Concept de traitements antibiotiques suppressifs – quand et comment ?

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Centre de Référence des IOA complexes de Lyon

Traitements antibiotiques suppressifs

- ***« Antibiothérapie sans limite de durée pour une infection bactérienne persistante »***

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- Comment peut-on imaginer cela en 2018 ?

Traitements antibiotiques suppressifs

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Limiter la prescription d'antibiotique
Limiter la durée de l'antibiothérapie

Limiter le coût
Limiter la survenue d'effets indésirables
Limiter l'impact écologique
Lutter contre l'antibiorésistance

VS.

Problématique individuelle

Infection (potentiellement) persistante

Enjeu vital
Enjeu fonctionnel majeur

Quel type d'infection ?

- **Infections bactériennes <u>sur implant</u>**
  - Infection sur prothèse articulaire
  - Infection sur matériel vasculaire/endovasculaire
  - Infection sur matériel neurologique

Quel type d'infection ?

- **Infections bactériennes <u>sur implant</u>**
  - Infection sur prothèse articulaire
  - Infection sur matériel vasculaire/endovasculaire
  - Infection sur matériel neurologique

- **Lorsque la stratégie médico-chirurgicale choisie expose le patient malgré tout à un risque de rechute important**

  ET

- **Que la rechute soit associée à un risque vital ou une perte fonctionnelle majeure**

Cas clinique 1

Quel % de risque d'infection persistante ? — **20-50%**

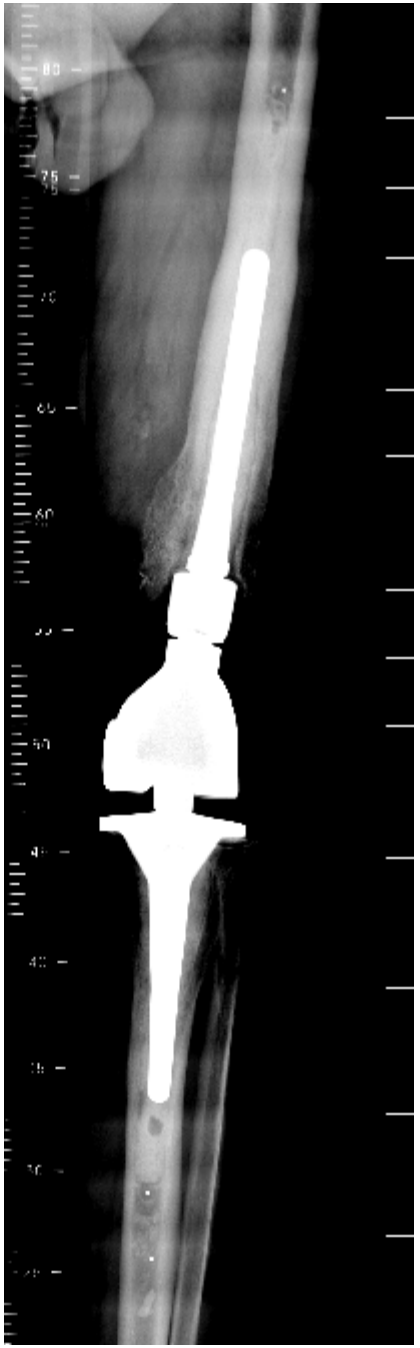
Sensibilité du germe — **Sensible**

Quel statut fonctionnel ? — **Excellent**

Quel traitement en cas d'échec ? — **Amputation transfémorale**

Quelle durée pour l'antibiothérapie ?

- 6 semaines ?
- 3 mois ?
- 6 mois ?
- **Suppressif ?**



Traitements antibiotiques suppressifs

- ***« Antibiothérapie sans limite de durée pour une infection bactérienne persistante »***
- Comment peut-on imaginer cela en 2018 ?

Problématique

Limiter la prescription d'antibiotique

- ***« Antibiothérapie sans limite de durée pour une infection bactérienne présumée persistante engageant le pronostic vital ou fonctionnel, que l'on ne peut simplement éradiquer »***

Lutter contre l'antibiorésistance

Enjeu fonctionnel majeur

Long-Term Suppressive Antimicrobial Therapy for Intravascular Device-Related Infections

LARRY M. BADDOUR, MD; AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA'S EMERGING INFECTIONS NETWORK

- Etude rétrospective
- 51 patients avec **matériel vasculaire** sans possibilité d'enlever le matériel
- La majorité des patients (45 patients) **n'ont pas été opéré**
- Antibiotique utilisé (***β*-lactam 39%**; co-trimoxazole, fluoroquinolone, clindamycin)
- Duration: from 3 to 120 months; in at 50%, least 50% the duration was >1 year
- **Rechute : 3/41 (7%)**
  - In 1 case, infection relapse under ciprofloxacin with ***P. aeruginosa*** **that had developed resistance**
  - In the other 2 cases, coagulase-negative staphylococci caused relapsing infections; **both isolates remained susceptible to the suppressive agents used**

Am J Med Sci **2001;322(4):209–212**

Outcome of patients over 80 years of age on prolonged suppressive antibiotic therapy for at least 6 months for prosthetic joint infection

Virginie Prendki [a,b,c,*], Valérie Zeller [b,c,d], Dorick Passeron [c,d], Nicole Desplaces [c,e], Patrick Mamoudy [c,d], Jérôme Stirnemann [a], Simon Marmor [c,d], Jean-Marc Ziza [b,c]

