Ospedale San Paolo
Polo Universitario

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

Università degli Studi di Milano

PANDORA 5.0
Esperienze a confronto in Malattie Infettive 2018

Utilizzo di Dalbavancina nelle infezioni dei tessuti molli e in casi off label

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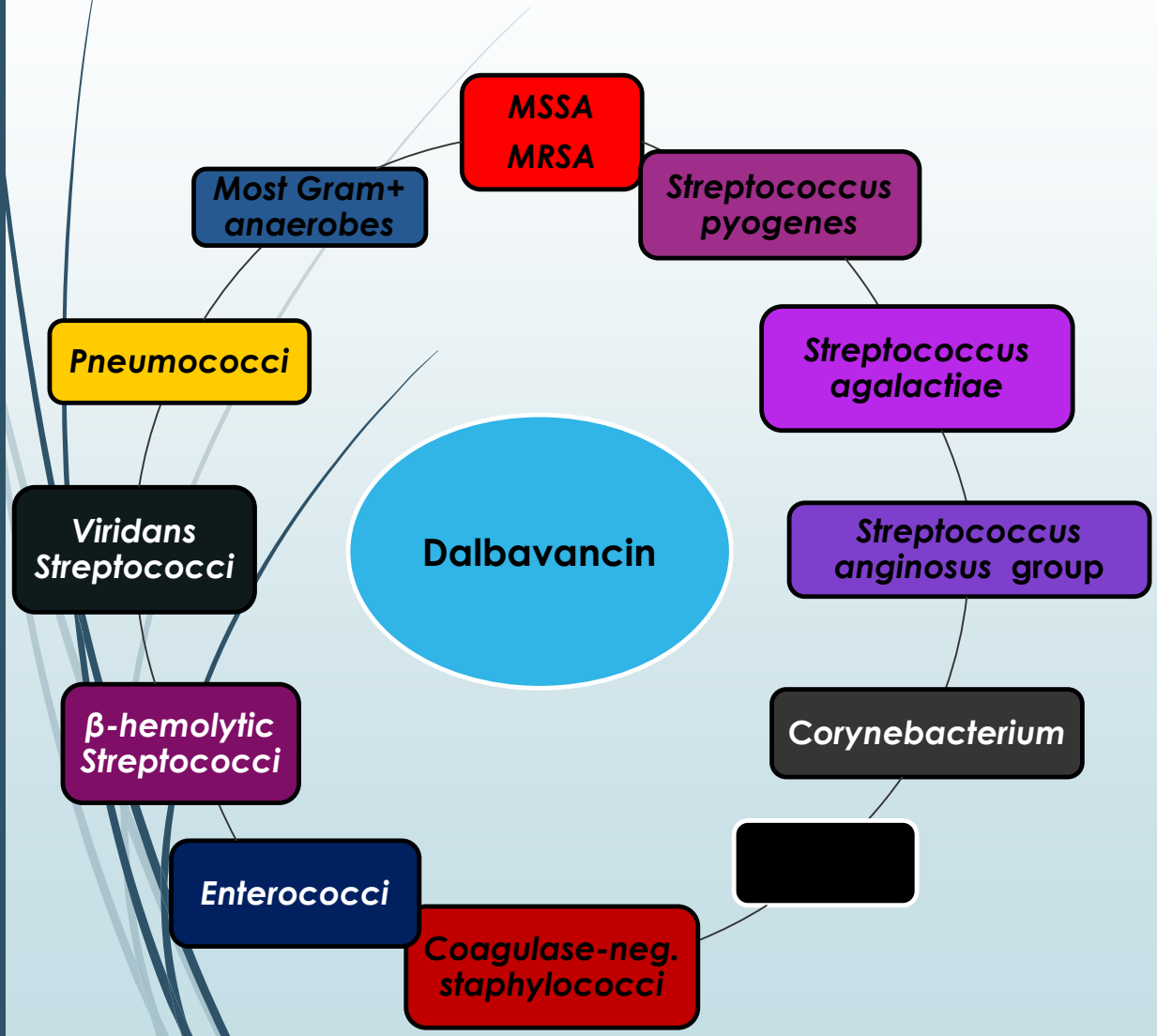
Outline

- Dalbavancina
- Dati di real life in letteratura
- Utilizzo off label e dati disponibili
- L'esperienza dell'H San Paolo

Dalbavancina



- La dalbavancina è **un lipoglicopeptide** (glicopeptide semisintetico strutturalmente correlato alla teicoplanina) con effetto **battericida.**
- Il suo meccanismo d'azione sui batteri Gram positivi sensibili consiste **nell'interruzione della sintesi della parete cellulare**, attraverso il legame al terminale D-alanil-D-alanina dell'estremità peptidica nel peptidoglicano della parete cellulare nascente, prevenendo il cross-linking (transpeptidazione e transglicolazione) delle subunità del disaccaride

Dalbavancina

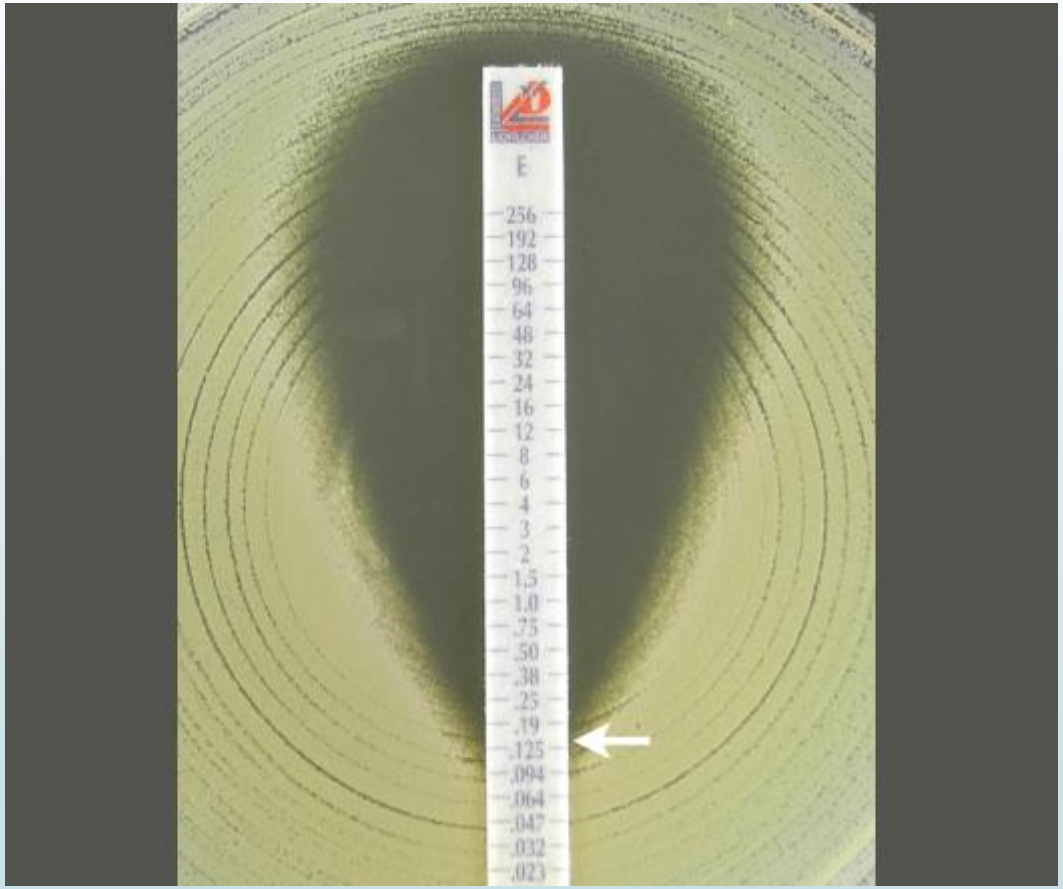
Microbiologia:

- I valori di MIC stabiliti da EUCAST sono:

  S ≤0,125 mg/L per Staphylococcus spp., e Streptococchi beta-emolitici di gruppo A, B, C, G e St. anginosus.

- **La R** tra i batteri Gram positivi sembra essere limitata a certe specie **intrinsicamente resistenti ai glicopeptidi e a batteri che esprimono il fenotipo VanA**.

- NB sembra esista un certo grado di **cross-resistenza all'interno della classe dei glicopeptidi.**



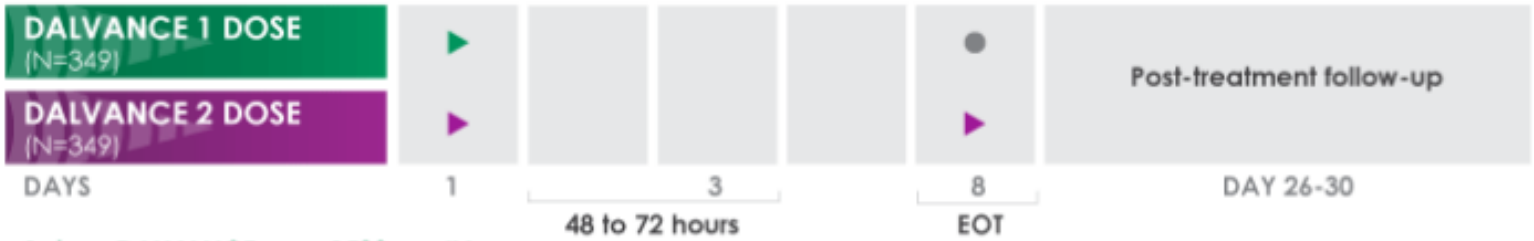
Dalbavancina

FARMACOCINETICA

- **L'emivita è di 372 or**
- La dalbavancina si l
  umane, principalme
  plasmatiche della d
  dalla sua concentra
  la somministrazione
  circa un 30% della d
  un 20% nelle feci.

