

Complicated skin and soft tissue infections: literature review of evidence for and experience with daptomycin

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Abstract: Skin and soft tissue infections (SSTIs) are the second most common infection encountered in hospitals. Management decisions have become increasingly complex due to the prevalence of resistant pathogens, the wide array of licensed antimicrobials and the availability of potent oral agents and of out-patient parenteral antibiotic therapy. Daptomycin is one of the newer therapeutic agents licensed for complex SSTI management. Rapid cidal activity, good soft tissue penetration, once daily IV bolus administration and activity against resistant Gram-positive infections make daptomycin an attractive option both in hospitalized and community treated patients. A comprehensive review of the evidence for and experience with daptomycin and its use in SSTIs is presented.

Keywords: SSTI, MRSA, OPAT, outpatient parenteral antibiotic therapy, lipopeptide

Introduction

Daptomycin is the first cyclic lipopeptide and many of its qualities favor its use in complicated skin and soft tissue infections (cSSTIs). It was approved at a dose of 4 mg/kg for this indication by the Food and Drug Administration (FDA) in the United States in 2003 and subsequently in Europe in 2006.¹ Daptomycin also has approval for use in *Staphylococcus aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg. Beiras-Fernandez et al have provided a fuller review of daptomycin's other clinical applications previously in this journal.² Herein we review published data and experience with daptomycin in cSSTI.

Skin and soft tissue infections: clinical features and microbiology

Skin and soft tissue infections (SSTIs) can be defined as a suppurative microbial invasion of the epidermis and subcutaneous tissues that induce either a local or systemic host response. SSTIs are characterized by induration, erythema, warmth and pain or tenderness³ and range from mild self-limiting furunculosis to life-threatening necrotizing fasciitis.

Complicated SSTIs (cSSTIs) are those either involving deep soft tissue, or requiring significant surgical intervention (such as infected ulcers, burns, and major abscesses), or those in which a significant underlying disease state complicates the response to treatment (for example diabetes mellitus, obesity, immune deficiency, or underlying venous or arterial insufficiency).⁴ Various severity stratifications have been developed including one by Eron et al,³ forming the basis of the UK and CREST guidelines,

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and one by Ki and Rotstein in Canada.⁵ Such classifications are designed to alert the clinician to the level of care required and the need for ancillary therapies, as well as guiding the choice and route of administration of antibiotic therapy, but they remain to be validated. A recent retrospectively validated severity classification, using an adaptation of the Eron classification, stratifies patients with SSTI based on the presence of the systemic inflammatory response and the physiological standardized early warning score (SEWS) and suggests that the presence of co-morbidities is less significant in predicting outcome.⁶

The main etiological agents implicated in SSTIs are the Gram-positive organisms, *Staphylococcus aureus* (*S. aureus*), and the beta-hemolytic streptococci (Groups A, B, C and G). Methicillin-resistant *S. aureus* (MRSA) infections have risen in prominence over the last 20 years, comprising 59% of *S. aureus* isolates in a recent study in the USA⁷ and >10% of isolates in 19 out of the 28 countries in the 2009 European Antimicrobial Resistance Survey.⁸ The 2 distinct epidemiological forms of MRSA, community acquired (CaMRSA) and healthcare associated (HaMRSA) have quite different clinical features, largely as a consequence of the presence of the Panton Valentine leucocidin toxin in CaMRSA (Table 1). Increasingly however, considerable clinical overlap has been observed as HaMRSA presents in the community and CaMRSA emerges and spreads in healthcare facilities. Local prevalence of MRSA is not only important from the infection control perspective but also the empirical choice of antibiotic for SSTI. UK MRSA guidelines state that if the local prevalence of MRSA exceeds 10% of *S. aureus* isolates, then empirical treatment of a suspected *S. aureus* infection (including SSTI) should include anti-MRSA activity.⁹

Antibiotic therapy for SSTI

Beta lactam antibiotics, in particular the penicillinase stable penicillins (flucloxacillin and cloxacillin) remain the mainstay of treatment for suspected streptococcal and methicillin-sensitive *S. aureus* infections. Combination therapy with flucloxacillin and benzyl penicillin, although still widely practiced, is outdated.¹⁰ In proven penicillin-sensitive infection, rationalization to benzyl penicillin remains appropriate. Addition of intravenous clindamycin in rapidly progressive infections is advised as beta lactam antibiotics may be less effective in the static growth phase as characterized by severe streptococcal infections. Additional Gram-negative cover may also be considered in severe hospital-associated cSSTIs.

Vancomycin, discovered more than 50 years ago, has been the mainstay of therapy in MRSA infections and for patients intolerant or allergic to the beta lactams. Emerging data however suggest slower bacterial clearance and poorer clinical response in vancomycin-treated patients with methicillin-sensitive *S. aureus* (MSSA infection) compared to those treated with beta lactam agents.¹¹ There are also increasing reports of intermediate vancomycin resistance by a variety of mechanisms.¹² These factors, as well as concerns over potential vancomycin toxicity, have led to the development of new anti-MRSA agents such as the oxalodindiones (linezolid), new beta-lactam agents (eg, ceftobiprole and cef-taroline), new glycopeptides (dalbavancin and telavancin), the glycycline tigecycline and daptomycin. In addition there is renewed interest in older agents with anti-MRSA activity such as trimethoprim-sulfamethoxazole, clindamycin, sodium fucidate and tetracyclines, particularly in the context of CaMRSA. Of all these agents, linezolid and daptomycin have the largest evidence base supporting their efficacy and

