Infezioni difficili e pazienti difficili: il mistero delle ABSSSI

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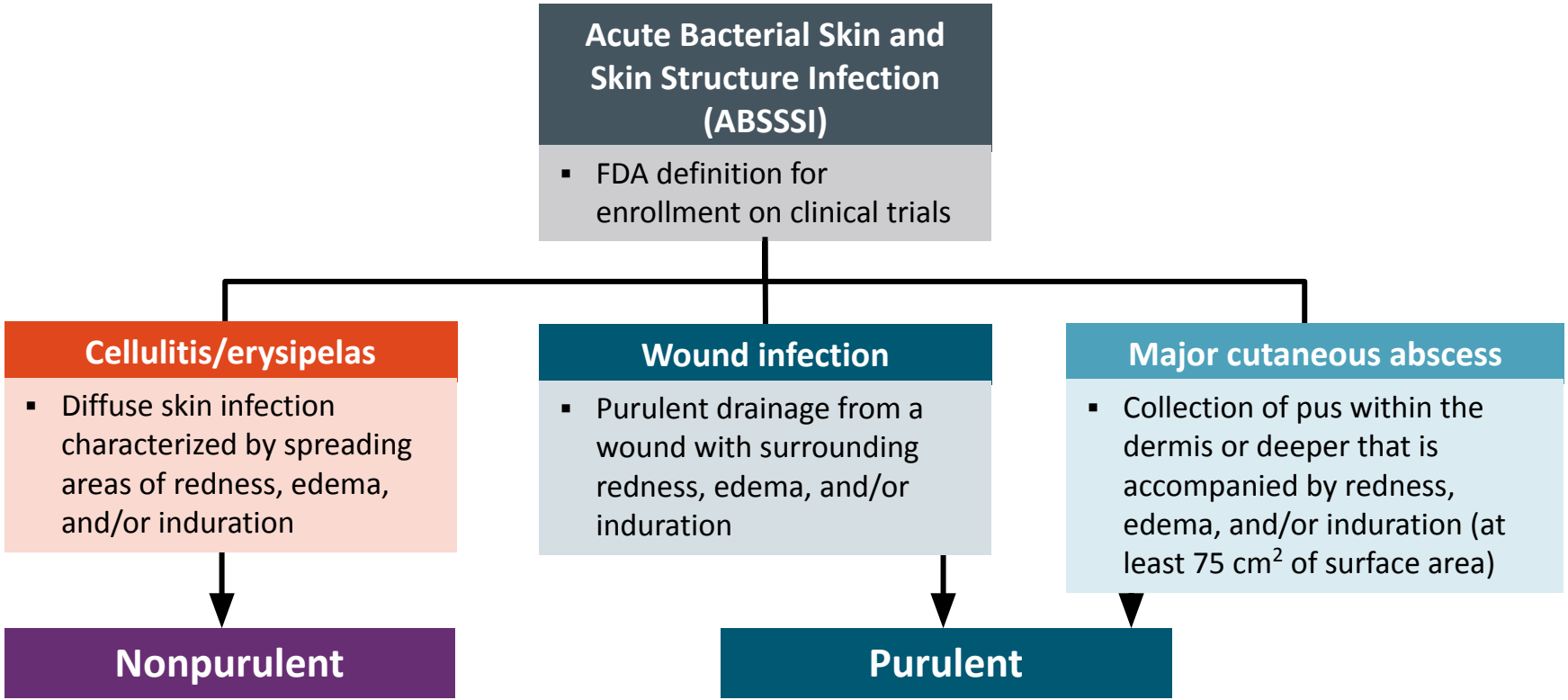
Disclosures

- ABBVIE
- GILEAD
- VIIV
- ANGELINI
- PFIZER
- MENARINI
- ASTRA ZENECA
- GSK

Topic

- Acute bacterial infections involving the skin and underlying tissues are becoming a growing and challenging problem
- Significant healthcare cost and important amount of hospital stays
- SSTIs represent a significant burden on the healthcare system and are among the most commonly encountered infections in EDs and a frequent reason for ambulatory visits

Definitions



www.fda.gov/files/drugs/published/Acute-Bacterial-Skin-and-Skin-Structure-Infections---Developing-Drugs-for-Treatment.pdf