1 dose study design[1,2]

- Phase 3, randomized, double-blind, noninferiority trial evaluated the efficacy and safety of 1 dose DALVANCE vs the 2 dose DALVANCE regimen[1]



- 1 dose DALVANCE arm: 1500 mg IV
- 2 dose DALVANCE arm: 1000 mg IV followed one week later by 500 mg IV
- Placebo

- The ITT population included 698 randomized adult patients* with documented ABSSSI[1]
- Patient selection criteria: patients with cellulitis, abscess, or wound infection with a lesion size ≥75 cm^2 and at least one systemic sign of disease at baseline, defined as[2]:
  - Temperature ≥38°C,
  - WBC count >12,000 cells/mm^3, or
  - ≥10% band forms on WBC differential

Dalbavancina

Gli effetti avversi più frequenti sono stati:

- **nausea (4.7%),**
- **cefalea (3.8%)**
- **diarrea (3.4%).**

Da segnalare:

Hypersensitivity Reactions : serious hypersensitivity (anaphylactic) and skin reactions have been reported with glycopeptide antibacterial agents. Exercise caution in patients with known hypersensitivity to glycopeptides due to the possibility of cross-sensitivity. If an allergic reaction occurs, treatment with DALVANCE should be discontinued.
Infusion-related Reactions: Rapid intravenous infusion can cause reactions, including flushing of the upper body, urticaria, pruritus, and rash.
Hepatic Effects ALT elevations were reported in clinical trials.
Clostridium difficile-associated Diarrhea: Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agent, with severity ranging from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs.

Dalbavancina

- **FDA Indications: ABSSI -**

DISCOVER1 e DISCOVER2—
Dalbavancin for infections of the skin compared to Vancomycin/Linezolid

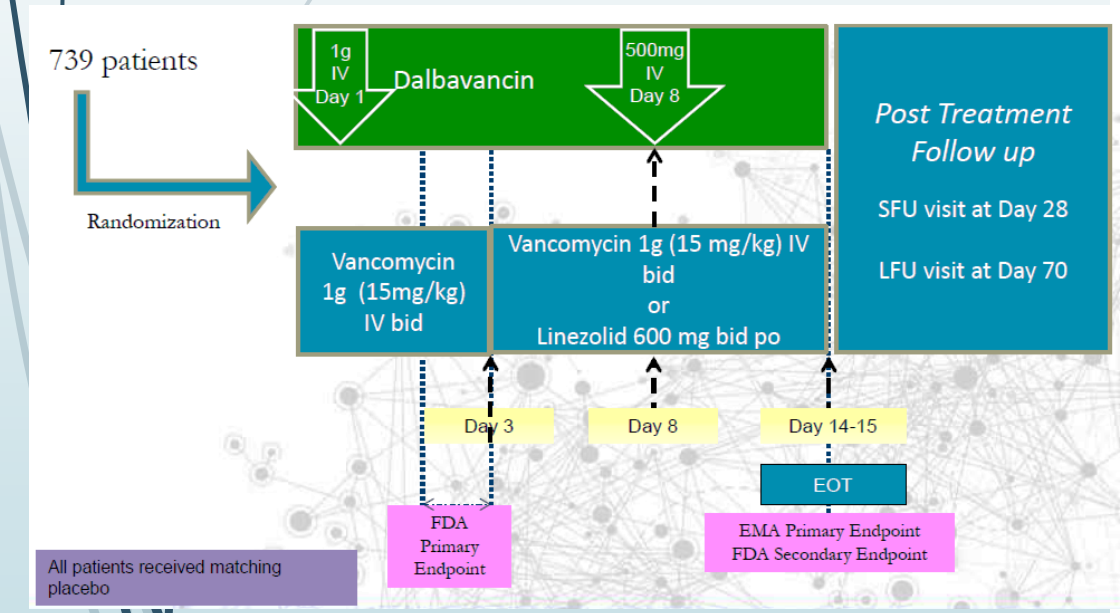


Table 2. Primary and Secondary Efficacy End Points.*

End Point	Dalbavancin	Vancomycin–Linezolid	Absolute Difference (95% CI)
	number/total number (percent)		*percentage points*
Primary end point			
DISCOVER 1	240/288 (83.3)	233/285 (81.8)	1.5 (–4.6 to 7.9)
DISCOVER 2	285/371 (76.8)	288/368 (78.3)	–1.5 (–7.4 to 4.6)
Both trials	525/659 (79.7)	521/653 (79.8)	–0.1 (–4.5 to 4.2)
Sensitivity analysis			
DISCOVER 1	259/288 (89.9)	259/285 (90.9)	–1.0 (–5.7 to 4.0)
DISCOVER 2	325/371 (87.6)	316/368 (85.9)	1.7 (–3.2 to 6.7)
Both trials	584/659 (88.6)	575/653 (88.1)	0.6 (–2.9 to 4.1)
Secondary end point			
Clinical status	517/570 (90.7)	502/545 (92.1)	–1.5 (–4.8 to 1.9)
Sensitivity analysis of clinical status†	533/570 (93.5)	517/545 (94.9)	–1.4 (–4.2 to 1.4)
Investigator's assessment of outcome	547/570 (96.0)	527/545 (96.7)	–0.7 (–3.0 to 1.5)

Primary Endpoint: early response at 48-72 hours post initiation of therapy cessation of spread of the erythema of the lesion, and resolution of fever.
Secondary Endpoint: Clinical Status at End of Therapy (Day 14-15, EMA primary endpoint).

Extended-Duration Dosing and Distribution of Dalbavancin into Bone and Articular Tissue

Michael W. Dunne,[a] Sailaja Puttagunta,[a] Craig R. Sprenger,[c]* Chris Rubino,[b] Scott Van Wart,[b] James Baldassarre[a]

Durata Therapeutics, Inc., Branford, Connecticut, USA[a]; Institute for Clinical Pharmacodynamics, Latham, New York, USA[b]; PRACS Institute, Ltd., Fargo, North Dakota, USA[c]

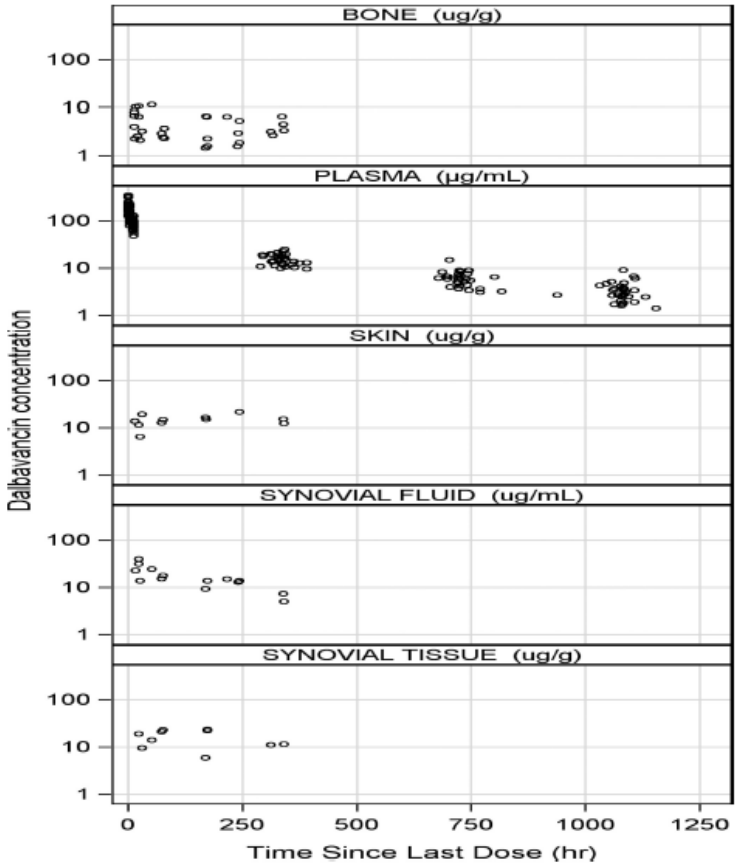


FIG 2 Dalbavancin concentrations in plasma, bone, and related tissues. Semi-log scatterplots: one skin concentration and eight synovial tissue concentrations were greater than the upper limit of quantification of the assay and do not appear in these plots.

