Top 5 papiers

Antibiothérapie suppressive

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DIUIOA 2023 Session de Lille

Généralités

- **Prise en charge des IPOAs : codifiée**
  - *Chirurgicale*
    - Maintien de prothèse : Synovectomie-lavage (DAIR)
    - Changement de prothèse 1 / 2 temps; résection arthroplastique
  - *Médicale*
    - ATB curative 6 à 12 semaines
    - Active biofilm / bonne diffusion
- **Objectif : rémission (éradication)**

Indications du DAIR

- Infection post-opératoire < 12 semaines (précoce)
- Durée des symptômes d'infection ≤ 3 semaines (aiguë)
- Infection hématogène (tardive) aiguë
- Implants stables
- État cutané satisfaisant
- Traitement par rifampicine (staphylocoques) ou fluoroquinolones (bacille à gram négatif) envisageable

Consensus Société Espagnole d'Infectiologie 2017

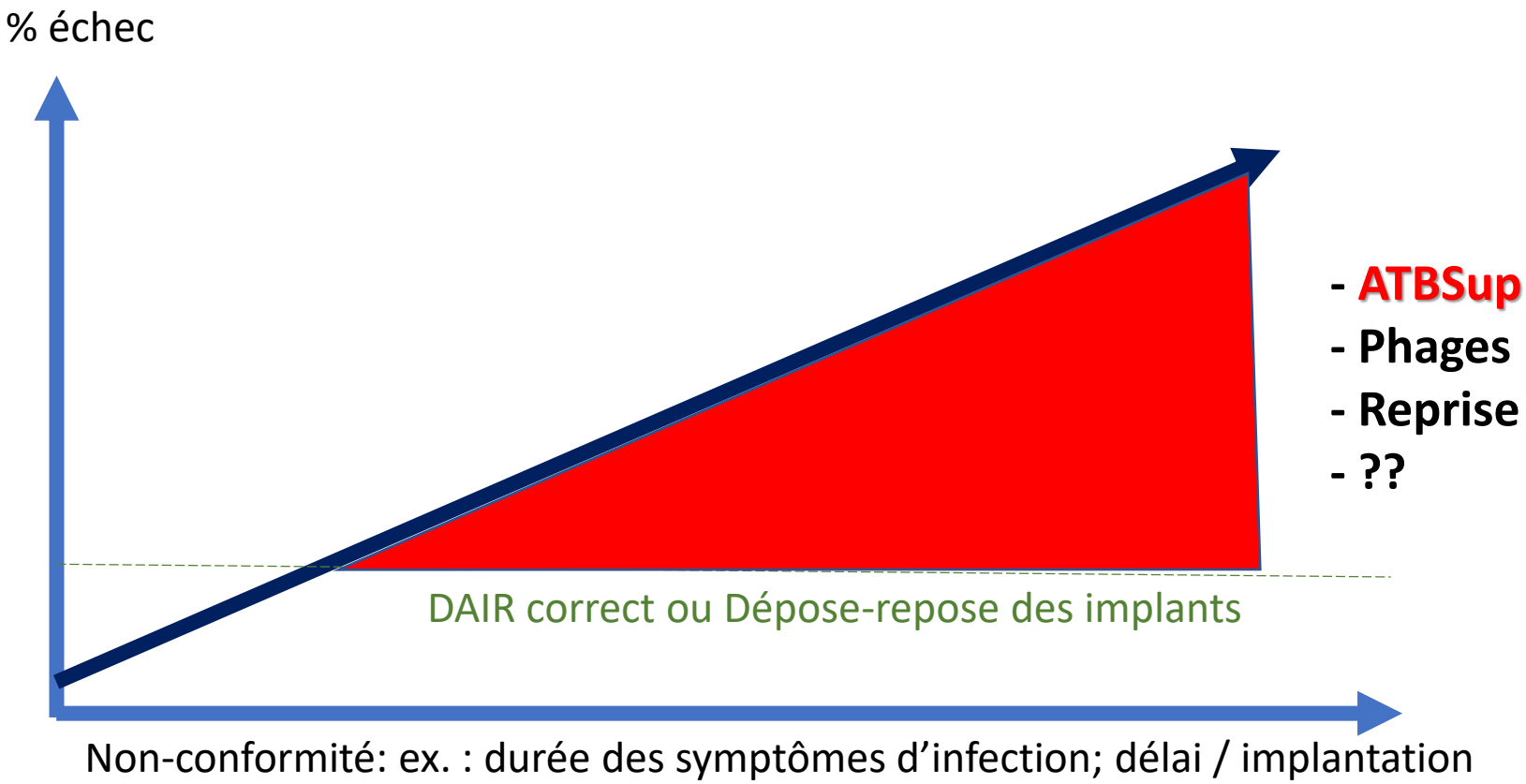
Situation non idéale :

- ❑ Maintien des implants non conforme
  - comorbidités / AG impossible
  - type de prothèse / matériel (PTG, mégaprothèses, etc…)
  - refus patient, etc…

- ❑ Autre : antibiothérapie curative sub-optimale

- ➢ L'objectif d'éradication ne peut pas être atteint

Conséquences de la non-conformité de prise en charge d'une IPOA



Antibiothérapie suppressive

- Objectifs :
  1. Maintenir un patient en état de rémission d'une infection alors que l'on estime le risque de récidive infectieuse anormalement élevé en raison d'un traitement non optimal = pour le patient c'est une assurance complémentaire pour l'avenir
     - « anormalement » élevé : supérieur au risque attendu si le patient avait été traité de façon optimale?

  2. Éviter ou ralentir une dégradation de la situation infectieuse et/ou fonctionnelle chez un patient en échec = pour le patient, c'est essayer de « limiter la casse »

