

# TREATMENT OF COMPLICATED SKIN AND SOFT-TISSUE INFECTIONS CAUSED BY RESISTANT BACTERIA: VALUE OF LINEZOLID, TIGECYCLINE, DAPTOMYCIN AND VANCOMYCIN

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## Abstract

Antibiotic-resistant organisms causing both hospital- and community-acquired complicated skin and soft-tissue infections (cSSTI) are increasingly reported. A substantial medical and economical burden associated with MRSA colonisation or infection has been documented. The number of currently available appropriate antimicrobial agents is limited. Good quality randomised, controlled clinical trial data on antibiotic efficacy and safety is available for cSSTI caused by MRSA. Linezolid, tigecycline, daptomycin and vancomycin showed efficacy and safety in MRSA-caused cSSTI. None of these drugs showed significant superiority in terms of clinical cure and eradication rates. To date, linezolid offers by far the greatest number of patients included in controlled trials with a strong tendency of superiority over vancomycin in terms of eradication and clinical success.

Tigecycline is an alternative in polymicrobial infections except by diabetic foot infections. Daptomycin might be a treatment option for cases of cSSTI with MRSA bacteremia. cSSTI caused by resistant Gram-negative bacteria are a matter of great concern. The development of new antibiotics in this area is an urgent priority to avoid the risk of a postantibiotic era with no antimicrobial treatment options. An individual approach for every single patient is mandatory to evaluate the optimal antimicrobial treatment regimen.

## INTRODUCTION

Skin and soft tissue infections (SSTI) are amongst the most common bacterial infections in humans. They represent one of the most common indications for antibiotic treatment and represent about 10% of hospital admissions in the US [1]. Amongst the broad spectrum of skin and soft tissue infections treatment is mainly delivered out of hospital. SSTI have a broad range of aetiology, clinical manifestation and severity [2, 3]. At one end of the spectrum the outcome may be spontaneous resolution without antibiotics, but at the other end it may present with sepsis with lethal outcome. SSTI at 10% is the third most frequent focus for severe sepsis or septic shock, after pneumonia (55-60%) and abdominal infections (25%) [4].

This review aims to discuss the currently available antibiotics active against resistant bacteria (primarily MRSA, VRE, ESBL-producing bacteria and carbapenem-resistant strains) in terms of mechanisms of action, eradication rates and most important clinical outcome.

## CLASSIFICATION OF SKIN AND SOFT TISSUE INFECTIONS

The classification of skin and soft tissue infections is often confusing. Specific SSTI can be sub-categorised according to the causative microbial agents, the main tissue layer affected (i.e. skin, subcutis, fascia and muscle) or according to clinical signs and symptoms. It is to be differentiated, whether the infection is localised or generalised. Useful classifications are those which differentiate SSTI according to urgency of surgical intervention [5, 6]. Three categories can be differentiated: Infections treated conservatively (i.e. erysipelas), infections with the need for surgical intervention (i.e. infective diabetic foot) and severe skin and soft tissue infections that require urgent surgery (i.e. necrotising fasciitis).

Another classification, provided by the FDA and frequently used for clinical trials differentiates between uncomplicated and complicated SSTI, whereby the latter group is characterised by either deep soft tissue involvement with signs of systemic sepsis, severe patient immunosuppression or the necessity for major surgical intervention [7].

The key to successful treatment of many severe soft tissue infections is based on early detection, adequate calculated antibiotic treatment and prompt surgical debridement.

## AETIOLOGY AND SPECTRUM OF BACTERIA

SSTI can be caused by a multitude of bacterial agents. The most important pathogenic agents are Gram-positive bacteria, primarily *S. aureus* and group A streptococci. In recent studies more than 50% of all SSTI were caused by staphylococcal or streptococcal species [8-11]. The aetiological spectrum also includes enterococci, Gram-negative and anaerobic bacteria with necrotising, gangrenous infections and those close to the trunk as well as bite injuries [12-14].

The past two decades have witnessed a massive increase in infections caused by pathogens that are resistant to commonly used antimicrobial agents [15-17]. The emergence and spread of drug-resistant bacteria has been facilitated by the selective pressure induced by intensive use of antibiotics both in hospitalized and out-patients. A growing number of invasive procedures, performed in increasingly multi-morbid patient populations and sometimes with inadequate infection control measures, have added to the problem [18]. Other factors driving the process include greater movement of people and the agricultural usage of antimicrobials [19].