- Etude rétrospective
- 38 patients âgés avec **infection de prothèse articulaire**
- ***Staphylococcus spp.*** were the most common pathogens (72.1%)
- Median follow-up 24 months
- **Failure in 6 patients (16%) :**
  - 1 persistance (MRSA/cotrimoxazole)
  - 3 relapses (MSSA/cloxacillin)
  - 1 related death
  - 1 treatment discontinuation

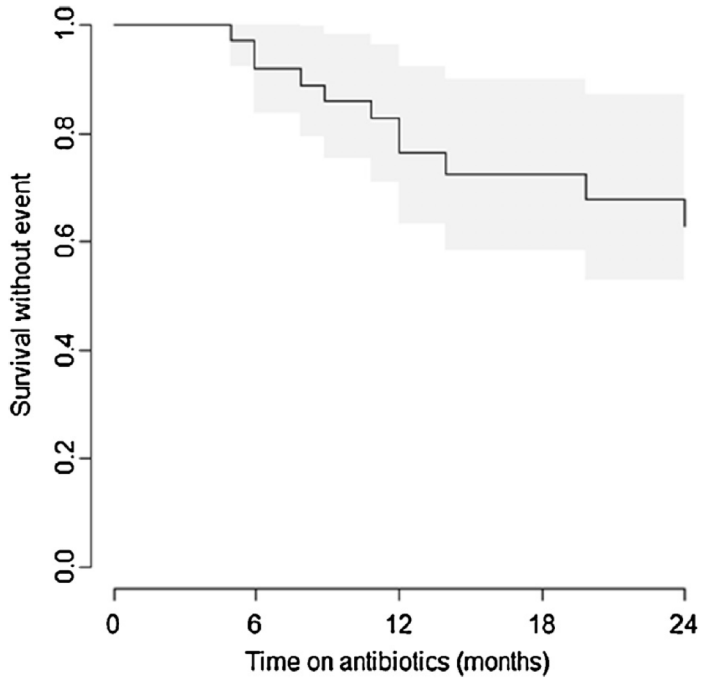


Figure 1. Clinical outcome of 38 patients with prosthetic joint infections treated with prolonged suppressive antibiotic therapy. Kaplan–Meier curve showing survival without event (95% confidence interval in grey). Events are defined as failure and unrelated death.

International Journal of Infectious Diseases 29 (2014) 184–189

Outcome of patients over 80 years of age on prolonged suppressive antibiotic therapy for at least 6 months for prosthetic joint infection

Virginie Prendki [a,b,c,*], Valérie Zeller [b,c,d], Dorick Passeron [c,d], Nicole Desplaces [c,e], Patrick Mamoudy [c,d], Jérôme Stirnemann [a], Simon Marmor [c,d], Jean-Marc Ziza [b,c]

Table 3
Agents used for chronic suppression in 38 patients with prosthetic joint infections (low-dose oral antibiotic therapy)

Agents used for oral PSAT	Daily dosage	Number of patients (%)	Microorganism (number of patients treated)
Amoxicillin	1000 mg tid	14 (37)	*Streptococcus spp* (7), *Enterococcus faecalis* (2), *Campylobacter fetus* (2), *Propionibacterium acnes* (3)
Cloxacillin	1000 mg tid	10 (26)	MS *Staphylococcus aureus* (6), MS coagulase-negative Staphylococcus (4)
Clindamycin	600 mg tid	8 (21)	MS *Staphylococcus aureus* (3), MR *Staphylococcus aureus* (2), MR coagulase-negative Staphylococcus (1), *Finegoldia magna* (1), *Campylobacter fetus* (1)
TMP–SMX	800 mg–160 mg bid	3	MR *Staphylococcus aureus* (1), *Enterobacter cloacae* (1), *Citrobacter koseri* (1)
Fusidic acid[a]	500 mg tid	2	MS *Staphylococcus aureus* (1), MR *Staphylococcus aureus* (1)
Doxycycline	100 mg bid	1	MR *Staphylococcus aureus* (1)

PSAT, prolonged suppressive antibiotic therapy; tid, three times daily; bid, twice daily; MS, methicillin-susceptible; MR, methicillin-resistant; TMP–SMX, trimethoprim–sulfamethoxazole.

[a] Fusidic acid is not recommended as single therapy.

International Journal of Infectious Diseases 29 (2014) 184–189

Suppressive antibiotic therapy with oral tetracyclines for prosthetic joint infections: a retrospective study of 78 patients

M. Pradier[1,5] · O. Robineau[1,2,5] · A. Boucher[1,2,5] · M. Titecat[2,3,5] · N. Blondiaux[1,5] · M. Valette[1,5] · C. Loïez[3,5] · E. Beltrand[1,5] · S. Nguyen[4] · H. Dézeque[3,5] · H. Migaud[2,3,5] · Eric Senneville[1,2,3,5]

- Etude rétrospective
- 78 patients avec **infection de prothèse articulaire** traité par cyclines en suppressif
- *Staphylococcus spp.* were the most common pathogens (72.1%)
- **Surgery in all cases** (DAIR in 76% of them)
- **Doxycycline (200 mg once daily)** in 94%; minocycline 100 mg twice daily in 6%
- Adverse events were reported in 14 patients (18%), leading to SAT discontinuation in 6 of them (8%)
- **A total of 22 (28.2%) patients had failed including 3 cases (3.8%) with documented acquisition of tetracycline resistance in initial pathogen(s).**

Infection **(2018) 46:39–47**

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Table 5 Compared outcome of patients treated with 2-year versus continued suppressive antibiotic therapy (SAT) for prosthetic joint infections