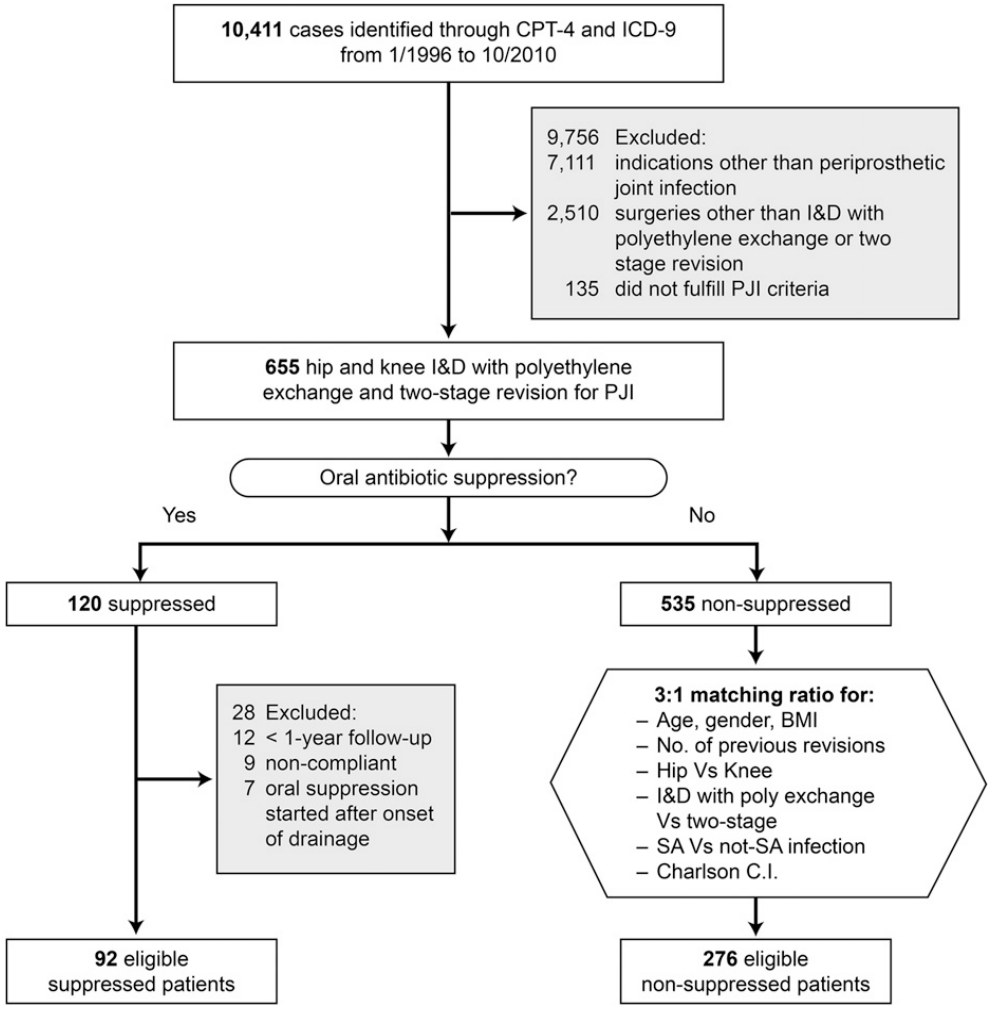
SUPPRESSIF

PALLIATIF

Top 5

- Siqueira M *et al*. J Bone Joint Surg Am. 2015;97:1220
- Cobo J *et al.* Antibiotics 2021; 10, 743
- Escudero-Sanchez R *et al*. Clin Microbiol Infect 2020;26:499
- Leijtens B *et al*. JBJI 2019; 4(6): 268
- Lensen KJ *et al.* JBJI 2021 ; 6: 313

Chronic Suppression of Periprosthetic Joint Infections with Oral Antibiotics Increases Infection-Free Survivorship



Siqueira M *et al*. J Bone Joint Surg Am. 2015;97:1220

TABLE I Results of Univariate Analyses Comparing Baseline Characteristics Between Suppression and Non-Suppression Groups

Variable	Suppression Group (N = 92)	Non-Suppression Group (N = 276)	P Value
Charlson comorbidity index*	4 [3, 5]	4 [2, 5]	0.34
Age† *(yr)*	63.7 ± 11.7	64.2 ± 11.5	0.72
BMI† *(kg/m²)*	33.6 ± 9.2	33.2 ± 8.6	0.71
Sex‡			0.90
Female	36 (39.1)	112 (40.6)	
Male	56 (60.9)	164 (59.4)	
Index surgery‡			0.63
Irrigation and debridement with polyethylene exchange	54 (58.7)	152 (55.1)	
2-stage revision	38 (41.3)	124 (44.9)	
No. of previous revisions*	1 [0, 3]	1 [0, 2]	0.37
Pathogen‡			0.33
S. aureus	44 (47.8)	114 (41.3)	
Non-*S. aureus*	48 (52.2)	162 (58.7)	
Joint‡			0.94
Knee	71 (77.2)	210 (76.1)	
Hip	21 (22.8)	66 (23.9)	
Duration of symptoms* *(days)*	30 [7, 90]	14 [5, 45]	0.024
Duration of intravenous antibiotic therapy* *(wk)*	6 [6, 6]	6 [6, 6]	0.17
Previous joint infection anywhere‡	41 (44.6)	130 (47.1)	0.76
Infecting organism class‡			0.21
Virulent§	54 (58.7)	147 (53.2)	
Indolent#	31 (33.7)	55 (20.0)	
Fungal and acid-fast bacilli	0	1 (0.3)	
Miscellaneous and contaminants	5 (5.4)	22 (7.2)	
Multiple organisms‡	18 (19.6)	35 (12.7)	0.13

Siqueira M *et al*. J Bone Joint Surg Am. 2015;97:1220

- SAT = treatment with oral antibiotics for ≥ 6 months following the initial course of intravenous antibiotics
- The decision of whether to offer this treatment was individualized
- SAT in case of virulent microbiology* if risk factor for reinfection :
  - a history of multiple joint infections
  - previous failed surgery for periprosthetic joint infection
  - retained implants and/or immunosuppression
- SAT in case of less virulent pathogens or negative cultures if :
  - had multiple risk factors for reinfection
- The primary outcome variable :
  - infection-free prosthetic survival, with additional surgery due to infection or death as the end points

Siqueira M *et al*. J Bone Joint Surg Am. 2015;97:1220

* MRSA, polymicrobial, fungi

Results

- The five-year infection-free prosthetic survival rate was **68.5%**(95% confidence interval [CI] = 59.2% to 79.3%) for the antibiotic-suppression group compared with **41.1 %** (95% CI = 34.9%to 48.5%) for the non-suppression group (HR = 0.63, p = 0.008)