This increase in infections is in contrast to a decrease in the number of novel antimicrobial therapeutic options with activity against drug-resistant pathogens [20]. The Antimicrobial Availability Task Force of the Infectious Diseases Society of America (IDSA), recently identified vancomycin-resistant *Enterococcus faecium* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and extended spectrum  $\beta$ -lactamase (ESBL)-producing *Enterobacteriaceae* as particularly problematic pathogens [21, 22].

An increased likelihood of drug-resistant organisms as causative pathogens has been reported in both hospital- and community-acquired complicated skin and soft-tissue infections (SSTI) [23]. A substantial medical and economical burden evoked by MRSA colonization or infection has been documented [24, 25]. In the US, community acquired MRSA (CA-MRSA) is the most frequent isolated bacteria in cSSTI [26]. Cases of necrotizing cSSTI caused by CA-MRSA are reported [27]. The epidemiological shift towards drug-resistant pathogens in the settings of complicated SSTI together with the limited number of currently available appropriate antimicrobial agents thus translates into relevant problems in a population of seriously ill patients.

### LINEZOLID

Linezolid is an oxazolidinone antibiotic active against many resistant and susceptible Gram-positive organisms (including MRSA, VRE and macrolide-resistant streptococci [28]). Linezolid has an oral and an intravenous formulation with a bioavailability of 100%. The tissue penetration into soft tissues in comparison to serum concentrations is 105% [29]. Linezolid has been approved for the treatment of adult patients with complicated skin and skin structure infections with suspected or proven infections due to Gram-positive organisms including MRSA and VRE by the FDA and the EMA.

Linezolid has been studied extensively in the treatment of a broad range of skin infections [30-35]. A recently published systematic review and meta-analysis of linezolid versus vancomycin for MRSA skin and soft tissue infections [28] included four trials: three for clinical outcome ( $n = 174$ ) and three for microbiological outcome ( $n = 439$ ). For clinical outcomes there were non-significant trends in favour of linezolid (RR 0.34; 95% CI 0.04, 2.89;  $p = 0.32$ ). For microbiological outcome there was weak evidence of linezolid outperforming vancomycin (RR 0.55; 95% CI 0.30;  $p = 0.05$ )

[28]. In one study designed to evaluate the potential for linezolid to provide superior efficacy to vancomycin in the treatment of cSSTI caused by known or suspected MRSA, a subgroup analysis of patients who had culture-proven MRSA indicated that linezolid might offer advantages over vancomycin, suggesting the need for a definitive study in this subgroup [33]. Therefore, a phase 4 clinical trial was designed to better define the relative efficacy of linezolid against appropriately dosed vancomycin for the treatment of cSSTI proven to be caused by MRSA. To address several design limitations of the previous trials, only patients with documented MRSA infections were included and the vancomycin dose was titrated according to patient weight, changing renal function, and vancomycin troughs [35]. 240 patients in the linezolid group and 221 patients in the vancomycin group were analyzed, representing the by far greatest number of patients with proven cSSTI caused by MRSA that has been investigated to date. The clinical success rate was significantly higher in linezolid-treated patients in the modified intent-to-treat population ( $p = 0.048$ ). The microbiological success rate was higher for linezolid at the end of treatment ( $p < 0.001$ ) and was similar at the end of the study ( $p = 0.127$ ).

Linezolid offers the possibility of early switch to oral therapy and, consequently, early discharge, which may be of possible economic advantage, particularly in the field of cSSTI. This is discussed elsewhere in this issue.

Linezolid has been available for ten years now and is well established as an effective agent in cSSTI [15]. A dose reduction is not necessary in renal insufficiency. Its side effects of thrombocytopenia (2.2%) and anaemia (4.8%) are considered mild, reversible and duration dependent [36]. Mostly in patients treated longer than the recommended duration of 28 days, reversible and irreversible peripheral and optic neuropathy, lactic acidosis and serotonin syndrome have been observed [37].

### DAPTOMYCIN

Daptomycin, a fermentation product of *Streptomyces roseosporus*, is a cyclic lipopeptide antibiotic with a rapid concentration-dependent bactericidal activity against Gram-positive bacteria in vitro including resistant and susceptible strains [38]. The good tissue penetration into soft tissues is another pharmacokinetic advantage. It is only available as an intravenous infusion.