- **SSTIs**
- **Differentiation of necrotizing soft tissue infections (NSTIs)** from **non-necrotizing infections**.
- **This differentiation is critical, because necrotizing infections warrant prompt aggressive surgical debridement**

“Hard Clinical Signs”

- Bullae
- Crepitus
- Gas on radiograph
- Hypotension with systolic blood pressure less than 90 mm Hg
- Skin necrosis

Distinguishing Nonpurulent Cellulitis From Necrotizing Fasciitis

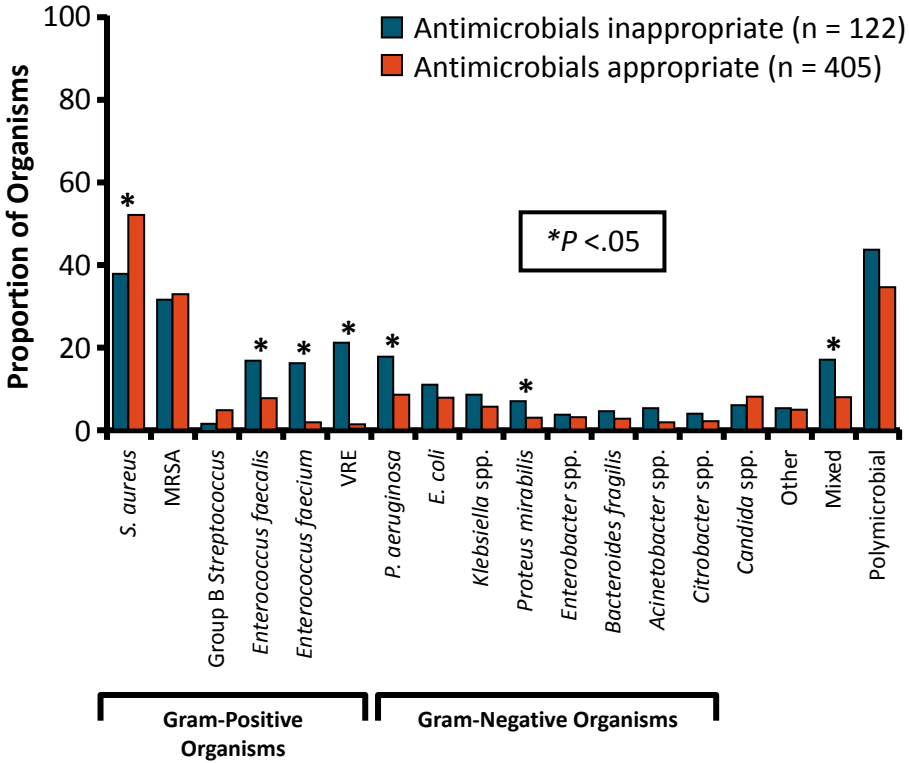
Feature	Nonpurulent Cellulitis	Necrotizing Fasciitis
Origin	May be obvious (trauma, recent surgery, ulceration), but often breaks in skin are clinically unapparent	Extension from skin lesion (minor abrasion, insect bite, injection site)
Systemic signs of infection	± SIRS criteria	SIRS criteria + disorientation and lethargy
Physical exam findings	Skin surface resembles orange peel or red, smooth and warm, subcutaneous tissues are palpable and yielding	Wooden-hard induration of subcutaneous tissues, fascial planes and muscle groups cannot be discerned by palpation
Pain	Appropriate considering findings on physical exam	Out of proportion
Bacteriology	Majority group A streptococci, but also other groups	Polymicrobial

Stevens. Clin Infect Dis. 2014;59:e10.

Etiology of SSTI

- **Most typically implicated:**
  S. aureus and β-hemolytic streptococci
  - 80% of culture-positive infection[1]
  - **CA-MRSA:** in patients who lack classic risk now most prevalent cause of staphylococcal SSTI[2]
- **Less frequently implicated:**
  Gram-negative organisms, anaerobes, yeast and mixed infections
  - Inappropriate choice of antimicrobials

Distribution of Pathogens Among Hospitalized Patients With Culture-Positive Complicated SSTI Treated With Appropriate or Inappropriate Empiric Therapy[3]



1. Ray. BMC Infect Dis. 2013;13:252. 2. Stryjewski. Clin Infect Dis. 2008;46:S368. 3. Kaye. Clin Infect Dis. 2019. 68:S193.

