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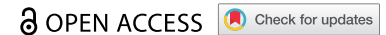


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REVIEW



Direct or early Discharge of Acute Bacterial Skin and Skin Structure Infection patients from the Emergency Department/Unit: place in therapy of dalbavancin

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ABSTRACT

Introduction: Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) are a common reason of Emergency Department (ED) access and account for a considerable number of hospital admissions and a high economic burden for the healthcare system. The long-acting lipoglycopeptides (LALs) allow for an outpatient management of subjects with ABSSSIs, still requiring parenteral therapy, but who do not need hospitalization.

Areas covered: The following topics were addressed: i) microbiological activity, efficacy, and safety of dalbavancin, ii) critical steps for the management of ABSSSIs in the ED (decision to hospitalize, risk of bacteremia and infection recurrence), iii) feasibility of direct/early discharge from the ED and potential advantage of dalbavancin.

Expert opinion: Authors' expert opinion was focused on drawing the profiles of patients who could benefit most from an antimicrobial therapy with dalbavancin in the ED and positioning this drug as a direct or early discharge strategy from the ED in order to avoid hospitalization and its complications. We have provided a therapeutic and diagnostic algorithm based on evidence from the literature and authors' expert opinion and suggest the use of dalbavancin in patients with ABSSSIs who are not eligible for oral therapies or Outpatient Parenteral Antibiotic Therapy (OPAT) programs and who would have otherwise been hospitalized only for antibiotic therapy.

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Acute Bacterial Skin and Skin Structure Infection (ABSSSI); dalbavancin; Direct discharge; early discharge; emergency department; emergency unit; long-acting lipoglycopeptides

1. Introduction

Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) are a common reason of Emergency Department (ED) access, accounting for a considerable number of hospital admissions and translating into a high financial burden for the health care system [1–5].

The most common causative pathogens of ABSSSI are β -hemolytic streptococci and *Staphylococcus aureus*; methicillin resistance in *S. aureus* characterizes 20–44% of the isolates, according to the epidemiological setting [6–11]. Although being especially prevalent among patients with previous health-care contacts, methicillin resistance is no longer an exclusive feature of these patients [12]. In Italy, where the prevalence of methicillin-resistant *S. aureus* (MRSA) is among the highest in Europe, MRSA was the most represented cause of ABSSSI when a microbial isolate was available [7,11,13].

While hospitalization is generally required for unstable or severely infected patients, or those with significant and active comorbidities, the need for intravenous antibiotics was the sole reason for admission in approximately 40% of the patients in one study [4,14–17].

In this setting, the advent of long-acting lipoglycopeptides (LALs) potentially allows for an outpatient management of subjects with ABSSSI, still requiring parenteral therapy, but who do not need hospitalization [18–20].

Dalbavancin is a semisynthetic lipoglycopeptide antibiotic with activity against Gram-positive pathogens including MRSA, which has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of ABSSSIs [21]. Its favorable pharmacokinetic profile and the long elimination half-life represent a key advantage over other intravenous drugs requiring multiple daily doses or oral antibiotics, which require patients' adherence and may be encumbered by adverse events [22].

This article aims to review the current literature on dalbavancin for ABSSSIs and draw the profiles of patients who could benefit most from an antimicrobial therapy with dalbavancin in the ED, allowing an early discharge. Furthermore, we propose a diagnostic-therapeutic algorithm for the management of patients presenting to the ED with ABSSSI.

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Article highlights

- Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) are a common reason of access to the Emergency Department (ED), account for a considerable number of hospital admissions and exhibit a high financial burden for the health care system
- Long-acting lipoglycopeptides (LALs) allow for an outpatient management of subjects with ABSSSI, still requiring parenteral therapy, but who do not need hospitalization
- Dalbavancin is a LAL with activity against Gram-positive pathogens including MRSA and has been approved by the FDA and EMA for the treatment of ABSSSIs
- In registration and observational studies, dalbavancin showed high efficacy and a remarkably good safety profile for the treatment of ABSSSIs
- Crucial steps in the management of patients with ABSSSIs at the ED include the decision to hospitalize and the risk of bacteremia and/or infection recurrence
- Dalbavancin may be considered as a strategy for a direct or early discharge from the ED of eligible patients with ABSSSIs
- Dalbavancin's favorable pharmacokinetic profile and its long elimination half-life represent a key advantage over other intravenous drugs requiring multiple daily doses or oral antibiotics, which require patients' adherence and may be encumbered by adverse events
- Dalbavancin use is cost-effective by reducing in-hospital length of stay and saving additional indirect costs related to the need of multiple daily infusion of antimicrobials, laboratory monitoring of potential toxicities and nurse assistance
- A diagnostic and therapeutic algorithm for the management of ABSSSI at the ED is proposed

2. Methods

In the first round of discussion among the authors, the following topics were identified to be addressed in this review: i) classification of ABSSSIs and LALs, with a main focus on dalbavancin and its microbiological activity, efficacy and safety profile, ii) assessment of critical steps for the management of ABSSSI in the ED (decision to hospitalize, risk of bacteremia and infection recurrence), iii) feasibility of direct/early discharge from the ED and potential advantage of dalbavancin in this setting and iv) the economic impact of dalbavancin in the ED for the treatment of ABSSSIs.

Afterwards, publications were searched through the MEDLINE/PubMed database using the following terms, used alone or combined with each other, as appropriate: 'ABSSSIs,' 'Acute Bacterial Skin and Skin Structure Infections,' 'LALs,' 'long-acting lipoglycopeptides,' 'Dalbavancin,' 'Emergency Department,' 'Early Discharge,' 'Microbiological activity,' 'In vitro activity,' 'Efficacy,' 'Effectiveness,' 'Safety,' 'Blood Cultures,' 'Bacteremia,' 'Bacteremia Risk Score,' 'Bacteremia Score of Cellulitis,' 'OPAT,' 'Economic evaluation,' 'Budget Impact Analysis,' 'Telehealth medicine.'

We excluded abstracts or articles not written in English. Publications regarding the use of dalbavancin in the pediatric

population were also excluded, since it is the topic of a specific publication [23].

No limitations to publication dates were considered, although the literature search was completed at the end of October, 2022.

All the found articles were then selected for their relevance during subsequent rounds of discussion among the authors.

The preliminary draft was shared among authors and then organized in the final version, which was finally reviewed and approved by all the authors.

3. Classification of ABSSSIs

ABSSSIs represent a special subgroup of complicated skin and soft tissue infections (SSTIs), and have been defined by the FDA as a bacterial infection of the skin with a lesion size of at least 75 cm² (lesion size measured by the area of redness, edema, or induration) to facilitate evaluation of new molecules in randomized clinical trials (RCT) [11,24]. ABSSSIs include cellulitis/erysipelas, wound infections, and major cutaneous abscesses (Table 1) [24]. Despite this classification, ABSSSIs represent an extremely heterogeneous group of diseases in terms of prognosis, ranging from mild to potentially life-threatening conditions [22,23].

Cellulitis is one of the most common ABSSSI, followed by erysipela, surgical site and diabetic foot infections, and abscesses [11,25–28].

Due to the prevalence of Gram-positives as causative agents of ABSSSIs, empiric antibiotic treatment is mainly targeted at covering Staphylococci and Streptococci, including MRSA in the presence of risk factors or if the prevalence of MRSA in the community is high [22]. However, conditions possibly complicating the efficacy of antimicrobials are the involvement of adjacent structures, such as bone and/or joints and biofilm formation on implants [29].