Daptomycin has been approved for the treatment of adult patients with complicated skin and skin structure infections by the FDA and the EMA. In two phase III studies 534 patients have been treated with daptomycin in a dosage of 4 mg/kg body weight once daily for cSSTI. The clinical success rate for daptomycin was 83.4% in the daptomycin group and 84.2% in the comparator group (vancomycin 1 g bid and penicillinase-binding semisynthetic penicillin 4-12 g daily, respectively). The clinical success rate in MRSA-caused infections was 75% (21 of 28 patients) in the daptomycin group versus 69% in the vancomycin group. The percentage of patients with a successful therapy (clinical cure or improvement) of only 4-7

days was significantly higher in the daptomycin group (63%) than in the vancomycin group (33%,  $p < 0,0001$ ) [10]. In a randomized trial with patients suffering from diabetic foot infections ( $n = 103$ ) the treatment success with daptomycin and vancomycin was 71,4% and 69,4%, respectively [39]. A sub-analysis of patients with evidence of MRSA has not been performed. Specific trials addressing the efficacy and safety of daptomycin in cSSTI proven to be caused by MRSA have not been published yet. Daptomycin showed good efficacy in the treatment of MRSA caused bacteremia and / or infective endocarditis [40, 41]. Consequently, daptomycin has been recommended as a possible treatment option in patients with cSSTI caused by MRSA and a high risk or evidence for bacteremia [80].

Daptomycin is safe and well tolerated when administered once daily according to on label dosage (4 mg/kg body weight). The most frequent documented side effects are of gastrointestinal origin (nausea, vomiting) [10, 41]. In higher dosages (6 mg/kg body weight) an increasing number of CPK elevations has been observed. This led to discontinuation of the drug in some cases [41]. A dose reduction is not necessary in renal insufficiency. In comparison to vancomycin, daptomycin was associated with a significantly lower rate of nephrotoxicity (6,7% daptomycin versus 18,1% vancomycin) [10, 41]. Its activity is independent of the cytochrome p450 system.

### TIGECYCLINE

Tigecycline is a novel glycylycline antibiotic for systemic use with broad-spectrum activity against aerobic and facultative Gram-positive and Gram-negative bacteria and anaerobic bacteria [42]. Tigecycline is active in vitro against antibiotic-resistant bacteria such as VRE (*Enterococcus faecalis* and *E. faecium*), MRSA, ESBL-producing Gram-negative and carbapenem-resistant bacteria [43, 44].

Tigecycline has been approved for the treatment of adult patients with complicated skin and skin structure infections by the FDA and the EMA. The patient population in the 2 phase III studies evaluating the use of tigecycline in cSSTI presented with a comparatively low mean (APACHE) II score [9].

There is a lack of data on the treatment of severely ill patients from the pivotal trials with tigecycline. Available data on the use of tigecycline in severely ill patients are mostly from retrospective analyses [45, 46] or studies with a focus on identified pathogens rather than the clinical picture [47-49].

Recently, data from prospective controlled trials on the efficacy and safety of tigecycline in the treatment of severely ill patients with complicated infections were published [50, 51]. In one monocenter study including 207 patients (mean APACHE II score: 21) 8% of the patients treated with tigecycline were found to suffer from cSSTI. The clinical success rate was 76% [50]. In a prospective observational multicenter trial including 656 patients (mean APACHE II score: 19) with tigecycline mono- or combination therapy, 102 patients (15,5%) were defined as cSSTI. The spectrum of isolated bacteria frequently included resistant organisms (MRSA: 65% of all *S. aureus* isolates, VRE:

14% of all enterococcal isolates, ESBL *E. coli*: 28%). The clinical success rate was 82% [51].

Although in vitro activity has been proven [52], Tigecycline failed to reach non-inferiority over the comparator substance in a trial with patients suffering from diabetic foot infection (data on file). Therefore, the drug is to date not approved for this indication. Tigecycline is in general a well tolerated substance. Frequently observed side effects are of gastrointestinal origin (nausea, vomiting). Cases of acute pancreatitis following the administration of tigecycline have been observed [53]. A trend towards a higher mortality rates in patients treated with tigecycline in comparison to control subjects has been noticed [54]. The data from the pivotal trial with tigecycline versus vancomycin-aztreonam in cSSTI revealed a non-significant difference in mortality of 0.7% [9].

