REVIEW ARTICLE

Current and future trends in antibiotic therapy of acute bacterial skin and skin-structure infections

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Abstract

In 2013 the US Food and Drug Administration (FDA) issued recommendations and guidance on developing drugs for treatment of skin infection using a new definition of acute bacterial skin and skin-structure infection (ABSSSI). The new classification includes cellulitis, erysipelas, major skin abscesses and wound infection with a considerable extension of skin involvement, clearly referring to a severe subset of skin infections. The main goal of the FDA was to better identify specific infections where the advantages of a new antibiotic could be precisely estimated through quantifiable parameters, such as improvement of the lesion size and of systemic signs of infection. Before the spread and diffusion of methicillin-resistant *Staphylococcus aureus* (MRSA) in skin infections, antibiotic therapy was relatively straightforward. Using an empiric approach, a β-lactam was the preferred therapy and cultures from patients were rarely obtained. With the emergence of MRSA in the community setting, initial ABSSSI management has been changed and readdressed. Dalbavancin, oritavancin and tedizolid are new drugs, approved or in development for ABSSSI treatment, that also proved to be efficient against MRSA. Dalbavancin and oritavancin have a long half-life and can be dosed less frequently. This in turn makes it possible to treat patients with ABSSSI in an outpatient setting, avoiding hospitalization or potentially allowing earlier discharge, without compromising efficacy. In conclusion, characteristics of long-acting antibiotics could represent an opportunity for the management of ABSSSI and could profoundly modify the management of these infections by reducing or in some cases eliminating both costs and risks of hospitalization.

Keywords: Acute bacterial skin and skin-structure infection, complicated forms of skin and soft-tissue infections, early discharge, long-acting antibiotics, methicillin-resistant *Staphylococcus aureus*
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Introduction

Acute bacterial skin and skin-structure infection (ABSSSI) is a frequent cause of morbidity in both the community and hospital settings. *Staphylococcus aureus* is the most frequent cause of these infections, and methicillin-resistant *S. aureus* (MRSA) represents the first resistant pathogen involved in complicated forms of skin and soft-tissue infections (cSSTI) [1,2]. This review addresses the changing definition, classification and aetiology from cSSTI to ABSSSI and the clinical profile of patients with ABSSSI; it also evaluates recent advances in the treatment of this various group of conditions. In particular, we explore the management of MRSA infections analysing the different new and old therapeutic options.

Definition and classification

The severity of SSTI is dependent on various factors, and the clinical spectrum ranges from mild forms to life-threatening variants. The definition of cSSTI identifies patients who need complex management including surgical procedures and antibiotic treatment, and/or who have significant underlying co-morbidities such as diabetes, systemic immunosuppression or neurological diseases [3,4]. This category includes both healthy individuals with severe infections and patients with co-morbidities and relatively minor infections. However, several classifications of SSTI have been proposed and heterogeneous syndromes, irrespective of the severity and the extension of the disease, have been categorized as cSSTI [5,6]. This terminology has been widely used in clinical trials, with partial benefits deriving from broad inclusion criteria. However, there was a lack of clear evidence to evaluate the patients whose conditions were improving quickly. Therefore, in 2013 the US Food and Drug Administration (FDA) issued new guidelines on developing drugs for treatment of cSSTI and introduced the new definition of ABSSSI, which now includes cellulitis, erysipelas, major skin abscesses and wound infections with a minimum lesion surface area of 75 cm^2. Diabetic foot ulcers, burns and chronic wound infections are excluded from this new definition (see Table 1). The main goal of the FDA was to better identify specific infections for which the advantages of a new antibiotic could be precisely estimated through quantifiable parameters, such as improvement of the lesion size and of systemic signs of infection [7].

