Early clinical assessment of response to treatment of skin and soft-tissue infections

Nathwani, Dilip; Dryden, Matthew; Garau, Javier

Published in:
International Journal of Antimicrobial Agents

DOI:
10.1016/j.ijantimicag.2016.04.023

Publication date:
2016

International Journal of Antimicrobial Agents 48 (2016) 127–136

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Early clinical assessment of response to treatment of skin and soft-tissue infections: how can it help clinicians? Perspectives from Europe

Dilip Nathwani [a,*], Matthew Dryden [b], Javier Garau [c]

[a] Ninewells Hospital and Medical School, Ward 42, East Block, Dundee DD1 9SY, UK
[b] Royal Hampshire County Hospital, Romsey Road, Winchester SO22 5DG, UK
[c] Hospital Universitari Mutúa de Terrassa, Plaza Dr Robert 5, Barcelona 08221, Spain

ARTICLE INFO

Article history:
Received 9 November 2015
Accepted 19 April 2016

Keywords:
Skin and soft-tissue infection
Antibiotic treatment
Clinical assessment
Early discharge

ABSTRACT

Skin and soft-tissue infections (SSTIs) are a common indication for antibiotic use in Europe and are associated with considerable morbidity. Treatment of SSTIs, occasionally complicated by infection with meticillin-resistant *Staphylococcus aureus*, can be resource intensive and lead to high healthcare costs. For patients treated in an inpatient setting, once the acute infection has been controlled, a patient may be discharged on suitable oral antibiotic therapy or outpatient parenteral antibiotic therapy. The recently confirmed efficacy of single-dose (e.g. oritavancin) and two-dose (e.g. dalbavancin) infusion therapies as well as tedizolid phosphate, a short-duration therapy available both for intravenous (i.v.) and oral use, for treating SSTIs has highlighted the need for clinicians to re-evaluate their current treatment paradigms. In addition, recent clinical trial data reporting a novel endpoint of early clinical response, defined as change in lesion size at 48–72 h, may be of value in determining which patients are most suitable for early de-escalation of therapy, including switch from i.v. to oral antibiotics, and subsequent early hospital discharge. The aim of this paper is to review the potential impact of assessing clinical response on clinical decision-making in the management of SSTIs in Europe, with a focus on emerging therapies.

1. Introduction

Skin and soft-tissue infections (SSTIs) encompass a wide spectrum of clinical presentations, depending on the anatomical site of infection [1]. They range in severity from mild superficial forms to severe life-threatening infections that penetrate the deep subcutaneous tissues and/or require hospitalisation [2]. A variety of acronyms and definitions are used to describe SSTIs, which can lead to confusion among clinicians, including prescribers [3]. For example, skin and skin-structure infection (SSSI) is a commonly used term that can be considered synonymous with SSTI [4]. The term complicated SSTI (cSSTI) is used to describe infections that are at the extreme end of the clinical spectrum; cSSTIs are often accompanied by some evidence of systemic sepsis [1]. The US Food and Drug Administration (FDA) has introduced the term acute bacterial skin and skin-structure infection (ABSSSI) to help delineate the types of skin infections that should be assessed in registration trials of new antibiotics [4]. ABSSSIs include cellulitis/erysipelas, wound infections and major cutaneous abscesses, but exclude infections resulting from animal or human bites, necrotizing fasciitis, diabetic foot infection and decubitus ulcer infection [4]. For clarity, the term SSTI will be used here to describe all types of skin infection except where specifically stated otherwise.

The aim of this article is to review how early assessment of the patient's response to treatment can help clinicians in Europe improve the patient journey, such as shortening the hospital length of stay (LOS) and optimising outpatient therapy, thereby addressing important antimicrobial stewardship goals. To achieve this aim, clinical trials of recently licensed antimicrobials for the treatment of SSTI (due both to susceptible and resistant strains of *Staphylococcus aureus*) will be considered.

1.1. Clinical burden and epidemiology

SSTIs are a common indication for antibiotic use in Europe and are associated with considerable morbidity [5]. Data from the European Centre for Disease Prevention and Control (ECDC) estimated that 4% of all healthcare-acquired infections (HAIs) reported between 2011 and 2012 were SSTIs, with surgical-site infections being the second most frequently reported HAI (19.6%) [5]. During 2008 and 2009 there were 82,113 cellulitis hospital admissions in England and

* Corresponding author. Ninewells Hospital and Medical School, Ward 42, East Block, Dundee DD1 9SY, UK. Tel.: +44 138 266 011; fax: +44 1382 4965547.
E-mail address: dilip.nathwani@nhs.net (D. Nathwani).

http://dx.doi.org/10.1016/j.ijantimicag.2016.04.023

Wales with a mean hospital LOS of 7.2 days, and an estimated £133 million (€170 million; US$209 million) of costs were due to direct inpatient bed stay [6].

In Europe, the most frequently isolated Gram-positive pathogens in SSTIs are *S. aureus* [including meticillin-resistant *S. aureus* (MRSA) and meticillin-susceptible *S. aureus* (MSSA)], followed by β-haemolytic streptococci [1,7,8]. In skin infections that have a more complex aetiology, such as those resulting from necrotizing fasciitis, diabetic foot infection and ecthyma gangrenosum, the range of pathogens is numerous and is dependent on the clinical setting [4,9].

The prevalence of MRSA varies greatly across Europe, with much higher frequencies seen in southern and southeastern countries [10]. Based on the European Antimicrobial Resistance Surveillance Network (ERAS-Net), the European population-weighted mean percentage for MRSA was 17.4% in 2014, ranging from 0.9% in the Netherlands to 56.0% in Romania [10].

1.2. Resource implications

Treatment of hospitalised patients with SSTI in Europe is resource intensive and is associated with prolonged hospital LOS and high healthcare costs [11,12]. The drivers of increased LOS are described in Table 1. Patients with MRSA-SSTI experience a longer LOS compared with patients with MSSA-SSTI, which can be further prolonged when the initial antibiotic treatment fails [12]. The acquisition cost of antibiotics represents a relatively small proportion of the overall cost of managing cSSTIs in hospitals. A 2009 study estimated that for linezolid-treated patients, the per-patient total treatment cost (comprising hospitalisation, antibiotic, inpatient tests and aftercare charges) was €7778 [14]. The cost of the antibiotic itself was €1595, representing ≈ 20% of the total. The same study demonstrated that vancomycin treatment was associated with a higher overall cost (€8777) despite the comparatively lower cost of this drug (€964; ≈ 11% of the total) [14].

For inpatients, once the acute infection has been controlled and there are no other reasons for continued hospitalisation, it should be possible to discharge patients on suitable oral antibiotic therapy or outpatient parenteral antibiotic therapy (OPAT) [15–17]. Treatment outside of the hospital setting is generally preferred by patients, is relatively low cost and is aligned with antimicrobial stewardship strategies [16,18]. Three new antibiotics (oritavancin, dalbavancin and tedizolid phosphate) could offer additional opportunities for early discharge of cSSTI patients [19–21], in keeping with antimicrobial stewardship initiatives. Oritavancin and dalbavancin offer, respectively, a single-dose or two-infusion dose of treatment, representing a novel paradigm for treating such infections [22,23]. Tedizolid phosphate offers both intravenous (i.v.) and oral treatment options for a 6-day treatment duration [24,25]. Phase 3 trials of tedizolid phosphate demonstrated that 6 days of therapy, which is a shorter duration than that recommended for most other antibiotics for this indication [26–29], was non-inferior to 10 days of therapy with linezolid [24,25], providing evidence-based reassurance for clinicians to consider shorter durations of treatment with this antibiotic.

Table 1
Drivers of increased length of stay for hospitalised patients with complicated skin and soft-tissue infections (cSSTIs) (adapted from Nathwani et al) [13].

