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Daptomycin

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Contents

Abstract

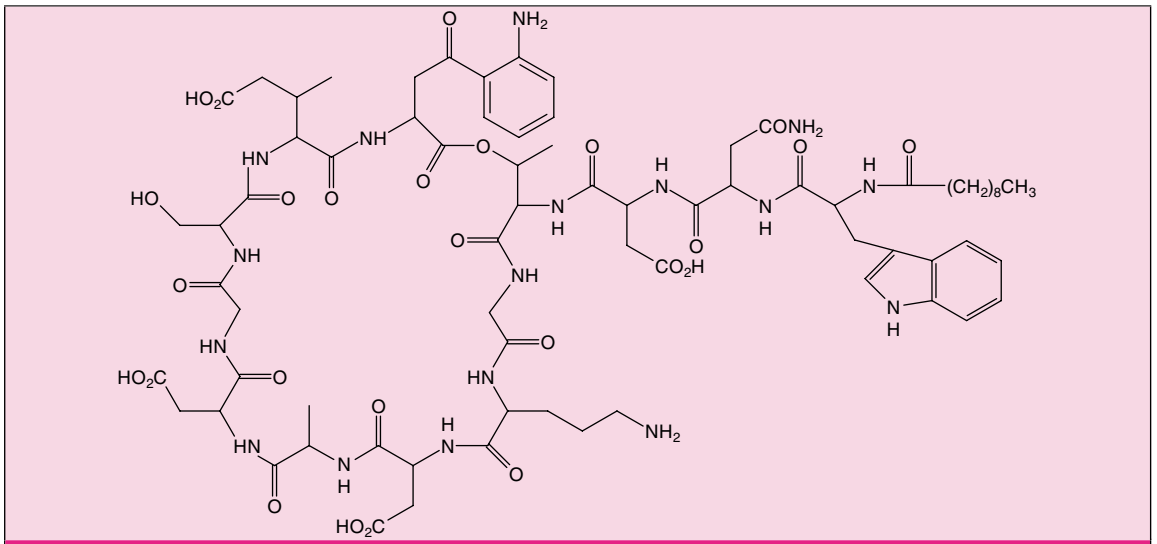
▲ Daptomycin is a lipopeptide antibacterial with rapid *in vitro* activity against Gram-positive cocci. It is approved for use in patients with complicated skin and skin structure infections (cSSSIs) caused by specified Gram-positive cocci.

▲ *In vitro*, daptomycin was active against *Staphylococcus aureus* (including meticillin-resistant strains), *Streptococcus pyogenes*, *S. agalactiae*, group C and G β-haemolytic streptococci and vancomycin-susceptible *Enterococcus faecalis*. Bactericidal activity *in vitro* was rapid and concentration dependent.

▲ In two randomised, investigator-blinded, multicentre trials in patients with cSSSIs, intravenous daptomycin 4 mg/kg once daily was as effective as standard therapy (intravenous semi-synthetic penicillin 4–12 g/day or vancomycin 1g 12-hourly). Clinical success rates assessed 6–20 days after treatment end were 82.1% in daptomycin recipients and 82.9% in recipients of standard therapy (pooled data).

▲ In patients with cSSSIs, the adverse event profiles of daptomycin and vancomycin were similar. Creatine phosphokinase (CPK) levels increased in 2.8% of daptomycin recipients and 1.8% of patients who received standard therapy; only one daptomycin recipient (0.2%) experienced increased CPK levels and muscle symptoms that were not associated with any comorbid factors.

Features and properties of daptomycin (Cubicin™)	
Indication	
Complicated skin and skin structure infections	
Mechanism of action	
Disruption of bacterial cell membrane potential	
Dosage and administration	
Recommended dosage	4 mg/kg once daily
Route of administration	Intravenous infusion
Duration of administration	7–14 days
Pharmacokinetic profile (4 mg/kg once daily at steady state)	
Mean maximum plasma concentration	57.8 μg/mL
Mean area under the plasma concentration-time curve from 0–24h	494 μg • h/mL
Plasma protein binding	92%
Volume of distribution	≈0.1 L/kg
Mean elimination half-life	8.1h
Most common adverse events	
Constipation, injection-site reactions, nausea, headache, diarrhoea and vomiting	



Daptomycin (Cubicin™[1]) is a cyclic lipopeptide antibacterial derived from *Streptomyces roseosporus*[1] that was recently approved in the US for use in the treatment of complicated skin and skin structure infections (cSSSIs).[2] An SSSI is defined as complicated if it requires surgical intervention and/or is known or suspected to involve deeper soft tissue layers of muscle and fascia.[3] Complicated infections are mostly caused by Gram-positive cocci, particularly *Staphylococcus aureus* and *Streptococcus pyogenes* (group A β-haemolytic streptococci), although enterococci, coagulase-negative staphylococci and other β-haemolytic streptococci (groups B, C or G) may also be involved.[3,4]