ABSSSIs may also require surgical interventions such as debridement, if necrotic tissue is present, or incision and drainage, if an abscess is detected [30]. In the latter condition, point-of-care ultrasound (POCUS) represents a rapid, noninvasive, painless, and easy-to-repeat method able to distinguish between abscess and cellulitis [31,32]. When the presence of an abscess is clinically irrefutable, the role of POCUS may be questionable; however, in cases where differentiating abscess from cellulitis by means of clinical examination alone is difficult, POCUS exhibited a crucial role and resulted in management changes – to perform or not perform a drainage – in approximately 25% of the patients with suspected, but not clinically obvious, abscesses [33–36].

Table 1. Classification of acute bacterial skin and skin structure infections (ABSSSIs) according to the FDA definitions [25].

Classification of ABSSSIs	Description	Therapeutic approach
Cellulitis/erysipelas	Diffuse skin infection with spreading areas of redness, edema, and/or induration	Antibiotics
Wound infection	Purulent drainage from a wound with surrounding redness, edema, and/or induration	Antibiotics ± debridement if necrotic tissue is present
Major cutaneous abscess	Collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration	Antibiotics + incision and drainage

4. Long-acting lipoglycopeptides

4.1. Types of LALs

Three LALs are currently available, telavancin, dalbavancin, and oritavancin. While telavancin is not approved in Europe, dalbavancin and oritavancin obtained approval by the FDA and EMA for the treatment of ABSSSIs caused by Gram-positive cocci in 2014 and 2015, respectively [21,37].

Dalbavancin is a lipoglycopeptide antibiotic with a chemical structure similar to teicoplanin; however, compared to teicoplanin, the presence of an extended lipophilic side chain allows for a better anchorage to the bacterial cell membrane and therefore enhances its potency and prolongs its terminal half-life up to 14.4 days [38,39]. The amidated carboxyl side group enhances the agent's anti-staphylococcal activity [39–41]. The distribution of the drug allows to reach adequate concentrations in skin, synovial fluid, and bone, which are higher than the MICs₉₀ of the principal pathogens causing ABSSSIs [42,43]. In a pharmacokinetic study carried out among healthy volunteers, the penetration rate into skin blister fluid after administration of a single 30-min 1000 mg iv dose was approximately 60% [43,44]. Dalbavancin does not interact with cytochrome P450 enzymes, showing a low likelihood for drug – drug interactions with other drugs [44–46].

Principal features and main differences among the three LALs are depicted in Table 2.

4.2. Microbiological activity of dalbavancin

Dalbavancin exhibits an *in vitro* activity higher than vancomycin or teicoplanin against several Gram-positive pathogens (Table 3) [54,55]. Dalbavancin regularly shows MIC values against *S. aureus* and MRSA isolates at ≤ 0.06 mg/L [47,56]. Large comparative studies on *S. aureus*, including isolates with decreased susceptibility to vancomycin, telavancin, teicoplanin, and linezolid showed that only 0.01% of the isolates were categorized as dalbavancin nonsusceptible [48,49,57]. Notably, against vancomycin-intermediate *S. aureus* (VISA), with a vancomycin MIC of 4–8 $\mu\text{g/ml}$ and heteroresistant VISA (hVISA), dalbavancin MICs were typically 4- to 8-fold lower than vancomycin and 16 to 32-fold lower than linezolid [48]. Moreover, population data from US medical centers reported a low percentage of staphylococcal (0.3%) and streptococcal isolates (4%) with dalbavancin MIC values above the currently proposed FDA breakpoint [50,51]. Thus, nonsusceptible staphylococci are rare, reported in less than 1% of the cases. In support of these *in-vitro* findings, several studies have confirmed that dalbavancin exerts a potent *in vivo* activity against *S. aureus* strains, including those with reduced susceptibility to vancomycin [58,59]. Notably, dalbavancin activity against enterococci largely depends on vancomycin activity. In vancomycin-susceptible enterococci (VSE), dalbavancin is active (MIC₉₀, 0.06 $\mu\text{g/ml}$) against both *E. faecalis* and *E. faecium* (MIC ≤ 0.125 $\mu\text{g/ml}$). Conversely, vancomycin-resistant enterococci (VRE) isolates are less susceptible to dalbavancin, regardless of species [50,51].

Dalbavancin showed *in-vitro* activity against the anaerobic Gram-positive and *Corynebacterium* species [52]. Moreover,

previous *in vitro* studies revealed that dalbavancin had significantly lower MICs against *Clostridioides difficile* than vancomycin [52,53].

It is worth noting that dalbavancin has demonstrated *in vitro* synergistic activity in combination with oxacillin and ceftaroline against staphylococci, including MRSA, VISA, and enterococci [60–62]. The combination of dalbavancin plus linezolid was highly synergistic *in vitro* against MRSA, with no antagonistic effect [63]. Therefore, combination therapy may represent an effective option in difficult-to-treat MRSA or *Enterococcus* spp, particularly in patients with device-associated infections [64]. As device-associated infections are at high risk of developing biofilm, the observed dalbavancin activity on biofilm eradication appears as a promising feature of this drug [30,65,66].

4.3. Efficacy and safety of dalbavancin for ABSSSIs: evidence from clinical studies

The two identically designed non-inferiority phase 3 trials DISCOVER-1 and DISCOVER-2 included 652 individuals with ABSSSIs receiving two doses of dalbavancin (1000 mg on day 1, followed by 500 mg on day 8), compared with 651 receiving intravenous vancomycin for at least 3 days (1 g every 12 h), with the option to switch to oral linezolid to complete 10–14 days of treatment [21]. The primary endpoint was clinical success measured at 48–72 h of therapy. Non-inferiority of dalbavancin was demonstrated in both trials [21].

Afterwards, a randomized clinical trial including 698 ABSSSI patients compared the classic two doses regimen with a 1500 mg single-dose. The authors found non-inferiority of the single dose regimen and no significant increase in the adverse events rate [67]. Accordingly, the regulatory agencies FDA and EMA also expanded their approval to the single-dose schedule.

In a sub-analysis of the phase III trial, dalbavancin showed similar efficacy as a single dose and a two-dose regimen in the outpatient and inpatient subgroups, with outpatients reporting significantly greater satisfaction with antibiotic treatment and care setting compared with inpatients [68].

In another *post-hoc* analysis specific on people who inject drug (PWID) ($n=212$), dalbavancin efficacy was similar between the single and two-dose therapy groups in the PWID and non-PWID populations at all time points [69].

Nadipelly et al conducted an open-labeled prospective randomized study including 200 patients with ABSSSIs who were randomized to receive either a single dose of 1500 mg intravenous dalbavancin (Group I) or intravenous telavancin 10 mg/kg every 24 h for 6 days (Group II). Clinical success, defined as a complete resolution of clinically meaningful signs and symptoms of infection was observed in 86.6% of the patients receiving dalbavancin and in 81.5% of the patients receiving telavancin (Table 4) [70].

In the subsequent years, several observational studies evaluated the real-life effectiveness of dalbavancin for the treatment of ABSSSIs (Table 4) [1,5,7,15,71–77]. Although the majority of the studies also included patients with infections different from ABSSSIs, the clinical efficacy of dalbavancin was

Table 2. Main features of the long acting lipoglycopeptides for the treatment of Acute Bacterial Skin and Skin Structure Infection (ABSSSI).