Hospital Admission for SSTI Increasing but Unnecessary

- **Hospitalizations doubled** and **costs increased** by 118% between 1998 and 2013[1]
- Associated with **low mortality** (<0.5%)[2]
  - Life-threatening infections occur in 6% of hospitalized patients[3]
- Administration of IV antibiotics is the ***only*** reason for hospital admission in **42%** of patients[3-4]
  - 535,100 hospital admissions could be avoided in the US
  - **Opportunity to improve healthcare efficiency and patient satisfaction, and decrease costs**

1. Baxa. Am J Emerg Med. 2020;38:321. 2. Talan. Acad Emerg Med. 2021;28:1108.
3. Talan. West J Emerg Med. 2015;16:89. 4. Lodise. Hosp Pract. 2015;43:137.

Emergency department

- More than 2 million patients are seen for SSTIs in US emergency departments every year
- Community-acquired methicillin-resistant Staphylococcus aureus is the primary cause in more than 60% of cases
- up to 50% of patients with SSTIs suffer from recurrences

ABSSSI Patient Journey

- Outpatient setting
- Inpatient setting
- Emergency department

Severity Classification: Purulent SSTI

***S. aureus*, including MRSA,** cause large % of infections

Purulent SSTI

eg, furuncle, carbuncle, abscess

Mild

No systemic signs of infection

Moderate

Systemic signs of infection but hemodynamically stable

Severe

Failed I&D + PO antibiotics OR multiple systemic signs + acute hypotension/organ dysfunction OR immunocompromised

Systemic signs of infection include:

- Temperature (>38°C)
- Tachycardia (HR >90 beats/min)
- Tachypnea (RR >24 breaths/min)
- Abnormal white blood cell count (>12,000 or <400 cells/µL)

Stevens. Clin Infect Dis. 2014;59:e10.

Severity Classification: Nonpurulent SSTI

Streptococci cause vast majority of infections

Nonpurulent SSTI

eg, necrotizing infection, cellulitis, erysipelas

Mild

No systemic signs of infection

Moderate

Systemic signs of infection but hemodynamically stable

Severe

Failed PO antibiotics OR multiple systemic signs + acute hypotension or organ dysfunction OR immunocompromised
OR signs of deeper infection (eg, bullae, skin sloughing)

Systemic signs of infection include:

- Temperature (>38°C)
- Tachycardia (HR >90 beats/min)
- Tachypnea (RR >24 breaths/min)
- Abnormal white blood cell count (>12,000 or <400 cells/µL)

Stevens. Clin Infect Dis. 2014;59:e10.

