Tufts UNIVERSITY | School of Medicine

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Le terapie antibatteriche soppressive croniche: quando e perché?

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SAT: Suppressive Antibiotic Treatment

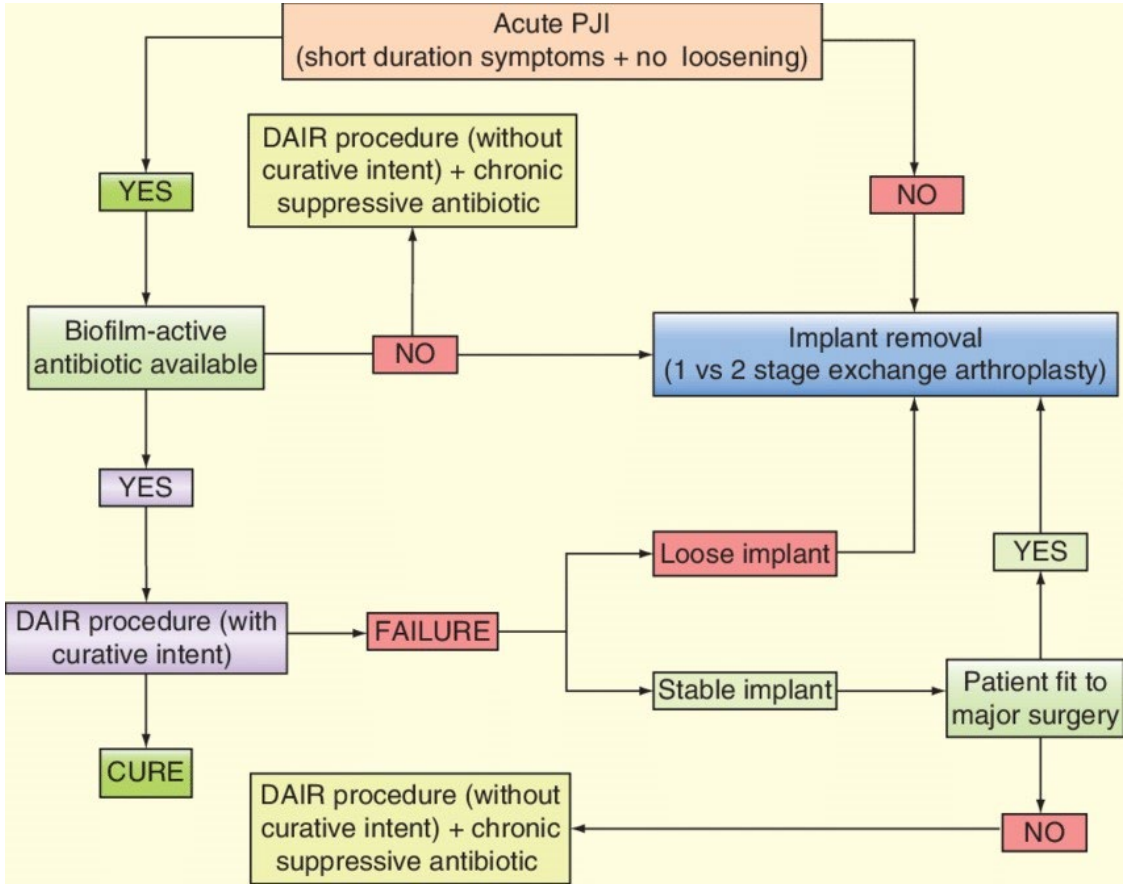
Cobo et al Antibiotics 2021; Penfield et al Clin Inf Dis 2023

- Administration of antibiotics in the long term or indefinitely over time
- SAT is considered a “noncurative” strategy, in which antimicrobials are administered with the aim:
  - reducing symptoms
  - delaying or preventing the progression of infections that needs a surgical procedure to be cured that will not be performed (at least for a prolonged period of time)
- SAT can be used in situations in which adequate surgical treatment is performed and the probability of cure is considered very low.
- Infrequent therapeutic option (5-14%)
- Interpretation of results in term of efficacy is very difficult for the absence of controlled studies, definition of criteria
- Majority of data from prosthetic joint infections and these recs can be applied to other clinical setting

SAT for PJI

Cobo et al Antibiotics 2021; Penfield et al Clin Inf Dis 2023; IDSA guidelines 2013

- Consider for acute PJI for whom conservative treatment (DAIR) has failed
- Patients with chronic-late PJI whose implants are not going to be removed or replaced due to any of these circumstances:
  - Unacceptable anticipated functional results
  - Surgical sequelae (or risks) disproportionate to the symptoms
  - Presence of another disease or condition that makes it advisable to substantially delay the intervention
  - Short life expectancy
  - Major surgical contraindication
  - Patient's refusal of the intervention
  - Chronic PJI managed with partial replacement of components.
- Early PJI managed with DAIR and high risk of failure:
  - immunosuppressed patients on chemotherapy
  - patients managed by arthroscopic debridement and/or without replacement of modular components,
  - suboptimal antimicrobial therapy (multidrug-resistant organisms).



How We Approach Suppressive Antibiotic Therapy (SAT) Following Debridement, Antibiotics, and Implant Retention for Prosthetic Joint Infection

Penfield et al Clin Inf Dis 2023

- For PJI treated with DAIR, the 2013 IDSA guidelines recommended 4–6-week antibiotic durations, extended in staphylococcal infections up to 3 months for hips and 6 months for knees.
- Consideration of chronic suppression was suggested, but with little guidance regarding whom to suppress, which antimicrobials to use, or how long uppression should continue.
- Narrative review
- Q1: Which patients are at highest risk of treatment failure after DAIR?
- Q2: Does SAT reduce the incidence of treatment failure?
- Q3: What are the rates of treatment failure or adverse events leading to a treatment discontinuation in patients receiving SAT for PJI?

- SAT definition « antimicrobial therapy > 6 months» in pts with PJI managed with DAIR

Q1: Which patients are at highest risk of treatment failure after DAIR?

- Staphylococcal infection
- Cirrhosis, higher initial CRP values, and bacteremia
- Revision versus primary arthroplasty
- Fracture as indication for primary arthroplasty
- Late (hematogenous) versus early postoperative infection
- Symptom duration before diagnosis or surgery
- More than 1 debridement
- Suboptimal surgical source control (eg, arthroscopic vs open DAIR, or not performing polyethylene liner exchange).

Penfield et al Clin Inf Dis 2023

Q1: Which patients are at highest risk of treatment failure after DAIR?

