Long-acting and Outpatient Parenteral Antimicrobial Therapy (OPAT): challenges and opportunities

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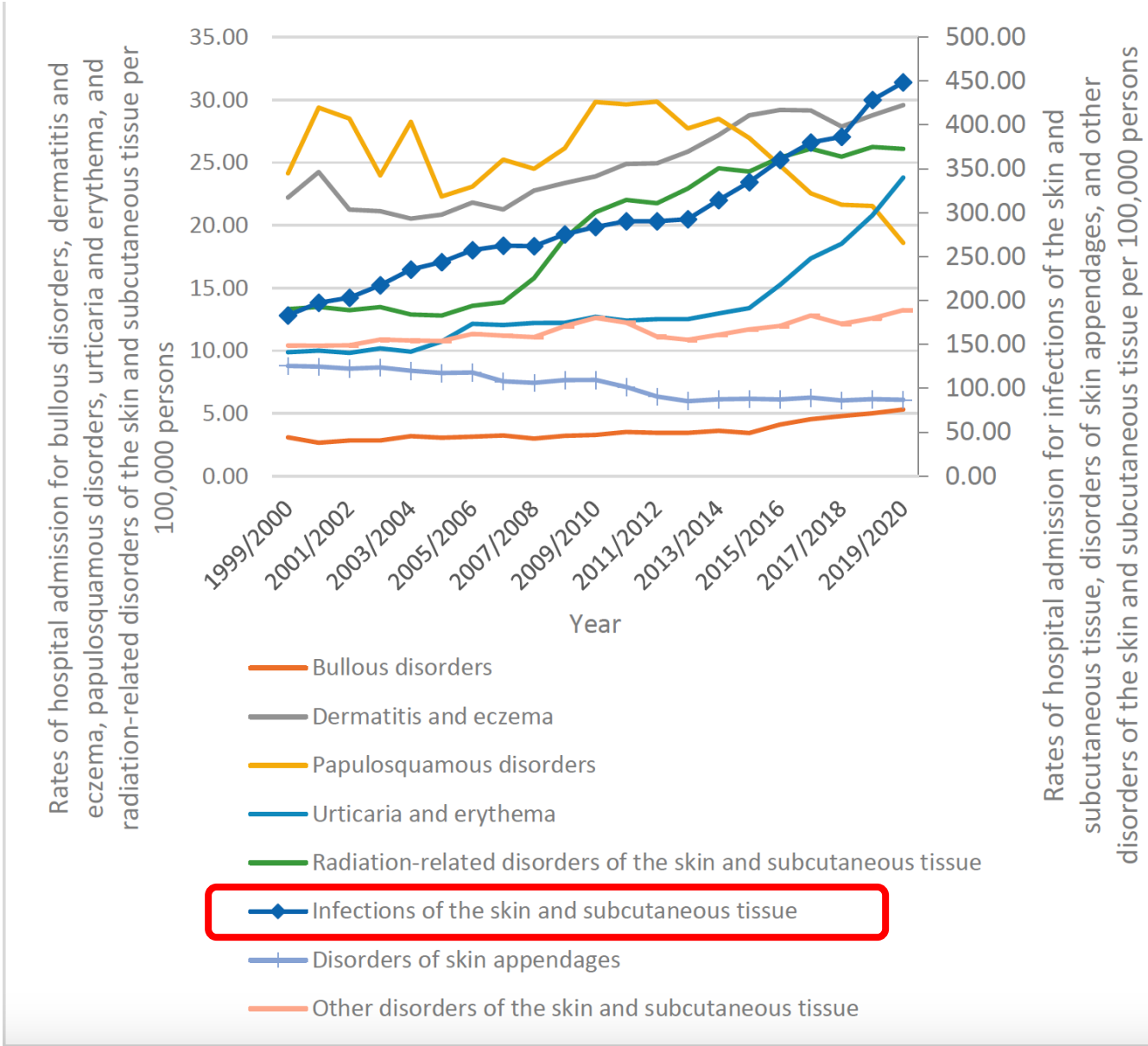
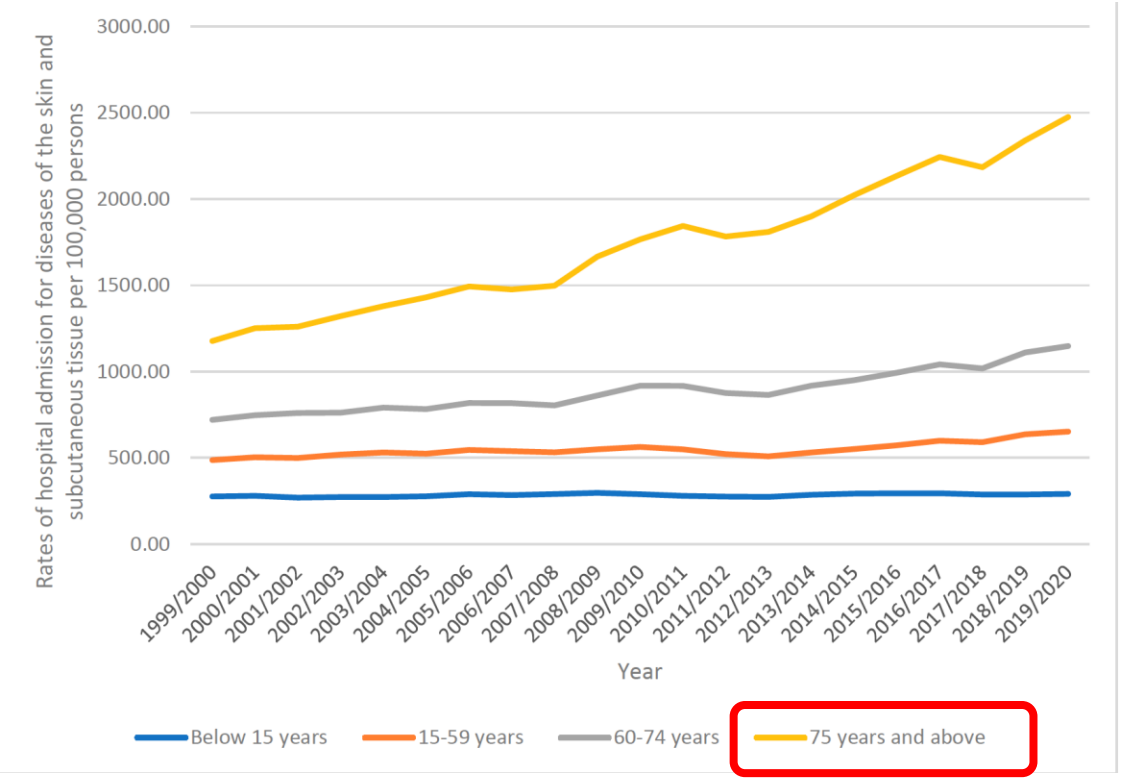
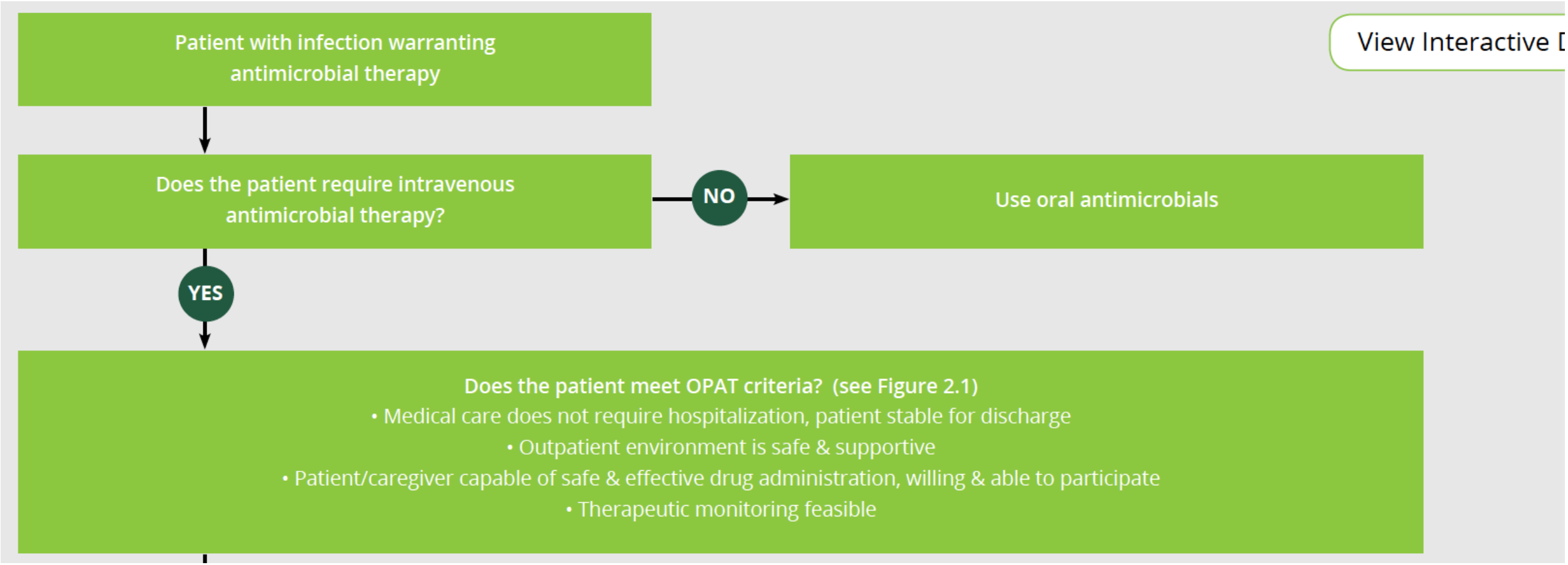
Outline

