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Étude rétrospective multicentrique sur les infections de prothèses articulaires monomicrobiennes à *Cutibacterium acnes*: différences cliniques entre membres supérieurs et membres inférieurs et impact du choix de l'antibiothérapie sur la guérison

Antoine Eyraud

► To cite this version:

Antoine Eyraud. Étude rétrospective multicentrique sur les infections de prothèses articulaires monomicrobiennes à *Cutibacterium acnes*: différences cliniques entre membres supérieurs et membres inférieurs et impact du choix de l'antibiothérapie sur la guérison. Médecine humaine et pathologie. 2023. dumas-04286419

HAL Id: dumas-04286419

<https://dumas.ccsd.cnrs.fr/dumas-04286419v1>

Submitted on 15 Nov 2023

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UNIVERSITE DE MONTPELLIER
FACULTE DE MEDECINE MONTPELLIER-NIMES

THESE

Pour obtenir le titre de
DOCTEUR EN MEDECINE

Présentée et soutenue publiquement

Par

Antoine EYRAUD

le 27/09/2023

TITRE

Étude rétrospective multicentrique sur les infections de prothèses articulaires monomicrobiennes à *Cutibacterium acnes* : différences cliniques entre membres supérieurs et membres inférieurs et impact du choix de l'antibiothérapie sur la guérison.

Directeur de thèse : Pr LE MOING Vincent

JURY

Président : Pr LE MOING Vincent

Assesseurs :

1er assesseur : Pr LAVIGNE Jean-Philippe

2ème assesseur : Pr MAKINSON Alain

Membre invité :

4ème membre de jury : Dr HAMOUI Mazen

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Remerciements :

Aux membres de mon jury :

À Monsieur le Professeur Vincent LE MOING : je vous remercie de m'avoir proposé ce sujet de travail de thèse, mais aussi de me faire l'honneur de présider cette thèse. Vous avez sagement su équilibrer l'accompagnement de ce travail au cours du temps et je vous en remercie. Je vous remercie également d'avoir été mon tuteur au cours de cet internat et d'avoir su me guider parfaitement au cours de cet internat.

À Monsieur le Professeur Jean Philippe LAVIGNE : je suis très heureux de vous avoir aujourd'hui comme membre de mon jury. Je vous remercie pour m'avoir accueilli dans votre service qui a été en plus d'avoir été très formateur et été un moment très agréable de mon internat.

À Monsieur le Professeur Alain MAKINSON : je vous remercie d'avoir accepté de faire partie de mon jury, je suis très heureux d'avoir pu apprendre avec vous lors de mon internat notamment pendant mon 2^e semestre.

À Monsieur le Docteur Mazen HAMOUI : je vous remercie d'avoir accepté de participer à ce travail ; votre expertise de chirurgien orthopédiste me semble indispensable dans ce travail.

À ceux qui ont participé à l'élaboration de ce travail :

Au docteur Yann DUMONT, qui a réalisé l'extraction des données bactériologiques, et donc sans qui ce travail n'aurait pas pu avoir lieu.

Au docteur Lionel MOULIS, qui a apporté un soutien méthodologique tout au long de cette thèse.

A tous les médecins, chirurgiens, Infirmiers et paramédicaux mais aussi patients qui ont permis la réalisation de ce travail.

Famille :

Mes parents, grâce à vous deux, j'ai eu une enfance parfaite et débordante d'amour. J'ai eu l'éducation rêvée, la plus parfaite à mes yeux, des valeurs, de l'empathie, de la curiosité, de la créativité, de l'esprit critique et j'en passe ! Toutes ces choses-là, c'est vous, par vos actes, par votre amour que je sais sans limite, que je les ai acquises. Tous les deux, vous vous êtes battus, donnés, et même sacrifiés pour que j'en arrive là. Vous avez toujours, été attentif, et malgré quelques difficultés, vous avez toujours trouvé un moyen de me soutenir. Il y en eut des trajets en voiture pour moi, l'orthophoniste, la psychomotricienne ect... Mais aussi la quasi-centaine d'aller-retour entre Annecy et Grenoble pendant 2 ans pour me soutenir pendant LES PACES ; je vous en aurais fait baver quand même ! Il y a eu aussi des choses plus simples ces années-là, comme notre petite routine au restaurant chinois, les petits tupperwares chaque semaine... Et ce sont tous ces « petits » détails qui ont compté. Si j'en suis là aujourd'hui, c'est grâce à vous.

