Treatment options for skin and soft tissue infections caused by meticillin-resistant *Staphylococcus aureus*: oral vs. parenteral; home vs. hospital

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Abstract

Although meticillin-resistant *Staphylococcus aureus* (MRSA) is recognized as a significant cause of nosocomial infections, it is also becoming an increasingly common cause of infections in the community. Overall, the most common infections caused by MRSA are those involving the skin and skin structures. These infections are difficult to treat and are associated with high morbidity and substantial cost. This article summarizes the current oral and parenteral therapeutic options, of which there are several, and the optimal site of care for the management of these infections. Defining the severity of the illness is central to improving the decision-making process about the route of administration and site of care.

1. Introduction

Meticillin-resistant *Staphylococcus aureus* (MRSA) was first described in 1961, and since then has become a worldwide problem [1,2]. Nowadays, MRSA is the most common nosocomial bacterial pathogen isolated in many parts of the world [3]. Recent evidence has shown that MRSA surgical site infections are associated with higher mortality, greater length of stay, and greater costs than meticillin-sensitive *S. aureus* (MSSA) infections [4].

During the past decade there has been a marked increase in the prevalence of community-acquired MRSA (CA-MRSA) infection. Overall, the most common infections caused by CA-MRSA are those involving the skin and skin structures (skin and soft tissue infections; SSTIs) [5]. Recently, Klein et al. used data concerning hospitalization and bacterial resistance to estimate the annual number of hospitalizations and deaths associated with *S. aureus* and MRSA in the USA from 1999 to 2005 [6]. During this period the most frequent primary diagnoses associated with *S. aureus* infections were cellulitis and abscess, followed by postoperative infection. The rate of diagnosis of cellulitis increased by >25% each year, from 22,451 (95% CI: 17.0–27.9) to 87,500 cases (95% CI: 75.5–99.5), a nearly fourfold increase. Frazee et al. determined the prevalence of MRSA among emergency department (ED) patients with SSTIs. Of 137 subjects, 18% were homeless, 28% injected illicit drugs, 63% presented with a deep or superficial abscess and 26% required admission for the infection. MRSA was present in 51% of infection-site cultures. Of 119 *S. aureus* isolates (from infection site and nares), 89 (75%) were MRSA [7].

In a retrospective chart review of 399 sequential cases of culture-confirmed *S. aureus* SSTIs, including 227 outpatients cases of MRSA SSTI, Szumowski et al. showed that the proportion of *S. aureus* SSTI due to MRSA increased significantly between 1998 and 2005 (P < 0.0001). Overall, 54/227 (23.8%) MRSA SSTI cases occurred in patients with a previous culture-confirmed MRSA SSTI [8]. In another, similar, retrospective study Pallin et al. showed that in 1993 SSTIs were diagnosed at 1.2 million visits (95% CI: 0.96–1.5 million) vs. 3.4 million in 2005 (95% CI: 2.8–4.1 million; P < 0.001). As a proportion of all ED visits, such infections were diagnosed at 1.35% in 1993 (95% CI: 1.07–1.64%) vs. 2.98% in 2005 (95% CI: 2.40–3.56%; P < 0.001). When antibiotics were prescribed at such
visits, one typically active against CA-MRSA was rarely chosen from 1993 to 2001, but increasingly thereafter, reaching 38% in 2005 (95% CI: 30–45%; P < 0.001) [9]. This paper will briefly touch upon the oral and parenteral treatment options for SSTIs and the site of care, i.e. home or hospital.

