Pre-clinical experience with daptomycin

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Daptomycin is a broad-spectrum, bactericidal agent active against Gram-positive bacteria, acting largely and unusually through membrane depolarization. Activity is markedly affected in vitro by the availability of calcium ions, and its high molecular weight with associated poor diffusion means that conventional disc diffusion testing is not reliable (and as a consequence not available). In order to allow susceptibility categorization, it is recommended that the MIC be determined in the presence of a defined calcium concentration. The activity of daptomycin is concentration-dependent with a prolonged post-antibiotic effect. It has linear pharmacokinetics, with a half-life of 8–9 h, the primary route of excretion is renal, it exhibits serum protein binding of ~92% and there is no interaction with the P450 cytochrome. Daptomycin is inactivated by surfactant in the lung and, in consequence, is not recommended for the treatment of respiratory infections. Daptomycin is currently licensed for the treatment of complicated skin and soft tissue infections and for bacteremia and right-sided endocarditis due to methicillin-susceptible and -resistant Staphylococcus aureus. To date, daptomycin-resistant bacteria have rarely been isolated from patients, although increases in vancomycin MIC may be linked to reduced susceptibility to daptomycin. Close monitoring of resistance is essential to maintain the clinical utility of the drug. Using once-daily dosing, daptomycin has been generally well tolerated; however, weekly monitoring of creatinine phosphokinase is recommended, as myopathy in skeletal muscles has been seen, albeit rarely. The rapid bactericidal action of daptomycin makes it a useful addition to the therapeutic armamentarium for the treatment of Gram-positive infections, providing a valuable alternative to vancomycin when it is inappropriate or resistance is a problem.

Keywords: Gram-positive infections, mode of action, MIC, pharmacokinetics

Development of compound

The cyclic lipopeptide group of antibiotics was developed as potentially more potent and safer alternatives to vancomycin. Daptomycin (LY146032) was discovered in the late 1970s by Eli Lilly & Co. through the classical approach of screening bacterial fermentation extracts for antibiotic activity. Early clinical trials in which daptomycin was administered at 2 mg/kg every 24 h or 3 mg/kg every 12 h were prematurely suspended in the late 1980s because of unexpected treatment failures. In an attempt to improve the clinical efficacy, the dose was increased to 4 mg/kg every 12 h, but clinical studies were again discontinued in 1991, this time because of reports of skeletal muscle toxicity with this higher dose. However, in 1997, the development of daptomycin recommenced when Cubist Pharmaceuticals Inc. (Cubist) licensed the worldwide rights from Lilly. Studies in dogs suggested that toxicity to skeletal muscle was increased with fractionated doses when compared with once-daily administration, and it was subsequently shown in both licensing studies and clinical use that administering daptomycin to patients once a day resulted in only rare instances of skeletal muscle toxicity. Following the completion of two randomized Phase 3 clinical trials using once-daily dosing of 1092 adult patients with complicated skin and soft tissue infections (cSSTIs), the FDA approved daptomycin for the treatment of cSSTIs caused by susceptible strains of Gram-positive organisms in 2003. These Phase 3 studies compared daptomycin (4 mg/kg iv once daily for 7–14 days) with vancomycin (1 g iv 12 hourly) or penicillinase-resistant penicillins (4–12 g daily) and reported not only non-inferiority to the comparators, but also a significantly shorter duration of therapy (4–7 days) in 63% of the patients. In 2006, daptomycin received approval for an expanded label as once-a-day therapy at 6 mg/kg for the treatment of Staphylococcus aureus bacteremia and right-sided endocarditis caused by methicillin-susceptible and -resistant S. aureus. It was approved for the treatment of cSSTIs in Europe in 2006, followed by an approval in September 2007 for right-sided endocarditis. This article will review the pre-clinical
and in vitro data for daptomycin. Other articles in the Supplement will review the clinical data.