- Increased length of intravenous (i.v.) therapy
- History of i.v. drug abuse
- High number of co-morbidities
- Patients with deep or extensive cellulitis (versus patients with a surgical site or post-traumatic wound infection)
- Infection in the torso or abdomen (versus upper extremity infection)
- Infection developed ≥4 days after admission
- Severe sepsis
- Surgery
- Late initiation of antibiotic treatment (≥3 days after the date of cSSTI diagnosis)
- Failed/inappropriate initial/empirical therapy
- No i.v.-to-oral antibiotic switch options and/or lack of corresponding protocol
- Not discharged from the hospital with outpatient parenteral antibiotics
- Cultural attitudes of physicians toward completion of i.v. course in hospital
- Healthcare system reimbursement policies
- Lack of awareness of treatment/administration options

2. Management of skin and soft-tissue infections

Management of SSTIs is dependent on the clinical presentation and the severity of the infection [2]. In general, a combination of surgical debridement or drainage and antibiotic treatment is used to treat the infection [1], although incision and drainage, without the need for antibiotics, is usually sufficient for treating simple abscesses or boils [30]. Determining the level of disease severity is an important first step in the clinical management of SSTIs in order to determine the type of care and empirical therapy [31]. Failure to do this can lead to inappropriate prescribing, with overtreatment of mild SSTIs and undertreatment of severe SSTIs having been reported previously [32,33]. For non-necrotizing SSTIs, including those caused by MSSA, commonly used antibiotics include penicillin G, cloxacillin, ceftriaxone and clindamycin [3]. The Infectious Diseases Society of America (IDSA) recommends early empirical therapy with an anti-MRSA agent for all hospitalised patients with SSTI [2]. These treatments are discussed below.

In Europe, where there are vast disparities in the prevalence of MRSA between countries [10], emphasis should be placed on understanding local epidemiology patterns for MRSA to ascertain the level of risk and the requirement for antibiotic therapy directed towards this pathogen [3]. Initial treatment of SSTIs is usually empirical because microbial culture results are generally not available for several days, and patients with SSTI benefit from rapid initiation of appropriate therapy [34]. The importance of early treatment for MRSA-SSTI was underscored by a recent retrospective study showing that patients who received therapy 1 day or 2 days after their date of diagnosis with cSSTI had a significantly shorter duration of i.v. therapy and hospital LOS than patients whose treatment was initiated ≥3 days after their date of cSSTI diagnosis [13].

The first-line antibiotic treatments recommended for MRSA-cSSTI in Europe are the glycopeptides vancomycin and teicoplanin. Additional antibiotics recommended by guidelines for cSSTI with proven or suspected MRSA involvement include linezolid, daptomycin and tigecycline (Table 2), with 7–14 days of therapy generally being recommended [35,36,38,40–43]. Several new antibiotics approved in Europe for the treatment of ABSSSIs (oritavancin, dalbavancin and tedizolid phosphate) [19–21] or cSSTI (ceftaroline) [44] are not yet discussed in European guidelines. The use of inappropriate initial antibiotic treatment can be associated with adverse clinical outcomes, increased morbidity and mortality, and increased hospital LOS or costs [41,45–48], highlighting the importance of establishing a microbiological diagnosis promptly.

3. Treatment patterns in Europe

The REACH study was a large, multicentre observational study that examined treatment patterns, healthcare resource utilisation and clinical outcomes for hospitalised patients with cSSTI ($n = 1995$) in 10 European countries from 2010 to 2011 [8,12,49]. This analysis revealed that of cSSTI patients managed with antibiotics, 60.3% received penicillin with or without a β-lactamase inhibitor, 5.2% received vancomycin, 4.4% received daptomycin and 1.9% received linezolid as their initial antibiotic treatment [8], whereas teicoplanin and tigecycline were less commonly used.

A survey conducted in 2014 among 350 respondents from European infection societies indicated that the preferred initial i.v.

Table 2
Antibiotic options available for the treatment of meticillin-resistant *Staphylococcus aureus* complicated skin and soft-tissue infections (cSSTIs) according to European guidelines [a] [34–38].

Antibiotic	Route	Dosing regimen	Mechanism of action	Indications	Reference
Vancomycin	i.v.	500 mg q6h or 1 g q12h	Cell-wall synthesis inhibitor	Severe infection caused by Gram-positive bacteria susceptible to vancomycin that cannot be treated with, or failed to respond to, or are resistant to other antibiotics such as penicillins and cephalosporins	[28]
Teicoplanin	i.v. and i.m.	6 mg/kg q12h for three administrations followed by 6 mg/kg once daily (for cSSTI) (treatment duration dependent on clinical response)	Cell-wall synthesis inhibitor	cSSTI, bone and joint infection, hospital-acquired pneumonia, complicated urinary tract infection, infective endocarditis, peritonitis associated with continuous ambulatory peritoneal dialysis, and bacteraemia that occurs in association with any of the indications listed above	[27]
Linezolid	i.v. and oral	600 mg twice daily for 10–14 days	Protein synthesis inhibitor	Pneumonia (nosocomial and community-acquired) and cSSTI due to Gram-positive pathogens	[29]
Daptomycin	i.v.	cSSTI without *S. aureus* bacteraemia: 4 mg/kg once daily for 7–14 days cSSTI with *S. aureus* bacteraemia: 6 mg/kg once daily for 14 days	Inhibition of protein, DNA and RNA synthesis	cSSTI, right-sided infective endocarditis due to *S. aureus*, and *S. aureus* bacteraemia when associated with right-sided endocarditis or with cSSTI	[26]
Tigecycline	i.v.	100 mg followed by 50 mg q12h for 5–14 days	Protein synthesis inhibitor	cSSTI (excluding diabetic foot infection) and complicated intra-abdominal infections	[39]

i.v., intravenous; q6h, every 6 h; q12h, every 12 h; i.m., intramuscular.
[a] Newer options such as tedizolid phosphate, oritavancin, dalbavancin and ceftaroline are approved for use in Europe for the treatment of cSSTI, but are not yet discussed in guidelines.

treatment choice for a SSTI patient with MRSA was glycopeptides (34.5% vancomycin, 20.3% teicoplanin) [50]. Clinical efficacy was the main driver behind the respondents' choice of antibiotic [50]. The majority (79%) would switch to oral therapy once the patient was stable, whilst 21% would have the patient complete the treatment with the same i.v. antibiotic (7% in hospital and 14% in OPAT). Interestingly, 70% of respondents believed that ≥10 days was the optimum duration of therapy for patients with MRSA-cSSTI [50].

Country-specific variations in MRSA-cSSTI treatment patterns across 12 European countries were also evaluated in a recent retrospective medical chart review [18]. Of the 1502 patients identified between 2010 and 2011, 1468 (97.7%) received confirmed MRSA-targeted therapy and most patients (81.5%) received i.v. therapy only. Only 10.7% were switched to an oral antibiotic (in-hospital i.v.-to-oral switch rates ranged from 2.0% to 20.2% by country). Overall, 32.7% of patients were discharged from hospital on MRSA-targeted therapies (ranging from 18.0% to 49.7%), and 92.7% and 7.3% of these patients were discharged on oral therapy and OPAT, respectively [18]; however, large variation was found in antibiotic treatment patterns across Europe (Fig. 1).

4. Opportunities for a change in antibiotic management

In modern clinical practice, there is a drive to promote prudent and rational use of antimicrobials to select the most effective, safe and narrow-spectrum antimicrobial agent that has the least capacity for the emergence of resistance or healthcare-associated infections, within a framework of antimicrobial stewardship [51]. However, approaches to antimicrobial stewardship vary considerably among countries [52]. With specific regard to MRSA infections, there appears to be no single European-wide approach to antimicrobial stewardship (e.g. disparities in the availability of discharge, i.v.-to-oral switch and OPAT protocols), although there are signs that clinicians are becoming more familiar with the relevant concepts and standards [50].

The need to provide more cost-effective healthcare, an additional antimicrobial stewardship objective [52], has stimulated a change in healthcare delivery in Europe. This is illustrated by a significant reduction in inpatient bed capacity, paralleled by investment in and support for outpatient hospital care, ambulatory therapy centres and home care [53]. Many approaches to the management of cSSTI are aimed at reducing LOS as a means of increasing the efficiency and cost effectiveness of the hospital [54,55].