### VANCOMYCIN

Vancomycin, a glycopeptide, has bactericidal activity against Gram-positive organisms in vitro including multiple-resistant (MRSA) and susceptible (MSSA) strains. It is only available as an intravenous infusion. The tissue penetration into soft tissue is poor (Table 1) [55]. It has been the gold standard for the treatment of MRSA infections for many years when no other drugs were available.

Vancomycin has been the comparator substance for numerous clinical trials of new substances (linezolid, daptomycin, tigecycline) for the treatment of cSSTI suspected or proven to be caused by MRSA (Table 2). Despite the pharmacokinetic weaknesses and the poor clinical results from other MRSA infections treated with vancomycin, none of these drugs showed significant superiority over vancomycin regarding clinical cure and eradication rates [8, 9, 10, 35]. This probably reflects the paramount importance of surgical source control in many cSSTI, which in part masks the real clinical value of an antibiotic. Moreover, the study design (non-inferiority) and the study population (many studies did not meet the FDA criteria for complicated SSTI) may have prevented detection of significant differences [56]. Consequently, vancomycin is still an option in mild to moderate cSSTI caused by MRSA (Table 3).

Due to poor clinical results in treatment of MSSA and MRSA pneumonia and sepsis, there is increasing concern about the use of vancomycin in serious infections [57]. These data have led to the recommendation of combination with other drugs (primarily rifampicin), on the assumption that a combination might improve clinical outcome. However, the combination of vancomycin and rifampicin is not based on controlled clinical data. Potential side effects are interaction with the cytochrome P450 system and frequent development of resistance against rifampicin [58].

There have been efforts for optimising the dosage of vancomycin. A trough level of  $>15 \mu\text{g/ml}$  has been recommended as desirable [59]. However, in a recently published trial comparing linezolid and vancomycin for the treatment of cSSTI caused by MRSA, the vancomycin dose was titrated according to patient

Table 1. General characteristics of antibiotics with activity against MRSA.

Antibiotic	Route	Mechanism of action	tissue penetration (% of serum concentration)	In vitro Spectrum of activity against resistant bacteria	Dose adjustment necessary in renal impairment
Linezolid	i.v., oral	bacteriostatic	105 %	MRSA, VRE	No
Tigecycline	i.v.	bacteriostatic	91%	MRSA, VRE, ESBL, CRB	No
Daptomycin	i.v.	bactericidal	68,4%	MRSA, (VRE)	No
Vancomycin	i.v.	bactericidal	8-10%	MRSA	Yes
TMP-SMX	i.v., oral	bactericidal	n.a.	MRSA	Yes
Rifampicin	i.v., oral	bactericidal	n.a.	MRSA	Yes
Fosfomycin	i.v.	bactericidal	91%	MRSA	Yes
Clindamycin	i.v., oral	bacteriostatic	95%	MRSA	No
Quino./dalfo	i.v.	bactericidal	n.a.	MRSA, (VRE)	Yes

CRB = carbapenem resistant bacteria

TMP-SMX = trimethoprim-sulfamethoxazole

(VRE) daptomycin = increasing number of treatment failures and emergence of resistance under therapy for VRE

(VRE) quinopristin/dalfopristin = no activity against *E. faecium*

Table 2. Assessment of antibiotics with activity against MRSA according to clinical data.

Antibiotic	Randomized controlled studies	Eradication rate (%)	Eradication rate (n)	reference	Toxicity in on label use	Daily cost
Linezolid	Yes	85,4	205/240	[35]	+	+++
Tigecycline	Yes	78,1	25/32	[9]	+	+++
Daptomycin	Yes	75	21/28	[10]	+	+++
Vancomycin	Yes	68,8	152/221	[35]	++	++
TMP-SMX	No	53	26/49	[64]	+	+
Rifampicin	No	53	26/49	[64]	+	+
Fosfomycin	No	n.a.	n.a.	n.a.	+	+
Clindamycin	No	n.a.	n.a.	n.a.	+	+
Quino./dalfo	No	n.a.	n.a.	n.a.	+++	+++