Evaluation

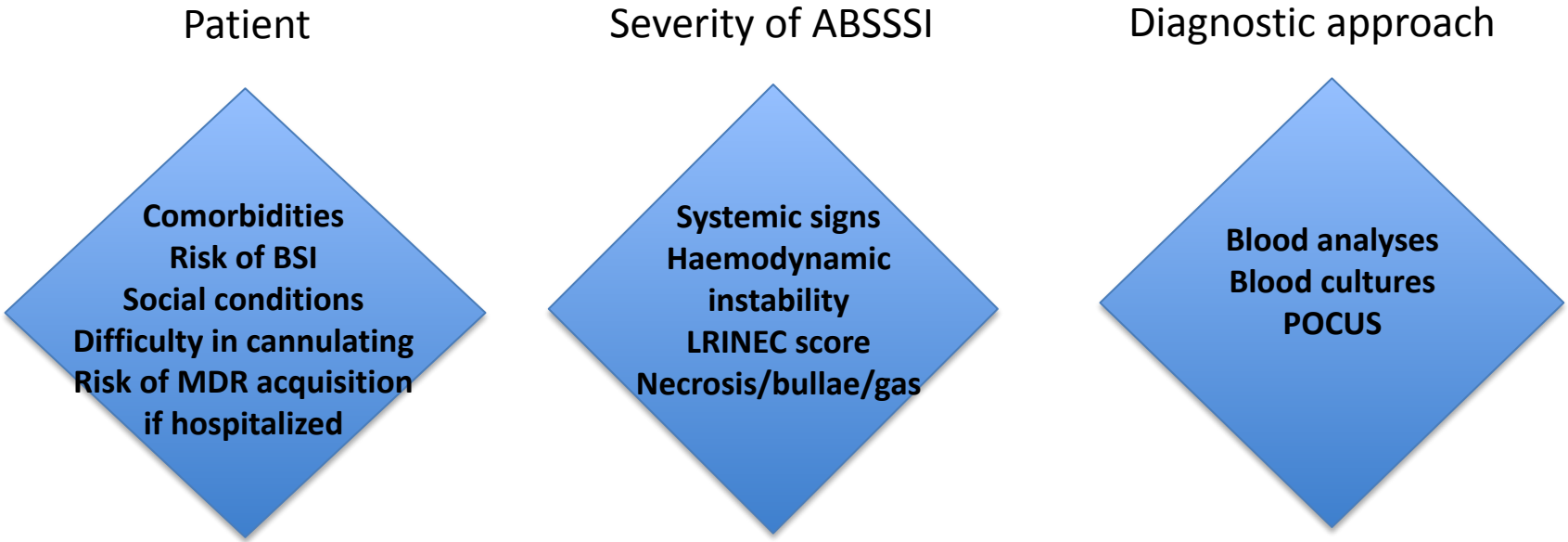
Anamnestic data

Clinical features

Laboratory/EGA exams

Bedside ultrasonography

ABSSSI Risk Profile



Hospitalization vs early discharge

Determinants of SSTI complicated

- Patient
  - Immunosuppression (IV drug user, steroids, DM)
  - Acute deterioration (Sepsis, shock)
- Wound
  - Large size (> 75cm2), deep invasion, rapid progresson, virulent bacteria, resistant bacteria
- Therapy
  - In-hospital treatment, surgical intervention, IV antibiotic therapy, failure of initial Abtx

Determinants of prognosis of cSSTs

Comorbidity

- Obesity
- diabetes mellitus
- Peripheral vasculopathy

Local lesion

- Edema
- Deepness
- Necrosis

Systemic signs

- Fever
- SIRS
- Shock

ABSSSI treatment
Outpatient setting

- **Advantages**
  - Reduced hospital stays and costs
  - Satisfactory for patients
- **Disadvantages**
  - Adherence issues
    - Elderly
    - Cognitive impairment
    - IV Drug user

ABSSSI treatment
Inpatient setting

- **Advantages**
  - Close monitoring adherence, clinical outcome and laboratory follow-up

- **Disadvantages**
  - Hospital costs
  - Adverse effects correlated with hospitalization

ABSSSI treatment
Emergency department

- **Advantages**
  - Reduced hospital stays and associated costs
  - Treatment adherence ensured