- Receipt of a fluoroquinolone in gram-negative PJI was associated with greater treatment success in all 3 studies examining this association.
- For staphylococcal PJI, 2 studies found that receipt of rifampin was associated with greater treatment success (1 study examining the specific combination of rifampin plus a fluroquinolone and 1 study examining any receipt of rifampin, the latter's benefit significant in knee PJI only).

Penfield et al Clin Inf Dis 2023

Q2: Does SAT reduce the incidence of treatment failure?

- 21 PJIs occurred in 138 patients receiving SAT (15.2%) and 111 PJIs occurred in 173 patients not receiving SAT (64.2%)

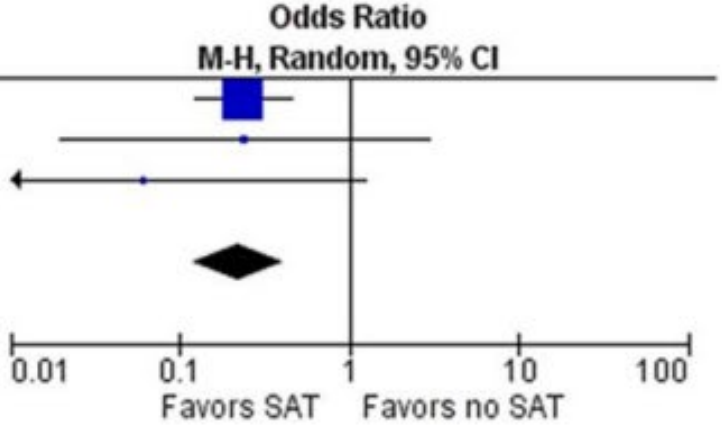
→ receipt of SAT associated with lower odds of recurrent PJI

(OR: 0.22; 95% CI: .12, .42)

	SAT		No SAT			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Siquiera 2015	19	54	106	152	89.7%	0.24 [0.12, 0.45]	2015
Bryan 2017	2	69	1	9	6.1%	0.24 [0.02, 2.94]	2017
Renz 2019	0	15	4	12	4.2%	0.06 [0.00, 1.27]	2019
Total (95% CI)		**138**		**173**	**100.0%**	**0.22 [0.12, 0.42]**	
Total events	21		111				

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 2 (P = 0.69); I² = 0%

Test for overall effect: Z = 4.73 (P < 0.00001)



Penfield et al Clin Inf Dis 2023

Evidence of SAT efficacy

Cobo et al Antibiotics 2021

- Evidence is scarce and interpretation of efficacy is very difficult
- Success rate from 23% to 84%
- A cohort study in which patients with stable PJI (69% with implants for <90 days) were managed with implant retention and prolonged antibiotic therapy for more than 1 year showed that the failure rate was 4 times higher in patients who discontinued antibiotic treatment (Prendkti et al Int. J. Infect. Dis. 2017)
- Siqueria et al: controlled study SAT Vs NO SAT matched with propensity score: SAT had a better 5 year outcome (68% Vs41%)
- Escudero et al : largest series, SAT effective in 75% of cases at 2 years

Reference	Number of Patients	Type of Infection	Aetiology (%)	Follow-Up (Months)	Criteria for Success	Success Rate	Toxicity
Siqueira, 2015 [16]	92	61% chronic 39% acute	*S. aureus* (48%), CoNS (35%)	69.1	Absence of the following: Subsequent surgical intervention for infection after the index procedure, persistent sinus tract, drainage, or joint pain at the last follow-up visit, or death related to the PJI	69%	No data
Prendki, 2017 [10]	136	No data	*S. aureus* (62%), CoNS (21%)	24	Absence of the following: Local or systemic progression of the infection, death, or discontinuation because an adverse drug reaction	61%	18.4% discontinued antibiotics, but in half of cases, the antibiotic could be replaced by another.
Pradier, 2017 [8]	39	61% delayed or late 39% acute	*S. aureus* (79%), CoNS (10%)	24	Absence of the following: Signs of infection assessed ≥24 months after the end of the curative treatment and then at the last contact with the patient, or death related to the PJI	74%	15% (photo-toxicity and gastrointesti-nal intolerance)
Escudero-Sánchez, 2019 [19]	302	73% chronic 11% haematoge-nous 16% early postopera-tive	*S. aureus* (31%), CoNS (33%)	36.5	Absence of the following: Appearance or persistence of a sinus tract, need for debridement or replacement of the prosthesis due to persistence of the infection, or the presence of uncontrolled symptoms, death related to PJI	59%	17% gastroin-testinal 5% cutaneous

Table 3. Factors We Suggest Guide Prescription of Suppressive Antibiotic Therapy Following DAIR

Factors strongly suggesting benefit from SAT after DAIR (the authors would offer SAT to most patients with at least 1 of these factors)
• Limited options for arthroplasty revision (ie, recurrent infection would require amputation, arthrodesis, or difficult wound coverage and likely result in a substantially worse functional outcome)a
• Recurrent PJI/prior PJI treatment failureb
• Infection with difficult-to-treat pathogens (*S. aureus*b and possibly othersa, eg *Pseudomonas aeruginosa* or Candida)
• Severe immunocompromise (ie, solid-organ or stem cell transplant, active chemotherapy, chronic systemic steroid therapy, TNF-inhibitor therapy, advanced HIV)a
• Underwent arthroscopy instead of open DAIR, or polyethylene liner was not exchangedb
Factors that may suggest benefit from SAT after DAIR (the authors would consider SAT in patients with at least 1 of these factors)
• Major end-organ disease predisposing to poor outcome (ie, cirrhosis, ESRD, or heart failure)b
• Age >75 y b or estimated life expectancy <10 ya
• Late hematogenous infection (onset >2 y after initial arthroplasty), particularly if associated with active bacteremiab
• Gram-negative infection that cannot be treated with a fluoroquinoloneb
• Patient strongly values the potential benefits of SAT over the potential risks after both have been explained in an informed shared-decision-making conversationa
Factors suggesting little benefit from SAT (the authors would not offer SAT to most patients with these factors)
• Completion of >6 wk of adjunctive rifampin for susceptible, monomicrobial coagulase-negative *Staphylococcus* spp. infection (as part of a minimum 3–6 mo total antibiotics)b
• Completion of a fluoroquinolone-based regimen for a gram-negative infectionb
• Culture-negative infectionb

Abbreviations: DAIR, debridement, antibiotics, and implant retention; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; PJI, prosthetic joint infection; SAT, suppressive antibiotic therapy; TNF, tumor necrosis factor.

[a]Based on the consensus opinion of the authors, but not directly supported by the data identified in this review.

[b]Based on retrospective data identifying this as a risk factor for treatment failure.