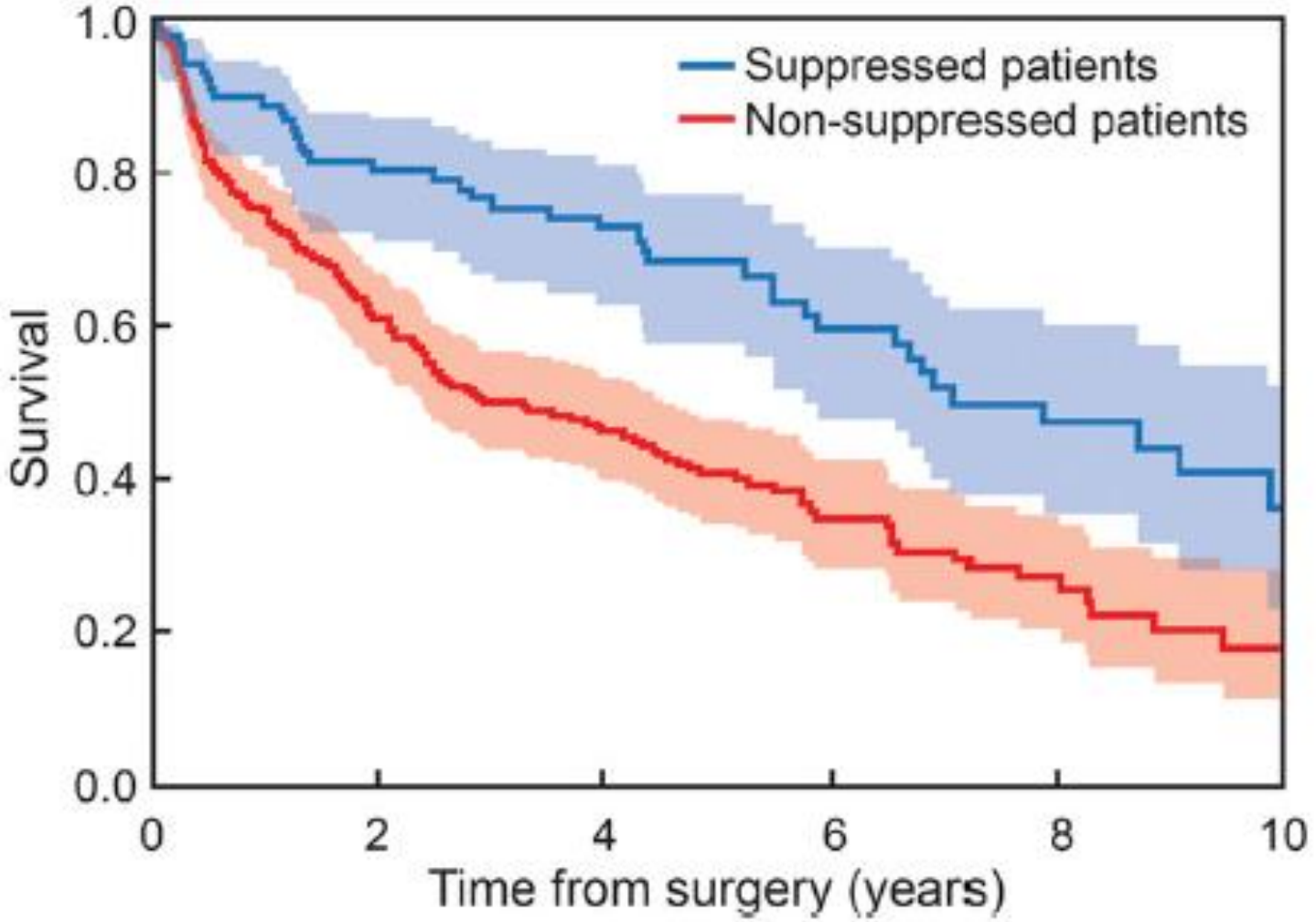
Siqueira M *et al*. J Bone Joint Surg Am. 2015;97:1220

Facteurs de risque de l'échec

TABLE IV Cox Proportional Hazards Model Estimates of Survival, with Adjustment for Matching Covariates

Variable	HR	95% CI	P Value
Chronic suppressive antibiotics	0.48	0.34-0.67	<0.001
No. of previous revisions	1.12	1.04-1.21	0.005
Non-*S. aureus* infection	0.69	0.51-0.94	0.018
Age (per year)	1.01	1.00-1.03	0.11
Hip joint	0.86	0.59-1.24	0.42
Charlson comorbidity index (per index point)	1.02	0.92-1.14	0.67
Male sex	1.05	0.78-1.40	0.76
BMI (per index point)	1.00	0.99-1.02	0.92

Siqueira M *et al*. J Bone Joint Surg Am. 2015;97:1220



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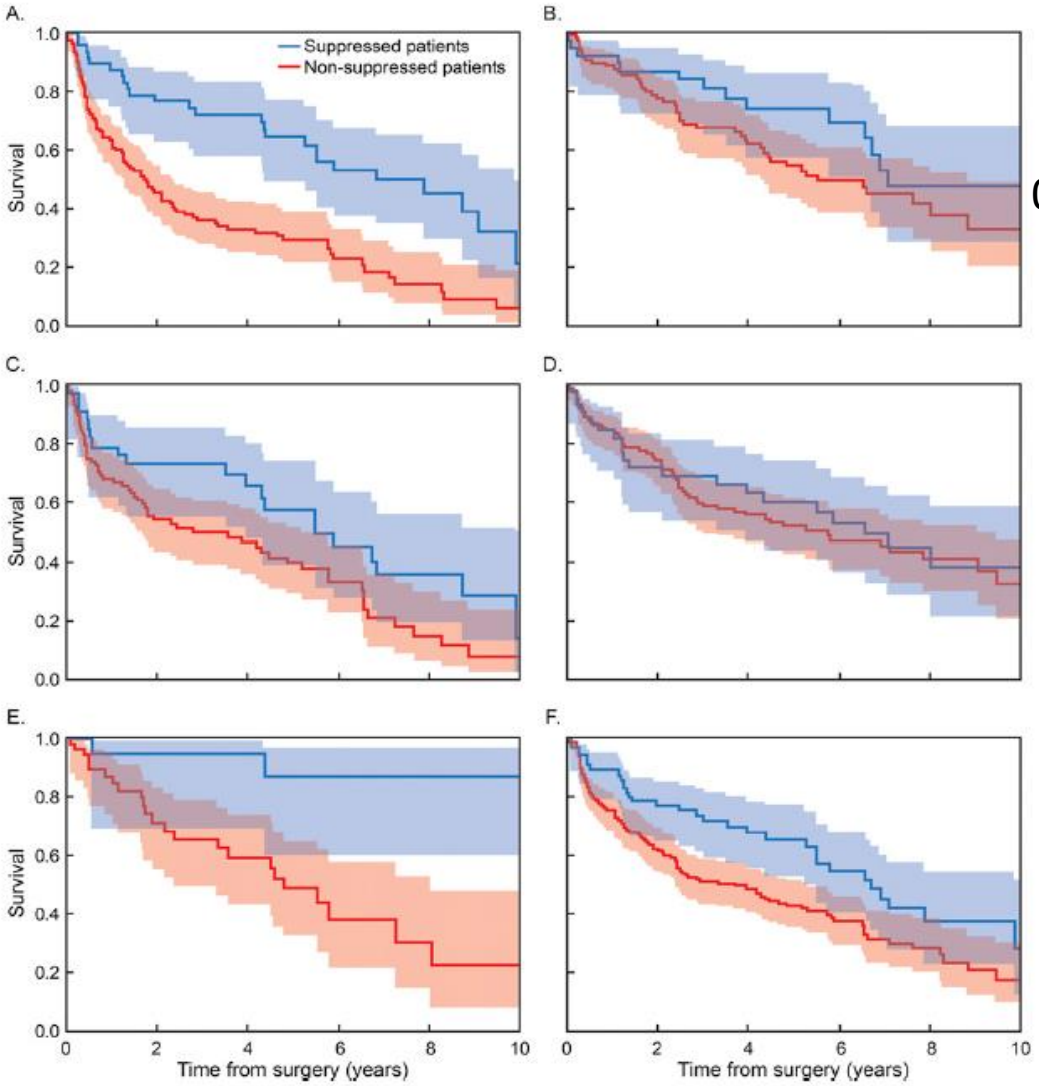
<0,0001 (DAIR + CPM)