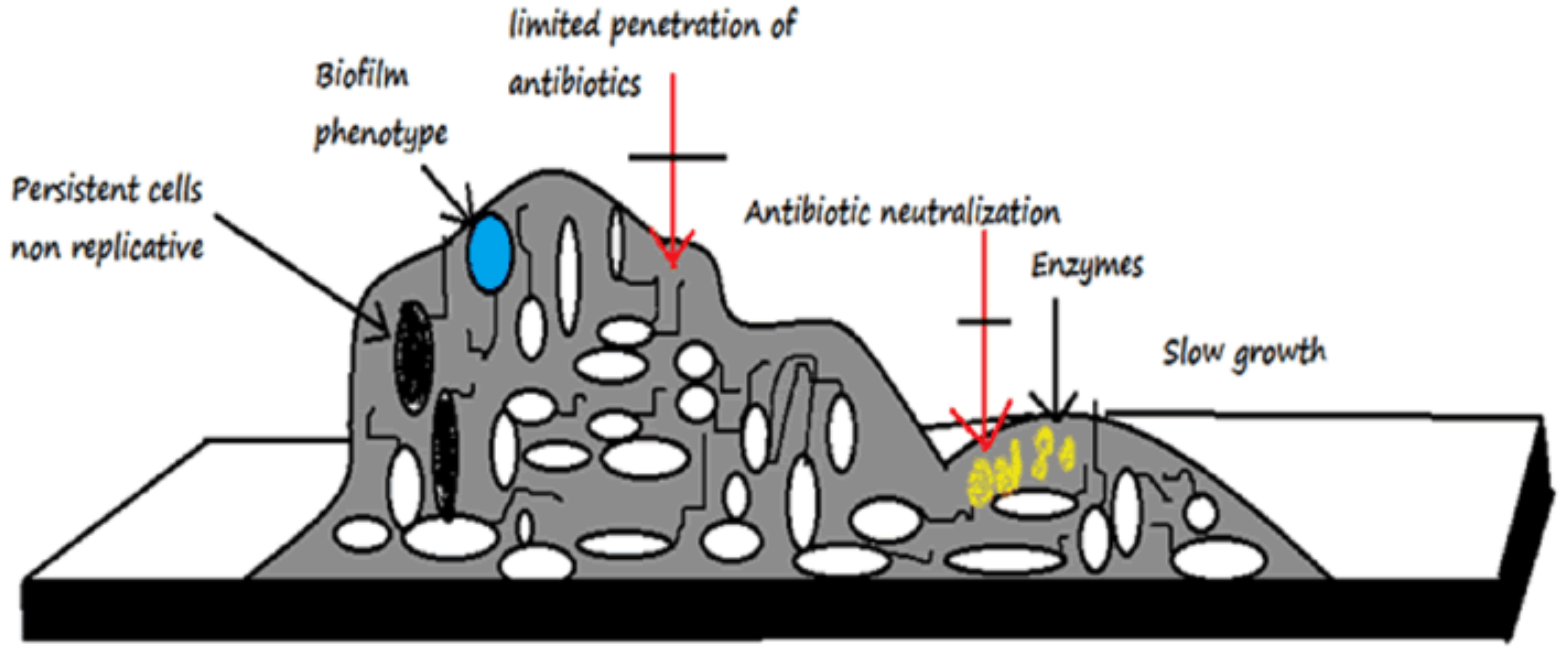
The concentrations of dalbavancin in bone are expected to be relevant to treatment of osteomyelitis. Dalbavancin in the serum is 93% protein bound, mostly to albumin, and the bone/plasma ratio is 13%. The drug levels measured in bone are very similar to the calculated simult
in serum, and as a
be free and availa
concentrations of
uninfected subjec
tions in infected b
higher than those

The concentrations of dalbavancin in other tissues were also assessed. In synovium and synovial fluid, the levels of the drug were even higher than those in bone. Due to the limited number of samples of evaluable synovial fluid, synovial tissue, and skin concentrations, it was not possible to model the time course of dalba-
vancin conce
However, pa
hibited signi
dalbavancin

These data provide evidence that dalbavancin distributes in the bone, skin, and articular tissue at concentrations that are expected to exceed the MIC for *S. aureus* for extended periods of time after a significantly shortened dosing regimen. Pharmacokinetic modeling provides direction to the selection of a therapeutic dosing regimen for treatment of infections in these tissues and justifies further study in prospective clinical trials.

Bacterial biofilms

	Components	Percentage of matrix
1	Microbial cells	2-5%
2	DNA and RNA	<1-2%
3	Polysaccharides	1-2%
4	Proteins	<1-2% (including enzymes)
5	Water	Up to 97%



. Description of the key mechanisms involved in antibiotic resistance such as enzyme causing neutralizations,presence of persistent (non-dividing) cells and biofilm phenotype

Hall-Stoodley L. et al.: Nat Rev Microbiol. 2004 Feb;2(2):95-108.

Dalbavancina e Biofilm

Eur J Clin Microbiol Infect Dis (2017) 36:677–680
DOI 10.1007/s10096-016-2845-z

ORIGINAL ARTICLE

Dalbavancin reduces biofilms of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE)

D. Knafl[1] · S. Tobudic[1] · S. C. Cheng[2] · D. R. Bellamy[3] · F. Thalhammer[1]

Medical devices, such as intravenous catheters, prosthetic heart valves, and vascular or joint prostheses, have contributed to reducing morbidity and mortality for numerous patients every year [1]. However, they are fraught with the risk of leading to surface-associated infections through formation of bacterial or fungal biofilms [1]. Although explantation of the

From the results of this study, dalbavancin shows in-vitro activity against biofilms with MRSA and MRSE in concentrations between 1 and 16 mg/l, which are concentrations easily reached in vivo, as mean plasma concentrations have been shown to be > 35 mg/l for 7 days after one dose of 1,000 mg

Only when dalbavancin was combined with rifampicin could reduction of biofilm MRSA be observed [7]. We suspect this

7. Baldoni D, Furustrand Tafin U, Aeppli S et al (2013) Activity of dalbavancin, alone and in combination with rifampicin, against methicillin-resistant *Staphylococcus Aureus* in a foreign-body infection model. Int J Antimicrob Agents 42:220–225

Dalbavancina e Biofilm

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In vitro activity of dalbavancin against biofilms of staphylococci isolated from prosthetic joint infections

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[d] Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester,

ABSTRAC

The in vitro activity of dalbavancin was tested against biofilms of 171 staphylococci associated with prosthetic joint infection.

Dalbavancin minimum biofilm bactericidal concentration (MBBC) values were:
MBBC50 for Staphylococcus aureus and Staphylococcus epidermidis, **1 µg/mL;**
MBBC90 for S. aureus**, 2 µg/mL**;
MBBC90 for S. epidermidis, **4 µg/mL.**

previous study for the same set of isolates, showing that the
vancomycin MBBC50 and MBBC90 were both ≥128 µg/ml
tedizolid MBBC50 and MBBC90 were both >32 µg/ml (Schmidt-Malan et al., 2016).

Can dalbavancin be used as a catheter lock solution?

Authors: Cristina Díaz-Ruíz[1], Beatriz Alonso[2,3], Emilia Cercenado[2], Raquel Cruces[2,3], Emilio Bouza[4], Patricia Muñoz[2,3], María Guembe[2,3]

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JOURNAL OF **MEDICAL MICROBIOLOGY**
The full breadth of clinical microbiology

Purpose. The new lipoglycopeptide dalbavancin has only been approved for acute bacterial skin and skin structure infections. However, its alternative use as a catheter lock solution could facilitate the conservative management of catheter-related bloodstream infection. Our objective was to assess the stability and activity of dalbavancin alone and in combination with heparin against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE) biofilms. We also compared the results with those obtained with vancomycin alone and in combination with heparin.

Methodology. We used a 96-well plate *in vitro* model based on 24 h biofilms of MRSA and MRSE (ATCC 43300, ATCC 35984 and one clinical strain of each). The biofilms were exposed to dalbavancin (0.128 mg ml^{-1}) and vancomycin (5 mg ml^{-1}) alone and in combination with heparin (60 IU). The median percentage reductions in metabolic activity, biomass, bacterial load, and cell viability for each solution were compared.

Results. Dalbavancin combined with heparin significantly reduced the median [interquartile range (IQR)] percentage of metabolic activity in MRSA biofilms compared with vancomycin [90.0% (70.4–92.9%) versus 35.0% (14.8–59.6%), *P*=0.006]. For the remaining variables studied, the combination was not inferior to vancomycin for MRSA and MRSE.

Conclusions. Dalbavancin proved to be active against MRSA and MRSE biofilms. The combination of dalbavancin with heparin is a promising catheter lock solution that has the advantage of locking the catheter at home for 7 days.

Preview this:

Real Life Experience

International Journal of Antimicrobial Agents 51 (2018) 571–577

Dalbavancin in the treatment of different gram-positive infections: a real-life experience

Emilio Bouza [a,b,c,d], Maricela Valerio [a,*], Alex Soriano [e], Laura Morata [e], Enrique García Carus [e], Carmen Rodríguez-González [b,f], Ma Carmen Hidalgo-Tenorio [g], Antonio Plata [h], Patricia Muñoz [a,b,c,d,*], Antonio Vena [a,b,d] on behalf of the DALBUSE Study Group (Dalbavancina: Estudio de su uso clinico en España)

- **Observational retrospective study** developed in 29 hospitals from 14 urban centres in Spain.
- Centres taking part were invited to include all cases of **infections treated with dalbavancin** from January 2016 to January 2017.
- Clinical outcome: considered successful when patients had **no clinical** (resolution of signs and symptoms related to bacterial infection) **or microbiological evidence of infection during the follow-up period.**

Dalbavancin in the treatment of different gram-positive infections: a real-life experience

Table 1
Baseline patient characteristics ($n = 69$).

Characteristic	n (%) [a]
Age (years) [median (IQR)]	63.5 (49.3–72.0)
Male sex	40 (58.0)
Department	
Medical	36 (52.2)
Surgical	29 (42.0)
Outpatient setting	4 (5.8)
Underlying diseases	
Diabetes mellitus	23 (33.3)
Cardiovascular disease	22 (31.9)
Respiratory tract disease	15 (21.7)
Neurological disorder	14 (20.3)
Immunosuppressive therapy	9 (13.0)
Solid-organ malignancy	8 (11.6)
Gastrointestinal disease	7 (10.1)
Haematological malignancy	3 (4.3)
HIV infection	2 (2.9)
Bone marrow transplant	1 (1.4)
Solid-organ transplant	1 (1.4)
Renal function	
Chronic renal failure	15 (21.7)
Haemodialysis	4 (5.8)
Liver disease [b]	7 (10.1)
A	3 (4.3)
B	3 (4.3)
C	1 (1.4)
Charlson comorbidity index [median (IQR)]	3 (1–5)
McCabe score	
Non-fatal	52 (75.4)
Ultimately fatal	14 (20.3)
Rapidly fatal	3 (4.3)

IQR, interquartile range; HIV, human immunodeficiency virus.
[a] Data are *n* (%) unless otherwise stated.
[b] Child–Pugh score.