- Selezione dei pazienti per OPAT e Switch a terapia orale
- Infezioni cutanee (ABSSSI) come principali infezioni da trattare con OPAT
- Identificare pazienti con infezione mild/moderate/severe
- Pazienti con infezione moderata: terapia con long acting
- Dalbavancina e Oritavancina

Increased rates of hospital admission for ABSSSI







- Criteria for **oral** antibiotic treatment
  - Criteria for selecting patients

Antimicrobial agent	Oral bioavailability
Amoxicillin/cephalexin	75-95%
Doxycycline	90-100%
Metronidazole	95%
Azithromycin	35-50%
Clarithromycin	50-60%
Clindamycin	70-85%
Fluoroquinolones	85-100%

Healthcare Improvement Scotland | SAPG

Out-patient parenteral antibiotic therapy (OPAT) pathway for the management of adults with complicated skin and soft tissue infections (SSTI) affecting their upper or lower limb(s) or face (erysipelas)

Patients' selection

Severity Assessment

Category 1 (NEWS 0-1)

Patients with no uncontrolled co-morbidities requiring in-patient assessment

And

not systemically unwell

And

not yet tried oral antibiotics

Category 2 (NEWS 0-1)

Patients with no uncontrolled co-morbidities requiring in-patient assessment

And

mild systemic illness

Or

well with condition complicating or delaying infection resolution, eg peripheral vascular disease, chronic venous insufficiency or morbid obesity

Or

well but cellulitis progression despite appropriate choice and dose of oral antibiotic

Category 3 (NEWS ≥ 2)

Patients with significant systemic upset, eg acute confusion, tachycardia, tachypnoea, hypotension or persistent pyrexia

Or

unstable co-morbidities, eg acute kidney injury (AKI), uncontrolled blood sugar or cardiac decompensation

MILD

MODERATE

SEVERE

OPAT Suitability Assessment

Give oral antibiotics

Flucloxacillin 1g 6 hourly

Alternative in patients with penicillin allergy: Doxycycline 100mg 12 hourly

Total duration 5 days (Check BNF for interactions, including cation interactions: see page 2, point 5)

Requires IV Antibiotics

Is patient ambulatory and self-caring or has appropriate carer support and access to OPAT does not delay

No

In-patient IV antibiotics required

See local in-patient infection management guidelines

Yes

OPAT Suitability Assessment

Does patient require additional assessment or have any exclusion criteria?

No

Additional Assessment Required

Patients in the groups below may be suitable for OPAT but require discussion with or assessment by OPAT medical staff and, potentially, adjustment of antibiotic regimen:

- ❑ Recent hospital admission
- ❑ Diabetic foot ulcer with cellulitis
- ❑ eGFR <30 ml/min/1.73 m^2
- ❑ People who inject drugs (PWIDs)
- ❑ Pregnant or breast feeding
- ❑ Immunosuppressed
- ❑ Previous or current MRSA
- ❑ Human or animal bite cellulitis

Discuss with specialist surgical or orthopaedic team in case further intervention required if the patient has:

- ❑ Surgical site infection
- ❑ Hand trauma
- ❑ Possible bone/joint infection or bursitis

OPAT Exclusion Criteria

Patients in these groups not eligible for OPAT:

- ❑ Under 18 years (consider paediatric pathway, if available)
- ❑ Pain out of proportion to skin changes, or skin changes that are rapidly evolving or blistering
- ❑ Unstable co-morbidities, eg AKI, cardiac decompensation or uncontrolled blood sugars
- ❑ Current *Clostridioides difficile* infection
- ❑ (Peri)-orbital cellulitis
- ❑ Other medical problems requiring in-patient management

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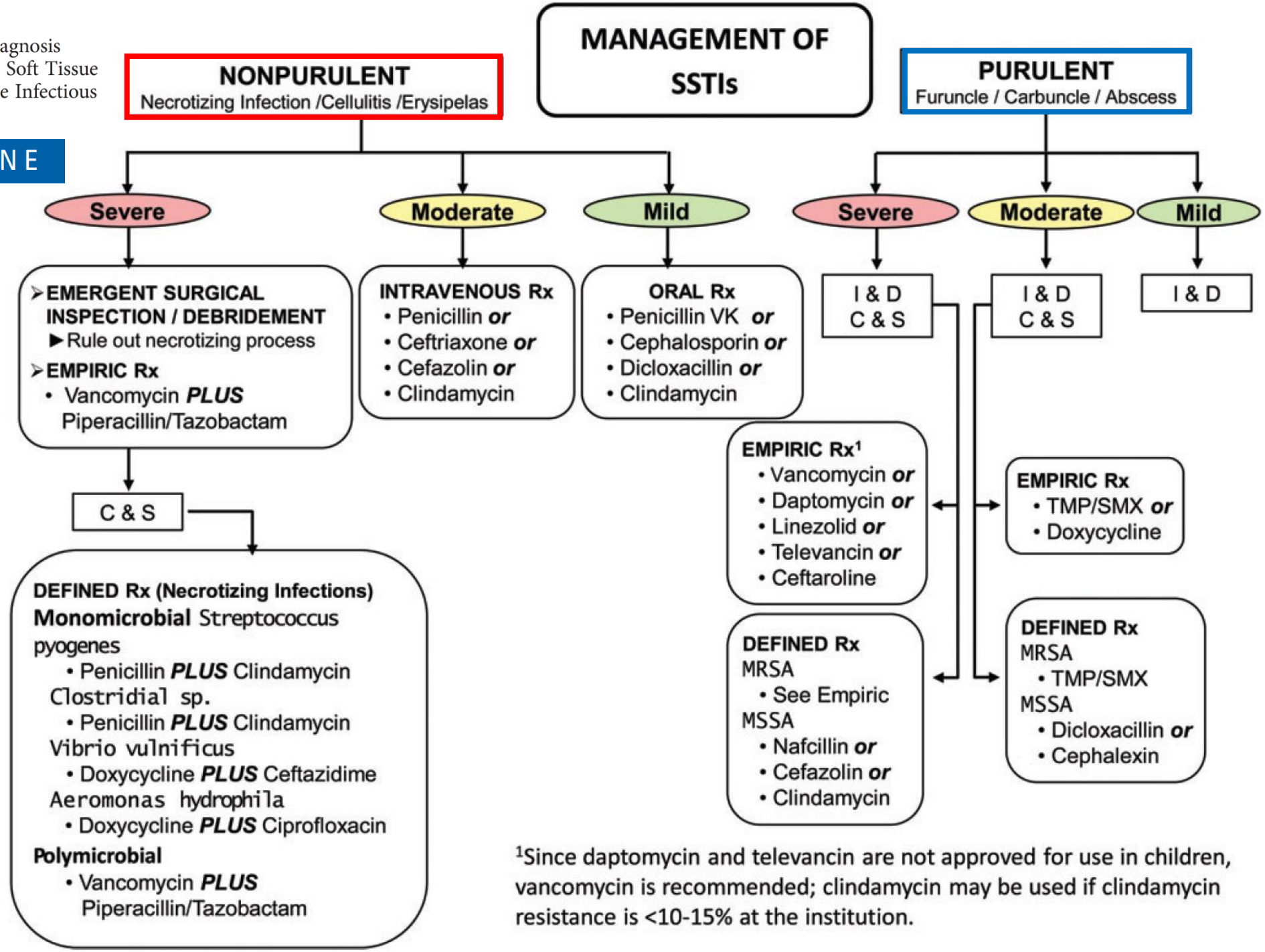
Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

IDSA GUIDELINE



[1]Since daptomycin and televancin are not approved for use in children, vancomycin is recommended; clindamycin may be used if clindamycin resistance is <10-15% at the institution.