Toxicity: + = mild to moderate, ++ = moderate to severe, +++ = severe

Daily cost: + = 5-25 Euro/day, ++ = 25-50 Euro/day, +++ ≥ 50 Euro/day

TMP-SMX = trimethoprim-sulfamethoxazole

weight, changing renal function, and vancomycin troughs. There was no correlation found between vancomycin trough levels (0-5, >5-10; >10-15, >15 µg/ml) and clinical or microbiological outcome [35]. Moreover, with high (>15 µg/ml) trough levels the risk for nephrotoxicity is substantially increasing [60]. When vancomycin is combined with aminoglycosides, the creatinine rise may be as high as 35% [61]. Finally, unfavourable clinical outcomes under vancomycin therapy have been shown to be referred to an increasing resistance with a minimum inhibitory concentration (MIC) >1 µg/ml [62]. Unfortunately, many clinicians are not provided with MIC data of vancomycin when clinical decisions have to be made. Taking all these issues together, it appears to be a reasonable approach to dispense with vancomycin as a first-line treatment for severe cSSTI and to use it only if other treatment options are not tolerated or available (Table 3).

#### ANTIBIOTICS WITHOUT DATA FROM CONTROLLED TRIALS (TRIMETHOPRIM-SULFAMETHOXAZOLE, RIFAMPICIN, FOSFOMYCIN, CLINDAMYCIN, QUINOPRISTIN/DALFOPRISTIN)

The good tissue penetration, the oral formulation and the low costs make trimethoprim-sulfamethoxazole (TMP-SMX) an attractive alternative to newer more expensive drugs or those which require intravenous application (glycopeptides, daptomycin, tigecycline). In vitro TMP-SMX is rapidly bactericidal against MRSA and has been shown to have a better in vitro bactericidal activity against MRSA than linezolid, rifampicin, clindamycin or minocycline [63]. Unfortunately we were unable to find prospective studies of TMP-SMX in treating patients with cSSTI caused by MRSA. The only available randomized double-blinded trial compared TMP-SMX (1g twice daily)



Table 3. Clinical decision-making for the choice of antibiotic with activity against MRSA according to the severity of disease.

severity of infection	characteristics	setting	preferred route	substances
mild	- limited local signs - no systemic signs - no surgery required - patient stable	outpatient	oral	TMP-SMX ± rifampicin clindamycin*◇ linezolid*
moderate	- marked local signs - systemic signs measurable - surgery required - patient stable	hospitalized, general ward	initially i.v.  sequential oral treatment	linezolid* tigecycline# daptomycin vancomycin linezolid* clindamycin* ◇ TMP-SMX ± rifampicin
severe	- massive local and/or systemic signs - surgery required - patient unstable	inpatient, intensive care	initially i.v.  sequential oral treatment	linezolid* daptomycin [bacteremia] tigecycline # [polymicrobial inf.] (vancomycin) linezolid* clindamycin*◇ TMP-SMX± rifampicin

\* preferred in cMRSA infections

# not indicated in diabetic foot infections

◇ = if susceptible

TMP-SMX = trimethoprim-sulfamethoxazole

(vancomycin) = to be used only if other drugs are not tolerated or not available

plus rifampicin (300 mg twice daily) versus novobiocin (500 mg twice daily) and rifampicin 300 mg twice daily) for MRSA-decolonization [64]. The eradication rate was 53% (TMP-SMX plus rifampicin) and 67% (novobiocin plus rifampicin), respectively. During therapy, 14% (7/49 patients) of the TMP-SMX group developed emergence of resistance to rifampicin.

Fosfomycin has an in vitro bactericidal activity against MRSA. The pharmacokinetic properties of the drug (excellent tissue penetration) make it appear reasonable to use fosfomycin for MRSA caused cSSTI, particularly in combination with other substances [65-67]. To the best of our knowledge there are only limited controlled clinical data on the use of fosfomycin in cSSTI caused by MRSA from a compassionate use study [67, 68]. Unsolved questions of dosage, a rapid development of resistance under treatment and potential severe side effects (liver failure) are matters of concern [69].

Quinopristin/dalfopristin (Q/D) is a semisynthetic mixture of two streptogramin antibiotics. Both substances have a bacteriostatic mechanism of action against Gram-positive bacteria, but in combination bactericidal activity can be observed [70]. It is inactive against *Enterococcus faecalis*. We could not find any controlled data regarding the use of Q/D for MRSA-caused cSSTI. There are only retrospective data for the treatment of VRE infections [71]. The substantial

side effect profile (severe myalgia, severe venous irritation, rapid emergence of resistance, interaction with cytochrome P450 system) have led to the abandonment of the Q/D [72].