OPAT programmes enable patients to receive i.v. antibiotics after hospital discharge, but require additional resources and are not available to all patients in Europe [56–58]. A variety of old and new agents are available for once-daily i.v. treatment [42], and these can be suitable for use as part of an OPAT programme or within the emergency department setting [59].

Evidence also suggests that many patients who require at-home antibiotic therapy can be treated with an oral agent after hospital discharge [16]. Early switch (ES) strategies promote switching patients from i.v. to oral antibiotics, and early discharge (ED) strategies enable patients to finish treatment after hospital discharge. The eligibility criteria for i.v.-to-oral switch of antibiotic therapy and ED are described in Table 3. ES and ED strategies lead to reductions in the volume of antibiotic use, reduce the risk of healthcare-associated complications and infections, require few additional resources and are considered to be relatively low-cost and high-impact antimicrobial stewardship strategies [13,18]. Although healthcare systems vary significantly across European countries, a criteria-based approach could provide ES and ED opportunities for certain patients with cSSTI, thereby improving both economic and patient outcomes [13,18].

The potential benefits of ES and ED strategies for hospitalised patients with MRSA-cSSTI were illustrated in a retrospective medical chart review of patients ($n = 1542$) from 12 European countries in 2010–2011. This study found that patients with MRSA-cSSTI who switched from i.v. to oral antibiotic therapy had 5.3 fewer i.v. days ($P < 0.001$) and 1.9 fewer inpatient days ($P = 0.162$) compared with those who received i.v. therapy for the entire treatment duration [61]. In addition, the authors estimated that more than one-third of patients were eligible for ES and ED, which could result in substantial reductions in i.v. days and bed-days, with potential savings of €2000 per ED-eligible patient [61]. Implementing clear strategies to evaluate patients for ES/ED eligibility can result in improved antibiotic stewardship, a reduction in volume of antibiotic use, more rapid i.v.-to-oral switch, a reduction in LOS and overall cost savings [16].

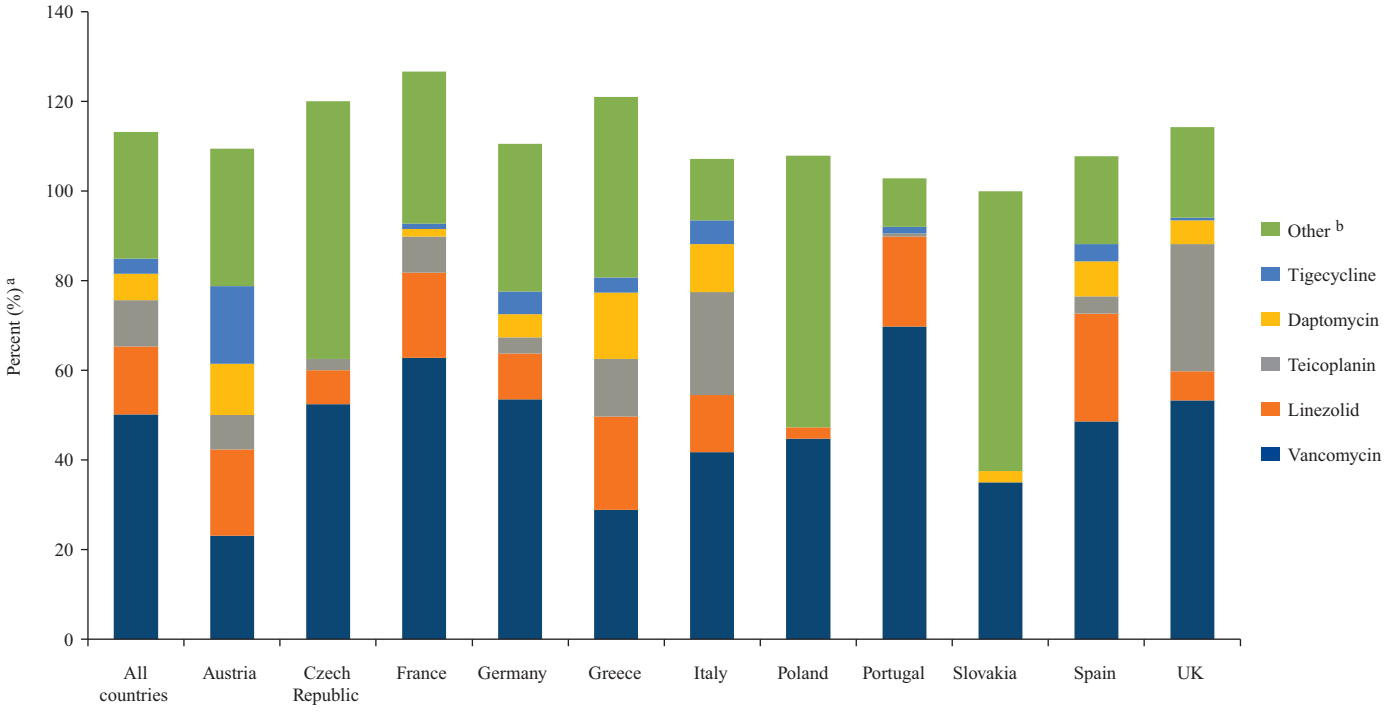

Fig. 1. Country-specific initial antibiotic treatment patterns for complicated skin and soft-tissue infections (cSSTIs) due to meticillin-resistant *Staphylococcus aureus* (MRSA) (adapted from Eckmann et al) [18]. Note: percentages calculated from a denominator based on the number of patients with MRSA-active therapy. [a] Drug groups were not mutually exclusive; multiple medications could be used simultaneously. [b] Includes clindamycin, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin), rifampicin, trimethoprim/sulfamethoxazole, doxycycline, ertapenem, fusidic acid, gentamicin, imipenem, meropenem, minocycline, pristinamycin, quinupristin/dalfopristin and trimethoprim.

5. Early assessment of response to therapy

When treating a patient with SSTI with i.v. antibiotics, it is good clinical practice to review the response to treatment on a daily basis. However, a clinical review at 48–72 h post-initiation is critical for deciding whether to stop or continue with the current treatment, to switch to an oral antibiotic, to change the antibiotic or to initiate OPAT, as outlined in the 'Start Smart—Then Focus' antimicrobial stewardship initiative from Public Health England [15]. Clinical outcomes around Day 3 have strong therapeutic importance. Early indication of treatment failure can guide necessary changes to antibiotic treatment, thus avoiding prolonged use of inappropriate treatment, which has been reported to increase overall morbidity and mortality [48]. In addition, the optimal time to re-assess the antibiotic treatment plan is on Days 2–3 of i.v. therapy when culture results, which were taken on initiation of antibiotic therapy, have been made available [60], along with other diagnostic information and assessments of patient response.

Recent FDA guidance on the conduct of clinical trials for SSTIs has suggested changes to clinical trial design and conduct [4,62]. Notable revisions included new disease state definitions, new primary endpoint definitions, early assessment of these endpoints and updated guidance on patient inclusion/exclusion criteria (Table 4). The primary efficacy endpoint in non-inferiority studies for SSTIs in Europe and the USA has historically been resolution of signs and symptoms of infection 7–14 days after the end of therapy (EOT) [9,63]. The new primary endpoint for clinical studies of ABSSSI, referred to as early assessment of clinical response, is a ≥20% reduction in lesion size at 48–72 h compared with baseline. It is recommended that clinical trials for ABSSSIs should also incorporate the key secondary endpoints of sustained clinical response at EOT and 7–14 days after EOT [referred to as post-therapy evaluation (PTE)] [4]. Such an approach would enable the use of the trial results for supporting licensing submissions to multiple regulatory authorities, including the European Medicines Agency (EMA) [64].