Potential antibiotic strategies for patients with SSTI

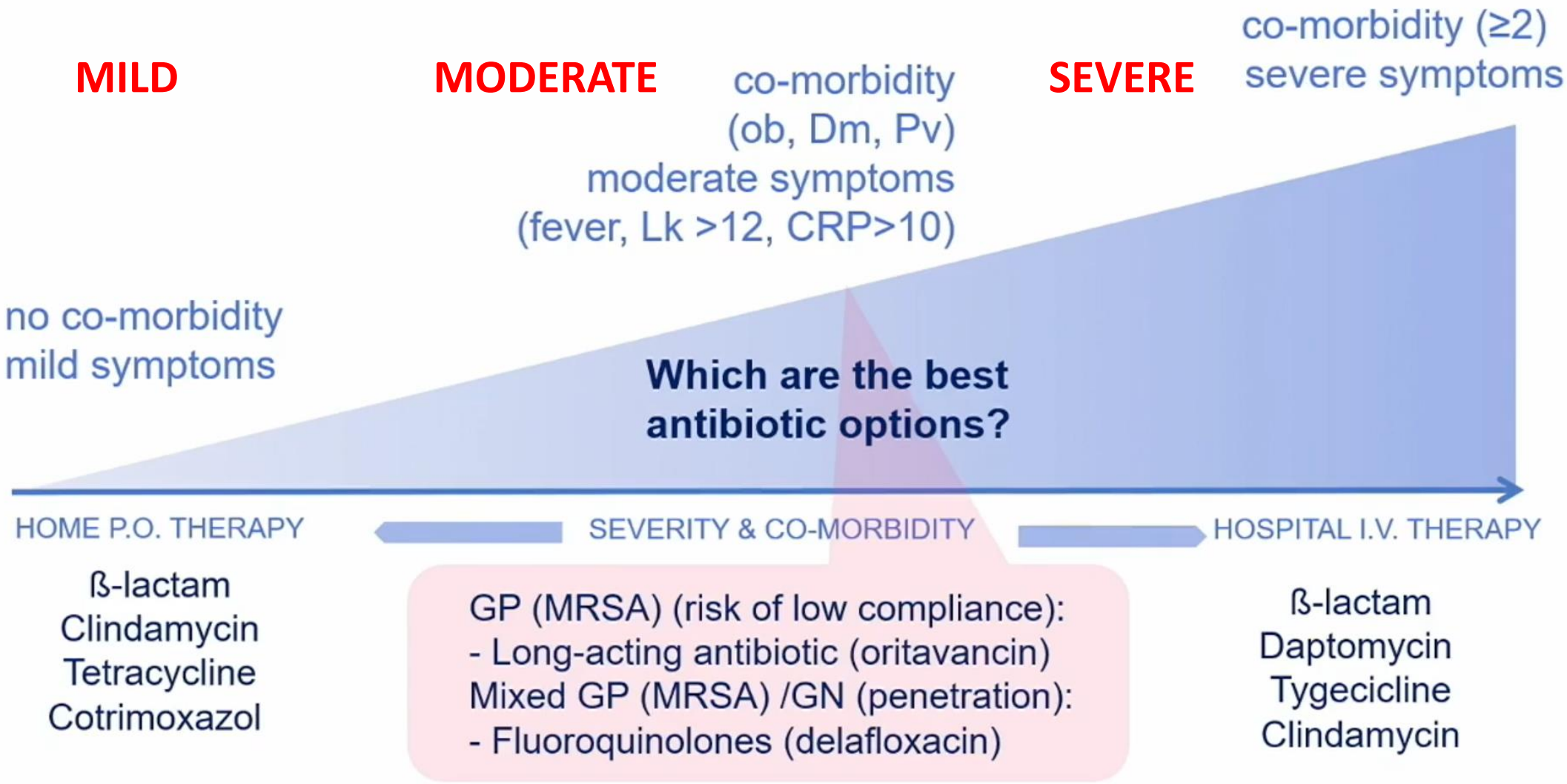


Tabella 16.1 - Patogeni più frequentemente associati a infezioni cutanee (in ordine decrescente di frequenza)

Maggioranza dei casi	Più raramente (ad esempio in pazienti immunocompromessi e/o diabetici, lesioni cutanee traumatiche)	Casi con esposizioni ambientali specifiche
Streptococcus pyogenes (*Streptococcus* di gruppo A), soprattutto nel caso di erisipela *Staphylococcus aureus* (compreso MRSA)	Enterobacterales (compresi ceppi multiresistenti come quelli che producono ESBL e carbapenemi) *Pseudomonas aeruginosa* (compresi ceppi multiresistenti come quelli che producono ESBL e carbapenemasi) Anaerobi **15-30%**	*Aeromonas hydrophila* (esposizione all'acqua dolce) *Erysipelothrix rhusiopathiae* (contatto con animali colonizzati con l'organismo, principalmente suini e pesci) *Vibrio vulnificus* (esposizione all'acqua di mare)

ESBL: beta-lattamasi ad ampio spettro; MRSA: *Staphylococcus aureus* meticillino-resistente.

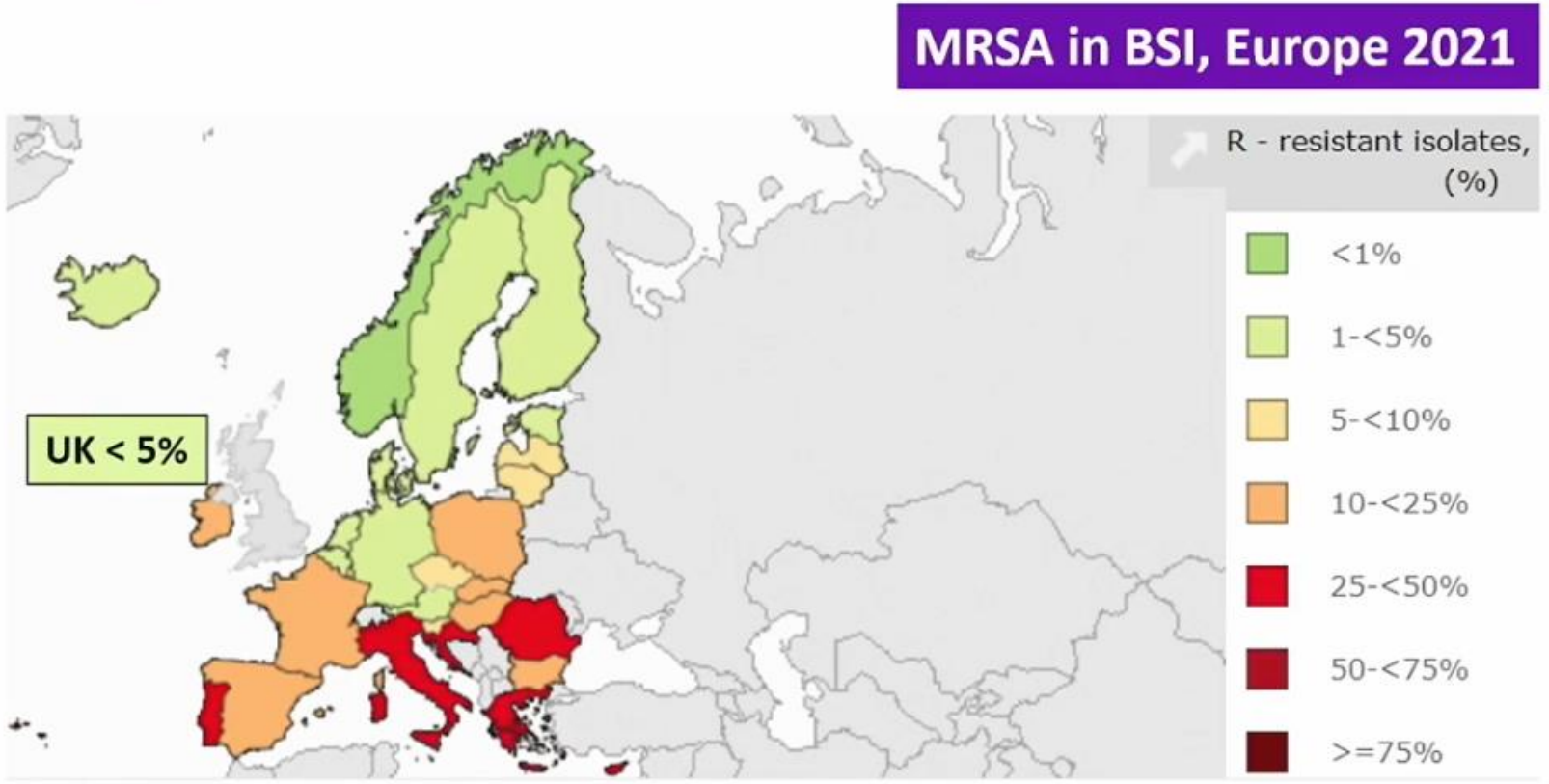
Diabetes
Immunodeficiences
Wound infections
Perianal/genital area

Pasteurella spp
Capnocytophaga c.
Eikenella c.
Anaerobes

Animal bites

Cellulitis, erysipelas, and abscesses are primarily caused by Gram-positive bacteria, including *S. aureus*, *Streptococcus pyogenes*, and other beta-hemolytic streptococci.[5,6,24–27] Coverage against Gram-positive bacteria therefore seems sensible as an initial empiric therapy for these conditions. The presence or absence of pus can be used to alert the clinician to the probability of an infection being staphylococcal (purulent) or streptococcal (non-purulent).[6,7]

Prevalence of MRSA influences treatment decisions in SSTI management



34%

European Centre for Disease Prevention and Control. (2021). Surveillance Atlas o Infectious Disease. Available at: https://atlas.ecdc.europa.eu/public/index.aspx?Dataset=27&HealthTopic=4

**FATTORI DI RISCHIO PER MRSA:

- ospedalizzazione nei 3 mesi precedenti
- paziente in struttura di lungodegenza o dializzato
- pregresso intervento chirurgico
- pregressa terapia antibiotica nei 3 mesi precedenti
- pregressa colonizzazione da MRSA
- tossicodipendenza ev
- tatuaggi e piercing

1. **Consider SSTI mimics/other dermopathies**

   Note: Bilateral skin changes are usually **not** cellulitis.