Penfield et al Clin Inf Dis 2023

Practical aspects of SAT

Cobo et al Antibiotics 2021; Penfield Clin Inf Dis 2023

- Is debridment mandatory?
  - Reduction of inoculum favour the success of SAT
  - No data describing failire in the absence of previous debridment
  - Useful for microbiological samples (culture from sinus tract non usually representative of actual etiology)
- What are the most suitable antibiotics?
  - Not possible to infer recs
  - No studies about optimal dosage (higher is better)
  - No antibiotics free periods
  - Long term safety and few side effects needed
  - Data available for:
    - Tetracyclines and rifampin
    - Monotherapy with betalactams
    - Long acting (dalbavancin, oritavancin)

Possible setting for SAT cUTI & colangitis

Clinical case 1

APR

- 2006 Adenocarcinoma prostatico (pT3aNx, GS 3+4) sottoposto a prostatectomia radicale
  - Luglio 2020 ritenzione urinaria acuta da stenosi uretrale posteriore/neocollo vescicale: posizionamento di CistoCath e successiva uretrotomia endoscopica laser (08/2020) con posizionamento di catetere siliconato.
  - Dal 2020 Infezioni urinarie recidivanti con pielonefrite:
  - Ultimo ricovero (10/2021) per infezione urinaria da **K pneumoniae ESBL pos + Enterococco Faecium amp R**

APP

- Accesso in DEA e successivo ricovero c/o Medicina per febbre (T 39.6°C) con brivido e dolore al fianco sin.
  - Emocolture (neg) e urocoltura pos per E. coli multisensibile.
  - Visita urologica: IVU da sospetta stenosi anastomosi uretero-ileale ds, di derivazione con pielostomia ds.

  Start Ceftriaxone, in accordo con i Colleghi infettivologi (12/01) con indicazione a proseguirla per un totale di tre settimane.
  - Stante il quadro flogistico acuto è stata posta indicazione Urologica a procrastinare il posizionamento del monoJ destro per via anterograda tra circa due mesi con contestuale valutazione per rimozione pielostomia.

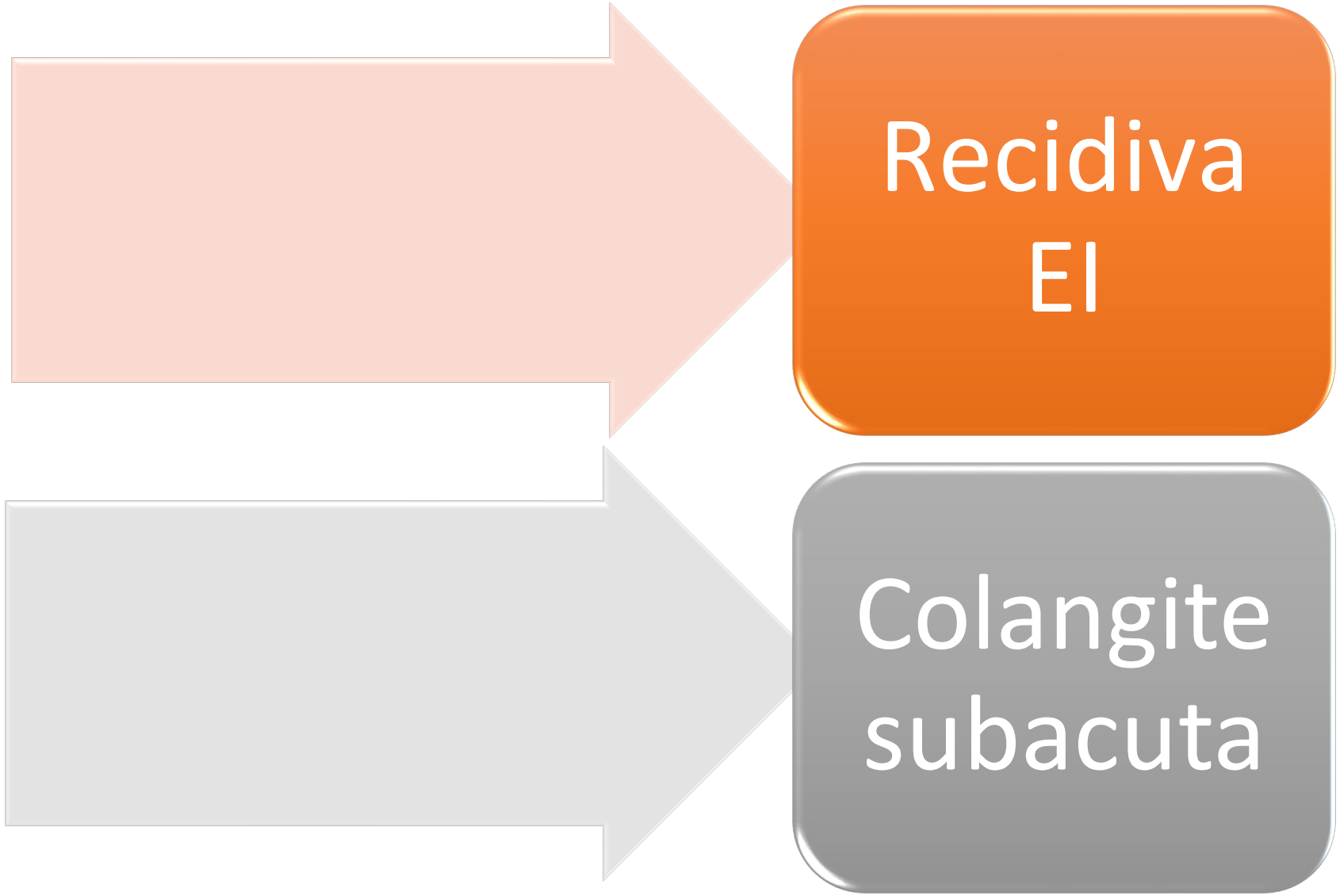
Follow up febbraio 2022

- Nuovo episodio di infezione urinaria (con evidenza di Pielonefrite bilaterale con ascessualizzazione) in paziente portatore di Urostomia sec Bricker e stenosi dell'anastomosi uretero-ileale ds, sottoposta a derivazione pielostomica Infezione da E. coli multisensibile
- Paziente già più volte valutato in occasione dei precedenti ricoveri. Attualmente ricoverato per IVU con riscontro di dilatazione e necessità di pielostomico.
- Impostata terapia con Ceftriaxone ed Amikacina con ottima risposta clinica. Sulla base della buona risposta alla terapia in corso, si consiglia di proseguirla fino a dopo l'introduzione del monoJ già prevista (per la quale nulla osta).
- **Successivamente inizia Cefixima 400 mg die in terapia "soppressiva», presa in carico da day hospital medicina interna**