	Telavancin	Dalbavancin	Oritavancin
Recommended dosage	10 mg/kg i.v. every 24 h	1500 mg i.v. single dose or 1000 mg d1 followed by 500 mg d8 i.v.	Single dose 1200 mg i.v.
US/Europe approval	Yes/No	Yes/Yes	Yes/Yes
Mechanism of action	<ul style="list-style-type: none"> Inhibition of cell wall biosynthesis by binding to late-stage peptidoglycan precursors, including lipid II, which prevents polymerization of the precursor into peptidoglycan and subsequent cross-linking events. Depolarization of membrane potential and increase in membrane permeability resulting in inhibition of protein, RNA, and lipid synthesis 	Interruption of cell wall synthesis by binding to the terminal D-ala-D-ala of the stem peptide in nascent cell wall peptidoglycan, preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits resulting in bacterial cell death	<ul style="list-style-type: none"> Inhibition of the transglycosylation step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors; Inhibition of the transpeptidation (cross-linking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; Disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and rapid cell death
Activity against VRE	No	No activity against Van-A Partial activity against Van-B	Activity against Van-A and Van-B
Intracellular concentration	Yes (alveolar macrophages)	No	Yes (liver, kidney, spleen and lung macrophages)
AUC in skin blister fluid (% of plasma AUC)	40	60	20
Volume of distribution (L/kg)	0.1	0.14–0.18	1
Protein binding (%)	90	93	85
Mean terminal half-life (hours)	8	372 (333–405)	245
Elimination	Urine, 76%, unchanged; Feces, <1%	Urine, 33%, unchanged; Feces, 20%	Urine, <5% Feces, <1%
Renal adjustment	<ul style="list-style-type: none"> Dose adjustment is required for patients with creatinine clearance ≤ 50 mL/min Contraindicated if acute renal failure or creatinine clearance < 30 mL/min or haemodialysis 	<ul style="list-style-type: none"> No dose adjustments in patients with mild/moderate renal impairment (creatinine clearance 30–79 mL/min) or haemodialysis Dose adjustment for patients with creatinine clearance < 30 mL/min 	<ul style="list-style-type: none"> No dose adjustment in patients with mild/moderate renal impairment (creatinine clearance 30–79 mL/min) No data in patients with severe renal impairment (creatinine clearance < 30 mL/min) or undergoing haemodialysis
Hepatic adjustment	<ul style="list-style-type: none"> No dose adjustment in patients with mild-to-moderate hepatic impairment (Child-Pugh Class A-B) No data in patients with severe hepatic impairment (Child-Pugh Class C) 	<ul style="list-style-type: none"> No dose adjustment in patients with mild hepatic impairment (Child-Pugh A). Caution in patients with moderate or severe hepatic impairment (Child-Pugh B, C) 	<ul style="list-style-type: none"> No dose adjustment in patients with mild-to-moderate hepatic impairment (Child-Pugh Class A-B) No data in patients with severe hepatic impairment (Child-Pugh Class C)
Interactions with CYP enzymes	<ul style="list-style-type: none"> No interaction with CYP enzymes QT interval prolongation 	<ul style="list-style-type: none"> No interaction with CYP enzymes 	<ul style="list-style-type: none"> Weak inhibition of CYP2C9 and CYP2C19 Weak induction of CYP3A4 and CYP2D6
Duration of infusion	60 min	30 min	3 hours
Interference with laboratory testing	Prolongation of PT, INR and aPTT up to 18 h after telavancin administration	No	<ul style="list-style-type: none"> Prolongation of aPTT for up to 120 h after oritavancin administration Prolongation of PT and INR for up to 12 h after oritavancin administration
Contraindications	<ul style="list-style-type: none"> Hypersensitivity or history of glycopeptide hypersensitivity Intravenous unfractionated heparin sodium 	<ul style="list-style-type: none"> Hypersensitivity or history of glycopeptide hypersensitivity 	<ul style="list-style-type: none"> Hypersensitivity or history of glycopeptide hypersensitivity Intravenous unfractionated heparin sodium for 120 h (5 days) after oritavancin administration

Note: VRE: vancomycin-resistant Enterococci; aPTT: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio.

overall demonstrated, with clinical cure rates ranging from 80% to 98%.

Interestingly, dalbavancin showed a remarkably good safety profile [78]. In the DISCOVER trials, adverse events, including nephrotoxicity, were reported in fewer patients treated with dalbavancin than in those treated with vancomycin or linezolid [21]. Similar findings were found in a safety data

analysis including 1778 patients treated with dalbavancin and 1224 patients receiving a comparator agent [79]. The duration of adverse events was similar for dalbavancin and the comparator regimens; therefore, the long half-life of dalbavancin did not lead to safety concerns [79].

Observational studies confirmed the low incidence of adverse events, ranging from 2% to 13% of the study

Table 3. Antimicrobial activity of dalbavancin against Gram-positive pathogens.

Organisms	MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)	MIC range (µg/ml)	Susceptible (%)	References
<i>S. aureus</i>					
MSSA	0.03	0.06	≤0.015–0.12	100	[47]
MRSA	0.03	0.06	≤0.015–0.12	100	[47]
CoNS	0.03	0.12	≤0.015–1	99.6	[47]
<i>S. aureus</i> with decreased susceptibility to:					
• Daptomycin	0.06	0.12	≤0.03–0.50	95.8	[48]
• Vancomycin	0.06	0.12	≤0.03–0.50	99.3	[48]
• Telavancin	0.06	0.25	≤0.03–0.50	90.4	[48]
Vancomycin-susceptible <i>E. faecalis</i>	0.03	0.06	≤0.015–0.25	100	[49]
Vancomycin-susceptible <i>E. faecium</i>	0.06	0.12	≤0.015–0.25	99.8	[49]
Vancomycin-resistant enterococci (VRE)	>4	>4	≤0.03–>4	7.5	[50,51]
VRE <i>vanA</i>	>4	>4	0.25–>4	0	[50,51]
VRE <i>vanB</i>	≤0.03	0.12	≤0.03–0.12	100	[50,51]
<i>S. pneumoniae</i>	0.015	0.015	≤0.002–0.06	-	[49]
<i>Corynebacterium</i> spp.	0.125	0.5	0.015–1	-	[52]
<i>Propionibacterium</i> spp.	0.25	0.5	0.03–0.5	-	[52]
<i>Clostridium</i> spp.	0.125	0.5	0.015–1	-	[52]
<i>Clostridium difficile</i>	0.016	0.03	0.002–0.250	-	[53]

populations. Most of these adverse events were of mild entity [1,5,7,15,71–77].

5. ABSSSIs at the emergency department: decision to hospitalize, risk of bacteremia and infection recurrence

In the ED setting, crucial importance is represented by the appropriateness of hospitalization. An analysis of more than 600,000 patients with ABSSSIs found that 60% of those hospitalized could potentially have been treated as outpatients [80]. Of note, the need for intravenous antibiotics administration represented the unique reason for hospitalization in approximately half of patients [14]. Therefore, the current hospitalization rate appears undue, leading to high costs for the health-care system and possible related iatrogenic complications, especially in older patients [81–84].

In one study, hospitalization rates were higher in the presence of a history of fever, extension of infection, history of failed treatment and age >65 years [14]. Also, abnormal imaging results, systemic inflammatory response syndrome, diabetes, previous infection at the same location and an infection involving the hand were associated with worse outcomes [85,86].

Identification of these criteria may therefore enable clinicians to better assess the need for hospital admission and, at the same time, identify patients who receive only little benefit from hospitalization and would otherwise be better treated in an outpatient setting [85].

Another crucial step is the assessment of the risk of bacteremia, by evaluating patients who should have blood cultures (BCs) done in the ED [87]. Indeed, patients with bacteremia experience a longer duration of hospitalization and a higher rate of infection recurrence [88–90]. However, the role of BCs in the management of ABSSSIs remains still controversial, since performing BCs in all patients seems to be not cost effective and have only marginal clinical advantage [91–94]. Furthermore, a significant rate of BC contamination may occur [95]. The incidence of bacteremia during ABSSSIs widely varies,

ranging from 2% to 21.3% among patients for whom BCs are performed [25,87,96].