   - **Common:** Venous eczema, dependent rubor in venous insufficiency, superficial thrombophlebitis, irritant or allergic contact dermatitis, deep vein thrombosis, septic arthritis.
   - **Less common:** Erythema nodosum, pyoderma gangrenosum, erythema multiforme, leukocytoclastic vasculitis.

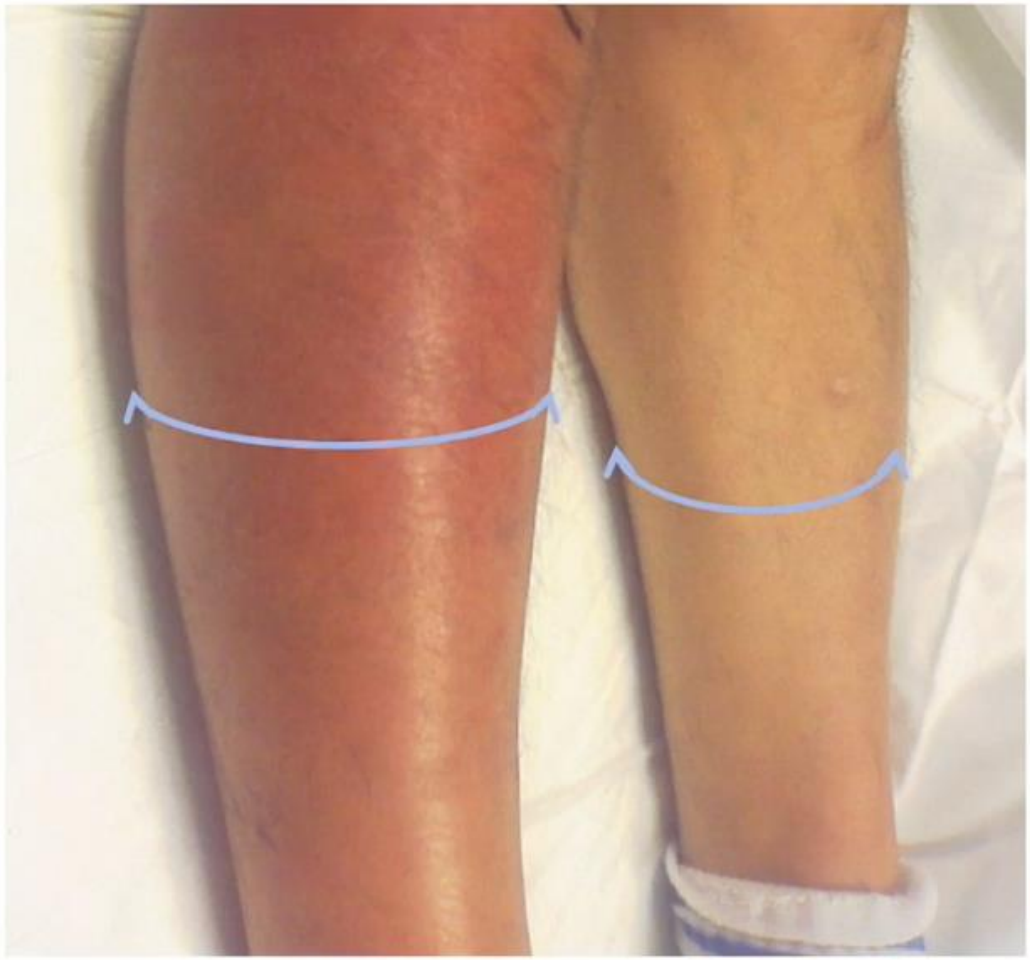
> Narrow spectrum penicillins targeting streptococci and staphylococci (in the case of purulent infection) should be the mainstay of antimicrobial therapy
>
> ---
>
> The natural history of cellulitis is one of slow resolution. Fever and inflammation often persist during the first 72 hours of treatment. Management should include limb elevation and continuing narrow-spectrum antimicrobial therapy alongside treatment of comorbid conditions exacerbating the cellulitis (oedema, diabetes, vascular disease)
>
> ---
>
> Outpatient parenteral antimicrobial therapy (OPAT) (including ambulatory care) is often appropriate in patients requiring intravenous therapy, but presents challenges in terms of antimicrobial agents used. Daily review and early switch to oral therapies is optimal
>
> ---
>
> In patients with recurrent episodes of cellulitis, risk factors should be addressed and consideration given to prophylaxis

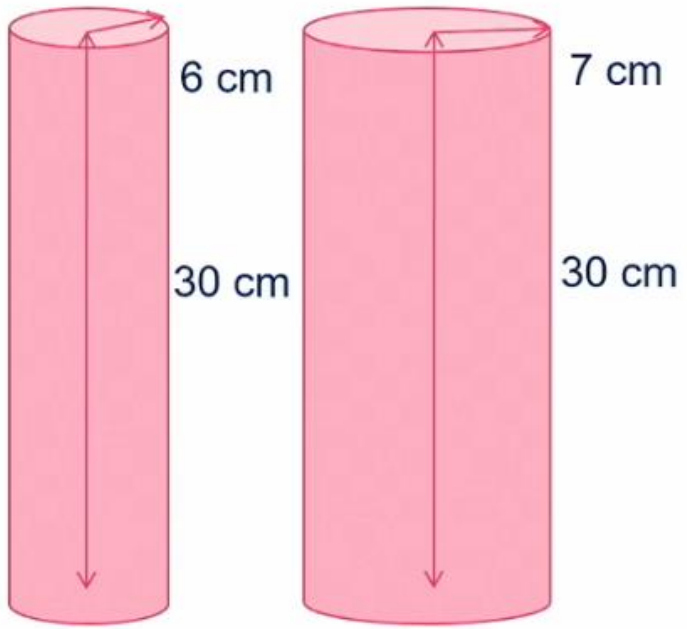
Determinants of the prognosis of complicated skin and soft tissue infections

co-morbidity	local lesion	systemic signs
obesity	edema-extension	fever
diabetes mellitus	deepness	SIRS
peripheral vasculopathy	necrosis	shock

Low antibiotic concentration in soft tissue

Modified from: Eron, L.J. et al (2003). Managing skin and soft tissue infections: expert panel recommendations on key decision points. The Journal of Antimicrobial Chemotherapy. 52(suppl S1): 3-17.