Table 3
Patient eligibility criteria for i.v.-to-oral switch of antibiotic therapy and early discharge (adapted from Mertz et al [60] and Nathwani et al [61]).

Early switch is recommended if all inclusion criteria are fulfilled, all exclusion criteria are absent and if an appropriate oral regimen is available
Eligible for oral switch
• i.v. antibiotics for >24 h
• Afebrile (temperature <38 °C) for >24 h
• Clinical improvement or stable infection
• WBC count normalising, WBC count of 4×10^9/L to 12×10^9/L
• No unexplained tachycardia
• Systolic blood pressure ≥100 mmHg
• Patient tolerates oral fluids/diet and is able to take oral medications with no gastrointestinal absorption problems
Not eligible for oral switch
• Cutaneous abscess not treated with incision and drainage; severe soft-tissue infection; osteomyelitis; septic arthritis
Eligible for early discharge
• All early switch eligibility criteria listed above have been met
• No other reason to stay in hospital except for infection management
• Stable mental status
• Stable co-morbid illness
• Stable social situation

i.v., intravenous; WBC, white blood cell.

6. Antibiotic agents that have been evaluated using the new FDA endpoints

Three new antibiotics (oritavancin, dalbavancin and tedizolid phosphate) recently approved in the USA and Europe for the

Table 4
Summary of key points of the 2013 US Food and Drug Administration (FDA) guidance on clinical trials of acute bacterial skin and skin-structure infections (ABSSSIs) [4].

Inclusion criteria
- Patients with cellulitis/erysipelas, wound infection or major cutaneous abscess
- Lesions should have a minimum surface area of 75 cm^2 (lesion size measured by the area of redness, oedema or induration)

Exclusion criteria
- Patients with medical conditions that would alter the interpretation of a primary endpoint (e.g. patients with neutropenia)
- Patients with suspected or confirmed osteomyelitis
- Patients with suspected or confirmed septic arthritis
- Patients who received >24 h of effective antibiotic therapy for treatment of current ABSSSI
- Number of patients enrolled with major cutaneous abscesses should be ≤30% of the total study population
- Primary endpoint is ≥20% reduction in primary lesion size at 48–72 h compared with baseline (early assessment)
- Secondary endpoint is resolution of ABSSSI evaluated at 7–14 days after completion of therapy (post-therapy evaluation)

treatment of ABSSSIs in adults were studied in phase 3 clinical trials that were designed largely in line with the new FDA guidance (Table 5). Whilst the oritavancin, dalbavancin and the first tedizolid phosphate (ESTABLISH-1) phase 3 trials used the 2010 FDA draft guidance [22,23,25,66], the tedizolid phosphate ESTABLISH-2 trial was prospectively designed to reflect all of the key elements of the 2013 final guidance [24]. Both the draft and final guidance recommended early assessment at 48–72 h [4,68]. The primary endpoint in the 2010 draft FDA guidance was cessation of spread or reduction in size of the lesion at 48–72 h compared with baseline as well as resolution of fever [68]. The primary endpoint in the 2013 final guidance was a ≥ 20% reduction in ABSSSI lesion size at 48–72 h compared with baseline [4].

Oritavancin is a lipoglycopeptide with bactericidal activity against Gram-positive pathogens [21]. In the phase 3 SOLO I and II trials, a single 1200 mg dose of oritavancin was shown to be non-inferior to twice-daily vancomycin administered for 7–10 days for the treatment of ABSSSIs caused by Gram-positive pathogens [23,66]. In addition, there was >85% concordance (agreement correlation) between success at the 48–72-h assessment and the PTE [69]. The positive predictive values (PPVs) of the approaches to assess early clinical response [(i) cessation of spreading or reduction in size of baseline lesion, absence of fever and no rescue antibiotics at 48–72 h and (ii) ≥20% reduction in lesion area at 48–72 h] were ≈ 95%, and the negative predictive values (NPV) were ≈ 20% [69]. Although early positive clinical response at 48–72 h was highly predictive of clinical cure of ABSSSI at 7–14 days post-therapy, lack of early clinical response was only rarely predictive of clinical failure [69], which was expected, since overall cure is dependent on antibiotic treatment as well as the natural course of the infection.

Dalbavancin, also a lipoglycopeptide, is bactericidal in vitro against Gram-positive pathogens [19]. DISCOVER 1 and 2 were identically designed non-inferiority phase 3 trials of dalbavancin (1000 mg dose, followed 1 week later by 500 mg) for the treatment of ABSSSIs [22]. Patients received dalbavancin i.v. on Days 1 and 8 or vancomycin i.v. for ≥3 days with the option to switch to oral linezolid to complete 10–14 days of therapy. Analysis of the primary endpoint of early clinical success showed non-inferiority of dalbavancin in both DISCOVER 1 and 2. Patients achieving cessation of lesion spread after 72 h of antibiotic treatment had a >90% chance of being cured at EOT [70]. All combinations of response assessed (cessation of spread, cessation of spread plus absence of fever, cessation of spread plus worsening pain, absence of fever and >20% reduction in lesion

Table 5
Antibiotics indicated for skin and soft-tissue infection (SSTI) that have been assessed in newer clinical trials that evaluated both early clinical response as well as end of therapy (EOT) and/or post-therapy evaluation (PTE) response.

Antibiotic [a]	Dosing regimen in clinical trials	Potential option for oral switch therapy	Potential option for OPAT	Clinical response: Early assessment vs. EOT or PTE
Tedizolid phosphate	200 mg once daily for 6 days	Yes	Yes	Pooled ESTABLISH-1 and -2 studies [65]: 81.6% tedizolid phosphate vs. 79.4% linezolid in the ITT population at 48–72 h vs. 86.7% tedizolid phosphate vs. 86.8% linezolid in the ITT population at PTE (7–14 days after EOT)
Oritavancin	Single 1200 mg dose	No	Yes	SOLO I study [23]: 82.3% oritavancin vs. 78.9% vancomycin in the MITT population at 48–72 h vs. 79.6% oritavancin vs. 80.0% vancomycin in the MITT population at PTE (7–14 days after EOT) SOLO II study [66]: 80.1% oritavancin vs. 82.9% vancomycin in the MITT population at 48–72 h vs. 82.7% oritavancin vs. 80.5% vancomycin in the MITT population at PTE (7–14 days after EOT)
Dalbavancin	1000 mg followed 1 week later by 500 mg	No	Yes	Pooled DISCOVER 1 and 2 studies [22]: 79.7% dalbavancin vs. 79.8% vancomycin/linezolid in the ITT population at 48–72 h vs. 90.7% dalbavancin vs. 92.1% vancomycin/linezolid in the per-protocol population at EOT
Ceftaroline	600 mg every 12 h for 5–14 days	No	Yes	Pooled CANVAS 1 and 2 studies [67]: 74.0% ceftaroline vs. 66.2% vancomycin plus aztreonam in the E-MITT population at Day 3 vs. 87.3% ceftaroline vs. 85.4 % vancomycin plus aztreonam in the E-MITT population at TOC visit (8–15 days after EOT)

OPAT, outpatient parenteral therapy; ITT, intent-to-treat; MITT, modified intent-to-treat; E-MITT, exploratory modified intent-to-treat; TOC, test-of-cure.
[a] All four of these antibiotics are approved in Europe for the treatment of cSSTI [19–21,44].

size) had ≥88% sensitivity and PPV. The NPV ranged from 28% to 80% because some early failures were ultimately successes at EOT. Addition of the criterion 'worsening of pain relative to baseline' improved the NPV to 80% and the specificity of the Day 3 assessment of cessation of spread [70]. Thus, in these trials patients who did not achieve cessation of spread at 72 h and had worsening of pain had an 80% chance of ultimately failing therapy [70].