Mode of action

Daptomycin is the first of a new class of antibiotics, the cyclic lipopeptides, and has a novel mode of action. It consists of a 13-member amino acid cyclic lipopeptide containing a hydrophilic core with a lipophilic tail (Figure 1). Its large carbon- and nitrogen-based structure is derived from a fermentation product of Strepromics roseosporus. The mode of action of daptomycin is a subject of continuing interest, despite a number of research studies over the last 20 years. The earliest studies suggested that peptidoglycan synthesis was a target, although this was not confirmed, and interference with lipoteichoic acid synthesis was suggested, but subsequently disproved.8 Other early studies suggested a completely different mode of action, namely, membrane depolarization.9 A more recent study showed a correlation between membrane depolarization and bactericidal activity and also demonstrated K⁺ release, giving a potential mechanism of inhibition of membrane potential (∆Ψ).10 These workers proposed a model in which the lipid tail of daptomycin is inserted in a calcium-dependent manner into the cell wall membrane, followed by oligomerization of daptomycin molecules forming a channel for K⁺ to move from the cell leading to a loss of ∆Ψ (Figure 2).10 This is further supported by the observation that the stationary phase cells of S. aureus are killed by daptomycin.11 The analysis of changes in gene expression in response to exposure to daptomycin has produced intriguing data.12 The transcriptome of S. aureus exposed to daptomycin showed that the expression of the cell wall stress stimulation genes was significantly raised, as it was when the cell wall-active antibiotics vancomycin and oxacillin were tested. In contrast, the membrane depolarizing agents carbonyl cyanide m-chlorophenylhydrazone (CCCP) and nisin showed little or no induction of cell wall stress stimulation genes. However, daptomycin and CCCP also induced expression of a wide range of genes not induced by vancomycin or oxacillin, suggesting that daptomycin also has a membrane depolarizing effect, which in turn affects a wide range of cell machinery. Indirect support for the additional mode of action of daptomycin comes from a study showing killing of S. aureus without lysis, although transmission electron microscopy showed that >95% of the cells had altered cell wall morphology, consistent with aberrant cell division and an action on peptidoglycan synthesis.13

![Figure 1. Structure of daptomycin.](image1)

![Figure 2. Mode of action of daptomycin.](image2)

In vitro activity

Daptomycin is a broad-spectrum anti-Gram-positive agent. It has no activity against Gram-negative bacteria. Physiological concentrations of calcium are required for the in vitro detection of the antibacterial activity of daptomycin. When two different concentrations were studied (25 and 50 mg/L Ca²⁺), a significant difference was seen in the MICs for staphylococci, streptococci and enterococci, with Mueller–Hinton broth supplemented with 50 mg/L Ca²⁺ being recommended.14 Fuchs et al.15 demonstrated a variation in the Ca²⁺ content of commercial Mueller–Hinton agar, such that the then-used tentative disc susceptibility breakpoints were outside the quality control limits for staphylococci. In consequence, commercial discs were never released, and an MIC breakpoint has been set at 1 mg/L by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).16 A recent evaluation of the agar diffusion MIC (Etest) method for daptomycin and a commercial freeze-dried broth microdilution system (Sensititre Just One Strip, Accumet International Inc., West Lake, OH, USA) showed concordance within one dilution of the reference methods, and both were deemed suitable for monitoring the rare emergence of daptomycin resistance in clinical isolates.17

Daptomycin is rapidly bactericidal against most Gram-positive pathogens. In vitro studies have shown activity against multidrug-resistant- and -susceptible Gram-positive organisms (Table 1).18–20 Among European18 and North American19 isolates, all S. aureus strains were inhibited at a daptomycin MIC of ≤1 mg/L (100% susceptible), with an MIC₅₀ of 0.25 mg/L and an MIC₉₀ of 0.5 mg/L. A slight trend towards higher daptomycin MICs was observed for methicillin-resistant
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Table 1. In vitro activity of daptomycin against European clinical isolates of Gram-positive bacteria

<table>
<thead>
<tr>
<th>Organism (number of isolates)</th>
<th>Daptomycin MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>S. aureus (MRSA) (1946)</td>
<td>0.25</td>
</tr>
<tr>
<td>OXA-susceptible (146)</td>
<td>0.25</td>
</tr>
<tr>
<td>OXA-resistant (800)</td>
<td>0.25</td>
</tr>
<tr>
<td>CoNS</td>
<td></td>
</tr>
<tr>
<td>OXA-susceptible (268)</td>
<td>0.25</td>
</tr>
<tr>
<td>OXA-resistant (673)</td>
<td>0.25</td>
</tr>
<tr>
<td>E. faecalis</td>
<td></td>
</tr>
<tr>
<td>VAN-susceptible (640)</td>
<td>0.5</td>
</tr>
<tr>
<td>VAN-resistant (6)</td>
<td>0.5</td>
</tr>
<tr>
<td>E. faecium</td>
<td></td>
</tr>
<tr>
<td>VAN-susceptible (252)</td>
<td>2</td>
</tr>
<tr>
<td>VAN-resistant (55)</td>
<td>2</td>
</tr>
</tbody>
</table>

Adapted from Sader et al.18
OXA, oxacinil; CoNS, coagulase-negative staphylococci; VAN, vancomycin.
*Based on CLSI breakpoints.