0,14 (T2)

0,047 (*S. aureus*)

0,62 (non-*S. aureus*)

0,001 (PTH)

0,01 (PTG)

Fig. 3

Kaplan-Meier infection-free prosthetic survival curves for subset cohorts. The blue line represents the suppression group, and the red line represents the non-suppression group; the shaded areas surrounding the lines represent the 95% CI. **Fig. 3-A** Individuals who underwent irrigation and debridement with polyethylene exchange ($p < 0.0001$ for the difference between the suppression and non-suppression groups). **Fig. 3-B** Individuals who underwent a two-stage revision ($p = 0.14$). **Fig. 3-C** Individuals with an *S. aureus* infection ($p = 0.047$). **Fig. 3-D** Individuals with a non-*S. aureus* infection ($p = 0.62$). **Fig. 3-E** Individuals with an infection in the hip ($p = 0.001$). **Fig. 3-F** Individuals with an infection in the knee ($p = 0.01$).

Siqueira M *et al*. J Bone Joint Surg Am. 2015;97:1220-32

Conclusions

- SAT resulted in superior infection-free survival rates after surgical treatment for PJIs compared with those observed without suppression
- Greatest benefit if DAIR and exchange of the mobile parts and/or *S. aureus* infection
- TKP and multiple revisions prior inclusion associated with treatment failure

Siqueira M *et al*. J Bone Joint Surg Am. 2015;97:1220

Suppressive Antibiotic Treatment in Prosthetic Joint Infections: A Perspective

Concept and Definition of Suppressive Antibiotic Treatment (SAT)

- The term "suppressive antibiotic treatment" (SAT) refers to the administration of antibiotics in the long term or indefinitely over time. In the area of PJI, SAT is considered a noncurative" strategy, in which antimicrobials are administered with the aim of reducing symptoms and delaying or preventing the progression of PJI that needs a surgical procedure to be cured that, for some reason, will not be performed (at least for a prolonged period of time).
- SAT can also be used in situations in which adequate surgical treatment is performed and the probability of cure is considered very low.

Cobo J *et al.* Antibiotics 2021, 10, 743

- SAT is intended to reduce local symptoms (presence of a sinus tract, inflammation, pain, etc.) and thus delay or elude a surgical intervention that has been rejected or is intended to be avoided.
- It is possible that SAT may delay or prevent prosthetic loosening by reducing the local peri-implant inflammatory process, although no studies have evaluated this potential effect.
- Additionally, SAT can be considered a general benefit for the patient's health as a result of the reduction in persistent chronic inflammation

Cobo J *et al.* Antibiotics 2021, 10, 743

Relevant clinical questions

- Is a Debridement Mandatory before Starting SAT?
- What Are the Most Suitable Antibiotics for SAT? Is a Combination of Antibiotics Necessary?
- Is Intravenous Treatment Necessary at the Beginning of SAT?
- Can There Be Periods Without Treatment?
- Is SAT safe?

Cobo J *et al.* Antibiotics 2021, 10, 743

Suppressive antibiotic therapy in prosthetic joint infections: a multicentre cohort study

- Retrospective, multicentre, cohort study of patients with PJI who were managed with SAT.
- PJI : if at least one of the following conditions occurred:

  (a) a fistula communicating with the prosthesis

  (b) local inflammatory signs together with elevated C-reactive protein (CRP), radiological signs of infection and positive cultures

  (c) synovial fluid count >4.3 G/L with >80% neutrophils (hip) or >1.1 G/L with >64% neutrophils (knee) in chronic infections

  (d) the same microorganism was isolated from at least two samples of intraoperative cultures

Escudero-Sanchez R *et al*. Clin Microbiol Infect 2020;26:499

- We defined SAT as the indefinite administration of antibiotics with a non-curative intention, in the context of either a PJI for which cure would require complete removal of the implant (as occurs for late chronic infections) or an acute infection for which conservative treatment such as DAIR has failed.

- SAT failure was indicated by the appearance or persistence of a fistula, the need for debridement or replacement of the prosthesis due to persistence of the infection or the presence of uncontrolled symptoms.

Escudero-Sanchez R *et al*. Clin Microbiol Infect 2020;26:499

Results

- A total of 340 patients with PJI participated in the study. Twenty-one cases were excluded due to insufficient or confounding data, and 17 cases were excluded because they did not meet the inclusion criteria. Therefore, 302 cases were finally analysed.

Escudero-Sanchez R *et al*. Clin Microbiol Infect 2020;26:499

Results

- Success in 177 patients (58.6%)
- The most frequent reason for failure (125) was a need to remove the prosthesis (48.8%), fistula (24.8%), need for debridement in 19 patients (15.2%), and poor symptom control in 14 patients (11.2%)

- The median follow-up to a failure event or death was 25 months (IQR 12e40]). In total, 46/ 302 patients (15.2%) died during the follow-up period, none for a reason directly related to the PJI.

- Success rates of approximately 75% and 50% were observed at 2 years and 5 years, respectively.

Escudero-Sanchez R *et al*. Clin Microbiol Infect 2020;26:499

Results

- Reported causes for failure :

  - suspension of SAT in 21/125 patients (16.8%)
  - development of resistance in 15 patients (of 65, 23.1% of microbiologically documented cases); (= 4.9%)
  - appearance of an unsuspected microorganism in 14/65 patients (21.5% of microbiologically documented cases)
  - poor adherence to treatment in 9/125 patients (7.2%)
  - in 67/125 patients (53.6%), the cause of the SAT failure was unknown

Escudero-Sanchez R *et al*. Clin Microbiol Infect 2020;26:499

- During the follow-up period, 104 adverse effects were recorded in 81/302 patients (26.8%); the majority of these were gastrointestinal (16.9%) and cutaneous (5.3%).
- Overall, 23 patients presented more than one adverse effect.
- SAT was suspended in only 17/302 patients (5.6%), while 46/302 (15.2%) changed antibiotics to avoid the adverse effect. Only 3/302 patients (1%) developed *Clostridium difficile* infection.