Risk factors for the development of bacteremia include advanced age, fever, elevated White Blood Cells (WBC), signs of Systemic Inflammatory Response Syndrome (SIRS), length of illness, lymphedema, and comorbidities, such as chronic renal disease and liver cirrhosis [25,95]. In particular, age (≥65 years), involvement of non-lower extremities, liver cirrhosis, and SIRS were included in the Bacteremia Score of Cellulitis: a cutoff value of 2 was able to discriminate patients with cellulitis at low or high risk of bacteremia [25]. Besides, the extension and severity of cellulitis emerged as risk factors for bacteremia, suggesting that the size of the infection area should be measured in the ED, and that patients with large cellulitis should be more carefully monitored [95–97]. Likewise, the presence of a device or prosthesis accounted for the highest risk of bacteremia [95–98]. Furthermore, it seems reasonable to perform BCs in patients with malignancy, neutropenia, and/or immunosuppression [99].

Recurrence is a common phenomenon in patients with cellulitis, especially in countries with a high prevalence of MRSA [100,101]. Lymphedema, chronic venous insufficiency, peripheral vascular disease, and deep vein thrombosis, which contributed to the creation of the recently proposed Cellulitis Recurrence Score (CRS), were risk factors of recurrence [102].

The 30-day ED return rate after the first ED visit ranges between 8.3% and 28% [71,77,103], and is higher in patients with abnormal WBC count at initial presentation, congestive heart failure, hypertension, and diabetes mellitus [77].

6. Early discharge in the ED: potential advantage of dalbavancin

Patients may be considered suitable for an early discharge from the ED or the ED short stay/observation unit by means of a reassessment at 48–72 h after treatment initiation. Indeed, culture results may be available and patients' clinical

Table 4. Registration and observational studies of dalbavancin for the treatment of acute bacterial skin and skin structure infections (ABSSSI).

Author, year	Study Population and Intervention	Type of study	Number of patients	Outcomes/Clinical efficacy	Safety	Isolated pathogens	Reasons for Dalbavancin use	Reference
Boucher, 2014	Adults with ABSSSIs who were thought to require at least 3 days of intravenous therapy. Patients were randomized to receive either Dalbavancin (1000 mg on day 1, followed by 500 mg on day 8) or Vancomycin (1000 mg, or 15 mg/kg every 12 hours) for at least 3 days, with an option to switch to oral Linezolid (600 mg every 12 hours) to complete 10 to 14 days of therapy	Double-blind, dummy, international, multicenter, randomized trials conducted from 2011 through 2012 (DISCOVER 1 and DISCOVER 2).	1303 (652 patients in the Dalbavancin group and 651 in the Vancomycin-Linezolid group)	The primary end point was measured at 48 to 72 hours of therapy and was defined as cessation of spread of the erythema associated with the infection (i.e. no increase in the surface area as compared with baseline) and a temperature of 37.6C or lower at three consecutive readings performed 6 hours apart. DISCOVER 1: treatment success 83.3% in the Dalbavancin group and 81.8% in the Vancomycin-Linezolid group. DISCOVER 2: treatment success 76.8% in the Dalbavancin group and 78.3% in the Vancomycin-Linezolid group.	Any event — (32.8% in Dalbavancin group versus 37.9% in Vancomycin-Linezolid group (p<0.05))	MSSA 356/666 (53.4%) MRSA 157/666 (23.6%) <i>Streptococcus pyogenes</i> 73/666 (10.9%)	NA	[21]
Dunne, 2016	Patients aged >18 years with ABSSSIs treated with Dalbavancin between April 2014 and March 2015. Patients were randomized to receive single intravenous infusion of 1500 mg of Dalbavancin or the 2-dose regimen (1000 mg on day 1, followed by 500 mg on day 8)	Double-blind, pharmacist-unblinded, randomized trial	698 (349 single dose, 349 double-dose)	The primary endpoint was a ≥20% reduction in the area of erythema at 48–72 h after initiation of study drug. Treatment success: Dalbavancin single-dose (81.4%) vs Dalbavancin 2-dose regimen (84.2%)	Treatment-emergent AE: 20.1% single-dose vs 19.9% 2-dose regimen	MSSA 199/430 (46.3%) MRSA 97/430 (22.5%) Gram-negative aerobic organisms 47/430 (10.9%)	NA	[67]
Gonzalez, 2018	PWID versus non-PWID receiving Dalbavancin for ABSSSIs between April 2014 and March 2015. Patients were randomized to receive single intravenous infusion of 1500 mg of Dalbavancin or the 2-dose regimen (1000 mg on day 1, followed by 500 mg on day 8)	Sub-analysis of randomized, double-blind international, multicenter trials	213 (105 PWID single-dose group, 107 PWID 2-dose group)	The primary efficacy outcome measure was a comparison of the proportion of patients with ≥20% reduction in erythema associated with the infection at 48–72 hours after the start of treatment in the intent-to-treat population. Clinical response: 89.5% single-dose regimen vs 86.0% 2-dose regimen	Treatment-emergent AE: 22 (21%) single dose vs 23 (21.7%) 2 doses	MSSA 199/430 (46.3%) MRSA 97/430 (22.5%) Gram-negative aerobic organisms 47/430 (10.9%) <i>Streptococcus ariginosus</i> group 53/430 (12.3%) <i>Streptococcus pyogenes</i> 36/430 (8.4%) MRSA 47/200 (23.5%)	NA	[69]
Nadipelly, 2018	Patients with ABSSSIs from January 2016 to May 2016. Patients were randomized to receive a single dose of Dalbavancin 1500 mg or Telavancin 10 mg/kg every 24 hours for six days	Open labeled prospective randomized study	200 (100 Dalbavancin, 100 Telavancin)	Clinically successful treatment was defined as complete resolution of clinically meaningful signs and symptoms of infection, including SIRS score of 0. The outcome measure was the percentage of patients with SIRS score of 0 on day 7 (clinical success). Clinical success: 86.6% Dalbavancin group versus 81.5% Telavancin	2.17% Dalbavancin group vs 1.11% Telavancin group	NA	NA	[70]

(Continued)

Table 4. (Continued).

Author, year	Study Population and Intervention	Type of study	Number of patients	Outcomes/Clinical efficacy	Safety	Isolated pathogens	Reasons for Dalbavancin use	Reference
Rappo, 2019	Outpatients versus inpatients treated with Dalbavancin between April 2014 and March 2015 Patients were randomized to receive single intravenous infusion of 1500 mg of Dalbavancin or the 2-dose regimen (1000 mg on day 1, followed by 500 mg on day 8)	Sub-analysis of randomized, double-blind international, multicenter trials	698 (386 outpatients, 312 inpatients).	The primary endpoint was defined as a 20% reduction in erythema associated with the infection at 48–72 h after the start of treatment in the intent-to-treat population. Outpatients: 82.1%/82.7% single-dose/2-dose Inpatients: 80.5%/86.3% single-dose/2-dose	Treatment-emergent AE: 23.7%/15.7% outpatients/inpatients receiving a single dose 21.2%/18.3% of outpatients/inpatients receiving the two-dose regimen.	MSSA 199/430 (46.3%) MRSA 97/430 (22.5%) Gram-negative aerobic organisms 47/430 (10.9%)	NA	[68]
Bouza, 2018	All patients receiving at least one dose of Dalbavancin from January 2016 to January 2017 Dalbavancin dosage: – 1000 mg d1 followed by 500 mg doses (on a weekly basis): 40 pts – Single 1500 mg: 17 pts – Single 1500 mg +1500 mg every 2 weeks: 2 pts – Single 1000 mg: 3 pts – 500 mg every 4 or 8 weeks: 2 pts	Observational retrospective study developed in 29 hospitals in Spain	69 patients ABSSSI 21.7%, PJI 29%, osteomyelitis 17.4% CR-BSI 11.6%	Clinical outcome was considered successful when patients had no clinical (resolution of signs and symptoms related to bacterial infection) or microbiological evidence of infection during the follow-up period. Overall clinical success rate: 84.1% (ABSSSI 80.0% vs 88.9% for off-label use) Re-admission rate: 3/69 (4.3%) (2 with ABSSSI)	13% (mainly of mild intensity)	MSSA 11/62 (17.7%) MRSA 16/62 (25.8%) CoNS 24/62 (38.7%) Enterococcus spp. 11/62 (17.7%)	Easy antibiotic administration 51 (73.9%), Previous antibiotic failure 21 (30.4%) Bone marrow toxicity 14 (20.3%) Antimicrobial resistance to previous antibiotic 13 (18.8%) Antibiotic allergy 10 (14.5%) Renal failure related with previous antibiotic 8 (11.6%) Poor compliance 3 (4.3%) Other reasons 8 (11.6%)	[6]
Koziatek, 2018	All adult patients with cellulitis and treated with Dalbavancin in the ED or ED observation unit between July 1, 2015 and June 30, 2017. No data on dalbavancin dosage	Retrospective cohort study	23 6: ED 17: ED observation unit	The primary outcome of interest was a cellulitis-related return to the ED within one week of initial ED arrival Cellulitis-related return to the ED within one week: 2/23 (8.7%)	No data	No data	No data	[71]