Table 1 Clinical and epidemiological differences between healthcare associated and community acquired MRSA infection

	Healthcare associated MRSA infection	Community acquired MRSA infection
Prior hospitalizations/healthcare contact	Yes	No
History of prior antibiotic use	Yes	No
Chronic medical conditions, eg, diabetes mellitus, chronic kidney disease, vascular disease, decubitus ulcers	Yes	No
Contact sport, or living/working in crowded and/or unsanitary conditions	No	Yes
Men who have sex with men	No	Yes
Surgical site infections	Yes	No
Furuncles, boils and abscesses (recurrent)	Not typically	Typical
Severe necrotizing pneumonia	No	Yes
Panton Valentine leucocidin toxin producing	No	Yes
Antimicrobial resistance	Multidrug resistance	Beta-lactam resistance alone

safety in cSSTIs.^{13–16} Linezolid is highly effective in SSTI therapy and has an advantage over other agents used in severe SSTI in that it has an oral formulation which facilitates early IV to oral switch and the potential for earlier hospital discharge. Myelo- and mitochondrial toxicity, along with various drug interactions can reduce its utility, particularly when longer term therapy is required.¹⁷ Evidence for daptomycin use in SSTI, is discussed below.

Pharmacology of daptomycin

Pharmacodynamics

Daptomycin demonstrates rapid, concentration-dependent, bactericidal activity in vitro against susceptible and resistant Gram-positive cocci, including MRSA, glycopeptide- and linezolid-resistant *S. aureus* and vancomycin-resistant enterococcal species.^{18,19} It has a novel mode of action, inducing cell death by calcium-dependent efflux of potassium following insertion of its lipophilic tail into the cell membrane.²⁰ It shows a strong post-antibiotic effect against *S. aureus*, and in contrast to the beta lactam antibiotics maintains its activity against bacteria in stationary-phase growth.²¹

Daptomycin has been shown, in experimentally induced blister fluid in healthy volunteers, to have 68% dermal penetration as measured by the ratio under the concentration-time curve over 24 hours.²² A case report describing daptomycin concentrations in synovial fluid shows similar levels of tissue penetration, with synovial daptomycin levels found to be 70% of those in the serum.²³ Furthermore, a recent pharmacokinetic study of daptomycin 6 mg/kg in 10 patients with diabetic foot infection found free plasma concentrations equilibrating completely with soft tissue and metatarsal bone within 3 hours of the start of a 30 minute infusion, and this was not affected by inflammation.²⁴

Daptomycin has no Gram-negative activity, and although there are some data showing in vitro activity against anaerobic Gram-positive organisms, this is difficult to assess due to lack of clinical data to support breakpoints.²¹ This highlights the need to consider additional antimicrobials when used for cSSTIs where suspicion of mixed infection is high, eg, in necrotic diabetic foot infections.

Daptomycin is highly protein bound (91%) and renally excreted. Normally given as a once daily bolus according to patient weight, it is dosed 48 hourly in patients with a creatinine clearance (CrCl) of <30 mL/minute²⁵ or following dialysis.

Elevation in creatinine phosphokinase (CPK) and associated myopathy was frequently seen in early clinical

studies when the daptomycin was administered via multiple daily injections. CPK elevation is rare in short term treated patients receiving 4 mg/kg.^{15,26} In the Fowler et al study of daptomycin use in bacteremia and endocarditis where it was used at a dose of 6 mg/kg/day, CPK elevations were seen in 6.7% of the daptomycin treated group, but led to discontinuation of therapy in only 3 of the 120 patients (2.5%).²⁷ CPK levels should be monitored weekly, or more often in those with myalgia, or concomitant renal failure, or when drugs associated with elevated CPK levels and myopathy are co-administered.²¹ The FDA has also recently published a drug safety communication highlighting the potential for developing eosinophilic pneumonia during treatment with daptomycin.²⁸ The pharmacokinetics, safety and efficacy in children have not been established and are under investigation.²⁹ It is pregnancy category B.

Daptomycin's potential for true pharmacokinetic interactions is low as it does not undergo significant metabolism in vivo, and does not induce or inhibit the cytochrome P450 pathway.¹ Although not a drug–drug interaction or side-effect per se, daptomycin may cause a spurious rise in the measured prothrombin time due to an interaction with some test reagents. This can lead to difficulties in therapeutic monitoring for warfarin. The effect can be minimized by drawing the international normalized ratio (INR) blood sample just before the daptomycin is given^{30,31} or by using alternative reagents.

Review of comparative clinical studies assessing daptomycin use for cSSTIs (Tables 2 and 3)

The initial data supporting the use of Daptomycin 4 mg/kg/day in cSSTIs came from two Phase III randomized, investigator blinded, controlled clinical trials, comparing it with vancomycin or a semi-synthetic penicillin. The study population was adults (mean age 51) with cSSTIs who were judged to require hospitalization and parenteral antibiotics for ≥96 hours.¹⁵ In total, 1092 patients were included across 139 sites in the USA, Europe, South Africa, Australia and Israel between 1999 and 2001. Exclusion criteria included minor infections, third-degree burns, known bacteremia at enrolment, concomitant infection at another site (osteomyelitis, septic arthritis, or endocarditis) or a requirement for curative surgery (eg, amputation). The primary efficacy end point was the non-inferiority of daptomycin to the comparator in clinical success (resolution of signs and symptoms such that no further antibiotic therapy was required) in the clinically evaluable and intent-to-treat (ITT) populations at