Table 3
Previous treatment characteristics and dalbavancin treatment information ($n = 69$).

Variable	n (%) [a]
Prior antibiotic therapy	
Received previous antibiotic	67 (97.1)
Days of antibiotics before dalbavancin therapy [median (IQR)]	18 (9.8–50.5)
Number of antibiotics received before dalbavancin therapy [median (IQR)]	2 (1–3)
Type of treatment	
Empirical therapy	7 (10.1)
Targeted therapy	61 (88.4)
Secondary prophylaxis	1 (1.4)
Main reasons for dalbavancin use	
Easier antibiotic administration	51 (73.9)
Previous antibiotic failure	21 (30.4)
Bone marrow toxicity	14 (20.3)
Antimicrobial resistance to previous antibiotic	13 (18.8)
Antibiotic allergy	10 (14.5)
Renal failure related with previous antibiotic	8 (11.6)
Poor compliance	3 (4.3)
Other reasons [b]	8 (11.6)
Adequate control of the infection source [c]	31/42 (73.8)
Dalbavancin therapy	
Days of dalbavancin therapy [median (range)]	21 (7–168)
Concomitant antibiotic therapy	25 (36.2)

Dalbavancin in the treatment of different gram-positive infections: a real-life experience

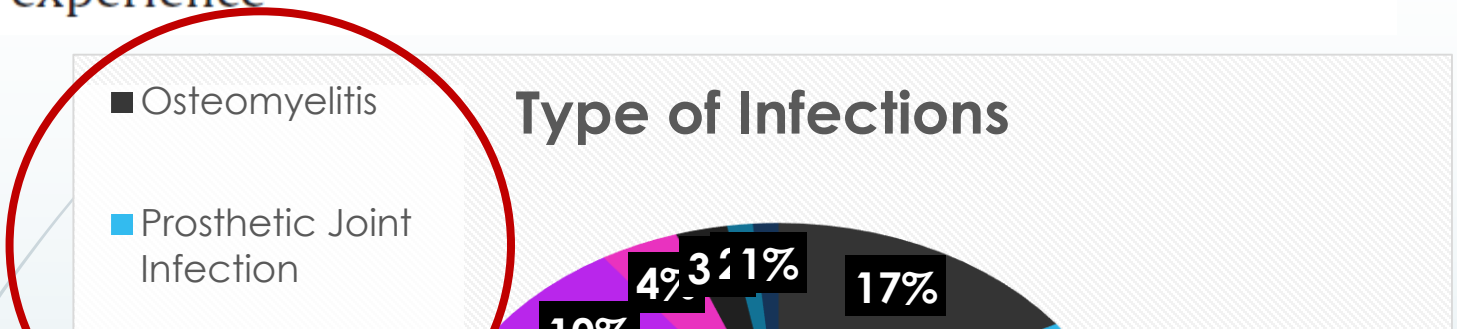


Table 2
Type of ns.

Infecti	MRSA	MSSA	CoNS	*Enterococcus* spp.	*Streptococcus* spp.	Other [a]	Negative culture
Prosth	3	1	13	1	0	1	1
ABSSS	5	6	3	1	0	0	1
Osteo	3	1	3	2	0	3	1
Cathe	3	2	3	1	0	0	0
Endoc	1	0	2	2	1	0	1
Intra-	0	0	0	3	0	0	0
Other	1	0	0	1	0	0	0
Septic	0	1	0	0	0	0	0
Sinusi	0	0	0	0	1	0	0
Overa	16	11	24	11	2	4	4

Dalbavancin in the treatment of different gram-positive infections: a real-life experience

Outcomes

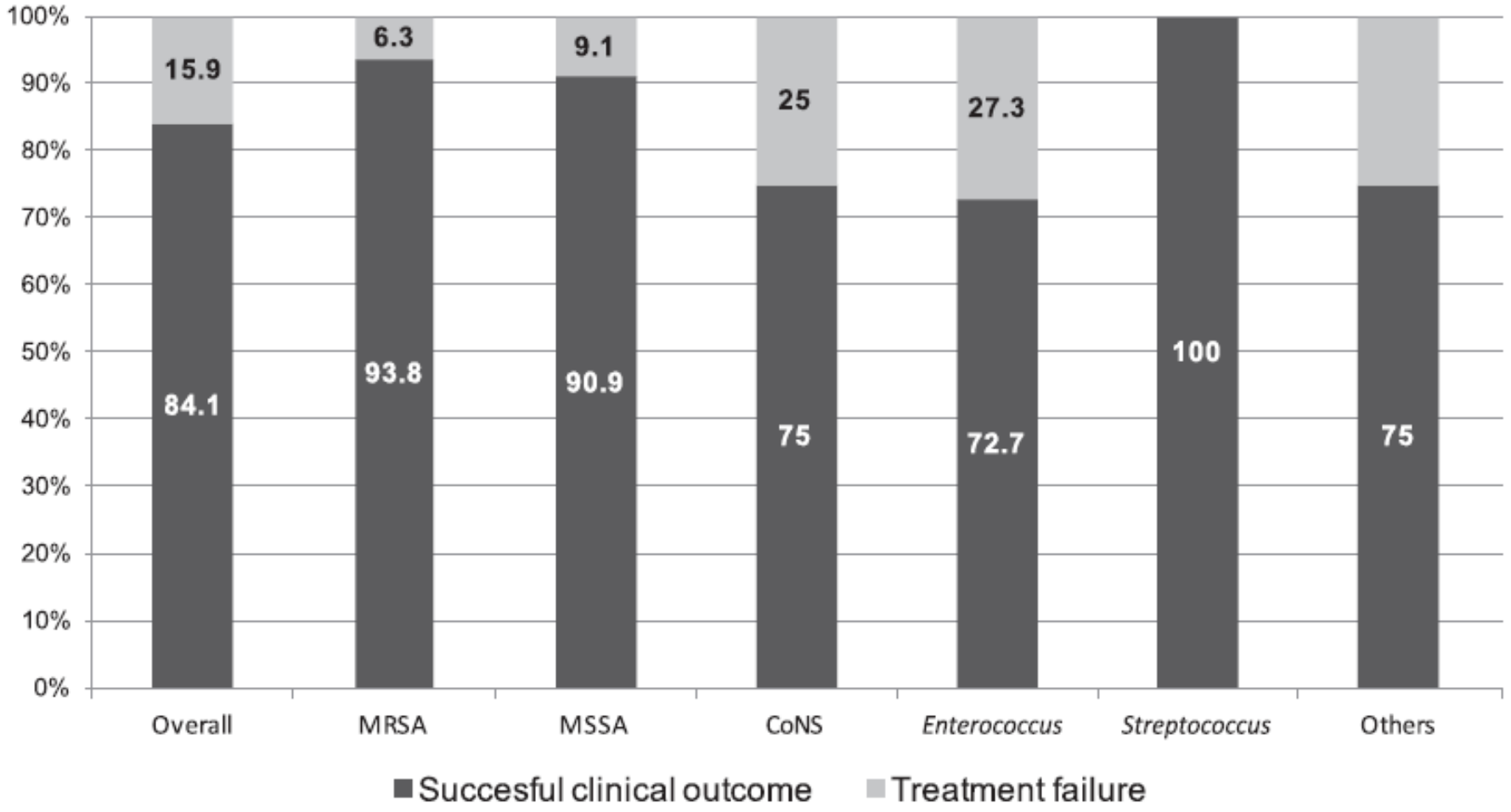


Fig. 2. Treatment outcomes by micro-organism type. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; CoNS, coagulase-negative staphylococci.

Fig
rel

Dalbavancin in the treatment of different gram-positive infections: a real-life experience

Outcomes

Use of concomitant antibiotics with dalbavancin was common (25 patients; 36.2%); with the most common accompanying agents being β-lactams (14; 20.3%), rifampicin (9; 13.0%), fluoroquinolones (4; 5.8%) and oxazolidinones (3; 4.3%).

For patients who received concomitant antibiotic treatment, the response rate was 68.0% (17/25 patients) compared with 93.2% (41/44 patients) receiving dalbavancin monotherapy.

Of the 11 patients (15.9%) who experienced clinical failure during dalbavancin therapy, 4 had a prosthetic joint infection (without prosthetic replacement therapy), 3 had polyr ABSSSI, 2 had catheter-related bacteraemia and 1 each h carditis and osteomyelitis. Except for one patient witl related bacteraemia that failed to resolve, all patients had in source control of the infection during dalbavancin therapy this, only 2 of 11 patients died during antibiotic therapy (with ABSSSI and 1 with CVC-related bacteraemia caused b *coccus* sp.). No superinfections or resistance occurred during dalbavancin therapy.

Dalbavancin tolerability was not a problem. Only in one patient was a second dose not administered due to an AE (rectal bleeding). Treating physicians reported at least one potential AE in 9 patients (13.0%). The most common AEs were rash (2; 2.9%), tachycardia (2; 2.9%) and impaired renal function (2; 2.9%) (Table 4). According to study definitions, AEs were considered as mild (7; 10.1%) or severe (2; 2.9%).