Daptomycin is approved for use in cSSSIs that are proven or strongly suspected to be caused by *S. aureus* (including meticillin-susceptible and meticillin-resistant strains; MSSA and MRSA), *S. pyogenes*, *S. agalactiae* (group B β-haemolytic streptococcus), *S. dysgalactiae* subspecies *equisimilis* (group C β-haemolytic streptococcus, sometimes classified as group G or group L), or *Enterococcus faecalis* (vancomycin-susceptible strains only).[1,5] Daptomycin has *in vitro* activity against most clinically relevant Gram-positive bacteria. This includes those listed above, as well as *Corynebacterium jeikeium*, vancomycin-resistant *E. faecalis*, *E. faecium* (including vancomycin-resistant strains), *S. epidermidis* (including meticillin-resistant strains) and *S. haemolyticus*. However, this profile focuses on the activity of daptomycin against the Gram-positive cocci for which it is approved and its use in the treatment of patients with cSSSIs.

1. Pharmacodynamic Profile

Mechanism of Action

● Daptomycin has a distinct mechanism of action.[5] The binding of daptomycin to bacterial cell membranes results in disruption of the membrane potential.[5,6] The synthesis of protein, DNA and RNA is inhibited by this disruption,[5,7,8] leading to bacterial cell death.

Antibacterial Activity

In vitro antibacterial activity of daptomycin was generally assessed according to the minimum inhibitory concentration (MIC) required to inhibit growth of the specified micro-organism, with focus on the

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

minimum concentration required to inhibit 90% of bacterial strains (MIC_{90}). MIC susceptibility breakpoints (the MIC at which daptomycin inhibits growth of susceptible isolates) specified in daptomycin prescribing information are ≤1 μg/mL for *S. aureus*, *S. pyogenes*, *S. agalactiae* and *S. dysgalactiae* subspecies *equisimilis* and ≤4 μg/mL for vancomycin-susceptible *E. faecalis*.[5]

In *in vitro* studies, daptomycin required Ca^{2+} at concentrations of 45–55 mg/L, about equivalent to the physiological free concentration of 1.15–1.31 mmol/L, to be fully effective.[9-12] Dilution method susceptibility testing for daptomycin should be undertaken using a minimum calcium chloride concentration of 50 mg/L in Mueller-Hinton broth or 28 mg/L in Mueller-Hinton agar,[5] and US National Committee for Clinical Laboratory Standards (NCCLS) MIC quality control ranges for daptomycin reflect the MICs obtained when Mueller-Hinton broth contains Ca^{2+} supplementation to a final concentration of 50 μg/mL.[13] Unless specified otherwise (some studies reported as abstracts did not comment on calcium supplementation[14,15]), all susceptibility results reported are based on testing in media supplemented with additional calcium. For testing according to British Society for Antimicrobial Chemistry (BSAC) standards, isotonic agar with an adjustment to 50 mg/L Ca^{2+} was used.[16] Most reports specified that *in vitro* testing methods otherwise complied with NCCLS or BSAC standards.

In Vitro Activity

Numerous studies have examined the *in vitro* activity of daptomycin against the Gram-positive cocci for which the use of daptomycin is approved;[9,11,14-20] most studies used clinical isolates.[11,14-20] Studies were conducted in North America[9,11,15,17,19] (two studies in the US only[15,17]) and Europe[14,16,18,20] (one study in the UK only[16]). Study isolates were mostly collected between 1999 and 2001; in two studies, less common isolates were collected over the previous 10 years.[16,19] Some of the studies included in this section are available as abstracts and/or posters.[14,15,20]