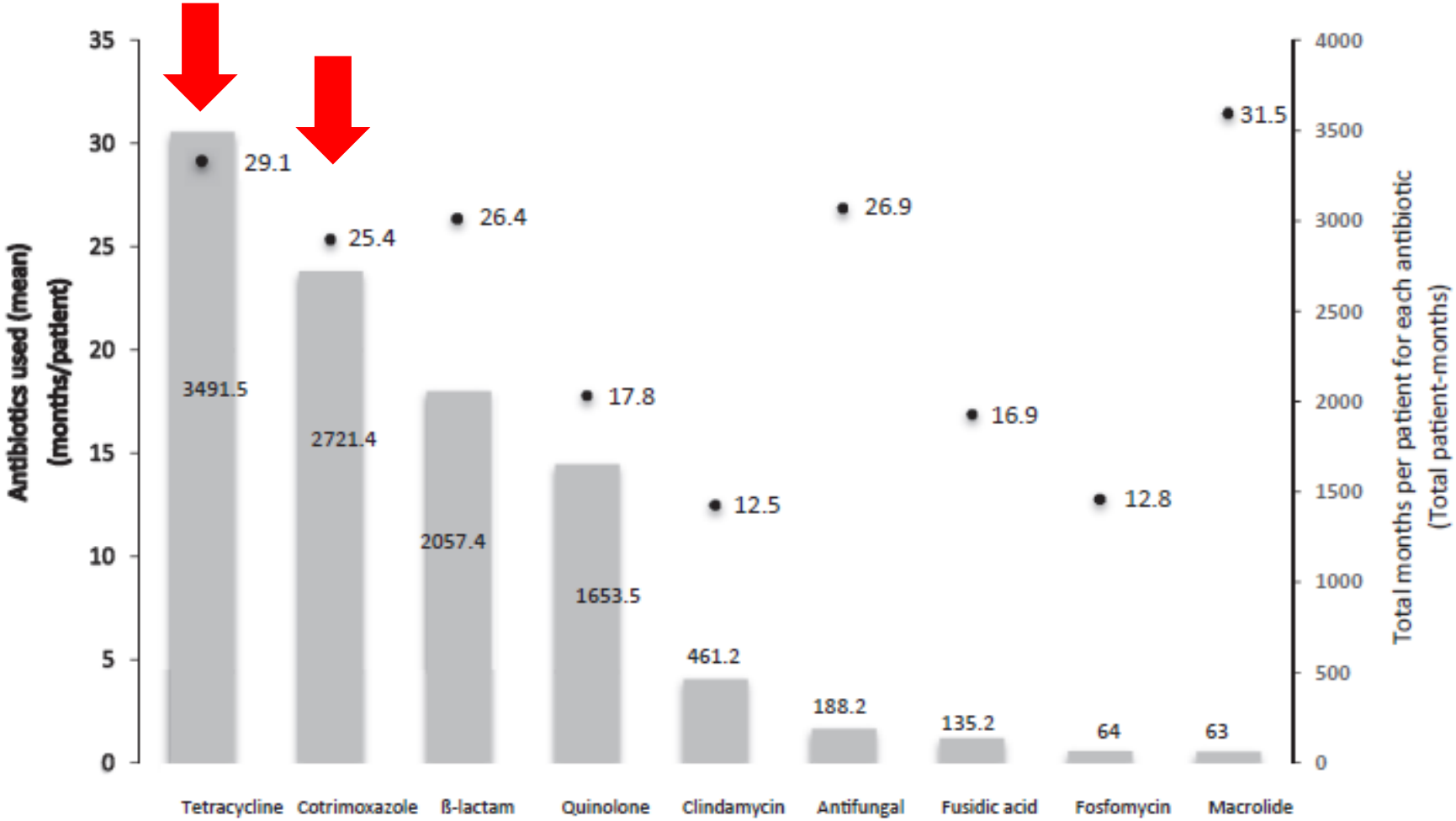
Escudero-Sanchez R *et al*. Clin Microbiol Infect 2020;26:499