Table 2 Characteristics of Daptomycin comparative SSTI studies

Study	Design	Patient characteristics	Daptomycin (dose, treatment duration)	Comparator (type, dose, treatment duration)
Arbeit ¹⁵	2 multicenter evaluator-blinded RCTs	N = 1092, adults with Gram-positive cSSTIs requiring hospitalization and IV antibiotics for ≥ 4 days	4 mg/kg IV once daily for 7–14 days	Vancomycin IV 1 g bd for 7–14 days or penicillinase-resistant penicillin IV 4–12 g IV q.d in equally divided doses
Davis ³⁶	Prospective open label	N = 56, hospitalized adults, cSSTIs at risk of MRSA, prospectively enrolled; 212 historical controls treated with vancomycin	4 mg/kg IV once daily for 3–14 days	Vancomycin IV dosed according to trough concentrations ≥ 3 days switched to semi-synthetic penicillin in absence of MRSA infection
Katz ³⁵	Multicenter, semi-single blinded RCT	N = 100, adults with cSSTIs at risk of MRSA, requiring IV antibiotics	10 mg/kg IV once daily for 4 days	Vancomycin IV 1 g bd or semi-synthetic penicillin IV 2 g q4h for ≤ 14 days
Pertel ³⁴	Multicenter, evaluator-blinded RCT	N = 103, adults with SSTI requiring hospitalization/iv antibiotics	4 mg/kg IV once daily for ≤ 14 days	Vancomycin IV standard doses for 7–14 days
Gollnick ³³	Phase IIIb multicenter RCT	N = 189, adults with cSSTI requiring hospitalization	4 mg/kg once daily for 4–14 days	IV Vancomycin or Teicoplanin for 4–14 days

Abbreviations: CE, clinically evaluable; ITT, intent-to-treat (all patients who received one or more doses of study medication); RCT, randomized controlled trial; IV, intravenous; cSSTI, complicated skin and soft tissue infections.

a test of cure (TOC) visit (6–20 days after the last dose of therapy).

Baseline characteristics were similar with wound infection comprising 44% of underlying diagnoses, 24% with major abscesses, 12% infected diabetic ulcers and 37% with a systemic inflammatory response (SIRS). Over 80% of patients had the infecting organism identified, 70% of which were *S. aureus* (10% were MRSA).

The two trials, both individually and collectively, met the predefined statistical criteria for non-inferiority of

daptomycin against comparator therapy (<10% difference in the upper limit of the 95% confidence interval between the groups' success rates). Success in the clinically evaluable and microbiologically evaluable populations was comparable, and no organism-specific difference was observed in response to treatment. In particular daptomycin was as effective as both vancomycin against MRSA (clinical success in 75% of those in the daptomycin arm, 69% in the comparator arm), and penicillinase-resistant penicillin against methicillin-sensitive *S. aureus* (MSSA) (clinical

Table 3 Summary of outcomes in published comparative studies of daptomycin in patients with cSSTIs

Study	Median duration of therapy with study drug (days)		Clinical success for CE population, n/N (%)		Clinical success in patients with MRSA infections		Patients with treatment-related AEs, n/N (%)	
	D	C	D	C	D	C	D	C
Arbeit ¹⁵ Phase III multicenter RCTs	Not known	Not known	372/446 (83)	384/456 (84)	21/28 (75)	25/36 (69)	94/534 (18)	119/558 (21)
Davis ³⁶ Prospective open-label, vs historical controls	4	7	41/53 (77)	89/212 (42)	15/15 (100)	30/30 (100)	0/56 (0)	0/212 (0)
Katz ³⁵ Multicenter RCT	4 ^a	8 ^a	32/39 (82)	37/39 (95)	24/31 (77)	27/28 (96)	20/48 (42)	11/48 (23)
Pertel ³⁴ Multicenter RCT	6.1*	6.2*	47/47 (100)	46/47 (98)	NR	NR	3/50 (6)	1/51 (2)
Gollnick ³³ Phase IIIb Multicenter RCT	8~	7~	53/58 (91.4)	41/47 (87.2)	NR	NR	55/97 (56.7)	51/92 (55.4)

Notes: ^aStudy designed to assess outcomes in a group of patients receiving high-dose daptomycin for 4 days versus comparator for ≤ 14 days; *Mean length of IV therapy –IV therapy was for at least 4 days.

Abbreviations: CE, clinically evaluable; MRSA, Methicillin-resistant *Staphylococcus aureus*; AE, adverse events; NR, not recorded; NA, not applicable.

success in 86% of those in the daptomycin arm, 87% in the comparator arm).¹⁵

This study was not designed to assess differences in duration of parenteral therapy between groups, however a post hoc analysis of the study population that received only intravenous therapy (89.8% of the total), found that 63% of the daptomycin-treated group required only 4–7 days of therapy compared with 33% of the comparator arm ($P < 0.0001$). A further analysis of a subset of the South African enrolled patients with \leq one co-morbidity showed that the median duration of therapy was shorter in the daptomycin group (7 versus 8 days for the comparator group, $P < 0.0001$).³²