Outcome	2-year SAT ($n = 26$)	Continued SAT ($n = 52$)	p value
Discontinuation for SAT-related adverse effect	2 (7.7%)	4 (7.7%)	1
Death	2 (7.7%)	2 (3.85%)	0.47
Failure	11 (42.3%)	11 (21.2%)	0.05

Infection (2018) 46:39–47

Eur J Clin Microbiol Infect Dis (2017) 36:1577–1585
DOI 10.1007/s10096-017-2971-2

ORIGINAL ARTICLE

Prolonged suppressive antibiotic therapy for prosthetic joint infection in the elderly: a national multicentre cohort study

V. Prendki[1] · T. Ferry[2] · P. Sergent[3] · E. Oziol[4] · E. Forestier[5] · T. Fraisse[6] · S. Tounes[7] · S. Ansart[8] · J. Gaillat[9] · S. Bayle[10] · O. Ruyer[11] · F. Borlot[11] · G. Le Falher[11] · B. Simorre[11] · F.-A. Dauchy[12] · S. Greffe[13] · T. Bauer[14] · E. N. Bell[15] · B. Martha[16] · M. Martinot[17] · M. Froidure[18] · M. Buisson[19] · A. Waldner[20] · X. Lemaire[21] · A. Bosseray[22] · M. Maillet[23] · V. Charvet[24] · A. Barrelet[25] · B. Wyplosz[26] · M. Noaillon[27] · E. Denes[28] · E. Beretti[29] · M. Berlioz-Thibal[30] · V. Meyssonnier[31] · E. Fourniols[32] · L. Tliba[33] · A. Eden[34] · M. Jean[34] · C. Arvieux[35] · K. Guignery-Kadri[36] · C. Ronde-Oustau[37] · Y. Hansmann[38] · A. Belkacem[39] · F. Bouchand[40] · G. Gavazzi[41] · F. Herrmann[42] · J. Stirnemann[43] · A. Dinh[44,45,46]

136 patients (83 years)

A single antimicrobial drug was prescribed in 96 cases (70.6%).

There were 46 (33.8%) patients with an event:

- 25 (18%) with an adverse drug reaction
- 8 (5.9%) with progression of sepsis
- 13 died (9.6%)

Among patients under follow-up, the survival rate without an event at 2 years was 61%

In the multivariate Cox analysis, patients with higher World Health Organization (WHO) score

Table 3 Agents used for first-line PSAT in 136 patients with PJIs (96 with single and 40 with double therapy)

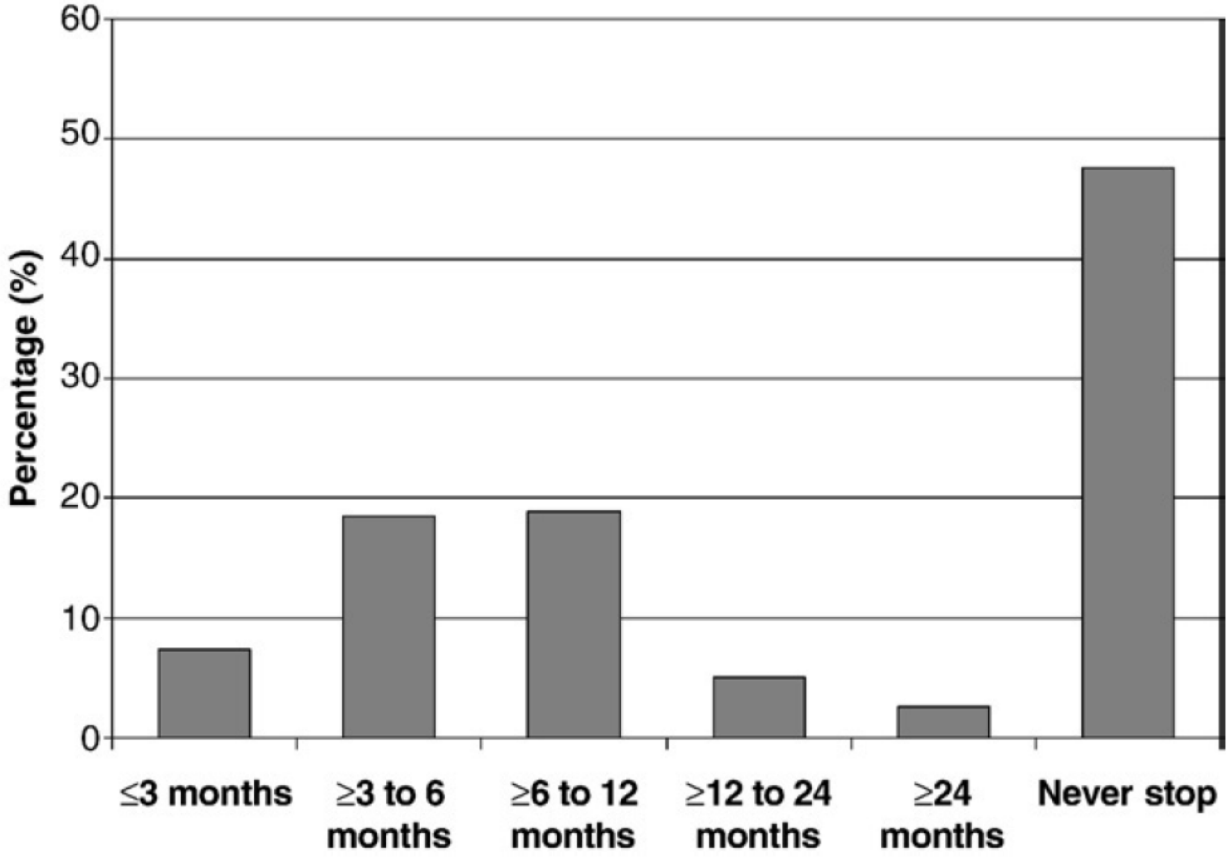
Agents used for PSAT	Daily dosage	No. of patients (%)	Micro-organisms found (*n* patients treated)
Penicillin			
Amoxicil			
Oxacillin			
Cloxacill			
Amoxicil			
Imipenem			
Cephalos			
Cefazolin			
Cephalex			
Cefadroxi			
Cefixime			
Cefpodox			
Ceftriaxo			
Sulpham trimeth			
Fluoroqu (%)			
Ofloxacin			
Ciproflox			
Levoflox			
Clindamy			
Rifampin			
Pristinam			
Doxycycline, *n* (%)	100 mg qd–100 mg bid	11 (8.1)	MSSA (2), MRSA (2), CNS (4), *Yersinia* (1), *Streptococcus* (1)
Fusidic acid[b], *n* (%)	500 mg tid	6 (4.4)	CNS (2), MRSA (2), MSSA (1)
Teicoplanin, *n* (%)	600 mg tid–1200 mg tid per week (IV)	5 (3.7)	CNS (3), MRSA (2)