- **Disadvantages**
  - Proper selection of patients
  - Organization issues

Not eligible for early discharge

Cutaneous abscess not treated with incision and drainage

Severe soft-tissue infection

Osteomyelitis

Septic arthritis

Presence of underlying hardware

Concomitant bloodstream infection/endocarditis

Early discharge criteria

Long acting i.v. therapy or oral antibiotic therapy

Temperature <38 °C for 24 h

Clinical improvement or stable infection

WBC count and inflammation indexes improving

No unexplained tachycardia

Systolic blood pressure ≥ 100 mmHg

Patient tolerates oral fluids/diet

No other reason to stay in hospital except for infection management

Stable mental status

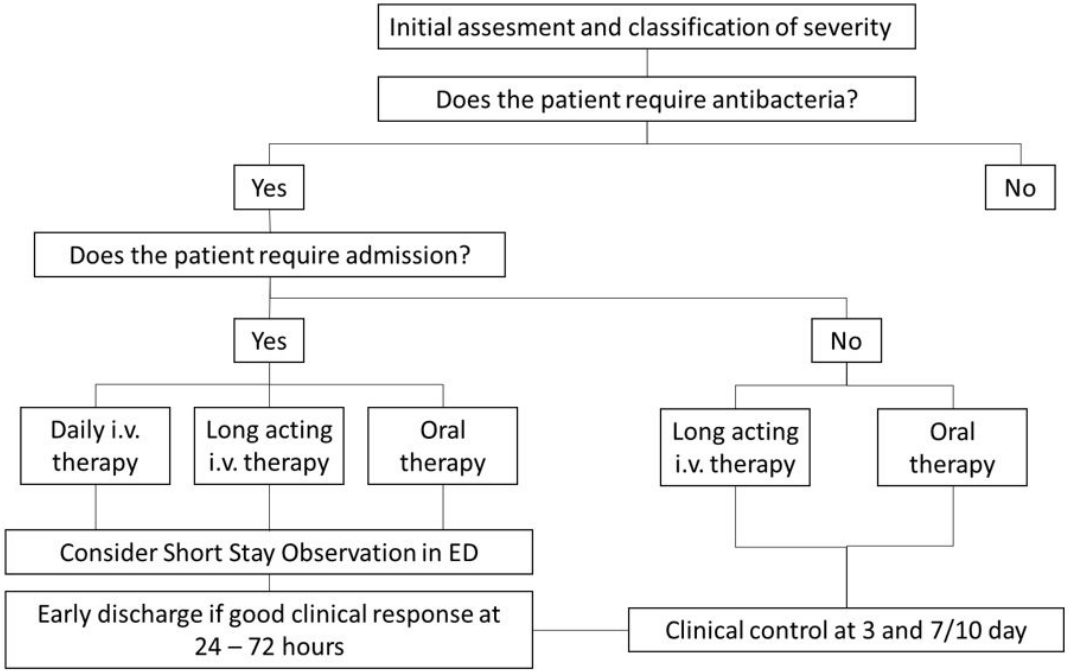
Stable co-morbid illness

Stable social situation

Principles of antimicrobial treatment

- Choice of antimicrobial agent and route of administration are contingent on **classification of ABSSSI** and **severity stratification**
- **Oral antimicrobials preferred** for definitive therapy in patients with mild/moderate ABSSSI, but **safety profile should be assessed**
- When use of oral antimicrobials prohibitive or when severity might otherwise warrant observation, **long acting antibiotic are a valuable alternative** to avert inpatient admission or eliminate adherence concerns

Treatment algorithm for managing skin and soft-tissue infections (SSTIs) in ED



Modified from Nathwani et al.

Adherence to Oral SSTI Treatment Is Low and Associated With Poor Clinical Response

- Prospective cohort study of 87 patients with confirmed *S. aureus* SSTI being discharged with oral antibiotic to complete therapy
  - Self-reported adherence to oral regimen 96% vs 57% confirmed by electronic bottle cap (P <.0001)

46% participants had a poor clinical response after 30 days of follow-up

In the multivariable analysis, lower adherence was an independent risk factor for poor clinical outcome (OR: 0.16; 95% CI: 0.02-0.99)

Eells. Antimicrob Agents Chemother. 2016;60:2941.

Complications to Be Ruled Out Prior to Treatment

- **Necrotizing fasciitis**
- Osteomyelitis/septic arthritis
- Tenosynovitis/bursitis/myositis
- Presence of underlying hardware
- Decubitus/chronic ulcers
- Concomitant bloodstream infection/endocarditis

Role of Incision and Drainage vs Antimicrobials

Purulent

- **I&D** is mainstay of therapy
- Antibiotics may be used in conjunction with I&D for patients with systemic signs of infection or situations where I&D may pose more risk than benefit[1]
- Role of antibiotics in mild, small abscesses (≤5 cm) uncertain (unless abscess undrained)[2]

Nonpurulent

- Primary treatment is **antimicrobial therapy** for all severities

1. Stevens. Clin Infect Dis. 2014;59:e10. 2. Daum. NEJM. 2017;376:2545.

Patients candidates to long acting antibiotics

- Pts with multiple comorbidities at risk for negative consequences of hospitalization (ie, risk of MDRO)
- Pts with expected poor adherence to oral therapy (ie, social conditions, homeless, PWID)
- Pts with contraindications to oral therapy (ie, drug-drug interaction)

Potential Uses of LAL for ABSSSI

Single-dose agents may have a role in reducing hospitalization and improving adherence in nonadherent patient populations

Avert inpatient admission

Facilitate early discharge

Long-Acting Lipoglycopeptides: Defining a Target Patient Population

Consider if

- Prohibitive safety profile of available PO options
- GI absorption issues based on physiology and nutrition
- **Significant doubts about adherence to PO therapies**
  - Homelessness, incarceration, rural location
  - Poor mental/physical health
  - **People who inject drugs**
- Mild/moderate systemic signs of infection where traditional IV therapies may have been considered, to avoid inpatient admission or line placement

Avoid in

- Hemodynamic instability or severe sepsis/shock
- **Lipoglycopeptide** allergy
- Emergent surgery
- Concern for **necrotizing fasciitis** or other infection besides SSTI (polymicrobial infection, LAL spectrum of activity inadequate)
- Orbital cellulitis

Krsak. Pharmacotherapy. 2020;40:469. Bosso. Hosp Pract. 2016;44:183.

