Nuove terapie antibiotiche nel trattamento delle SSTI …e non solo!

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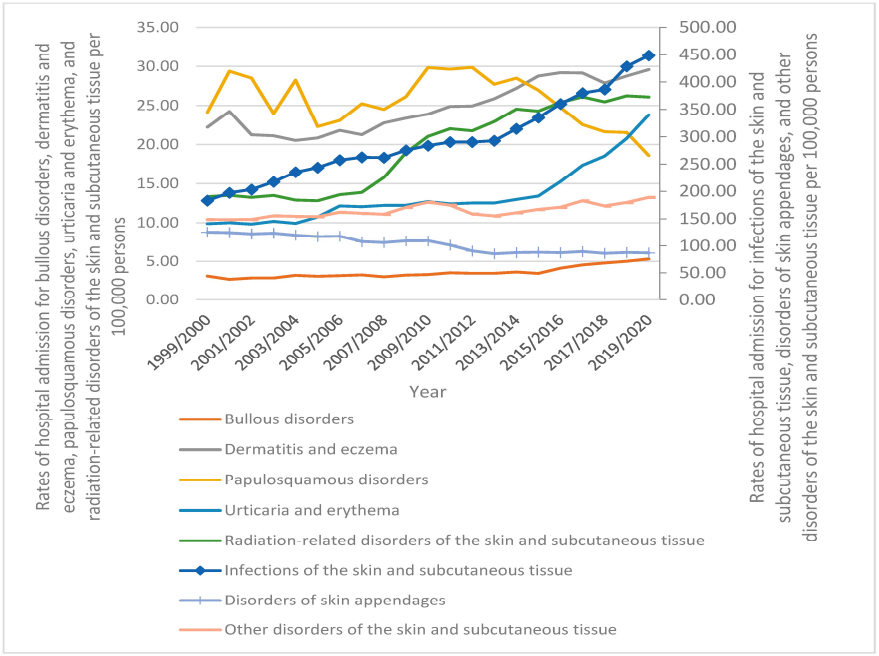
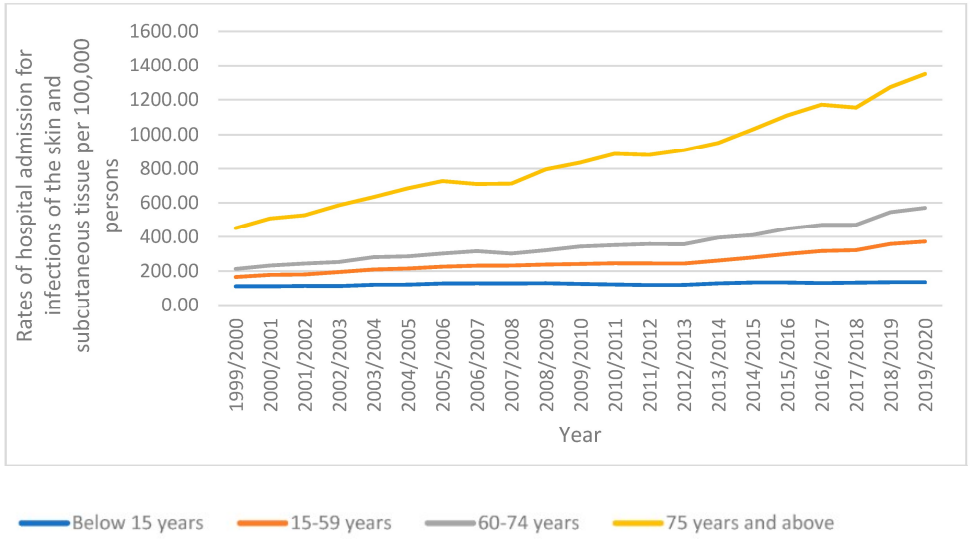
Admissions with SSTI are increasing



145% increase

Older age

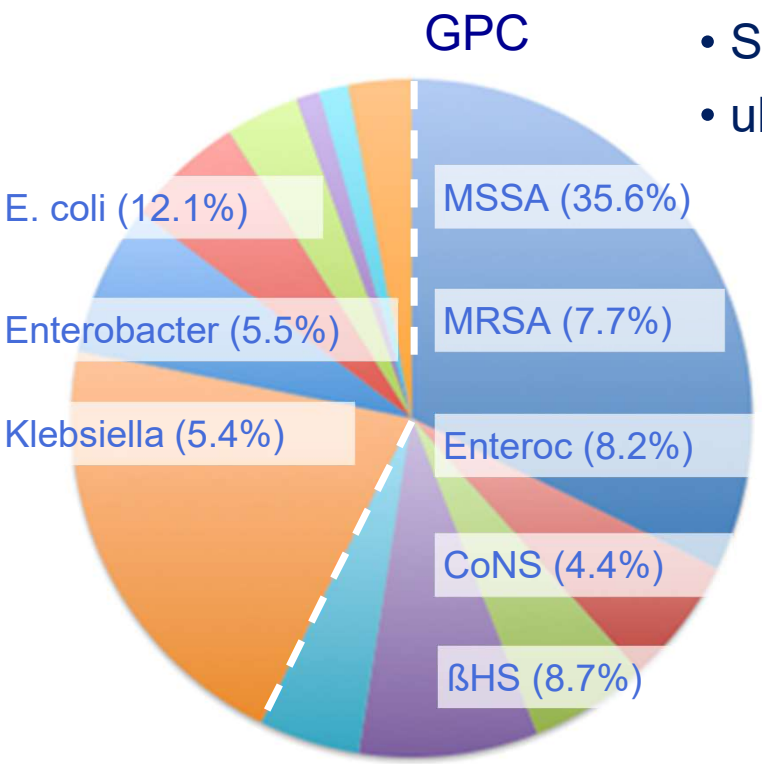


Samannodi, M. (2022). Hospital Admissions Related to Infections and Disorders of the Skin and Subcutaneous Tissue in England and Wales. Healthcare. 10(10):2028.

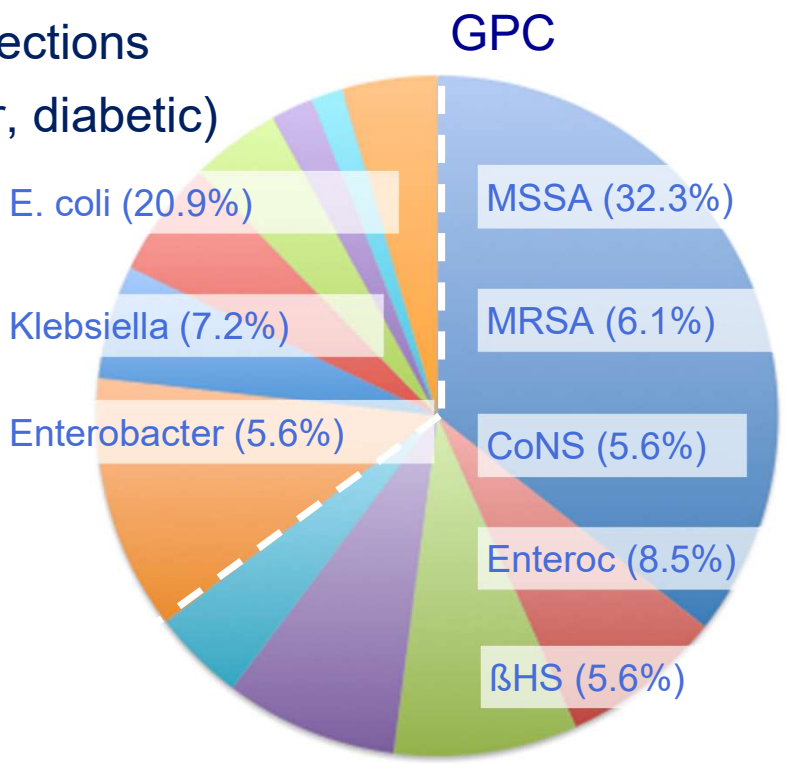
Bacterial isolates from patients hospitalised with skin and soft tissue infections in Europe

- Surgical site infections
- ulcers (vascular, diabetic)

Western Europe (3250 isolates)



Eastern Europe (839 isolates)

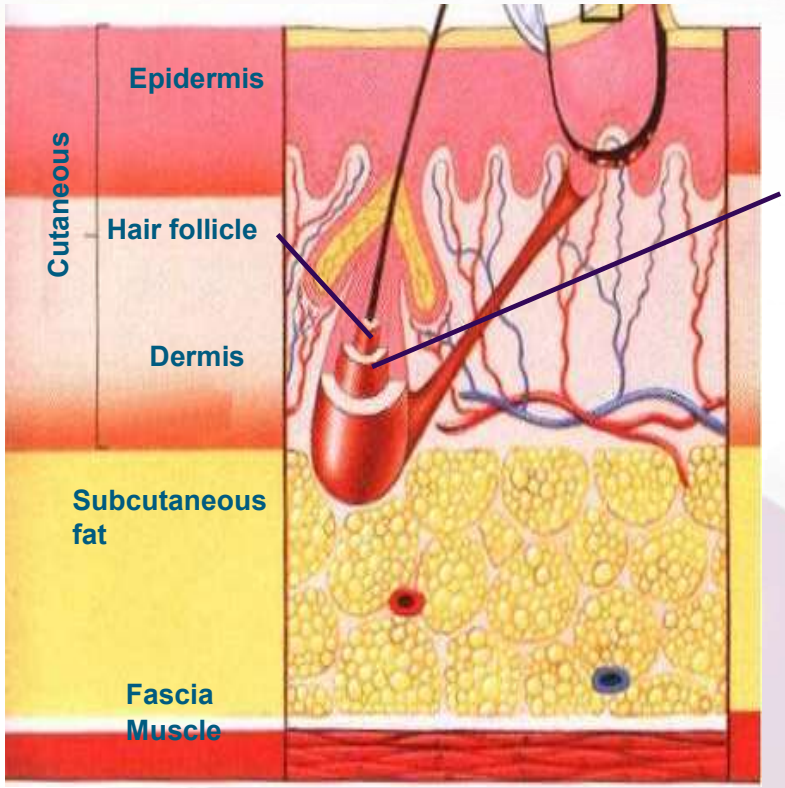


Sader, H. et al (2019). Frequency and antimicrobial susceptibility of bacterial isolates from patients hospitalised with community-acquired skin and skin-structure infection in Europe, Asia and Latin America. Journal of Global Antimicrobial Resistance. 17: 103-108.

Complicated skin and soft tissue infections (cSSTIs)

SSTIs are classified as <u>complicated</u> if either:

- **deeper tissues than subcutaneous**
- **necrotizing infection**
- **require surgical intervention more complex than simple incision/drainage.**
- **significant co-morbidities that complicates the response to treatment**



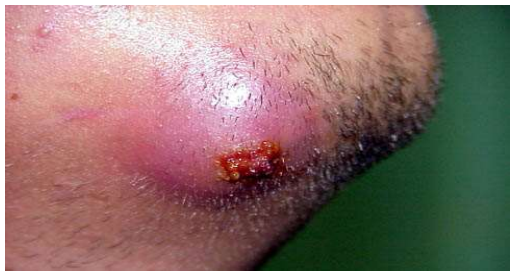
- May AK, et al. Surg Infect 2009; 10: 467–99;
- Garau J et al. Clin Microbiol Infect 2012;18(Suppl 3):24
- May AK et al. Surg Infect (Larchmt) 2009;10:467–499;
- Moet GJ et al. Diagn Microbiol Infect Dis. 2007;57:7–13

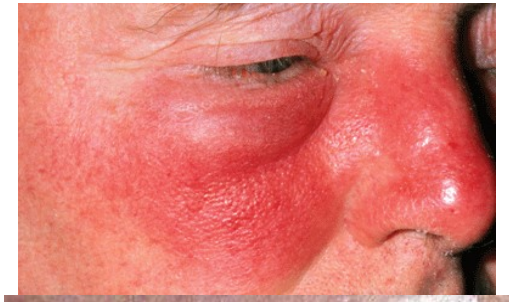
- IDSA 2005
- US SIS 2012
- US- FDA

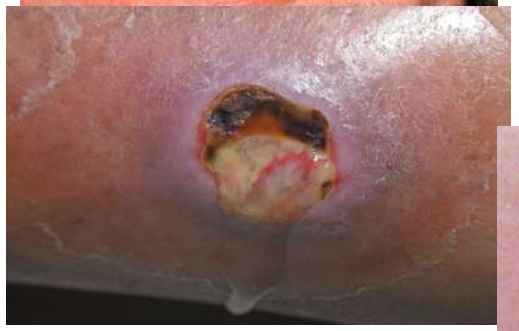
SSTIs - Definitions

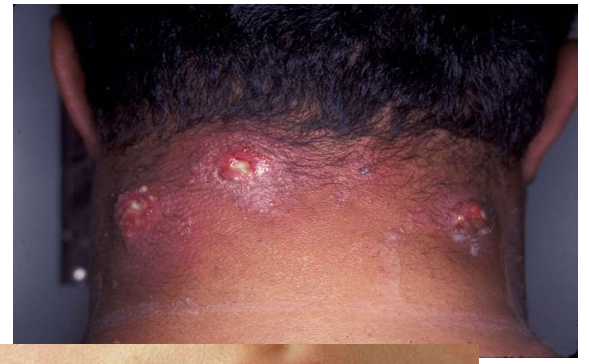
Uncomplicated :

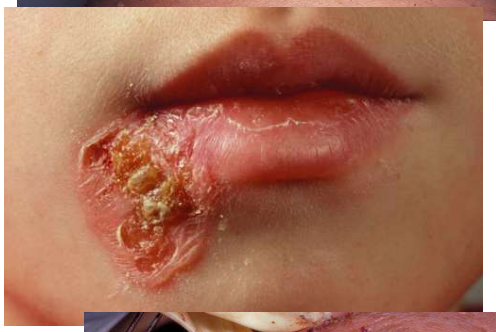
- **foruncle / carbuncle**
- **impetigo**
- **erysipela**
- **cellulitis**
- **ecthyma**
- **simple skin abscess** (< 5 cm)

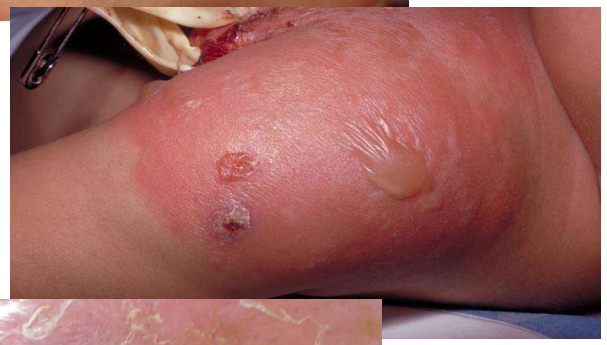


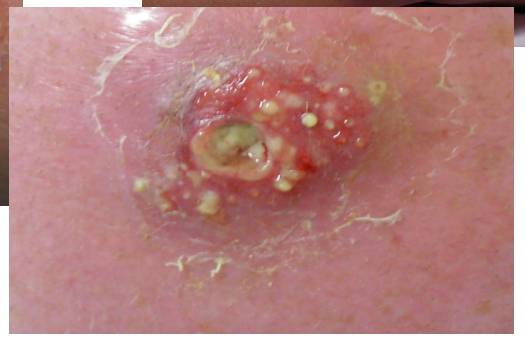






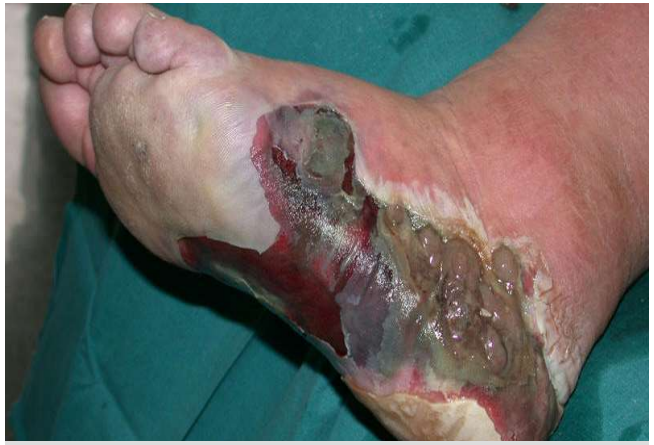






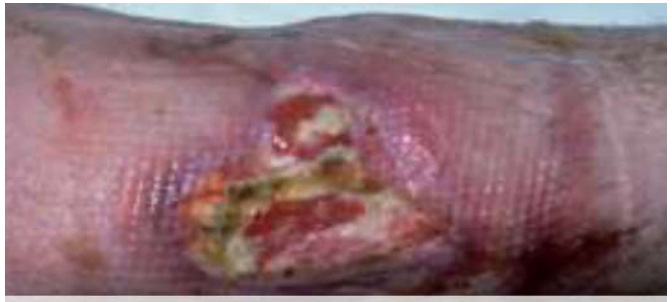
SSTIs - Definitions

Complicated :



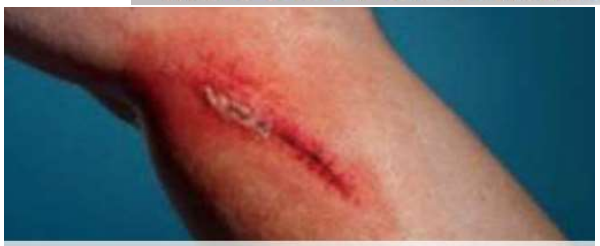
Diabetic Foot Infection

Infected ischaemic ulcer

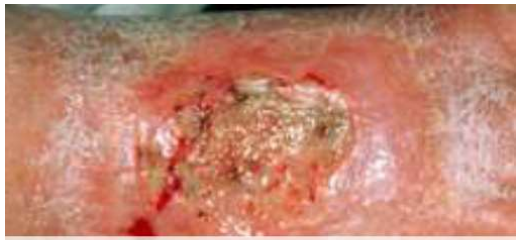


Infected decubitis ulcer

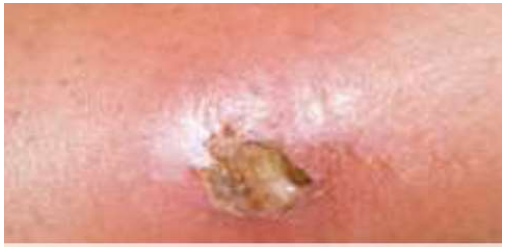
Infected venous stasis ulcer[a]



Surgical site infection[a]



Trauma infection



Bite-related infection

SSTIs (Skin & Soft Tissues Infections) vs. ABSSSIs (Acute Bacterial Skin & Skin-Structures Infections)

FDA 1998	FDA 2013
SSTI Skin and Soft Tissue Infections	**ABSSSI** Acute Bacterial Skin and Skin Structure Infections
uSSTI: cellulite, lesioni impetiginizzate, foruncolo, ascesso minore **cSSTI**: ulcere infette, ustioni infette, ascessi maggiori	-cellulite/erisipela -infezione di ferita -ascessi maggiori
Nessuna definizione di dimensioni minime, ascesso «maggiore» non definito	**Almeno 75 cm^2**, in base a questa dimensione distinzione ascesso «maggiore» da ascesso «minore»
Non necessaria contemporanea presenza di segni sistemici di infezione	Non necessaria contemporanea presenza di febbre (per non sottostimare pazienti anziani, diabetici, immunocompromessi)
Endpoint primario di trattamento: **guarigione alla visita a 7-14** giorni dopo il termine della terapia	Endpoint primario di trattamento: **Almeno il 20% di riduzione della dimensione della lesione a 48-72 h** rispetto al baseline