2. Severity of the illness

Defining the severity of an infection plays a central role in the correct choice of the route of administration of antibiotics and the site of care (Fig. 1) [10]. The first, and economically most important, decision in treating SSTIs concerns the need for hospitalization. It largely depends on the severity of the illness at presentation and the likelihood of disease progression. These factors are assessed on the basis of the history, the presence of co-morbidities, the physical examination and the results of laboratory studies and other tests. Most uncomplicated SSTIs do not require hospitalization. Complicated infections often require admission, especially if muscle or fascial involvement is suspected, the process is rapidly progressing, signs of toxaemia are developing, the diagnosis or prognosis is in doubt, exploratory surgery is contemplated or the patient cannot adequately comply with outpatient treatment [11]. In 2003 an expert panel described a system for the classification and management of SSTIs. These infections were divided into four classes according to the severity of local and systemic signs and symptoms of infection, and the presence and stability of any co-morbidities. Class 1 patients have no signs or symptoms of systemic toxicity, no uncontrolled co-morbidities that may complicate treatment and usually can be managed with topical or oral antimicrobials on an outpatient basis. Class 2 patients are either systemically ill, but any co-morbidities they may have are stable, or are systemically well, but have one or more co-morbidities that may complicate or delay the resolution of their SSTI. Class 3 patients may appear toxic, e.g. having changes in mental status, tachycardia, tachypnoea or hypotension, or they may appear non-toxic but have unstable co-morbidities that may interfere with their response to therapy. Class 4 patients have sepsis syndrome or serious life-threatening infections. Figure 2 shows an algorithm for managing SSTIs according the Eron classification [12].

3. Oral agents for treating SSTIs due to MRSA

3.1. Clindamycin

Clindamycin has been widely used by paediatricians for treating SSTIs, including those due to CA-MRSA [13]. A potential advantage of clindamycin is that it suppresses the production of Panton-Valentine leukocidin and other virulence factors in MRSA [14,15]. Only few clinical data are available. Martinez-Aguilar et al. compared the outcome of therapy for invasive infections caused by MRSA or MSSA in children treated with clindamycin, vancomycin or β-lactam antibiotics. The sites of infection for MRSA vs. MSSA isolates, respectively, were: bacteraemia 3 vs. 6; osteomyelitis 14 vs. 14; septic arthritis 5 vs. 7; pneumonia 11 vs. 3; lymphadenitis 7 vs. 14; other 5 vs. 8. Among MRSA patients, 39 received clindamycin and 6 received vancomycin as primary therapy. Among MSSA patients, clindamycin, nafcillin or other β-lactam antibiotics were used in 24, 18 and 9 cases, respectively. The median number of febrile days was three and two for MRSA and MSSA patients, respectively (P = 0.07).
The median number of days with positive blood cultures was two for MRSA patients and one for MSSA patients \( (P = 0.04) \). The authors concluded that clindamycin was effective in treating children with invasive infections caused by suscepti-
ble CA-MRSA isolates [16]. Recently, Drekonja et al. studied the outcome of 87 patients affected by non-life-threatening MRSA infections (85% skin/musculoskeletal; 15% urinary tract infection) who received alternative (non-vancomycin, non-
linezolid) antimicrobial agents. Eight patients were treated with clindamycin. Treatment was clinically successful in 77 (89%; 95% CI: 78–96%) and unsuccessful in 10 (11%) [17].

However, organisms that exhibit resistance to erythromycin and susceptibility to clindamycin may quickly develop resistance to clindamycin, either because of efflux or via inducible expression of the MLS\(_b\) gene. These organ-
isms will appear to be susceptible by clinical microbiology laboratory testing, but treatment will result in clinical failure [5,18,19].

### 3.2. Trimethoprim–sulfamethoxazole

At present in the USA, trimethoprim–sulfamethoxazole (TMP–SMX) and clindamycin are the most commonly used antimicrobial drugs for the outpatient treatment of CA-MRSA infections [5]. Szumowski et al. showed that at the beginning of the study period in 1998 most patients with MRSA SSTI empirically treated with antibiotics received a \( \beta\)-lactam, whereas by 2005, 76% received TMP–SMX \( (P < 0.0001) \). Infections treated with TMP–SMX were associated with a more favourable response than those treated with agents to which the organisms were resistant (odds ratio [OR] 5.91; 95% CI: 3.14–11.13). Moreover, resistance to TMP–SMX was uncommon. Of the 399 \( S.\ aureus \) SSTI, 386 had known TMP–SMX sensitivity and only 10 isolates (2.6%) were resistant. Of these, five were HIV-infected, and three of these were receiving prophylactic TMP–SMX. Nine isolates were MSSA and one was MRSA. Only one (0.5%) of the 216 MRSA skin and soft tissue isolates with known TMP–SMX sensitivity was resistant to TMP–SMX [8].