Aetiology of ABSSSI

Globally, the most common cause of SSTI is *S. aureus*, which also includes MRSA. Although *S. aureus* is the predominant pathogen, *Streptococcus pyogenes* and other streptococci, enterococci and Gram-negative bacteria can also be involved in ABSSSI [8–10]. *Staphylococcus aureus* is rated as the main pathogen in all regions across North America, Latin America and Europe [11], and is also the most common cause of cSSTI in Europe. A study of more than 3000 cSSTI-associated isolates, sampled from 19 countries in and around Europe during 2008–2009, found that almost one-third were *S. aureus* and, of those, approximately one-half were MRSA [12]. Recent epidemiological data of the European Antimicrobial Resistance Surveillance (EARS) Network from 28 participating countries suggested that, overall, MRSA accounted for 16.7% of all *S. aureus* isolates and rates of >25% were reported from Cyprus, Greece, Italy and Malta (see Fig. 1). Gram-negative aetiology is more common in surgical-site infections: in the SENTRY programme (1998–2004) *Pseudomonas aeruginosa* was the second most important pathogen, followed by *Escherichia coli* [8].

TABLE 1. Disease manifestations of acute bacterial skin and skin-structure infection (ABSSSI)[a]

Included in the definition of ABSSSI	Excluded from the definition of ABSSSI
Cellulitis/erysipelas	Impetigo and minor cutaneous abscess
Wound infections	Animal or human bites
Major cutaneous abscess	Necrotizing fasciitis
	Diabetic foot infection
	Burns
	Chronic wound infection
	Myonecrosis
	Ecthyma gangrenosum

[a]Lesions should have a minimum surface area of 75 cm^2; erythema and/or induration should extend ≥5 cm from the peripheral margin of the infection; systemic signs of infection (such as fever) and/or proximal lymphadenopathy.

Patients with MRSA frequently present with a previous history of MRSA infection, advanced age, chronic open wounds, underlying chronic disease and repeated contact with a healthcare facility (see Table 2 for a more complete list of risk factors) [13]. Compared with hospital-associated MRSA, community-acquired MRSA tends to be more virulent and may carry genes that encode the Panton–Valentine leucocidin, as well as many other exotoxins that are associated with tissue necrosis and a greater severity of disease [14,15]. However, community-acquired MRSA seems to be less problematic in Europe than in the USA [16,17].

Recognition of ABSSSI as a tool to measure clinical cure

The FDA definitions place some emphasis upon signs of systemic involvement or regional involvement (such as lymph node enlargement) as part of the initial clinical presentation. The current guidelines only cite fever as a systemic sign; other signs and symptoms include leucocytosis, and increased serum C-reactive protein levels, procalcitonin levels, and erythrocyte sedimentation rates [18]. Clinical therapeutic success is based on objective criteria such as reduction of the initial lesions and their size (length, width and area) ≥20% in the size of the lesion within 48–72 h plus resolution of fever (i.e. temperature <37.7°C at three consecutive recordings using the same methodology every 6 h between 48 and 72 h). Importantly, the timing of the primary efficacy assessment should be done 48–72 h after the beginning of the therapy, to minimize the confounding influence of the immune response. Subsequently, the secondary end-point should be the assessment of efficacy after 7–14 days of therapy [19].

As aforementioned, the primary concern in ABSSSI is MRSA, which is the specific target of most recent antimicrobials studied under the new FDA guidance. It is also important to highlight that inadequate treatment of MRSA is an important risk factor for recurrent infections [20].