VANTAGGI:
-definizione dimensionale della lesione
-omogeneità del tipo di lesioni
-standardizzazione dei trial clinici
-definizione di criteri di inclusione ed esclusione
-definizione precoce endpoint primario di trattamento

SVANTAGGI:
-esclusione del piede diabetico
-esclusione della fascite necrotizzante
-minore applicabilità alla pratica clinica
-misurazioni soggettive
-profondità non considerata

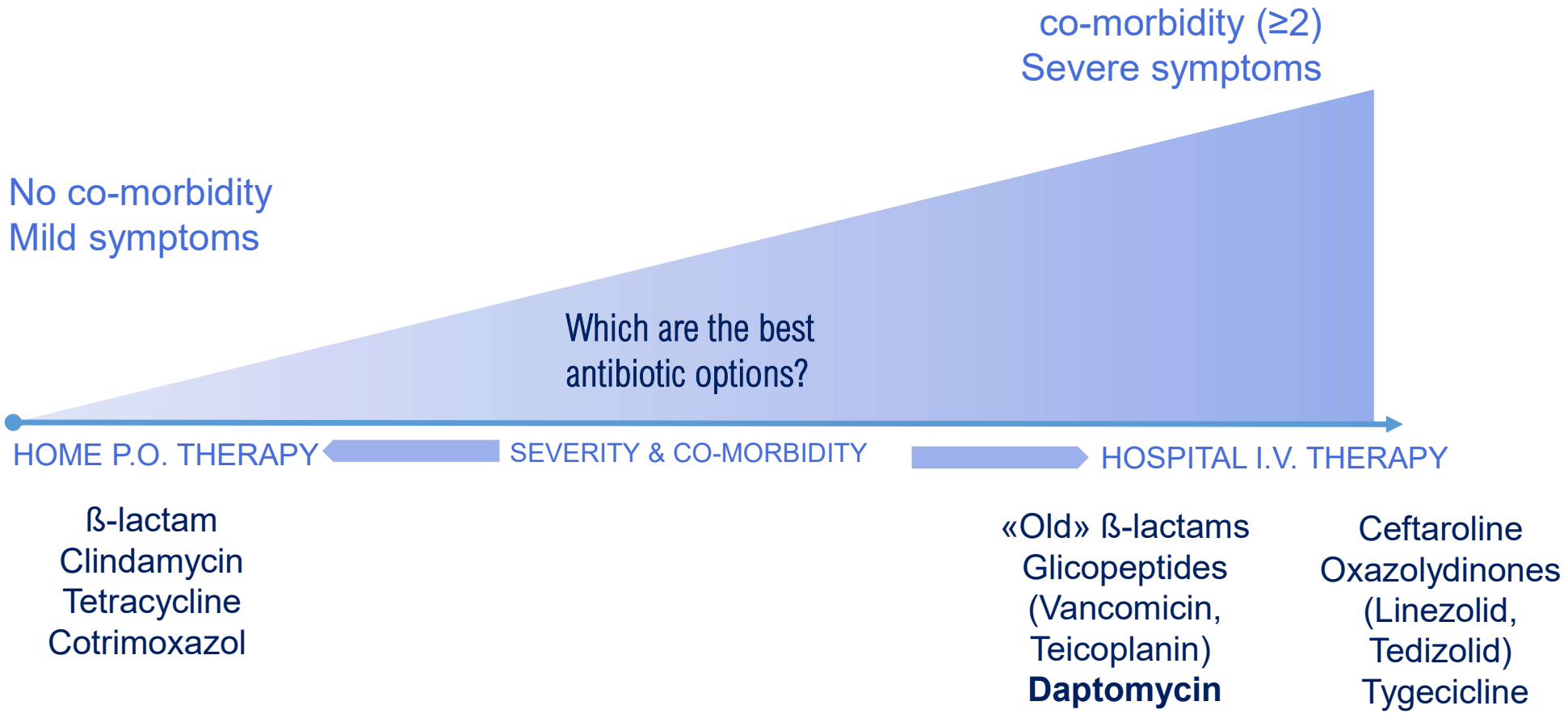
Falcone M. et al Acute bacterial skin and skin structure infections in internal medicine wards: old and new drugs. Intern Emerg Med (2016) 11:637–648

Determinants of the prognosis of skin and soft tissue infections

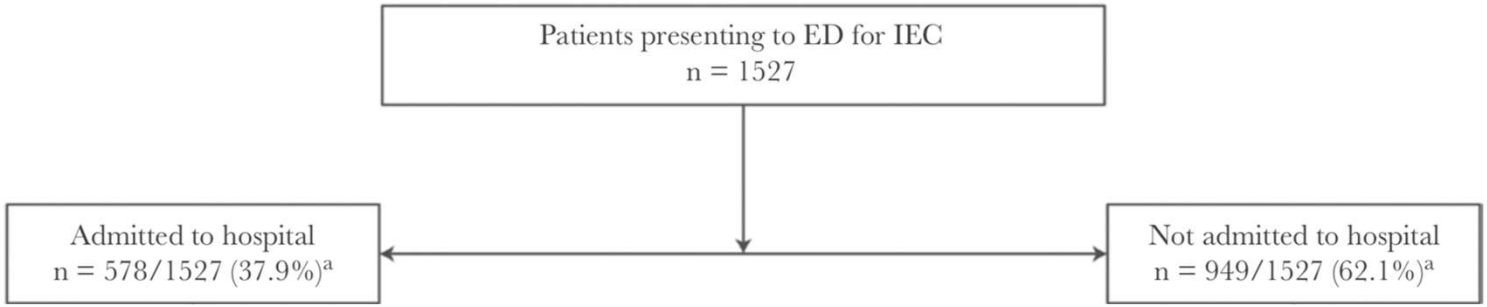
co-morbidity	local lesion	systemic signs
obesity	edema-extension	fever
diabetes mellitus	deepness	SIRS
peripheral vasculopathy	necrosis	shock

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.

Potential antibiotic strategies for patients with SSTI



Impact of outpatient vs inpatient ABSSSI treatment



Older
Cellulitis vs abscess
Higher BMI
Higher CCI
More SIRS

ED, emergency department. IEC, initial episode of care, BMI, body mass index. SIRS, sistemic inflammatory response sindrome. CCI, Chalrson comorbidity index

Bookstaver, P.B. et al (2018). Impact of Outpatient vs Inpatient ABSSSI Treatment on Outcomes: A Retrospective Observational Analysis of Medical Charts Across US Emergency Departments. Open Forum Infectious Diseases. 5(7): ofy109.

Identification of potentially avoidable hospitals admissions through a retrospective database analysis

	Group 1 (n = 8636)	Group 2 (n = 30,123)	Group 3 (n = 572,108)
CCI = 0, n/N (%)	2,668/3,183 (83.8%)	6,240/16,405 (38.0%)	54,421/477,692 (11.4%)
CCI = 1, n/N (%)	1,502/1,627 (92.3%)	3,067/4,491 (68.3%)	20,834/57,580 (36.2%)
CCI = 2, n/N (%)	1,281/1,343 (95.4%)	2,564/3,062 (83.7%)	11,152/18,792 (59.3%)
CCI ≥3, n/N (%)	2,408/2,483 (97.0%)	5,746/6,165 (93.2%)	13,860/18,044 (76.8%)
Total, n/N (%)	7,859/8,636 (91.0%)	17,617/30,123 (58.5%)	100,267/572,108 (17.5%)

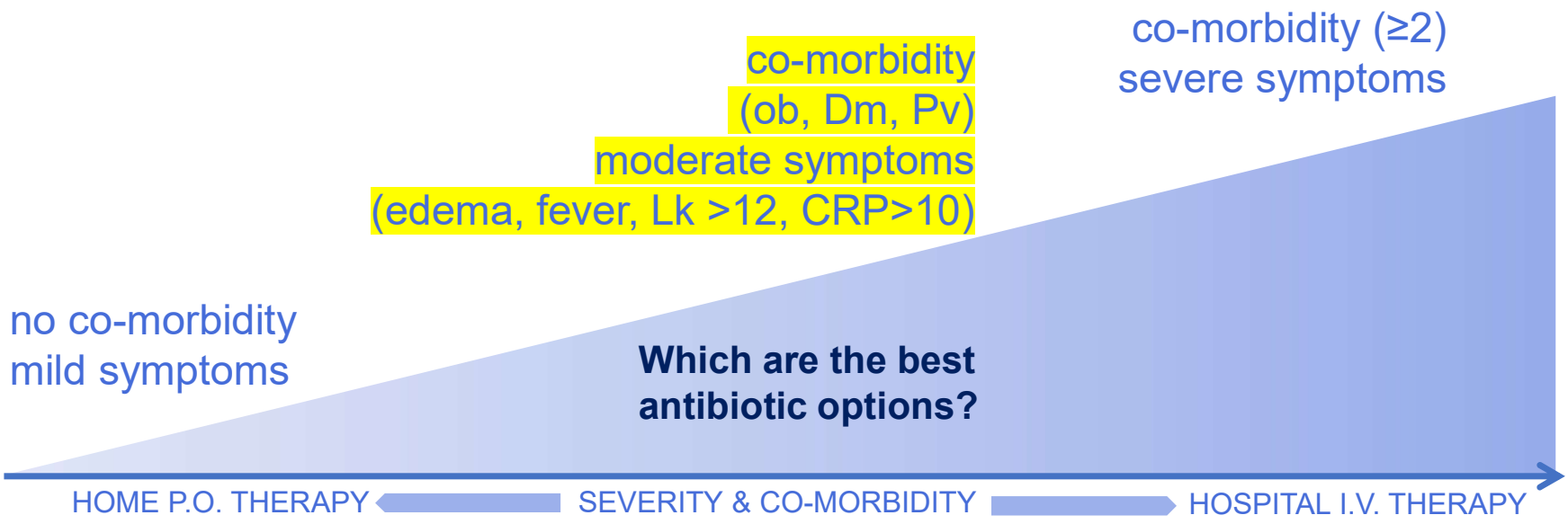
Group 1: Patients with life-threatening conditions.
Group 2: Patients with systemic symptoms but no life-threatening conditions.
Group 3: Patients without life-threatening conditions or systemic symptoms.
Abbreviations: CCI = Charlson Comorbidity Index; SSTI = Skin and soft tissue infection.

610.867 patients with SSTI from 520 US hospitals, 125.743 (20.6%) required hospital admission.

Admitted for intravenous antibiotic treatment but without strict criteria for being hospitalized

Lodise, T.P. et al (2015). Hospital admission patterns in adult patients with skin and soft tissue infections: Identification of potentially avoidable hospital admissions through a retrospective database analysis. Hospital Practice (1995). 43(3): 137-143.

Potential antibiotic strategies for patients with SSTI



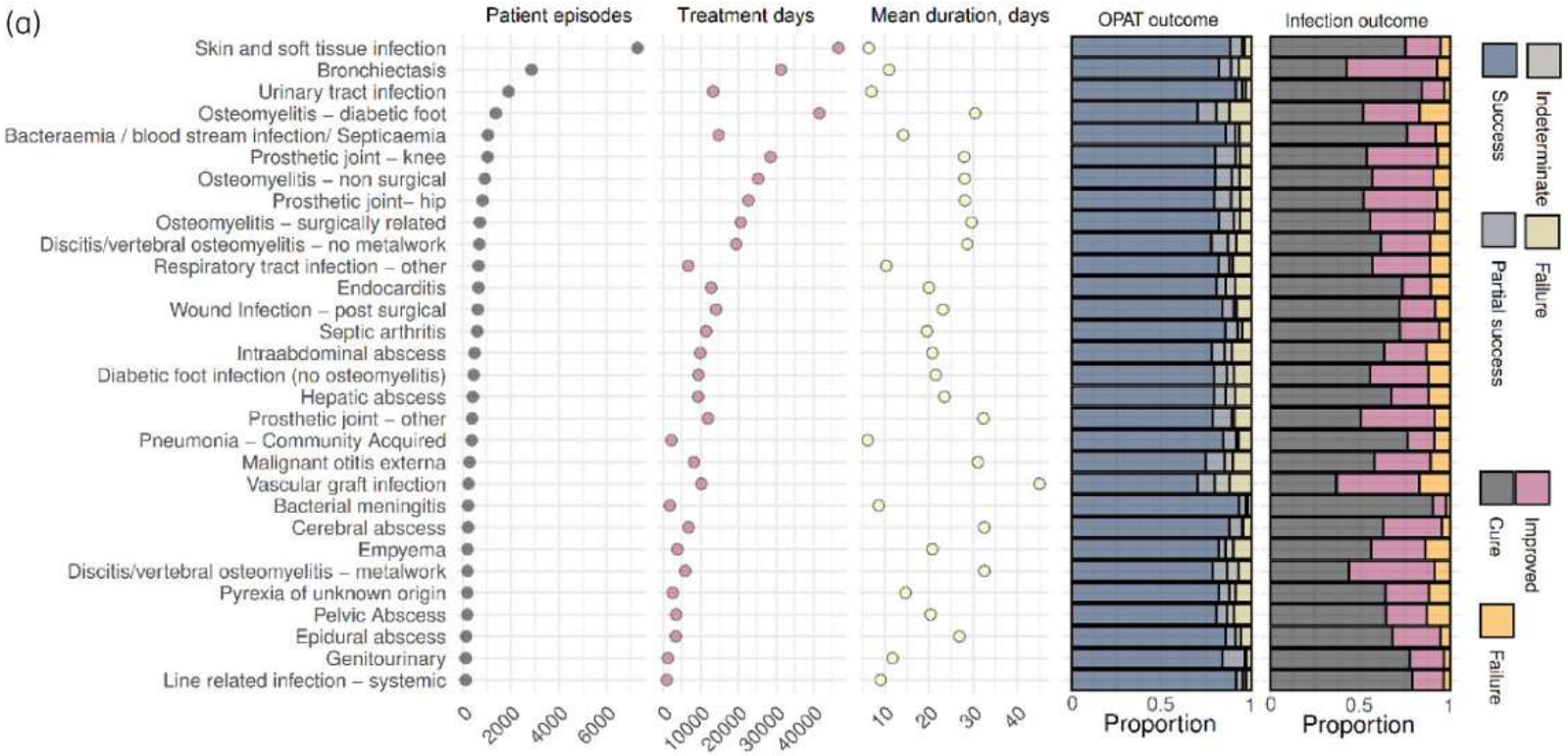
ß-lactam
Clindamycin
Tetracycline
Cotrimoxazol

Possible home-based I.V. Tx

«Old» ß-lactams
Glicopeptides
(Vancomicin,
Teicoplanin)
Daptomycin

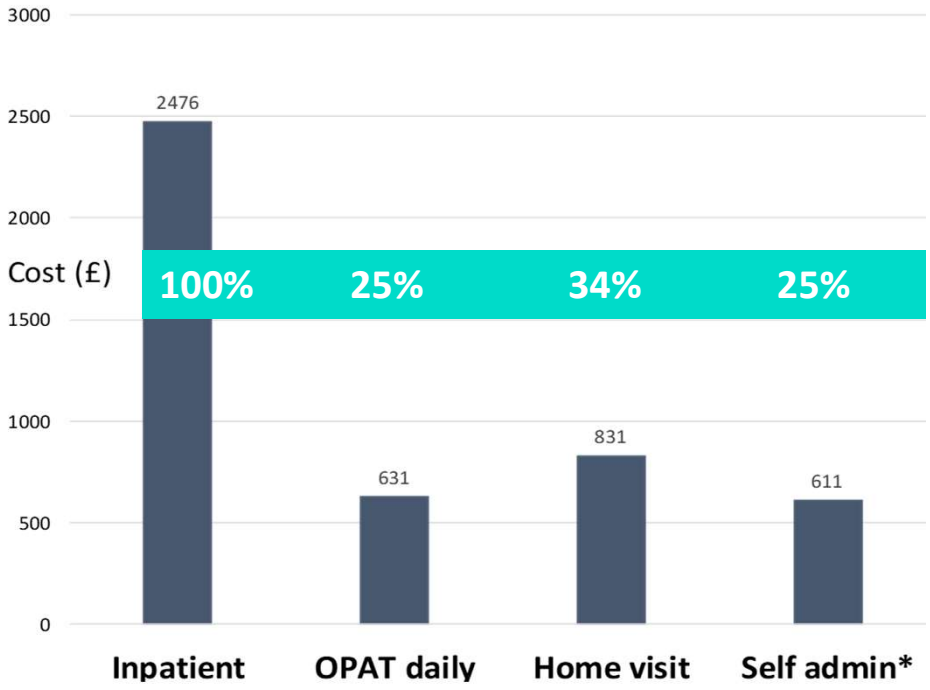
Ceftaroline
Oxazolydinones
(Linezolid,
Tedizolid)
Tygecicline

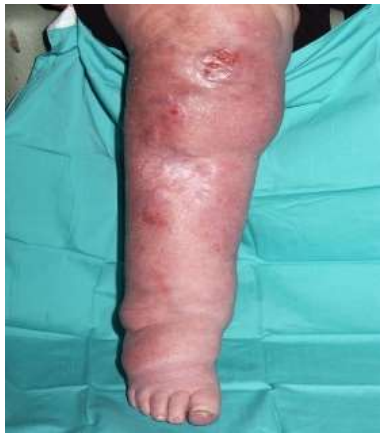
Skin and soft tissue infections are the commonest indication for OPAT (Outpatient Parenteral Antibiotic Therapy)

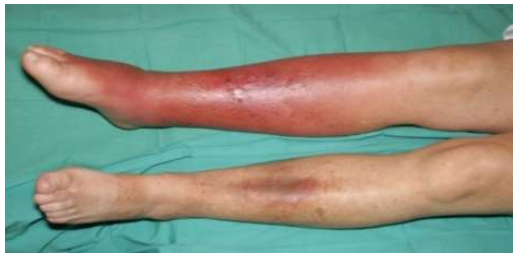


Gilchrist, M. et al. on behalf of BSAC OPAT Initiative (2022). Outpatient parenteral antimicrobial therapy (OPAT) in the UK: findings from the BSAC National Outcomes Registry (2015–19), Journal of Antimicrobial Chemotherapy, 77(5): 1481–1490. Available at: https://doi.org/10.1093/jac/dkac047

Cost of traditional OPAT models of care vs inpatient stay for short-term skin and soft tissue infections





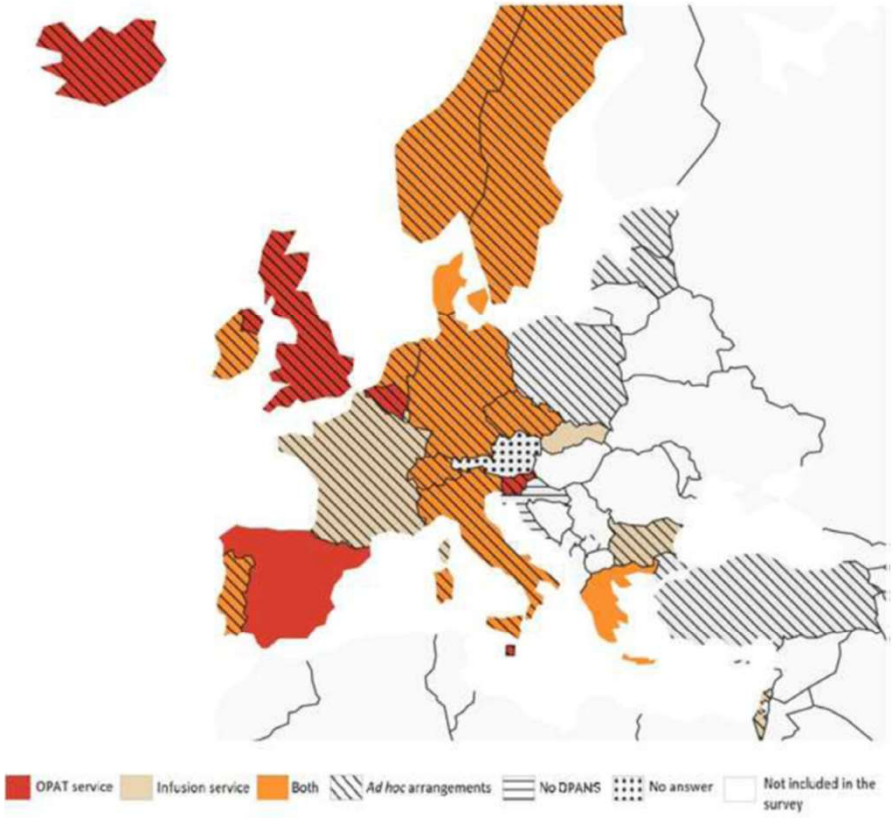


Dimitrova, M. Gilchrist, M. & Seaton, R. A. (2021). Outpatient parenteral antimicrobial therapy (OPAT) versus inpatient care in the UK: a health economic assessment for six key diagnoses. BMJ Open. 11(9):e049733.