Characteristics of the patients

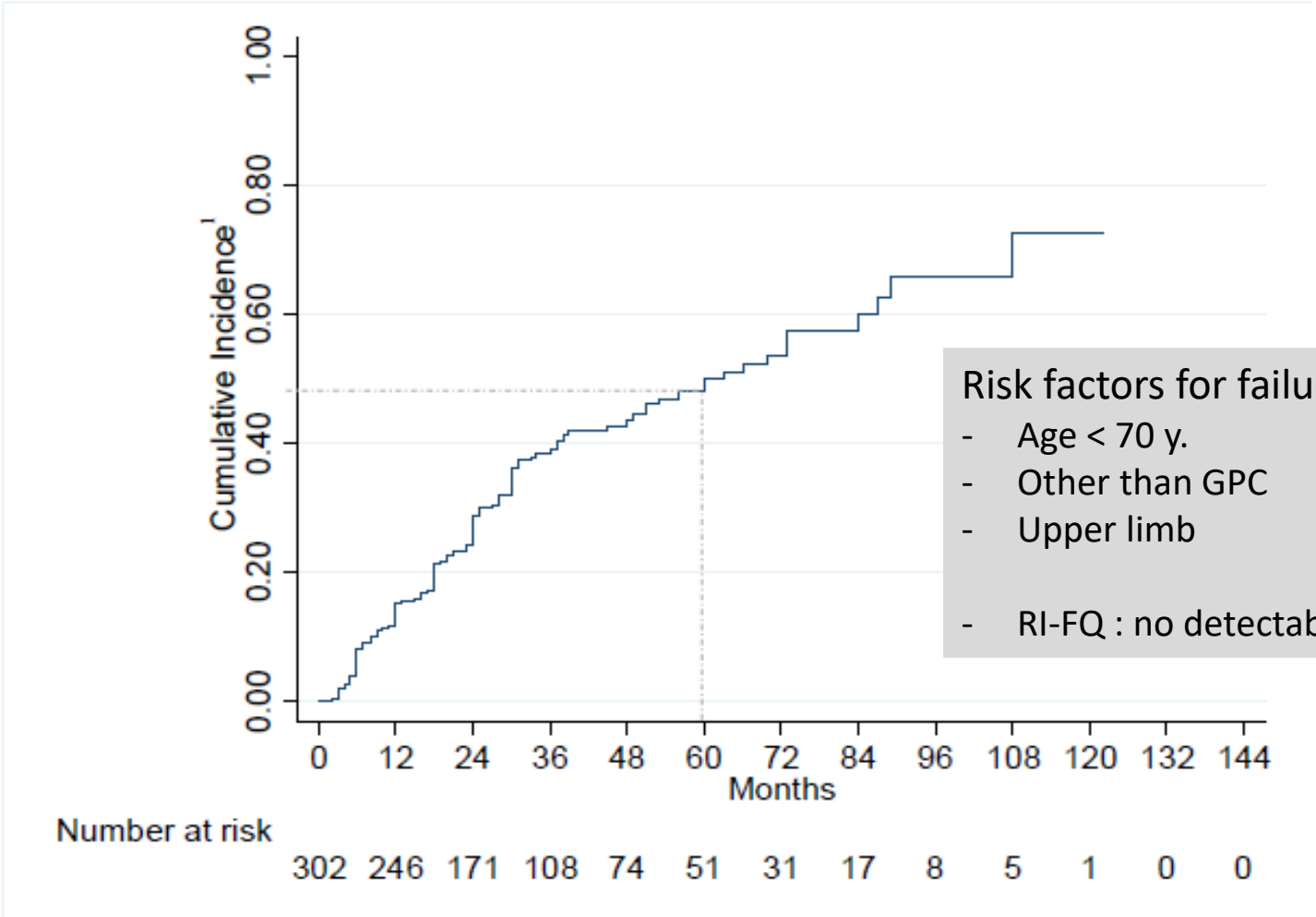
	n (302)	%
Sex Male	122	40.4
Age (years) (mean, SD)	75.5 ± 13.9	—
>70 years	220	72.8
>85 years	85	28.1
Prosthesis		
Knee	157	52.0
Hip	136	45.0
Upper limb	9	3.0
Number of prostheses placed in the same localization		
Primary	162	53.6
Secondary	108	35.8
Tertiary or more	29	9.6
Classification		
Early postoperative[a]	48	15.9
Late chronic	220	72.8
Haematogenous[a]	34	11.3
Diagnostic criteria		
Fistula	133	44.0
Inflammatory and radiological signs, with elevated CRP and positive culture	107	35.4
Synovial fluid count[b]	73	24.2
Positive culture	280	72.8
Characteristics of the prostheses		
Cemented	106	64.6[c]
Loose	51	23.2[c]
Comorbidity		
Charlson index (median, IQR)	4 (3–6)	—
Diabetes	68	22.5
Solid neoplasm	37	12.3
Congestive heart failure	33	10.9
Kidney failure	31	10.3
Liver failure	18	6.0
Initial clinical symptoms		
Asymptomatic	38	12.6
Pain	180	59.6
Impaired walking	167	55.3
Fistula	133	44.0
Local inflammation	127	42.1
Joint effusion	56	18.5
C-reactive protein (mg/L) (mean, SD)	51.7 ± 63.3	—
Management		
Debridement with partial removal	24	7.9
Debridement without removal	143	47.4
Non-surgical	132	43.7
Reason for non-curative surgical management		
Decision of the surgeon	82	27.2
High surgical risk	80	26.5
Advanced age	71	23.5
Patient's decision	70	23.2
Anticipation of poor functional results	69	22.8
Presence of minor symptoms	35	11.6

Aetiology of prosthetic joint infections

Microorganism	n (%)
CoNS	98 (32.5)
S. aureus	94 (31.1)
MSSA	73 (24.1)
MRSA	21 (7.0)
Streptococcus sp.	28 (9.3)
Enterococcus sp.	17 (5.6)
Enterobacteriaceae	26 (8.6)
Escherichia coli	8 (2.6)
Proteus sp.	6 (2.0)
Klebsiella sp.	5 (1.7)
Morganella sp.	3 (1.0)
Enterobacter sp.	2 (0.7)
Citrobacter sp.	1 (0.3)
Non-fermenting GNB	20 (6.6)
Pseudomonas sp.	19 (6.3)
Acinetobacter sp.	1 (0.3)
GPB	10 (3.3)
Cutibacterium sp.	8 (2.6)
Clostridium sp.	2 (0.6)
Fungi	6 (2.0)
Negative culture	22 (7.3)
Polymicrobial	41 (13.6)
High virulence	144 (47.7)



Escudero-Sanchez R *et al*. Clin Microbiol Infect 2020;26:499



Risk factors for failure :

- Age < 70 y.
- Other than GPC
- Upper limb

- RI-FQ : no detectable effect

R. Escudero-Sanchez *et al*. Clin Microbiol Infect 2020;26:499

Conclusion

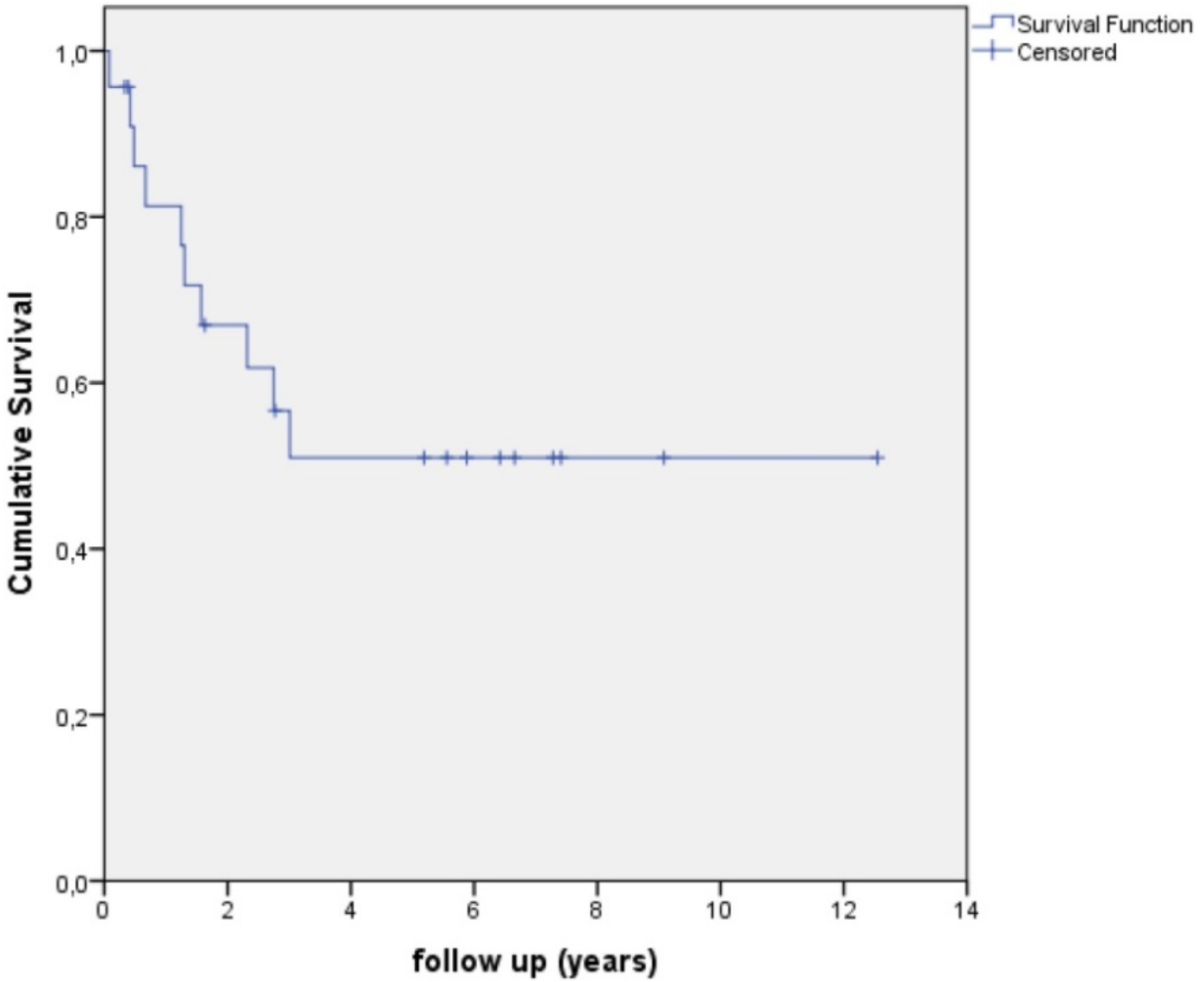
- when prescribed by experts who can anticipate the toxicities and interactions that may occur during antibiotic treatment, SAT offers acceptable results in terms of its efficacy and safety for patients for whom surgical treatment is insufficient or is contraindicated due to disproportionate risks including death and/or amputation