Tedizolid phosphate is an oxazolidinone antibiotic drug with bactericidal activity in vivo and bacteriostatic activity in vitro against Gram-positive pathogens [20,71]. In ABSSSI, the recommended dosage of tedizolid phosphate is 200 mg administered once daily for 6 days, either orally (with or without food) or as an i.v. infusion over 1 h [20]. ESTABLISH-1 (oral only dosing) [25] and ESTABLISH-2 (i.v.-to-oral dosing; optional oral step-down could occur 24 h after treatment initiation if pre-defined conditions were met) [24] were non-inferiority phase 3 trials of tedizolid phosphate for the treatment of ABSSSIs. Clinical response in these trials was analysed using varied endpoint definitions and criteria, therefore allowing an opportunity to evaluate the concordance between primary endpoints assessed in clinical trials and those more commonly used in clinical practice. In a combined analysis of the two ESTABLISH trials, high concordance (93%) between early clinical response at 48–72 h and clinical success at PTE was observed [65]. In addition, early clinical response (e.g. 20% lesion area reduction) was strongly associated with investigator-assessed treatment success (based on resolution of signs and symptoms) at the PTE visit, regardless of ABSSSI type or hospitalisation status, with a high PPV of >96% and a low NPV ranging mostly from 11% to 30% [72]. These findings support the validity of a positive early response as an indicator of long-term success. In contrast, early clinical failure based on lesion area assessments had a low predictive ability for investigator-assessed treatment failure at the PTE visit [72]. Since changes in lesion size are generally not assessed in clinical practice, the potential utility of this approach for making real-world treatment decisions is limited. However, the ESTABLISH data also suggested that patients assessed as improving or stable at 48–72 h based on the investigator's clinical judgement had a high likelihood of investigator-assessed success at the PTE visit (PPV > 94%) [65]. The high concordance between programmatic early clinical response and late response at PTE strongly support the use of early clinical response to replace late response at PTE as a new regulatory primary endpoint. In addition, the high PPV of investigator-assessed early clinical response for late response at PTE means that clinician assessment of early clinical response could possibly be useful in making treatment decisions (e.g. if a patient is stable after 48–72 h of antibiotic treatment, the physician may be confident that the patient will have an overall cure with this therapy at EOT and no change in therapy would be necessary). Further investigation of investigator-assessed early clinical response is required.

7. Perspective on the real-world utility of early clinical assessment of treatment outcomes in complicated skin and soft-tissue infections and potential impact on early discharge

Following the release of the 2010 draft FDA guidance on the conduct of clinical trials for ABSSSIs, the IDSA, which represents >9000 clinicians, reported a lack of clinical relevance of the early assessment endpoint and stated that the endpoint was irrelevant to clinical success and was only indicative of clinical failure [73]. However, as described above, consistency between early and post-therapy clinical responses was shown in six different phase 3 clinical trials, thus supporting the relevance of this assessment to clinical practice. Furthermore, in a study of management practices in European hospitals, cSSTI patients who showed an early response to treatment [<72 h; defined as (i) resolution of fever AND some indication of lesion improvement or stability, or (ii) lesion improvement or stability OR resolution of local signs and symptoms] were less likely to require therapy modification and showed improved clinical outcomes and lower resource use than patients without an early response [49]. Finally, whilst there are no formal recommendations for early assessment in the UK, it is common practice to accommodate patients with SSTI who do not have sepsis in a short-stay ward, limited usually to a 24-h period. If they have shown clinical response within that time, further treatment in an outpatient setting can be considered. Specific criteria for early assessment with early appropriate discharge and the cost implications of this strategy in the UK have been published [16,17].

For patients with documented clinical improvement and who are able to tolerate oral therapy, the aim should be to step-down (streamline) therapy to the oral route as soon as possible [50]. Options for oral switch in the treatment of suspected or documented MRSA-cSSTI include linezolid and tedizolid phosphate. Some clinicians consider oral therapy with trimethoprim/sulfamethoxazole (cotrimoxazole), and although effective in many circumstances (e.g. MRSA-bacteraemia [74]), its efficacy in severe cSSTI has not been shown in randomised clinical trials [75]. To provide an illustrative example for i.v.-to-oral switch, a case study is presented in Box 1.

In choosing an appropriate step-down oral antibiotic, the same active antibiotic in oral form and high bioavailability could also be considered. Clinical trials have shown that linezolid and tedizolid phosphate have high oral bioavailability and comparable clinical success rates [24,25]. Whilst the overall incidence of adverse events was similar, patients who received tedizolid phosphate for 6 days reported fewer gastrointestinal disorders (nausea, vomiting and diarrhoea) than patients who received linezolid for 10 days [65]. Tedizolid also led to a lower incidence of abnormally low platelet and neutrophil counts 7–9 days after the start of therapy and at EOT (Days 11–13) [65]. This is of importance because myelosuppression is a known adverse event associated with the use of linezolid after

Box 1. Skin and soft-tissue infection (SSTI) case report of intravenous (i.v.)-to-oral switch.

A 57-year-old female with type 2 diabetes mellitus presented with swelling, redness and pain in her left lower leg. There was no fluctuation, but the infected soft tissue was erythematous and indurated with early development of a blister but no discharge. The patient had a temperature of 38 °C, a pulse of 84 beats per min and a blood pressure of 140/85 mmHg. Early blood tests showed a white blood cell count of 10.2×10^9/L with slight neutrophilia and a C-reactive protein of 112 mg/L. Other parameters were within normal ranges.

The patient had previously been colonised with meticillin-resistant *Staphylococcus aureus* (MRSA) in the nose and had a previous MRSA wound infection. She had a history of penicillin allergy (rash) but was administered a single dose of 2 g ceftriaxone in the emergency department. On the ward, the patient was switched to oral linezolid as she no longer met the systemic inflammatory response syndrome criteria, could take oral medication, and had a history of penicillin allergy and previous MRSA. The patient responded well over the next 24 h with improvement of the erythema and fever and was discharged early to complete the course of linezolid for 7 days in the community.

2 weeks of drug administration; of note, these adverse events did not result in clinical complications of bleeding or discontinuation of treatment in either treatment group. The clinical relevance of these differences with regards to longer duration of tedizolid phosphate dosing is unknown.

High concordance between early and late clinical response could facilitate ED of patients on i.v. or oral therapy, leading to important positive cost implications. The clinician may be able to use early response, along with other clinical parameters, to assess patients for ES/ED. OPAT has been championed as an approach to ED because it may reduce the cost of treatment and is preferred by patients over i.v. administration in a hospital [76]. However, the use of OPAT with many of the current parenteral agents is challenged by the availability of oral formulations of linezolid and tedizolid phosphate and by longer-acting agents such as oritavancin and dalbavancin, which either avoid or minimise the need for additional infusions. Considerations such as patient preference and adherence are also relevant in the choice of i.v. versus oral therapy. In a small survey of UK patients treated for antibiotic-resistant Gram-positive infections ($n = 12$), there was a preference for discharge on oral over i.v. therapy, albeit this was dependent on the formulations being of equal efficacy [77]. There are limited data on adherence to oral therapies for cSSTI; however, findings for other infections indicate that adherence is higher with once-daily doses and shorter treatment regimens [78–83].