OPAT (Outpatient Parenteral Antibiotic Therapy) in Europe: variable distribution, organisation and governance

28 European countries surveyed
17 (61%) countries have OPAT

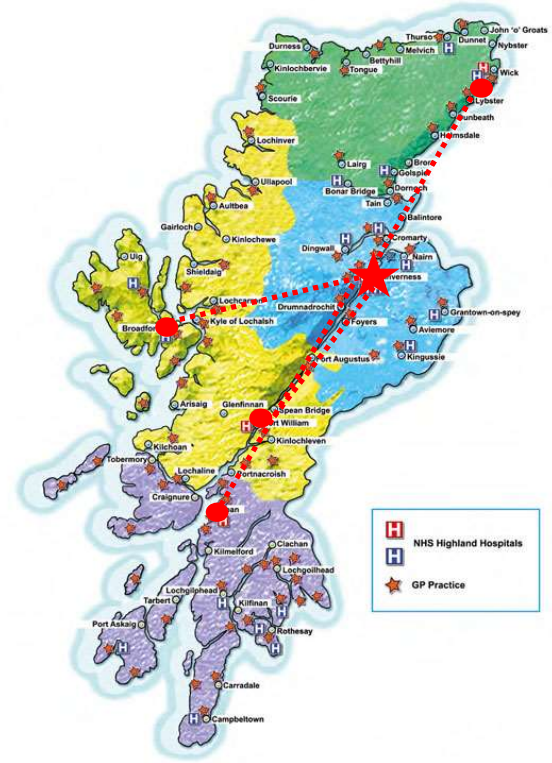
- 5 (UK, Denmark, Ireland, Spain, Netherlands) - national OPAT guidelines/good practices recommendations
- 12 - OPAT services to adults and children
- 6 - specifically trained staff
- 4 - no structured services but practiced OP IV Rx via *ad hoc* arrangements



Emilie, C. et al. (2022). Survey of delivery of parenteral antimicrobials in non-inpatient settings across Europe. International Journal of Antimicrobial Agents. 59(4):106559.

Tackling OPAT Equity in remote and rural Scotland

- **Sparsely populated, large land mass**
- **Hub and spoke model management rural general and other hospitals**
- Ensuring good clinical governance
- Improved access in those areas to appropriate care and management
- Utilise national SAPG pathway
- Support and leadership for teams
- Nursing education on management and review of patients

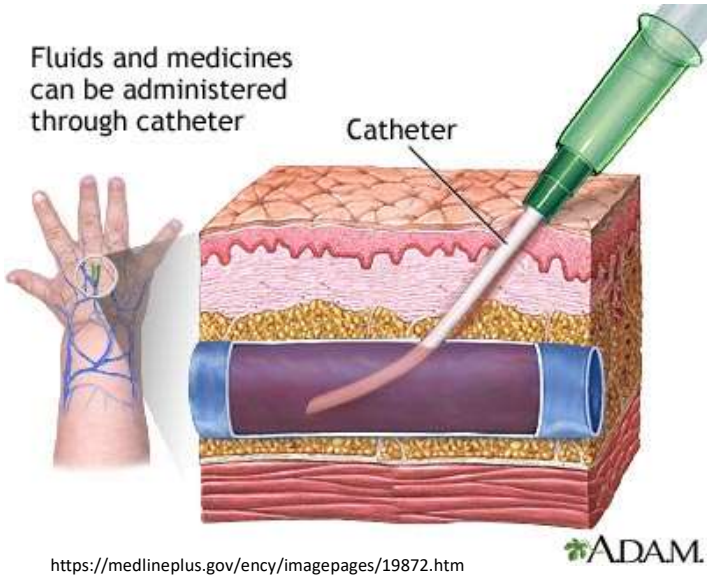


MacDonald, A. & Beadles, W. (2022) 'Developing an OPAT Skin and Soft Tissue Pathway Across NHS Highland' [PowerPoint]. Available at: https://opat-conference.com/wp-content/uploads/2022/09/BSAC-OPAT-conference-Glasgow-Alison.pdf (Accessed: 20 March 2023)

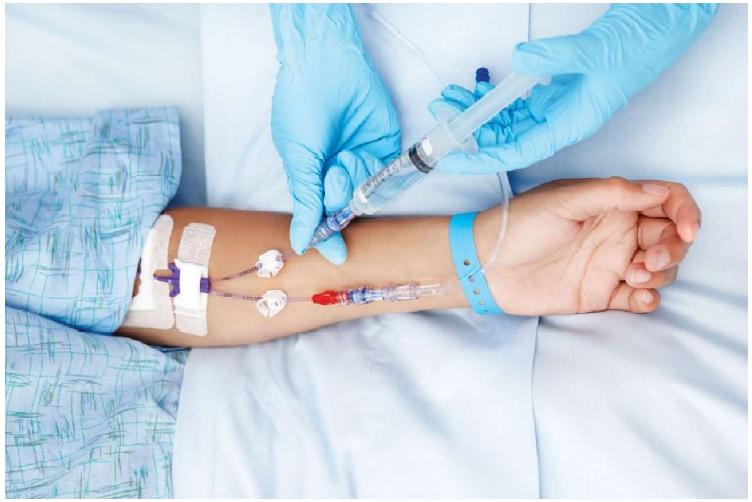
STUDY RATIONALE

Poliseno M, Bavaro DF, …, Carbonara S. Clin Drug Investig. 2021 May;41(5):437-448.

- **a daily IV Tx, delivered either in-hospital or in an outpatient setting, implies additional issues, including:**
  - ✓ the need for long-lasting **intravenous line**
  - ✓ risk of several **local and systemic complications** (e.g., thrombophlebitis, cellulitis, bacteremia, endocarditis, sepsis; often Health-care associated) [5],
  - ✓ **patient discomfort** & reduced **quality of life** [6], especially if has to be "restricted" in hospital or in a long-care facility
  - ✓ **impaired adherence** to therapy



https://medlineplus.gov/ency/imagepages/19872.htm



https://www.google.com/search?q=intravenous+line&rlz=1C1ASRM_enIT942IT942&source=lnms&tbm=isch&sa=X&ved=2ahUKEwimkqSgh8P2AhV1gP0HHXzpDK8Q_AUoAXoECAIQAw&biw=911&bih=572&dpr=1.5#imgrc=rvTEie4RwfpElM

Long-acting lipoglicopeptides:

- **Active vs. most Gram+ bacteria**
  - ✓ **including several drug-resistant strain**
  - ✓ **Rapid bactericidal activity**
  - ✓ **Anti-biofilm activity**
- **Very long half-life ➔ long-lasting activity ➔ Single dose (ABSSIs)**

  Possible advantages:
  - ✓ useful in the **patient requiring parenteral therapy** but who **does not otherwise need to be hospitalized**

    ➔ **early hospital discharge** or **avoidance of hospitalization**
  - ✓ **avoidance of long-term intravascular catheter** access & related **complications**
  - ✓ **Improved adherence to therapy** (esp. in difficult-to-treat subjects)
  - ✓ **Saving of working days**
  - ✓ **improved quality of life**

Individual level:

🡻Morbidity/mortality

🡹 QoL

Society level:

🡻 Organizational burden

🡻 Costs

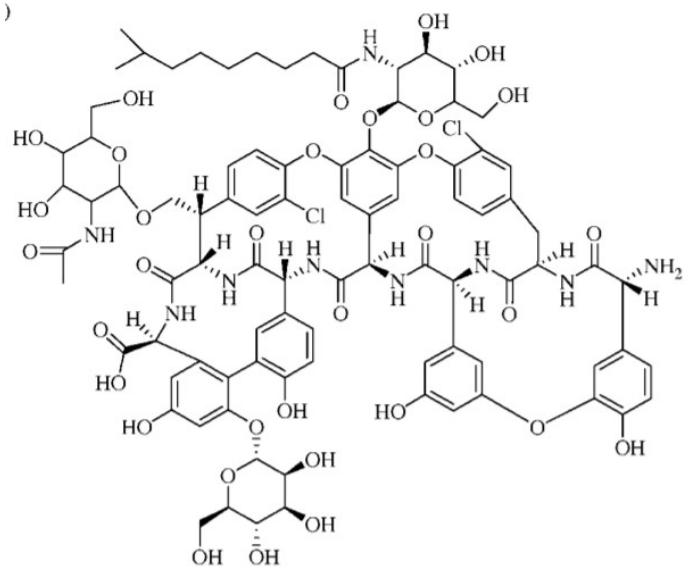
LIPOGLICOPEPTIDI: proprietà farmacocinetiche

Table III. Pharmacokinetic parameters for lipoglycopeptides at usual human doses.[23,57–60]

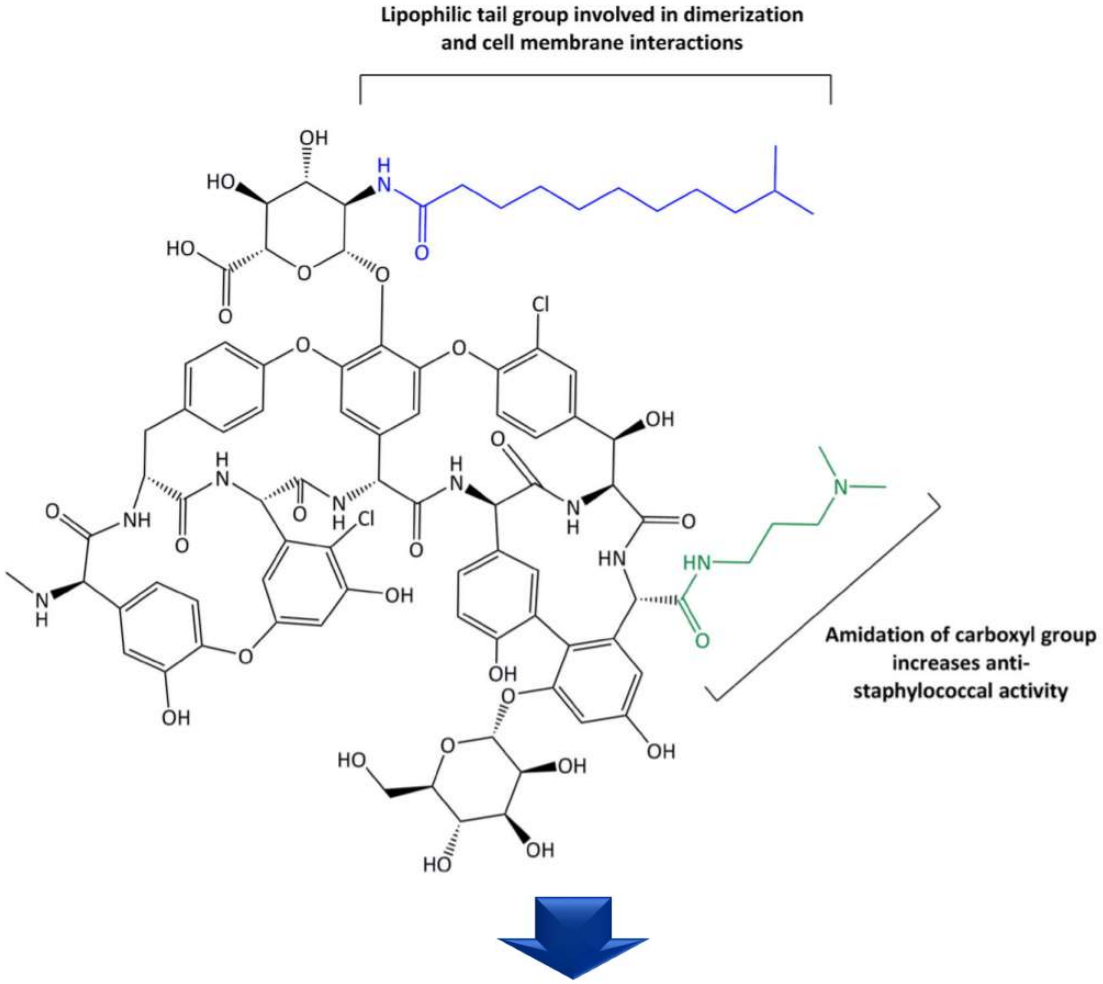
Parameter	Telavancin (10 mg/kg)	Oritavancin (1200 mg)	Dalbavancin (1 g on day 1, 500 mg on day 8)	Vancomycin (15 mg/kg BID)
C_{max}, mg/L	88–101	138	312	20–50
AUC, mg · h/L	776–858	1110	27,103	260
V_d, L/kg	0.1–0.12	1	0.11	0.3
Protein binding, %	93	86	90	10–55
Terminal half-life, h	7–9	245 (10 gg)	187 (8 gg)	4–8

Klinker KP, Borgert SJ. Beyond Vancomycin: The Tail of the Lipoglycopeptides. Clin Ther. 2015 Dec 1;37(12):2619-36

Dalbavancina



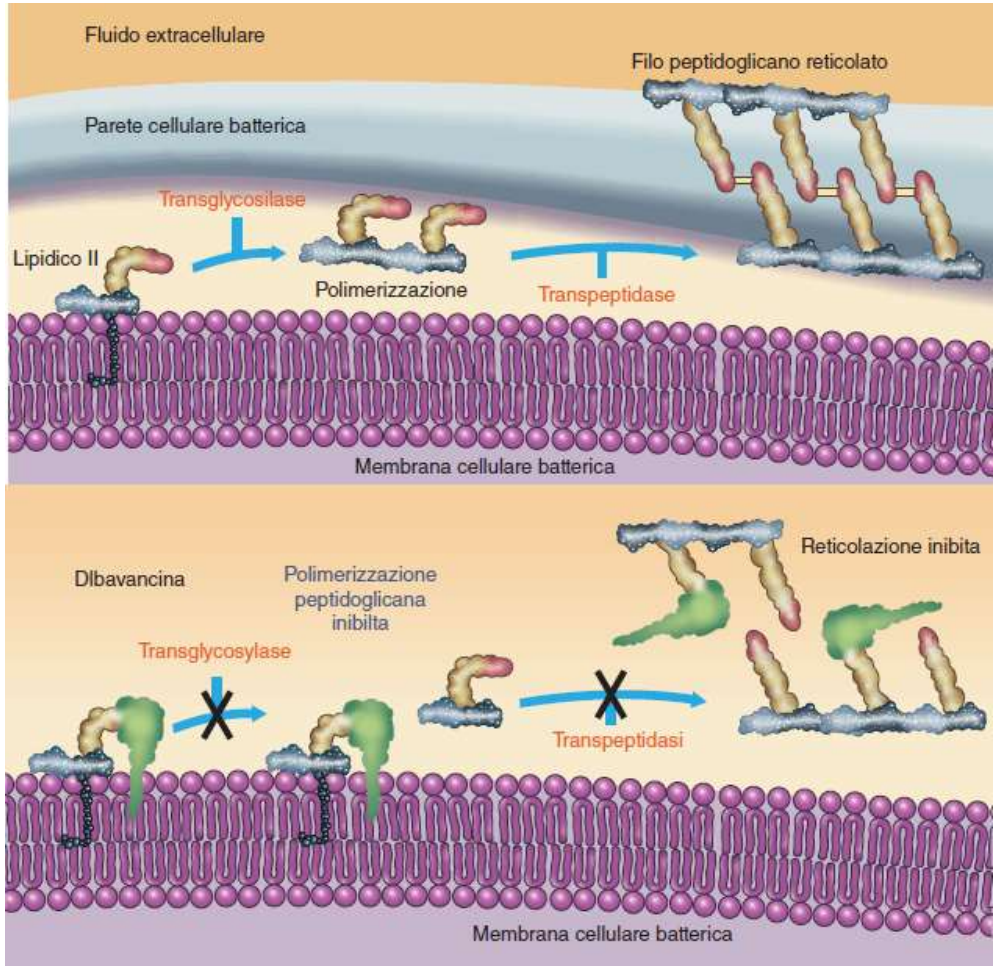
A-40926
Antibiotico naturale simil-teicoplanina
derivato da *Nonomuria spp.*



Ancoraggio alla membrana e aumento dell'attività antistafilococcica

Smith et al., Infect Dis Ther (2015) 4:245–258

Meccanismo d’azione



1. Blocca il legame di **transpeptidazione** e di **transglicosilazione** legando il dimero D-ala – D-ala

2. La catena lipofilica laterale permette la **dimerizzazion**e: dalbavancina si ancora al Lipide II nella membrana cellulare, **aumentando il suo legame al dimero D-ala – D-ala**

Jennifer L. Bailey, Kelly M Summers Published 2008 in American journal of health-system pharmacy

Dalbavancina - Spettro d'azione

POTENTE ATTIVITÀ in *vitro* contro Staphylococcus spp.

Staphylococcus aureus

- *MSSA*
- *MRSA*
- *hVISA*
- *MDR-MRSA/VISA*
- *<suscettibilità a altri farmaci (Vanco, Dapto, Telavancina, Teicoplanina, Linezolid e Rifampicina)*

Staphylococchi coagulasi negativi (CoNS)

- *S. epidermidis*
- *S. haemolyticus*
- *S. hominis*
- *S. lugdunensis*
- *S. schleiferi*
- *S. saprophyticus*
- *S. xylosus*
- Anche **MDR**

POTENTE ATTIVITÀ *in vitro* contro Streptococcus spp.

Streptococcus pneumoniae (R pencilline e ceftriaxone):

- MIC90 0.016 - 0.03 mg/L

Streptococchi beta emolitici:

- MIC che inibiscono tutti i ceppi <0,12 ug/ml

Streptococcus pyogenes (Gruppo A):

- MIC90 0,03ug/ml

Streptococcus agalactiae (Gruppo B):

- MIC90 0,12 ug/ml

Streptococchi viridanti (VGS) (anche MDR):

- MIC che inibiscono tutti i ceppi <0,12 ug/ml

Attività *in vitro* contro Enterococci spp.