Clinical case 2

- Donna 84 anni ricovero per FUO
- APR:
  - 2003 colecistectomia laparoscopica complicata da fistola biliare e stenosi dotto epatico per cui sottoposta ad anastomosi dotto epatico digiuno
  - Maggio 2021 FUO ricovero in Medicina interna sospetta endocardite infettiva su valvola nativa (PET+), ceftriaxone 2 gr die per 6 settimane
    - PET ancora positiva a fine terapia, isolamento di E. coli multi S su emocolture ripreso ceftriaozone per ulteriori 6 settimane, PET neg stop terapia
- APP:
  - Ottobre 2021 febbre con brivido scuotente, arriva in DEA
  - Emocolture in PS positive per E. coli multi S, start ceftriaxone
  - Eco addome: neg; PET: ipercaptazione epatica lobo destro
  - Colangio RMN: dilatazione dotti epatici dx e sx e stenosi dotto epatico sx, area incremento di segnale in S5 esiti di colangite

Diagnosi differenziale



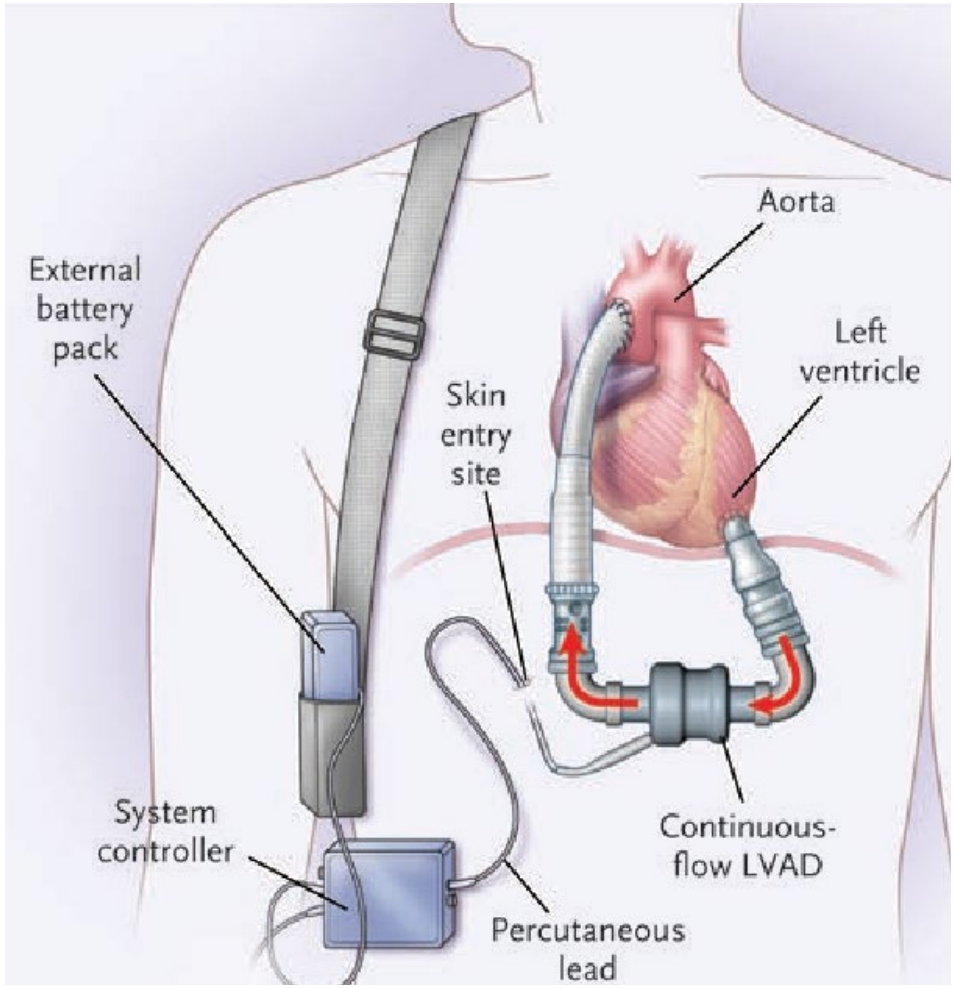
Consulenza infettivologica

- Verosimile BSI da E. coli multi S in colangite subacuta complicante pregressa anastomosi bilio digestiva su ansa alla Roux
- Inizia terapia soppressiva cronica con cefixima 400 mg die
- Indicazione a follow up ambulatoriale con controllo clinico e laboratoristico seriato

Possible setting for SAT
L-VAD

INFEZIONI del VAD

"qualunque infezione che si manifesta in presenza di un VAD"



INFEZIONI VAD-SPECIFICHE:
interessano qualunque componente del dispositivo

-Infezione della ***driveline*** (12-35%)

-Infezione della **tasca della pompa** (2-10%)

-Infezione della **cannula o pompa** (<1%)

INFEZIONI VAD-RELATE: possibile complicanza della procedura chirurgica, delle infezioni VAD-specifiche

- Infezioni **torrente circolatorio** (8-36%) NB. 85% non correlate al *device*

-**Endocardite** (0,5-1%)

-**Mediastinite** (2%)

INFEZIONI NON VAD-CORRELATE:
infezioni non correlate alla presenza del *device* (infezione delle vie urinarie, polmonite, infezione da *C. difficile*, colecistite…)

Zinoviev, R. et al Open Forum Infectious Disease (2020); International Society for Heart and Lung Transplantation, ISHLT]

Contemporary Management Strategies in VAD Infection

Phadke et al Current Heart Failure Reports 2020

- High-quality data to support many of the routine therapeutic strategies currently used for VAD infections:
  - suppressive antibiotic therapy
  - surgical debridement/device exchange
  - novel antimicrobials for emerging multidrug-resistant organisms—remain limited
- For BSI and other endovascular infectious syndromes, the need for SAT is generally presumed (for BSI not thought to be originating from a VAD source suppressive therapy may be deferred under select conditions)
- Any retained material, should be considered a potential source of recrudescent infection and should be removed, if feasible, at the time of device explantation; otherwise, these may require continuation of suppressive antibiotic therapy indefinitely.