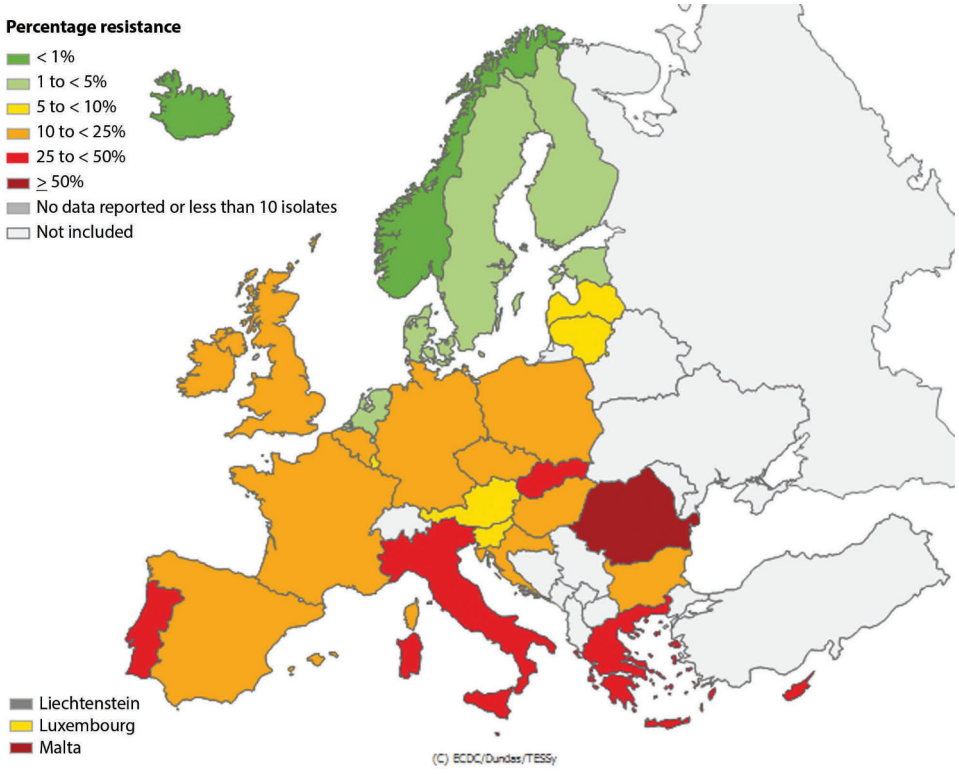

FIG. 1. Proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in participating countries in 2013.* European Antimicrobial Resistance Surveillance (EARS) Network [70]. *Reproduced with permission from the European Centre for Disease Prevention and Control.

Acknowledging these important steps, an important goal of management of ABSSSI should be to reduce inpatient hospital stay and readmissions through seamless transitions of care from the emergency department to hospital wards and then to discharge. The final target is to optimize the healthcare system through appropriate management and empiric antibiotic treatment of ABSSSI [21].

Diagnosis of ABSSSI

Microbiological diagnosis of SSTI and in particular of ABSSSI is often an object of concern for physicians. Surface cultures of wounds usually represent colonizing microbes, which cannot be easily differentiated from the underlying aetiological agent and are not indicative of infections such as cellulitis or subcutaneous abscesses. In addition, the sensitivity of blood cultures, especially in patients with cellulitis, is low. Tissue biopsies after deep debridement are the most valuable tool and the specimen of choice is a biopsied sample of the advancing margin of the lesion. Pus on a surface swab is inadequate and does not represent the disease process. In contrast, cultures are indicated for the patient who presents exudates or abscess and requires operative incision and drainage after debridement and cleansing of necrotic tissues. This procedure should be performed considering the high risk for deep structures and underlying tissues. Radiological imaging is particularly important in patients with ABSSSI. Ultrasonography is the most common and easiest method for assessing the presence of abscesses and can be used to guide therapeutic aspiration of deeper abscesses. Computed tomography scans can also be used in the diagnosis of deeper infections, while magnetic resonance imaging can detect soft-tissue alterations and is the most sensitive non-invasive method to determine the extent of tissue involvement and whether an infection is necrotizing [22].