Dalbavancina è considerata attiva contro gli isolati VSE

Parzialmente attiva contro i VRE:

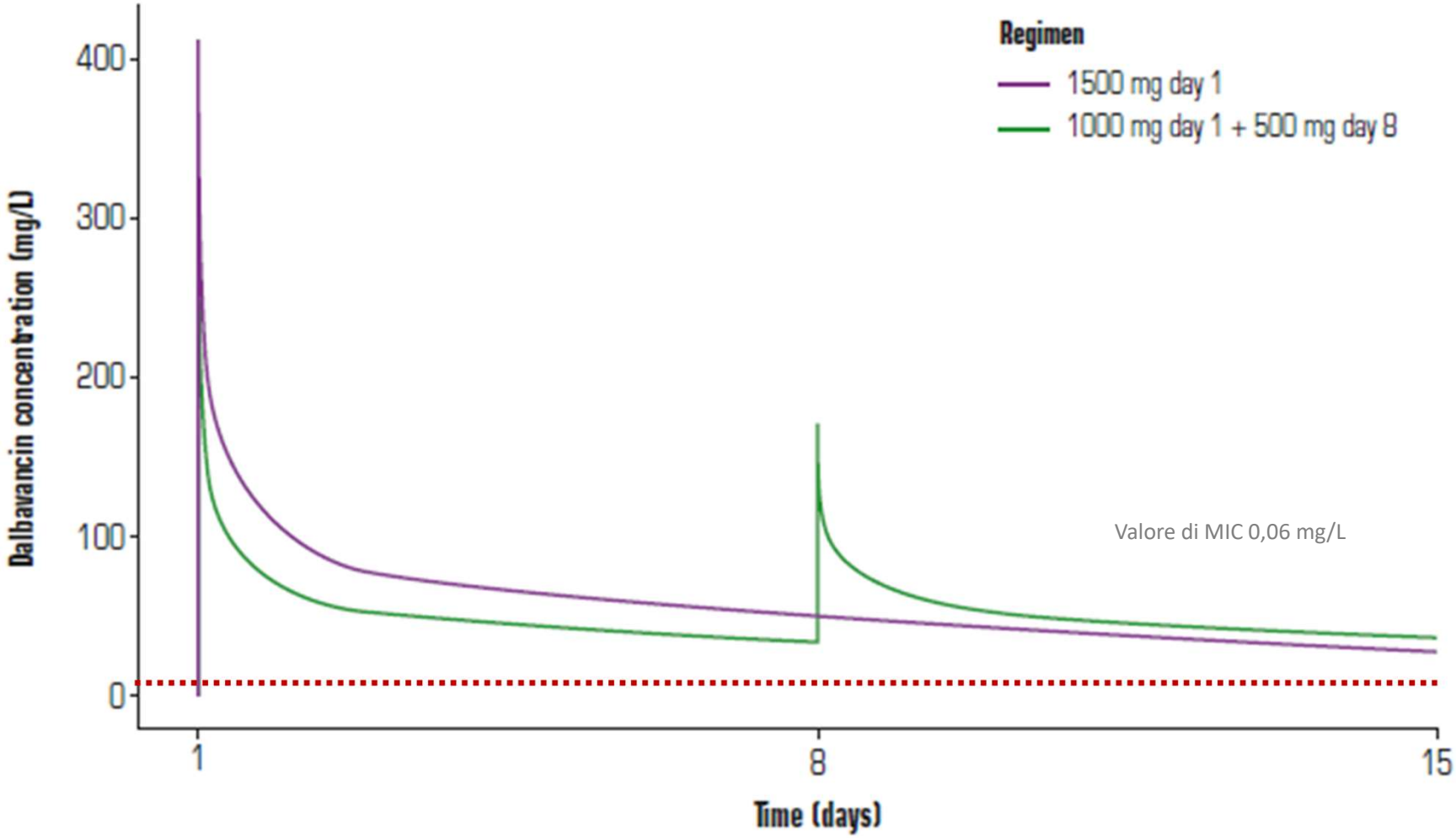
- non esercita alcuna azione contro gli isolati con fenotipo VanA
- è solo parzialmente attiva sui ceppi con fenotipo VanB

Attività di dalbavancina e dei farmaci di confronto in 39.824 isolati di *S.aureus* negli USA (2002-2012)[7]

Farmaco	MIC (µg/ml)			%S / %I / %R*	
	50%	90%	Range	CLSI	EUCAST
Dalbavancina	0.06	0.06	≤0.03-0.5	- / - / -	- / - / -
Vancomicina	1	1	≤0.12-4	>99.9/<0.1/0.0	>99.9/0.0/<0.1
Teicoplanina	≤2	≤2	≤2-8	100.0/0.0/0.0	99.7/0.0/0.3
Oxacillina	>2	>2	≤0.25->2	47.5/0.0/52.5	17.5/0.0/52.5
Eritromicina	>2	>2	≤0.2->2	35.9/0.9/63.2	36.1/0.4/63.5
Clindamicina	≤0.25	>2	≤0.25->2	76.5/0.2/23.3	76.1/0.4/23.5
Daptomicina	0.25	0.5	≤0.12-4	99.9/-/-	99.9/0.0/0.1
Levofloxacina	≤0.5	>4	≤0.5->4	56.6/1.1/42.3	56.6/1.1/42.3
Linezolid	1	2	≤0.25->8	99.9/0.0/<0.1	>99.9/0.0/<0.1
Tetraciclina	≤4	≤4	≤4->8	95.1/0.5/4.4	89.7/0.4/9.9

** Criteri pubblicati dal Clinical and Laboratory Standards Institute (CLSI), M100-S23- Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement e da The European Committee on Antimicrobial Susceptibility Testing – EUCAST2013.*

Dalbavancina-Farmacocinetica



Dalbavancina – Studi Clinici

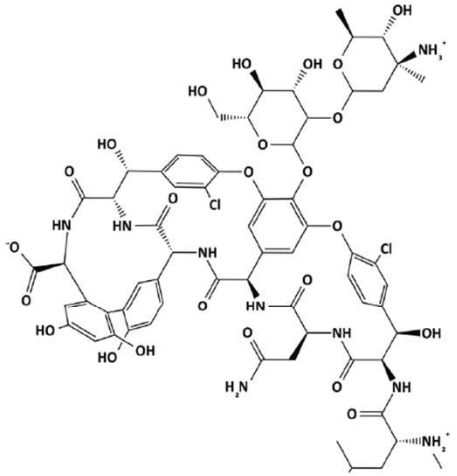
Studio	Criterio di inclusione	Intervento	Competitor	N. di pazienti	Efficacia clinica	Eventi avversi correlati
Jauregui LE et al., 2005 [44]	Suspected or confirmed SSSI due to gram-positive pathogens	Dalbavancin 2-dose regimen **Day 1: 1.000 mg + Day 8: 500 mg**	Linezolid 600 mg q12h	Total: 854 pts Pts clinically evaluable at the TOC visit: 660	88.9% (dalbavancin) versus 91.2% (comparator)	25.4% (dalbavancin) versus 32.2% (linezolid) Most frequent: nausea, diarrhea
Boucher H et al., 2014 [19] DISCOVER 1 and 2	Patients with ABSSSIs needed iv therapy	Dalbavancin 2-dose regimen	Vancomycin 1 g (or 15 mg/kg) q12h, eventually de-escalated to linezolid 600 mg q12h	Total: 1312 pts (659 versus 653 comparator)	79.7% (dalbavancin) versus 79.8% (comparator), Weighted difference -0.1% (95% CI, -4.5 to 4.2	32.8% (dalbavancin) versus 37.9% comparator, p=0.05 Most frequent: nausea, diarrhea
Dunne MW et al., 2016 [45]	Patients with ABSSSIs needed iv therapy	Dalbavancin 2-dose regimen **Day 1: 1.000 mg + Day 8: 500 mg**	Dalbavancin single-dose regimen **Day 1: 1.500 mg**	Total: 698 pts (349 2-dose regimen versus 349 single dose regimen)	84.2% (2-dose regimen) versus 81.4% (single dose regimen) Absolute difference -2.9% (95% CI -8.5, 2.8)	19.9 (2-dose regimen) versus 20.1% (single dose regimen) Most frequent: nausea

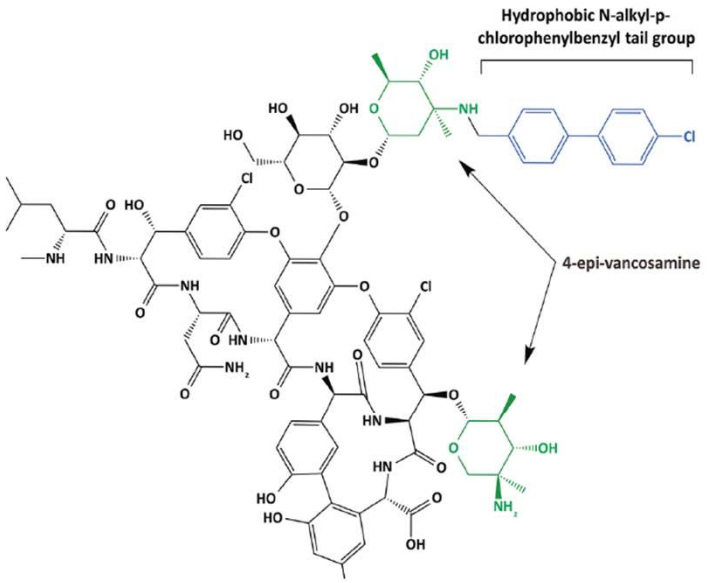
Studio registrativo
non inferiorità VS SoC

Confronto tra i due regimi posologici

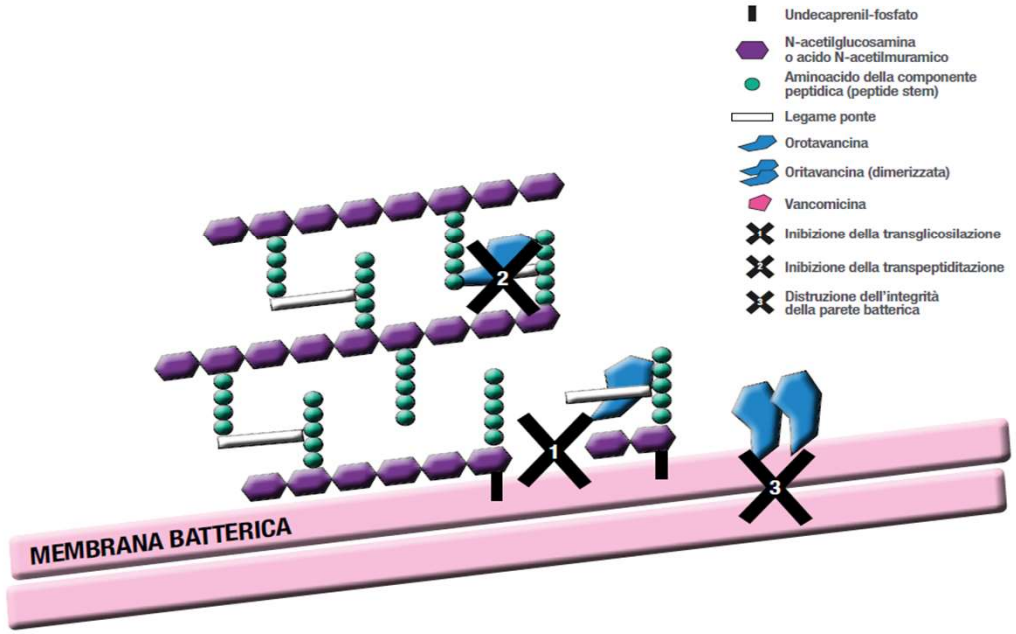
Oritavancin

- **Semisynthetic lipoglycopeptide** (LGP)
  - ✓ Derivato della <u>vancomicina</u>, da cui differisce per 2 molecole di un monosaccaride (4-epi-vancosamina) ed **una catena lipofila**





- **MoA:**
  - ✓ Inhibition of <u>transglycosylation</u> step of cell wall synthesis
  - ✓ Inhibition of cell wall <u>transpeptidation</u> (crosslinking) step of cell wall synthesis
  - ✓ <u>Disruption of the integrity of the bacterial membrane</u>
  - ➢ Rapid bactericidal activity



Brade KD, Rybak JM, Rybak MJ. Oritavancin: A New Lipoglycopeptide Antibiotic in the Treatment of Gram-Positive Infections. Infect Dis Ther. 2016 Mar;5(1):1-15

Zhanel GG, Schweizer F, Karlowsky JA. Oritavancin: mechanism of action. Clin Infect Dis. 2012 Apr;54 Suppl 3:S214-9

J Molec Biol 377: 281, 2008.

Oritavancin

- **Active vs. all Gram+ cocci, incl. MDR:**
  - ✓ ***Staphilococcus aureus, incl.*** MSSA, **MRSA, VRSA** (no clinical data)
  - ✓ **CoNS, incl. MR**
  - ✓ ***Streptococcus*** *spp., incl. pyogenes, anginosus* group, viridans, *agalactiae, gr. C,F.G*
  - ✓ ***Enterococcus*** *spp.,* ***incl. VRE, both VanA & VanB*** *(no clinical data)*
  - ✓ *P.acnes, Peptostreptococci*

- Indication (EMA,FDA): ABSSSI in adults & paediatric patients aged 3 months and older

Oritavancin

PK:

- long acting IV lipoglycopeptide ➔single dose therapy.
  - ✓ serum half-life of 245 hours (10 days)
  - ✓ useful in patient requiring parenteral therapy but who does not otherwise need to be hospitalized
    - ➔ early hospital discharge or avoidance of hospitalization
- **Two IV formulations:**
  - ✓ Tenkasi **fl. 400 mg: 1.200 mg/1000 D5W (NO SALINE!!), infusion 3 hr**
  - ✓ Kimyrsa (**FDA approved, not yet EMA approv.): fl 1.200 mg/250 mL D5W or NS, infusion 1h**.

- Renal /Hepatic Adjustment:
  - ✓ No adjustment needed in patients with mild or moderate renal or hepatic insufficiency.
  - ✓ The pharmacokinetics in patients with severe renal or hepatic impairment have not been evaluated.
  - ✓ Oritavancin is not removed from blood by hemodialysis.
- Obesity: No dosage adjustment necessary.

Oritavancin

Adverse Effects

- Most common, reported in ≥3% of recipients: nausea, vomiting, diarrhea, headache.
- Acute urticaria/flushing/pruritis have occurred.
  - **Red man syndrome,** similar to histamine-release syndrome reported with Vancomycin. If reactions do occur, discontinue therapy. In many patients with similar reactions to Vancomycin, it was possible to reinstitute therapy at a slower rate of infusion.
    - ➔ preferable to dilute 1 vial at a time
- *C. difficile* colitis.

Oritavancin has **no effect on the coagulation system *in vivo***, *but* can artificially **alter laboratory coagulation tests:**

- ✓ Oritavancin binds to, and prevent the action of, the phospholipid reagents
- ✓ PT and INR are prolonged for up to 12 hrs.
- ✓ prolonged aPTT for up to 120 hrs (5 days) after drug administration
  - ➔ Administration of IV unfractionated heparin is contraindicated
- ✓ D-dimer concentrations are artificially elevated for up to 72 hours.

Oritavancin bactericidal activity on VRE biofilm

Diagnostic Microbiology and Infectious Disease 91 (2018) 348–350

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Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

In vitro activity of oritavancin against planktonic and biofilm states of vancomycin-susceptible and vancomycin-resistant enterococci☆

Qun Yan [a,b], Melissa J. Karau [a], Robin Patel [a,c,*]

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[b] Department of Clinical Laboratory, Xiangya Hospital of Central South University, Changsha, Hunan, China
[c] Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, MN

Table 1
Oritavancin minimal inhibitory concentration (MIC), minimal biofilm inhibitory concentration (MBIC) and minimum biofilm bactericidal concentration (MBBC) of enterococc

	MIC (μg/ml)											MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2		
VSE (n = 60)													
E. faecalis (n = 52)	25 (48.1)	6 (11.5)	11 (21.2)	7 (13.5)	1 (1.9)	2 (3.8)						0.004	0.015
E. faecium (n = 8)	8 (100)											NA	NA
VRE (n = 27)													
VanA *E. faecalis* (n = 3)							1 (33.3)	1 (33.3)	1 (33.3)			NA	NA
E. faecium (n = 17)					1 (5.9)	6 (35.2)	6 (35.2)	3 (17.6)	1 (5.9)			0.12	0.25
VanB *E. faecalis* (n = 3)		1 (33.3)		1 (33.3)	1 (33.3)							NA	NA
E. faecium (n = 4)	4 (100)											NA	NA

	MBIC (μg/ml)											$MBIC_{50}$ (μg/ml)	$MBIC_{90}$ (μg/ml)
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2		
VSE (n = 60)													
E. faecalis (n = 52)	2 (3.8)	1 (1.9)			1 (1.9)	4 (7.7)		4 (7.7)	14 (26.9)	22 (42.3)	4 (7.7)	0.5	1
E. faecium (n = 8)	2 (25)		3 (37.5)	3 (37.5)								NA	NA
VRE (n = 27)													
VanA *E. faecalis* (n = 3)					1 (33.3)				1 (33.3)	1 (33.3)		NA	NA
E. faecium (n = 17)	4 (23.5)	1 (5.9)			1 (5.9)		2 (11.8)	1 (5.9)	6 (35.3)	2 (11.8)		0.25	1
VanB *E. faecalis* (n = 3)								1 (33.3)	2 (66.6)			NA	NA
E. faecium (n = 4)	3 (75)			1 (25)								NA	NA

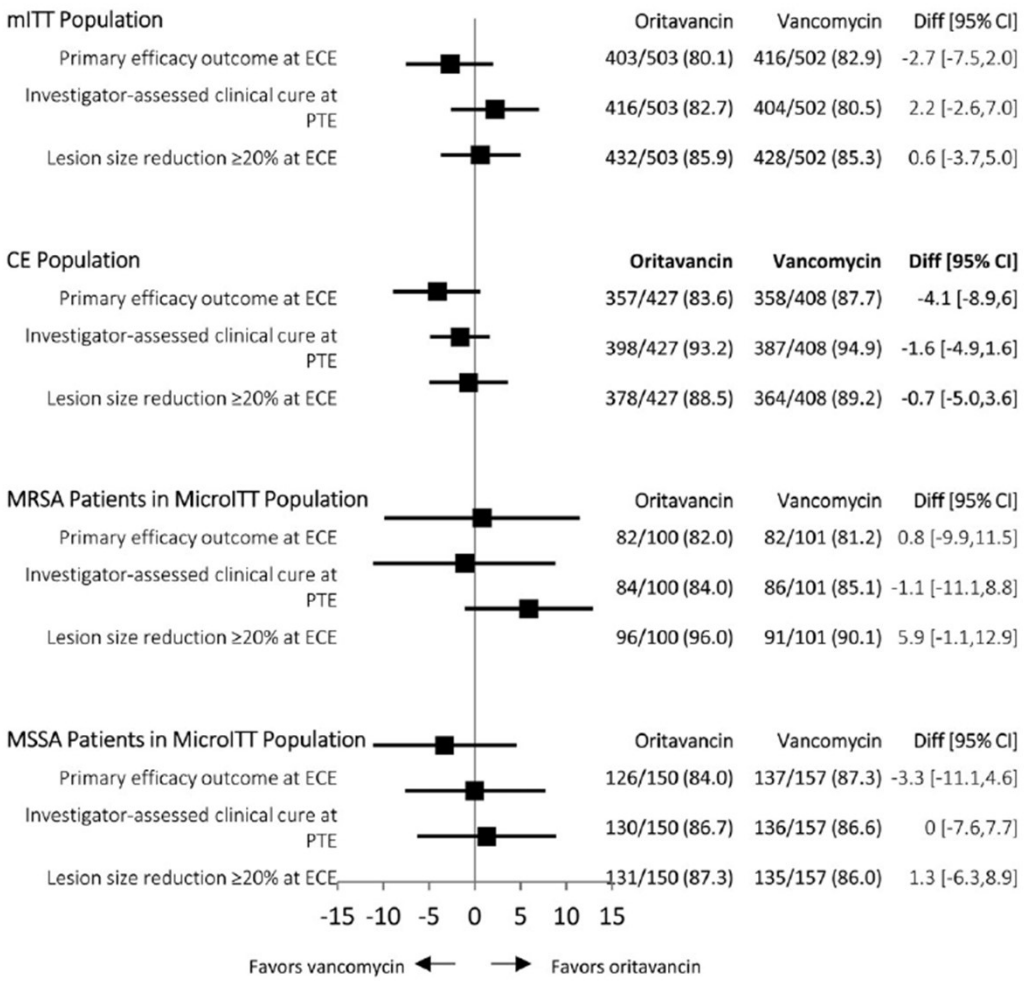
	MBBC (μg/ml)											$MBBC_{50}$ (μg/ml)	$MBBC_{90}$ (μg/ml)
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2		
VSE (n = 60)													
E. faecalis (n = 52)		1 (1.9)	2 (3.8)			2 (3.8)	1 (1.9)	2 (3.8)	6 (11.5)	22 (42.3)	16 (30.8)	1	2
E. faecium (n = 8)		2 (25)		1 (12.5)	3 (37.5)	2 (25)						NA	NA
VRE (n = 27)													
VanA *E. faecalis* (n = 3)								1 (33.3)	1 (33.3)		1 (33.3)	NA	NA
E. faecium (n = 17)	2 (11.8)			1 (5.9)	2 (11.8)		2 (11.8)	1 (5.9)	3 (17.6)	6 (35.3)		0.5	1
VanB *E. faecalis* (n = 3)										2 (66.6)	1 (33.3)	NA	NA
E. faecium (n = 4)	2 (50)	1 (25)				1 (25)						NA	NA

VSE = vancomycin-susceptible enterococci, VRE = vancomycin-resistant enterococci, NA = not applicable (fewer than 10 isolates).