Efficacy and Safety of Weekly Dalbavancin Therapy for Catheter-Related Bloodstream Infection Caused by Gram-Positive Pathogens

Issam Raad,[1] Rabih Darouiche,[2] Jose Vazquez,[3] Arnold Lentnek,[4] Ray Hachem,[1] Hend Hanna,[1] Beth Goldstein,[5] Tim Henkel,[5] and Elyse Seltzer[5]

[1]The M. D. Anderson Cancer Center and [2]Veterans Affairs Medical Center, Houston, Texas; [3]Harper University Hospital, Detroit, Michigan; [4]Wellstar/Kennestone Hospital, Marietta, Georgia; and [5]Vicuron Pharmaceuticals, King of Prussia, Pennsylvania

Methods. A phase 2, open-label, randomized, controlled, multicenter study of 75 adult patients with CR-BSIs compared treatment with intravenous dalbavancin, administered as a single 1000-mg dose followed by a 500-mg dose 1 week later, with intravenous vanc… …eria isolated in this study included coagulase-… …ng methicillin-resistant *S. aureus* (MRSA).

In this phase 2, open-label, randomized, multicenter study, a 2-dose regimen of parenteral dalbavancin provided highly efficacious treatment of CR-BSIs caused by gram-positive bacteria. Compared with vancomycin—a standard antibiotic used for this indication—dalbavancin, administered as an initial 1000-mg dose followed 1 week later by a second infusion of 500 mg, achieved a significantly higher overall success rate. Dalbavancin also demonstrated higher response rates than vancomycin when stratified according to the strategy of catheter management (removal or replacement).

Clinical Infectious Diseases

BRIEF REPORT

Dalbavancin as Primary and Sequential Treatment for Gram-Positive Infective Endocarditis: 2-Year Experience at the General Hospital of Vienna

- Retrospective cohort study performed from **January 2015 to December 2016** in the University Hospital of Vienna, Austria.
- screened retrospectively adult patients with **gram-positive bacteremia with IE treated by ≥1 dose ofdalbavancin**.

Gram-positive bacteremia was defined as ≥1 positive blood culture with *S. aureus*, *Streptococcus* spp., or *Enterococcus* spp. For coagulase-negative staphylococci or *Aerococcus urinae*, 2 positive blood cultures were required.
IE was defined according to the modified Duke criteria

The primary end point was defined as clinical cure or failure.
Clinical cure was defined as resolution of all clinical signs and symptoms of infection, no additional antibiotic therapy required for the indication initially treated with dalbavancin, absence of Gram-positive bacteraemia at the end of dalbavancin therapy and no microbiological relapse in follow-up 6 months after completion of treatment.
Failure was defined as worsening of current infection or new or recurrent signs and symptoms of infection requiring either a change or addition of antibiotic therapy.

Table 1. Duration of Dalbavancin Therapy Stratified by Type of Infective Endocarditis, Pathogen, Duration of Therapy Before Dalbavancin, Reason for Change to Dalbavancin Therapy, Weekly Regimen, Adverse Effects, and Outcome of Dalbavancin Therapy

Duration of Dalbavancin Therapy, wk	Patient No.	Types of IE	Pathogen	Therapy Before Dalbavancin (Duration, wk)	Reason for Change to Dalbavancin Therapy	Failure of Dalbavancin Treatment	Adverse Effects	Regimen (Once or Twice Weekly)
1 (n = 1)	1	Prosthetic valve	*Enterococcus faecalis*	Vancomycin (3)	Not documented	Death	No	Once
2 (n = 3)	2	Native valve	*Staphylococcus aureus*	Flucloxacillin and fosfomycin (2) cefazoline and daptomycin (4)	Poor venous access	No	No	Once
	3	Native valve	*S. aureus*	Flucloxacillin and daptomycin (5)	OPAT	No	No	Twice
	4	Native valve	*S. aureus*	Cefuroxime and daptomycin (4)	Poor venous access	No	No	Twice
4 (n = 5)	5	Native valve	*E. faecalis*	Ceftriaxone and ampicillin (2)	OPAT	No	No	Once
	6	Prosthetic valve	*Streptococcus equi*	Penicillin G (1)	OPAT	No	Nausea	Twice
	7	CDE	*Staphylococcus epidermidis*	Cefazoline and fosfomycin (4)	OPAT	No	No	Twice
	8	CDE	*S. epidermidis*	Daptomycin (4)	OPAT	No	No	Twice
	9	Native valve	*Streptococcus mitis*	Ceftriaxone and gentamycin (2)	OPAT	No	No	Twice
6 (n = 10)	10	Prosthetic valve	*S. aureus*	Flucloxacillin and rifampicin (2)	OPAT[a]	No	No	Once
	11	Native valve	*Staphylococcus hominis*	Flucloxacillin and daptomycin (2)	OPAT	No	No	Once
	12	CDE	*Streptococcus* spp., *S. epider*	Daptomycin (5 d), vancomycin (2)	OPAT	No	No	Once
	13	Prosthetic valve	*Streptococ*					
	14	Suspected prosthetic valve	*Streptococ*					
	15	Native valve	*E. faecalis*					
	16	Native valve	*Aerococcus*					
	17	Native valve	*S. aureus*					
	18	Native valve	*S. aureus*					
	19	Native valve	*S. sanguini*					
>6 (n = 8)	20	Native valve	*E. faecalis*					
	21	Native valve	*S. sanguini*					
	22	CDE	*S. epiderm*					
	23	CDE	*S. aureus*					
	24	Native valve	*S. aureus*					
	25	Prosthetic valve	*S. aureus*	Flucloxacillin and rifampicin (1)	OPAT	No	No	Twice
	26	Prosthetic valve	*S. sanguini*					
	27	Native valve IE	*Staphyloco*					

Abbreviations: CDE, cardiac device–related endocarditis; IE, infective endocarditis; OPAT

[a]In combination with rifampicin.

Microbiological and clinical successes were reached in **25 (92.6%) of the 27 patients who received dalbavancin as primary or sequential treatment for IE**.

In fact, **24 patients (88.9%) were previously treated with other antimicrobial agents. In all those patients, negative blood cultures were obtained before the first dose of dalbavancin was administered**.

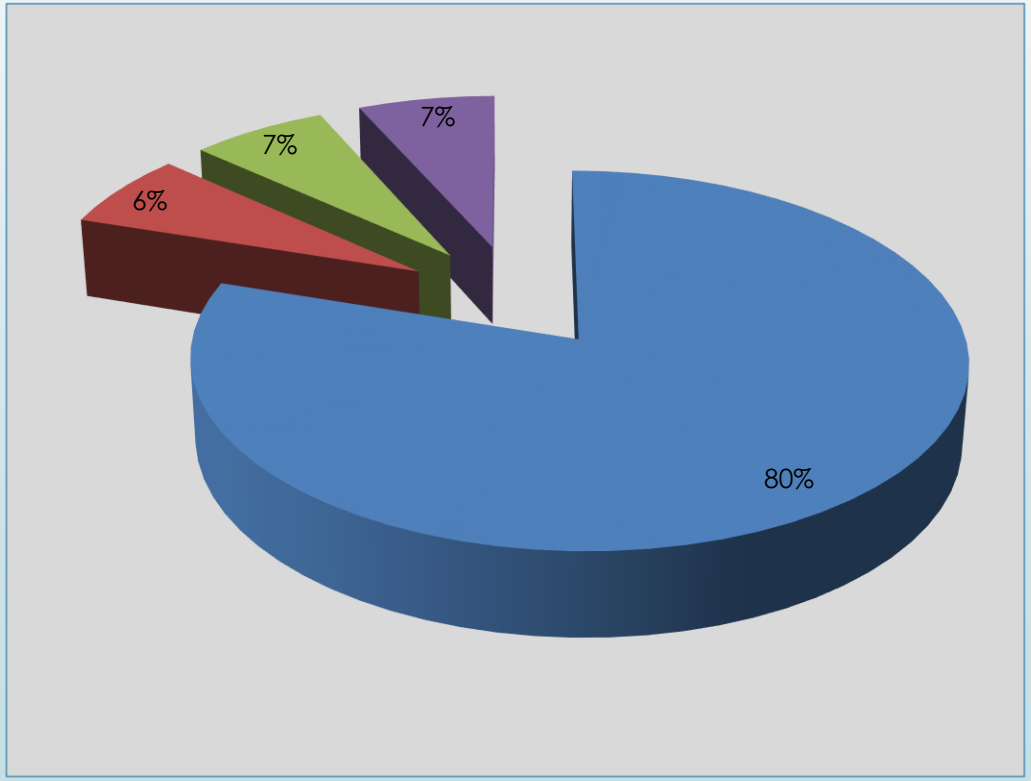
The majority of our patients (**92.6%) were infected by a β-lactam-sensitive gram-positive isolate.**

What's next?

Status	Study Title	Conditions	Interventions	Locations
Active, not recruiting	Evaluation of Intravenous and Intraperitoneal Pharmacokinetics of **Dalbavancin** in Peritoneal Dialysis Patients	• Infectious Peritonitis	• Drug: **Dalbavancin** via Intravenous Administration • Drug: **Dalbavancin** via Intraperitoneal Administration	• University of Colorado Hospital Aurora, Colorado, United States
Recruiting	**Dalbavancin** For The Treatment of Gram Positive Osteoarticular Infections	• Bone Infection • Osteomyelitis • Septic Arthritis • (and 2 more...)	• Drug: **Dalbavancin** • Drug: Vancomycin	• Infectious Diseases Physicians, Inc. Annandale, Virginia, United States
Terminated	Efficacy and Safety of **Dalbavancin** Compared to Standard of Care Antibiotic Therapy for the Completion of Treatment of Patients With Complicated Bacteremia or Infective Endocarditis	• Infective Endocarditis, Bacteremia	• Drug: **Dalbavancin** • Drug: Standard of Care	• Midway Immunology and Research Center Fort Pierce, Florida, United States • Infectious Disease Specialists of ATL, PC Decatur, Georgia, United States • University of Kansas Medical Center Research Institute Kansas City, Kansas, United States • (and 16 more...)