S. aureus (MRSA) (52.8% and 77.9% at 0.25 mg/L and 24.9% and 18.3% at 0.5 mg/L in European isolates and North American isolates, respectively) compared with oxacillin (methicillin)-susceptible S. aureus (70.7% and 80.7% at 0.25 mg/L and 24.9% and 11.9% at 0.5 mg/L, respectively). This trend was less apparent for coagulase-negative staphylococci (CoNS), where the frequencies of oxacillin (methicillin)-susceptible (MS-CoNS) and oxacillin (methicillin)-resistant (MR-CoNS) isolates inhibited at 0.25 mg/L were 48.1% and 47.3% (European) and 59.2% and 62.3% (North American), respectively, whereas at 0.5 mg/L, the frequencies were 33.6% and 43.2% (European) and 23.2% and 27.1% (North American). Among European isolates, one MS-CoNS isolate exhibited an elevated daptomycin MIC of 4 mg/L, with all other CoNS from both studies being inhibited by ≤1 mg/L daptomycin.

Among both European and North America isolates of Enterococcus faecalis (MIC50 0.5 mg/L, MIC90 1 mg/L, 100% susceptible), the highest daptomycin MIC was only 2 mg/L (2.2% and 2.0% of the strains tested, respectively).18,19 In the case of Enterococcus faecium (MIC50 2 mg/L, MIC90 4 mg/L, 100% susceptible, Europe; MIC50 1 mg/L, MIC90 2 mg/L, 100% susceptible, North America), the highest MIC was 4 mg/L (19.9% and 1.3% of the strains in Europe and North America, respectively).18,19 Daptomycin has good activity against glycopeptide-intermediate S. aureus (GISA)21,22 and other Gram-positive bacteria with decreased susceptibility or resistance to vancomycin (Table 2). Two reports of vancomycin-resistant S. aureus (VRSA) from Pennsylvania and Michigan recorded daptomycin MICs of 0.5 and 1 mg/L, respectively, whereas time–kill studies demonstrated rapid bactericidal activity of daptomycin against a panel of GISA, heterogeneous GISA (hGISA) and VRSA strains.25 Although the presence of serum resulted in a modest elevation of daptomycin MICs, its bactericidal activity was unaffected. It has been recently suggested that the extent of daptomycin protein binding when calculated from arithmetic mean MICs may be lower than previously thought, correlating with the effect noted in the previous study.26

Daptomycin demonstrates rapid, concentration-dependent bactericidal activity against Gram-positive bacteria. For S. aureus (including MRSA), daptomycin (at 2–4× MIC) achieves a 3 log10 reduction in viable organisms within 1 h (Figure 3).27 Daptomycin has a dose-dependent prolonged antibiotic effect on E. faecalis (0.6–6.7 h) and S. aureus (1.0–6.3 h) in the presence of physiological free calcium concentrations28 and may also exert some antimicrobial effects at sub-MIC concentrations.27 Small-colony variants (SCVs) of S. aureus are thought to be important in maintaining intracellular survival in difficult-to-treat chronic infections such as osteomyelitis, endocarditis, intravascular and extravascular infections associated with prosthetic material and cystic fibrosis. When the activity of daptomycin, gentamicin and rifampicin was investigated against SCVs both in broth and macrophages, extracellular daptomycin was (with or without gentamicin) the most effective, and for intracellular activity, a combination of either daptomycin or gentamicin with rifampicin was best.29 Daptomycin has also been demonstrated to show a marked reduction in biofilm production in vitro for both S. aureus and Staphylococcus epidermidis, although this study did not compare the effect of daptomycin with other antibiotics.30 These in vitro findings are consistent with the excellent performance of daptomycin compared with vancomycin in the rabbit aortic valve model of endocarditis using MRSA, hGISA and GISA strains.31