A subsequent Phase IIIb multi-center randomized assessor-blinded study³³ compared the efficacy and safety of daptomycin versus vancomycin or teicoplanin for the treatment of cSSTIs. The primary objective was to compare daptomycin to its comparator at day 7–14 for clinical success (complete resolution of clinical signs and symptoms or improvement requiring no additional therapy). Patients with cSSTIs were included if they were expected to receive at least 4 days of IV therapy before step down to oral therapy, if needed, and were randomized (1:1) and stratified by age (≥ 65 years) and systemic inflammatory response syndrome (SIRS) to receive either daptomycin (4 mg/kg IV once daily [OD]) or a glycopeptide (vancomycin 1 g IV BD or teicoplanin 400 mg IV OD). 189 patients (97 in the daptomycin arm, 92 in the comparator) from 29 centers across Europe received treatment. Baseline demographics were similar, with 1/3 of patients ≥ 65 years old and SIRS present in 58.8% in the daptomycin arm and 56.5% in the pooled comparator. In this study the median time to switch to oral therapy or end therapy

was the same in both groups (8 days), and success rates in the clinically evaluable population were similarly high in both groups (91.4% for daptomycin and 87.2% for the pooled comparator) although in elderly patients there was a trend to a higher clinical success rate with daptomycin than with the pooled comparator (88.9% versus 76.5%, respectively, (Confidence interval [CI] –22.4, 45.1).³³

A summary of the outcomes from these 3 studies along with the other main comparative studies discussed in this review are presented in Table 3.

Meta-analysis of daptomycin therapy for cSSTIs

Three randomized controlled trials (RCTs) and 1 prospective comparative study (included in Tables 3 and 4) were included in a recent meta-analysis comparing the effectiveness of daptomycin with other agents in the treatment of SSTIs.¹⁶ Three studies only included patients with cSSTIs whilst one included non-complicated SSTIs.³⁴ Vancomycin and semi-synthetic penicillins were the comparator agents used. Short-term high-dose daptomycin therapy (10 mg/kg/day for 4 days) was evaluated in one study.³⁵ In total 1557 patients were evaluated (688 in the daptomycin group). No statistically significant difference in clinical success or toxicity in the clinically evaluable or ITT populations was noted. No firm conclusions on the comparative efficacy of daptomycin versus vancomycin in MRSA infection could be drawn due to significant differences between the studies in the proportion of patients infected with MRSA.

Two studies have specifically examined duration of IV therapy as an outcome but results have been inconclusive: In a nonrandomized study utilising retrospective vancomycin

Table 4 Characteristics of SSTI patient population included in CORE 2004, 2005 and EU-CORE 2006–'08

Characteristic	CORE 2004 SSTI subgroup ⁴⁰ (n = 522)%	CORE 2005 SSTI subgroup ^{41,42} (n = 486)%	EU-CORE 2006–2008 ^{39,44} (n = 484)%
Age > 66~	24	21	53
CrCl < 30 mL/minute	26	12	9
Diabetes	27	30	41
cSSTIs	64	70	100
Bacteremia	3	5	NR
Prior antibiotic therapy	67	74	62
Prior vancomycin	Not reported	49	22*
MRSA [#]	63	52	33
Enterococcal sp	19	Not reported	10
VRE**	8	Not reported	3

Notes: ~Age ≥ 65 in EU-CORE group; NR, not recorded; *Percent of all EU-CORE data from this time period ie, includes the non-SSTI patients; #Percent of all positive isolates that were MRSA positive; **Including both vancomycin resistant *Enterococcus faecium* and *faecalis*.

Abbreviations: VRE, vancomycin resistant enterococcus; MRSA, methicillin resistant *Staphylococcus aureus*; SSTI, skin and soft tissue infections; cSSTI, complicated skin and soft tissue infections; CrCl, creatinine clearance; CORE, Cubicin Outcomes Registry and Experience program; EU-CORE, European Cubicin Outcomes Registry and Experience program.

treated controls,³⁶ median duration of time of IV therapy, as well as time to clinical cure and length of stay was less (4 days [range 2–13] versus 7–8 days [range 3–19]) in the daptomycin arm. Notably a higher proportion of patients with MRSA received daptomycin (Table 4). In a setting of high MRSA prevalence, an unusual study was employed whereby 96 patients were randomized to 4 days of high dose daptomycin (10 mg/kg/day) or 8 days of intravenous vancomycin with the option to switch to a semi-synthetic penicillin in sensitive isolates.³⁵ Both arms could switch to oral therapy following clinical improvement. The study was not statistically powered to detect differences between treatment groups, but a trend towards better outcome in the comparator group with longer therapy was observed. Differences were more pronounced in the MRSA subgroup, which itself has previously been identified as an independent predictor of longer hospital stays and poorer clinical outcome irrespective of therapy.³⁷

A further meta-analysis has looked at the comparative effectiveness of antibiotics for the treatment of MRSA complicated skin and soft tissue infections using a Bayesian statistical approach which enables combining of evidence to handle indirect comparisons.³⁸ It compared treatment of cSSTI by vancomycin, linezolid, daptomycin, tigecycline and the novel glycopeptides dalbavancin and telavancin. Following a literature search which initially identified 1632 papers, it included 13 studies within which they could specifically look at the subset of patients with confirmed MRSA-related cSSTIs. Of these however it only included one paper on daptomycin,¹⁵ which only included 28 patients with MRSA infection. No difference in effect between daptomycin (success rate of 78.1%; 95% Bayesian confidence interval [CrI_{95%}]: 54.6%–93.2%) and vancomycin (pooled success rate of 74.7%; CrI_{95%}: 64.1%–83.5%) was demonstrated.