- Daptomycin demonstrates *in vitro* activity against Gram-positive cocci implicated in cSSSIs. Against *S. aureus* (including oxacillin- and meticillin-resistant strains), daptomycin MIC_{90} values were 0.25–1.0 μg/mL (10–888 isolates).[9,11,14,16-19] In a study examining the susceptibility to daptomycin of *S. aureus* with glycopeptide intermediate susceptibility (GISA), the MIC_{90} was 4 μg/mL (19 isolates).[19] Furthermore, daptomycin showed *in vitro* activity (MIC = 1.0 μg/mL) against a vancomycin-resistant *S. aureus* clinical isolate (vancomycin MIC >32 μg/mL).[21]
- Daptomycin MIC_{90} values for *S. pyogenes* were 0.06 μg/mL (50–484 isolates),[9,11,15,17] and for *S. agalactiae* were 0.25–0.5 μg/mL (31–367 isolates).[9,11,16-18] Data concerning the activity of daptomycin against *S. dysgalactiae* subspecies *equisimilis* are lacking, although daptomycin is generally active against group C and G β-haemolytic streptococci (MIC_{90} 0.06–0.12 μg/mL [10–83 isolates]).[9,15]
- Against vancomycin-susceptible isolates of *E. faecalis*, MIC_{90} values for daptomycin were 0.5–2.0 μg/mL (10–2049 isolates).[9,11,16-18,20] In an *in vitro* study using 20 isolates of vancomycin-susceptible *E. faecalis*, daptomycin showed synergistic activity with ceftriaxone, cefepime and imipenem against 65%, 35% and 35% of isolates, respectively.[22]
- For *S. aureus*, MRSA, *S. pyogenes*, *S. agalactiae*, and vancomycin-susceptible *E. faecalis*, (n = 31–57) and 19 group C and G β-haemolytic streptococci, susceptibility rates to daptomycin were all 100%.[9]
- Several studies compared the *in vitro* activity of daptomycin with that of other antibacterials commonly used in the treatment of cSSSIs.[9,16-18] In addition to a 100% susceptibility to daptomycin,[9,16-18] 99.9–100% of *S. aureus* isolates (n = 80–1222) were susceptible to vancomycin,[9,16-18] teicoplanin,[9,17,18] linezolid[17,18] or quinupristin/dalfopristin;[17,18] 100% of MRSA isolates (n = 29 and 51) and 100% of group C and G streptococci isolates (n = 8 and 19) were susceptible to vancomycin[9,16] or teicoplanin;[9] 100% of *S. pyogenes* isolates (n = 50–484) were susceptible to vancomycin,[9,16,17] teicoplanin,[9] linezolid[17] or quinupristin/dalfopristin;[17] 100% of *S. agalactiae* isolates (n = 31–367) were susceptible to vancomycin,[9,16-18] teicoplanin,[9] linezolid[17,18] or quinupristin/dalfopristin;[17,18] 100% of vancomycin-susceptible *E. faecalis* isolates (n = 30–2049) were susceptible

to vancomycin,[9,16-18] teicoplanin[9,17,18] or linezolid.[17,18]

• *In vitro*, the bactericidal activity of daptomycin against *S. aureus* was rapid and concentration dependent.[12,23-26] At four times the MIC, daptomycin killed a mean 99.9% of 25 isolates of each of MSSA and MRSA at 24 hours, and was more bactericidal than all comparator drugs, including meticillin and vancomycin.[23] However, at the MIC, daptomycin killed a mean 76.8% of MSSA, but only a mean 32.3% of MRSA isolates at 24 hours.[23]

• Enhanced bactericidal activity occurred with the combination of daptomycin and gentamicin against MSSA and *E. faecalis*, (log_{10} decrease at 4 hours 5.7–>5.9 vs 4.6–4.8 for MSSA and ≥5.9 vs 4.5–5.3 for *E. faecalis*) but not *S. pyogenes*, *S. agalactiae* or MRSA.[12]

• At 4 hours, the combination of daptomycin and oxacillin 32 μg/mL was bactericidal at ≤1 times the MIC for daptomycin against 17 of 18 strains of MRSA, all of which were resistant to oxacillin but susceptible to daptomycin. At 24 hours, synergy and bactericidal activity against all 18 isolates at 0.5 times the daptomycin MIC also occurred.[27]

• The *in vitro* bactericidal effect of daptomycin against *S. aureus* was diminished by the addition of albumin.[26,28] This effect was more pronounced at low than at high daptomycin concentrations[26] and reflects the high protein binding of daptomycin (see also section 2).

Animal Models

• In murine neutropenic thigh models of MSSA[29] or MRSA[30] infection, the maximum bacterial kill with intraperitoneal[29] or subcutaneous[30] daptomycin was >4 log_{10} CFU/mL[30] or CFU/g;[29] bacterial levels at 24 hours were 3.97 log_{10} CFU/g in tissues treated with intraperitoneal daptomycin versus 8.26 log_{10} CFU/g in untreated controls.[29]

• The maximum bacterial kill in a murine neutropenic thigh model of vancomycin-susceptible *E. faecalis* infection was 2 log_{10} CFU/mL.[30]

• In a rat foreign body *S. aureus* infection model, intraperitoneal daptomycin significantly reduced bacterial counts in tissue cage fluids by 1.11 log_{10} CFU/mL ($p = 0.001$), compared with those in control rats.[31]

Pharmacodynamic/ Pharmacokinetic Considerations

• Modelling studies determined that the effective daptomycin dose required to achieve an 80% reduction in the *in vitro* bacterial density of MRSA at 48 hours was 3.1 mg/kg,[32] and that a daptomycin dosage of 4 mg/kg once daily had an 80.4% probability of achieving maximal kill of MRSA (study available as an abstract).[33]

• In murine neutropenic thigh models of MSSA[29] or MRSA[30] infection, the area under the serum concentration-time curve (AUC) to MIC ratio was the parameter best correlated with outcome.