Pharmacokinetics and pharmacodynamics

Daptomycin is given intravenously at a dose of 4–6 mg/kg once daily. Daptomycin has linear pharmacokinetics with a half-life of 8–9 h and steady state is reached by day 3.32 The primary route of excretion is via kidneys with ~78% urinary recovery (~50% as active compound) and little faecal excretion (~5%).33,34 Protein binding is ~92% and reversible in vitro (in contrast to the irreversible binding to the bacterial membrane), so protein-bound daptomycin is bioavailable and is
Daptomycin does not interact with the P450 cytochrome, and consequently, there are no known cytochrome P450-mediated drug–drug interactions between daptomycin and other drugs.32,33,35 The volume of distribution is low (\(\frac{C24}{0.1 \text{ L/kg}}\)) and corresponds to the concentration of the drug in plasma and interstitial fluid.33,35 Table 3 summarizes the tissue distribution. Daptomycin is inactivated by surfactant in the lung and is not indicated for the treatment of pneumonia.36 Daptomycin does not cross the blood–brain barrier.37

Bactericidal activity has been demonstrated at 4 h in an in vitro pharmacodynamic model of endocarditis using a high inoculum of pathogens, in which daptomycin demonstrated significant bactericidal (99.9% kill) activity equivalent to that seen with nafcillin, vancomycin and linezolid (decreases of 3.34 ± 1.1, 3.28 ± 0.4 and 3.34 ± 0.8 log10 cfu/g, respectively).38

Pharmacodynamic and toxicology studies were pivotal in establishing the once-daily dose regimen. Using a canine model, Oleson et al.4 established that the skeletal muscle effects of daptomycin were related to dosing interval rather than to the maximum concentration of the drug in plasma or the area under the concentration–time curve, concluding that once-daily dosing should minimize the potential for daptomycin-related skeletal muscle effects. Cha et al.39 reported that doses ranging between 3 and 7 mg/kg produced significant bactericidal activity (effective dose ED80) against multidrug-resistant S. aureus and E. faecium isolates. A Monte Carlo prediction model determined that the probability of achieving an AUCfree/MIC ratio of 189 to achieve 80% maximal kill (ED 80) in patients with normal renal function. Using a pharmacodynamic model of impaired renal function to investigate the impact of a prolonged half-life on the pharmacodynamics of daptomycin against methicillin-susceptible S. aureus and MRSA, an equivalent bactericidal killing at 4, 6 and 8 mg/kg delivered at an 8 and 30 h \(t_{1/2}\) was reported by Huang and

### Table 2. Comparative activity of daptomycin, linezolid, quinupristin/dalfopristin (QD) and vancomycin against Gram-positive bacteria

<table>
<thead>
<tr>
<th>Organism (n)</th>
<th>Antimicrobial agent</th>
<th>50%</th>
<th>90%</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSV(^a) S. aureus (19)(^b)</td>
<td>daptomycin</td>
<td>2</td>
<td>8</td>
<td>1–8</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>2</td>
<td>4</td>
<td>1–8</td>
</tr>
<tr>
<td></td>
<td>QD (\leq 0.5)</td>
<td>(\leq 0.5)</td>
<td>(\leq 0.5)–2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>4</td>
<td>8</td>
<td>4–8</td>
</tr>
<tr>
<td>DSV CoNS (17)(^c)</td>
<td>daptomycin</td>
<td>1</td>
<td>4</td>
<td>0.25–4</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>2</td>
<td>2</td>
<td>1–2</td>
</tr>
<tr>
<td></td>
<td>QD (\leq 0.5)</td>
<td>(\leq 0.5)</td>
<td>(\leq 0.5)–1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>4</td>
<td>4</td>
<td>4–8</td>
</tr>
<tr>
<td>VR(^d) E. faecium (63)</td>
<td>daptomycin</td>
<td>4</td>
<td>8</td>
<td>2–8</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>2</td>
<td>4</td>
<td>2–4</td>
</tr>
<tr>
<td></td>
<td>QD (\leq 0.5)</td>
<td>(\leq 0.5)</td>
<td>(\leq 0.5)–1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vancomycin (\geq 128)</td>
<td>(\geq 128)</td>
<td>(\geq 128)</td>
<td></td>
</tr>
<tr>
<td>Enterococci, other(^e) (27)</td>
<td>daptomycin</td>
<td>2</td>
<td>8</td>
<td>0.5–8</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>4</td>
<td>4</td>
<td>2–4</td>
</tr>
<tr>
<td></td>
<td>QD</td>
<td>2</td>
<td>16</td>
<td>(\leq 0.5)–32</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>8</td>
<td>(\geq 128)</td>
<td>1 to (\geq 128)</td>
</tr>
</tbody>
</table>

Adapted from Jevitt et al.,21 with permission from Mary Ann Liebert, Inc. publishers.

\(^a\)DSV, decreased susceptibility to vancomycin.