Microbiology of LVAD infections

Zinoviev R. Open Forum Infectious Diseases 2020;

S. aureus 14-56%; CNS 7-56%, *P. aeruginosa* 3-28%

Table 1. Frequency of Bacterial (A) and Fungal (B) Pathogens in LVAD Infections as Percentage of Bacterial and Fungal Infections, Respectively

A, Reported Frequency of Bacterial Organisms Among Patients With Bacterial LVAD Infections				
Bacterial Pathogen	Reported Frequency, %			
	DLI	PPI	IE	BSI
Staphylococcus aureus	10–43	8–22	20–25	33
MSSA	4–30	11–25	8–21	0
MRSA	44–56	21	0	14
Unspecified				
Coagulase-negative *Staphylococcus*	7–29	17–50	21–40	33–56
Enterococci	5–15	11–26	8–29	8–17
Corynebacterium	2–14	2	8–20	0
Pseudomonas aeruginosa	4–28	3–25	17–20	3
Klebsiella species	2–13	5–7	7–8	5
Escherichia coli	1–4	5–11	0	0
B, Reported Frequency of Fungal Organisms Among Patients With Fungal LVAD Infections				
Fungal Pathogen	Reported Frequency, %			
Candida albicans	28–45			
C. glabrata	14–23			
C. kruseii	14–19			
Other *Candida* species	13			
Aspergillus species	28			

Data are listed as a range between the lowest and highest reported frequencies per pathogen [6, 7, 9, 11, 14, 23, 26, 28, 29].

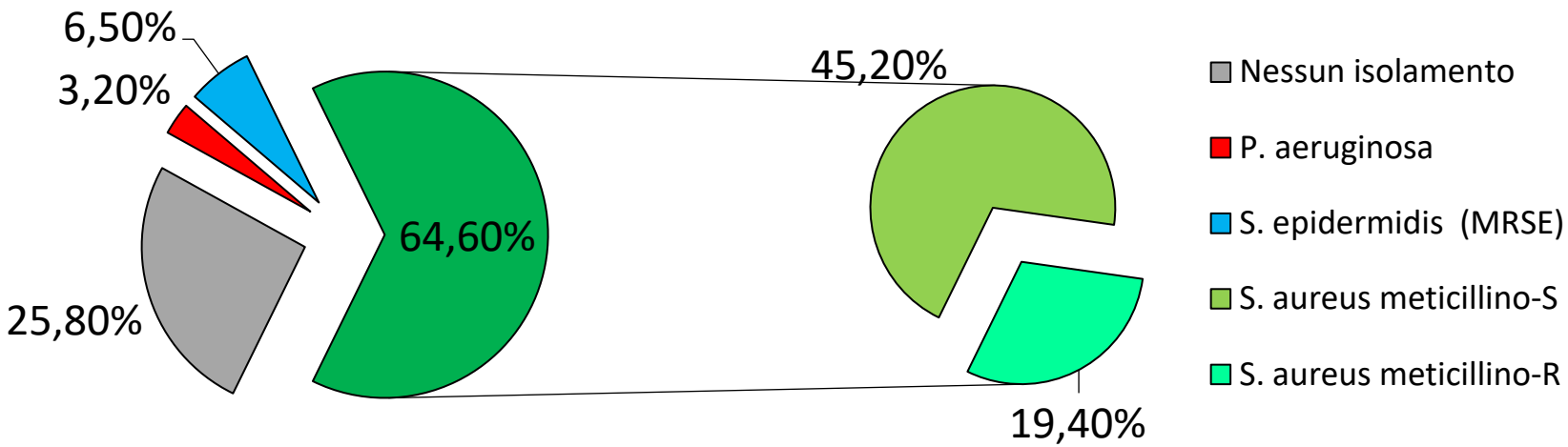
Abbreviations: BSI, bloodstream infection; DLI, driveline infection; IE, infective endocarditis; LVAD, left ventricular assist device; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PPI, pump pocket infection.

Epidemiologia CDDS

INFEZIONI VAD-SPECIFICHE

Infezione della *driveline:* 31 pz (37%)

Isolamenti microbiologici *exit site* (primo isolamento)



Secondo isolamento (6): 3 Gram negativi (2 *K. pneumoniae* KPC+)

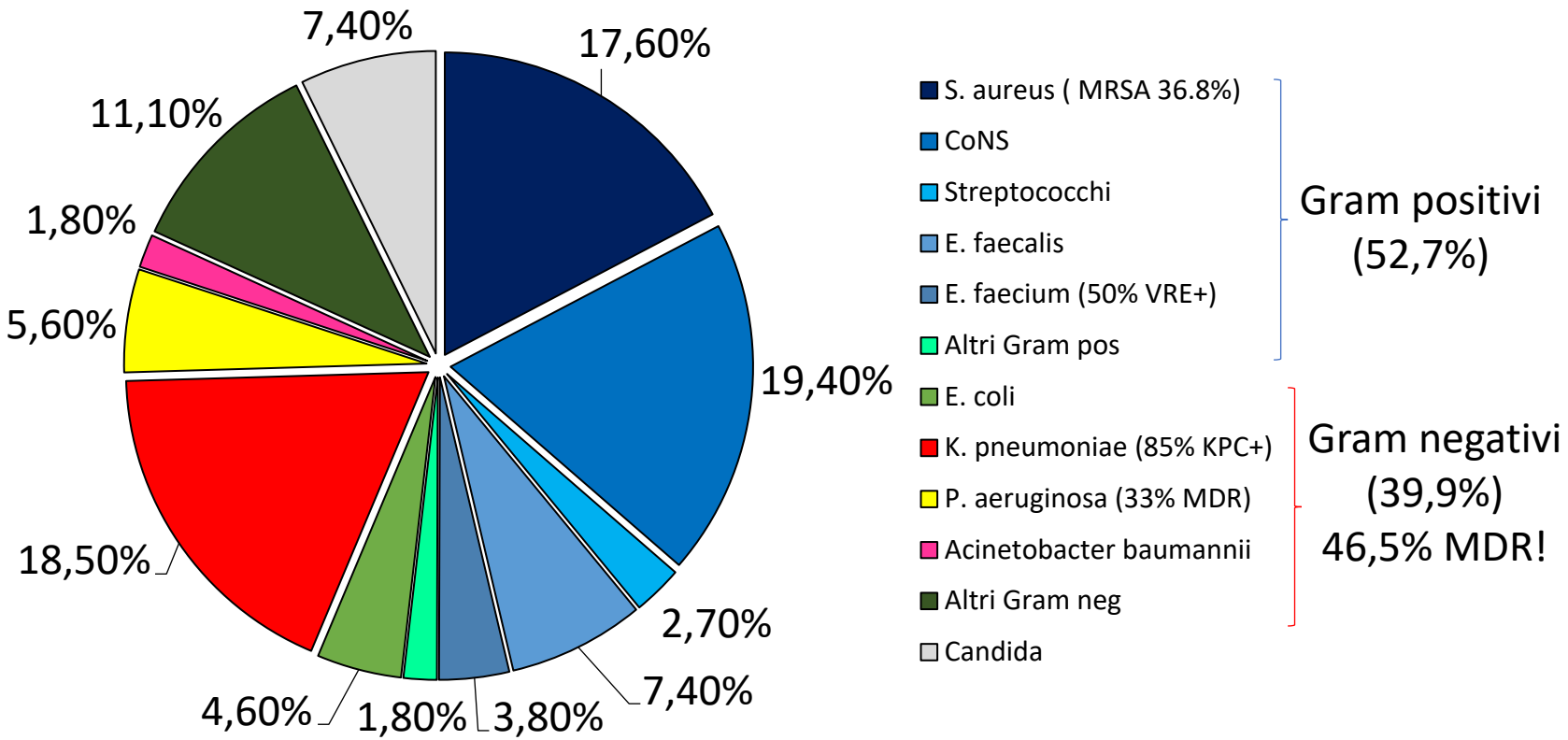
Impianto di LVAD nel periodo Gennaio 2010 – Giugno 2019 presso l'Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, centro di riferimento regionale;