Dalbavancina: l'esperienza dell'Ospedale San Paolo

Da Gennaio 2017 - Marzo 2018:
15 infezioni trattate con dalbavancina



DALBAVANCINA in ABSSSI – Caratteristiche dei pazienti

Paziente	Età	Sesso	Comorbilità	Infezione
1 2 Episodi ABSSSI	55	F	-Psoriasi -Neoplasia cervice uterina → istero-annessiectomia e linfoadenectomia inguinale (1999) -Linfedema cronico con ABSSI recidivanti	Erisipela AI dx recidivante
2	70	F	-Malattia di Darier -Gastrite cronica -Adenocarcinoma della testa del pancreas→ duodenocefalopancreasectomia (12/2016), CT adiuvante con gemcitabina in corso	Erisipela AAII
3	61	M	-Psoriasi -Asportazione di melanoma (2012) -Carcinomi spinocellulari recidivanti (30 interventi con 8 innesti cutanei)	Infezione avambraccio sx in recente asportazione ca spinocellulare
4	82	M	-Basalioma padiglione auricolare sinistro recidivante (10 interventi con chirurgia ricostruttiva) -Carcinoma spinocellulare sottopalpebrale (2011)	Erisipela emivolto sinistro

DALBAVANCINA in ABSSSI – Caratteristiche dei pazienti

Paziente	Età	Sesso	Comorbilità	Infezione
5	57	F	-Infezione da HVS-2 recidivante -Intervento di mastoplastica additiva con iniezione di silicone in Ucraina (1997) -Intervento di asportazione del QIE mammella per mastite granulomatosa con reazione gigantocellulare da corpo estraneo (12/2016)	Mastite con ascesso nel muscolo grande pettorale
6	59	M	-Poliomielite con paralisi flaccida AI sx -Osteopetrosi con calcificazioni nei tessuti molli -Frattura traumatica tibia dx trattata chirurgicamente con mezzi di sintesi (2006) -Insufficienza venosa cronica AI dx	Erisipela AI dx recidivante
7	51	M	-Mastite ricorrente -Infezione tessuti molli inguinale (2016)	Mastite
8	74	M	-Tenosinovite in tendinopatia degenerativa della cuffia dei rotatori - infiltrazione 09/2017	Artrite settica con infezione tessuti molli peri-articolari
9	56	M		Fascite muscolo pettorale dx
10	30	M		Cellulite coscia destra
11		F		Mastite

ABSSSI – Caratteristiche dell'infezione

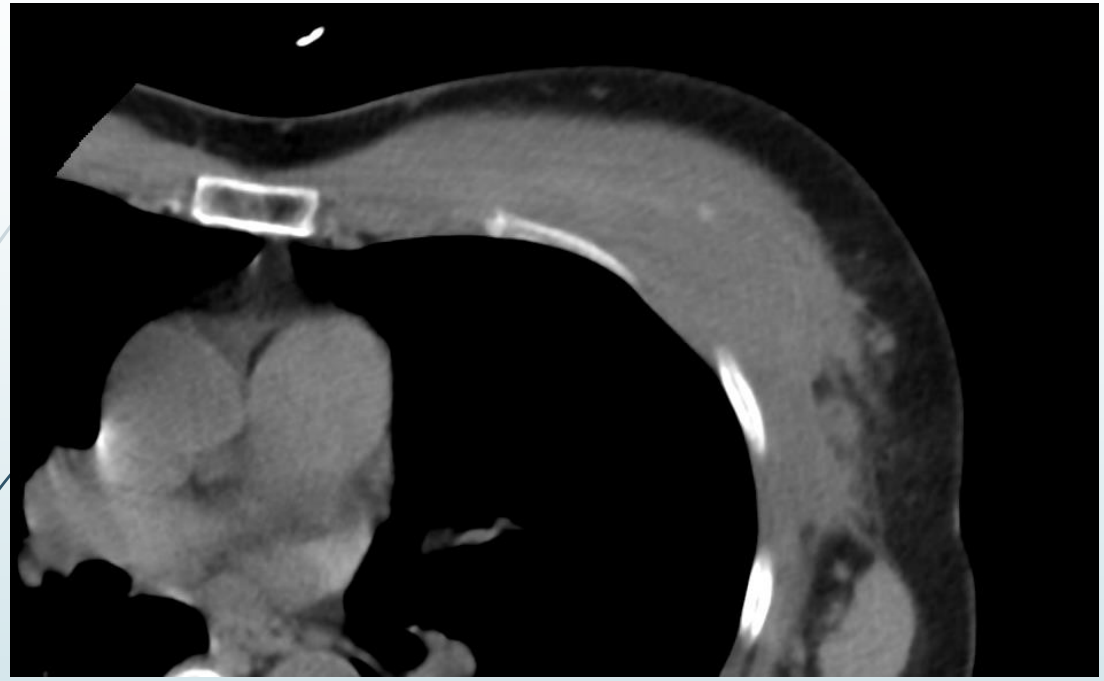
	Sede Infezione	Tipo	GB/ %Ne	PCR/PCT	Fx renale/ epatica/LAC	Sintomi sistemici
EP-1	Erisipela AI	Comunitaria	14000/ 90%	136/-	NR	Febbre
EP-2	Erisipela AI	Comunitaria	11490/ 93%	122/-	NR	Febbre
EP-3	Erisipela AI	HC			R	Febbre
EP-4	Avambraccio	HC			R	no
EP-5	Erisipela volto	NC			R	no
EP-6	Mastite + ascesso pettorale	NC			R	Febbre
EP-7	Erisipela AI	C			R	no
EP-8	Mastite	C			R	no
EP-9	Braccio + artrite settica	HC			ea 3.8	Febbre
EP-10	Fascite pettorale	C			I/107-45	Febbre
EP-11	Cellulite coscia	C			AST-ALT e bil. R =1.7 PTLs =90000	Febbre
EP-12	Mastite	Comunitaria				

Tipo di Infezione:
40% Erisipela
25% Mastite
35% Altro

60% Comunitaria
25% HCA
15% Nosocomiale

60% Presenza di febbre
66% Leucocitosi
80% Incremento PCR
25% Alterazioni funzionalità epatica, renale o emocoagulative

ABSSSI – Imaging – Source control -EP6

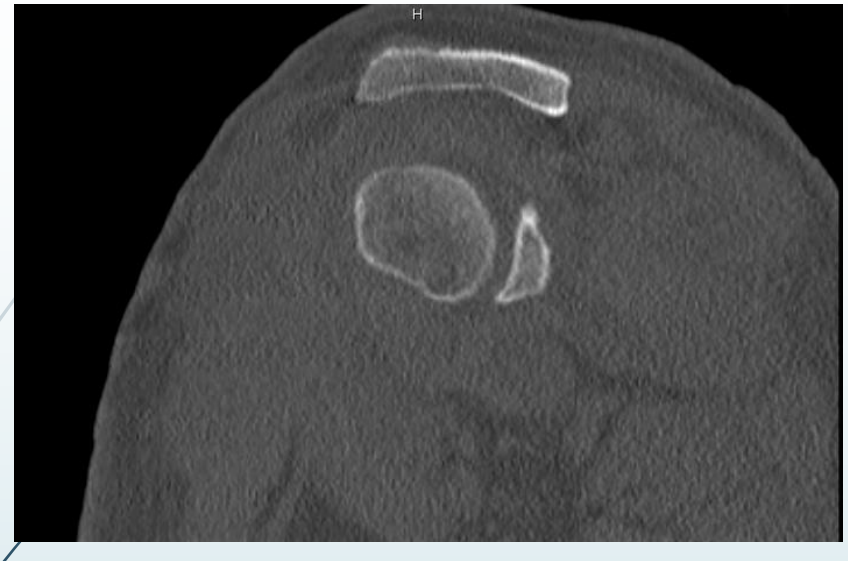


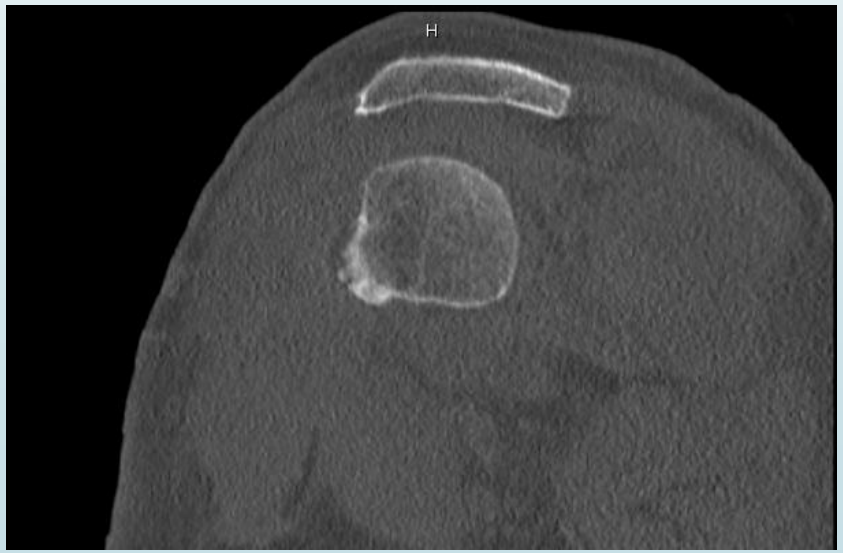
Presenza di tumefazione della parete toracica laterale sinistra che si dispone tra i muscoli della scapola (grande dorsale e dentato) e i muscoli pettorali , coinvolgendo anche la ghiandola mammaria.
Diffuso ispessimento di tessuti adiposi e i piani muscolari, sino alle coste.