In the retrospective study conducted by Pallin et al., TMP–SMX was rarely prescribed in 1993, but 51% of SSTIs treated received TMP–SMX in 2005 [9]. Recently, Cenizal et al. conducted a prospective randomized trial of empirical therapy with TMP–SMX or doxycycline for outpatient SSTIs in an area of high prevalence of MRSA. Of the 34 subjects included in the study, 14 received TMP–SMX (8 with MRSA) and 20 received doxycycline (15 with MRSA). One subject with MRSA was lost to follow-up in the doxycycline group. Three of the 33 subjects (9%) with data at 10–14 days were classified as clinical failures. All three occurred in the TMP–SMX group, with none in the doxycycline group. By culture, two of the clinical failures with TMP–SMX had MRSA and one had \( S.\ milleri \). However, there was no significant difference between the clinical failure rate of empirical TMP–SMX therapy and that of doxycycline therapy [20]. Drawbacks with TMP–SMX include its relative lack of activity against streptococci, Stevens-Johnson syndrome and blood dyscrasias [21].

### 3.3. Tetracyclines

Few data are available on the use of these agents for this indication. Older studies found that tetracyclines are potent in vitro anti-staphylococcal agents (minocycline more so than doxycycline) [22]. In a small case-series on the role of long-acting tetracyclines for MRSA infections (complicated SSTIs 67%), Ruhe et al. achieved a clinical cure in 20 of 24 patients (83%) [23]. The same authors performed a retrospective cohort study of 276 patients with 282 episodes of MRSA SSTI who presented to the emergency room or outpatient clinic at two tertiary medical centres. Abscesses constituted the majority of clinical presentations (75%), followed by furuncles or carbuncles (13%) and cellulitis originating from a purulent focus of infection (12%). A total of 225 patients (80%) underwent incision and drainage. Doxycycline or minocycline was administered in 90 episodes (32%). On logistic regression analysis, receipt of a \( \beta\)-lactam agent was the only clinical characteristic associated with treatment failure \( (OR: 3.94; 95\% CI: 1.28–12.15; P = 0.02) \). Moreover, the median percentage of patients infected with MRSA strains that were susceptible to tetracycline was 95% [24]. However, staphylococcal resistance to tetracyclines is conferred by two mechanisms: active efflux, which is mediated by the plasmid-located \( tetK \) and \( tetL \) genes, and ribosomal protection, which is mediated by chromosomal or transposonal \( tetM \) or \( tetO \) genes [25]. The presence of these genes gives cross-resistance to all tetracyclines. Therefore, tetracycline-resistant strains of MRSA should be considered resistant to all tetracycline class members unless testing for specific minocycline susceptibility is performed [23].

### 3.4. Fusidic acid and rifampicin

Fusidic acid and rifampicin are useful oral antimicrobials with excellent anti-staphylococcal activity. MRSA strains must be treated with a combination of these agents because resistance develops rapidly if they are used singly [26]. However, a limited number of small clinical studies have shown good clinical efficacy [27,28].

### 3.5. Linezolid

Linezolid is the only currently available oxazolidinone. It has been approved by the US Food and Drug Administration for the treatment of complicated skin infections caused by MRSA. Linezolid can be administered both orally and parenterally. After oral administration, the maximum peak plasma concentration occurs within 1–2 h. Orally adminis-
tered linezolid is virtually completely bioavailable [29].