Yan, Q. et al (2018). In vitro activity of oritavancin against planktonic and biofilm states of vancomycin-susceptible and vancomycin-resistant enterococci. *Diagnostic Microbiology and Infectious Disease.* **91**(4): 348-350.

RISULTATI – SOLO II

Oritavancina in singola somministrazione è risultata non inferiore a Vancomicina per tutti gli endpoint di efficacia



Corey GR, Good S, Jiang H, et al; SOLO II Investigators. Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. Clin Infect Dis. 2015 Jan 15;60(2):254-62.

Corey GR, Loutit J, Moeck G, et al; SOLO I and SOLO II investigators. Single Intravenous Dose of Oritavancin for Treatment of Acute Skin and Skin Structure Infections Caused by Gram- Positive Bacteria: Summary of Safety Analysis from the Phase 3 SOLO Studies. Antimicrob Agents Chemother. 2018

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
https://doi.org/10.1080/14787210.2023.2214727

2023 May 31;1-19.

Taylor & Francis
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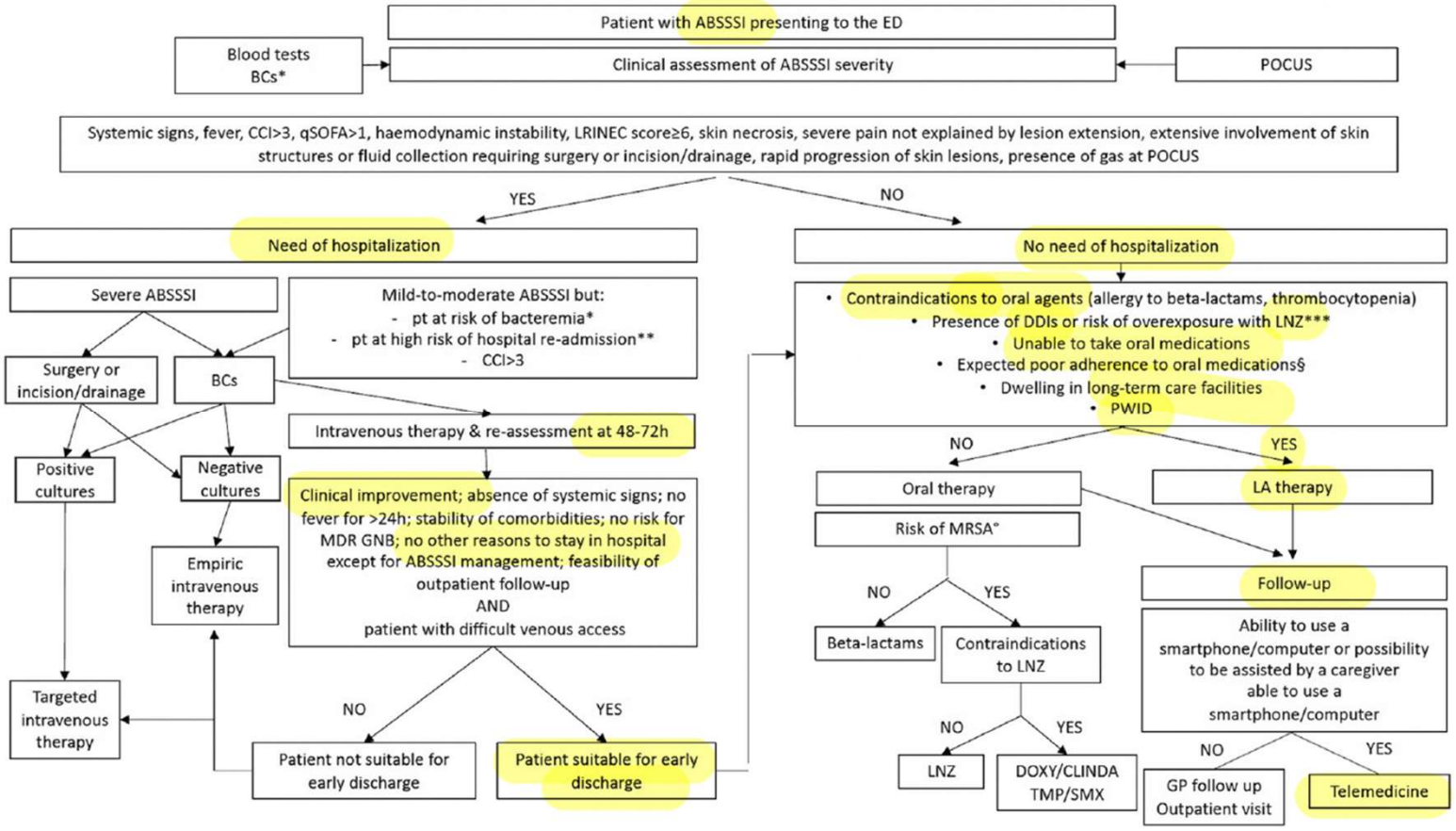
REVIEW

OPEN ACCESS Check for updates

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

Alessandra Oliva [a], Sergio Carbonara [b], Vito Cianci [c], Massimo Crapis [d], Enea Gino Di Domenico [e], Marco Falcone [f], Gioacchino Galardo [g], Emanuele Durante-Mangoni [h,i*] and Mario Venditti [a*]



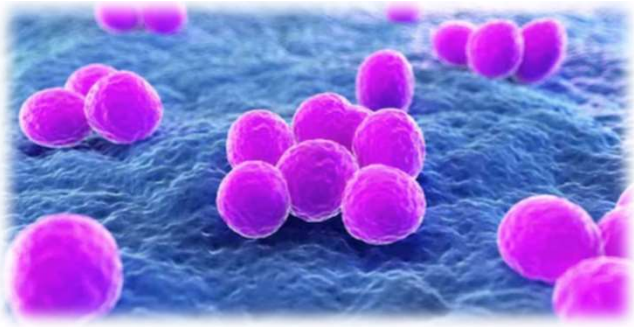
Our algorithm suggest the ***use of dalbavancin*** *in patients with ABSSSIs* ***who are not eligible for oral therapies or Outpatient Parenteral Antibiotic Therapy (OPAT)*** *programs and who* ***would have otherwise been hospitalized only for antibiotic therapy****.*

LIPOGLYCOPEPTIDES –

OFF-LABEL USES

STUDY RATIONALE

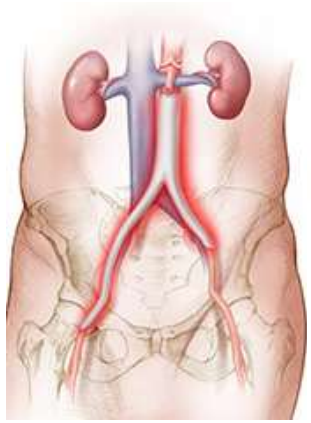
Poliseno M, Bavaro DF, …, Carbonara S. Clin Drug Investig. 2021 May;41(5):437-448.



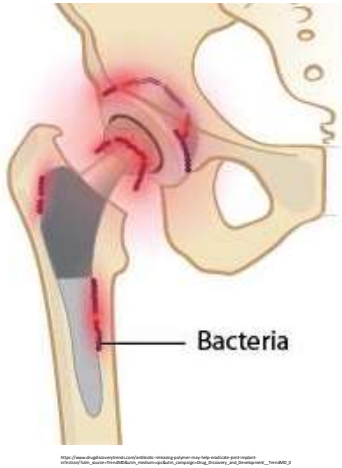
Gram+ bacteria represent a frequent, well-recognized cause of HCA & CA infections in Europe, with an estimated expense for European healthcare systems of € 380 ML only for MRSA infections, which affect about 150,000 people per year [1]

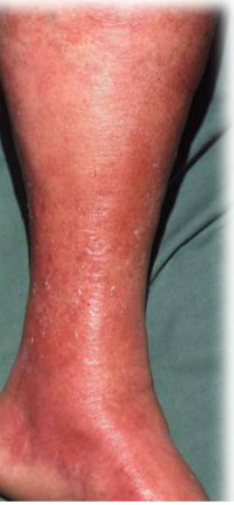
ABSSI vs. CV/OA Infections

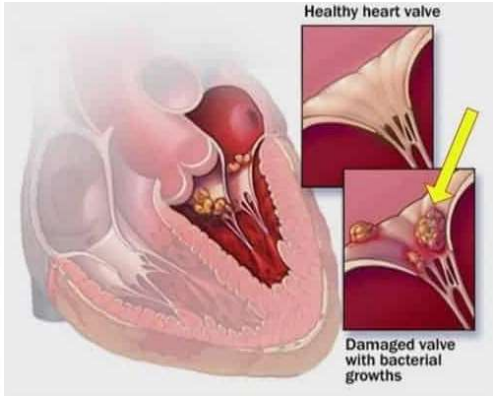
- CV/OA Infections more frequently observed in our ID settings than ABSSIs
- Despite being ABSSSI the most common Gram+ IDs, **the major burden in terms of morbidity, mortality, prolonged hospitalizations and costs is sustained by Gram+ related cardiovascular (CV) and osteoarticular (OA) infections, especially when implants are involved** [2,3].



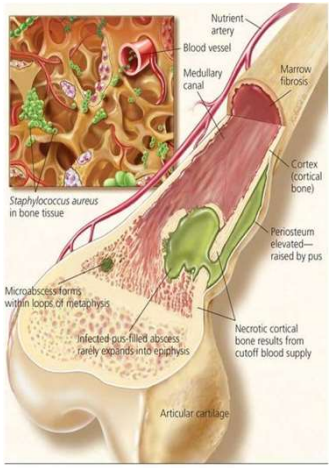
https://www.cryolife.com/products/vascular-reconstructive-surgery/infected-fields/infected-abdominal-aortic-grafts/



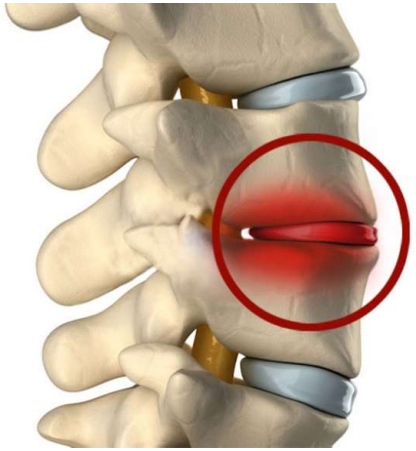




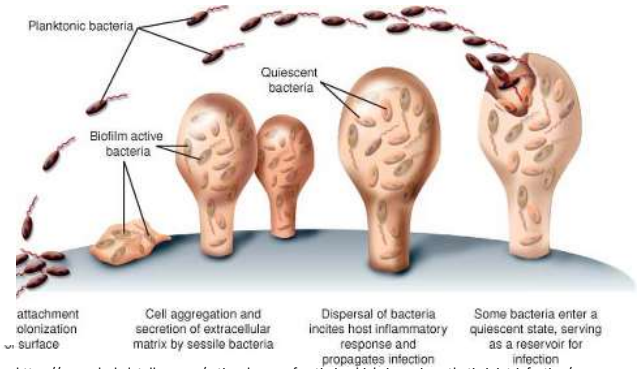
https://medicoapps.org/infective-endocarditis-2/



https://www.pinterest.it/pin/115756



http://www.spine-center-rischke.ch/portfolio/spondylodiszitis/?lang=en

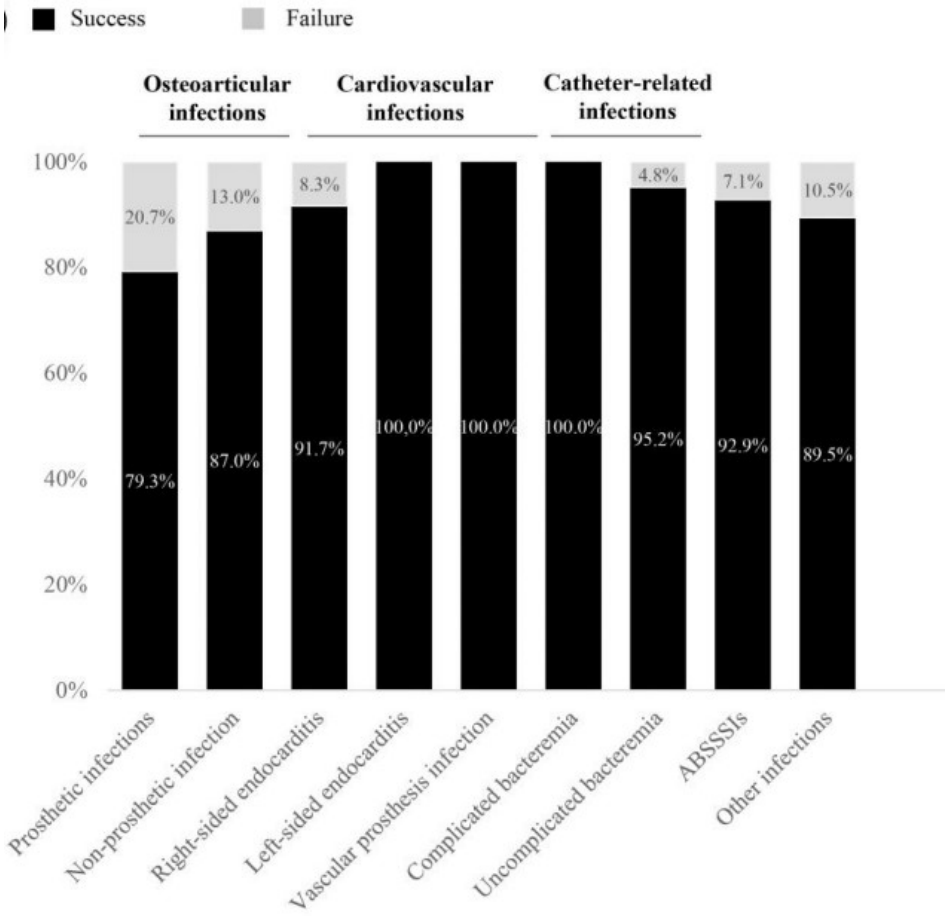


JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac120

Antimicrobial Resistance

Dalbavancin in clinical practice in Spain: a 2 year retrospective study

Laura Morata[1], José María Aguado[2], Miguel Salavert[3], Juan Pasquau[4], Enrique Míguez[5], Patricia Muñoz[6], Irantzu Rosselló[7] and Benito Almirante[8*9]



Pazienti: arruolati 187 pazienti che hanno ricevuto almeno una dose di Dalbavancina. Precedentemente trattati con altri antibiotici: 94,7%
età media: 64 anni
CCI medio: 4.

- ✓ Comorbidità: CVD (27.3%), diabete mellito (23.5%), tumori solidi (15.0%) and insufficienza renale cronica (11.8%)
- ✓ Infezioni osteoarticolari: 28.3%, ABSSSI: 22.5%, infezioni cardiovascolari: 20.9%, infezioni correlate a catetere: 18,2%, altre infezioni: 10%
- ✓ Agenti eziologici: *S. aureus* (31.3% MRSA), CoNS (32.6%) ed enterococchi. (12.8%)

Table 4. Clinical success and safety by patient subgroups

	Number of patients (*N*)	Clinical success (%)	Relapses (%)	AE (%)
Overall	187	91.4	6.5	3.2
Diabetes	44	88.6	9.1	2.3
Cardiovascular disease	51	94.0	3.9	3.9
Over 60 years	113	91.2	6.2	0.9
No comorbidities at baseline	27	96.3	3.7	7.4
S. aureus infection	64	92.2	6.3	3.1
Enterococcus infection	24	91.7	8.3	0.0

RESULTS

Poliseno M, Bavaro DF, …Carbonara S. Clin Drug Investig. 2021 May;41(5):437-448.

Antimicrobial treatment and clinical outcome of Study population.

Variable	Total (n=50)	ABSSSI (n= 12)	Complicated ABSSSI (n = 8)	Bone and joints infections (n=18)	CIED/Vascular grafts infections (n=12)
In- hospital antimicrobial regimens, n (%)					
Daptomycin based	**38 (76)**	**7 (60)**	**5 (64)**	**15 (83)**	**11 (19)**
Glycopeptide based	**4 (8)**	**2 (16)**	**1 (12)**	**1 (5)**	**-**
Beta-lactams based	**3 (6)**	**2 (16)**	**1 (12)**	**-**	**-**
Other combinations [a]	**5 (10)**	**1 (8)**	**1 (12)**	**2 (12)**	**1 (9)**
Source control, n (%)	**15 (30)**	**3 (25)**	**2 (25)**	**2 (11)**	**8 (66)**
Indications to Switch to Dalbavancin, n (%)					
Early hospital discharge	**44 (88)**	**11 (92)**	**6 (75)**	**15 (83)**	**12 (100)**
Failure of initial therapy	**5 (10)**	**1 (8)**	**2 (25)**	**2 (11)**	**-**
Adverse events to initial therapy	**1 (2)**	**-**	**-**	**1 (5)**	**-**
Dalbavancin doses (1.500mg-dose), median (IQR)[b]	**1 (1 – 3)**	**1 (1 - 1)**	**2 (2 - 4)**	**1 (1 - 3)**	**3 (1 - 3)**
Outcome of antimicrobial treatment, n (%)					
Clinical success	**49 (98)**	**12 (100)**	**8 (100)**	**17 (95)**	**12 (100)**
Treatment failure (due to adverse events)	**1 (2)**	**-**	**-**	**1 (5)**	**-**
Outcome at follow-up (FU), n (%)					
Days of follow up, median (IQR)	**150 (30-180)**	**-**	**-**	**-**	**-**
Relapses, n (%)	**3 (6)**	**1 (8)**	**1 (12)**	**-**	**1 (8)**
Lost to FU, n (%)	10 (20)	5 (41)	1 (12)	3 (16)	1 (8)

RESULTS

Poliseno M, Bavaro DF, …Carbonara S. Clin Drug Investig. 2021 May;41(5):437-448.

Actual and hypothetical duration of antimicrobial therapy and hospital-stay in 50 patients with different Gram+ infections.