Epidemiologia CDDS

INFEZIONI VAD-RELATE

Infezione del torrente circolatorio: 50 pz (61,7%) – 108 episodi

(7,4% polimicrobici)



Impianto di LVAD nel periodo Gennaio 2010 – Giugno 2019 presso l'Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, centro di riferimento regionale;

Long-Term Antibiotic therapy in non-surgical Prosthetic valve Endocarditis (L-TAPE study)

RATIONALE:

Management of PVE non susceptible to surgical intervention may be very heterogeneous among European centres with clinicians that may prescribe LTAT due to missed surgical source control and others that conclude antibiotic treatment after the pre-established 4-6 weeks as recommended by most of guidelines on management of PVE.

OBJECTIVES:

1- Describe the management of PVE non susceptible of surgery

2- to compare outcome of patients treated with and without LTAT for PVE or TAVI-PVE not susceptible of surgical valve replacement

3- Assess the occurrence of *C. difficile* infections and other adverse event during antibiotic treatment

METHODS:

Retrospective, international, multicenter study.

All adult patients (<18 year) with diagnosis of definitive or possible left-sided PVE or TAVI (transcatheter aortic valve implantation)-PVE not eligible for surgery. Patients must have already received at least 4-6w of antibiotic treatment for endocarditis.

All patients will be followed up for 1 year after PVE diagnosis.

Long-term antibiotic therapy (LTAT) is defined as antibiotic treatment for endocarditis lasting >=12 weeks

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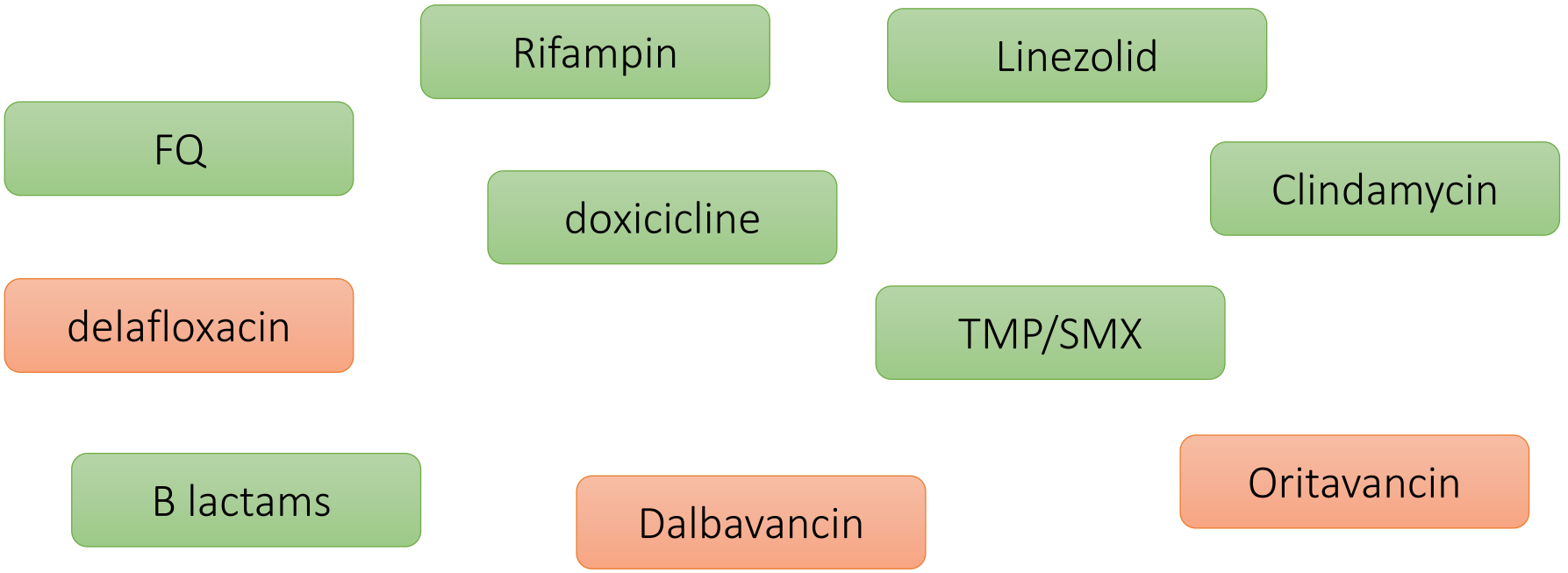
Which drugs?

Treatment Options for SAT



- Limitations of some agents include:
  - Emerging resistance, changing susceptibilities
  - Bacteriostatic rather than bactericidal activity
  - Decreased penetration or inactivity in some tissues
  - Side effects/toxicity
  - Good adherence

Dalbavancin as suppressive antibiotic therapy in patients with prosthetic infections: efficacy and safety

Ruiz Sancho et al. Front Pharmacol 2023

- Adult patients with documented vascular or orthopedic chronic prosthetic infections, who received dalbavancin as SAT between 2016 and 2018 from four Spanish hospitals were reviewed for inclusion
- 8 patients were eligible for inclusion, where six patients had prosthetic vascular infections (aortic valve) and two patients had knee prosthetic joint infections.
- The most common pathogens were methicillin-susceptible Staphylococcus aureus and Enterococcus faecium.
- The median number of dalbavancin doses was 29 (IQR, 9–61) and concomitant antibiotic use (n = 5, 62.5%).
- Clinical success was reported in 75% (n = 6) of patients.
- Adverse events were reported in two patients (mild renal and hepatic impairment).
- The median estimated cost savings due to the avoided hospital days was €60185 (IQR, 19,916–94984) per patient.