In adults with complicated SSTIs requiring hospitalization, linezolid 600 mg q12h intravenously (iv) followed by the same dosage given orally after initial improvement was as clini-
cally and microbiologically effective as intravenous oxacillin followed by oral dicloxacillin [30]. Wilcox et al. compared linezolid and teicoplanin in a randomized controlled trial (RCT) in patients with suspected or proven Gram-positive infection. Clinical cure rates at the end of treatment were higher for the linezolid than the teicoplanin group for each baseline diagnosis: SSTI (96.6% vs. 92.8%); pneumonia (96.2% vs. 92.9%); bacteraemia (88.5% vs. 56.7%) [31]. In another
RCT, Weigelt et al. showed that linezolid outcomes (124/140 patients; 88.6%) were superior to vancomycin outcomes (97/145 patients, 66.9%) at the test-of-cure visit for patients with MRSA infections ($P < 0.001$) [32].

More recently, Falagas et al. performed a meta-analysis of RCTs. Overall, twelve RCTs involving 6093 patients were included. In a sub-analysis on SSTIs linezolid was more effective than comparators (OR: 1.67; 95% CI: 1.31–2.12) [33]. However, linezolid has drawbacks including adverse haematological effects and peripheral and optic neuropathy with prolonged use, and it is only bacteriostatic against staphylococci.

4. Parenteral agents for the treatment of SSTIs due to MRSA

4.1. Glycopeptides

Vancomycin or teicoplanin remain the gold standard of therapy for serious MRSA infections [5]. However, there is great controversy over the current utility of these agents, the backbone of treatment for MRSA infections [34]. The poor pharmacokinetic/pharmacodynamic parameters—poor tissue distribution, slow cidal activity and high protein binding—predict poor patient outcome, even without the advent of resistant strains, and may explain the higher mortality of MRSA infections and the poorer outcome even of MSSA infections when treated with vancomycin. Moreover, there is a growing body of evidence indicating that glycopeptide minimum inhibitory concentrations (MICs) have a real impact on patient outcomes [35].

In a 5 year microbiological study, Wang et al. observed that the percentage of S. aureus isolates with a vancomycin MIC of 1 mg/mL in 2004 was significantly higher than the percentage of isolates in 2000 (70.4% vs. 19.9%; $P < 0.01$) [36]. In a small study, Sakoulas et al. found a statistically significant relationship between treatment success with vancomycin and decreases in both vancomycin MICs ($\leq 0.5$ mg/mL vs. 1.0–2.0 mg/mL; $P = 0.02$) and degree of killing (reduction in log10 CFU/mL) by vancomycin over 72 h incubation in vitro ($P = 0.03$). For MRSA isolates with vancomycin MICs $\leq 0.5$ mg/mL, vancomycin was 55.6% successful in the treatment of bacteraemia, whereas it was only 9.5% effective in cases in which vancomycin MICs for MRSA were 1–2 mg/mL [37]. In another study comparing infections caused by MRSA with a vancomycin MIC of $\geq 2$ mg/mL with infections due to MRSA with a MIC of $<2$ mg/mL, the response was significantly lower (62% vs. 85%; $P = 0.02$) and infection-related mortality was higher (24% vs. 10%) in the high MIC group. In addition, a high MIC for vancomycin was an independent predictor of poor response in multivariate analysis of these MRSA infections [38]. More recently, Soriano et al. found a significantly higher mortality for this disease when vancomycin was used empirically and the vancomycin MIC was 2 mg/mL [39].

4.2. Tigecycline

Tigecycline is a novel, broad-spectrum, glycylcycline antibiotic with activity against a broad range of Gram-positive, Gram-negative, atypical, anaerobic and antibiotic-resistant bacteria, including MRSA. All of the staphylococci tested in vitro were inhibited by $\leq 2$ mg/mL of tigecycline and against MSSA and MRSA (including community-acquired strains) tigecycline MIC90 values were 0.12 and 0.25 mg/mL, respectively. Tigecycline is only available as an intravenous preparation, is administered twice daily (although its long half-life and post-antibiotic effect may make once-daily dosing possible), appears to have good tissue penetration (e.g. skin) and requires no adjustment in the presence of renal or hepatic diseases [40]. The safety and efficacy of tigecycline vs. vancomycin-aztreonam were determined in two phase 3, double-blind studies in hospitalized adults with complicated SSTIs. Clinical responses to tigecycline and vancomycin-aztreonam at test-of-cure evaluation were similar: 79.7% (95% CI: 76.1–83.1%) vs. 81.9% (95% CI: 78.3–85.1%), as were the responses of the clinically evaluable population: 86.5% (95% CI: 82.9–89.6%) vs. 88.6% (95% CI: 85.1–91.5%) [41].