(Continued)

Table 4. (Continued).

Author, year	Study Population and Intervention	Type of study	Number of patients	Outcomes/Clinical efficacy	Safety	Isolated pathogens	Reasons for Dalbavancin use	Reference
Wunsch, 2019	<p>Patients who received Dalbavancin in Austria from September 2016 to March 2018.</p> <p>Dalbavancin dosage:</p> <ul style="list-style-type: none"> - Single 1500 mg dose: 24 (23.8%) - 1500 mg d1 and d8: 14 (13.9%) - 1500 mg d1, d8+week 8: 3 (3%) - 1000 mg +500 mg weekly: 43 (42.6%) - 1000 mg every 14 days: 3 (3%) - Others: 14 (13.9%) 	Multicenter retrospective study	101	<p>Clinical success was presumed when patients had no clinical, laboratory or microbiological evidence of persistent or recurring infection during the follow-up period.</p> <p>Clinical success rate at 90-d: 89%</p>	3/101 (2.97%)	<p>MSSA 14 (16%)</p> <p>MRSA 8 (9%)</p> <p>CoNS 28 (33%)</p> <p>Enterococci 7 (8%)</p> <p>Streptococci 5 (6%)</p> <p><i>Propionibacterium acnes</i> 4 (5%)</p> <p>Mixed infection (gram-positive plus gram-negative) 5 (6%)</p> <p>MSSA 27/72 (37.5%)</p> <p>MRSA 6/72 (8.3%)</p> <p>MSSE 5/72 (6.9%)</p> <p>MRSE 3/72 (4%)</p> <p><i>Enterococcus</i> spp 3/72 (4%)</p> <p><i>Streptococcus</i> spp 11/72 (15.3%)</p> <p><i>Cutibacterium acnes</i> 3/72 (4%)</p> <p>Mixed infections 4/72 (5.5%)</p>	<p>Long half-life of dalbavancin 58%</p> <p>Treatment failure of previous antibiotics 12%</p> <p>Antibiotic allergy 9%</p> <p>Resistance of pathogens 8%</p> <p>Non-compliance 5%</p> <p>Side effects of prior therapies 3%</p> <p>Other reasons 5%</p>	[72]
Tobudic, 2019	<p>Adult patients with gram-positive infections who received at least one dosage of Dalbavancin between 2015 and 2017</p> <p>Dalbavancin dosage:</p> <ul style="list-style-type: none"> - Initial dose 1500 mg +1000 mg each 14 days: 51 pts (71%) - 1000 mg d1 + 500 mg every 7 days: 17 pts - 1500 mg day 1, day 8 and in individual cases repetition of 1500 mg: 5 pts 	Retrospective case series	72	<p>The primary endpoint was defined as clinical cure or failure. Clinical cure was defined as resolution of all clinical signs and symptoms of infection, no additional antibiotic therapy required for the indication initially treated with dalbavancin and no microbiological relapse during the follow-up period of 6 months after completion of treatment.</p> <p>Clinical cure: 64%</p> <p>SSTI: 20/26 (77%)</p> <p>Osteomyelitis: 13/20 (65%)</p> <p>Spondylodiscitis: 7/14 (50%)</p> <p>Septic arthritis: 4/4 (100%)</p> <p>PJI: 6/8 (75%)</p>	5%	<p>MSSA 14 (19%)</p> <p>Salvage treatment 39 (54%)</p> <p>Simplification due to outpatient option 19 (27%)</p>	[73]	
Bartoletti, 2019	<p>Patients with deep sternal wound infection (DSWI) treated with Dalbavancin from March 2016 to April 2018 in Italy</p> <p>Dalbavancin dosage:</p> <ul style="list-style-type: none"> - 1000 mg and 500 mg: 9 (60%) - 1000 mg +500 mg every week: 5 (33%) - 2 doses of 1500 mg: 1 (7%) 	Retrospective, observational, cohort study	15	<p>Outcome variables included death, hospital length of stay (LoS), relapse of DSWI within 6 months after treatment, and hospital readmission. Relapse of DSWI within 6 months: 1 (7%) The remaining 14 patients (93%) showed no relapse of DSWI, did not received any further course of antibiotics and were not readmitted to hospital for other causes.</p>	No data	<p>MRSA 7/15 (47%)</p> <p>MSSE 6/15 (40%)</p> <p>CoNS 2/15 (13%)</p>	<p>Lack of oral antibiotics based on susceptibility test results (5, 33%)</p> <p>Decision of the attending physician (5, 33%)</p> <p>Previous failure with other treatments (3, 20%)</p> <p>History of allergy to other drugs (2, 13%)</p>	[74]

(Continued)

Table 4. (Continued).