Table 4 Description of events in 136 patients with PJIs treated with PSAT

Type of event	Total (136)	Median delay (months) [IQR]
All events, *n* (%)	46 (33.8)	6.3 [2.7; 19.7]
Adverse effect leading to discontinuation or switch of PSAT	25 (18.4)	8.6 [3.2; 21.2]
All deaths	13 (9.6)	7 [1.9; 29.1]
Death due to infection	2 (1.5)	1.5 [1.3; 1.7]
Failure		
Systemic progression of sepsis	5 (3.7)	39 [36.9; 53.5]
Development of sinus tract	2 (1.5)	18.2 [17.6; 18.7]
Worsening of the inflammation	1 (0.7)	11.7

Treatment approaches to prosthetic joint infections: results of an Emerging Infections Network survey☆

Birgir Johannsson[a,*], James Taylor[a], Charles R. Clark[b], Hala Shamsuddin[c], Susan E. Beekmann[a], Philip Polgreen[a,d]
on behalf of the Infectious Diseases Society of America Emerging Infections Network



Diagnostic Microbiology and Infectious Disease 66 (2010) 16–23

Recommandations de pratique clinique

Infections ostéo-articulaires sur matériel

(prothèse, implant, ostéo-synthèse)

2009

- **Définition :** « antibiothérapie orale dans la grande majorité des cas pour une durée indéterminée »
- **But :** « Inhiber la multiplication bactérienne autour de la prothèse »
- Elle ne s'applique qu'aux situations pour lesquelles :
  - La documentation bactérienne est connue
  - L'infection persiste chez un **malade inopérable**
  - Ayant une prothèse non descellée.
- Elle ne se conçoit qu'avec des molécules bien supportées, d'administration aisée (voie orale) et pour lesquelles une monothérapie est possible

Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America[a]

2013

IDSA
Infectious Diseases Society of America

Douglas R. Osmon,[1] Elie F. Berbari,[1] Anthony R. Berendt,[2] Daniel Lew,[3] Werner Zimmerli,[4] James M. Steckelberg,[1] Nalini Rao,[5,6] Arlen Hanssen,[7] and Walter R. Wilson[1]

What is the medical treatment for a patient with PJI **following debridement and retention of the prosthesis**?

- The decision to offer chronic suppressive therapy must take into account the individual circumstances of the patient including:
  - The ability to use rifampin in the initial phase of treatment
  - The potential for progressive implant loosening and loss of bone stock
  - The hazards of prolonged antibiotic therapy

it is therefore generally reserved for patients who are unsuitable for, or refuse, further exchange revision, excision arthroplasty, or amputation.

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Table 3. Common Antimicrobials Used for Chronic Oral Antimicrobial Suppression (B-III Unless Otherwise Stated in Text)[a,b]

Microorganism	Preferred Treatment	Alternative Treatment
Staphylococci, oxacillin-susceptible	Cephalexin 500 mg PO tid or qid or Cefadroxil 500 mg PO bid	Dicloxacillin 500 mg PO tid or qid Clindamycin 300 mg PO qid Amoxicillin-clavulanate 500 mg PO tid
Staphylococci, oxacillin-resistant	Cotrimoxazole 1 DS tab PO bid Minocycline or doxycycline100 mg PO bid	
β-hemolytic streptococci	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid
Enterococcus spp, penicillin susceptible	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	
Pseudomonas aeruginosa	Ciprofloxacin 250–500 mg PO bid	
Enterobacteriaceae	Cotrimoxazole 1 DS tab PO bid	β-lactam oral therapy based on in vitro susceptibilities
Propionibacterium spp	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or qid Minocycline or doxycycline 100 mg PO bid

Clinical Infectious Diseases 2013;56(1):e1–25

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β-hemolytic streptococci	or Amoxicillin 500 mg PO tid	ephalexin 500 mg PO tid or qid
Enterococcus spp, penicillin susceptible	Amoxicillin 500 mg PO tid	
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Enterobacteriaceae		β-lactam oral therapy based on in vitro susceptibilities
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Clinical Infectious Diseases 2013;56(1):e1–25

Consensus document

2017

Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

- Some patients may be considered **unsuitable for implant removal**, either because they present with too many baseline conditions, or because a poor functional outcome is foreseen. In these patients, prolonged or **indefinite antimicrobial therapy aiming to control the infection may be considered**. This strategy is known as SAT (suppressive antimicrobial therapy).