Papa : on pourrait dire que ce n'est pas lié au hasard que je suis devenue docteur en médecine, un arrière-grand-père pharmacien sur l'avenue de la République à Lyon, une arrière-grand-mère infirmière pendant la guerre, un père médecin. On aurait cela dans le sang ! Je n'en suis pas si sûr... Je pense surtout avoir attrapé la maladie médicale par toi. Si aujourd'hui, je suis si épanoui dans ma voie, c'est grâce à toi. Je t'aime papa.

Maman : tu m'as couvert d'amour, une véritable mère poule : « Cot, cot » ! Je t'aime profondément, tu m'as toujours encouragé et soutenu dans ma voie, et sans toi, je n'y serais jamais arrivé.

Mes 4 grands-parents, qui hélas n'auront jamais vu leur petit-fils devenir docteur, j'ai une pensée pour chacun d'entre vous.

Les frères et sœurs (on le fait à l'ancienneté pas de favoritisme.) :

Julien : c'est toi qui m'as donné tout petit le surnom de « too-toon », car je rigolais comme un personnage de dessin animé (et parlais déjà BEAUCOUP trop fort). Je te rassure rien a changé, il faudra juste m'appeler « Dr Tootoon » maintenant. Pense à rentrer plus souvent de la Réunion.

Sophie : même si le temps et les événements, nous aurons éloigné, je pense fort à toi.

Tristan : merci d'avoir fait le déplacement pour cet événement, cela me touche énormément. Je n'arrive même pas à me souvenir combien de fois, je t'ai embêté, mais promis, je vais rester tranquille.

Quentin : c'est bien parce que tu vis à l'autre bout de la planète que tu es excusé pour ne pas être présent, PS si tu deviens milliardaire, je ne rechignerai pas à recevoir quelques millions.

Siyuan, je suis très heureux de te compter parmi les présents, et oui, tu es ma sœur maintenant !

À ma Pauline : que dire... Tu es rentrée dans ma vie comme une balle en plein cœur, et tu es resté logé là. Notre comportement d'inséparable a fini par nous faire percevoir comme une seul et même personne par nos amis. Pourtant, au départ, comme tu l'as dit toi-même, tu avais le choix entre la peste et le choléra ! En est-il qu'en moins de 1 mois d'internat, tu as choisi la pestouille... Tu le sais, ma vie mes choix, et mon avenir tourne autour de toi. Sans toi, ces années d'internats auraient été totalement différentes. Tu es la chose la plus importante pour moi et tu guides ma vie, ou plutôt notre vie. Je t'aime.

À ma belle-famille, Laurence et Rodrigue, merci pour ces kilos d'aïolis.

Mes Co-internes de DES :

À mes super co-internes de promo ; Tristan et Fanny, j'ai été plus que ravi de vous avoir rencontré, on a été un super trio ; d'un complémentaire assez dingue. J'ai adoré tous les moments passés avec vous pendant cet internat. Merci Tristan d'avoir supporté la charge de référent, et désolé de ne pas t'avoir pas beaucoup aidé. Merci Fanny de m'avoir supporté pendant 2 semestres, tu détiens le record bravo !

Merci aussi à Jordan qui a n'en pouvais plus de m'entendre crier dans le service, Charlotte qui a été notre modèle de travail à tous, Boris et son légendaire accent franc comtois, Taïma et les staff interminable de réa, Agathe la super-DJ, Sophie et ses galères de thèses, Alice qui ferra toujours parti de la bande, Kieffer et ses platines enflammées, Mais aussi Joshua et Bruce, et les plus jeunes que je ne connais pas encore assez.