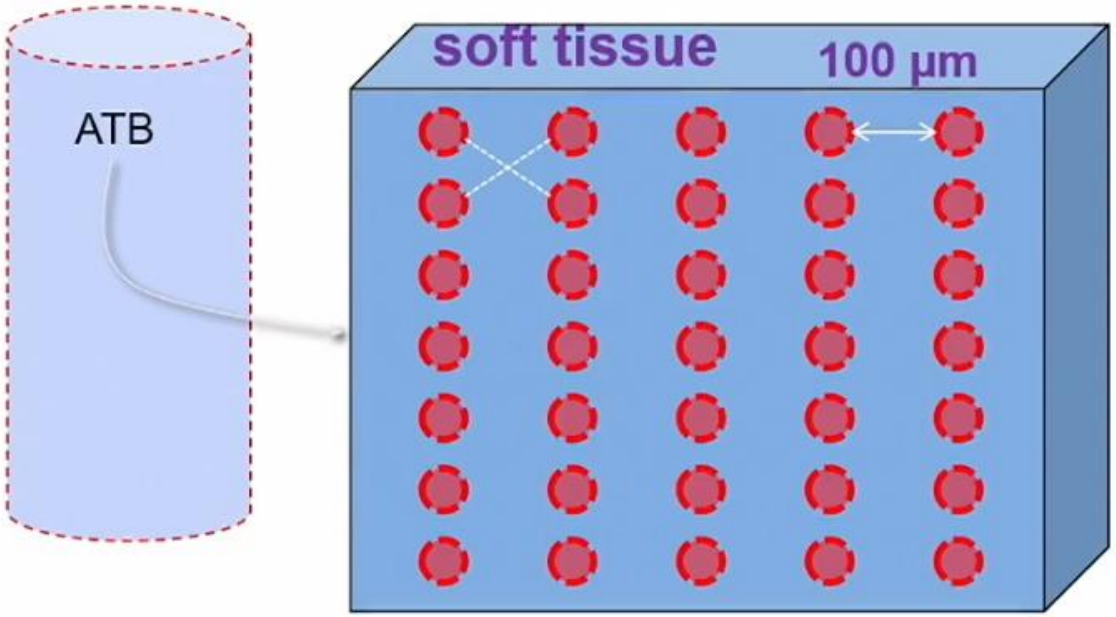
$$V = h \times r^2 \times \pi$$

$V_1 = 3.3\ L$

$V_2 = 4.6\ L$

$\Delta\ 25\%$

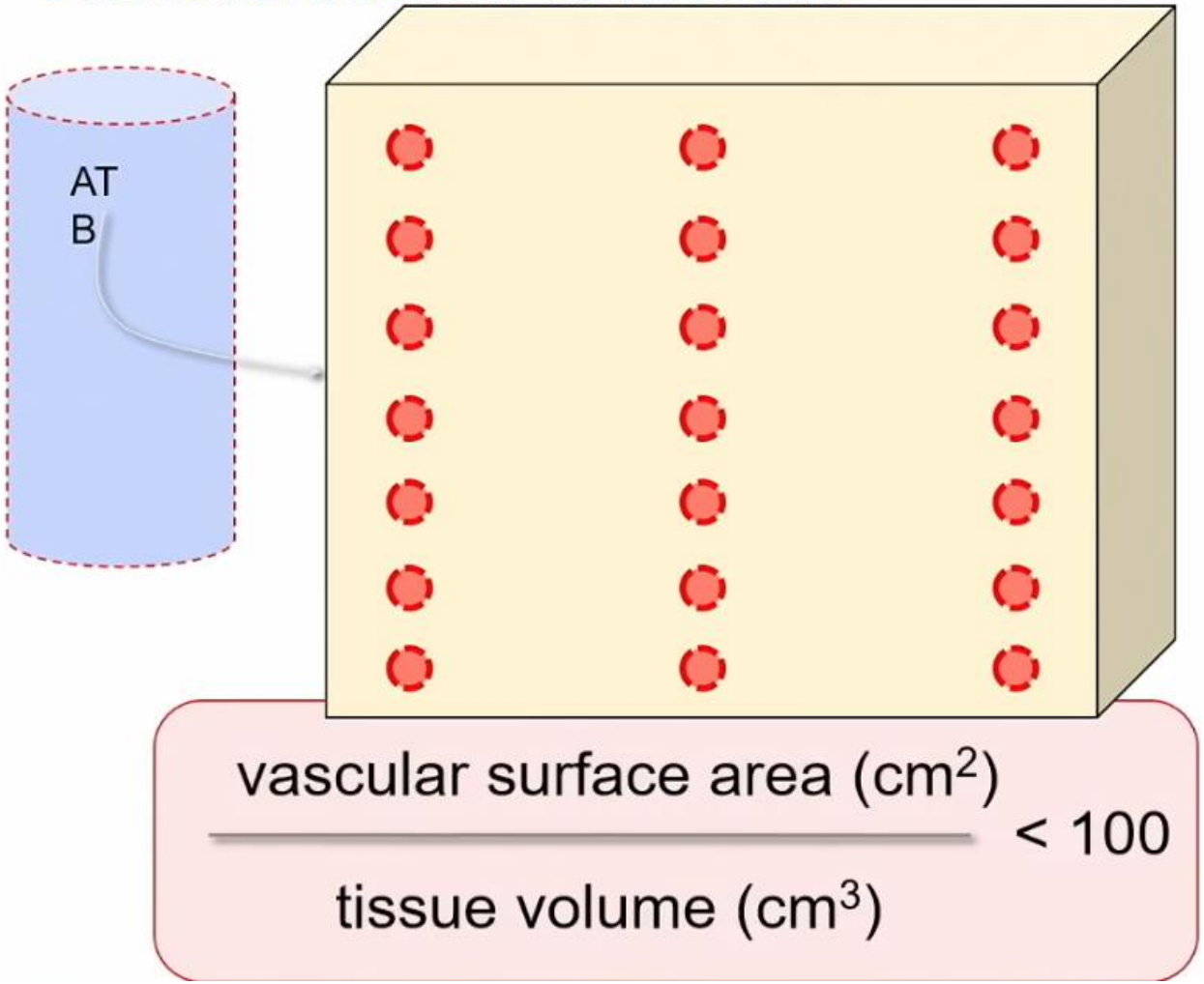
Factors determining the antibiotic concentration in soft tissue



Time needed to achieve the equilibrium with serum concentration is <u>< 15 minutes</u>

$$\frac{\text{vascular surface area } (cm^2)}{\text{tissue volume } (cm^3)} > 100$$

Factors determining the antibiotic concentration in soft tissue



Time needed to achieve the equilibrium with serum concentration is > hours/days

OPAT treatment for ABSSSI

Treatment

OPAT first line: Ceftriaxone 2g IV and review daily (Note: not for in-patient use)

Alternative if patient has severe anaphylaxis or other life-threatening penicillin or beta-lactam allergy or *C. difficile* concern (including episode in previous 3 months)

Daptomycin IV 4-6mg/kg and review daily
See page 2 for notes on daptomycin dosing, some OPAT services may use Teicoplanin (Note: not for in-patient use).

If daily IV administration is not possible for logistical reasons *eg* geographically remote, care home resident, people who inject drugs, or with alcohol dependency, or a significant mental health morbidity or a history of deliberate self-harm.
IV dalbavancin 1g once and review on day 7, or sooner if required. Discuss with pharmacy for patients with extremes of weight (Note: not for in-patient use)

*CRITERI DI ELEGGIBILITA' A LONG ACTING:

- individui con necessità di assistenza per assunzione della terapia
- tossicodipendente attivo e/o in trattamento con metadone
- senza fissa dimora
- migrante senza assistenza sanitaria
- pregresso fallimento antibiotico domiciliare
- condizioni di non fattibilità SOC: deficit di accessi venosi periferici, fallimento terapie precedenti, impossibilità di ospedalizzazione

Delafloxacin

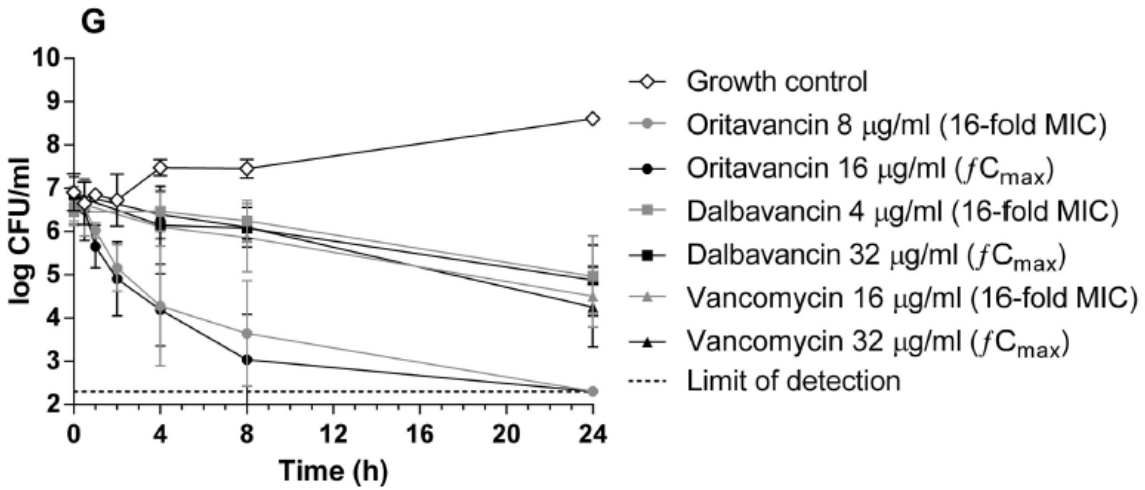
Delafloxacin is a new-generation anionic fluoroquinolone that has good Gram positive coverage: **MRSA**, MSSA, CONS (S. haemolyticus, S. lugdunensis), Streptococcus spp. (S. pyogenes, S. agalactiae, S. anginosus group), Enterococcus faecalis; Gram-negative activity: E. coli, K. pneumoniae, E. cloacae and **P. aeruginosa**.

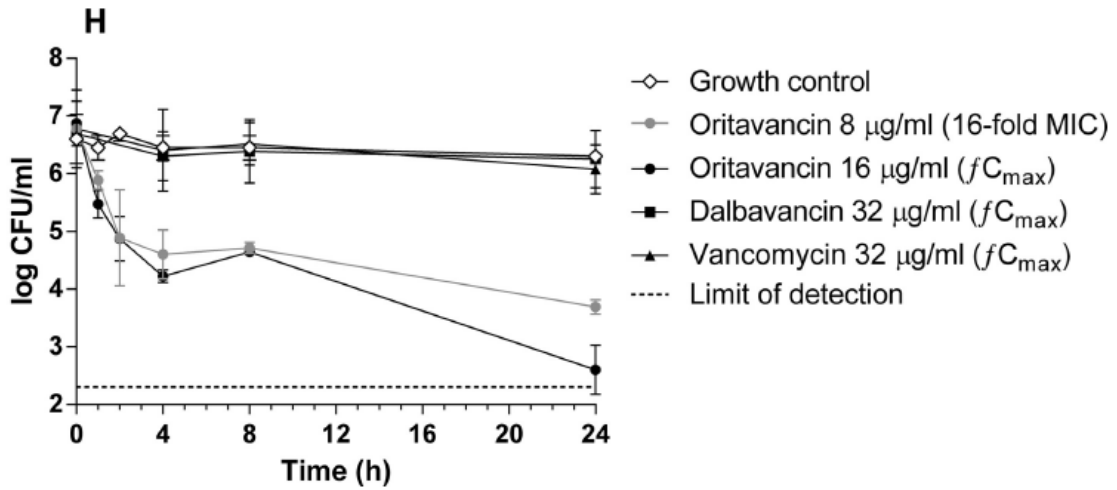
It has received its FDA approval for SSTIs in June 2017 based on two double-blind randomized controlled trials (RCTs) PROCEED 1 and 2, wherein delafloxacin showed noninferiority to vancomycin as well as aztreonam for cSSTI treatment