Consensus document

2017

Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

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- Thus, the main medical and surgical strategies to be considered in a patient with PJI are:
  a) Attempted eradication with implant retention and antibiotics (DAIR).
  b) Attempted eradication with implant removal and antibiotics:
  c) Implant retention and long-term suppressive antibiotics (SAT), without attempted eradication.

Consensus document

2017

Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

Is it necessary to perform a surgical debridement before initiating SAT?

- It is reasonable to think that **reducing the bacterial inoculum** and debriding the infected tissues **may favour the success of SAT**.
- Another important advantage of performing surgical debridement is the possibility of **obtaining valuable samples for culture**.

RECOMMENDATIONS

- A **surgical debridement before beginning SAT** is recommended, if feasible (C-III).
- Obtaining a valid sample for culture before starting SAT is particularly important (C-III).

Consensus document

2017

Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

What are the most appropriate antibiotics for SAT? Are combinations of antimicrobials convenient or necessary? What is the role for rifampin?

- In published case series, the most frequently reported antibiotics are the combination of **minocycline** plus rifampin or **β-lactams** alone. Other less frequently antibiotics used are **co-trimoxazole**, **clindamycin**, and **fluoroquinolones**.

RECOMMENDATIONS

- For the choice of the specific antibiotic for SAT, the antimicrobial susceptibility of the microorganism causing the infection, the **safety of the drug** and the **observance** of the treatment must be considered (C-III).
- Except for some particular cases, the use of combinations (and therefore the use of rifampin) is not recommended (D-III).

Consensus document

2017

Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

Is it necessary to administer intravenous antibiotics at the beginning of SAT?

In addition to the surgical debridement, an initial intravenous antimicrobial treatment may contribute to reducing the bacterial inoculum, thus favouring good evolution. Nevertheless, it seems unlikely that prolonged intravenous treatment is really relevant for the success or failure of SAT, since its efficacy is based on its indefinite administration.

RECOMMENDATIONS

- In cases undergoing surgical debridement, **an initial intravenous treatment for at least 7 days** is recommended. Nevertheless, prolonged intravenous treatment is not necessary when deciding on SAT management (C-III).