Clinical profile of patients with ABSSSI

Although ABSSSI is a common cause of admission to the emergency department, the majority of patients can be treated effectively as outpatients with or without surgical intervention. For patients with more severe ABSSSI who actually need hospital admission, an effective communication and care transition between the emergency department and the hospital ward is crucial. However, an easy and well-defined clinical and therapeutic algorithm that evaluates the need for hospitalization,

TABLE 2. Risk factors for different bacterial skin and soft-tissue infections

Methicillin-resistant *Staphylococcus aureus*	**Gram-negative, anaerobes and polymicrobial**
Anamnestic factors:	**Surgical site infections:**
Previous colonization	Axillary cavity
Contact with patients colonized	Gastrointestinal tract
Antibiotic therapy in the previous 12 months	Perineum
Hospitalization in the previous 12 months	Female genital tract
History of previous infection	
Recent travel in Latin America, Africa, South East Asia	
Residence in long-term care facilities	
Previous intensive care unit admission	
Co-morbidities:	**Co-morbidities:**
Cardiovascular disease	Diabetes mellitus
Diabetes mellitus	Cirrhosis
Peripheral vascular disease	Intravenous drug abuse
Chronic wounds	Subcutaneous drug abuse
Immunodepression	
Central venous catheter	
Chronic renal disease	
Dialysis	
Intravenous drug abuse	

subsequent discharge and inpatient management has not been established. Such an algorithm should provide an appropriate pathway for case management while minimizing complications, readmissions, and inappropriate antibiotic use.

Clinical decision-making for ABSSSI in the emergency department is based on risk stratification [23]. For patients with ABSSSI who are unstable, an appropriate antimicrobial therapy should be started immediately.

In the majority of ABSSSI, an empiric antibiotic therapy is administered while in the emergency department and cultures are rarely collected. The aetiology of cellulitis without a wound or drainage is unclear because of the difficulty of obtaining an adequate sample for culture. Treatment should be guided by recognition of the most common pathogens, which in most cases are Gram-positive cocci. In contrast, antibiotic therapy for Gram-negative bacteria is not generally indicated in the treatment of most cases of ABSSSI [24,25].

The assessment of lesions that require surgery is essential. Inadequate drainage is often a reason for the apparent failure of an initial outpatient antibiotic regimen. In larger and more indurated lesions, ultrasound may provide valuable information. Patients with large and deep abscesses that require extensive debridement may require hospitalization for operative treatment and more intensive therapies.

Once a patient is admitted to the hospital, physicians play a key role in optimizing the choice of an appropriate antimicrobial regimen and evaluating the need for surgical intervention. After antibiotic treatment has been initiated empirically, physicians must follow the culture results and start a targeted antibiotic therapy as soon as possible. Physicians should try to reduce the duration of therapy and identify possibilities for an early switch to oral therapy or to outpatient parenteral antimicrobial therapy. Infectious disease specialists can provide recommendations for an optimal empiric and de-escalation therapy and for a switch to an outpatient antimicrobial therapy [26]. Oral therapy is recommended for patients who have had no fever for more than 24 h, show a normalized white blood cell count, and have the ability to take oral medications [27]. Once oral therapy is initiated, patient discharge should be planned (see Table 3). Typically, patients who are afebrile for at least 48 h and physically independent are ready to be discharged [28].

In internal medicine wards, elderly patients with high rates of co-morbidities are frequently hospitalized for long periods [29]. In this setting, an early discharge to home or other wards or hospitals, such as long-term care facilities, should be encouraged [30]. Multidisciplinary ABSSSI evaluation and management programmes can potentially contribute to better outcomes and coordination of care from the emergency department to the hospital (for patients requiring admission), and from the wards to the outpatient setting. Frequently, patients hospitalized with ABSSSI are prescribed an inadequate initial therapy, which is more common when the patient is older (>65 years) and presents co-morbidities, has difficulty in taking oral drugs, has recurrent or nosocomial infections, or has MRSA infection or septic shock [31,32].

On this basis, the use of an empiric antibiotic therapy tailored to the clinical features and risk factors of each patient might be the right approach for the management of ABSSSI. Moreover, an early switch to oral therapy or the use of long-acting antibiotics seems to be the best strategy to obtain an early discharge to home or to other facilities.