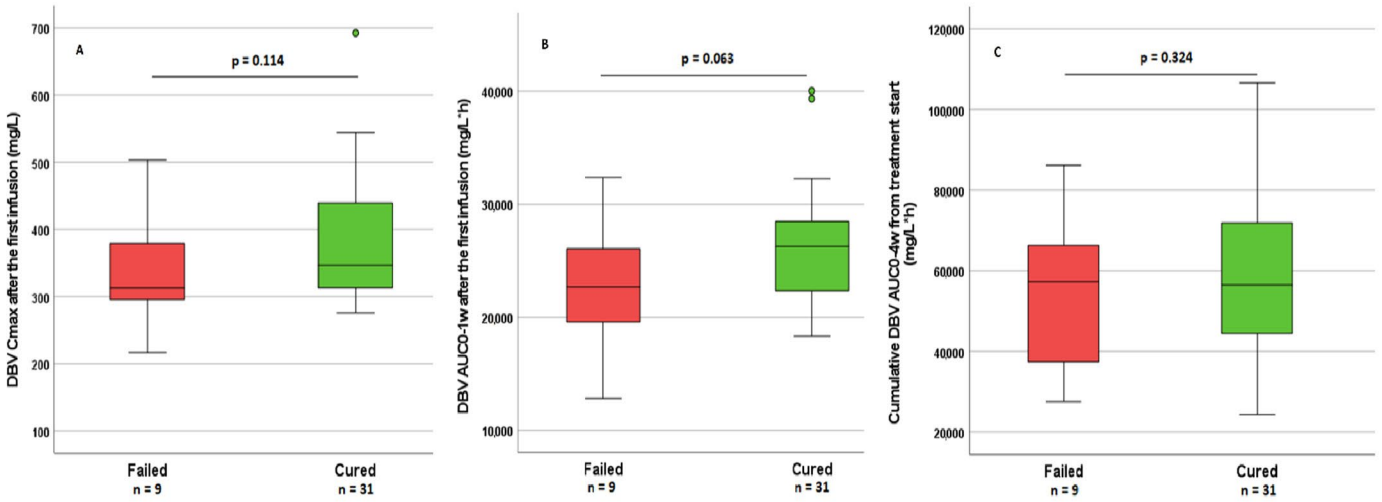
Clinical Effectiveness and Pharmacokinetics of Dalbavancin in Treatment-Experienced Patients with Skin, Osteoarticular, or Vascular Infections

Stroffolini et al Pharmaceuticals 2022

Table 2. Main clinical and microbiological characteristics and outcomes.

	Overall (76)	*Intensive PK Study (n = 41)*			
		Group 0 (n = 17)	*Group 1 (n = 9)*	*Group 2 (n = 13)*	*Group 3 (n = 2)*
Type of infection (n, (%))	ABSSSIs: 16 [21] LVAD: 3 [4] Endocarditis: 3 [4] OAs: 54 [71] Osteomyelitis: 13 [25] Spondylodiscitis: 8 [15] Septic arthritis: 5 [11] PJI: 27 [49]	ABSSSIs: 7 LVAD: 2 Septic Arthritis: 1 Osteomyelitis: 2 Prosthetic infection: 5	Septic arthritis: 1 Osteomyelitis: 4 Spondylodiscitis: 3 Endocarditis: 1	ABSSSIs: 2 Septic arthritis: 1 Osteomyelitis: 3 Spondylodiscitis: 2 PJI: 5	Spondylodiscitis: 1 PJI: 1
Aetiology (n, (%))	MSSA: 32 [42] MRSA 23 [30] MRSE 7 [9.2] MSSE 2 [2.6] S. Lugdunensis 1 [1.3] Streptococcus spp.: 3 [4.1]	MRSA: 4 MSSA: 8 MRSE: 3	MRSA: 3 MSSA: 3 MRSE: 1 S. dysgalactiae: 1	MSSA: 8 MRSA: 4 MSSE: 1	MRSA: 2
Outcome: cure (n, (%))	58/71 [82%]	14/17 [82]	9/9 [100]	7/13 [54]	2/2 [100]
Time to cure (days)	28 [28–56]	14 [14–56]	84 [49–105]	84 [84–112]	28 [28–84]

- Failure associated with lower C_{max}
- DBV C_{max} is a possible candidate for TDM purposes
- Dual-dose one-week-apart treatment as the optimal choice for OA infections



Dalbavacin as SAT in L-VAD: Molinette Experience

- Male;
- Age 62 years
- L-VAD colonization by Corynebacterium Striatum
- Waiting for heart transplant
- Previous therapy: Vancomycin 1g q12h

Administration	mg/L
Gg1 1500mg 2h inf	No blood sample
Gg 14 1500mg 2h inf	No blood sample
2 week blood sample Cthrough	41.83
5 week blood sample Cthorugh	11.09
5 week third adm. 1500mg	No blood sample
6weeks blood sample Cthrough	15.6
6weeks fourth adm. 1500mg	No blood sample
5weeks blood sample Cthrough	11.6
9 weeks 1500mg + blood sample pre administration	4.7
2 weeks blood sample Cthrough	40.2