Variable	Total (n=50)	ABSSSI (n= 12)	Complicated ABSSSI (n = 8)	Bone and joints infections (n=18)	CIED/Vascular grafts infections (n=12)	*p value*
Duration of antimicrobial therapy [days per patient, median (IQR)]						
Prior to Dalbavacin Tx	10 (4 – 23)	2 (2 – 4)	12 (5 - 32)	18 (16 - 32)	13 (8 - 28)	*<0.001*
After switch to DBV [a]	14 (14 - 42)	14 (14 - 14)	28 (28 - 56)	14 (14 - 42)	42 (14 - 42)	*0.033*
Hospital length-of-stay [days per patient, median (IQR)] [b]						
Actual	22 (11-33)	13 (10 - 23)	12 (6 - 25)	28 (19 - 38)	21 (14 - 33)	*0.053*
Hypothetical[c]	47 (35 - 67)	30 (24 - 42)	58 (41-68)	50 (40 - 74)	55 (35 - 76)	*0.009*
Reduction in hospital-stay	**14 (14 - 49)**	**14 (14 - 14)**	**28 (28 - 42)**	**21 (21 - 49)**	**42 (14 - 42)**	*0.015*

a. End of Dalbavancin therapy has been considered at 14 days after the last 1.500 mg Dalbavancin dose (see text, *"Definitions"* paragraph)

b. Overall length of stay since hospital admission included the time period prior to start of antimicrobial therapy and was possibly influenced by other clinical problems than the antibiotic Tx (e.g. comorbidities, diagnostic work-up, surgery, etc)

c. Hypothetical duration of hospitalization was estimated considering that the initial standard antimicrobial treatment would have been in-hospital administered, without switching to Dalbavancin, until the end of therapy (see text, "*Methods*" section)

RESULTS

Poliseno M, Bavaro DF, …Carbonara S. Clin Drug Investig. 2021 May;41(5):437-448.

COSTS saved by switching standard antimicrobials to Dalbavancin *[€ per patient, median (IQR)].*

Variable	Total (n=50)	ABSSSI (n= 12)	Complicated ABSSSI (n = 8)	Bone and joints infections (n=18)	CIED/Vascular grafts infections (n=12)	*p value*
Antimicrobials	**530 (409 - 1,537)**	**385 (-872 - 530)**	**2,050 (1,025 - 2,076)**	**512 (482 -1,288)**	**1,144 (512 - 1,537)**	***0.005***
Infusion sets & accessories	19 (18– 20)	18 (18 - 19)	27 (4.56 - 35)	19 (17- 21)	18 (18 – 20)	*0.951*
Hospital accommodation	**7,846 (5,502 - 15,756)**	**5,383 (3,129 -6,719)**	**11,156 (10,108 - 13,216)**	**6,629 (5,502 - 15,756)**	**18,963 (7,742 - 23,226)**	***0.001***
Total cost saved	**8,259 (5,644 - 17,270)**	**5,034 (3,647 - 6,590)**	**12,882 (11,970 - 15,246)**	**7,131 (5,644 - 17,270)**	**20,084 (8,259 - 24,366)**	***0.007***

- ***Non quantificato: tempo infermiere risparmiato (diluizione e infusione ABX)***

CONCLUSIONS

Poliseno M, Bavaro DF, …Carbonara S. Clin Drug Investig. 2021 May;41(5):437-448.

An "early discharge" strategy based on the switch to Dalbavancin provides a significant reduction of both:

- ❖ patient hospital LOS, thus increasing the availability of hospital beds
  - ✓ especially useful in peculiar circumstances such as the current SARS-CoV-2 pandemic (shortage of hospital beds)
- ❖ costs

➢ These organizational and economic benefits were greater in patients with difficult Gram-positive infections requiring longer antimicrobial treatment, non-eligible to oral antibiotic therapies and for whom a daily OPAT is not feasible.

➢ the organizational & economical advantages are combined with an adequate clinical success and good tolerability.

Key Points

The switch to dalbavancin in patients hospitalized for diverse Gram-positive infections allowed a significant reduction both in the duration of hospital stay and in treatment-related costs, along with an overall good clinical outcome.

These benefits were greater for complex infections requiring prolonged antimicrobial treatment.

An even greater cost-saving than that observed in our study population could be obtained with the following DBV dose optimization, in difficult-to-treat infections:

➢ 1.500 mg (1^ dose) followed by **1,000 mg (**rather than 1.500 mg**) every 14 days** [31-37].

➢ **1,500 mg doses** of DBV **X 2** (**on day 1 and 8**, respectively) as an effective treatment of osteomyelitis and complicated bacteremia or endocarditis due to Gram-positive bacteria [14].

Dalbavancin - Analisi farmacocinetica per dosaggio in osteomieliti

Analisi farmacocinetiche su pazienti con infezioni ossee che ricevono Dalbanìvancina dopo fallimento con altre terapie e simulazioni Monte Carlo con lo scopo di **identificare il regime posologico che permette di rimanere nel range di concentrazione efficace** per trattare con successo infezioni OA da gram positivi.

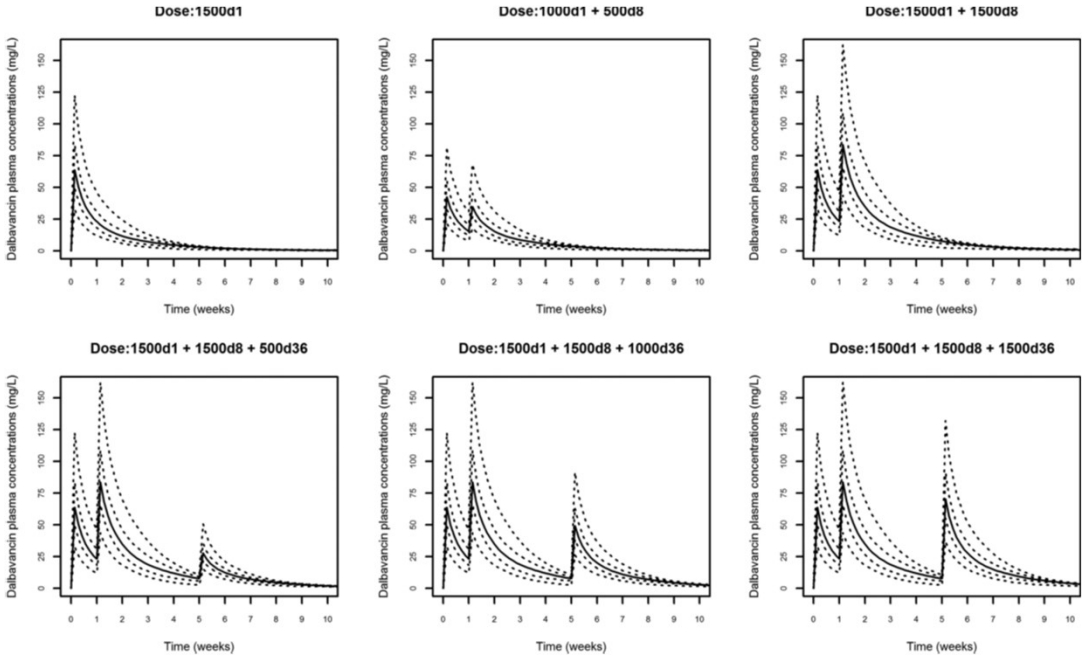
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Population Pharmacokinetics of Dalbavancin and Dosing Consideration for Optimal Treatment of Adult Patients with Staphylococcal Osteoarticular Infections

Pier Giorgio Cojutti,[a,b] Matteo Rinaldi,[c,d] Eleonora Zamparini,[c,d] Nicolò Rossi,[c,d] Sara Tedeschi,[c,d] Matteo Conti,[c] Federico Pea,[c,e] Pierluigi Viale[c,d]

6 regimi di dosaggio:



1 -1,500mg at day 1,
2 - 1,000mg at day 1 plus 500mg at day 8,
3 - 1,500mg at days 1 and 8,
4- 1,500mg at days 1 and 8 plus 500mg at day 36,
5- 1,500mg at days 1 and 8 plus 1,000mg at day 36, and
6 - 1,500mg at days 1 and 8 plus 1,500mg at day 36

SCHEMA POSOLOGICO	DURATA EFFICACIA STIMATA
1500 d1 + 1500 d8	5 settimane
1500 d1 + 1500 d8 + 500 d36	7 settimane
1500 d1 + 1500 d8 + 1000 d36	8 settimane
1500 d1 + 1500 d 8 + 1500 d36	9 settimane

ORITAVANCIN - Clinical Outcomes and Economic Impact of Oritavancin for Gram-Positive Infections: A Single Academic Medical Center Health System Experience

Lauren E. Brownell1 · Meagan L. Adamsick2 · Erin K. McCreary3 · Joshua P. Vanderloo1 · Erika J. Ernst4 · Emily R. Jackson1 · Lucas T Schulz1

Drugs - Real World Outcomes (2020) 7 (Suppl 1):S13–S19

Table 1 Baseline demographic and efficacy and safety outcomes

Indication	All patients ($n=75$)			Patients included in efficacy analysis ($n=73$)		
	Age (avg, years)	Male, *n* (%)	Weight (avg IBW, kg, avg ABW, kg)	Clinical cure or improvement[b], *n* (%)	Failure, *n* (%)	ADR, *n* (%)
All indications	**50**	**43 (57.3)**	**85.1, 65.6**	**68 (93.2)**	**5 (6.8)**	**9 (12)**
ABSSSI (all $n=25$; efficacy analysis $n=24$)	54	15 (60)	66.8, 92.8	23 (95.8)	1 (4.2)	4 (16.7)
Diabetic foot infection ($n=3$)	56	2 (66.7)	69.2, 100.4	3 (100)	0 (0)	0 (0)
Endocarditis ($n=4$)	37	3 (75)	67.8, 71.2	4 (100)	0 (0)	0 (0)
Line infection ($n=2$)	38	1 (50)	66.2, 55.5	2 (100)	0 (0)	1 (50)
Other[a] ($n=5$)	53	1 (20)	62.7, 93.3	4 (80)	1 (20)	0 (0)
Osteomyelitis/septic arthritis ($n=10$)	54	5 (50)	61.8, 83.4	10 (100)	0 (0)	2 (20)
Pneumonia ($n=5$)	48	3 (60)	66.7, 75.6	5 (100)	0 (0)	0 (0)
Prosthetic device infection (all $n=4$; efficacy analysis $n=3$)	48	1 (33.3)	59.2, 85.6	3 (100)	0 (0)	1 (33.3)
Sepsis ($n=5$)	47	4 (80)	67.9, 92.5	3 (100)	2 (40)	0 (0)
Surgical wound infection ($n=12$)	45	8 (66.7)	66.6, 76.5	11 (91.7)	1 (8.3)	1 (8.3)

IBW ideal body weight, *ABW* actual body weight, *ABSSSI* acute bacterial skin and skin structure infections, *IV* intravenous

[a]Other = left parotid sialadenitis with right parotid duct abscess with a large sialolith, infection of trigeminal neurotrophic ulceration infected with methicillin resistant *Staphylococcus aureus*, hepatic abscess, tenosynovitis

[b]34 patients were defined as having clinical cure and 34 patients were defined as having clinical improvement; 34 patients with clinical improvement received oral antibiotics after administration of oritavancin as IV to oral step-down therapy

Real-World Use of Oritavancin for the Treatment of Osteomyelitis.

Scoble PJ, Reilly J, Tillotson GS. Drugs. 2020 Jun;7(Suppl 1):46-54. doi: 10.1007/s40801-020-00194-8.

Table 5 Summary of the real-world experience using oritavancin for microbiologically positive osteomyelitis

Study	Patient background	Pathogens	Oritavancin dose and duration	Outcome	Adverse effects
Schulz et al. [32]	4 patients; median age 59 years (31–76); 25% male	MSSA	3 patients: 1200 mg × 1 dose, then 800 mg weekly ≥ 2 doses 1 patient: 1200 mg × 2/week	Success × 2 Improvement × 2	Anemia and leukopenia in 1 patient
Chastain et al. [36]	12 patients, median age 65 years (47–79), 67% male, 67% DM	MRSA	3 patients = 1200 mg × 1 dose 9 patients = 1200 mg × ≥ 2 doses	100% Success	None
Foster et al. [37]	57 y/o M with osteomyelitis secondary to prosthetic hip replacement	Daptomycin non-susceptible VRE	1200 mg once weekly × 6 weeks	Success	None
Delaportas et al. [31]	49 y/o F with right tibial osteomyelitis secondary to retained intramedullary nail	MSSA	1200 mg once weekly × 6 weeks	Success	None
Ruggero et al. [33]	46 y/o M with native vertebral osteomyelitis	MRSA	1200 mg every 2 weeks × 4 doses, then 1200 mg 1 month later	Improvement	None
Dahesh et al. [35]	59 y/o M with hardware-associated vertebral osteomyelitis	Vancomycin-resistant and daptomycin NS *E. faecium*	1200 mg weekly × 2 doses, then 800 mg weekly × 8 doses	Improvement	None
Stewart et al. [34]	26 y/o F with sacral joint osteomyelitis; IVDU	MSSA	1200 mg × 1 dose	Failure	None
CHROME Registry [38]	18 patients; mean age 58.4 years, 38.9% male, 77.8% prior antibiotics, 50% failure prior antibiotics	MRSA, MSSA, coagulase-negative *Staphylococcus, E. faecalis, E. faecium, S. pyogenes*	10 patients = 1200 mg × 1 dose 8 patients = 1200 mg × ≥ 2 doses	Clinical success: Single dose: 90% Multi-dose: 87.5%	Moderate, not serious infusion-related reaction (in multidose patient)

ORITAVANCINA: PENETRAZIONE A LIVELLO POLMONARE

Table 2. Antibiotic concentrations in ELF and alveolar macrophage cells comparing to serum levels

Antibiotic	Dose	Time (hr)	ELF (mg/L)	Cells (mg/L)	Serum (mg/L)	Free serum[a] (mg/L)	C_{ELF}/C_{fs}[b] or AUC_{ELF}/AUC_{fs}[c]	C_{cell}/C_{fs}[d] or AUC_{cell}/AUC_{fs}[e]	Comments
Iclaprim	1.6 mg/kg IV, single	AUC_6	40.9	67.7	1.8	0.13	323.9	536.8	Healthy Volunteers
Linezolid	600 mg q12 PO, 5doses	AUC_{24}	622.8	27.2	190.0	131.1	4.77	0.22	Healthy Volunteers
	600 mg q12 PO, 6 doses	2.9-7.5					12.1	1.03	Diagnostic BAL
	600 mg q12 IV, 2 days	Peak					1.52	0.5[f]	VAP
		Trough					1.51	0.5[f]	Patients
Oritavancin	800 mg q24 IV, 5 days	AUC_{24}	106	3,297	2,310	23.1	4.6	142.7	Healthy Volunteers
Teicoplanin	12 mg/kg q12-24, IV	Trough	4.9		15.9	3.7	1.5	7.4[f]	VAP Patients
Telavancin	10 mg/kg q24 IV, 3 days	AUC_{24}[g]	50	820		73	0.7	11.2	Healthy Volunteers
Tigecycline	50 mg q12 IV, 3 days	AUC_{12}	2.28	134	1.73	0.69	3.3	194.2	Healthy Volunteers
Vancomycin	1g q12 IV, 9 doses	AUC_{24}	92	926	367	165.2	0.56	5.6	Healthy Volunteers
	Target trough 15-20 mg/L	Trough	4.5		24	10.8	0.42	6.3[f]	Critically ill Patients
	1g q12 IV, 9 doses	AUC_{24}					0.91	6.3[f]	Healthy Volunteers

Kiem S, Schentag JJ. Interpretation of Epithelial Lining Fluid Concentrations of Antibiotics against Methicillin Resistant Staphylococcus aureus. Infect Chemother. 2014 Dec;46(4):219-25. doi: 10.3947/ic.2014.46.4.219. Epub 2014 Dec 29. PMID: 25566401; PMCID: PMC4285007.

Clinical Outcomes and Economic Impact of Oritavancin for Gram-Positive Infections: A Single Academic Medical Center Health System Experience
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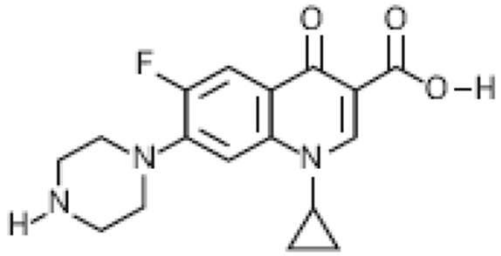
Drugs - Real World Outcomes (2020) 7 (Suppl 1):S13–S19

Table 4 Cost avoidance analysis of oritavancin in patients with hospital days saved

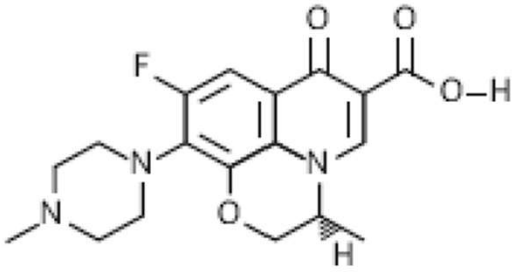
Indication	Average hospital day of oritavancin administration; *n* (range)	Average hospital days avoided; *n* (range)	Average cost avoidance associated with inpatient oritavancin administration; US$ amount	Patients with a positive return on investment per indication; *n* (%)
All indications (*n* = 20)	6 (2–20)	12 (3–48)	15,621	9 (45)
Cellulitis (*n* = 6)	5 (2–9)	6 (3–7)	5,252	1 (16.7)
Endocarditis (*n* = 3)[a]	7 (5–11)	18 (14–26)	47,246	3 (100)
Pneumonia (*n* = 3)	7 (6–9)	16 (8–30)	24,955	1 (33.3)
Prosthetic device infection (*n* = 1)	5	10	19,221	1 (100)
Surgical wound infection (*n* = 7)[a]	7 (3–20)	8 (3–14)	2,941	3 (42.9)

DELAFLOXACIN

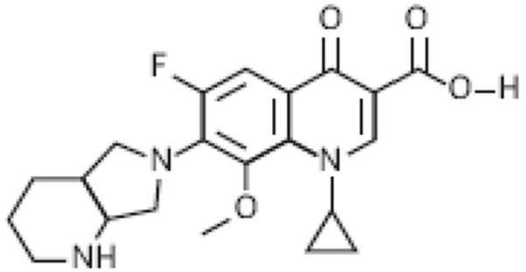
Differenze strutturali con altri FQs: il primo FQ anionico a pH neutro



Ciprofloxacin

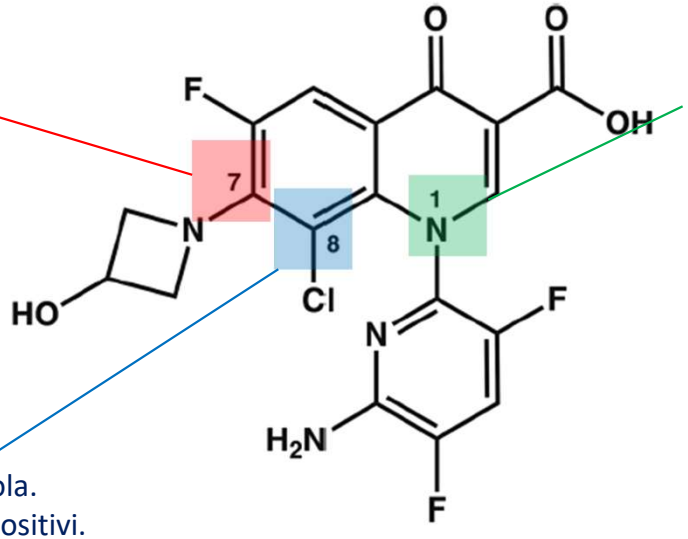


Levofloxacin



Moxifloxacin

Assenza gruppo basico in posizione C7:
Conferisce **carattere anionico** alla molecola a pH neutro