À mes amis :

Aux expatriés grenoblois : Yannis Y, avec toi, j'aurai fait les 400 coups depuis l'externat, promis, si tu as des ISO, je te répondrais, mais arrête de cracher dans les patients et lave toi les mains. À Lucas M et Marie S, merci pour ces soirées chez vous à boire beaucoup trop et jouer aux jeux de sociétés. Bob, j'attends comme prévu que tu deviennes directeur de l'ARS pour détourner l'argent public. JS et Solène, les Perpignanais malgré eux, j'arrive quand vous repartez, j'aurais vraiment rien compris. Et enfin, Lucas C avec qui on aura tout fait pour quasiment ne pas se voir.

À la coloc du love, ou des millions de rire ont raisonnés : à Paola ; que j'ai mis première pour poursuivre la blague de l'échelle. À Léna et sa fameuse playlist de musique sur lesquels on aura tous dansé/twerké des heures. À Sara, la tornade, qui était la seule capable de remettre tout en état. À Soufiane, devenu Dom juan depuis, mais qui met toujours des plombes à mettre ces chaussettes. À Camille, que j'ai mis dernière encore une fois pour la blague de l'échelle, parce que finalement, c'est surtout toi qui rappelles toujours cette histoire, alors voilà bien fait. Je remercie aussi les Coloc qui m'ont remplacé, mais jamais égalé (faut bien dire les choses) : Benoit et Loïc qui aura eu le mérite de guider Soufiane vers la luxure, je vous remercie tous pour ces bons moments, mais aussi pour les prochains.

À la quasi-coloc : Bénédicte, notre future PU-PH de pneumo, je te remercie de m'apprendre tous les jours de nouvelles expressions.

Aux Catalans : Arthur et Marie, mais aussi au petit Joseph, merci pour tous ces repas chez vous en terre catalanes et pour tous les prochains.

Aux amis « rapportés » : avec qui on aura fait finalement beaucoup de choses, et que je ne considère pas du tout de cette façon et donc merci à Marine A, Marine B Rodolphe, Laura, Paul-Henri, Octavie, Marine L, Clément, Aude et Joris.

À tous mes co-internes : qui ont dû me supporter au quotidien, merci.

Enfin, je ne remercie pas le SARS-COV-2, pour avoir pourri mon internat et nos vies sociales.

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Titre

Multicentric and retrospective study of monomicrobial *Cutibacterium acnes* prosthetic joint infections: clinical differences between upper and lower limbs and impact of choice of antibiotic therapy on successful healing.

Abstract

Background : *Cutibacterium acnes* prosthetic joint infection affects mainly, but not exclusively, the shoulder. There is limited or no data in the literature comparing clinical setting and failure rates between shoulder implants (SI) and lower limb implants (LLI).

Method : Comparative, multicentric, and retrospective study including monomicrobial *Cutibacterium acnes* prosthetic joint infections of the shoulder, knee, and hip occurring between 2012 and 2022 at the Montpellier and Nîmes University Hospitals. We compared clinical data and failure rates between SI infection and ILM. We also conducted an analysis of predictive factors for failure.

Results : We included 56 patients. Pain was significantly more frequent and presentation more frequently acute in LLI. The most frequently antibiotic prescribed was clindamycin (> 7 days in 87.5% of patients). Amoxicillin was used in 16.5% of patients. Rifampicin was associated in 28.6%. Failure rate was high, particularly for LLI (10/27, 37.0%) compared with 5/24 (20.8%) for SI (P-value=0.235). The reason for failure appeared to be different according to infected joint, with significantly more relapses with the same germ in SI (16.7% vs 0.0% P=0.043), and more new infections for LLI (29.6% vs 4.2% P=0.026). The only factor significantly associated with failure was acute infection. There was insufficient data to conclude on antibiotic therapy, but failures tended to be less frequent in patients who received amoxicillin (12.5%).

Conclusion : The high frequency of new infections in failures in LLI infections suggests that the isolation of only *C. acnes* in LLI infection should be considered with caution. Our data are insufficient to suggest ways of optimising antibiotic strategy to improve the poor outcome of *C. acnes* PJI.

Introduction

Shoulder prosthesis implantation has increased significantly since the advent of reverse prosthesis. Reverse prostheses provide better functional recovery with improved range of motion [1]. However, they seem to present a higher risk of complications, particularly infectious, with a 5% rate of prosthetic joint infection (PJI) [2]. Shoulder PJI have a particular bacteriological feature compared to other PJIs. They are more frequently chronic PJI due to *Cutibacterium acnes* (*C. acnes*) [3].