Drug name	Drug class	Date of FDA approval for SSTIs	Mechanism of action	Type of activity	Half-life (h) - Oral bioavailability (%)	Formulations	Doses, frequency and duration	Excretion	Doses adjustments not required for	References
Delafloxacin (Baxdela)	New-generation anionic fluoroquinolone	June 2017	Inhibits both bacterial topoisomerase IV and DNA gyrase (topoisomerase II) enzymes Possesses enhanced bactericidal activity because of ability to accumulate in bacteria	Bactericidal	8 - 58.8	Oral IV	Orally: 450 mg IV: 300 mg over 60 min Every 12 h For 5–14 days	If oral: Faeces: 28% Urine: 65% If IV: Faeces: 48% Urine: 50%	Body weight Hepatic impairment Mild-to-moderate renal impairment	[20]

Ceftaroline (Teflaro) exhibits good activity against MSSA, MRSA and streptococci, including *S. pyogenes* and multidrug-resistant *S. pneumoniae* as well as Gram-negative bacteria such as *Haemophilus influenzae* and *Moraxella catarrhalis* [40]. Ceftaroline has exhibited a low potential for resistance selection *in vitro* for drug-resistant Gram-positive organisms, including MRSA [40]. The AWARE global surveillance programme for bacteria causing SSTIs and lower respiratory infections in Middle East and African countries from 2015 to 2018 did not identify ceftaroline-resistant MRSA [41▪]. It is the only FDA-approved cephalosporin with good activity against MRSA. It received its FDA approval for SSTIs in October 2010 [40] based on two RCTs, CANVAS 1 and 2, wherein ceftaroline was found to be noninferior to vancomycin plus aztreonam when used in hospitalized patients with cSSTIs [42,43]. In addition, the CAP-

Dalbavancina/Oritavancina	Dalbavancina	Oritavancina
Long elimination half life	*346 hrs*	*245 hrs*
Type of killing and activity	Bactericidal, concentration dep	Bactericidal, concentration dep
Combined hydrophilic and lipophilic		
High protein binding	93%	85-90%
Large volume of distribution (optimal tissue penetration)		
Broad antimicrobial spectrum	Strepto MRSA, VISA – VRSA (poor) VRE (VAN B) Gram-pos MDR	Strepto MRSA, VISA - VRSA VRE (**VAN B e VAN A**) Gram-pos MDR
Few drug/drug interactions	No interactions with CP450	**Interaction with CP450** (warfarin, omeprazole)
Optimal safety		
No hepatic adjustment (Child A-B)	**Renal adjustment (CL crea <30)**	No renal adjustment
Infusion	Infusion in 30 min-1 hr	**Infusion in 3 hrs**
Cost	1.414.46 euro 500 mg	**4.243.36 euro** 400 mg





Comparative *In Vitro* Activities of Oritavancin, Dalbavancin, and Vancomycin against Methicillin-Resistant *Staphylococcus aureus* Isolates in a Nondividing State

Adam Belley, David Lalonde Seguin, Francis Arhin, Greg Moeck
The Medicines Company, Ville St-Laurent, Quebec, Canada

In conclusion, the current study demonstrates the bactericidal activity of oritavancin against MRSA and MRSA-hVISA isolates in a nondividing state *in vitro*, conditions in which the antibacterial activities of dalbavancin and vancomycin are diminished. Despite the observed interisolate variability, oritavancin consistently exerted bactericidal activity at pharmacologically relevant exposures. The maintenance of killing by oritavancin against nondividing bacteria is likely linked to its disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and cell death (5). This differential property may be of benefit for infection sites that typically harbor bacteria in the nondividing state.

Dalbavancin: tissue penetration

Site (subject type)	Dose	Measurement method	Mean concentration (mg/L)	Mean AUC			Penetration (% site/plasma) [%]
				Time period (days)	Plasma (mg·h/L)	Site (mg·h/L)	
Skin [35] (human)	1000 mg	LC–MS/MS	–	0–7	10,806	6438	59.6
Epithelial lining fluid [39] (human)	1500 mg	LC–MS/MS	–	0–7	Total: 21,087 Free: 1476	527[a]	35.7
Bone [38] (human)	1000 mg	LC–MS/MS	–	0–14	NR	NR	13.1
Cerebrospinal fluid [37] (rabbit)	20 mg/kg	LSC	24 h: 0.05 µg/g 72 h: BDL	–	–	–	–
Peritoneal dialysate fluid [41] (human)	1500 mg	LC–MS/MS	–	0–14	40,573	2125	5.2

In small non-clinical PK studies, dalbavancin appears to **achieve adequate tissue penetration to skin, bone and joints, lung tissues, and peritoneal space**, resulting in concentrations above the MIC for susceptible Gram-positive pathogens; however, corroborative clinical data are needed for treatment of infections at other sites.

Bone penetration

Dalbavancin

Penetration of 20 mg/kg of IV dalbavancin was studied in noninfected bone and joint tissues of rabbits (Solon et al., 2007). Concentrations were above the MIC for common Gram-positive pathogens when measured 12–336 h after dosing. Concentrations were the highest in bone marrow with a mean of 13.4 μg/mL and reached the lowest in cortical bone with a mean of 4.2 μg/mL. Moderate-to high concentrations were reached in synovial space and surrounding tissues.

Oritavancin

In an *in vivo* study, 21 rabbits were administered 20 mg/kg of oritavancin (Lehoux et al., 2015). C_{max} in tibia, bone matrix, and bone marrow were 38.8, 65.6, and 27 μg/mL, respectively. Calculated AUC in were 1,792.1, 2,779.5, and 5,136.3 g h/g, respectively, which were 1.1, 1.7, and 3.1-fold higher than that in the serum, respectively. Oritavancin concentration in bone remained above the MIC_{90} against *S. aureus* throughout the 168 h study duration.

Dalbavancin: TDM

Three cases of Necrotizing fascitis cause by high-level aminoglycoside-resistant *Enterococcus faecalis,* MRSA, MR-CONS

Antibiotic treatment (combination therapy to cover Gram-pos, Gram-neg, anaerobes): Dalbavancin (1-3 doses) in combination (meropenem, linezolid, clindamycin; vancomycin, clindamycin, piperacillin/tazobactam; vancomycin, clindamycin, piperacillin/tazobactam)

Clinical improvement after 4-7 days: negative blood cultures, 80% procalcitonin reduction

TABLE 2. Dalbavancin Pharmacokinetic Parameters Measured in the Three Patients

Parameters	Patient 1	Patient 2	Patient 3	Reference*
Cmax, mg/L	336.5	242.7	55.1	250–350
AUC, mg × h/L	27,718	19,947	4491	22,000–28,000
Vd, L	4.5	6.2	27.2	6.0–12.0
CL, L/h	0.054	0.075	0.334	0.04–0.06
MIC	0.0125	0.064	0.05	

*From studies in healthy volunteers.
Cmax, peak plasma concentrations; Vd, volume of distribution; CL, clearance.