Consensus document

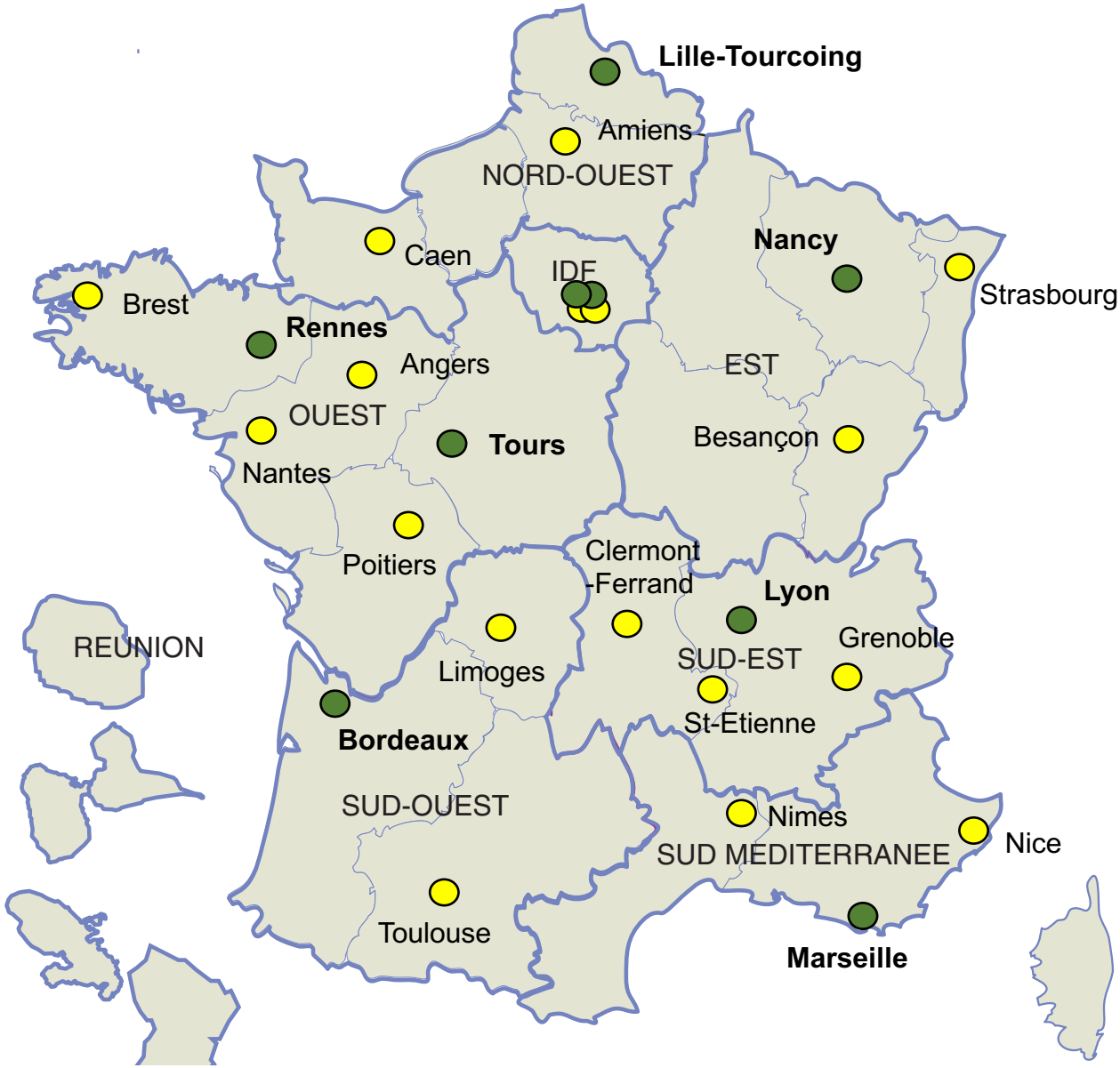
2017

Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

Is SAT safe? What about its effect on the microbiota?

RECOMMENDATIONS

- The prescription and control of a SAT must be performed by an **expert in antimicrobial therapy, who will periodically follow up the clinical evolution** of the infection and assess the possible occurrence of adverse events (B-III).
- The **use of linezolid is discouraged** in SAT due to high risk of toxicity, which limits its prolonged administration (E-I).
- The use of **β-lactams, or low doses of co-trimoxazole**, is recommended. Alternatively, other antimicrobials such as **minocycline** or **clindamycin** may be administered (C-III).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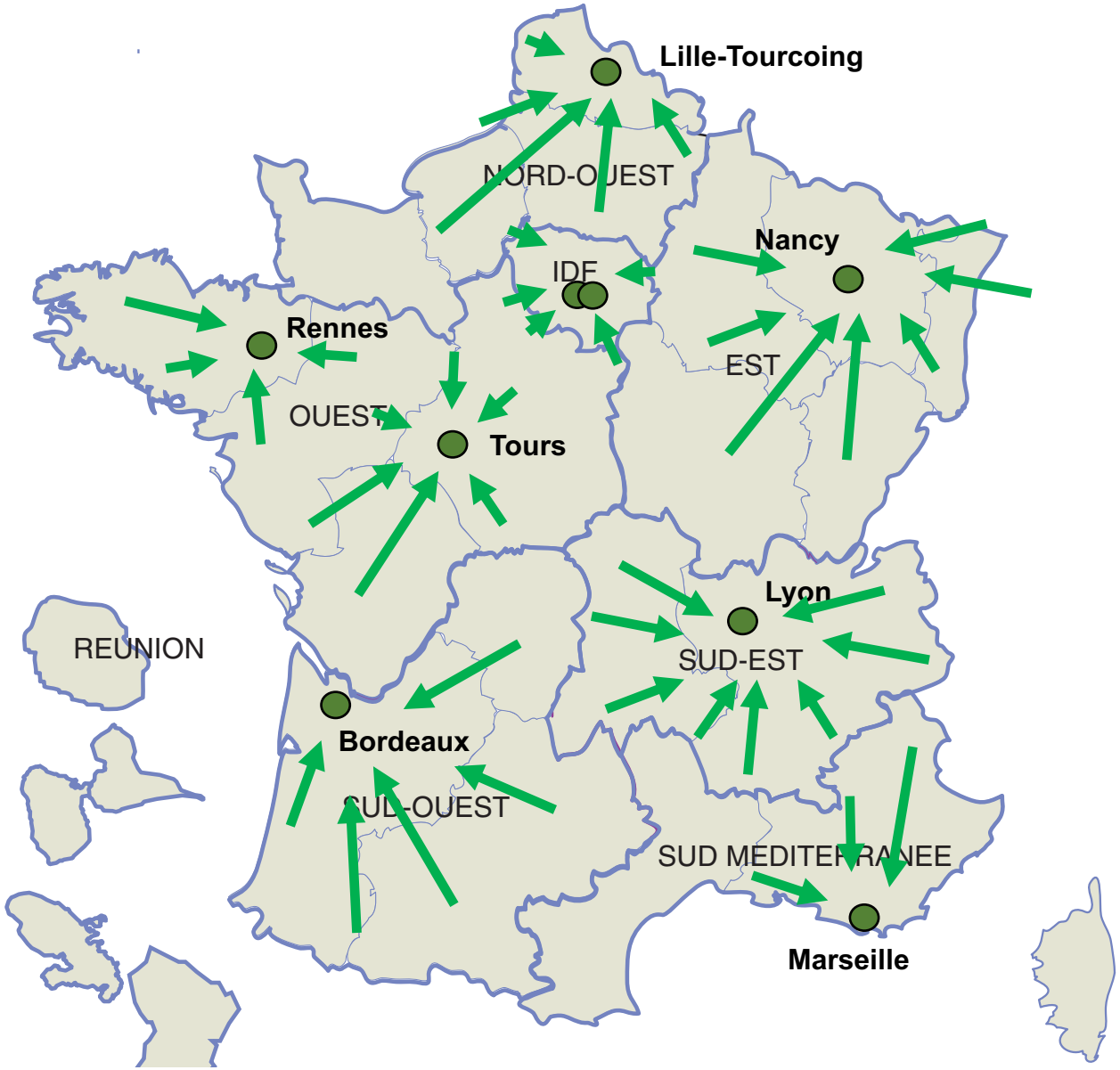

Recruitement of **the most <u>complex</u> <u>patients</u>**

In the CRIOAc network

To increase the <u>knowledge</u> and <u>skill</u> of dedicated surgeons and physicians