• Against *S. aureus*, the post-antibiotic effect (PAE) of daptomycin (at clinically achievable concentrations) was dose dependent, and ranged from 1.0 to 6.3 hours (*in vitro* study).[10] In a murine neutropenic thigh model of *S. aureus* infection, the *in vivo* PAE of daptomycin was 4.8–7.3 hours (study available as an abstract).[34]

• *In vitro*, the PAE of daptomycin (at clinically achievable concentrations) against *E. faecalis* was dose dependent, and ranged from 0.6 to 6.7 hours.[10] PAEs were reduced in the presence of albumin.[10]

Resistance Development

• Resistance of *S. aureus* to daptomycin has been demonstrated in laboratory strains,[35] although few cases have been reported in clinical trials.[5,36] Among the laboratory strains, no spontaneously resistant mutants occurred; one mutant was obtained through serial-passage mutagenesis and 11 through chemical mutagenesis.[35] The daptomycin MIC against the mutants increased 8- to 32-fold compared with those for the wild type; daptomycin retained its bactericidal activity at eight times the MIC.[35] The mechanism by which resistance to daptomycin develops has not been identified.[5]

Other Effects

Effects on Immune Function

• Given that serious infections often occur in immunocompromised patients, studies have been undertaken to assess the effect of daptomycin on immune function. To date, limited data from two *in vitro* studies using blood from healthy volun-

teers[37,38] and an *in vivo* study in Balb/c mice[37] have shown that at therapeutic concentrations, daptomycin had no detrimental effects on immune function.

Renal Effects

- Excretion of the renal tubular enzymes alanine aminopeptidase (AAP) and *N*-acetyl-β-d-glucosaminidase (NAG) increased significantly from baseline in six healthy men who received a single intravenous dose of daptomycin 2 mg/kg, tobramycin 1 mg/kg or daptomycin plus tobramycin in a crossover study.[39]
- AAP excretion increased from 12.2 U/day at baseline to 16.9, 18.8 and 17.8 U/day in the respective treatment groups, and NAG excretion increased from 2.6 U/day to 4.4, 4.2 and 3.9 U/day (all $p < 0.05$ vs baseline). Increased excretion of enzymes such as AAP and NAG is an early indicator of aminoglycoside-associated renal damage.[39] However, the effects of daptomycin and/or tobramycin were considered negligible and no change in pharmacokinetic parameters was seen[39] (see also sections 2 and 5).

Musculoskeletal Effects

- The risk of adverse skeletal muscle effects associated with daptomycin appears to be minimised by once-daily administration of the drug, according to a study conducted in dogs.[40] In dogs receiving intravenous daptomycin 25 mg/kg three times daily, the mean increase in creatine phosphokinase (CPK) activity was about four times that in dogs receiving 75 mg/kg once daily (administered for 20 days). The incidence of microscopic myofibre lesions increased 2-fold with daptomycin 25 mg/kg three times daily versus 75 mg/kg once daily (although not statistically significant, the increase was considered biologically significant).[40]
- In 2 of 5 volunteers who received daptomycin 4 mg/kg 12-hourly, transient muscle weakness and myalgia occurred 2–3 days after rapid elevations were seen in CPK.[41] Daptomycin was stopped and one day later CPK levels peaked at 10 000–20 000 IU/L, then subsided to almost baseline over the next week. Muscle symptoms resolved with the decline in CPK.[41]

In a study in 24 volunteers who received 7–14 days of once-daily intravenous daptomycin 4, 6 or 8 mg/kg or placebo, 2 of 18 daptomycin recipients (one each in the 4 and 8 mg/kg groups) developed mild elevations in serum CPK levels (≤2.5 times the upper limit of normal).[42] The recipient of daptomycin 8 mg/kg had performed intense physical activity the day before. Neither volunteer experienced muscle discomfort or weakness. Administration of daptomycin was continued, and CPK levels returned to normal in both volunteers. Data on the musculoskeletal effects of daptomycin in patients with cSSSIs are reviewed in section 4.