Clin Drug Investig. 2020 Apr;40(4):305-318. doi: 10.1007/s40261-020-00891-w.

Budget Impact Analysis of Dalbavancin in the Treatment of Acute Bacterial Skin and Skin Structure Infections in Three European Countries

Andrea Marcellusi [1] [2], Chiara Bini [3], Massimo Andreoni [4], Loredana Sarmati [4], Jaime Espin [5], Juan P Horcajada [6], Thomas Czypionka [7] [8], Davide Andretta [9], Paolo Sciattella [3], Giampiero Favato [10], Francesco S Mennini [3] [10]

The introduction of dalbavancin in a new patient pathway to treat non-severe ABSSSI could generate a significant reduction in hospitalized patients and the overall patient length of stay in hospital in Spain, Italy and Austria

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlad044

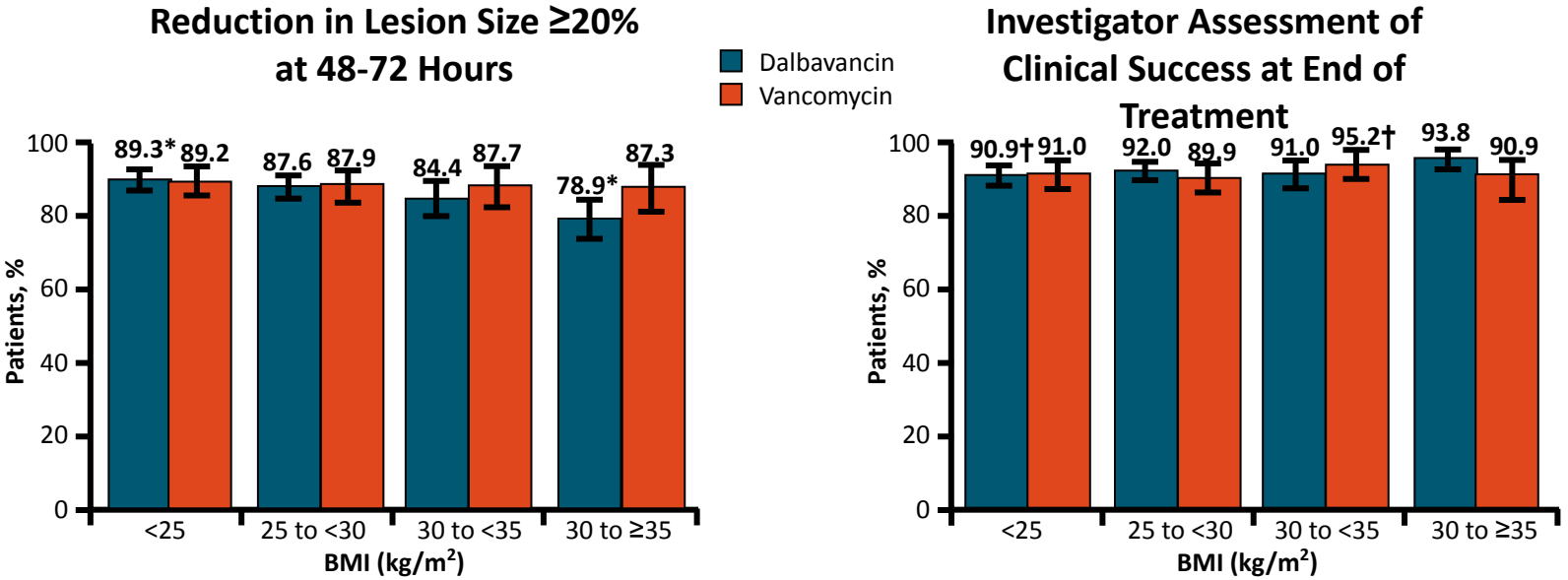
JAC-Antimicrobial Resistance

Cost analysis of dalbavancin versus standard of care for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in two Italian hospitals

Francesca Bai[1]†, Maria Mazzitelli [2]†, Sofia Silvola[3,4], Francesca Raumer[5], Umberto Restelli[3,6], Davide Croce[3,4], Giulia Marchetti[1]* and Anna Maria Cattelan[2]

Dalbavancin, when used as the primary and sole treatment, significantly cuts hospitalization time compared to standard care, resulting in cost reductions between €1,099 and €2,013.