ORITAVANCIN: Molinette Experience

G1: first administration 1200mg 6h of infusion	mg/L
T0	nd
T6	115.95
T10	77.89

G7:second adm. 800 mg 3h of infusion	mg/L
T0	1.06
T3	94.84
T4	87.63

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Previous therapy

G14: third adm. 800 mg 3h of infusion	mg/L
T0	3.00
T3	105.85
T5	76.83

4fl q8h

, followed b

G21:fourth adm. 800 mg 3h of infusion	mg/L
T0	3.27
T3	105.15
T5	78.78

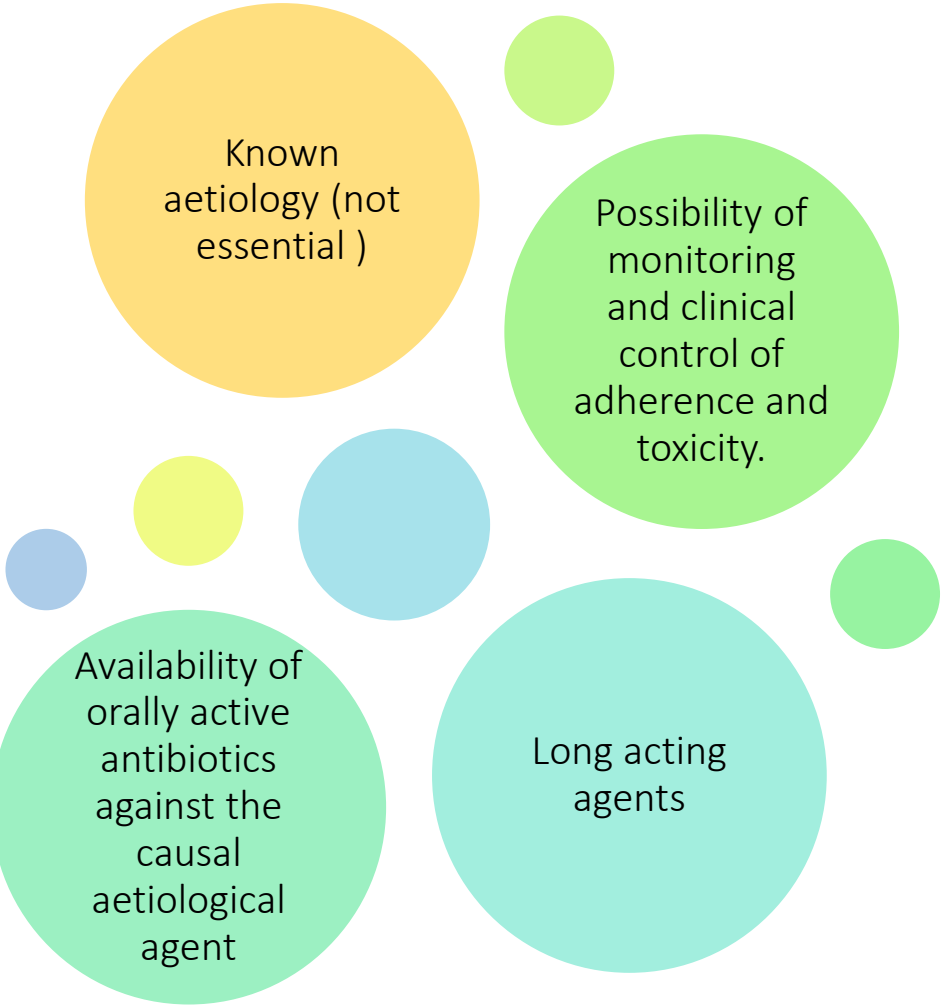
Clinical Breakpoint EUCAST for *S.aureus* ≤ 0.125 mg/L

Last administration

One month after G21 1200 mg 6h of infusion	Mg/L
T0	0.78
T6	139.83
T8	134.94

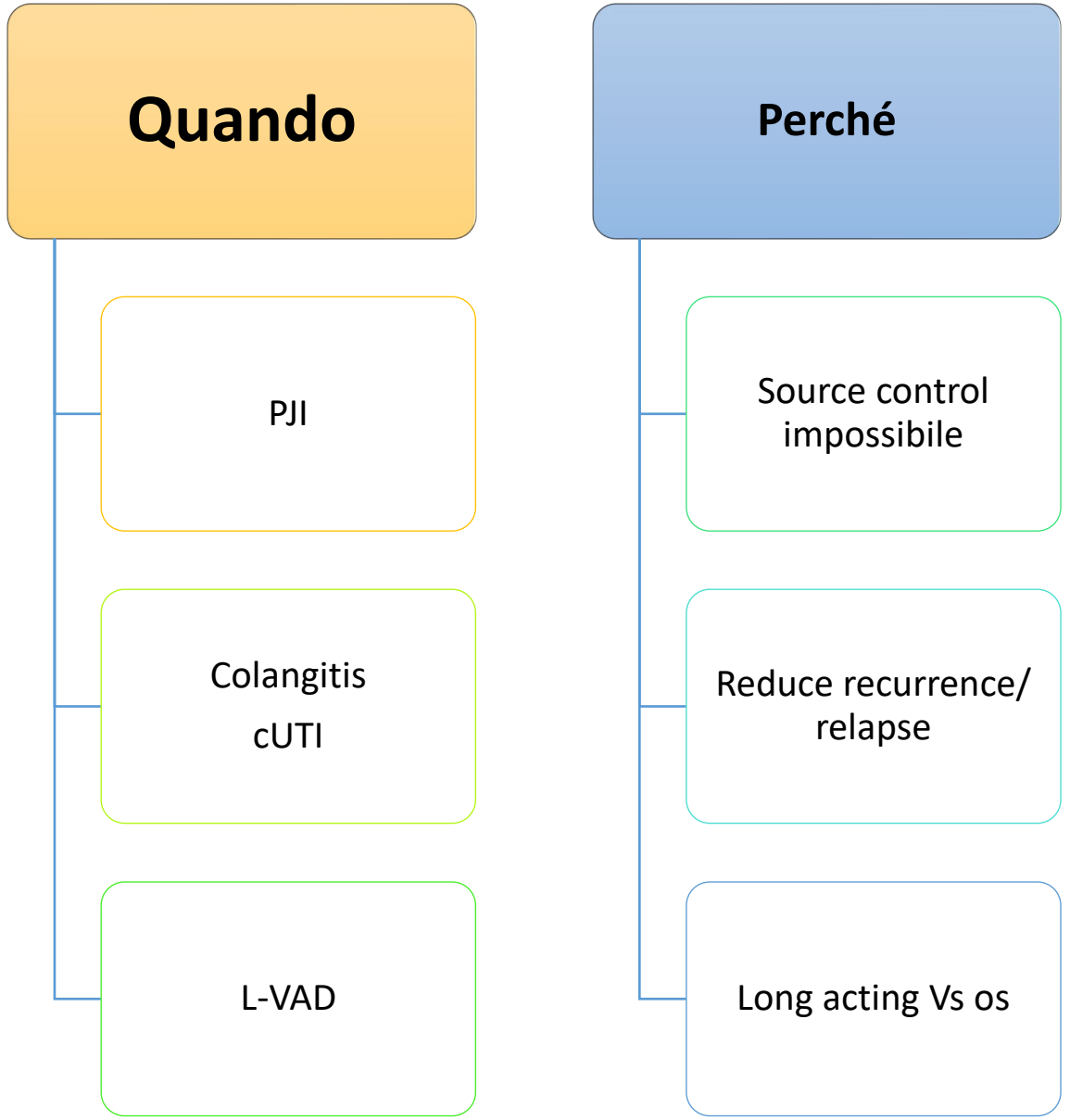
Follow up with PET resolution of fluid collection then switch to doxi plus rifa

SAT is easier if



Conclusion

- How long?
- Which drug works best?
- Long acting promising option
- Adherence and long term tolerability
- Follow up and personalized therapy (TDM)



Speakers' personal view