Review of non-comparative studies of daptomycin use in cSSTIs

There is now increasing experience with daptomycin worldwide, with over an estimated 1,000,000 treated patients by

mid-2010.³⁹ Clinical experience with daptomycin has been captured within the Cubist-sponsored Cubicin Outcomes Registry and Experience (CORE) programme: a multi-center retrospective observational programme based in the United States, and now by the Novartis Pharma AG-sponsored European registry (EU-CORE). Data have been collected on patients who have received daptomycin outside the trial setting, providing ‘real-life’ experience. The data produced should be interpreted with care due to their retrospective, observational nature and potential inclusion bias.

Patient characteristics and outcomes for those with cSSTIs from CORE 2004⁴⁰ and 2005,^{41–43} as well as from EU-CORE analysis for January 2006 to August 2008^{39,44} are presented here (Tables 4 and 5).

MRSA infections make up the majority of positive isolates in the earlier registry groups (63% in 2004, 52% in 2005), but a smaller proportion of the European group perhaps reflecting recent decline in MRSA in some participating European nations. Nonetheless, MRSA still accounted for over 50% of all *S. aureus* isolates. The high rate of prior antibiotic use has been notable across all registry groups, with glycopeptides and in particular vancomycin being the most common preceding antibiotic. Switch to daptomycin was most commonly observed following treatment failure. The EU-CORE data show similarly low failure rates whether daptomycin was prescribed as first- or second-line therapy (6% versus 8% respectively)³⁹ suggesting perhaps that prior vancomycin therapy does not increase the risk of daptomycin failure.

For patients treated for SSTI, a median dose of 4 mg/kg was observed most frequently with a higher mean dose used in cSSTIs compared with uSSTIs (4.5 mg/kg versus 4.2 mg/kg in 2004 ($P < 0.001$) and 4.7 mg/kg versus 4.4 mg/kg in 2005). In the most recent data from EU-CORE a significant proportion of those with cSSTIs (43%) received ≥ 6 mg/kg, possibly indicating the complexity of infections treated, and perhaps increasing confidence in daptomycin’s safety and tolerability at these doses.

Table 5 Clinical outcomes and treatment characteristics of patients treated with daptomycin for cSSTIs in CORE 2004, 2005, 2007 and EU-CORE 2006–‘08

Study	Patient group	Success rate in CE patients (%)	Success rate in MRSA infections (%)	Mean dose mg/kg (range)	Median duration of therapy (days)
CORE 2004 ⁴⁰	cSSTIs (n = 334)	96	136/144 (97)	4.5 (2.3–12)	14
CORE 2005 ^{41,42}	cSSTIs (n = 333)	93	Not known	4.7 (2–10)	13
EU-CORE 2006–2008 ^{39,44}	cSSTIs (484)	84	152/187 (81.5) ^a	Not known ^b	10

Note: ^aTotal MRSA population including non-cSSTIs; ^bMean/median dose not recorded, but 44% of patients received 4 mg/kg, and 43% received ≥ 6 mg/kg.

Abbreviations: cSSTI, complicated skin and soft tissue infection; CE, clinically evaluable; MRSA, methicillin resistant *Staphylococcus aureus*; CORE, Cubicin Outcomes Registry and Experience program; EU-CORE, European Cubicin Outcomes Registry and Experience program.

Overall clinical success was judged by local investigators as ‘cured’ where no further antibiotic therapy was required, and ‘improved’ where there was clinical improvement but further therapy was required following daptomycin.⁴⁵ Overall success was >90% in both the CORE 2004 and 2005 studies, and >80% in the EU-CORE registry (Table 5). High success rates were maintained in patients with confirmed MRSA infections. The median time to clinical response, as evidenced by signs and symptoms was 4 days (range 1–32) for patients with cSSTIs (2004 registry).

A multivariate analysis of the CORE 2005 cohort determined that sepsis, ICU stay and creatinine clearance <30 mL/minute were significantly associated with clinical failure.⁴³ However, a subsequent stepwise multivariate regression analysis of a larger data set of patients with *S. aureus* infections from CORE 2005 to 2007 found that the only independent predictors of clinical failure with daptomycin therapy were the presence of endocarditis, bacteremia, severe renal dysfunction (CrCl < 30 mL/minute) and diabetes mellitus.⁴⁶ Each of these factors have been found to be associated with increased infection-related complications and mortality in previous studies.^{27,47} This analysis also suggested that prior treatment with other antibiotics, including vancomycin, did not independently influence treatment outcomes with daptomycin, even if the reason for using daptomycin was prior treatment failure.⁴⁶

Daptomycin in specific cSSTIs

As previously noted cSSTIs comprise a diverse group of infections with similar etiology but varying environmental and host factors. Differing infection types may present diverse therapeutic challenges. Some of these have been investigated in sub groups of prospective clinical trials whilst others have been retrospectively evaluated in post-marketing studies.

Surgical site infections (SSI)

In the CORE 2007 population,⁴⁸ 118 of the 962 patients had SSI. Of these 104 (11%) met the criteria for an efficacy analysis. Positive microbiology was found in 73% and the majority were *S. aureus* (59%) with MRSA in 25 (24%). The majority of patients also received concomitant antibiotics however (54%), reflecting the potential polymicrobial nature of these infections.