C. acnes, previously named *Propionibacterium acnes*, is a bacilliform, anaerobic, Gram-positive bacteria commensal of the skin. This bacterium is more commonly found in seborrheic areas, and in particular in the axilla [4]. Antibiotic prophylaxis and skin decontamination are not very effective in preventing the occurrence of infection with this microorganism [5]. *C. acnes* produce biofilm [6], which contributes to the difficulty to treat osteoarticular infections with this germ.

There are few data on the efficacy of the antibiotic regimen in *C. acnes* osteoarticular infections. In the 2010 recommendations of the “Société de Pathologie Infectieuse de Langue Française” (SPILF) on osteoarticular prosthesis infections [7], the recommended antibiotic regimens are single therapy using amoxicillin, cefazolin, ceftriaxone, or clindamycin. In a 2015 review article focusing on anaerobic germ prosthesis infections [8], only intravenous treatments were proposed for a duration of 4 to 6 weeks, with either penicillin G or ceftriaxone proposed as the reference. The alternatives were clindamycin or vancomycin. In current practice in France, it is generally preferred to treat with oral therapy, and often for a longer duration compared to infections due to other bacteria. The optimal oral antibiotic strategy is however unknown. Observational studies suggest that the use of levofloxacin [9], or clarithromycin may increase the risk of failure [10]. But in the other end, another study focusing on clindamycin use do not suggest this trend [11]. Rifampicin was shown useful in an animal model to reduce the biofilm created by *C. acnes*, with a higher frequency of cured animals treated with a combined therapy including rifampicin [12]. Rifampicin based treatment did not show benefit in small retrospective observational studies [10-13]. However, a European multicentric study with more than 187 patients showed a non-significant positive trend in favour of rifampicin [14]. Therefore, with no strong data available, antibiotic therapy is not standardized, and differs from one centre to another.

C. acnes is often considered as a contaminant in lower limb surgery, but it can be responsible for true PJI in hip joint implant [15] and in knee joint implant [16]. Only a few studies compared the difference of clinical presentation and outcome between shoulder and lower limb *C. acnes* PJI. A recent study [17] tried to compare those different joints infection, but focused on radiologic and surgical management. Most studies that try to compare retrospectively the impact of antibiotic regimens in *C. acnes* PJI include only shoulder PJI [7;11;10;13], The studies [14-18] that included those 3 joints did not take in consideration the possible difference of clinical presentation and outcome according to the infected joint. Of note, the choice of antibiotic regimen may be different between those 3 joints, and thus bias the results.

The first aim of this study is to compare retrospectively clinical setting, antibiotic regimen and outcome of *C. acnes* PJI according to the location of infection, shoulder vs hip and knee.

Materials and Methods

Study population.

This retrospective multicentric study was carried in 2 centres (Montpellier University Hospital and Nîmes University Hospital) and included adult patients who contracted a monomicrobial *C. acnes* shoulder, hip or knee PJI between 2012 and 2022. At least 2 surgical samples positive for *C. acnes* were required, as well as the absence of isolation of other microorganisms. Samples were incubated for at least 14 days in both centres. We included patients who had undergone all type of surgery (1 or 2 stage replacement of the prosthesis, debridement and retention of prosthesis (DAIR) or explantation without reimplantation of prosthesis). To define the type of prosthesis infection we used a modified Tsukayama classification [19] : the PJI was considered acute when symptom occurred for less than 30 days, chronic if symptom occurred for more than 30 days; the PJI was considered as early if symptoms appeared within a year after implantation, late if symptoms appeared more than 1 year after implantation

Endpoints

The objective of this study was to compare clinical setting, antibiotic regimen and outcome between shoulder and lower limb (hips and knee) PJI.

For the outcome analysis, a failure was defined as the necessity of repeat surgery or new antibiotic treatment regardless of the infectious agent after the initial treatment. A relapse was defined as the necessity of repeat surgery or new antibiotic treatment with 2 new surgical samples positive for *C. acnes*. A new infection was defined as the necessity of repeat surgery or new antibiotic treatment with surgical samples positive for other germs than *C. acnes*. We also studied the impact of the choice of antibiotic regimen on the risk of failure, including rifampicin, amoxicillin and clindamycin and antibiotics of the fluoroquinolone class that have been grouped together for this study. Antibiotic regimens were considered in the analysis only if they were prescribed for 7 days or more.