2. Pharmacokinetic Profile

Three studies in healthy volunteers, including one in a cantharidin-induced inflammatory model,[43] defined the pharmacokinetics of daptomycin, administered as a 30-minute intravenous infusion.[42-44] Another report provided information on the pharmacokinetics of daptomycin in patients with renal impairment[45] and information has also been sourced from the daptomycin prescribing information.[5]

Absorption and Distribution

- A multiple-dose study in 24 healthy volunteers aged 25–43 years found once-daily dosages of daptomycin 4 mg/kg resulted in mean maximum plasma concentration (C_{max}) values of 54.6 μg/mL on day 1 and 57.8 μg/mL at steady state on day 7 (steady state was achieved by the third dose).[42] C_{max} occurred at the end of the 30-minute infusion (t_{max}) in this[42] and other studies.[43,44] C_{max} for an 8 mg/kg dose was more than twice that of the 4 mg/kg dose, but this slight non-linearity was not considered clinically relevant.[42]
- At steady state, the median trough daptomycin plasma concentration at a dosage of 4 mg/kg was 6.37 μg/mL.[42] After administration of daptomycin 4 mg/kg, the mean AUC_{∞} on day 1 was 425 μg • h/mL and, as with C_{max}, was slightly higher at steady state (AUC_{24h} of 494 μg • h/mL). The accumulation index for once-daily daptomycin 4 mg/kg administered for 7–14 days was about 1.2.[42]
- Daptomycin plasma protein binding was 92% and was independent of the drug concentration.[42] At all dosages, the volume of distribution was low (≈0.1 L/kg),[42,44] suggesting that daptomycin does

not easily move from plasma and interstitial fluid across some cell membranes.[44] Concentrations of ^{14}C-labelled daptomycin in whole blood were lower than in plasma, indicating that almost no drug crossed into erythrocytes.[44] Distribution was not complete until 4–6 hours after administration.[44]

- About 68% of a single dose of daptomycin 4 mg/kg penetrated inflammatory fluid in six healthy men.[43] Mean AUC_{24h} was 318 μg • h/mL; the difference between this value and plasma AUC could possibly reflect the lower protein content of inflammatory exudate (about 70% of that of plasma).[43] In inflammatory fluid, mean daptomycin concentrations at 1 and 3 hours were 9.4 and 14.5 μg/mL, with a mean C_{max} of 27.6 μg/mL occurring at a mean 3.7 hours.[43]

Metabolism and Elimination

- Daptomycin does not inhibit or induce the cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 *in vitro*.[5]
- The site of daptomycin metabolism is currently unknown.[5] In healthy volunteers, after a single dose of ^{14}C-labelled daptomycin 1 mg/kg, mean recovery of ^{14}C in urine over 144 hours was 78% (plus 5% in faeces) while that of unchanged ^{14}C-labelled daptomycin was only 51.7%.[44] Plasma concentrations of unchanged ^{14}C-labelled daptomycin and of total ^{14}C were, however, almost identical. This suggests that no circulating metabolites were present (if present, such metabolites would probably be large, highly polar and readily detectable). Thus, the plasma concentration may consist largely of parent drug, and renal metabolism, with rapidly excreted metabolites, may occur.[44] Beyond 4 days, <1% of the initial single dose of ^{14}C-labelled daptomycin was recovered from urine or faeces.[44]
- In healthy volunteers, the elimination half-life ($t_{1/2}$) of daptomycin 4 mg/kg was 7.4 and 8.1 hours after single or multiple doses; mean 24-hour urinary elimination after a single 4 mg/kg dose was 59.7%.[43] In six healthy volunteers who received a single dose of daptomycin 4 mg/kg, mean $t_{1/2}$ in inflammatory fluid was 17.3 hours but varied widely (6.32–30.9 hours).[43]
- The systemic clearance of daptomycin was low (9.6 and 8.3 mL/h/kg after single or multiple doses of 4 mg/kg); renal clearance of unbound daptomycin 4 mg/kg was 84.6 and 62.9 mL/h/kg on days 1 and 7.[42]

Special Patient Populations

- In six patients with severe renal impairment (creatinine clearance [CL_{CR}] <1.8 L/h [30 mL/min]) who received a single dose of daptomycin 4 mg/kg, mean AUC_∞ was increased to 1254–1474 μg • h/mL compared with 518–698 μg • h/mL in volunteers with normal renal function (statistical analysis not reported); mean C_{max} was unchanged.[45] The increased exposure to daptomycin reflected an extended mean $t_{1/2}$ of 29.4 hours and a reduced mean plasma clearance (CL_P) of 4.6 mL/min. This was in line with the reduced mean CL_{CR}, and dosage adjustment in patients with severe renal disease was recommended (see section 5).[45] In contrast, mean CL_P was 12.1 mL/min in volunteers with normal renal function (CL_{CR} >4.8 L/h [80 mL/min]).[45]
- Mean C_{max} was decreased to 39.7 μg/mL in six patients with end-stage renal disease treated with haemodialysis. However, in five patients with end-stage renal disease treated with peritoneal dialysis, mean C_{max} was 51.3 μg/mL, which was similar to that in patients with less severe disease (C_{max} 47.7–55.7 μg/mL).[45] There was no clinically significant alteration in pharmacokinetic parameters in patients with CL_{CR} 30–80 mL/min compared with those in individuals with normal renal function, and dosage adjustments are not required in these patients (see section 5).[45]
- The pharmacokinetics of daptomycin were not altered in ten patients with moderate hepatic impairment (Child-Pugh Class B).[5] No evaluation of daptomycin in patients with severe hepatic impairment has been undertaken.[5] In 12 healthy volunteers aged ≥75 years who received a single dose of daptomycin 4 mg/kg, mean total clearance was reduced by ≈35% and mean AUC_∞ increased by ≈58% compared with values for young healthy volunteers. No dosage adjustment is recommended in elderly patients.[5]