Overall success (cured or improved) was observed in 91.3% with SSI and no statistical difference was observed between pathogens except for the small number of infections caused by vancomycin-resistant *Enterococcus* species, where

success was observed in 5/8 (63%). On logistic regression vancomycin-resistant enterococcal infection was found to be an independent risk factor for failure (odds ratio 14.2, 95% confidence interval 1.3–154). This observation in a small number of patients has not been reflected in large international surveillance programmes.^{49–54}

Diabetic foot infections

Pharmacokinetic data have shown that daptomycin effectively penetrates the soft tissue and bone in patients with diabetic foot infections.²⁴ The clinical evidence supporting daptomycin use in diabetic foot ulcers (DFUs) largely comes from a subset analysis of the two international Phase III RCTs previously discussed.⁵⁵ In these studies, 133 patients (12% of the total) had DFU infection and 103 were clinically evaluable. 47 received daptomycin and 56 received either vancomycin or semi-synthetic penicillin. Most infections were monomicrobial and *S. aureus* was the predominant pathogen, with MRSA isolated in 18.2%. There were no statistically significant differences between the daptomycin and the comparator groups for either the overall clinical outcomes (66% versus 70% respectively) or when analysed by infecting organism.⁵⁵ Of the 39 patients treated for DFUs in CORE 2004, 35 (90%) were successful (cured or improved).¹⁵

Daptomycin in outpatient management of cSSTI

Outpatient parenteral antibiotic therapy (OPAT) is increasingly recognized as a cost-effective management option for patients with SSTIs where the appropriate guidance and expertise are available.³⁰ OPAT enables shorter length of hospital stay or even avoidance of admission in appropriate patients, conferring patient convenience, a significant reduction in hospital costs,⁵⁶ and also reduced risk of health care associated infection. However, a recent study in Glasgow, where OPAT is well established, shows that the service remains poorly accessed in patients with MRSA-associated SSTIs with only 10 (5.8%) of 173 patients receiving OPAT over a 16 month period and potentially one third of survivors having had the potential to be discharged earlier with either oral therapy or OPAT.⁵⁷

In the UK for OPAT-managed SSTIs when MRSA is not suspected and there is no history of beta lactam allergy, Ceftriaxone 1–2 g IV daily is the standard of care.⁵⁸ In suspected MRSA or allergy, teicoplanin is the usual alternative pending IV to oral switch. Current recommendations are for teicoplanin to be administered via a loading regimen of three 400 mg doses 12 hourly followed by daily dosing. As the loading regimen is most easily performed in hospital

the opportunity for an avoided admission may be lost. Also higher doses (600–800 mg/day) of teicoplanin are generally preferred by most UK infection specialists. In some centers higher doses of teicoplanin (10–15 mg/kg) are used with a daily loading regimen for 3 days followed by thrice weekly dosing until oral switch is feasible.⁵⁹ In a recently reported cohort of nearly 1000 OPAT-managed SSTIs (approximately 150 of whom received teicoplanin as per the above regimen), first line OPAT therapy with teicoplanin was identified as an independent risk factor for OPAT failure (as defined by either intolerance/allergy, progression of infection or readmission). Increased rates of failure were largely due to teicoplanin intolerance or allergy. Increased duration of therapy compared to ceftriaxone treated patients may have reflected the intermittent dosing regimen.⁶⁰

Daptomycin is well suited to OPAT use. It has proven clinical efficacy in cSSTIs and a low and predictable toxicity profile. A half-life of 8–9 hours and a prolonged post-antibiotic effect (>6 hours), allows once-daily IV bolus administration. There is growing clinical experience supporting daptomycin's use in the OPAT setting.

In CORE 2005, 539 (56.8%) of the clinically evaluable patients received OPAT, either de novo or following inpatient initiation.⁵⁶ One hundred and seventy seven (32.8%) OPAT treated patients had cSSTI. Proportionally more uncomplicated SSTIs were managed via OPAT (18.4% versus 8.8% managed solely via inpatient antibiotic therapy [IPAT], $P < 0.001$). cSSTI rates were similar in OPAT and IPAT groups. Cure or improvement was observed in 94.6% OPAT treated patients versus 86.3% for those treated with IPAT alone (chi-squared test <0.001). OPAT was also associated with fewer adverse events, reflecting patient selection for OPAT versus IPAT.

Within EU-CORE between 2006 and 2008,⁶¹ 153 (13.6%) received daptomycin via OPAT. Thirty four patients (22.1%) were treated for cSSTIs. Overall in OPAT 58 (37.9%) of infections were due to *S. aureus*, the majority of which were MRSA. Daptomycin was typically administered at 4 mg/kg ($n = 55$, 35.9%) and 6 mg/kg ($n = 79$, 51.6%) and clinical success at 30 days post-treatment was observed in 136 (88.9%). Possible adverse events were reported in 16 patients, but all were mild to moderate in severity.

Future developments and areas of controversy

Daptomycin resistance

Daptomycin resistance is rare, with more than 99% susceptibility of Gram-positive isolates in recent large European,

North and South American, as well as Australian and New Zealand surveillance studies, including amongst MRSA and vancomycin resistant enterococci (VRE).^{49–54} To our knowledge resistance has not been reported in patients with SSTIs, but there are several case reports of daptomycin non-susceptibility and/or resistance emerging during treatment in patients with deep-seated infections, highlighting the key role that surgical debridement has in these circumstances.^{27,62,63}

Although some in vitro data have led to concerns regarding increased risk of daptomycin resistance associated with intermediate susceptibility to vancomycin (VISA),^{64,65} recent clinical data have shown that in the vast majority of cases of VISA, daptomycin remained effective.⁶⁶ Animal data have shown that increasing the dose of daptomycin can improve its efficacy for *S. aureus* strains with reduced daptomycin susceptibility,⁶⁷ therefore using a higher dose may be advisable in these patients until evidence is available to guide management.