As a secondary analysis, we also planned to perform survival analyses according to the joint, the type of infection, some clinical setting and the antibiotic regimen, with a analyse of the failure rate at 2 years. Exclusion criteria for the analyse of failure consisted in a follow-up of less than 6 months and antibiotic therapy longer than 6 months.

An evaluation of adverse events related to antibiotic regimen was also carried out, adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Collected data

Eligible patients were identified by cross-referencing the bacteriology file (all osteoarticular samples isolating *C. acnes*) with clinical data from the infectious disease records.

We collected from the patient records general socio-demographic data such as age, sex, weight, BMI. We also collected medical data such as renal function, smoking status, presence of diabetes. We noted all the dates of the different surgeries related to the implantation and the revision(s) of the prosthesis.

Regarding the antibiotic therapy, we have gathered the name of the molecule(s) used, as well as the dosage, the administration methods, the start and end date of the probabilistic and adapted antibiotic therapy for each patient.

This study was approved by the local Institutional Review Board of the university hospital of Montpellier ; Agreement number : 202201150

Statistical analysis

Patients were compared for their clinical, sociodemographic and therapeutic characteristics according to the joint using a Chi-2 or Fischer's exact test for qualitative variables, a Student's t-test if the conditions of application allow it, or Mann Witney test for quantitative variables.

We used the Kaplan-Meier method to estimate survival probabilities and their pointwise 95% confidence intervals. The log-rank non-parametric test for comparison of survival distributions was used to compare survival differences between groups. The alpha risk was set to 5.0%. Statistical analysis was performed with EasyMedStat (version 3.27; www.easymedstat.com).

Results

Study population

We included 56 patients from 2 hospitals (29 from Montpellier 27 from Nimes). 69.6% of the patients were male with a median age of 67 years. In 48.2% of cases PJI affected a shoulder implant (SI), in 33.9% a hip prosthesis and in 17.9% a knee prosthesis. Main characteristics of the patients are described in Table 1.

Table 1. Patient demographics and baseline characteristics of the 56 patients and in function of the joint, Shoulder vs lower limb

		All patients	Shoulder	Hip (19) and Knee (10)	P-Value
Total		56	27	29	
General patient information					
Hospital of recruitment	Montpellier	29 (51.8%)	19 (70.4%)	8 (29.6%)	0.016
	Nimes	27 (48.2%)	10 (34.5%)	19 (65.5%)	
Sex	Male	39 (69.6%)	22 (81.5%)	17 (58.6%)	0.084
	Female	17 (30.4%)	5 (18.5%)	12 (41.4%)	
Age	(median, IQR)	67 (57 - 74)	71 (64 - 73)	63 (53 - 74)	0.096
Body mass index,	kg/m ² , (Median, IQR)	26.1 (23.9 - 28.3)	26.1 (23.4 - 28.6)	26.09 (24.1 - 28.2)	0.941
Diabetes mellitus	n, %	9 (16.1%)	7 (25.9%)	2 (6.9%)	0.073
smoking status	Active smokers	8/53 (15.1%)	2/26 (7.7%)	6/27 (22.2%)	0.081
	Former quitters	12/53 (22.6%)	9/26 (34.6%)	3/27 (11.1%)	
Renal insufficiency	(CrCl <60 mL/min) n, %	7 (12.5%)	2 (7.4%)	5 (17.2%)	0.424
Previous surgery*	n, %	37 (66.1%)	19 (70.4%)	18 (62.1%)	0.58
	Including prosthesis ^a n, %	22 (39.3%)	7 (25.9%)	15 (51.7%)	0.089
History of cured infection	n, %	8 (14.3%)	4 (14.8%)	4 (13.8%)	0.999
Planned surgery	n, %	50 (89.3%)	24 (88.9%)	26 (89.7%)	>0.999

Abreviation : IQR, interquartile ratio ; CrCl, Creatinine clearance.