Clindamycin may be an alternative in MRSA-caused cSSTI, although resistance to this agent is a problem. The penetration of the drug into soft tissues, that can be administered both i.v. and orally, is high. Clindamycin is an effective inhibitor of protein biosynthesis, making it like linezolid to a valuable drug particularly in cases of CA-MRSA [73]. Data from controlled trials do not exist to date, but efficacy has been shown in case series [74]. The toxicity profile of clindamycin is tolerable. The possible development of *Clostridium difficile*-associated colitis needs close clinical observation under therapy.

The lack of evidence from controlled studies with regard to efficacy and safety is a substantial flaw of all of the above mentioned compounds. Many of the randomized trials, that have been performed for approval of substances in cSSTI, were criticized not having met all of the FDA criteria for complicated SSTI [7, 56]. Nevertheless, as seen before the background of data from pivotal trials for linezolid, tigecycline, daptomycin and vancomycin [8-10, 35], the administration of drugs without evidence from controlled trials needs to be considered very carefully, particularly under medicolegal aspects.

## COLONISATION OR INFECTION?

The differentiation between colonisation and infection in cSSTI is of paramount clinical importance for the initiation of an antimicrobial treatment. The clinical differentiation between colonisation and infection can be extremely difficult even for experienced physicians. On one hand the recognition of an infection can be complicated in a case of a diabetic foot syndrome when classical local and systemic signs of infection are disguised by an ischemic component of the disease. On the other hand a substantial immunosuppression (e.g. leucopenia during chemotherapy) might be a reason for the initiation of an antibiotic treatment even in case of colonisation. In a Cochrane review the results of a treatment of MRSA colonization with topical or systemic administration of several agents in immunocompetent patients has been investigated. Six randomized studies with 384 patients were included. The authors did not find superiority for any drug over placebo except for the nasal decolonisation with mupirocin [75]. Development of resistance and toxicity were significantly more frequent in the verum group. Therefore, antibiotic treatment of colonisation of skin and soft tissues with MRSA is only indicated in rare cases.

### IS THERE A CLINICALLY RELEVANT DIFFERENCE BETWEEN BACTERIOSTATIC AND BACTERICIDAL DRUGS?

The general characteristics of anti-MRSA substances are listed in Table 1. In Table 2 the controlled clinical data of the compounds are listed. From the analyzed drugs, vancomycin, daptomycin, TMP-SMP, Q/D, fosfomicin and rifampicin are described as bactericidal, whereas linezolid, clindamycin and tigecycline as bacteriostatic. Bacteriostatic and bactericidal categorizations in clinical practice are not absolute and can lead to false assumptions concerning antimicrobial therapy, especially if major pharmacokinetic and pharmacodynamic parameters like tissue penetration and plasma protein binding are ignored. The bacteriostatic agent linezolid has shown non-significant superiority over the bactericidal vancomycin in every controlled study for the treatment of cSSTI caused by MRSA [8, 31, 35], whereas the rapidly bactericidal drug daptomycin has failed to reach superiority over comparator substances in cSSTI [10]. It is important to distinguish microbiological and clinical definitions. To date, there has not been found any significant advantage for bactericidal agents in the treatment of cSSTI. The ultimate guide to treatment of any infection must be clinical outcome [76].

### TREATMENT RECOMMENDATIONS FOR ANTIMICROBIAL THERAPY

The adequate empirical antibiotic treatment in cSSTI caused by MRSA has been shown to be a significant predictor for treatment success [77]. The antibiotic treatment of cSSTI is well reviewed in the published guidelines [78-81]. Any clinical guideline for antimicrobial treatment of (MRSA-caused) cSSTI should

follow the clinical presentation of the affected patient. Differentiation between outpatient treatment (preferably with oral agents), and hospitalised patients with or without sepsis (primarily intravenously, followed by oral treatment if possible) is set out in Table 3. Although concerns remain about the quality of randomized trials in cSSTI [56], linezolid, tigecycline, daptomycin and vancomycin have proven efficacy and safety in MRSA-caused cSSTI [8-10, 35]. None of these drugs showed significant superiority regarding clinical cure and eradication rates. To date, linezolid offers by far the greatest number of patients included in trials with cSSTI caused by MRSA and showed a strong tendency of superiority over vancomycin in terms of clinical success rates and eradication rates [34, 35]. Due to its pharmacokinetic unreliability, its toxicity and increasing resistance ("MIC-creep") and relatively poor results in the treatment of severely ill patients, the administration of vancomycin should be restricted only to cases of moderate severity of infection or if other treatment options are not tolerated or available [57].