Author, year	Study Population and Intervention	Type of study	Number of patients	Outcomes/Clinical efficacy	Safety	Isolated pathogens	Reasons for Dalbavancin use	Reference
Dinh, 2019	<p>Adult patients receiving at least one dose of Dalbavancin from 1 June 2017 to 31 September 2018 in France</p> <p>Dalbavancin dosage: - Single 1500 mg: 2 pts - Single 1000 mg: 2 pts - 1000 mg d1 + 500 mg d8: 1 pt - 1000 mg d1 + 1000 mg d8: 1 pt - 1500 mg d1 + 1500 mg d8: 31 pts - 1500 mg d1 + 1000 mg d14: 1 pt - 1500 mg d1 + 1500 mg d14: 7 pts - Other: 16 pts - Suppressive: 3 pts</p>	Retrospective multicenter study	75 BJI (64%) Endocarditis (25.3%) SSTI (17.3%) Vascular infection (6.7%) Catheter line infection (5.3%) BSI (4%) Mediastinitis (2.7%)	<p>Clinical cure was defined as the absence of clinical signs of infection and was confirmed by the physician in charge.</p> <p>Clinical cure: 54/68* (79.4%) BJI (76.1) Endocarditis (72.2) SSTI (81.8) Vascular infection (100) Catheter line infection (100) BSI (100) Mediastinitis (50)</p>	5/75 (6.6%)	MSSA 23/72 (31.9%) MRSA 14/72 (19.4%) CoNS 32/72 (44.4%) MRSE 15/72 (20.8%) Enterococcus faecalis 5/72 (6.9%) Corynebacterium spp. 5/72 (6.9%)	Clinical failure of previous antibiotic treatment 16 (21.3%) Microbiological failure of previous antibiotic treatment 4 (5.3%) Adverse event of previous antibiotic treatment 26 (34.7%) Multidrug-resistant bacteria 17 (22.7%) Impossible venous access 18 (24%) Patient autonomy 29 (38.7%) Early hospital discharge 26 (34.7%) Better compliance 21 (28%)	[75]
Arrieta Loitegui, 2020	<p>All patients treated with Dalbavancin from October 2016 to August 2019</p> <p>Dalbavancin dosage: - 1500 mg initial dose plus 500 mg: 60 pts - 1000 mg initial dose plus 500 mg: 8 pts - Others: 27 pts</p>	Retrospective observational study	102 SSTI (30.4%), CR-BSI (15.7%) Endocarditis (13.7%) BSI with suspected endocarditis (10.8%) PJI (10.8%) Osteomyelitis (10.8%) BSI (4.9%) Septic arthritis (1.9%) Febrile syndrome (1%)	<p>Effectiveness was assessed using the clinical and microbiological resolution of the infection and the absence of hospital admissions due to the same infection in the following 3 months</p> <p>Clinical and microbiological resolution: 89/95** (93.7%) No relapses in the 3-month follow-up period</p>	4 (3.9%)	Staphylococcus spp 72/102 (70.6%) Enterococcus spp 10/102 (9.7%) Streptococcus spp 4/102 (4%) Corynebacterium spp 1/102 (1%) Cutibacterium spp 1/102 (1%) Polymicrobial 3/102 (3%) No microbiological isolations 11/102 (10.7%)	Hospital discharge (79.4%, n = 81) Toxicity of the previous therapy (8.8%, n = 9) Ensure adherence (5.9%, n = 6) Poor venous access (4.9%, n = 5) Microbiological resistance (1%, n = 1)	[76]

(Continued)

Table 4. (Continued).

Author, year	Study Population and Intervention	Type of study	Number of patients	Outcomes/Clinical efficacy	Safety	Isolated pathogens	Reasons for Dalbavancin use	Reference
Durante-Mangoni, 2020	Patients who received Dalbavancin in Italy between 2016 and 2019 No data on dalbavancin dosage	Retrospective study	30 ABSSSI (8) osteomyelitis (4) PJI (12) CR-BSI (4) Endocarditis (2).	No definition of outcome Favorable outcome was observed for all 12 PJI cases	3/10 (10%)	MSSA 5/30 (16.7%) MRSA 5/30 (16.7%) CoNS 7/30 (23.3%) <i>E. faecalis</i> 2/30 (6.7%) Streptococcus spp. 3/30 (10%) Mixed infections 2/30 (6.7%) Negative cultures 6/30 (20%)	No data	[1]
Poliseno, 2021	All hospitalized patients switched to Dalbavancin for the treatment of Gram-positive infections from July 2017 to July 2019 Dalbavancin dosage: Dalbavancin 1500 mg dose, median (IQR) 1 (1–3)	Retrospective study	50 ABSSSIs: 12; complicated ABSSSIs: 8; osteoarticular infections 18; vascular graft or CIED-I, 12	Success was defined as stable remission, detected at the end of therapy (14th day after a single 1500 mg dose of dalbavancin, or, for longer treatments with repeated infusions of 1500 mg at 14-day intervals, as the 14th day after the last dose), of both symptoms and signs of infection recorded at patient presentation, along with a stable reduction of both C-reactive protein to a value <10 mg/L and procalcitonin to <0.5 ng/mL, if not altered for other reasons than the infection. Furthermore, cultures, when indicated either from blood or from other sites of infections, had to be negative. Overall clinical success: 49/50 (98%) 3-month clinical relapse: 7% (1 ABSSSI)	1/50 (2%) (stop of Dalbavancin)	<i>S. aureus</i> 17/50 (34%) CoNS 17/50 (34%) <i>E. faecalis</i> 3/50 (6%) <i>C. striatum</i> 1/50 (2%) <i>B. cereus</i> 1/50 (2%) No isolate 11/50 (22%) Oxacillin-R Staphylococci 19/50 (38%) Polymicrobial isolates 9/50 (18%)	Early hospital discharge 44 (88%) Failure of initial therapy 5 (10%) Adverse events to initial therapy 1 (2%)	[15]

(Continued)

Table 4. (Continued).

Author, year	Study Population and Intervention	Type of study	Number of patients	Outcomes/Clinical efficacy	Safety	Isolated pathogens	Reasons for Dalbavancin use	Reference
Bai, 2021	Adult patients treated with ≥1 Dalbavancin dose from 01/05/2016 to 30/06/2019 for any type of infection (ABSSSI and OTA***) Dalbavancin dosage: – 1500 mg in single dose 124 (60.2%) – Others: 82 (39.8%)	Retrospective, observational study in 11 hospitals in Italy	206 ABSSSI 124, 60.2% OTA 82, 39.8%	The primary outcome was clinical cure as evaluated by physicians at endo of treatment defined as improvement of lesions and resolution of signs and symptoms of infection. Overall clinical cure: 82.5% (ABSSSI 85.5% vs 75%, p = 0.459) Clinical relapse with hospitalization: 12/206 (5.8%) ABSSSI 5 (4%) OTA 7 (8.5%)	Non-serious AEs: 10 (4.9%) ABSSSI 5 (4%) OTA 5 (5.9%) Serious AE: 1 (0.5%) ABSSSI 0 (0%) OTA 1 (1.2%)	Overall population: MSSA 14/78 (18%) MRSA 25/78 (32%) CoNS 23/78 (29%) Subgroup of ABSSSIs: MSSA 4/23 (17.4%) MRSA 9/23 (39%) CoNS 4/23 (17.4%)	Easier way of administration (116, 56.3%) Failure to previous antibiotics (62, 30.1%) Antimicrobial resistance to previous regimens (2, 1%) Allergy 8 (3.9%) Poor compliance 4 (1.9%) Other reasons/missing data 14 (6.8%)	[7]
Dolan, 2022	Consecutive adult patients who received Dalbavancin at the ED for the treatment of ABSSSI from January 1, 2019 to June 1, 2021 Dalbavancin dosage: – 1500 mg single dose regimen	Retrospective cohort study	125	The primary aim of the study was to assess 30-day readmission rates after treatment with dalbavancin 30-d return to ED: 35 (28.0%) 30-d hospital admission: 16 (12.8%)	No data	No data	NA	[77]

Note: *: Patients who were lost to follow-up, died from noninfectious causes or were misdiagnosed were excluded. **: 95 patients included in efficacy analysis; ***: OTA included osteomyelitis, prosthetic joint infections, endocarditis, septic arthritis, sepsis, central venous line (CVC)-related bloodstream infections (BSI), endovascular stent infections, relapsing staphylococcal furunculosis, cutaneous patch, or breast implant infections. PJI: prosthetic joint infections; CR-BSI: catheter-related bloodstream infection. ED: Emergency Department; SSTI: skin and skin soft tissue infection; BJI: bone and joint infections; CIED-I: cardiovascular implantable electronic device infection; AE: adverse event.
NA: not applicable. PWID: People Who Inject Drugs. MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; CoNS: Coagulase-negative *Staphylococcus*; MSSE: methicillin-susceptible *Staphylococcus epidermidis*; MRSE: methicillin-resistant *Staphylococcus epidermidis*.

conditions may have improved or become stable during that time [104,105].

Oral options such as trimethoprim/sulfamethoxazole or linezolid/tedizolid may present limitations, such as myelotoxicity, potential for drug–drug interactions or risk of drug over-exposure, leading to the need for close laboratory follow-up [106–110]. Furthermore, patient's adherence to the therapy is needed. OPAT regimen is an alternative to oral therapy; however, this strategy may be limited by the need for daily use of an intravenous line, therapeutic drug monitoring and the low diffusion of OPAT programs [8,111,112].