\(^b\)Includes three S. aureus with vancomycin MICs of 8 mg/L.

\(^c\)Includes one CoNS with a vancomycin MIC of 8 mg/L.

\(^d\)Vancomycin-resistant.

\(^e\)Includes E. faecalis, Enterococcus casseliflavus, Enterococcus gallinarum and vancomycin-intermediate E. faecium.

### Figure 3. Bactericidal activity of daptomycin against S. aureus: in vitro time–kill assay. Adapted from Thorne and Alder,27 with permission from Elsevier.
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Table 3. Daptomycin tissue penetration

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Species</th>
<th>Maximum concentration</th>
<th>% of serum</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blist fluid</td>
<td>human</td>
<td>27.6 mg/L</td>
<td>68.4</td>
<td>Wise et al.63</td>
</tr>
<tr>
<td>Blood clot tissue</td>
<td>rat, rabbit</td>
<td>3.5 µg/g</td>
<td>72.7</td>
<td>Michiels and Bergeron64</td>
</tr>
<tr>
<td>Peritoneal tissue</td>
<td>rat</td>
<td>11.8 mg/L</td>
<td>35.1</td>
<td>Vaudaux et al.65</td>
</tr>
<tr>
<td>CSF</td>
<td>rabbit</td>
<td>5.2 mg/L</td>
<td>5.97</td>
<td>Cottagnoud et al.66</td>
</tr>
</tbody>
</table>

Adapted from Steenbergen et al.37

Rybak.40 No appreciable differences in the bactericidal activity or endpoints between full-dose daptomycin delivered either every 24 h for simulated normal renal function or every 48 h for simulated impaired renal function were reported. Among subjects not on dialysis, daptomycin clearance is estimated to be primarily a linear function of estimated creatinine clearance (CLCR).41 In subjects on dialysis, clearance is approximately one-third of that in non-dialysis subjects (0.27 versus 0.81 L/h).42 Further studies are ongoing to investigate the effects of renal impairment and dialysis. There is no dose adjustment recommended for patients with renal impairment and CLCR 30 mL/min. In patients with CL CR < 30 mL/min, the dose recommendation is 4 mg/kg every 48 h. In patients on haemodialysis or continuous ambulatory peritoneal dialysis, administration post-dialysis on dialysis days is recommended.34 In patients with mild to moderate hepatic impairment, the pharmacokinetics of daptomycin are not significantly altered and no dosage adjustment is necessary.34

Resistant mechanisms

Resistant bacteria have been isolated, albeit rarely, from patients treated with daptomycin as well as antibiotic-naive patients.43 Typically, in vitro emergence of resistance most commonly occurs by spontaneous mutations resulting from serial passage or chemical mutagenesis and involves alterations in the membrane structure, although the mechanism is not well understood.44 Of 35 965 isolates within the EUCAST database, none had an MIC of ≥ 2 mg/L (Figure 4).45 Mutations in mprF (which encodes lysylphosphatidylglycerol synthetase), yycG (which encodes the sensor histidine kinase) and rpoB and rpoC (which encode the β and β' subunits, respectively, of the RNA polymerase, the latter occurring later in the selection process) have been found in S. aureus isolates with daptomycin MICs greater than the susceptible range (MICs ≤ 1 mg/L).43 It is now appreciated that the exposure of S. aureus to vancomycin has a major influence on the physiology of the bacterium with alterations in the activity of global regulators such as the accessory gene regulator gene (agr), resulting in decreased susceptibility to vancomycin. There have been reports of linked increases in vancomycin and daptomycin MICs, possibly due to the increased cell wall thickness induced by vancomycin.46 The recent finding that daptomycin has an effect on peptidoglycan synthesis might also explain this effect.13 As yet, the clinical significance of this phenomenon is unclear.

To date, most of the resistant isolates have been derived from severely ill patients with serious underlying conditions, often immunocompromised, and in many cases pre-treated with other antibiotics or receiving an inappropriate dose. Recent in vitro studies using large bacterial inocula on solid and liquid media containing various daptomycin concentrations have demonstrated that the plasma daptomycin concentration is above the mutant prevention concentration throughout treatment using approved doses, a finding consistent with the comparative rarity of the selection of daptomycin-resistant mutants in the clinic.47 In the clinical setting, resistance has been associated with prolonged use,48,49 multiple co-morbidities,50 osteomyelitis,51,52 acute myeloid leukaemia53 and leucocyte adhesion deficiency syndrome.54 The impact of resistance on the use of daptomycin is not great at the current level of experience with the drug. Close monitoring of resistance is essential to manage the individual patient effectively and to maintain the utility of daptomycin by reducing the likelihood of the emergence of resistant strains. This has been illustrated in a study reporting pre- and post-treatment isolates from salvage therapy of persistent S. aureus bacteraemia when 6 of the 67 patients relapsed with resistant isolates (mean MIC 2 mg/L).55 It is important to put this observation in context in that resistant (MIC ≥ 1 mg/L) post-treatment isolates were found in 7 (13.2%) of the 53 patients treated with vancomycin as opposed to 7 (5.8%) of the 120 patients treated with daptomycin in a randomized prospective study of S. aureus bacteraemia/endocarditis.7