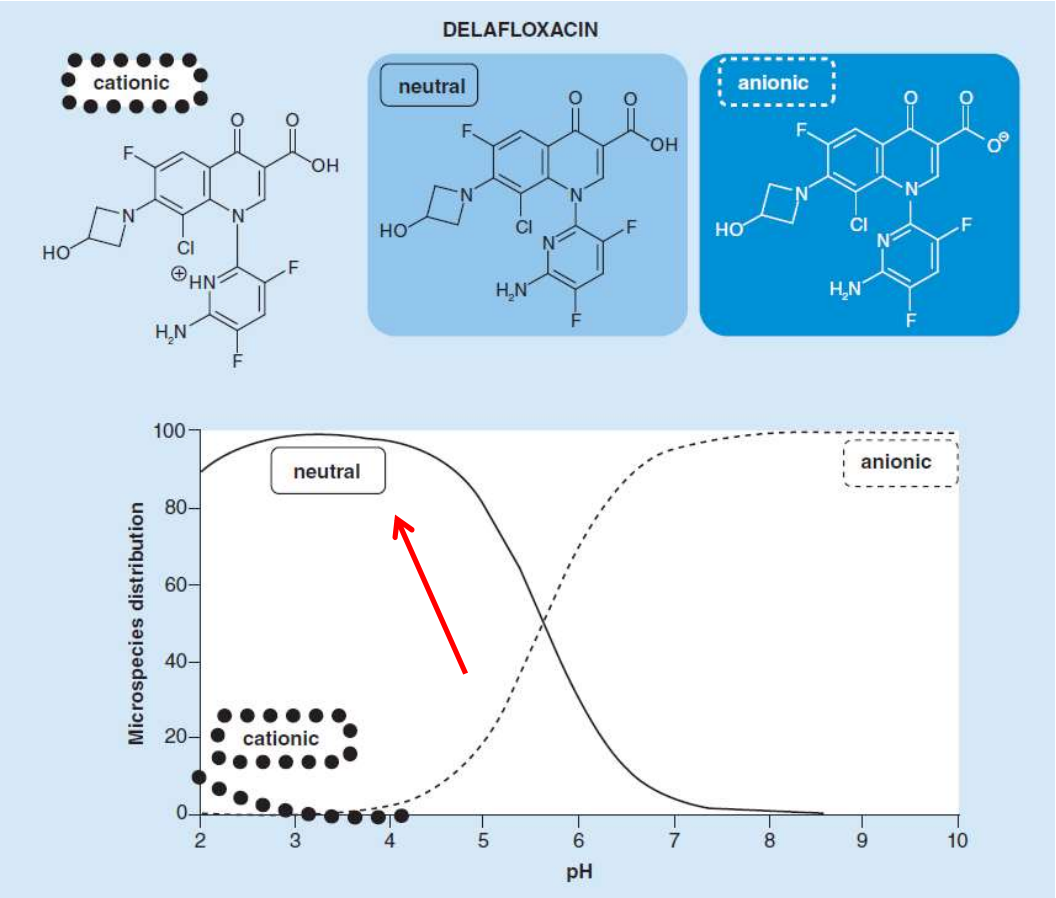


Anello eteroaromatico in posizione N1:
Si ritiene che la collaborazione tra questo sostituente e il gruppo debolmente polare in C8 possa influenzare la potenza contro i batteri gram-positivi resistenti ai chinoloni

Atomo di cloro in posizione C8:
Responsabile della debole polarità della molecola.
Contribuisce alla potenza verso i batteri gram-positivi.
Si ipotizza che questa sostituzione in C8 possa anche ridurre lo sviluppo di resistenze da parte di *S. aureus*

Mogle et al, J Antimicrob Chemother 2018; 73: 1439–1451; Jorgensen et al, Infect Dis ther (2018) 7:197-217

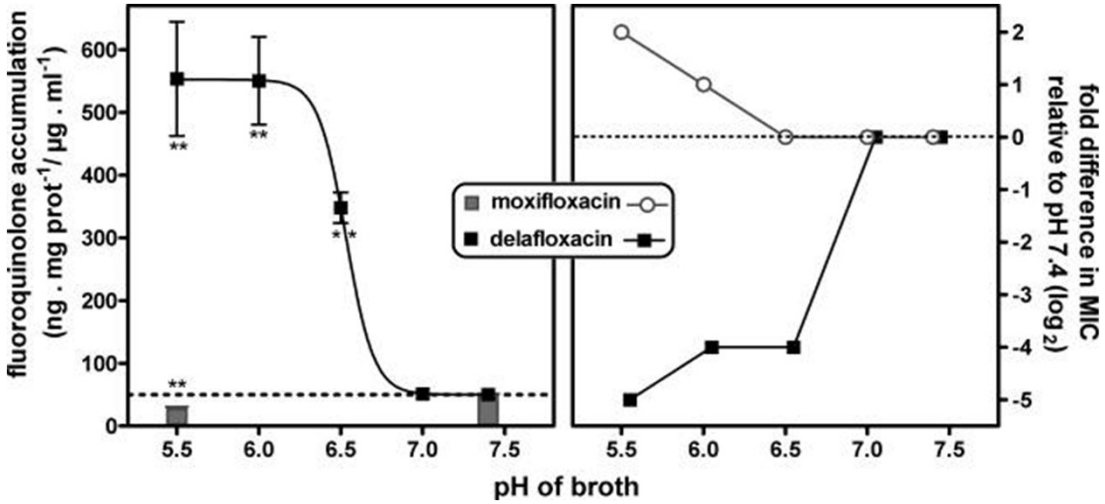
Comportamento di delafloxacina in funzione del pH: distribuzione microspecie



- **A pH fisiologico** (~7–7,4), delafloxacina si trova principalmente come **anione**, ma **a pH** leggermente **acido** (≤5,5), si trova soprattutto in forma **neutra**
- **Le condizioni acide** caratterizzano l'ambiente locale in molti siti di infezione: **tratto urinario, ascessi, ulcere da decubito, fluido di rivestimento epiteliale e fagolisosomi** di cellule infette, dove delafloxacina esiste prevalentemente in forma neutra
- **La forma neutra di un farmaco risulta la più diffusibile attraverso le membrane cellulari**
- Questa caratteristica differenzia delafloxacina da tutti gli altri FQ che esistono come zwitterioni a pH neutro e come cationi a pH acido

Van Bambeke et al, Future Microbiol. (2015) 10(7), 1111–1123

Ruolo del pH nell'accumulo dei fluorochinoloni all'interno dei batteri e sulla loro attività intrinseca



Questo studio ha valutato l'accumulo di Delafloxacina e Moxifloxacina e le loro MIC all'interno dello *S.aureus* a seguito (30 min) della variazione del pH da 7 a 5.5.

A pH neutro, l'accumulo intracellulare di moxifloxacina e delafloxacina sono risultati equivalenti

Quando invece il pH è sceso da 7.0 a 5.5, si è osservato un aumento dell'accumulo di delafloxacina (10 volte) e riduzione MIC (5 diluizioni) rispetto a Moxifloxacina

Lemaire S, et al. Antimicrob Agents Chemother. 2011;55(2):649-658.

Delafloxacina: meccanismo d'azione dual-target

Gli enzimi DNA girasi e topoisomerasi IV hanno la funzione di operare tagli temporanei e ricongiungimenti a livello della doppia elica del DNA durante la replicazione.
Quindi hanno quindi il *potenziale di frammentare il genoma batterico* (evento potenzialmente fatale).
I chinoloni legando l'enzima formano un **complesso ternario farmaco-enzima-DNA** (legame non covalente) impedendo quindi il normale controllo sul DNA da parte degli enzimi, causando quindi la morte della cellula batterica.

La resistenza ai fluorochinoloni deriva da mutazioni cromosomiche nelle regioni che determinano la resistenza ai chinoloni (*Quinolones resistance-determining regions,* QRDR) della DNA girasi (gene GyrA) e/o della topoisomerasi IV (gene ParC/GrlA).

I fluorochinoloni hanno una preferenza di legame per la DNA girasi nei batteri Gram-negativi e per la topoisomerasi IV nei Gram-positivi e questo viene indicato come il motivo principale dello sviluppo di resistenze.

A differenza degli altri fluorochinoloni **delafloxacina ha uguale affinità per entrambi gli enzimi sia nei Gram positivi che nei Gram negativi.**

Questo meccanismo ***dual target*** contribuisce a ridurre la selezione delle resistenze:
infatti dovrebbe esserci una mutazione in entrambi gli enzimi per ridurre significativamente la sensibilità del germe all'antibiotico.

Van Bambeke et al. Future Microbiol. (2015) 10(7), 1111–1123

Delafloxacina: forma farmaceutica, posologia e modalità di somministrazione

Infusione endovenosa	Compresse per via orale
300 mg ogni **12** h in infusione ev di **60** min	**450 mg** per os ogni **12** h
O SWITCH dalla formulazione endovenosa alla formulazione orale a discrezione del clinico	
La durata del trattamento è compresa tra 5 e 14 gg per le ABSSSI e 5-10 gg per le CAP	

Ricostituzione in condizioni asettiche, utilizzando 10,5 mL di destrosio (5%) soluzione iniettabile o Cloruro di sodio (0,9%) soluzione iniettabile per ciascun flaconcino da 300 mg.
La soluzione ricostituita deve essere diluita in una sacca per terapia endovenosa da 250 mL (cloruro di sodio 0,9% iniettabile o D5W).
Preparare la dose necessaria per l'infusione endovenosa prelevando un volume pari a 12 mL per Quofenix 300 mg e 8 mL per Quofenix 200 mg (ins. renale grave) dal flaconcino ricostituito.

Modificato da RCP Quofenix

Attività sui GRAM positivi

Table 1. Susceptibility of relevant Gram-positive pathogens to delafloxacin and other commercially available fluoroquinolones.

Species	Phenotype	Number of strains	Antibiotic	MIC_{50} (mg/l)	MIC_{90} (mg/l)	MIC range (mg/l)	Ref.[†]
S. aureus	All	681	Levofloxacin	0.12	>32	0.03–>32	[41]
		681	Delafloxacin	0.12	0.5	≤0.004–16	[41]
	FQ-S	70	Levofloxacin	0.25	0.5	0.06–0.5	[23]
		88		0.12	0.25	0.06–1	[42]
		70	Moxifloxacin	0.06	0.1	0.015–0.5	[23]
		70	Delafloxacin	0.004	0.008	0.002–0.008	[23]
		88		0.002	0.008	≤0.001–0.06	[42]
→	FQ-R	71	Levofloxacin	16	32	4–64	[23]
		100		4	8	2–32	[42]
		71	Moxifloxacin	4	8	0.25–16	[23]
		71	Delafloxacin	0.25	1	0.015–1	[23]
		100		0.006	0.12	0.015–2	[42]
S. epidermidis	FQ-S	9	Levofloxacin		0.25	0.12–0.5	[23]
		9	Moxifloxacin		0.12	0.03–0.12	[23]
		9	Delafloxacin		0.008	0.002–0.08	[23]
	FQ-R	10	Levofloxacin	16	16	4–128	[23]
		10	Moxifloxacin	2	2	1–>128	[23]
		10	Delafloxacin	0.5	0.5	0.12–1	[23]
Coagulase-negative staphylococci	All	19	Levofloxacin	0.12	>32	0.06–>32	[42]
		19	Delafloxacin	0.004	1	0.001–2	[42]
→	FQ-R	10	Levofloxacin	8	64	4–128	[18]
		10	Delafloxacin	0.25	0.5	0.03–0.5	[18]
β-hemolytic staphylococci	All	17	Levofloxacin	0.5	2	0.03–2	[42]
		17	Delafloxacin	0.008	0.015	≤0.002–0.015	[42]
S. pneumoniae	FQ-S	69	Levofloxacin	1	1	0.5–2	[23]
		69	Moxifloxacin	0.12	0.12	0.06–0.25	[23]
		69	Delafloxacin	0.008	0.015	0.004–0.015	[23]
→	FQ-R	33	Levofloxacin	16	32	2–32	[23]
		33	Moxifloxacin	2	4	0.25–8	[23]
		33	Delafloxacin	0.12	0.5	0.015–0.5	[23]
E. faecalis	FQ-S	18	Levofloxacin	1	1	0.5–2	[18,23]
		18	Moxifloxacin	0.25	0.5	0.12–0.5	[23]
		18	Delafloxacin	0.06	0.06	0.03–0.12	[23]
→	FQ-R	26	Levofloxacin	32	128	16–128	[23]
		26	Moxifloxacin	8	32	2–64	[23]
		26	Delafloxacin	0.25	8	0.06–32	[23]
E. faecium	FQ-S	14	Levofloxacin	1	4	0.5–4	[23]
		14	Moxifloxacin	1	2	0.12–4	[23]
		14	Delafloxacin	0.12	1	0.06–2	[23]
→	FQ-R	28	Levofloxacin	32	64	8–>128	[23]
		28	Moxifloxacin	16	16	1–32	[23]
		28	Delafloxacin	4	8	0.25–16	[23]
C. difficile	All	12	Levofloxacin	2	4	2–4	[18]
→		12	Delafloxacin	≤0.015	≤0.015	≤0.015	[18]

[†]Comparison of MIC distributions among antibiotics should be performed using data from a same bibliographic reference.
FQ-S: Fluoroquinolone susceptible; FQ-R: Fluoroquinolone resistant (based in most cases on CLSI susceptibility breakpoints for marketed comparators).

Le MIC di Delafloxacina rimangono basse anche contro i ceppi di GRAM POSITIVI resistenti ai fluorochinoloni incluso S. Aureus e S. Pneumoniae e Stafilococchi coagulasi negativi (Epidermidis) nel confronto con Levofloxacina e Moxifloxacina.

Valori **inferiori anche rispetto a quelli di moxifloxacina**, fino ad oggi considerato il più potente fluorochinolonico anti Gram-positivo disponibile

Sebbene più potente di altri fluorochinoloni contro gli enterococchi, le MIC possono raggiungere valori alti nei ceppi resistenti (soprattutto E. faecalis)

La delafloxacina è anche attiva sugli anaerobi, compreso *C. difficile (superiore a levofloxacina)*

Van Bambeke et al. Future Microbiol. 2015;10(7):1111-23

Attività sui GRAM negativi

Species	Phenotype	Number of strains	Antibiotic	MIC_{50} (mg/l)	MIC_{90} (mg/l)	MIC range (mg/l)	Ref.[†]
H. influenzae	FQ-S	110	Levofloxacin	0.015	0.03	0.002–0.5	[23]
		110	Moxifloxacin	0.015	0.06	0.004–0.12	[23]
		110	Delafloxacin	0.005	0.002	≤0.00025–0.004	[23]
	FQ-R	6	Levofloxacin			0.06–8	[23]
		6	Moxifloxacin			0.06–8	[23]
		6	Delafloxacin			0.004–0.5	[23]
M. catarrhalis	FQ-S	50	Levofloxacin	0.03	0.06	0.15–0.25	[23]
		50	Moxifloxacin	0.06	0.06	0.03–0.12	[23]
		50	Delafloxacin	0.002	0.004	0.0005–0.03	[23]
L. pneumophila	All	5	Levofloxacin	0.5	0.5	0.5	[18]
		5	Delafloxacin	0.12	0.12	0.12	[18]
M. pneumoniae	All	18	Levofloxacin	1	2	1–2	[18]
		18	Delafloxacin	0.5	0.5	0.25–0.5	[18]
H. pylori	All	45	Levofloxacin	0.5	0.5	0.12–1	[18]
		45	Delafloxacin	0.03	0.12	0.015–0.12	[18]
N. gonorrheae	All	100	Ciprofloxacin	≤0.015	8	≤0.015–16	[71]
		100	Delafloxacin	0.001	0.06	≤0.0005–0.06	[71]
E. coli	FQ-S	45	Ciprofloxacin	0.015	0.06	0.004–0.25	[23]
		10				0.008–0.25	[26]
		45	Delafloxacin	0.03	0.06	0.04–0.25	[23]
		10				0.016–0.25	[26]
	FQ-R	27	Ciprofloxacin	128	>128	4–>128	[23]
		21				64–>128	[26]
		27	Delafloxacin	4	8	1–16	[23]
		21				2–128	[26]

La delafloxacina si dimostra anche più potente della moxifloxacina e della levofloxacina contro altri patogeni respiratori come *H. influenzae, M. catarrhalis, L. pneumophila* o *Mycoplasma pneumoniae.*

Le sue MIC sono particolarmente basse anche verso *N. gonorrheae, H. pylori, E. Coli.*
In questi casi, attività ancora più elevata *in vivo* , a causa del pH particolarmente acido.

Van Bambeke et al. Future Microbiol. 2015;10(7):1111-23

Attività sullo Pseudomonas Aeurginosa

TABLE 1 Comparison of susceptibility of *Pseudomonas aeruginosa* to delafloxacin and ciprofloxacin

Ciprofloxacin	Ciprofloxacin MIC (mg/L) Mean ± SEM	Delafloxacin MIC (mg/L) Mean ± SEM [Paired with Ciprofloxacin comparator]	*p* value
Total isolate (n = 50)	3.20 ± 0.58	1.13 ± 0.16	0.0005***
Sensitive [S ≤ 0.5 mg/L] (n = 10)	0.27 ± 0.04	0.17 ± 0.02	0.01*;
Intermediate [I = 1.0 mg/L] (n = 12)	1.15 ± 0.10	0.78 ± 0.12	0.01*;
Resistant [R ≥ 2.0 mg/L] (n = 28)	4.89 ± 0.88	1.28 ± 0.21	0.001**
Reference Strain (ATCC 27 853)	0.19	0.25	–

Lo studio ha esaminato la sensibilità **in vitro** di Delafloxacina e Ciprofloxacina nei confronti di P. aeruginosa (n = 50 isolati da pazienti adulti con **fibrosi cistica)**.

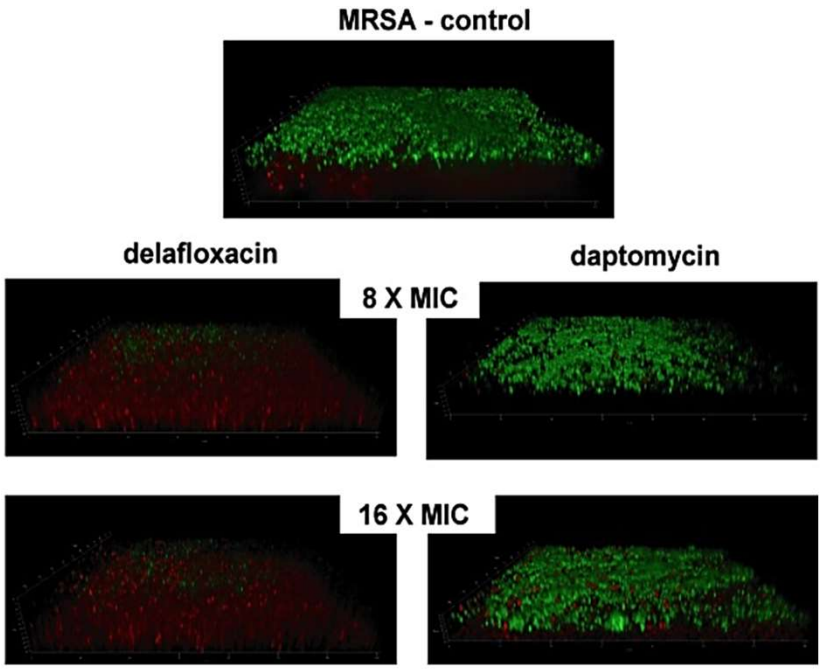
Nel complesso, **gli isolati erano statisticamente più sensibili a Delafloxacina (p = 0,0005) rispetto a Ciprofloxacina**.