In cSSTI caused by MRSA it is useful to differentiate between monomicrobial and polymicrobial infections [80]. In those cases, agents merely active against Gram-positive bacteria (linezolid, daptomycin, vancomycin) have to be combined with drugs showing activity against Gram-negative and anaerobic organisms. Tigecycline is an alternative in polymicrobial infections excluding diabetic foot infections [9]. Daptomycin appears to be a treatment option for cases of cSSTI and MRSA bacteremia [10, 80].

cSSTI caused by VRE have not been investigated under conditions of controlled trials. Treatment recommendations (linezolid, tigecycline) are based on in vitro data [8, 9] as well as personal experience and are summarized in Table 4 modified according to [81].

In cSSTI caused by resistant Gram-negative bacteria (primarily ESBL-producing or carbapenem-resistant strains), carbapenems (ESBL) and tigecycline (ESBL and carbapenem-resistant bacteria) are the only available in vitro effective drugs with a tolerable toxicity (Table 4). However, evidence from controlled trials is almost completely missing [50, 51]. Colistin has been shown to be associated with poorer survival compared to controls, a significantly higher rate of renal toxicity and a high rate of subsequent infections caused by *Proteus* spp. [82].

As long as more than one therapeutic alternative is available, the application of antibiotic diversity appears to be a very useful tool in order to reduce the antibiotic selective pressure on any substance as a part of an antibiotic stewardship program [15, 17].

Despite national and international recommendations and guidelines, it is important to stress that local epidemiology and antibiotic resistance patterns are important in determining empirical antibacterial therapy.

Treatment duration can usually be confined to 7 days, providing that the patient and wound have improved clinically and blood inflammatory signs (CRP, leucocytes) have substantially reduced. However, controlled clinical data regarding the duration of treatment in cSSTI are not available to date.

Table 4. Antibiotics against VRE, ESBL and carbapenem-resistant bacteria in cSSTI.

Organism	Antibiotic	Duration
VRE	Linezolid Tigecycline	7 days
ESBL	Carbapenem group 1 and 2 Tigecycline Fosfomycin+ Colistin	7 days
Carbapenem resistant bac.	Tigecycline Colistin	7 days

+ = combination therapy necessary

### SUMMARY

- The treatment of cSSTI caused by resistant bacteria relies on a combination of surgical and antimicrobial treatment. Good quality controlled clinical data for the efficacy and safety is only available for MRSA-caused cSSTI.
- Linezolid, tigecycline, daptomycin and vancomycin have shown efficacy and safety in MRSA-caused cSSTI. None of these drugs showed significant superiority regarding clinical cure and eradication rates. Linezolid offers to date by far the greatest number of patients included in controlled trials with a strong tendency of superiority over vancomycin.
- Tigecycline is an alternative in polymicrobial infections excluding diabetic foot infections.
- Daptomycin is an effective treatment option for cases of cSSTI and MRSA bacteremia.
- Due to its pharmacokinetic shortfalls, the toxicity and the increasing resistance and poor clinical results in the treatment of severe infections, the administration of vancomycin should be restricted only to cases of mild or moderate severity of infection or if other treatment options are not tolerated or available.
- cSSTI caused by resistant Gram-negative bacteria (mainly ESBL-producing or carbapenem-resistant strains) are a matter of great concern. Carbapenems (ESBL) and tigecycline (ESBL and carbapenem-resistant bacteria) are the only available effective drugs with a tolerable toxicity.
- The development of new antibiotics in this area is urgently required in order to avoid a postantibiotic era without any antimicrobial treatment option.
- An individual approach for every patient is essential to establish an optimal treatment regimen. As long as more than one therapeutic alternative is available, the application of antibiotic diversity is a useful tool in order to reduce the antibiotic selective pressure on particular agent.

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