Dosing of daptomycin in SSTIs

The current licensed dosing for SSTIs is 4 mg/kg in SSTIs¹⁵ and 6 mg/kg in bacteremia.²⁷ There are recent data supporting the safe use of daptomycin at doses up to 12 mg/kg, including in patients with a CrCl of < 30 mL/minute and on hemodialysis, when dosing interval is appropriately adjusted.^{67,68} Furthermore, the presence of bacteremia, endocarditis, severe renal dysfunction (defined as an initial CrCl < 30 mL/minute) and diabetes mellitus were the variables independently associated with clinical failure of daptomycin therapy.⁴⁶ Therefore, although the 4 mg/kg dose has been shown to be effective and is appropriate for the majority of patients with SSTIs, it has been suggested that higher dosing at 6 mg/kg should be considered in certain patient groups (Table 6).³⁰ In particular this includes patients at risk of, or proven to have bacteremia, which should include those presenting with a sepsis syndrome or requiring high dependency or intensive care

Table 6 Patients with SSTI in whom initial daptomycin dose should be ≥ 6 mg/kg

Associated sepsis syndrome
Otherwise suspected or confirmed bacteremia or endocarditis
Diabetic foot infection/infected ulcer
Suspected underlying osteomyelitis or septic arthritis
Intravenous drug user
Burns injury ^a
Glycopeptide intermediate-resistant MRSA
Consider when creatinine clearance < 30 mL/minute ^b

Note: ^aConsider doses of 10–12 mg/kg; ^bDosing interval should be increased to 48 hourly.

Abbreviation: MRSA, methicillin resistant *Staphylococcus aureus*.

due to cSSTI. In diabetic patients with a SSTI complicating a foot ulcer, the possibility of an osteoarticular infection can be difficult to exclude initially, and therefore higher doses would be advisable in these patients.⁶⁹ Patient groups at risk of SSTIs who are known to have altered drug pharmacokinetics are also likely to require higher doses. Intravenous drug users (IVDU) have increased drug clearance and are therefore likely to require the 6 mg/kg dose, although clinical data are not yet available to confirm this.²⁷ Another group is patients with burn injuries. In 2008 a pharmacokinetic study looked at nine patients with $\geq 18\%$ body surface area burns between 7 and 27 days after the burn injury. They demonstrated a decreased area under the curve (AUC), increased volume of distribution and more rapid clearance of daptomycin (as is seen with other antibiotics evaluated in burns patients) compared to normal controls. This is felt to reflect clearance of daptomycin through the burn wound itself. The AUC was reduced by 47% for burns patients with a 6 mg/kg dose, and as its pharmacokinetics are linear, the authors suggest that a dose of 10–12 mg/kg would be required in this group of patients to achieve similar drug exposures to those achieved in healthy volunteers.⁷⁰

Economics

Drug acquisition costs have been one of the major hurdles in daptomycin becoming a first line treatment option in countries where health care is state funded. However, in a recent Canadian review of cost drivers associated with MRSA infection, antimicrobial therapy only made up 4% of the total cost, while hospitalization was estimated to be by far the largest driver (at 81% of the cost per patient).⁷¹ The authors estimated that direct health care cost attributable to MRSA in Canada averaged \$82 million in 2004 and could reach \$129 million in 2010.

Daptomycin is highly suitable as an empirical parenteral antibiotic option in patients with cSSTI to enable OPAT, particularly when there is a suspicion of MRSA infection or serious beta lactam allergy. More rapid hospital discharge or admission avoidance for patients with SSTI in whom IV therapy is indicated, gives a distinct economic advantage. A study in Ohio reviewed outcomes of the first 50 consecutive patients treated with daptomycin in a community hospital, 31 of whom had cSSTI.⁷² Out of the 50 patients, 31 (62%) had confirmed MRSA infection. Fourteen patients (28%) transitioned to outpatient daptomycin therapy saving an estimated \$102,340 in hospital charges. In 48 (96%), infection resolved with daptomycin therapy. Although this study was limited by its observational retrospective nature,

it emphasises the significant cost savings that accompany shorter or no hospitalization in these patients.

Shorter duration of therapy could confer economic advantage, however to date the *in vitro* rapid cidal activity of daptomycin has yet to be translated into a demonstrably more rapid clinical response or shorter therapy duration.

More clinical and economic data are required to fully evaluate daptomycin's cost efficiency in comparison to the glycopeptides and to linezolid. Particularly important questions are whether daptomycin use can achieve quicker clinical improvement and hence shorter course IV therapy in both hospital and OPAT settings compared to the glycopeptides or linezolid and whether this, combined with OPAT use, can translate to shorter hospitalization. To date these questions have not been addressed in clinical trials.

Current international recommendations

The current international guidelines for the management of SSTIs in patients known to have, or at risk of MRSA are summarized in Table 7. Daptomycin is considered a first line option for cSSTIs in the UK^{14,73} and the USA²⁶ and second line in severe infections in Spain.⁷⁴ Daptomycin is recommended as one of the options for enabling OPAT in the UK.⁷³

Summary and recommendations

SSTIs form a substantial part of acute hospital care in all countries. Infections with MRSA, the presence of beta lactam allergy and declining efficacy of the glycopeptides requires that alternative antibiotics are available. For inpatients at risk of MRSA or with beta lactam allergy, glycopeptides are likely to remain the first line option in the majority of patients at present. The data presented to date have not demonstrated superiority of daptomycin over glycopeptides in cSSTI, however daptomycin is likely to remain an important second line agent in those failing or intolerant of the glycopeptides. If *in vitro* rapid cidal activity data translates to a more rapid clinical improvement in future studies, the significant benefits of shorter course therapy and shorter hospitalization could encourage greater empirical use of daptomycin in cSSTI in hospital. As clinicians become more experienced with the use of OPAT to manage SSTI, and aware of the substantial economic and psychosocial benefits derived from non-inpatient management, daptomycin may become increasingly used, particularly in patients at risk of infection with resistant Gram-positive pathogens. A proposed algorithm for management of cSSTI is shown in Figure 1.