Escudero-Sanchez R *et al*. Clin Microbiol Infect 2020;26:499

Clinical Outcome of Antibiotic Suppressive Therapy in Patients with a Prosthetic Joint Infection after Hip Replacement

- Retrospective monocentric cohort study
- All patients with a PJI in which treatment with AST was started between Jan. 1st, 2006 and Dec. 31st 2013 were included.
- We separately analyzed patients receiving at least 6 months of AST showing a success rate of 63.2% (12 out of 19 patients).

Leijtens B *et al*. JBJI 2019; 4(6): 268-276



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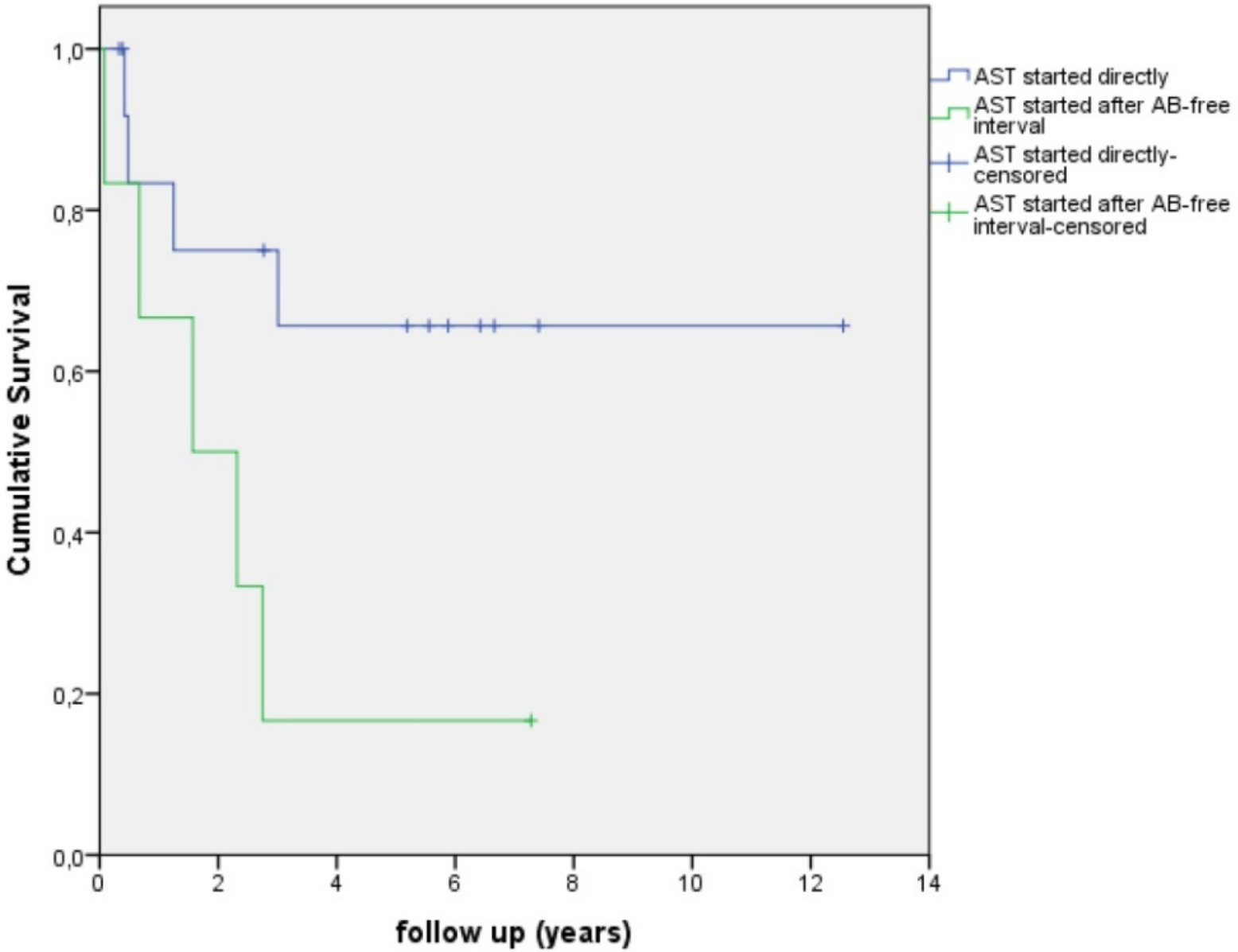


Leijtens B *et al*. JBJI 2019; 4(6): 268-276

Conclusions

- When considering the start of AST, one should be aware of a possible decreased success rate among patients
  - who had an antibiotic-free period before the start of AST
  - patients with high inflammatory parameters
  - *S. aureus* infections

Leijtens B *et al*. JBJI 2019; 4(6): 268-276

The efficacy of suppressive antibiotic treatment in patients managed non-operatively for periprosthetic joint infection and a draining sinus

- Multicentre retrospective observational cohort study.
- PJI patients with a sinus tract were eligible for inclusion when the sinus tract was diagnosed between Jan. 2008 and Jan. 2018 and when they were considered ineligible for a potential curative surgical strategy or the patients themselves refused surgery.
- Patients were excluded if the duration of follow-up was less than 2 years.