Potential Drug Interactions

- When daptomycin 2 mg/kg and tobramycin 1 mg/kg were coadministered in a single-dose, crossover study in healthy men (n = 5), there was no significant alteration in the pharmacokinetics of either agent.[39] However, given that the combination of tobramycin and the recommended dose of daptomycin (4 mg/kg) has not been assessed for possible interaction, caution is recommended when coadministering these agents.[5]
- No change in the C_{max} or AUC_{∞} of daptomycin 6 mg/kg or intravenous aztreonam 1000mg occurred when 15 healthy volunteers received both drugs together (single-dose study).[5] Similarly, probenecid 500mg four times daily did not alter the C_{max} or AUC_{∞} of a single dose of daptomycin 4 mg/kg.[5]
- There was no effect on the pharmacokinetics of either drug (or the international normalised ratio [INR]) when a single dose of warfarin 25mg was administered to 16 healthy volunteers after they had received daptomycin 6 mg/kg once daily for 5 days, but information on concomitant administration in patients is not available and close monitoring of the INR is recommended if the two drugs are coadministered.[5]

3. Therapeutic Efficacy

Two randomised, investigator-blinded, multicentre trials of intravenous daptomycin in >1000 adult patients with cSSSIs (e.g. wound infection, major abscess, ulcer infection) were reported as a combined analysis (trials 9801 and 9901)[46] or separately (trial 9901 only)[47,48] in abstracts and/or posters. Data were also obtained from the prescribing information.[5]

Only patients aged 18–85 years with cSSSIs known or suspected to be due to Gram-positive bacteria and requiring hospitalisation for intravenous antimicrobial therapy were included. Patients were excluded if they required surgery to cure the infection, if they had known bacteraemia prior to study entry, were primarily infected with Gram-negative organisms or bacteria known to be resistant to either vancomycin or daptomycin, or were expected to live <2 months.[46]

Trials were undertaken in the US and South Africa (trial 9801; n = 517)[46] and in South Africa, Europe, Russia, Israel and Australia (trial 9901; n = 562).[46-48] These patient numbers reflect the intention-to-treat (ITT) population, who received at least one dose of medication and had an appropriate infection (figure 1).[46] Patients in the ITT population with a Gram-positive infection at baseline were included in the modified ITT (MITT) analysis (n = 421 and 468 in studies 9801 and 9901) [figure 1]. Analyses of clinically and microbiologically evaluable patients were also reported (see figure 1 for definitions and patient numbers).[46] Bacteriological assessments based on cultures before and after treatment were not reported.

Patients were randomised for a planned treatment period of 7–14 days to daptomycin 4 mg/kg once daily or standard therapy with either semi-synthetic penicillin (cloxacillin, oxacillin, flucloxacillin or nafcillin, depending on local availability) 4–12 g/day or vancomycin 1g 12-hourly. In all treatment groups, aztreonam and/or metronidazole were added if appropriate.[46]

Before randomisation, the MRSA status of the patients was assessed. If an infection with MRSA was considered likely, the patients randomised to standard therapy were treated with vancomycin.[46]

The clinical success rate, assessed at a test-of-cure visit 6–20 days after the end of treatment, was the primary endpoint.[46]

Combined Analysis

- In the combined analysis, daptomycin produced clinical success rates similar to those with standard therapy regardless of analysis/population (82.1% vs 82.9% [clinically evaluable population]; 75.8 vs 76.2% [MITT population]; 68.8% vs 67.4% with vancomycin [patients with likely MRSA infection, MITT]; 84.3% vs 82.1% with semi-synthetic penicillin [MRSA not suspected, MITT]).[46] For daptomycin recipients in the clinically evaluable population, success rates were 81.1% and 85.8% for those with or without likely MRSA infection.[46]
- In the microbiologically evaluable population, daptomycin produced clinical success rates of ≈75–100% depending on the nature of positive base-