↓

Incisione della parete toracica con drenaggio di 2 raccolte saccate, fuoriuscita di abbondante materiale siero-purulento e materiale estraneo, asportazione di materiale necrotico e demolizione parziale del muscolo grande pettorale.

ABSSSI - Imaging - Source control - EP9

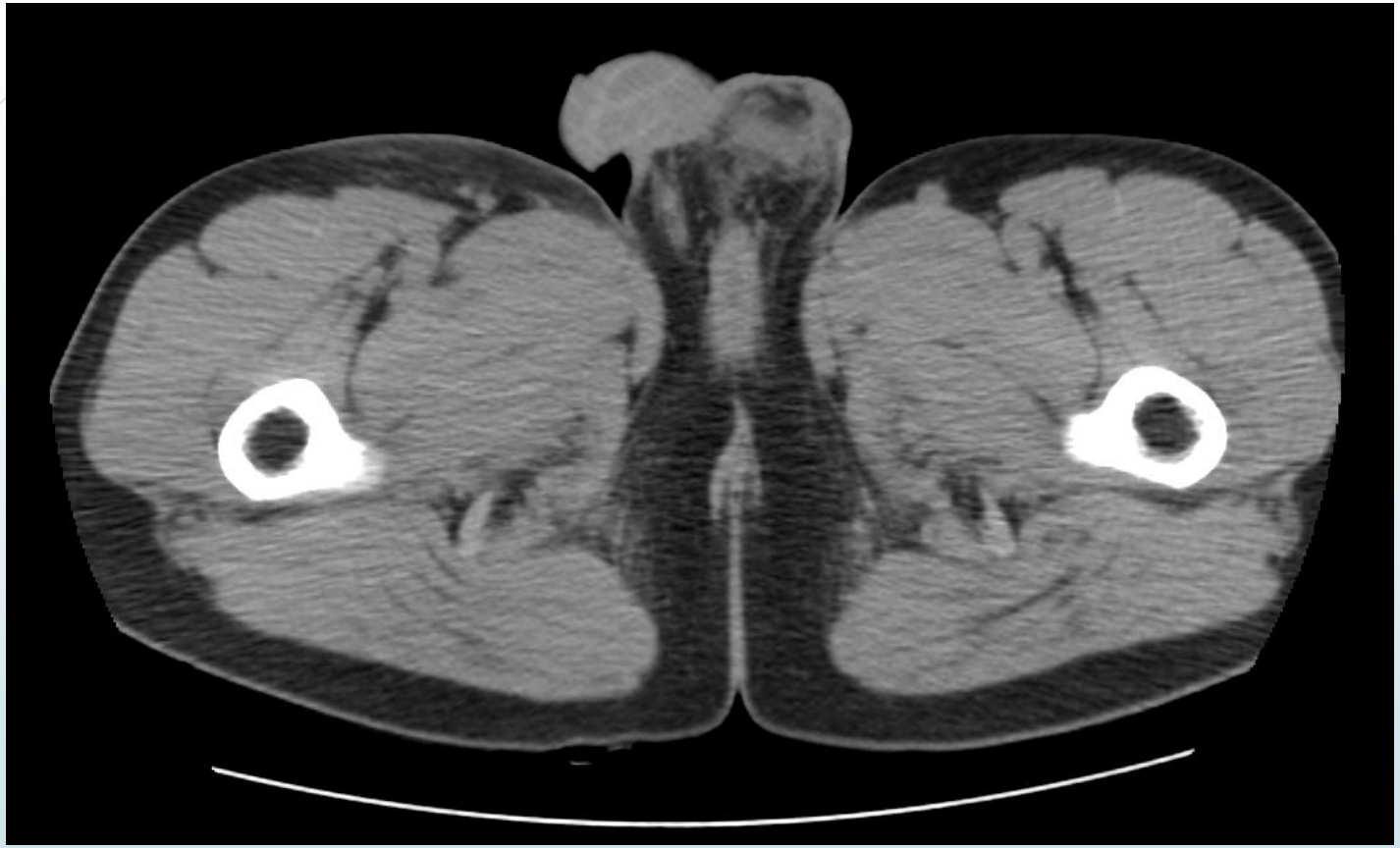




Millimetriche immagini aeree nel ventre deltoideo, in postumi di recenti iniezioni, in associazione a raccolta liquida periarticolare.

ARTROCENTESI → 120 cc di franco pus inviato in coltura, positivo per MSSA

ABSSSI – Imaging – EP11



Lieve disomogeneità dell'adipe sottocutaneo nella regione della radice della coscia destra a confronto con la controlaterale, possibile espressione di fatto flogistico.

ABSSSI – Caratteristiche dell'infezione

	Sede Infezione	Tipo	Isolamento	Precedente linea terapeutica	Durata	Motivo di switch a dalbavancina
EP-1	Erisipela AI	Comunitaria	NA	Levofloxacina	1g	Allergia penicillina
EP-2	Erisipela AI	Comunitaria	NA	Levofloxacina	10gg	Allergia a penicillina Inefficacia I linea
EP-3	Erisipela AI	HCA	NA	Amoxicillina/clavulanato → Ceftriaxone + Teicoplanina	5gg 10gg	Inefficacia I linea Recidiva dopo II linea
EP-4	Avambraccio	HCA	**MRSA**	Amoxicillina/clavulanato	1g	Epidemiologia di HCA
EP-5	Erisipela volto	Nosocomiale	NA	Nessuna		Epidemiologia
EP-6	Mastite + ascesso pettorale	Nosocomiale	**MSSA**	Piperacillina/tazobactam	6gg	Early discharge
EP-7	Erisipela AI	Comunitaria	NA	Ceftriaxone	1g	PS Discharge
EP-8	Mastite	Comunitaria	NA	Levofloxacina	9gg	Inefficacia
EP-9	Braccio + artrite settica	HCA	**MSSA**	Vancomicina Oxacillina	7gg 4gg	Early Discharge
EP-10	Fascite pettorale	Comunitaria	NA	Amoxicillina/clavulanato	2gg	
EP-11	Cellulite coscia	Comunitaria	NA	Ceftriaxone + Clindamicina	3gg	Early Discharge
EP-12	Mastite	Comunitaria	NA			

ABSSSI – Caratteristiche dell'infezione

	Sede Infezione	Tipo	Schema utilizzato	Setting	DEGENZA gg	MAC gg	OUTCOME CLINICO
EP-1	Erisipela AI	Comunitaria	1500	Deg. MAL INF	3gg		Guarigione
EP-2	Erisipela AI	Comunitaria	1000+500	Deg/MAC MAL INF	6gg	1g	Guarigione
EP-3	Erisipela AI	HCA	1000+500	MAC ONCO		2gg	Guarigione
EP-4	Avambraccio	HCA	1500	Deg.MAL INF	3gg		Guarigione
EP-5	Erisipela volto	Nosocomiale	1500	Deg.MED VI	24gg		Guarigione
EP-6	Mastite + ascesso pettorale	Nosocomiale	1500	Deg.MAL INF	6gg		Guarigione
EP-7	Erisipela AI	Comunitaria	1000+500	MAC MAL INF		2gg	Guarigione
EP-8	Mastite	Comunitaria	1000+500	MAC MAL INF		2gg	Guarigione
EP-9	Braccio + artrite settica	HCA	1000+500	Degenza/MAC MAL INF	13gg	1g	Guarigione
EP-10	Fascite pettorale	Comunitaria	1000	Deg.MAL INF	8gg		**Sospesa per tossicità**
EP-11	Cellulite coscia	Comunitaria	1000+500	Deg/MAC MAL INF	4gg		Guarigione
EP-12	Mastite	Comunitaria					

Caso clinico - Utilizzo off-label

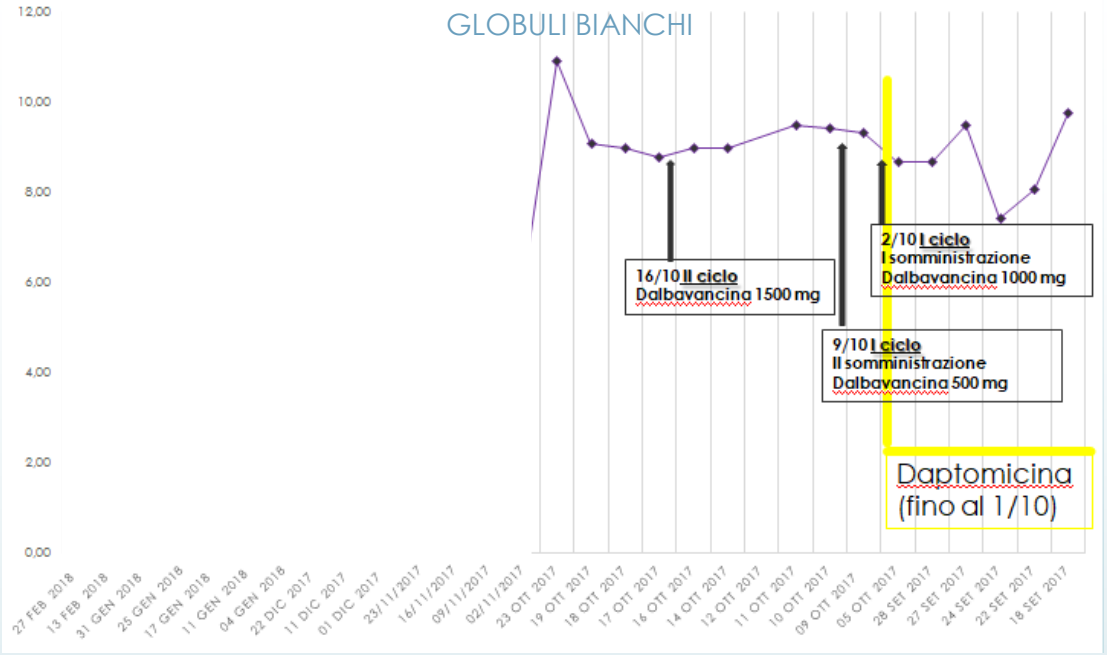
Dati anamnestici
M.M., F, anni 81
Comorbilità:
-Mieloma Multiplo
-2012 Protesi valvolare mitralica meccanica per stenosi post RAA
-PM impiantato nel 2011 per FA a lenta risposta ventricolare condizionante episodi sincopali e sostituito nel 2016
-Gozzo tiroideo multinodulare in terapia sostitutiva
-Lieve IRC (eGFR 45-50 mL/min/1,73m2)