Table 7 Current international MRSA SSTI guidelines

Guideline	Ist line	Alternative	OPAT	IVOST	Duration
Spain⁷⁴					
SSTI (mild)	Clindamycin Doxycycline	Co-trimoxazole	NA	NA	No comment
SSTI (more severe)	Linezolid, Vancomycin ± Clindamycin	Tigecycline (polymicrobial) Daptomycin (MIC ≥ 1.5)	No comment	Linezolid	No comment
UK^{14,73}					
SSTI (non-hospital)	Doxycycline Clindamycin Rifampicin + (Fusidate or Doxycycline or Trimethoprim)	Linezolid Co-trimoxazole	Glycopeptide Daptomycin	Yes	No comment
SSTI (hospital)	Glycopeptide Linezolid Daptomycin	Tigecycline (polymicrobial) Clindamycin	Glycopeptide Daptomycin	Clindamycin Linezolid	No comment
USA²⁶					
uSSTI	Clindamycin TMP-SMX Tetracycline Linezolid	No comment	Not applicable	Not applicable	5–10 days
cSSTI	Vancomycin Linezolid Daptomycin Telavancin Clindamycin	No comment	No comment	Linezolid Clindamycin	7–14 days

Abbreviations: NA, Not applicable; OPAT, Outpatient parenteral antibiotic therapy; IVOST, Intravenous to Oral antibiotic Switch Therapy; SSTI, skin and soft tissue infection; uSSTI, uncomplicated SSTI; cSSTI, complicated SSTI.

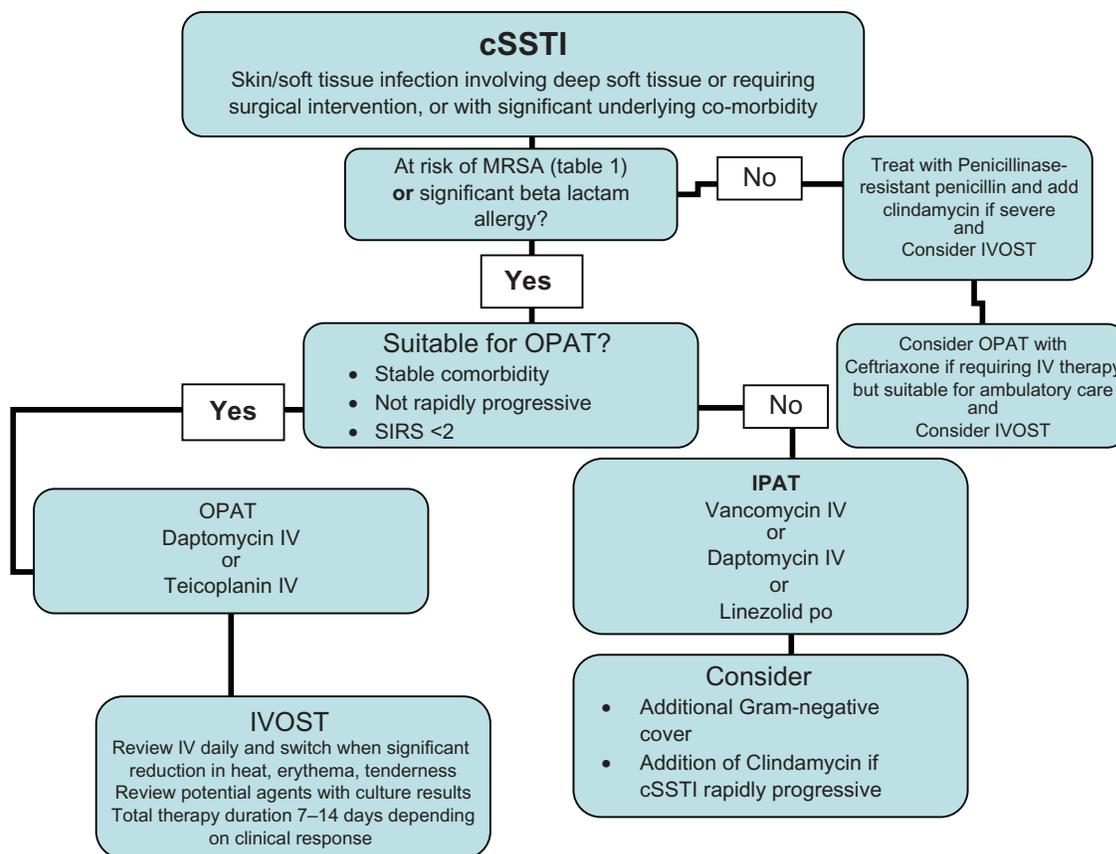


Figure 1 Proposed antibiotic management algorithm for MRSA cSSTIs.

Abbreviations: OPAT, Outpatient parenteral antibiotic therapy; IPAT, Inpatient parenteral antibiotic therapy; IVOST, Intravenous to oral antibiotic switch therapy.

Disclosure

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