Some patients with SSTI may be entirely managed in an outpatient setting. This approach to management may be particularly applicable to oral or longer-acting i.v. agents and may help to avoid hospitalisation. This approach may also provide an alternative when there is no OPAT service or the patient profile suggests a high probability of poor participation in OPAT or compliance with oral therapy [56,60,61]. However, the selection of appropriate patients is critical. In this context, longer-acting antibiotics (i.e. a single infusion of oritavancin or two doses of dalbavancin, 1 week apart, with review

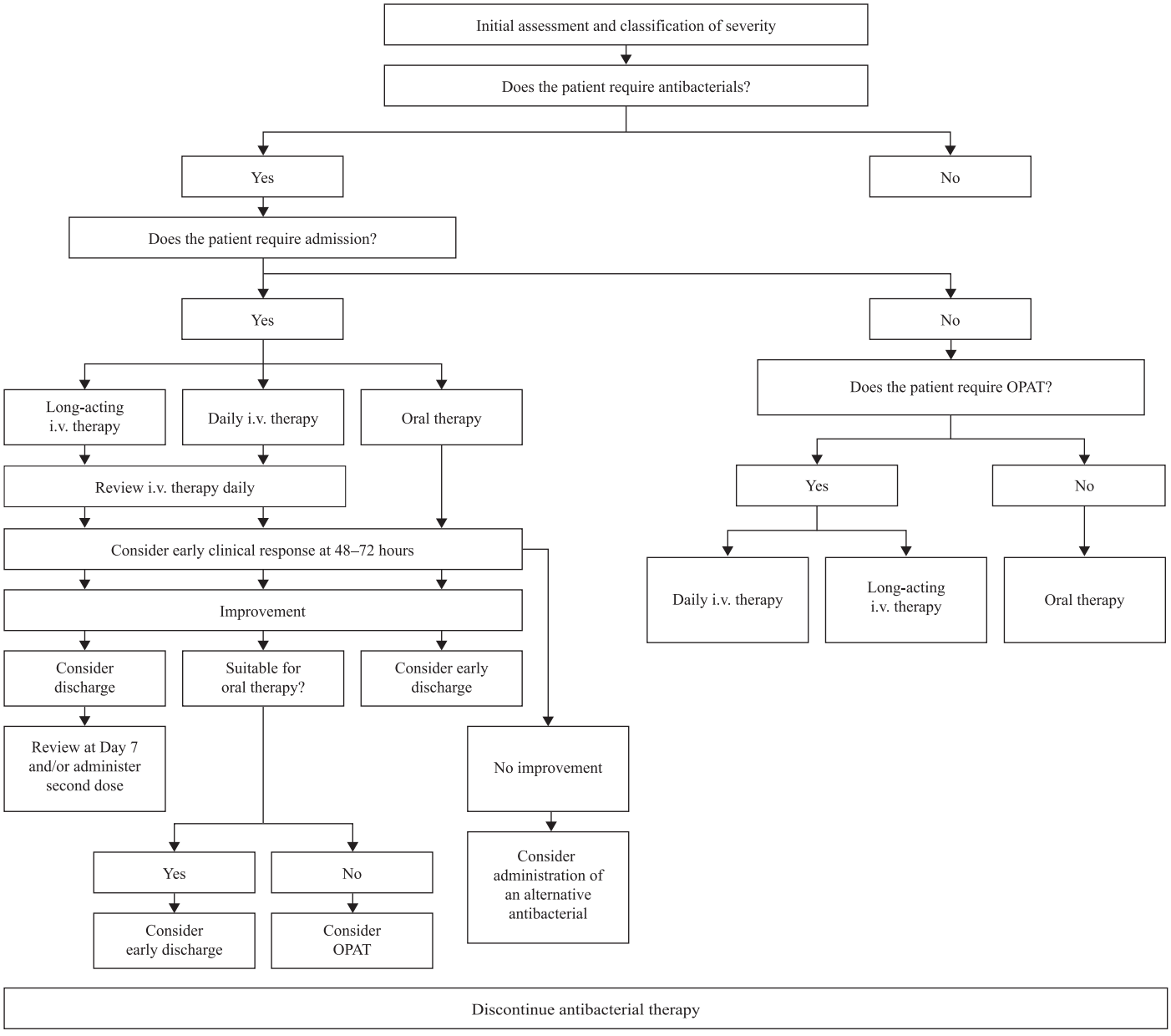

Fig. 2. Treatment algorithm for managing skin and soft-tissue infections (SSTIs) based on early clinical response. Note: long-acting infusion therapy, single dose of oritavancin or two doses of dalbavancin 7 days apart. i.v., intravenous; OPAT, outpatient parenteral antibiotic therapy.

at 48–72 h to ensure response) may be suitable for patients with limited access to or interaction with healthcare systems (e.g. the homeless, elderly, military personnel, i.v. drug abusers and those in rural areas).

In light of the new early clinical response endpoint and the data surrounding the relevance of utilising this endpoint, we updated the treatment algorithm pathway developed by Eron et al [84] for the management of SSTIs to include this assessment (Fig. 2). It shows how new drugs, either oral with short duration or i.v. once a week, may influence current decision-making in the management of cSSTIs. Our aim is to encourage further debate and research about introducing these new concepts and treatment paradigms into current care. We accept that further research (retrospective analysis of clinical practice and prospective, real-world studies) is required to address how clinicians can define and assess early clinical response in an easy and objective manner.

8. Conclusions

SSTIs require early recognition and prompt management as, depending on their severity, they can lead to considerable morbidity and mortality and represent a major economic burden to the healthcare system. Recent clinical trials have demonstrated concordance between early clinical response at 48 h and the PTE. In general practice, physicians may wish to consider an assessment of early clinical response as part of their overall decision-making process when assessing the likelihood of sustained response, so as to determine the most effective approach to reducing the patient's inpatient stay. Because these data will require further verification and understanding, clinicians should display caution and ensure appropriate means of patient monitoring/follow-up to minimise any unintended consequences of early changes in treatment. Initial findings from clinical studies with oxazolidinones suggest that early assessment of antibiotic treatment response by clinicians—without having to take the burdensome route of lesion area measurement—may be valuable in predicting late clinical response, and we recommend that this topic be investigated further in prospective studies. For example, it would be of great interest to study which routinely assessed patient and diagnostic factors may be useful for objectively determining early response in real-world clinical practice. Having this information available could greatly facilitate clinical decision-making in the management of cSSTIs, such as early hospital discharge or the potential to switch to an oral formulation of the same agent or step-down to a different antibiotic agent.

Acknowledgements

The authors would like to thank Hina Patel, PharmD, and Dominik Wolf (Merck & Co., Inc., Kenilworth, NJ) for helpful input during manuscript development. Medical writing and/or editorial assistance was provided by Christina Campbell, PhD, and Jean Turner of PAREXEL (Uxbridge, UK). This assistance was funded by Merck & Co., Inc.

Funding: Medical writing assistance was funded by Merck & Co., Inc. (Kenilworth, NJ).

Competing interests: DN has received speaker's and/or consultancy fees from Astellas, Basilea, Bayer, Durata, The Medicines Company, Pfizer, and Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Kenilworth, NJ); MD has received speaker's and/or consultancy fees from AstraZeneca, Bayer, Janssen-Cilag, Novartis, Pfizer, and Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.; JG has received research grants, speaking invitations and conference invitations from Astellas, AstraZeneca, Bayer, GlaxoSmithKline, Novartis, Pfizer, Vifor Pharma, and Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and has recent or on-going consultancies with Astellas, AstraZeneca, Bayer, Durata, GlaxoSmithKline, Janssen-Cilag, Novartis, Pfizer, Theravance and Vifor Pharma.

Ethical approval: Not required.