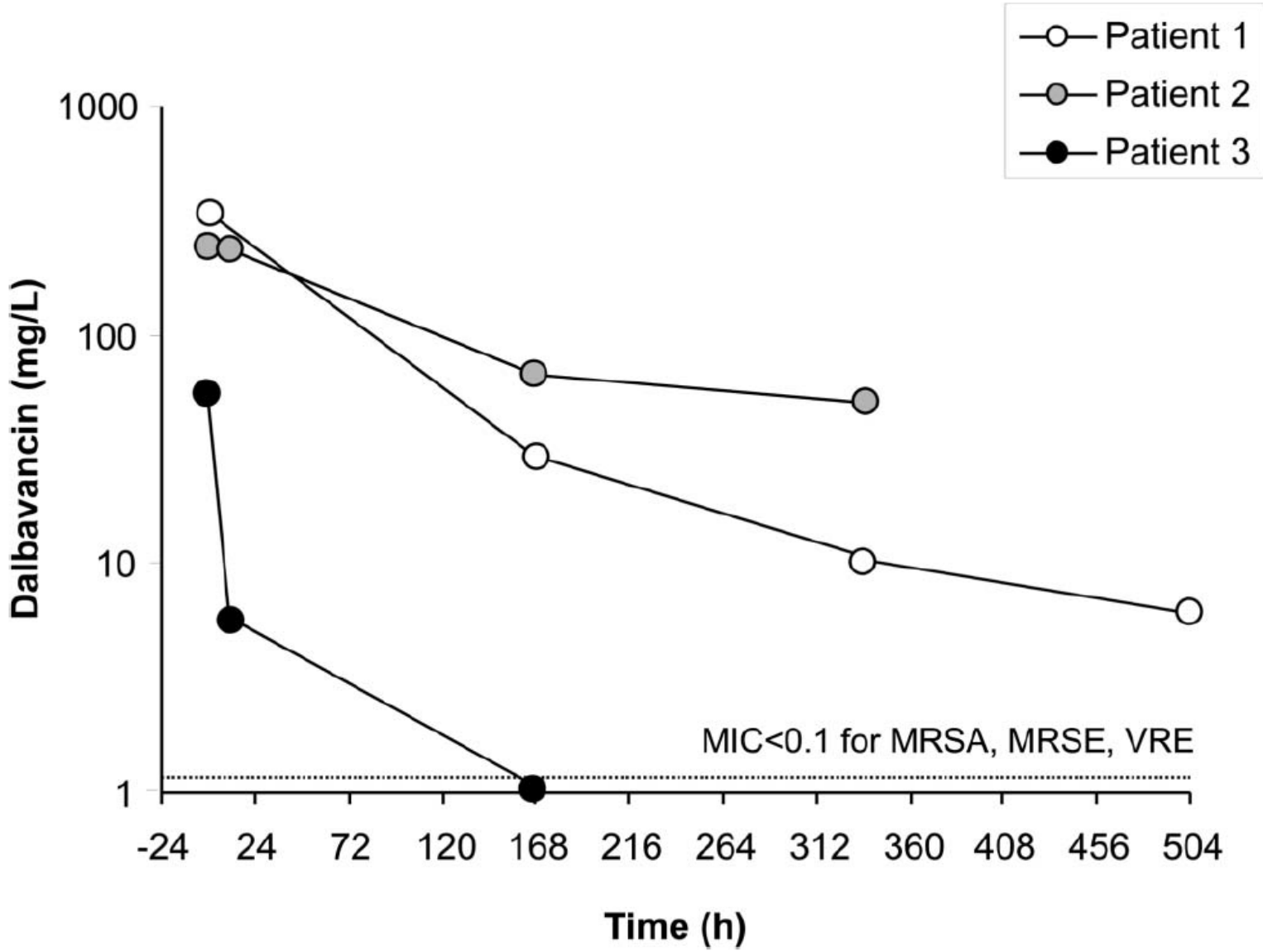


FIGURE 1. Time course of dalbavancin plasma concentrations measured in the 3 ICU patients.

Dalbavancin pharmacokinetics have been extensively characterized in healthy volunteers,[1] whereas data in ICU patients are lacking, despite of their well-known conditions (ie, hypoalbuminemia, hyper-filtration, capillary leaking, etc), eventually resulting in an altered antibiotic disposition.[11] On performing a TDM analysis, we observed that the main dalbavancin pharmacokinetic parameters, in the first 2 ICU patients, were comparable with healthy volunteers (Table 2).[1,12,13] The 2 patients demonstrated an optimal response to dalbavancin-based antibiotic therapy. Conversely, the third ICU patient showed reduced dalbavancin exposure and increased drug clearance.

Dalbavancin is characterized by >90% protein binding. Therefore, in case of severe hypoalbuminemia—like observed in patient 3 at the time of TDM assessment—increasing of unbound drug fraction may result in increased drug glomerular filtration and renal elimination and suboptimal antibiotic exposure.[14] Notably, in a recently published population pharmacokinetic model, serum albumin concentrations significantly correlated with dalbavancin clearance.[15]

Serum albumin concentrations

↓

Dalbavancin clearance

KEY POINTS

- The comorbidity of obesity is common in SSTIs, is expected to increase and demands specific antimicrobial management considerations.
- Pharmacokinetics and pharmacodynamics of antibiotics used for prevention and treatment of SSTIs may be altered in the presence of obesity, thus influencing their optimized dosing in the obese, as compared to normal weight population.
- In the face of scarce available data, the management of obese patients with SSTIs should be guided by combining knowledge regarding the pharmacokinetic and pharmacodynamic characteristics of relevant antimicrobials, clinical evidence and clinical judgment.

Case Report

Clinical failure of dalbavancin for MRSA bacteremia in patient with severe obesity and history of IVDU☆

Hannah Ritchie[a], Abhimanyu Aggarwal[b], Jennifer Schimmel[b], Michael P. Lorenzo[a,*]

Table 1. Pharmacokinetic and pharmacodynamic characteristics of antimicrobials relevant to usage in the obese population

PK/PD characteristic	Description of characteristic	Observed influence of obesity on characteristic
Absorption phase	The interval between the introduction of the antibiotic to the human body and reaching the bloodstream	Similar between obese and nonobese
Plasma protein binding	The proportion of an antimicrobial that is in a bound to plasma proteins vs. unbound form in the blood. Only the unbound form can exert effect	Increased serum concentrations of α1-acid glycoprotein, resulting in facilitated binding of some alkaline antibiotics
Volume of distribution (Vd)	The theoretical volume that would be necessary to contain the total amount of an administered antimicrobial at the same concentration that it is observed in the blood plasma	Plasma volume increases with bodyweight, but the Vd is additionally dependent on the distribution into tissues. Tissue distribution of lipophilic agents is generally increased, but the opposite is not the rule in case of hydrophilic drugs, because about 30% of the adipose tissue is water, which may result in an increased Vd of the latter drugs
Hepatic clearance	A quantitative measure of the amount of antimicrobial eliminated from the bloodstream during its passage through the liver	May be enhanced in obesity, especially through phase II reactions, or reduced when steatohepatitis and fibrosis secondary to obesity affect the liver
Renal clearance	A quantitative measure of the amount of antimicrobial eliminated from the bloodstream during its passage through the kidneys	Usually increased in obese patients, following increased kidney size and increased glomerular filtration rate
Efficacy of time-dependent antibiotics	To maximize efficacy, the goal is to optimize the fraction of time the antibiotic concentration is above the MIC ($fT>MIC$) throughout the body weight spectrum	This parameter is influenced by both clearance and the Vd, which can both be influenced by body size
Efficacy of concentration-dependent antibiotics	To maximize efficacy, the goal is to achieve a ratio of systemic maximum concentration (Cmax) to the minimal inhibitory concentration (MIC) that is comparable throughout the body weight spectrum	This parameter will be mostly related to the relationship of the Vd to body size
Efficacy of antibiotics that dependent on both concentration and time (exposure)	To maximize efficacy, the goal is to optimize the area under the curve (AUC/MIC) throughout the body weight spectrum	This parameter will be most influenced by the relationship of clearance to body size

Dalbavancin as sequential therapy for infective endocarditis due to Gram-positive organisms: a review

T. Fazili[a,*], E. Bansal[a], D. Garner[a], M. Gomez[a], N. Stornelli[b]

Dalbavancin is a parenteral lipoglycopeptide antibiotic derived from teicoplanin, an analogue of vancomycin. It is mainly used for skin and soft tissue infections. The sustained half-life of approximately 14 days makes dalbavancin a novel option for potential use as sequential treatment in infections such as infective endocarditis, which require prolonged antibiotic courses. However, only a few studies have been reported in the literature, and the use of dalbavancin remains limited. This article is a review of the currently available literature using dalbavancin for the treatment of infective endocarditis due to Gram-positive organisms. Almost all patients received dalbavancin as sequential therapy following standard-of-care antibiotics. The overall clinical efficacy of dalbavancin was approximately 90%, and it appeared to be well tolerated.

Table 1. OPAT-GAMES Criteria to Guide Indication of Outpatient Parenteral Antibiotic Treatment for Patients With Infective Endocarditis (Adapted From Pericàs et al. [18])

Inclusion criteria: All patients are potential candidates once the acute critical phase[a] has been overcome, except for those presenting with the following criteria:
Exclusion criteria:
1. Patients with Child B or C liver cirrhosis
2. Severe central nervous system emboli Multiple (>3), large (>2 cm), hemorrhagic, or with fixed neurologic deficits
3. Not drained large spleen or renal abscess
4. Vertebral abscesses requiring neurosurgery
5. Periannular complications or other severe conditions requiring surgery when this is contraindicated[b] Perivalvular abscess, fistula, perforation, pseudoaneurysm, severe pericardial effusion with signs of cardiac tamponade, etc.

6. Severe postsurgical complications

Ischemic stroke, brain hemorrhage, worsening of prior stroke/bleeding, hemodynamic collapse, surgical wound bleeding requiring new surgery, infection of the surgical wound (mediastinitis/osteomyelitis), ventilator-associated pneumonia, acute kidney failure requiring dialysis, cardiac blockade requiring pacemaker, critically ill–associated polyneuropathy

7. Highly difficult-to-treat microorganisms

Those requiring intravenous antibiotic combinations that cannot be administered by means of OPAT or that require strict monitoring of drug levels either in blood or in other fluids owing to their potential toxicity or narrow therapeutic index (eg, methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci also resistant to alternative drugs such as daptomycin and linezolid, multidrug or extensively drug-resistant gram-negative rods, highly penicillin-resistant viridans group streptococci, fungi other than *Candida* spp.)