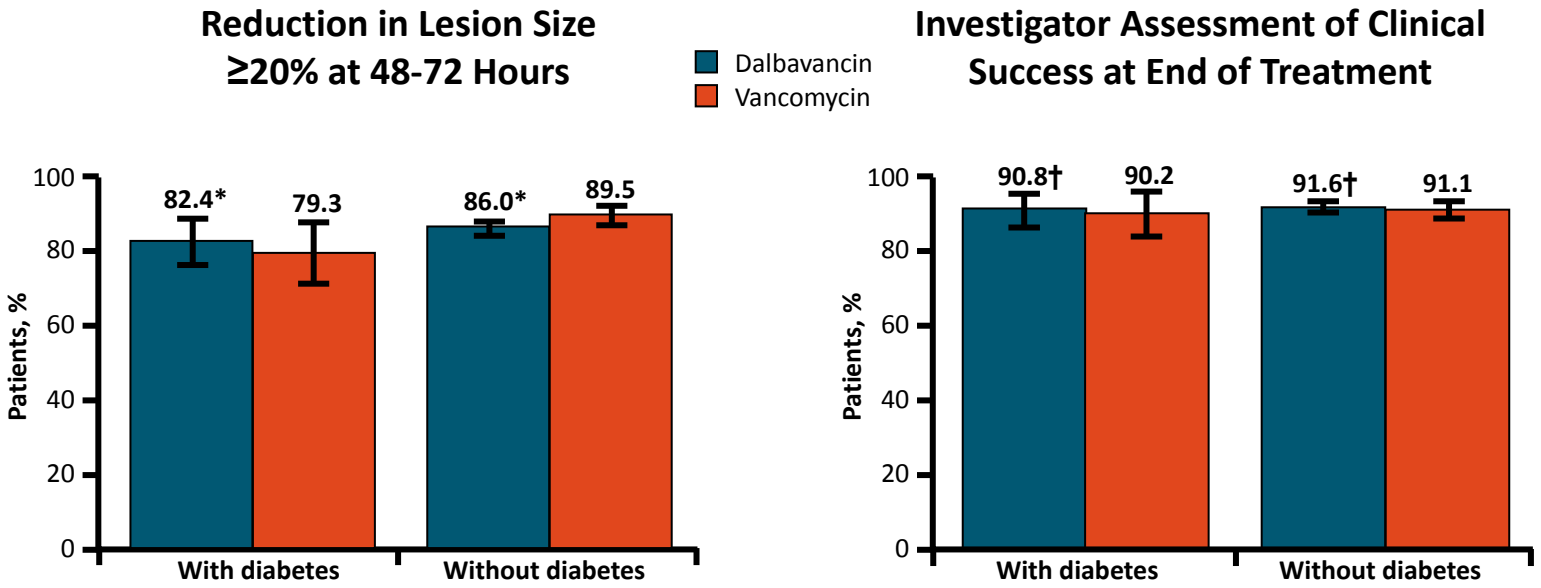
Dalbavancin in Patients by BMI: Pooled Phase 3 Subgroup Analysis



- *At earlier timepoint, lower clinical response with obesity may be explained by higher baseline incidence of cellulitis
- **†At end of treatment, clinical response was equivalent**

Riccobene. Open Forum Infect Dis. 2023;10:ofad256.

Dalbavancin in Patients by Diabetes Status: Pooled Phase 3 Subgroup Analysis



- *At earlier timepoint, lower clinical response with diabetes may be explained by higher baseline incidence of cellulitis
- **†At end of treatment, clinical response was equivalent**

Riccobene. Open Forum Infect Dis. 2023;10:ofad256.

Tailoring of the ideal patient

- Careful evaluation of patient characteristics upon ED admission and risk stratification for bacteraemia, infection recurrence, and potential ED readmission are crucial.

- This assessment helps to determine the necessity of hospital admission and identify individuals who could be observed for 48–72 hours before being safely discharged with continued dalbavancin treatment

- However, there are certain patient categories who should remain hospitalized and not be discharged with long-acting therapy, especially when follow-up appointments cannot be scheduled.