Treatment of ABSSSI and the role of new antibiotics

Before the spread and diffusion of MRSA in skin infections, empiric antibiotic therapy with a β-lactam was favoured and cultures were rarely obtained [33]. With the occurrence of MRSA in the community setting, initial ABSSSI management has been changed [34,35]. Three therapeutic approaches are favoured in treating skin infections: (a) surgical drainage and debridement, (b) wound culture with susceptibility testing, and (c) early and appropriate empiric antibiotic therapy [36]. Surgical drainage is recommended for abscesses or a purulent infection, whereas mechanical or chemical debridement is advised for

TABLE 3. Checklist for early discharge of patients with acute bacterial skin and skin-structure infection[a]

Discharge checklist	Comments
Results of blood cultures and other tests	Negative cultures, reduction of inflammatory indices, normalizing white blood cell count
Evaluation of all co-morbidities	No significant alterations of chronic diseases, glycaemic control in patients with diabetes, no systemic signs of infection
Switch to oral therapy or plan for outpatient parenteral antibiotic therapy	Plan for length of antibiotic therapy after discharge, access to day-hospital services, ability to take oral medications
Use of long-acting antibiotics	In empiric therapy or as early switch to these antibiotics
Follow up scheduled	Follow up within 7 days from discharge
Education to wound care	Correct management of chronic wounds
Continued cares in structures enabled or home-care evaluation	Transfer to long-term care facilities or evaluation by primary-care physician within 48 h from discharge

[a]Adapted by Amin et al. [69].

devitalized tissue in severe ABSSSI [37]. Wound cultures are highly recommended in patients with severe local infection and those who have failed on antibiotic treatment [38]. The rate of initial treatment failure may be considerably high for skin infections: in a study that reviewed data from more than 100 US hospitals, 16.6% of acute infections, 34.1% of chronic or ulcerative infections, and 26.7% of surgical site infections had initial treatment failure [39]. In particular, failure to initiate an antimicrobial therapy active against the causative pathogen within 48 h has been reported as an independent risk factor for treatment failure [40]. This is the main reason why the FDA guidance for ABSSSI suggested evaluation of clinical response 48–72 h after initiation of therapy, a tool that has proved useful in assessing therapeutic failure [41]. However, it is important to underline that Zervos et al. did not find an association between inappropriate therapy and outcomes, except in the subset of patients with ulcers [42]. Patients whose conditions deteriorate despite empiric antibiotic therapy should be treated more aggressively on the basis of Gram staining, culture and antibiotic susceptibility. Worsening of ABSSSI may indicate the presence of resistant pathogens, and therapy should be readdressed [43]. After initial treatment failure, MRSA should be considered as a possibility in hospitalized patients, and the choice of a new agent should be made on the basis of susceptibilities [44]. The need for source control, such as drainage or debridement, should also be carefully considered for patients not responding to antibiotic treatment.

Recently, the Infectious Disease Society of America developed new practice guidelines for the diagnosis and the management of SSTI [45]. SSTI were divided into two categories: purulent and non-purulent. Additionally, therapeutic indications were stratified on the basis of clinical manifestations, classified as mild, moderate and severe. Non-purulent infections include cellulitis and erysipelas, whereas abscesses fall into the purulent category. No differences are reported in the therapeutic approach to mild, moderate and severe purulent infections: cultures for test sensitivity, incision and drainage of the site of infection are considered the milestone of the treatment. Vancomycin, linezolid, tigecycline, daptomycin, ceftaroline and telavancin are considered the drugs of choice for severe infection [46,47]. Trimethoprim-sulfamethoxazole and doxycycline are used for moderate infections, and cefazolin and clindamycin are considered for severe infection due to methicillin-susceptible *S. aureus*. Recently, in a randomized trial on uncomplicated wound infection, trimethoprim-sulfamethoxazole was associated with a higher recurrence of infection compared with clindamycin [48].