8. Active intravenous drug users

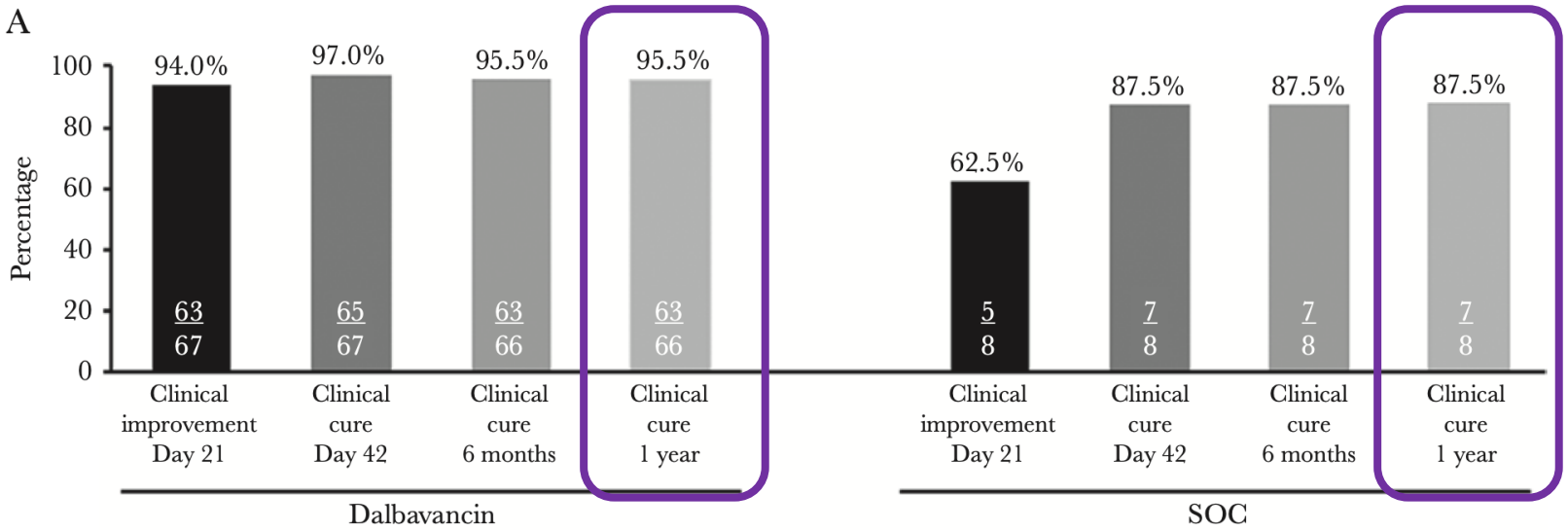
Dalbavancin for the Treatment of Osteomyelitis in Adult Patients: A Randomized Clinical Trial of Efficacy and Safety

Rappo Uet al, OFID 2018; 8(2):ofab721

Effectiveness of Dalbavancin Compared With Standard of Care for the Treatment of Osteomyelitis: A Real-world Analysis

Cain AR et al, OFID 2021; 9(2):ofab589

Results: A total of 132 patients received dalbavancin (n = 42) or SoC (n = 90). Baseline characteristics, including rates of surgical intervention, were similar between the 2 treatment groups. Treatment failure was similar between those who received dalbavancin and SoC (21.4% vs 23.3%; *P* = .81). Patients who received dalbavancin had a shorter hospital LOS (5.2 days vs 7.2 days; *P* = .01). There was no difference in the rates of infection-related readmission between the dalbavancin and the SoC group (31% vs 31.1%; *P* = .99). There were numerically fewer adverse events in the dalbavancin group compared with the SoC group (21.4% vs 36.7%; *P* = .08). Peripherally inserted central catheter line-related complications were reported in 17.8% of patients in the SoC group.



OFID. 2019 Nov; 6(11): ofz479.

Table 4. Clinical and Microbiologic Outcomes in 438 Evaluable Patients[a]

Outcome	Single Dose, no./No. (%)	Multiple Doses (Interrupted by ≤14 d), no./No. (%)	Overall, no./No. (%)
Clinical success[b]	356/406 (87.7)	30/32 (93.8)	386/438 (88.1)
Clinical cure	262/406 (64.5)	20/32 (62.5)	282/438 (64.4)
Clinical improvement	94/406 (23.2)	10/32 (31.3)	104/438 (23.7)
Clinical failure	50/406 (12.3)	2/32 (6.2)	52/438 (11.9)
Microbiological eradication[c]	28/37 (75.7)	1/37 (2.7)	29/37 (78.4)
Microbiological persistence[c]	7/37 (18.9)	1/37 (2.7)	8/37 (21.6)

Treatment of osteoarticular, cardiovascular, intravascular-catheter-related and other complicated infections with dalbavancin and oritavancin: A systematic review

International Journal of Antimicrobial Agents 56 (2020) 106069

Results: In total, 38 studies (18 randomized controlled trials/case series and 20 case reports) met the inclusion criteria. The most common off-label indication for oritavancin and dalbavancin was osteoarticular infection, with a median success rate of 73% [interquartile range (IQR) 58–85%] among the 14 studies with more than one patient. The success rate for endocarditis and cardiac-device-related infections was 68% (IQR 56–86%) among nine studies, and the success rate for catheter-related bloodstream infection was 75% (IQR 59–90%) among seven studies. Among the 16 studies of almost 700 patients receiving laLGPs, there were 98 reports of adverse events, resulting in 13% of treated patients reporting an event.

Conclusions: This review provides evidence that laLGPs are safe and efficacious for osteoarticular, cardiovascular, intravascular-catheter-related and other complicated infections. Further research is needed to confirm these results.

Utilizzo di dalbavancina nel trattamento soppressivo cronico di infezioni osteo-articolari e protesiche da Gram-positivi: proposta di armonizzazione della raccolta dati e monitoraggio farmacocinetico.

Il progressivo incremento di pazienti con plurime comorbilità, dovute all'invecchiamento della popolazione e al miglioramento dell'aspettativa di vita, ha ampliato il bacino di utenti con infezioni life-threatening non candidabili a procedure chirurgiche atte a ottenere adeguato source control, per cui la terapia antibiotica soppressiva cronica rimane l'unica alternativa.
Dalbavancina potrebbe rappresentare una valida alternativa nel trattamento cronico di infezioni da batteri Gram-positivi, rispetto a terapie endovenose e orali, grazie alla sua lunga emivita e a una migliore tollerabilità.

In ambito infettivologico, la therapeutic drug monitoring (TDM) è diventata un imprescindibile strumento per valutare l'esposizione al farmaco e ottimizzare la gestione clinica del paziente. Nello specifico, la TDM della dalbavancina può guidare lo schema di somministrazione del farmaco, personalizzandolo in base alle caratteristiche del singolo paziente. Alla luce di recenti evidenze, diversi sono gli schemi posologici raccomandati, uno di questi prevede due somministrazioni di farmaco al dosaggio di 1500 mg a distanza di una settimana[1]. A partire dalla seconda dose, in caso di necessità, è possibile con la TDM stimare la tempistica delle somministrazioni successive al fine di mantenere delle concentrazioni di farmaco ≥ 8.04 mg/L (valore associato ad una probabilità ≥90% di raggiungimento dell'obiettivo farmacodinamica ottimale di fAUC24h/MIC > 111,1 contro *Staphylococcus aureus*)[2].

Gli studi a oggi disponibili, riguardanti l'utilizzo di dalbavancina per indicazioni off-label come infezione osteo-articolari, sono caratterizzati da pochi dati relativi alla TDM e da una mancanza di informazioni sull'utilizzo dell'antibiotico in cronico.

Obiettivo di questa collaborazione è quello di armonizzare l'utilizzo della TDM e della raccolta dati sull'utilizzo di dalbavancina nella terapia soppressiva cronica, in modo da approfondire la conoscenza di tale molecola.

Proposta schema di prelievi per la TDM della dalbavancina:

Giorno 1:	Somministrazione I dose dalbavancina (1500 mg)
Giorno 8:	Prelievo basale per TDM dalbavancina (Cmin) Somministrazione II dose dalbavancina (1500 mg) 30-60 minuti dopo il termine dell'infusione: prelievo di picco (Cmax)
Dopo 14 +/- 5 giorni:	Prelievo per TDM dalbavancina
III° dose:	Prelievo basale per TDM dalbavancina (Cmin) Somministrazione III dose dalbavancina (1500 mg) 30-60 minuti dopo il termine dell'infusione: prelievo di picco (Cmax)
Dopo 14 +/- 5 giorni*:	Prelievo per TDM dalbavancina

***NB: Schema da ripetere fino a termine terapia**
Timing III dose e successive stabilito dal farmacologo (dott. Cattaneo) in base a TDM

GRAZIE per l'ATTENZIONE

- http://www.e-opat.com/
- https://www.futurelearn.com/courses/outpatient-patenteral-antimicrobial-therapy
- Linee guida IDSA - UK - Scotland

2018 Infectious Diseases Society of America Clinical Practice Guideline for the Management of Outpatient Parenteral Antimicrobial Therapy[a]

Anne H. Norris,[1] Nabin K. Shrestha,[2] Genève M. Allison,[3] Sara C. Keller,[4] Kavita P. Bhavan,[5] John J. Zurlo,[6] Adam L. Hersh,[7] Lisa A. Gorski,[8] John A. Bosso,[9] Mobeen H. Rathore,[10] Antonio Arrieta,[11] Russell M. Petrak,[12] Akshay Shah,[13] Richard B. Brown,[14] Shandra L. Knight,[15] and Craig A. Umscheid[16]