Safety

As stated earlier, early clinical trials with 12 hourly dosing caused reversible effects in the skeletal muscle as measured by the level of creatinine phosphokinase (CPK) isoenzymes released by the
skeletal muscle. A recent review of 4 year post-marketing data on daptomycin usage in the USA, involving 534 patients with cSSTIs who received daptomycin at 4 mg/kg, reported CPK elevation in 2.5% (11 of 435 patients) and myopathy in 0.2% (including one case of severe myopathy). The safety profile of daptomycin from the Clinical Outcomes Registry Experience (CORE) programme is reviewed elsewhere in this Supplement.51–55 In clinical trials using doses of 4–6 mg/kg, the rate of side effects reported is equivalent to standard therapy.5,6 High-dose daptomycin (12 mg/kg) administered to healthy volunteers was not associated with any toxicity. However, because of the potential for increase in the CPK levels in serum and myopathy, weekly monitoring of CPK levels is recommended. Post-marketing safety surveillance has demonstrated a very low frequency of adverse skeletal muscle effects (Peggy Webster, Senior Director of Pharmacovigilance, Cubist, personal communication). Ongoing clinical studies will confirm the tolerability of daptomycin in the clinical setting.

Conclusions

Infection caused by MRSA is one of the greatest—if not the greatest—challenge(s) to the infection community, not only in hospital-acquired infection but increasingly in a community setting. Although infection control can, if exhaustively applied, prevent the emergence of healthcare-associated infection caused by MRSA, as in the Netherlands, or result in reductions in MRSA bacteraemia rates as has been the experience in the UK recently, the role of effective chemotherapy is still substantial. Vancomycin has very much been seen as the mainstay of treatment in this area but increasing resistance, particularly at low levels, is undermining its perceived utility. Also, an increasing number of new agents are being introduced, many of which have advantages over vancomycin, and these will be used as alternatives. As with all antimicrobial agents, their usage will promote the development of resistance. Linezolid is an agent that has been in clinical use now for some time and has proved to be invaluable for certain patients, although resistance associated with the selection of mutations has been sporadic and never posed a significant clinical problem. A very recent report of plasmid-mediated resistance associated with the cfr gene, which encodes a novel methyl transferase resulting in the post-transcriptional methylation of ribosomal rRNA at position A2503 giving resistance, is disturbing as this resistance determinant could spread rapidly among MRSA strains. The new third-generation cephalosporins, which have marked anti-MRSA activity, such as ceftobiprole and ceftaroline, again look promising as bactericidal and safe drugs, but their impact on the hospital environment, particularly in relation to the selection of extended-spectrum β-lactamases and Clostridium difficile, may well prove to be a substantial problem. Tigecycline has proved to be a promising agent in specific areas, although disappointingly has not performed particularly well in comparative studies in hospital-acquired pneumonia and is largely used as a drug for use in treating complicated post-surgical skin and soft tissue infections and intra-abdominal infections when MRSA is suspected. It also has value in treating certain specific pathogens such as Acinetobacter baumannii. Daptomycin is an interesting novel agent with a new mode of action, for which resistance as yet appears not to be a substantial problem; it represents a valuable therapeutic agent, particularly for the treatment of MRSA and vancomycin-resistant enterococcus bacteraemia and associated endocarditis, although its lack of activity in the lung means that it is not suitable for the treatment of pneumonia. The rapid bactericidal action of daptomycin undoubtedly makes this agent of particular use in these bloodstream-associated infections. The drug appears to be safe when dosed once a day and to have favourable pharmacokinetic/pharmacodynamic properties. There is an extensive body of pre-clinical information that has been further backed up by clinical experience in the USA since September 2003, which shows that daptomycin is a valuable addition to our armamentarium for the treatment of infections caused by MRSA.

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