Therefore, in the case of contraindications to oral therapy or unavailability/unfeasibility of OPAT programs, dalbavancin may represent the optimal choice for the treatment of selected patients with ABSSSIs, allowing patients' early discharge [113–116].

Patients' categories, which may benefit most from the use of dalbavancin in the ED are those with expected poor oral adherence or with limited access to/contact with healthcare systems, such as homeless, elderly, prisoners, military personnel, people who inject drugs, people living in rural areas far away from hospitals, people with psychiatric disorders or alcohol abuse, frail categories including severely burned or oncologic patients [22,105,110,116–118].

Given their higher risk of recurrent ABSSSIs and worse outcomes, along with their noncompliant behavior, PWID represents one ideal candidate subgroup for LALs [69,118–120]. In PWID, dalbavancin efficacy was high and well tolerated, with similar rates of adverse events compared to the non-PWID population [69]. With a short-duration and single intravenous infusion, dalbavancin represents an optimal alternative to the placement of a permanent venous access or a central line, thereby reducing catheters' complications, such as line occlusion, venous thrombosis, infections or hematomas [15,121,122]. Patients' satisfaction may also be improved with dalbavancin: indeed, the majority of patients prefer a single-dose 30-min intravenous antibiotic over other antibiotic treatment options [15,68]. Avoiding prolonged hospitalization may further prevent complications usually associated with hospitalization itself, such as hospital-acquired infections or Multi-Drug Resistant Organisms (MDROs) colonization/infection [1,15].

7. Economic impact of dalbavancin in the ED for the treatment of ABSSSIs

A systematic review, network meta-analysis and cost analysis compared the newer lipoglycopeptides to standard care and to each other for the treatment of complicated SSTIs, estimating that using dalbavancin could save third-party payers \$ 1,442 to \$ 4,803 per case [123].

A recent study aimed to evaluate the direct costs associated with the management of severe ABSSSI patients from a national healthcare provider's perspective in Italy, Romania, and Spain. The hypothetical administration of dalbavancin rather than the Standard of Care (SoC) therapy (based on either vancomycin, teicoplanin, or linezolid) resulted in an estimated mean reduction in hospital stay of 3.3 days per

ABSSSI patient, with no significant incremental costs from a National Health System perspective [124].

A budget impact analysis considered national administrative databases of patients with non-severe ABSSSIs who accessed the ED in Italy, Spain, and Austria between 2006 and 2014, with an average calculated annual number of patients equal to 5,396, 7,884, and 1,788, respectively [125]. The model estimated that a hypothetical scenario in which an early single dose of dalbavancin (1500 mg) would have been administered rather than the SoC therapy actually prescribed would have allowed in the first year of its introduction a reduction in the total financial burden in Italy and Spain (– € 352,252 and –€ 233,991, respectively), while it increased the total economic burden in Austria (€ 80769); in the third year of its introduction, dalbavancin use would have reduced the total economic burden in all Countries (– € 1.1 million, –€ 810,650, and –€ 70269, respectively). This cost saving was mainly driven by the estimated increase in patients discharged directly by the ED combined to the reduced in-hospital length of stay for those who were hospitalized, following the hypothetical dalbavancin use rather than the actual SoC antimicrobial therapy: –1,332 days over 3 years in Italy, –1,187 in Spain, –1,537 in Austria.

Although providing remarkable insights, the above-mentioned studies present some limitations, including: the frequent lack of sufficient information; the estimation of costs for a whole, although large, study population rather than the calculation of actual costs paid for individual patients; the possible variation of tariffs between different regions of the same Country and even between different hospitals in a same region.

A real-life, individual patients-based study calculated that an early discharge strategy following the use of dalbavancin would have saved a median of € 5,034 (IQR 3,647–6,590) for each ABSSSI case compared to the actual antimicrobial therapy administered [15]. Other real-life studies estimated the cumulative cost saving driven by dalbavancin use of in ABSSSI along with other sites of infection, thus not allowing to extrapolate the saving quota attributable to ABSSSI only [6,126].

The reduced in-hospital length of stay represents a major driver for the cost-effectiveness of dalbavancin use across studies. Indeed, this parameter is associated with a high-cost burden, although it may differ between geographical areas. For instance, the cost of one day of hospitalization in an internal medicine ward in Spain in 2014 was € 325.01 and in an infectious disease ward in Italy € 361; the average cost estimated in 2020 of a day in a U.S. State-local government hospital is \$ 2,606 but varies from \$ 671 in Montana to \$ 5,557 in Connecticut [6,15,127].

Several indirect costs should be considered which could as well be saved using long-acting antibiotics. For instance, daily infusion of antimicrobials often requires indwelling middle-term venous access such as peripherally inserted central catheter (PICC), which poses an average per patient cost of \$ 873 for placement and \$ 205 for complications (e.g., infection, thrombophlebitis, malposition, malfunction);

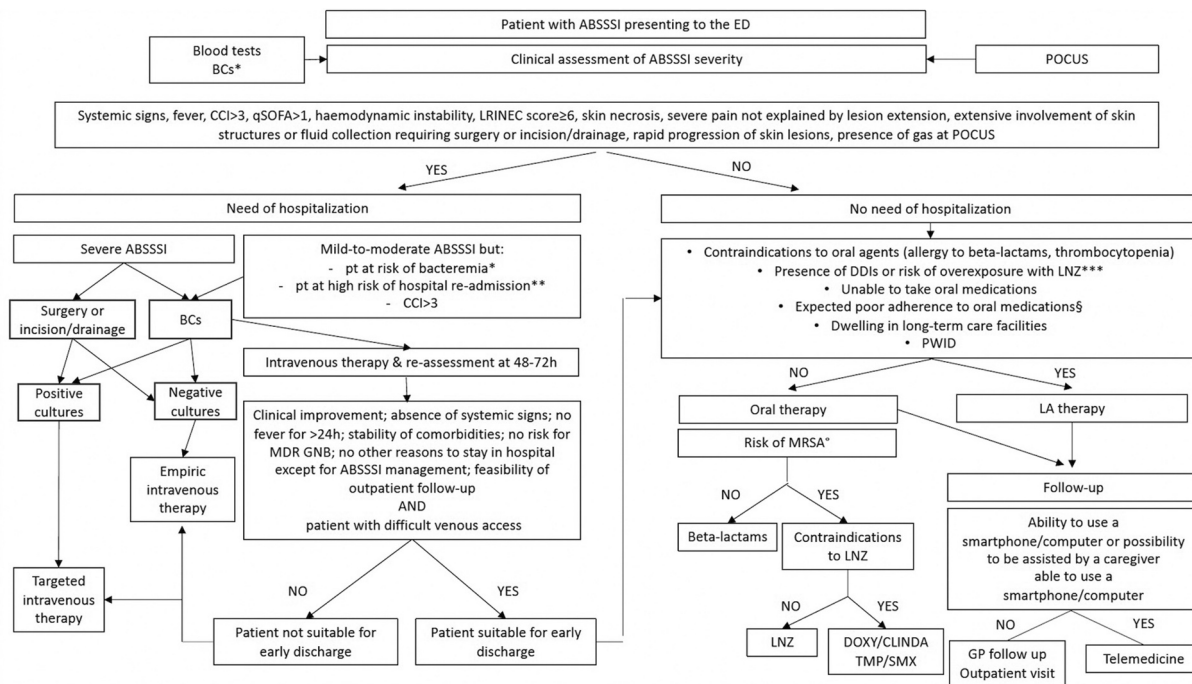


Figure 1. Proposal of a diagnostic and therapeutic algorithm for the management of Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) at the Emergency Department (ED).