4.3. Daptomycin

Daptomycin has rapid, concentration-dependent, bactericidal activity against most Gram-positive pathogens, including those that are multi-drug resistant. It is not active against Gram-negative organisms as it is unable to penetrate their outer membrane. The MIC of daptomycin for determining susceptibility is $\leq 1$ mg/mL for S. aureus (both meticillin-resistant and meticillin-susceptible strains) [42]. Daptomycin 4 mg/kg iv every 24 h for 7–14 days was compared with conventional antibiotics (penicillinase-resistant penicillins 4–12 g iv per day or vancomycin 1 g iv q 12 h) in two randomized, international trials involving 1092 patients with complicated SSTIs. Among 902 clinically evaluable patients, clinical success rates were 83.4% and 84.2% for the daptomycin- and comparator-treated groups, respectively (95% CI: -4.0 to 5.6). Among patients successfully treated with iv daptomycin, 63% required only 4–7 days of therapy, compared with 33% of comparator-treated patients ($P < 0.0001$). The frequency and distribution of adverse events were similar among both treatment groups. Overall, the safety and efficacy of daptomycin were comparable with conventional therapy [43].

5. Outpatient parenteral antibiotic therapy

SSTIs have been the main diagnosis of patients in outpatient parenteral antimicrobial therapy (OPAT) programmes for many years, as they can require antibiotic therapy administered parenterally at high dosages for a prolonged period. Currently, these infections are the most frequent indication for OPAT in the USA, the UK and Italy (Fig. 3) [44].

The initiation of OPAT requires that a physician determines that such a therapy is needed to treat a defined infection, that hospitalization is not needed to control the infection and that alternative routes of drug delivery are not feasible or appropriate [45]. According to Eron’s classification, some class 2 patients may require short-term hospitalization or observation in an infusion centre or emergency department. Class 3 patients usually require initial inpatient treatment with parenteral antimicrobials, but many of them can be quickly discharged on OPAT or oral therapy. Several other studies have shown that OPAT has the potential to greatly reduce costs and improve patient satisfaction, with outcomes that are equivalent or superior to those of inpatient treatment.
In a RCT comparing the efficacy, safety and acceptability of treatment with iv antibiotics for cellulitis at home and in hospital, Corwin et al. observed that the two treatment groups did not differ significantly with respect to the primary outcome of number of days to no advancement of cellulitis, with a mean of 1.50 days ($\pm 0.11$) for the group receiving treatment at home and 1.49 days ($\pm 0.10$) for the group receiving treatment in hospital (mean difference 0.01 days, 95% CI: $-0.3$ to 0.28). None of the other outcome measures differed significantly, except for patient satisfaction, which was greater in patients treated at home [46]. More recently, Martone et al. showed that successful outcomes for OPAT patients vs. inpatient parenteral antibiotic therapy (IPAT) patients were 94.6% and 86.3% respectively ($P < 0.001$). Success rates were higher in OPAT patients than in IPAT patients for both complicated and uncomplicated SSTIs (95.5% vs. 89.43% [P = 0.064] and 98.0% vs. 94.4% [P = 0.289], respectively) [47].

6. Conclusion

SSTIs are difficult to treat and are associated with high morbidity and substantial cost. Several oral and parenteral antibiotics, both established and new, are available for the management of these infections. Defining the severity of the illness is central to improving the decision-making process about the route of administration and site of care.

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