Vancomycin plus piperacillin/tazobactam is the first line of treatment for severe non-purulent infections, especially if a necrotizing or polymicrobial infection is suspected. A defined aetiology due to *Streptococcus pyogenes* requires treatment with a penicillin plus clindamycin. For moderate and mild infections the choice is between a penicillin, ceftriaxone, cefazolin or clindamycin (see Table 4). No sufficient or definitive data are reported concerning the use of teicoplanin in ABSSSI due to MRSA. Recently, Lawson et al. reported data from a retrospective study to characterize real-world dosing of weight-based intravenous antibiotic therapy in patients hospitalized for MRSA cSSTI [49]. The new recommended teicoplanin dose for patients with MRSA cSSTI is 400 mg (~6 mg/kg) every 12 h for three doses, followed by a daily dose of 6 mg/kg [50]. New data are necessary to assess the role of teicoplanin in the treatment of these infections.

Once culture and susceptibility results are available, antibiotic therapy must be de-escalated to avoid emergence of resistance. Although no definitive data are reported, recommended treatment duration for ABSSSI is at least 7–10 days, but according to international guidelines treatment should be extended if the clinical condition does not improve [51].

At present, different guidelines have been proposed by the national expert panels of different European countries. The rationale is to adapt the use of antibiotic therapy to the respective national epidemiological situation [34,52–55]. On this basis, monotherapy should be attempted if possible. Gram-negative coverage is not empirically indicated in most cases of ABSSSI; however, clinical risk factors for infections due to Gram-negative pathogens should be considered in every patient. This point is crucial: early discharge or a switch to outpatient therapy, especially in the era of long-acting antibiotics, could be delayed by the use of antibiotics for Gram-negative

TABLE 4. Antimicrobial therapy for skin and soft-tissue infection due to methicillin-susceptible or methicillin-resistant *Staphylococcus aureus*

Aetiology	Antibiotic	Dosage[a]	Comments
MSSA	Oxacillin	1–2 g every 4 h IV	Parenteral drug of choice; inactive against MRSA
	Cefazolin	1–2 g every 8 h IV	For penicillin-allergic patients
	Clindamycin	600 mg every 8 h IV or 300–450 mg qid PO	Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA
	Doxycycline or minocycline	100 mg bid PO	Bacteriostatic
	Trimethoprim/sulfamethoxazole	One or two double-strength tablets bid PO	Bactericidal, recurrent infections
MRSA	Tigecycline	100 mg loading dose, followed by 50 mg every 12 h	Bacteriostatic, no bacteraemic infections
	Teicoplanin	6–10 mg/kg every 12 h for three doses followed by a daily dose of 6–10 mg/kg	No data about the new licensed dosage; reported failure of therapy; expensive
	Vancomycin	30 mg/kg/day in two divided doses IV	For penicillin-allergic patients; parenteral drug of choice for treatment of infections caused by MRSA
	Linezolid	600 mg every 12 h IV or 600 mg bid PO	Bacteriostatic
	Clindamycin	See above	See above
	Daptomycin	4 mg/kg every 24 h IV	Bactericidal
	Ceftaroline	600 mg bid IV	Bactericidal
	Doxycycline or minocycline	See above	See above
	Trimethoprim/sulfamethoxazole	See above	See above

Abbreviations: SSTI, skin and soft-tissue infection; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; IV, intravenous; qid, four times daily; bid, twice daily; PO, by mouth.
[a]Dosage and frequency are based on patients with normal renal function.

infections. The variability in treatment administration patterns and hospital stay observed across countries may be due to a number of reasons, including differences in physician and patient expectations, and different healthcare systems [56,57]. For example, the variability in the rate of intravenous-to-oral antibiotic switch may be affected by different perceptions on whether oral antibiotics represent the standard of care for treating serious infections [58,59]. Oral MRSA-active drugs have been implemented in recent algorithms and guidelines for treatment of MRSA ABSSSI, further supporting the use of these agents [1]. The extent and severity of infections may have contributed to a reluctance to switch patients from i.v. to oral formulations or to discharge patients sooner.