Cas clinique 3

Homme de 71 ans
Vitiligo, coronarien

PTG droite changée à de multiples reprises

Fistule

Open Forum Infectious Diseases

ID CASE

Correction of Linezolid-Induced Myelotoxicity After Switch to Tedizolid in a Patient Requiring Suppressive Antimicrobial Therapy for Multidrug-Resistant *Staphylococcus epidermidis* Prosthetic-Joint Infection

Tristan Ferry,[1,2,3,4] Cécile Batailler,[2,3,4,5] Anne Conrad,[1,2,3,4] Claire Triffault-Fillit,[1,3,4] Frédéric Laurent,[2,3,4,6] Florent Valour,[1,2,3,4] and Christian Chidiac[1,2,3,4]; on behalf of the Lyon BJI Study Group

Cas clinique 3

Homme de 71 ans
Vitiligo, coronarien

PTG droite changée à de multiples reprises

Fistule

Arthrotomie-lavage
Antibiothérapie suppressive

Infection chronique à *Staphylococcus epidermidis* uniquement sensible vancomycine, daptomycine, linézolide

Open Forum Infectious Diseases

ID CASE

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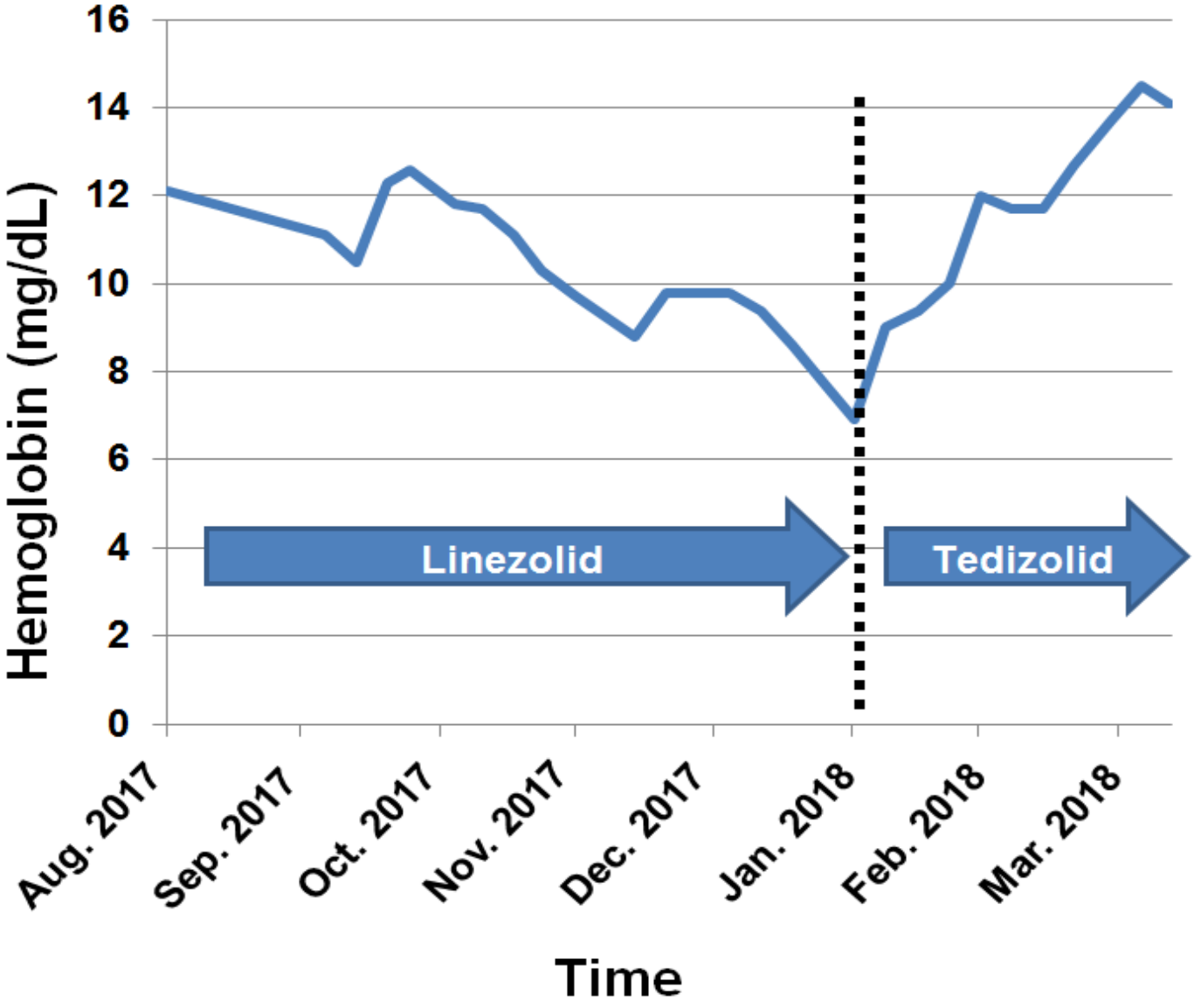

Figure 1. Hemoglobin during time, with continuous decrease under linezolid therapy, followed by a continuous increase after the switch to tedizolid.

