseudomonas aeruginosa*.61

### Conclusions

Treatment options for infections due to staphylococci and other Gram-positive bacteria are expanding rapidly, and the challenge is to determine whether and when these new options offer advantages. All these new agents have undergone or are undergoing trials in SSTIs, but daptomycin is unique in having been evaluated—with promising results—in staphylococcal bacteraemia and endocarditis.3 Its efficacy here reflects its bactericidal activity, and it is encouraging that trials are underway in other settings where this may be an advantage, notably enterococcal endocarditis and neutropenic fevers. Daptomycin’s utility in orthopaedic infections deserves early investigation, as a combination of cidality and activity against biofilms suggests potential.

While emerging resistance is rare, the scatter of reports in settings with high bacterial loads is of concern.32 To minimize the risk, three steps are advised: first to explore the potential for higher dosage, guaranteeing levels above a ‘mutant prevention concentration’; secondly, to recognize patients where surgical debridement is warranted; and thirdly, to prevent cross-infection with resistant organisms. Limited registry and volunteer data suggest that it may be possible to use daptomycin at significantly higher doses than the present 4–6 mg/kg, but side effects remain to be evaluated in large-scale clinical trials.

Finally, the background is changing in at least three ways, and these will affect the future of daptomycin and other new anti-Gram-positive agents. First, perceptions of vancomycin are changing, with growing doubt about its efficacy against MRSA isolates with MICs at the high end of the ‘susceptible’ range. Secondly, there have been recent and welcome falls in the incidence of MRSA bacteraemia in England.62 Thirdly, there is the emergence of new MRSA strains, particularly in the USA; these spread first in the community, causing infections associated with vigorous physical contact,63 but have now begun to disseminate in hospitals.64 These, and other future changes, will undoubtedly lead to changes in the demands placed upon antibiotics in the years to come.

### References


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**Daptomycin in the future**

Table 4. Vancomycin and MRSA bacteraemia: MIC distribution of vancomycin for MRSA from bacteraemias in the UK, from the BSAC bacteraemia surveillance, 2001–0660

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