For ABSSSI due to MRSA, increased hospital length of stay is the key cost driver [60]. Therefore, identification of early switch and early discharge opportunities for hospitalized patients with ABSSSI due to MRSA could lead to a significant reduction in length of stay, providing a mechanism for improving outcomes and increasing efficacy. Recent data were published on patients with MRSA ABSSSI from more than 400 hospitals throughout 12 European countries [61]: although most patients were treated with a targeted intravenous antibiotic therapy, 29% met the criteria for an early switch to oral antibiotics and could have been discontinued from their intravenous treatment roughly 9 days earlier. Moreover, 24% of intravenous-only and 16% of intravenous-to-oral treatment-switched patients met the criteria for early discharge, with a mean potential saving of 7 days. These data provide useful information on the potential for improving current management of these infections.

The new drugs already approved or in development for ABSSSI have an important activity against MRSA (see Table 5). Tedizolid was reported to be statistically non-inferior to linezolid in patients with ABSSSI for an early clinical response evaluated 48–72 h after the beginning of the therapy [62,63]. Due to their long half-life, dalbavancin and oritavancin have the potential to be dosed less frequently. Dalbavancin has a prolonged half-life of 6–10 days and can be administered with only two doses once weekly [64]. The DISCOVER 1 and DISCOVER 2 studies showed that once-weekly intravenous dalbavancin was not inferior to twice-daily intravenous vancomycin followed by oral linezolid for the treatment of ABSSSI. Adverse events were reported less frequently in patients treated with dalbavancin than in those treated with vancomycin–linezolid [30]. Of interest, Dunne and coworkers recently published a randomized clinical trial in which a single 1500 mg infusion of dalbavancin was reported as non-inferior to a two-dose regimen with a similar safety profile [65], and this single 1500-mg dosage was recently approved by European Medicine Agency [66].

Another lipoglycopeptide, oritavancin, is being investigated for use in ABSSSI and has the potential to be used as a single-dose therapy. The SOLO II trial (Oritavancin Versus IV Vancomycin for the Treatment of Patients With ABSSSI) evaluated oritavancin efficacy and recently published data reported similar efficacy between the single-dose oritavancin regimen and twice-daily vancomycin evaluated at early clinical and end-of-therapy time points [67].

The new long-acting antibiotics represent a potential opportunity for early discharge. These agents make it possible

TABLE 5. New antibiotics for the treatment of acute bacterial skin and skin-structure infection

Antibiotic	Dosage[a]	IV/PO	Frequency	Infusion time	Duration	Comments
Dalbavancin	1000 mg followed 1 week later by 500 mg	IV	Once a week × two doses	Over 30 min	Two doses, 1 week apart	Early discharge Bactericidal Not dialysable if toxicity emerges No definitive data versus enterococci
	1500 mg	IV	Once	Over 30 min	One time dose	
Oritavancin	1200 mg	IV	Once	Over 3 h	One time dose	Early discharge Bactericidal Not dialysable if toxicity emerges No definitive data versus enterococci
Tedizolid	200 mg	IV/PO	Once a day	Over 60 min	6 days	PO administration Low toxicity Adjustment not required in renal impairment

Abbreviations: IV, intravenous; PO, by mouth.
[a]Dosage and frequency are based on patients with normal renal function.

to treat patients with ABSSSI who might otherwise require hospitalization on an outpatient basis without compromising efficacy. This approach could profoundly modify the management of these infections by reducing or in some cases eliminating hospitalization costs and risks.

Given the available data, future clinical trials are needed to better define the safety and efficacy profile of these new antibiotics, especially in sicker patients and for more serious infections and to analyse economic aspects. However, the characteristics of long-acting antibiotics could represent an opportunity for a more targeted management of ABSSSI.

Conclusions

In conclusion, ABSSSI is a new definition for bacterial infections of the skin that includes cellulitis, erysipelas, major skin abscesses and wound infection with a considerable extension of skin involvement, and that is based upon quantifiable parameters such as improvement of the lesion size and of systemic signs of infection. Dalbavancin, oritavancin and tedizolid are new drugs already approved or in development for ABSSSI. In particular, dalbavancin and oritavancin are long-acting antibiotics that might create opportunities for early hospital discharge. This approach could modify the management of these infections with a considerable reduction of hospitalization costs and risks [68].

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