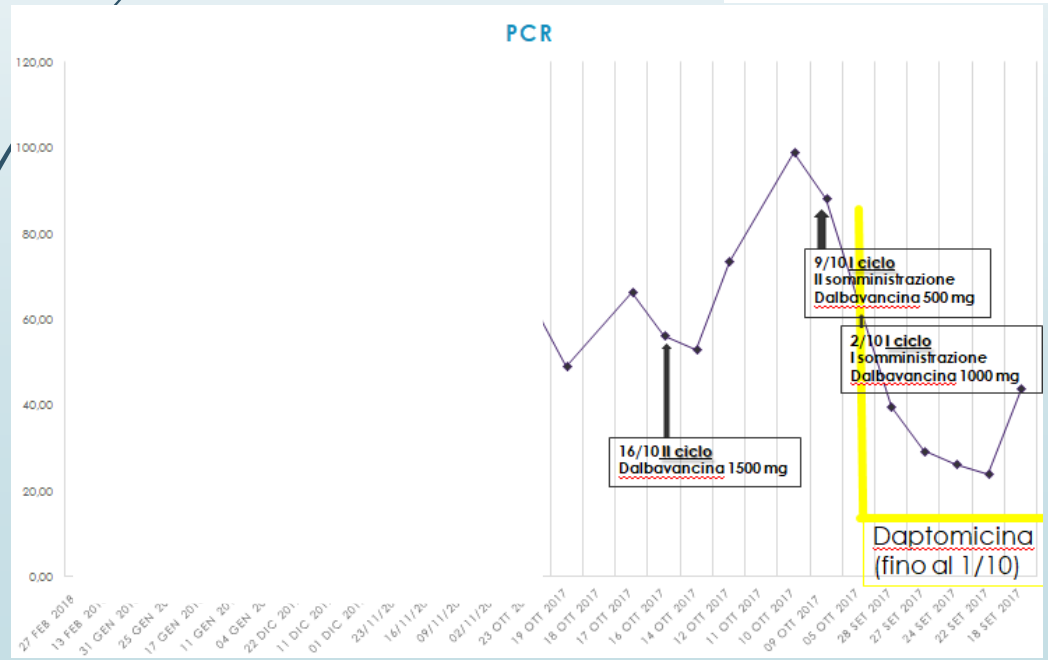
Febbraio 2017 → trasferita c/o la nostra UO per riscontro di sospetta endocardite aortica da *S. capitis* e *successivamente infezione di elettrocatetere non sostituibile secondo parere cardiochirurgico.*

Sottoposta quindi a varie linee terapeutiche:
-VANCOMICINA e GENTAMICINA in empirico sostituite con OXACILLINA sulla base dell'antibiogramma (6 settimane totali) con sviluppo di rash verosimilmente allergico;
-DAPTOMICINA E LINEZOLID (2 cicli);
-DAPTOMICINA per ulteriore batteriemia da S capitis, con iniziale tossicità (aumento CPK).

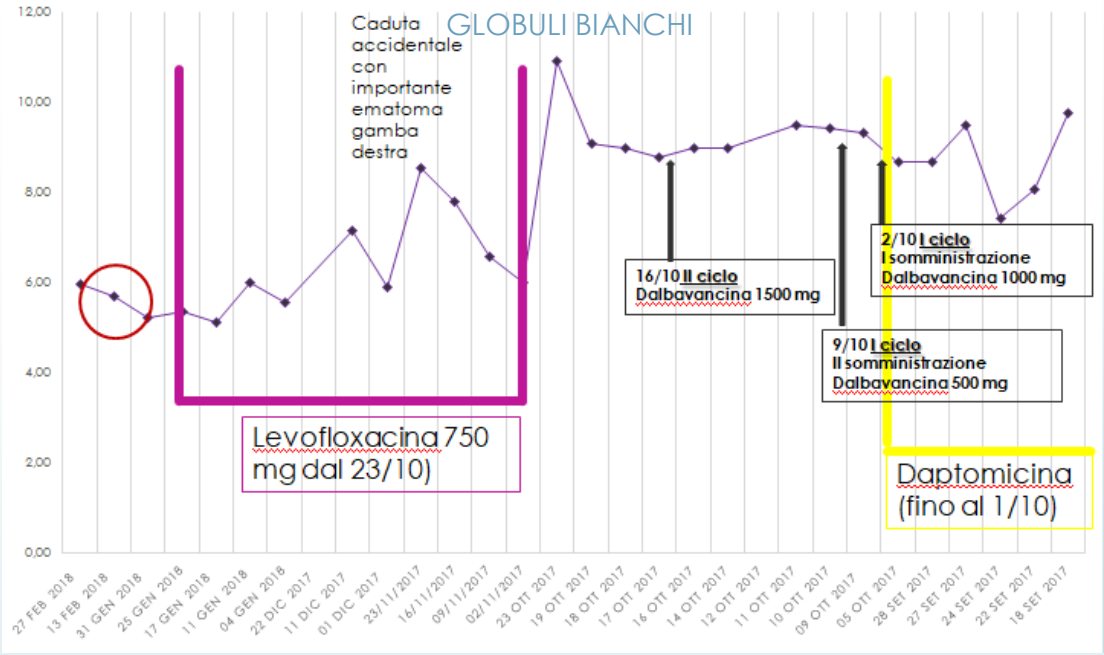
Veniva proposto ad ottobre 2017 trattamento con DALBAVANCINA (I ciclo 1000+500, II ciclo 1500 mg) nel tentativo di evitare una long linfe suppressive therapy.

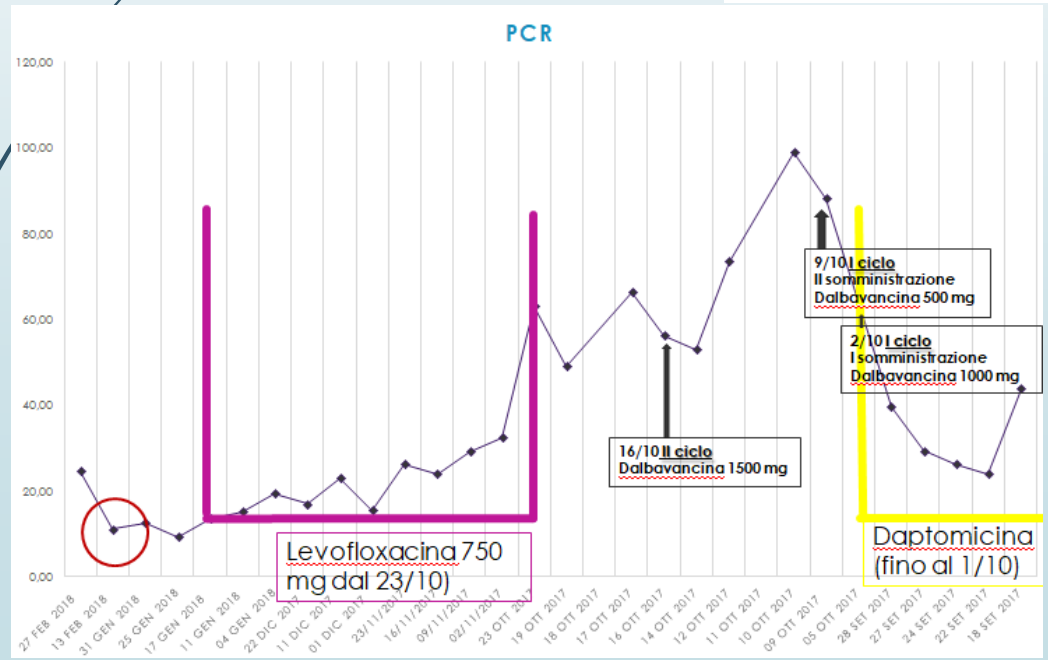
Durante il trattamento con dalbavancina, permanenza di febbre e incremento indici di flogosi.





Durante il trattamento con dalbavancina, permanenza di febbre e incremento indici di flogosi.





Iniziato pertanto il 23/10 trattamento con LEVOFLOXACINA come long life suppressive therapy con defervescenza della febbre e decremento dei GB e degli indici di flogosi.

Veniva successivamente sospeso il 17/01/18 per piastrinopenia iatrogena.

Dopo la sospensione dell'antibioticoterapia con levofloxacina, nuove EC positive per S. capitis.

In seguito a decisione collegiale si è deciso di sottoporre la paziente ad un tentativo di trattamento eradicante con DALBAVANCINA e LINEZOLID per 8 settimane.

Sono state effettuate 3 somministrazioni di dalbavancina 1500 mg a distanza di 15 giorni l'una dall'altra, ma, per sviluppo di sospetta reazione allergica ha poi proseguito con il solo linezolid.

A 10 giorni dal termine della terapia antibiotica, EC negative.
Clinicamente paziente apiretica, GB nella norma.

La paziente è poi partita per le vacanze in montagna…

Grazie per l'attenzione