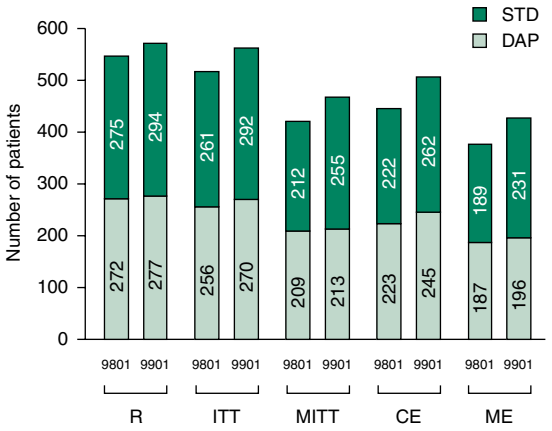


Fig. 1. Patient numbers reported in comparative trials of daptomycin (DAP) in complicated skin and skin structure infections (cSSSIs).[46-48] Of the 1118 patients initially randomised (R) in two clinical trials, the intention-to-treat (ITT) population included patients who received at least one dose of study medication and had a cSSSI infection known to be or probably caused by Gram-positive cocci. Patients with a Gram-positive infection isolated at baseline constituted the modified ITT (MITT) population.[46] Patients who met all major protocol requirements (appropriate infection, intravenous treatment for 7–14 days with either daptomycin 4 mg/kg/day or standard therapy (STD) of vancomycin 1g 12-hourly or semi-synthetic penicillin 4–12g daily, evaluated) were included in the clinically evaluable population (CE) and the subset of these who had a specific Gram-positive pathogen isolated from baseline cultures made up the microbiologically evaluable (ME) population.[46]

line cultures (figure 2) [no statistical analysis reported].[5]

Study 9901

In the individually reported trial (study 9901), 562 patients were included in the ITT population and 507 in the clinically evaluable population.[48] Patients were assessed according to eight clinical symptoms, each on a 0–3 scale, where 0 indicates no symptoms and 3 indicates severe symptoms, with a maximum cumulative score of 24.[48] Symptoms included tenderness, induration and purulence, and were assessed at baseline (median score of 13 for both groups), day 3 or 4 of therapy, at the end of therapy and at the test-of-cure assessment.[48]

- The median reduction in clinical scores in daptomycin recipients (ITT population) was 5 points on day 3 or 4, which was significantly better ($p < 0.05$) than the 4-point reduction in the standard therapy group, 85% of whom received a semi-synthetic penicillin.[48] The median duration of treatment with daptomycin was significantly shorter than with standard therapy (7 vs 8 days, $p < 0.05$). At the test-of-cure assessment, 81% of ITT patients in both groups achieved clinical success (95% CI −6.4 to 6.5).[48]
- In a separate abstract report on the 468 patients in the MITT population in trial 9901 (figure 1), clinical success rates were similar for daptomycin (84.4%) and standard therapy (83.2%).[47] Overall, the clinical success rate in patients with dual infection due to *S. aureus* and β-haemolytic streptococci was significantly lower than that in patients with all other infections (73.2% vs 86.5%, $p < 0.004$).[47]

4. Tolerability

Tolerability data were obtained from the prescribing information and pooled analysis of the two randomised, investigator-blinded studies in patients with cSSSIs discussed in section 3.[5,46] Data concerning skeletal muscle adverse events were obtained from another analysis of these studies.[49]

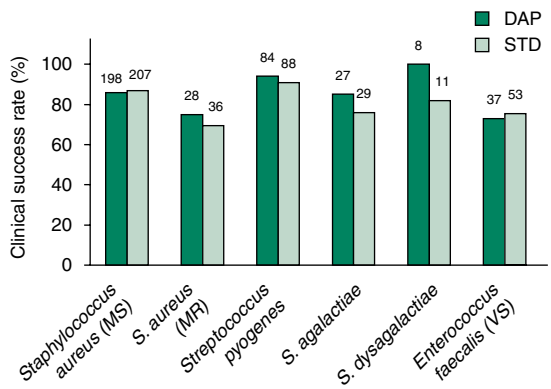


Fig. 2. Efficacy of daptomycin (DAP) in specified Gram-positive complicated skin and skin structure infections (cSSSIs).[5,46] Combined clinical success rates in two randomised, investigator-blinded trials in patients with confirmed Gram-positive cSSSIs, assessed at test-of-cure 6–20 days after planned treatment of 7–14 days with intravenous DAP 4 mg/kg once daily or standard therapy (STD) [vancomycin 1g 12-hourly or semi-synthetic penicillin 4–12 g/day]. Results are from the microbiologically evaluable population (patients who met all protocol inclusion criteria, including duration of therapy and evaluations and had Gram-positive pathogens isolated at baseline). Numbers above the bars are numbers of patients. **MR** = meticillin-resistant; **MS** = meticillin-susceptible; **VS** = vancomycin-susceptible.