*: BCs are indicated in patients with age ≥ 65 years, comorbidities, fever or signs of SIRS, malignancy, neutropenia and/or immunodeficiency or with involvement of non-lower extremities or an infected device/prosthesis, Bacteremia Risk Score > 7 [88] or, in patients with cellulitis, Bacteremia Score of Cellulitis ≥ 2 [26]. **: Risk factors for 30-d hospital re-admission include initial WBC count, congestive heart failure, diabetes mellitus [78]. ***: DDIs with inhibitors of MAO; SSRI; fentanyl; rifampin. Cautious use of LNZ in conditions at risk of LNZ over-exposure such as age ≥ 70 , HD, omeprazole, amiodarone, amlodipine, low dose acetylsalicylic acid [109,110]. §: homeless, PWID, patients with social isolation, residents in LTCF, dependent people, asylum seekers with difficult access to health service, patients with psychiatric illnesses, patients who do not understand local language [123]. °: previous infection/colonization by MRSA; previous exposure to antimicrobials; chronic open wounds; advanced age; recent hospitalization or repeated contacts with the health-care system; chronic conditions such as diabetes, chronic kidney diseases, cardiovascular diseases, immune suppression, HD; parenteral drug use; local MRSA prevalence $> 20\%$ [133–135]. ED: Emergency Department; ABSSSI: acute bacterial skin and skin structure infection; BCs: Blood Cultures; POCUS: point-of-care ultrasound; CCI: Charlson Comorbidity Index; MDR GNB: Multi-drug resistant Gram negative bacilli; DDI: drug–drug interaction; LNZ: linezolid; PWID: People who inject drugs; MRSA: methicillin-resistant *Staphylococcus aureus*; LA: long-acting; TMP/SMX: trimethoprim-sulfamethoxazole; DOXY: doxycycline; CLINDA: clindamycin; GP: general practitioner; MAO: monoamine oxidase; SSRI: selective serotonin reuptake inhibitors; HD: hemodialysis; LTCF: long-term facility.

if systemic and serious complications occur (e.g., bacteremia, endocarditis, sepsis) PICC-related costs markedly increase [128]. Furthermore, glycopeptides require a therapeutic drug monitoring, which may cost from 24 to 56 euros and can be complicated by a transient nephrotoxicity, which determines additional costs for its management and the prolonged in-hospital stay [124]. Moreover, daily intravenous antibiotics require nursing time related to drug dilution, positioning, and removing infusion line, and patient observation, which has variable costs across different hospitals/regions. Finally, in a single-center, real-life study, the introduction of dalbavancin use compared to usual antibiotics yielded significant improvements in work productivity and ability to complete daily activities, in addition to patient satisfaction, thus saving social costs as well [129].

8. Conclusions

Early discharge from ED of eligible patients with the use of dalbavancin could represent an effective and advantageous strategy for the management of patients with ABSSSIs who are not eligible for oral therapies or OPAT programs and who would have otherwise been hospitalized only for antibiotic therapy.

A rigorous assessment of patient characteristics at admission as well as the stratification of the existing risks of bacteremia, recurrence, and ED return could provide valuable information to discriminate the need for hospitalization and select patients who may, instead, benefit from a 48–72 h observation before being discharged on ongoing dalbavancin.

9. Expert opinion: proposal of a diagnostic and therapeutic algorithm for the management of ABSSSIs at the ED

ABSSSIs represent an important reason for hospital admission worldwide; a significant rate of admissions is due to the administration of intravenous antimicrobial therapy alone, accounting for an overall excess of hospitalizations [1–4,14]. Dalbavancin has proven to be highly effective and safe for the treatment of ABSSSIs in registration and observational studies and represents a potential attractive option for the direct or early discharge from the ED of patients with ABSSSIs who are not candidate for oral therapy or OPAT programs [4,21,71–77]. Indeed, dalbavancin's favorable pharmacokinetic profile and its long elimination half-life provide advantage over other intravenous drugs requiring multiple daily doses or oral antibiotics, which need patients' adherence and may be encumbered by adverse events [8]. Furthermore, in light of the increase of multi-drug resistance in

Gram-positive pathogens causing ABSSSIs, the activity of dalbavancin against MRSA represents an additional advantage, which renders dalbavancin a feasible option for selected patients for direct or early discharge from the ED [7]. However, evidence is still limited and highlights the need for further research in order to optimize this treatment strategy.

Figure 1 shows the study panel proposal for the diagnostic and therapeutic approaches of patients presenting at the ED with ABSSSI.

The first step is assessing infection severity and the need for hospitalization through clinical evaluation, laboratory tests and, when applicable, POCUS assessment [14,25,31,87,130]. Blood cultures should be reserved to patients considered at high risk of bacteremia, while surgical procedures and empirical intravenous therapy should not be delayed in the case of hospitalization [87]. If the patient meets the early discharge criteria at the 48–72 h clinical re-assessment, possible options include oral therapy or, if feasible, OPAT programs [105,131–134].

The use of dalbavancin as an early discharge strategy is suggested in the presence of contraindications to oral agents, inability to take oral medications, conditions leading to expected poor adherence to oral medications, such as PWID, homeless, residents in Long-Term Care Facility (LTCF), dependent people, patients with psychiatric illnesses [115].

After discharge, a close follow-up should be guaranteed, in order to early identify signs and symptoms indicating that the infection is not responding to therapy and that there is the need of further care [5,22]. Although its use is increasing and is currently proposed as a possible follow-up strategy, the telehealth approach is feasible for patients or caregivers who are able to use a smartphone/computer (i.e., to provide images of the involved skin area and/or wound) [4,18,19]. Otherwise, a more traditional follow-up with outpatient visits and/or the involvement of the general practitioner is suggested.

The panel believes that a similar approach to patients with ABSSSIs presenting at the ED may be easily implemented into clinical practice, following a strict collaboration between ED physicians, Infectious Diseases specialists and general practitioners for patients' follow-up. Further studies should be promoted to address the role of dalbavancin as a direct or early discharge strategy from the ED in order to avoid hospitalization and its complications by, at the same time, ensuring high efficacy and safety. Furthermore, the additional potential advantages of using dalbavancin in the ED rely on its cost-effectiveness by reducing in-hospital length, providing indirect economic savings and, eventually, contributing to the reduction of ED overcrowding.

List of abbreviations

(ABSSSIs)	Acute Bacterial Skin and Skin Structure Infections
(ED)	Emergency Department
(LALs)	long-acting lipoglycopeptides
(MRSA)	methicillin-resistant <i>S. aureus</i>
(FDA)	Food and Drug Administration
(EMA)	European Medicines Agency
(RCT)	randomized clinical trials

(POCUS)	point-of-care ultrasound
(VISA)	vancomycin-intermediate <i>S. aureus</i>
(hVISA)	heteroresistant VISA
(VSE)	vancomycin-susceptible enterococci
(VRE)	vancomycin-resistant enterococci
(PWID)	people who inject drug
(BCs)	blood cultures
(WBC)	White Blood Cells
(SIRS)	Systemic Inflammatory Response Syndrome
(CRS)	Cellulitis Recurrence Score
(OPAT)	Outpatient Parenteral Antibiotic Therapy
(MDROs)	Multi-Drug Resistant Organisms
(SoC)	Standard of Care
(PICC)	peripherally inserted central catheter
(LTCF)	Long-Term Care Facility

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Author contribution

Conceptualization of the study: MV, EDM; literature revision: AO, SC, VC, MC, EDD, MF, GG, EDM, MV; manuscript draft writing: AO, EDD, SC; supervision: MV, MF, EDM.

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