Antibiothérapie suppressive

- **Réelle** stratégie
  - Balance bénéfice/risque
  - Bétalactamines, doxycycline, cotrimoxazole, clindamycine
  - Validation RCP (CRIOAc)
- **Incertitudes**
  - Timing ? Doses initiales ? Doses minimales ?
  - Effet thérapeutique au long cours (biomarqueur d'infection résiduelle ?)
  - Impact sur le microbiote et l'environnement ?
- **Possibilités émergentes** (pathogènes résistants)
  - Antibiothérapie sous-cutanée
  - Linézolide -> Tédizolide

Hospices Civils de Lyon

CRIOAc LYON

Lyon 1

Lyon BJI Study group

Coordinator: Tristan Ferry
Infectious Diseases Specialists – Tristan Ferry, Florent Valour, Thomas Perpoint, André Boibieux, François Biron, Patrick Miailhes, Florence Ader, Sandrine Roux, Claire Triffault-Philit, Agathe Becker, Anne Conrad, Marielle Perry, Cécile Pouderoux, Marie-Elodie Langlois, Fatiha Daoud, Johanna Lippman, Evelyne Braun, Christian Chidiac;
Surgeons – Sébastien Lustig, Elvire Servien, Cécile Batailler, Romain Gaillard, Stanislas Gunst, Julien Roger, Charles Fiquet, Michel-Henry Fessy, Anthony Viste, Jean-Luc Besse, Philippe Chaudier, Lucie Louboutin, Sébastien Martres, Franck Trouillet, Cédric Barrey, Emmanuel Jouanneau, Timothée Jacquesson, Brice Gérenton, Ali Mojallal, Fabien Boucher, Hristo Shipkov;
Microbiologists – Frederic Laurent, Céline Dupieux, Laetitia Berraud, Camille Kolenda, Jérôme Josse
Nuclear Medicine – Isabelle Morelec, Marc Janier, Francesco Giammarile
PK/PD specialists – Michel Tod, Marie-Claude Gagnieu, Sylvain Goutelle
Clinical Research Assistant – Eugénie Mabrut

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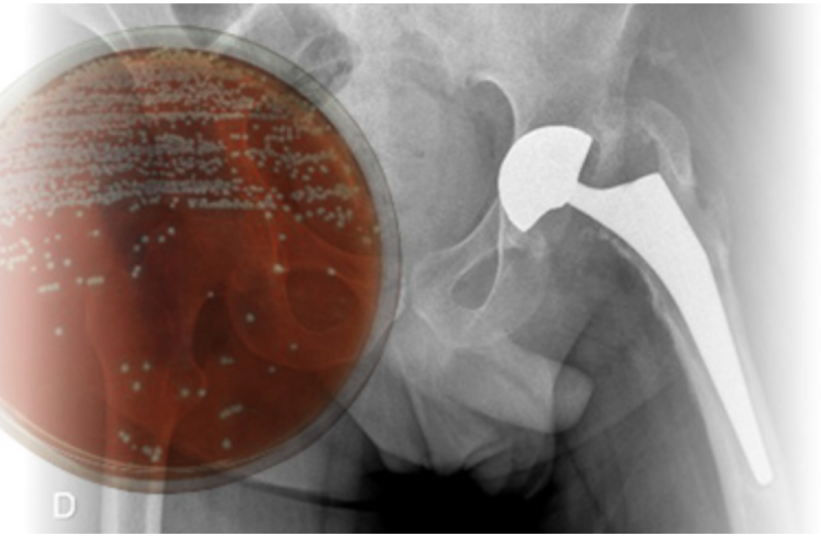

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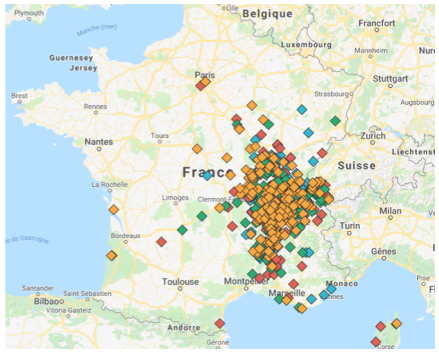
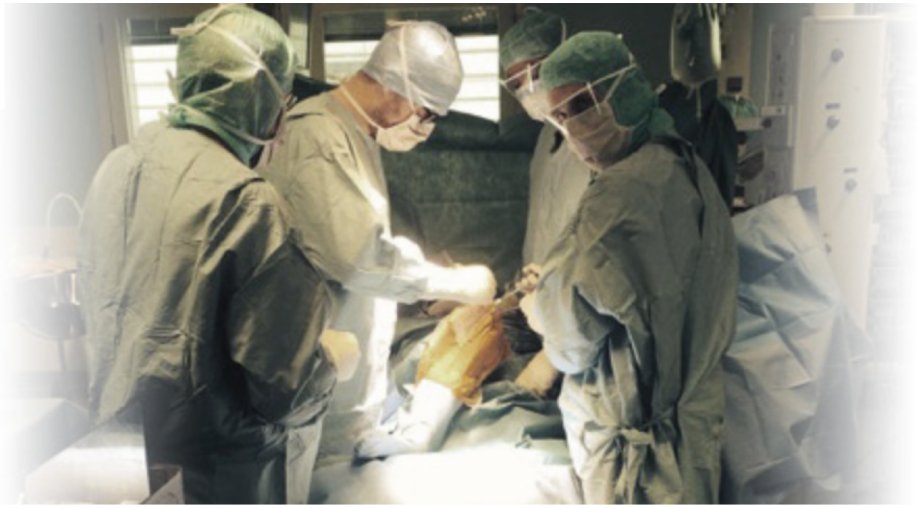
- All recommendations
- **Newsletter**





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