References

[1] Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother 2010;65(Suppl. 3):iii35–44.
[2] Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014;59:e10–52.
[3] Montravers P, Snauwaert A, Welsch C. Current guidelines and recommendations for the management of skin and soft tissue infections. Curr Opin Infect Dis 2016;29:131–8.
[4] US Food and Drug Administration. Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. Rockville, MD: FDA; 2013.
[5] European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012. Stockholm, Sweden: ECDC; 2013 <http://www.ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf> [accessed 20.01.15].
[6] Phoenix G, Das S, Joshi M. Diagnosis and management of cellulitis. BMJ 2012;345:e4955.
[7] Sader HS, Farrell DJ, Jones RN. Antimicrobial susceptibility of Gram-positive cocci isolated from skin and skin-structure infections in European medical centres. Int J Antimicrob Agents 2010;36:28–32.
[8] Garau J, Ostermann H, Medina J, Avila M, McBride K, Blasi F, et al. Current management of patients hospitalized with complicated skin and soft tissue infections across Europe (2010–2011): assessment of clinical practice patterns and real-life effectiveness of antibiotics from the REACH study. Clin Microbiol Infect 2013;19:E377–85.
[9] US Food and Drug Administration. Guidance for industry. Uncomplicated and complicated skin and skin structure infections—developing antimicrobial drugs for treatment. Rockville, MD: FDA; 1998.
[10] European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm, Sweden: ECDC; 2015.
[11] Hatoum HT, Akhras KS, Lin SJ. The attributable clinical and economic burden of skin and skin structure infections in hospitalized patients: a matched cohort study. Diagn Microbiol Infect Dis 2009;64:305–10.
[12] Ostermann H, Blasi F, Medina J, Pascual E, McBride K, Garau J, et al. Resource use in patients hospitalized with complicated skin and soft tissue infections in Europe and analysis of vulnerable groups: the REACH study. J Med Econ 2014;17:719–29.
[13] Nathwani D, Eckmann C, Lawson W, Solem CT, Corman S, Stephens JM, et al. Influence of real-world characteristics on outcomes for patients with methicillin-resistant staphylococcal skin and soft tissue infections: a multi-country medical chart review in Europe. BMC Infect Dis 2014;14:476.
[14] De Cock E, Sorensen S, Levrat F, Besnier JM, Dupon M, Guery B, et al. Cost-effectiveness of linezolid versus vancomycin for hospitalized patients with complicated skin and soft-tissue infections in France. Med Mal Infect 2009;39:330–40.
[15] Public Health England. Start smart—then focus: antimicrobial stewardship toolkit for English hospitals. London, UK: Public Health England; 2015.
[16] Dryden M, Saeed K, Townsend R, Winnard C, Bourne S, Parker N, et al. Antibiotic stewardship and early discharge from hospital: impact of a structured approach to antimicrobial management. J Antimicrob Chemother 2012;67:2289–96.
[17] Gray A, Dryden M, Charos A. Antibiotic management and early discharge from hospital: an economic analysis. J Antimicrob Chemother 2012;67:2297–302.
[18] Eckmann C, Lawson W, Nathwani D, Solem CT, Stephens JM, Macahilig C, et al. Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant *Staphylococcus aureus*: a plea for implementation of early switch and early discharge criteria. Int J Antimicrob Agents 2014;44:56–64.
[19] European Medicines Agency. Xydalba™ summary of product characteristics, <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002840/WC500183869.pdf> [accessed 10.08.15].
[20] European Medicines Agency. SIVEXTRO® summary of product characteristics, <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002846/WC500184802.pdf> [accessed 10.08.15].
[21] European Medicines Agency. Orbactiv® summary of product characteristics, <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003785/WC500186343.pdf> [accessed 10.08.15].
[22] Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med 2014;370:2169–79.
[23] Corey GR, Kabler H, Mehra P, Gupta S, Overcash JS, Porwal A, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. N Engl J Med 2014;370:2180–90.
[24] Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure

infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 2014;14:696–705.
[25] Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA 2013;309:559–69.
[26] Novartis Pharmaceuticals. CUBICIN® summary of product characteristics. Camberley, UK: Novartis Pharmaceuticals; 2014.
[27] Sanofi. Targocid® summary of product characteristics. Guildford, UK: Sanofi; 2014.
[28] Hospira UK Ltd. Vancomycin summary of product characteristics. Leamington Spa, UK: Hospira UK Ltd.; 2009.
[29] Pfizer. Zyvox® summary of product characteristics. Sandwich, UK: Pfizer; 2014.
[30] Sartelli M, Malangoni MA, May AK, Viale P, Kao LS, Catena F, et al. World Society of Emergency Surgery (WSES) guidelines for management of skin and soft tissue infections. World J Emerg Surg 2014;9:57.
[31] Ki V, Rotstein C. Bacterial skin and soft tissue infections in adults: a review of their epidemiology, pathogenesis, diagnosis, treatment and site of care. Can J Infect Dis Med Microbiol 2008;19:173–84.
[32] Marwick C, Broomhall J, McCowan C, Phillips G, Gonzalez-McQuire S, Akhras K, et al. Severity assessment of skin and soft tissue infections: cohort study of management and outcomes for hospitalized patients. J Antimicrob Chemother 2011;66:387–97.
[33] Marwick C, Rae N, Irvine N, Davey P. Prospective study of severity assessment and management of acute medical admissions with skin and soft tissue infection. J Antimicrob Chemother 2012;67:1016–19.
[34] National Institute for Health and Clinical Excellence. Surgical site infection prevention and treatment of surgical site infection. NICE; 2014.
[35] Esposito S, Bassetti M, Borrè S, Bouza E, Dryden M, Fantoni M, et al. Diagnosis and management of skin and soft-tissue infections (SSTI): a literature review and consensus statement on behalf of the Italian Society of Infectious Diseases and International Society of Chemotherapy. J Chemother 2011;23:251–62.
[36] Gould FK, Brindle R, Chadwick PR, Fraise AP, Hill S, Nathwani D, et al. Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United Kingdom. J Antimicrob Chemother 2009;63:849–61.
[37] Nathwani D, Morgan M, Masterton RG, Dryden M, Cookson BD, French G, et al. Guidelines for UK practice for the diagnosis and management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presenting in the community. J Antimicrob Chemother 2008;61:976–94.
[38] Pan A, Cauda R, Concia E, Esposito S, Sganga G, Stefani S, et al. Consensus document on controversial issues in the treatment of complicated skin and skin-structure infections. Int J Infect Dis 2010;14(Suppl. 4):S39–53.
[39] Pfizer. Tygacil® summary of product characteristics. Sandwich, UK: Pfizer; 2014.
[40] Schofer H, Bruns R, Effendy I, Hartmann M, Jappe U, Plettenberg A, et al. Diagnosis and treatment of *Staphylococcus aureus* infections of the skin and mucous membranes. J Dtsch Dermatol Ges 2011;9:953–67.
[41] Bassetti M, Baguneid M, Bouza E, Dryden M, Nathwani D, Wilcox M. European perspective and update on the management of complicated skin and soft tissue infections due to methicillin-resistant *Staphylococcus aureus* after more than 10 years of experience with linezolid. Clin Microbiol Infect 2014;20(Suppl. 4):3–18.
[42] Dryden MS. Novel antibiotic treatment for skin and soft tissue infection. Curr Opin Infect Dis 2014;27:116–24.
[43] Dryden MS. Alternative clinical indications for novel antibiotics licensed for skin and soft tissue infection? Curr Opin Infect Dis 2015;28:117–24.
[44] European Medicines Agency. Zinforo® summary of product characteristics, <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002252/WC500132586.pdf> [accessed 10.08.15].
[45] Berger A, Oster G, Edelsberg J, Huang X, Weber DJ. Initial treatment failure in patients with complicated skin and skin structure infections. Surg Infect (Larchmt) 2013;14:304–12.
[46] Lipsky BA, Napolitano LM, Moran GJ, Vo L, Nicholson S, Chen S, et al. Economic outcomes of inappropriate initial antibiotic treatment for complicated skin and soft tissue infections: a multicenter prospective observational study. Diagn Microbiol Infect Dis 2014;79:266–72.
[47] Eagye KJ, Kim A, Laohavaleeson S, Kuti JL, Nicolau DP. Surgical site infections: does inadequate antibiotic therapy affect patient outcomes? Surg Infect (Larchmt) 2009;10:323–31.
[48] Edelsberg J, Berger A, Weber DJ, Mallick R, Kuznik A, Oster G. Clinical and economic consequences of failure of initial antibiotic therapy for hospitalized patients with complicated skin and skin-structure infections. Infect Control Hosp Epidemiol 2008;29:160–9.
[49] Garau J, Blasi F, Medina J, McBride K, Ostermann H. Early response to antibiotic treatment in European patients hospitalized with complicated skin and soft tissue infections: analysis of the REACH study. BMC Infect Dis 2015;15:78.
[50] Dryden M, Andrasevic AT, Bassetti M, Bouza E, Chastre J, Baguneid M, et al. Managing skin and soft-tissue infection and nosocomial pneumonia caused by MRSA: a 2014 follow-up survey. Int J Antimicrob Agents 2015;45(Suppl. 1):S1–14.
[51] Gilchrist M, Seaton RA. Outpatient parenteral antimicrobial therapy and antimicrobial stewardship: challenges and checklists. J Antimicrob Chemother 2015;70:965–70.
[52] Howard P, Pulcini C, Levy HG, West RM, Gould IM, Harbarth S, et al. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. J Antimicrob Chemother 2015;70:1245–55.
[53] Hensher M, Edwards N. Hospital provision, activity, and productivity in England since the 1980s. BMJ 1999;319:911–14.
[54] Nathwani D. Impact of methicillin-resistant *Staphylococcus aureus* infections on key health economic outcomes: does reducing the length of hospital stay matter? J Antimicrob Chemother 2003;51(Suppl. 2):ii37–44.
[55] Nathwani D. Health economic issues in the treatment of drug-resistant serious Gram-positive infections. J Infect 2009;59(Suppl. 1):S40–50.
[56] Chapman AL, Seaton RA, Cooper MA, Hedderwick S, Goodall V, Reed C, et al. Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement. J Antimicrob Chemother 2012;67:1053–62.
[57] Matthews PC, Conlon CP, Berendt AR, Kayley J, Jefferies L, Atkins BL, et al. Outpatient parenteral antimicrobial therapy (OPAT): is it safe for selected patients to self-administer at home? A retrospective analysis of a large cohort over 13 years. J Antimicrob Chemother 2007;60:356–62.
[58] Tice AD, Rehm SJ, Dalovisio JR, Bradley JS, Martinelli LP, Graham DR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. Clin Infect Dis 2004;38:1651–72.
[59] Seaton RA, Sharp E, Bezlyak V, Weir CJ. Factors associated with outcome and duration of therapy in outpatient parenteral antibiotic therapy (OPAT) patients with skin and soft-tissue infections. Int J Antimicrob Agents 2011;38:243–8.
[60] Mertz D, Koller M, Haller P, Lampert ML, Plagge H, Hug B, et al. Outcomes of early switching from intravenous to oral antibiotics on medical wards. J Antimicrob Chemother 2009;64:188–99.
[61] Nathwani D, Eckmann C, Lawson W, Stephens JM, Macahilig C, Solem CT, et al. Pan-European early switch/early discharge opportunities exist for hospitalized patients with methicillin-resistant *Staphylococcus aureus* complicated skin and soft tissue infections. Clin Microbiol Infect 2014;20:993–1000.
[62] Itani KM, Shorr AF. FDA guidance for ABSSSI trials: implications for conducting and interpreting clinical trials. Clin Infect Dis 2014;58(Suppl. 1):S4–9.
[63] European Medicines Agency. Addendum to the guidelines on the evaluation of medicinal products indicated for treatment of bacterial infections. Committee for Human Medicinal Products (CHMP); 2013.
[64] Toerner JG, Burke L, Komo S, Papadopoulos E. A collaborative model for endpoint development for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. Clin Infect Dis 2012;55:1122–3.
[65] Shorr AF, Lodise TP, Corey GR, De Anda C, Fang E, Das AF, et al. Analysis of the phase 3 ESTABLISH trials: tedizolid versus linezolid in acute bacterial skin and skin structure infection. Antimicrob Agents Chemother 2015;59:864–71.
[66] Corey GR, Good S, Jiang H, Moeck G, Wikler M, Green S, et al. Single-dose oritavancin versus 7–10 days of vancomycin in the treatment of Gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. Clin Infect Dis 2015;60:254–62.
[67] Friedland HD, O'Neal T, Biek D, Eckburg PB, Rank DR, Llorens L, et al. CANVAS 1 and 2: analysis of clinical response at Day 3 in two phase 3 trials of ceftaroline fosamil versus vancomycin plus aztreonam in treatment of acute bacterial skin and skin structure infections. Antimicrob Agents Chemother 2012;56:2231–6.
[68] US Food and Drug Administration. Draft guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. Rockville, MD: FDA; 2010.
[69] Corey GR, Good S, Jiang H, Moeck G, Wikler M. SOLO 1 and SOLO II Investigators. Concordance between early and late clinical response with a single dose of oritavancin in the SOLO studies. In: 54th interscience conference on antimicrobial agents and chemotherapy (ICAAC); 5–9 September 2014. Washington, DC: ASM Press; 2014. p. abstract F-972.
[70] Dunne MW, Puttagunta S, Wilcox M, Tasaki O, Boucher HW, FIDSA. Concordance of clinical response at 48–72 hours after initiation of therapy and end of therapy (EOT) in patients with acute bacterial skin and skin structure infection (ABSSSI) in the DISCOVER studies. In: IDWeek 2013; 2–6 October 2013; San Francisco, CA, abstract 1340.
[71] Wong E, Rab S. Tedizolid phosphate (Sivextro): a second-generation oxazolidinone to treat acute bacterial skin and skin structure infections. P T 2014;39:555–79.
[72] Das A, Corey R, Nathwani D, Sandison T, De Anda C, Prokocimer P. Does early clinical response predict late clinical success in patients with acute bacterial skin and skin structure infections (ABSSSI)? Data from the ESTABLISH clinical trials. In: 25th European congress of clinical microbiology and infectious diseases (ECCMID); 25–28 April 2015. Copenhagen, Denmark. Basel, Switzerland: ESCMID; 2015. p. abstract EV0362.
[73] Infectious Diseases Society of America. IDSA comments on FDA's draft guidance for industry on acute bacterial skin and skin structure infections (ABSSSI), <http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Position_Papers/IDSA%20Comments%20re%20FDA%20ABSSSI%20Guidance%20111710.pdf> [accessed 01.08.15].
[74] Goldberg E, Paul M, Talker O, Samra Z, Raskin M, Hazzan R, et al. Co-trimoxazole versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia: a retrospective cohort study. J Antimicrob Chemother 2010;65:1779–83.
[75] Cotrimoxazole versus vancomycin for invasive methicillin-resistant *Staphylococcus aureus* infections, <https://clinicaltrials.gov/ct2/show/NCT00427076> [accessed 12.02.15].
[76] Marra CA, Frighetto L, Goodfellow AF, Wai AO, Chase ML, Nicol RE, et al. Willingness to pay to assess patient preferences for therapy in a Canadian setting. BMC Health Serv Res 2005;5:43.

[77] Bamford KB, Desai M, Aruede MJ, Lawson W, Jacklin A, Franklin BD. Patients' views and experience of intravenous and oral antimicrobial therapy: room for change. Injury 2011;42(Suppl. 5):S24–7.
[78] Vrijens B, Urquhart J. Patient adherence to prescribed antimicrobial drug dosing regimens. J Antimicrob Chemother 2005;55:616–27.
[79] Cals JW, Hopstaken RM, Le Doux PH, Driessen GA, Nelemans PJ, Dinant GJ. Dose timing and patient compliance with two antibiotic treatment regimens for lower respiratory tract infections in primary care. Int J Antimicrob Agents 2008;31:531–6.
[80] Kardas P. Comparison of patient compliance with once-daily and twice-daily antibiotic regimens in respiratory tract infections: results of a randomized trial. J Antimicrob Chemother 2007;59:531–6.
[81] Llor C, Sierra N, Hernandez S, Moragas A, Hernandez M, Bayona C, et al. The higher the number of daily doses of antibiotic treatment in lower respiratory tract infection the worse the compliance. J Antimicrob Chemother 2009;63:396–9.
[82] Kardas P. Once-daily dosage secures better compliance with antibiotic therapy of respiratory tract infections than twice-daily dosage. J Appl Res 2014;3:2001–6.
[83] Kauf T. Adults' adherence with anti-infectives. White paper. Lexington, MA: Cubist Pharmaceuticals; 2014.
[84] Eron LJ, Lipsky BA, Low DE, Nathwani D, Tice AD, Volturo GA. Managing skin and soft tissue infections: expert panel recommendations on key decision points. J Antimicrob Chemother 2003;52(Suppl. 1):i3–17.