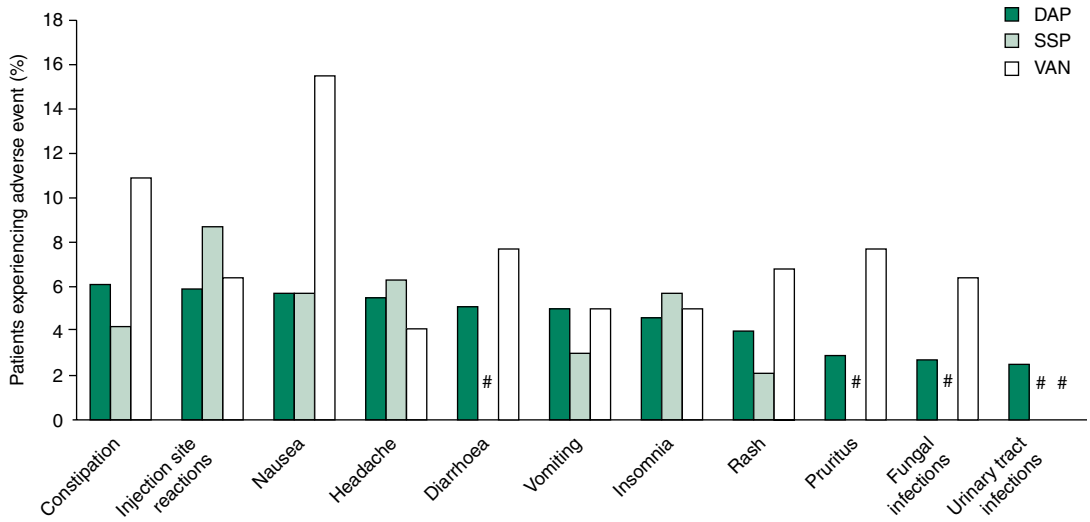


Fig. 3. Adverse events in patients receiving daptomycin (DAP). Events affecting ≥5% of patients in two randomised, evaluator-blinded, multicentre trials in complicated skin and skin structure infections where patients received DAP 4 mg/kg once daily, or either semi-synthetic penicillin (SSP) 4–12 g/day or vancomycin (VAN) 1g 12-hourly (all drugs administered intravenously), for a planned treatment period of 7–14 days.[46] **#** indicates an incidence <2%.

Both analyses are available as abstracts and posters.[46,49]

- Daptomycin 4 mg/kg administered intravenously once daily to patients with cSSSIs resulted in a similar incidence of adverse events to intravenous vancomycin 1g 12-hourly.[46] Adverse events reported by 5–6.1% of daptomycin recipients in the combined trial ITT population were constipation, injection-site reactions, nausea, headache, diarrhoea and vomiting; no statistically significant differences between treatment groups were reported (figure 3).[46]
- CPK levels increased in 15 of 534 (2.8%) daptomycin recipients and in 10 of 558 (1.8%) patients who received standard therapy (see also section 1).[49] Muscle cramps, muscle weakness (not otherwise specified), musculoskeletal pain or myalgia occurred in 0.2–0.9% of daptomycin recipients and in 0–0.4% of patients receiving standard therapy.[49]
- Only one daptomycin recipient (0.2%) experienced increased CPK levels of up to 10 320 IU/L and muscle symptoms (e.g. upper extremity pain, weakness) that were not associated with any comorbid clinical factors.[49] CPK levels peaked on day 11, one day after the patient's treatment was changed from daptomycin to levofloxacin, and declined to 75 IU/L by day 28.[49]
- Renal failure occurred in 2.2% of daptomycin recipients and 2.7% of recipients of standard therapy (vancomycin or semi-synthetic penicillin).
- Daptomycin 4 mg/kg once daily for 14 days did not alter the incidence of adverse events in 20 healthy volunteers receiving the HMG-CoA reductase inhibitor simvastatin 40 mg/day.[5] However, there is limited experience of the coadministration of HMG-CoA reductase inhibitors, which may cause myopathy, and daptomycin; suspension of treatment with HMG-CoA reductase inhibitors should be considered in patients receiving daptomycin.[5]

5. Dosage and Administration

Daptomycin is administered intravenously over 30 minutes. The approved dosage is 4 mg/kg once every 24 hours for 7–14 days.[5] A reduced dosage of 4 mg/kg once every 48 hours is recommended for patients with CL_{CR} <1.8 L/h (30 mL/min), including patients receiving haemodialysis or continuous ambulatory peritoneal dialysis.[5]

6. Daptomycin: Current Status

In two randomised, controlled trials, intravenous daptomycin 4 mg/kg was as effective as standard therapy in the treatment of cSSSIs and had a tolerability profile similar to that of vancomycin. Daptomycin 4 mg/kg once every 24 hours is approved in the US for cSSSIs proven or strongly suspected to be caused by susceptible *S. aureus* (including MSSA and MRSA), *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae* subspecies *equisimilis* or *E. faecalis* (vancomycin-susceptible strains only).[5]

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