Da questo studio è emerso inoltre che circa l'80% di isolati di P. Aeruginosa resistenti alla Ciprofloxacina non erano resistenti a Delafloxacina

Millar et al Clin Respir J. 2021 Jan;15(1):116-120

Delafloxacina ha una potente attività nei confronti del Biofilm da Stafilococco Aureo, incluso MRSA (modello sperimentale)

E’ stata studiata l'efficacia di vari antibiotici (vancomicina, acido fusidico, moxifloxacina, **daptomicina e delafloxacina**) sui biofilm di MSSA e MRSA



Verde: cellule vitali
Rosso: cellule morte

- Immagini tridimensionali da microscopia a scansione laser di biofilm da MRSA in condizioni di controllo o dopo esposizione a delafloxacina o daptomicina a concentrazioni 8 e 16 volte la rispettiva MIC per 48 ore

- **Delafloxacina è apparsa più efficace di Daptomicina ad entrambe le concentrazioni (8 e 16 volte la MIC) nel ridurre il Biofilm da MRSA in questo modello sperimentale**

Bauer J, et al. Antimicrob Agents Chemother. 2013;57(6):2726-2737.

Global overview on the microbiology of diabetic foot infection

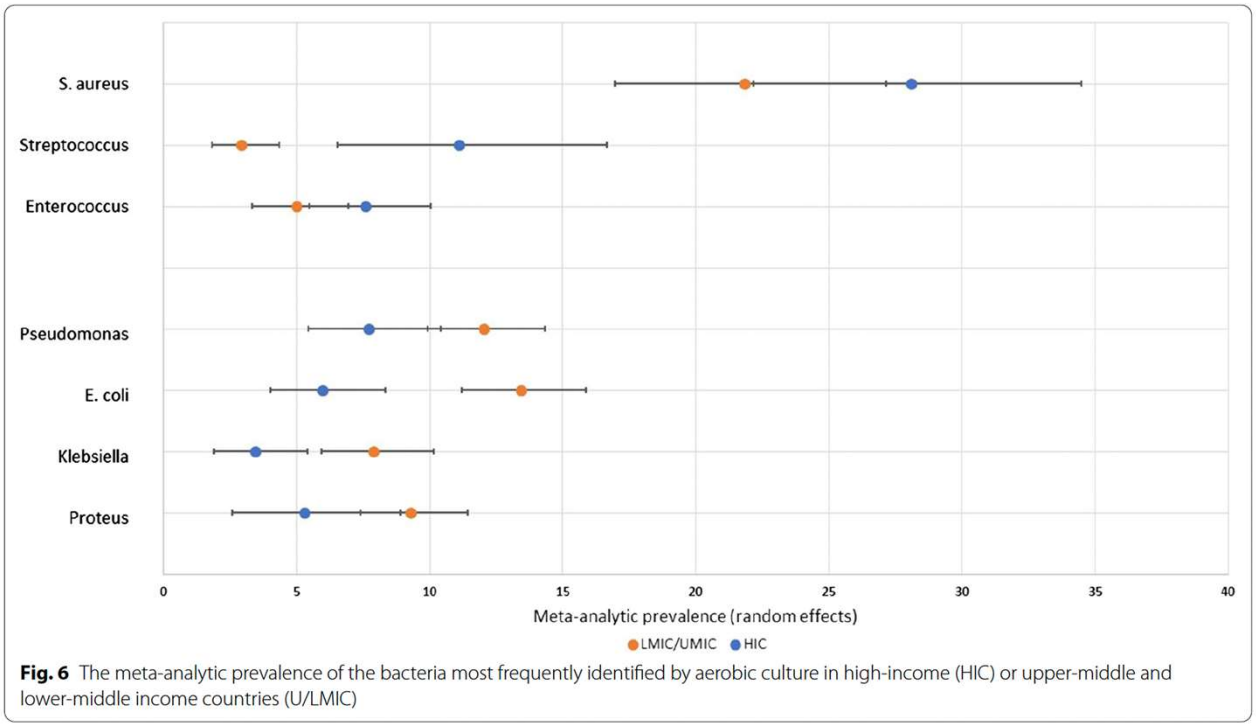


Fig. 6 The meta-analytic prevalence of the bacteria most frequently identified by aerobic culture in high-income (HIC) or upper-middle and lower-middle income countries (U/LMIC)

Macdonald *et al. BMC Infect Dis* (2021) 21:770
https://doi.org/10.1186/s12879-021-06516-7

BMC Infectious Diseases

RESEARCH Open Access

The microbiology of diabetic foot infections: a meta-analysis

Katherine E. Macdonald[1], Sophie Boeckh[2], Helen J. Stacey[3] and Joshua D. Jones[1*]

- The prevalence of **Streptococcal species** was significantly greater among high income countries (HICs).
- The prevalence of ***Enterococcus* spp.** and ***S. aureus*** was also higher among HICs, but not significantly so.
- ***Klebsiella* spp.** and ***E. coli*** were significantly more common among diabetic foot infections in upper-middle/lower-middle income countries than HICs.
- ***Proteus* spp. and *Pseudomonas* spp.** were also more prevalent among U/LMICs, but not significantly so.

BMC Infect Dis. 2021 Aug 9;21(1):770

Macdonald, K.E. et al (2021). The microbiology of diabetic foot infections: a meta-analysis. *BMC Infectious Diseases*. **21**(1): 770.

Antibiotic Tx

Major Limitations:

- **Drug-resistance**
- **ABX diffusion:**
  - ✓ **Abscesses/Fluids**
  - ✓ **Necrotic tissue**
  - ✓ **Biofilm/Devices**
  - ✓ **Osteomyelitis**
  - ✓ ***Vasculopathy/Hypoperfusion***
- **Other Host factors:**
  - ✓ **Decompensated Diabetes**
  - ✓ **Malnutrition**
  - ✓ **Smoking**

General management of cSSTIs

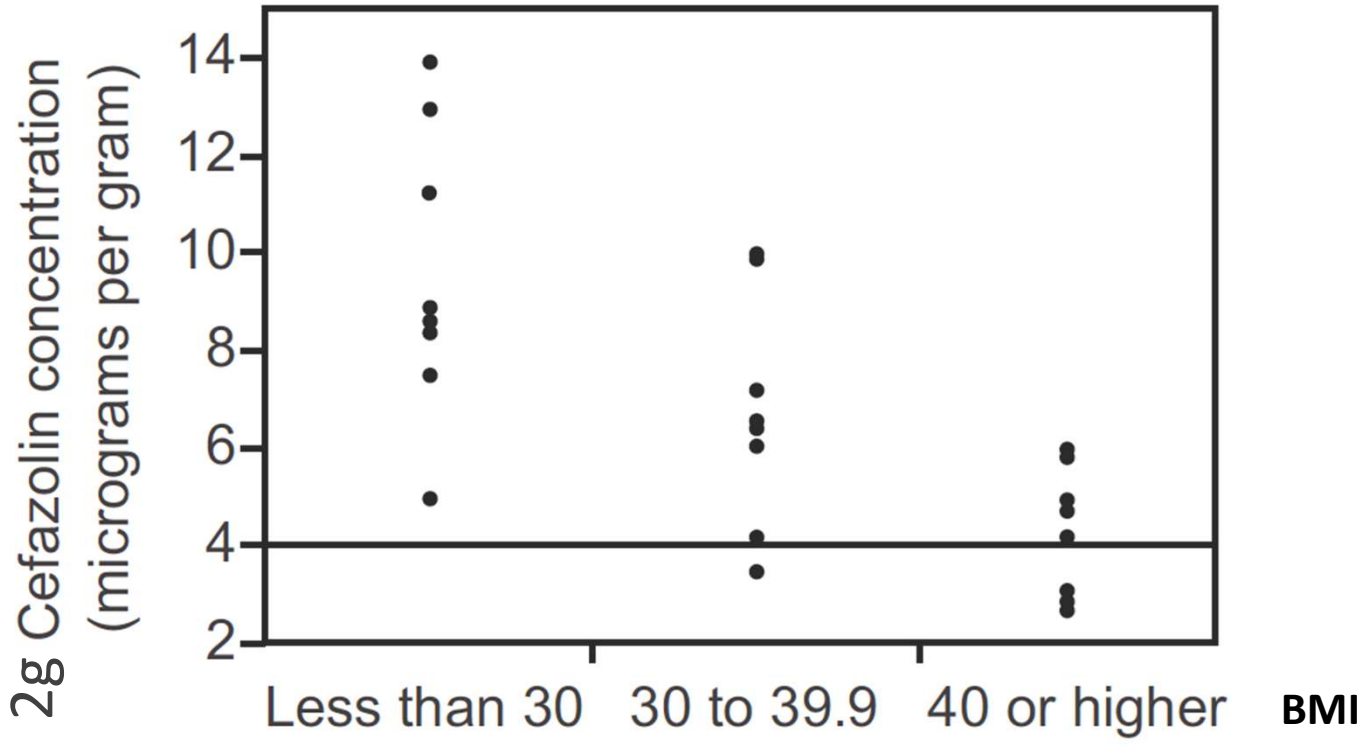
SOURCE CONTROL !!!

If indicated:

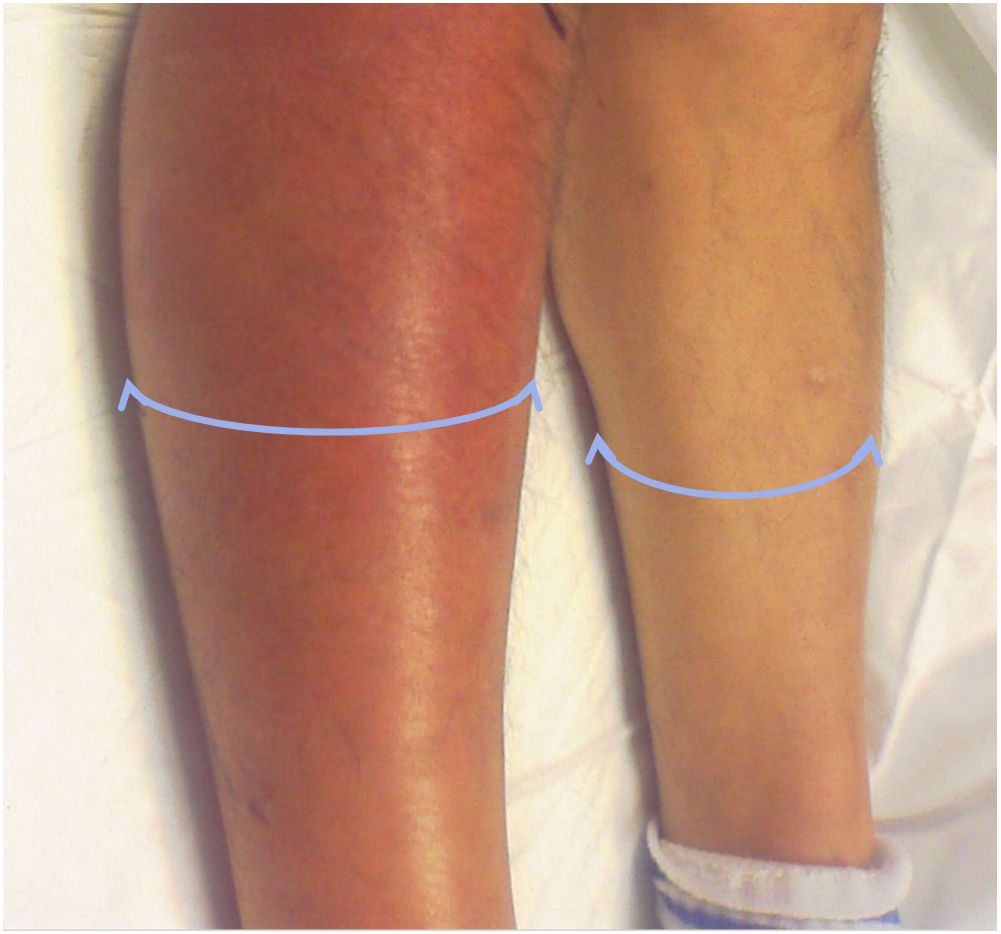
- **Incision and drainage**
- **Debridement**
  - **Including removal of foreign bodies if possible**
  - ***Extended to bone if osteomyelitis***
- **Local management**
  - **frequent detersion, antiseptics**
  - **if appropriate: advanced medications, VAC therapy**
- **Revascularization**

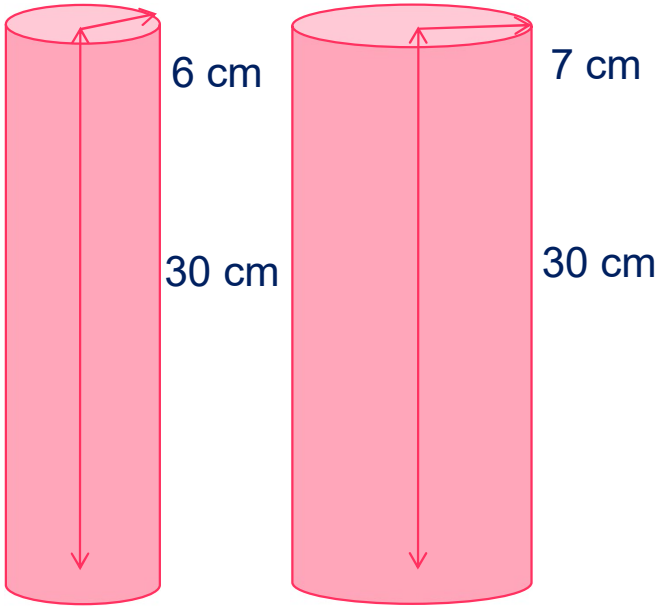
Adapted from Liu et al. Clin Infect Dis 2011;52:285-92;

Effects of Maternal Obesity on Tissue Concentrations of Prophylactic Cefazolin During Cesarean Delivery



Pevzner, L. et al (2011). Effects of Maternal Obesity on Tissue Concentrations of Prophylactic Cefazolin During Cesarean Delivery. Obstetrics & Gynecology. 114(4): 877-882.





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

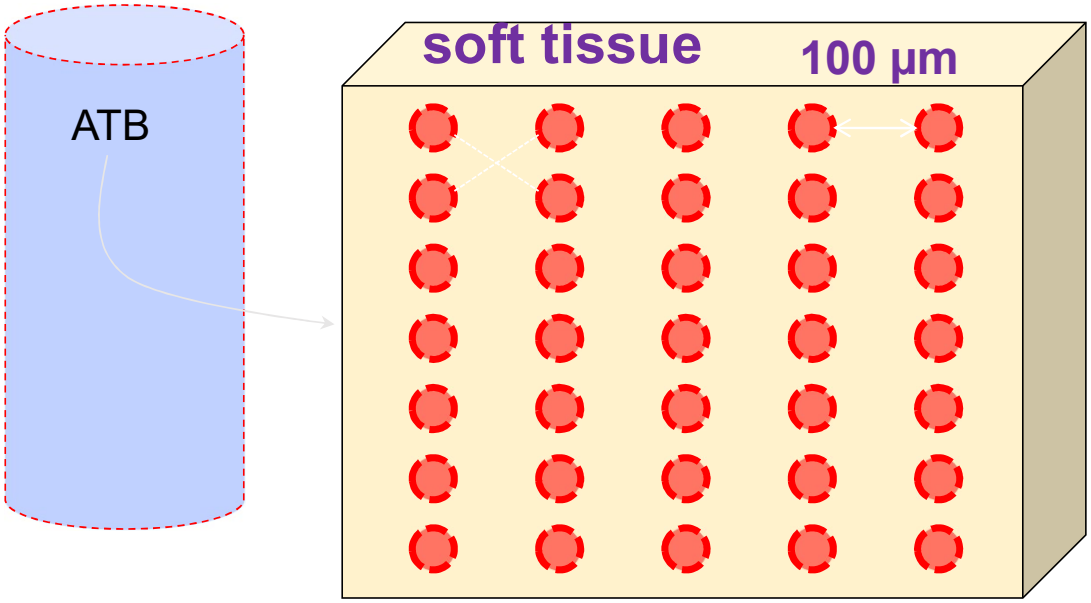
$V_1 = 3.3\ L$

$V_2 = 4.6\ L$

$\Delta\ 25\%$

Speaker's own opinion.

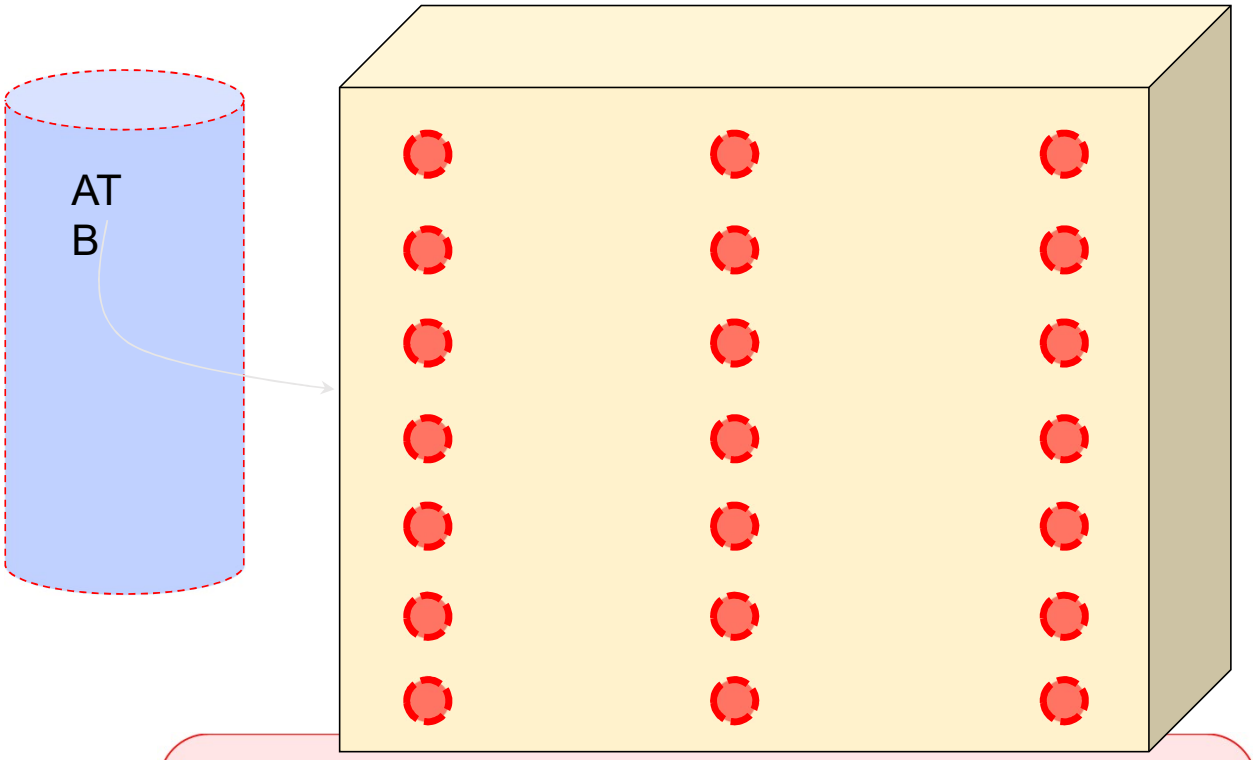
Factors determining the antibiotic concentration in soft tissue



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



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

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

Conclusions

- Healthcare systems under pressure
- Increasing admissions with SSTI
- Significant opportunities to avoid admission/ support early discharge
- OPAT service supervision ideal or local ambulatory care supported by AMS teams (guidance and governance)
- Service provision not consistent – no one size fits all approach
- Solutions for harder to reach populations where daily attendance is not possible are needed – role of well governed use of long acting IV agents