Lensen KJ *et al.* JBJI 2021 ; 6: 313-319

- The primary end point of this study was retention of the implant during follow-up.

- Secondary end points consisted of the prevention of prosthetic loosening in initially fixed implants, the need for surgical debridement during follow-up, closing of the sinus tract, resolution of pain, the development of bacteremia, the resolution of inflammation and anaemia, and side effects when treated with SAT.

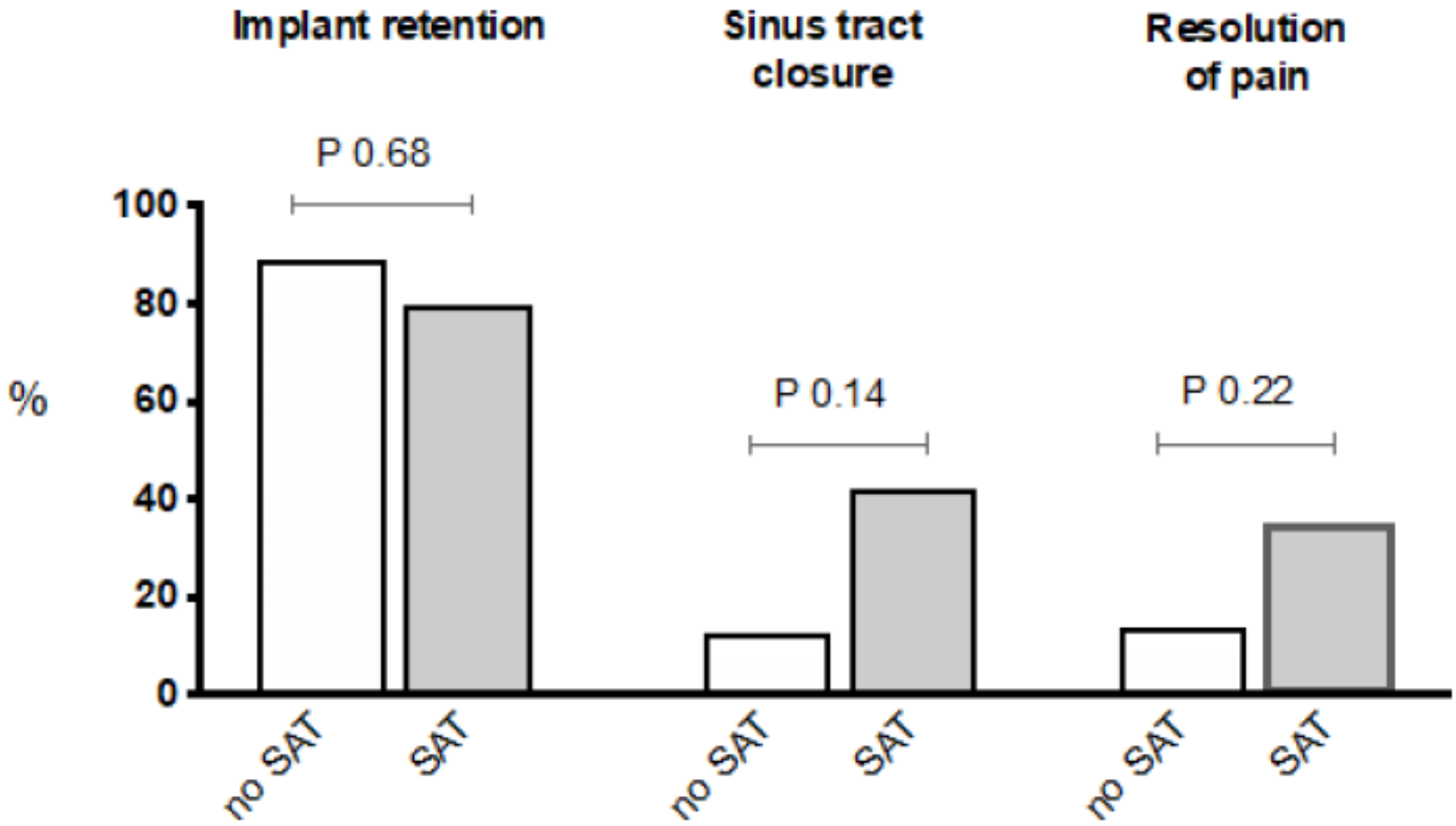
- For this study, SAT was defined as a period of >6 months of oral antibiotic therapy.

Lensen KJ *et al.* JBJI 2021 ; 6: 313-319

Results

- 72 patients (mean age 74 y.)
- SAT in 63 (87.5%)
- Mean time between onset of fistula and start of the fistula: 2 months (IQR 0-8)
- Diabetes in 21% of the patients
- Most of the studied variables did not significantly differ between both groups, but SAT was prescribed more often for those patients with a CRP above 50 mg/L (46% vs. 0 %; p = 0.02).

Lensen KJ *et al.* JBJI 2021 ; 6: 313-319



Lensen KJ *et al.* JBJI 2021 ; 6: 313-319

Conclusions

- Traitement suppressif : pas nouveau mais tendance
- Ça marche!
- Surtout lorsque le traitement est pris
- « à vie »!! (… des implants infectés)
- Doxy (mino) cycline
- Manque cruellement de données solides (indications, objectifs, efficacité au long cours, tolérance, microbiote)

Author	Year and Journal of publication	Number of patients	Mean follow-up (years)	Success rate (%)
Goulet et al [6]	1988, J. Arthroplasty	19	4.1	63.0
Tsukayama et al [7]	1991, J. Orthopedics	13	3.1	23.0
Segreti et al [8]	1998, Clin Inf Disease	18	4.1	83.0
Rao et al [9]	2003, CORR	36	4.4	86.2
Prendki et al [10]	2014, Int J Inf Disease	38	2.0	60.0
Siqueira et al [11]	2015, J Bone Joint Surg Am.	92	5.8	68.5
Wouthuyzen-Bakker et al [12]	2017, J Bone Joint Infect	21	1.8	67.0
Pradier et al [13]	2018, Infection	78	2.8	71.8

Leijtens B *et al*. JBJI 2019; 4(6): 268-276

Conclusions

- Le traitement suppressif reste une aberration
- Attention à la possible déviance « chirurgicale » (pas de chirurgie ou minimaliste et « les infectiologues mettront du suppressif »…)
- **Décision collégiale (RCP) ++++ encore et toujours**

Questions?