*All history of surgery on the joint that occur before the surgery that lead to the infection of this joint.

^aOnly history of placement or replacement of prosthesis on the joint that occur before the surgery that lead to the infection of this joint.

The clinical presentation of the infection and surgical management are described in Table 2. The infection was classified as acute (< 30 days of symptoms) in 8 patients (14.3%), and chronic (> 30 days of symptoms) in 48 patients (85.7%). Infection occurred within one year of implantation (early) in 39 patients (69.6%), and after 1 year (late) in 17 patients (30.4%). Infection was diagnosed before revision surgery in 34 patients (60.7%), during revision surgery in 6 (10.7%), and after revision surgery in 16 (28.6%). Median time between onset of symptoms and diagnosis of infection was 209 days. The revision surgery consisted of a 2-stage prosthesis change for 18 patients (32.1%), a 1-stage prosthesis change for 30 patients (53.6%), a DAIR for 8 patients (14.9%) and a removal without insertion of material for 1 patient (1.8%).

Table 2 : clinical presentation an surgical setting of the 56 patients and in function of the joint, Shoulder vs lower limb

Total		All patients 56	Shoulder 27	Hip (19) and Knee (10) 29	P-Value
Clinical presentation					
Pain		49 (87.5%)	21 (77.8%)	28 (96.6%)	0.048
	Including isolated pain ^a	16 (28.6%)	7 (25.9%)	9 (31%)	0.771
Other symptoms	Fistula	16 (28.6%)	8 (29.6%)	8 (27.6%)	>0.999
	Inflammatory signs ^b	15 (26.8%)	6 (22.2%)	9 (31.0%)	0.552
	Haematoma	5 (8.9%)	1 (3.7%)	4 (13.8%)	0.353
	Luxation	8 (14.3%)	4 (14.8%)	4 (13.8%)	>0.999
duration of the infection ^c	Acute	8 (14.3%)	1 (3.7%)	7 (24.1%)	0.052
	Chronic	48 (85.7%)	26 (96.3%)	22 (75.9%)	
time to onset ^d	Early	39 (69.6%)	16 (59.3%)	23 (79.3%)	
	Late	17 (30.4%)	11 (40.7%)	6 (20.7%)	0.147
CRP >15mg/L or positive ^e	n, %	27 (69.2%) N=39	12 (70.6%) N=17	15 (68.2%) N=22	>0.999
CRP >50mg/L	n, %	10 (28.6%) N=35	3 (23.1%) N=13	7 (31.8%) N=22	0.708
Surgery setting					
Time of diagnosis	Before surgery (n, %)	34 (60.7%)	18 (66.7%)	16 (55.2%)	0.544
	During surgery (n, %)	6 (10.7%)	4 (14.8%)	2 (6.9%)	0.414
	After surgery (n, %)	16 (28.6%)	5 (18.5%)	11 (37.9%)	0.143
Time to make the diagnosis ^f	In day (median, IQR)	209 (32.5 ; 520.75)	144 (26 ; 405.5)	251 (34 ; 749)	0.309
Surgical strategy	n, %	48 (85.7%)	23 (85.2%)	25 (86.2%)	>0.999
	1-stage exchange	30 (53.6%)	14 (51.9%)	15 (51.7%)	0.964
	2-stage exchange	18 (32.1%)	8 (29.6%)	10 (34.5%)	
	Explantation only	1 (1.8%)	1 (3.7%)	0 (0.0%)	
	DAIR	8 (14.9%)	4 (14.8%)	4 (13.8%)	

Abreviation : IQR, interquartile ratio ; CRP, C reactive protein ; DAIR, Debridement, antibiotics and implant retention.

^apatient for who the pain was the only symptom.

^bInflammatory symptom include: swelling, redness and warmth.

^cAcute when symptom occure for less than 30 days, chronic if symptom occure for more than 30 days.

^dEarly if symptom appear within a year after the surgery, late if symptom appear more than 1 year after the surgery.

^eInclude patient for who the CRP value was >15mg/L or for who it was write in the consultation file that the CRP was positive without the value known.

^fNumber of days between the infecting surgery and the diagnosis of infection

In terms of laboratory data, a preoperative joint puncture was performed in 26 patients (46.4%), and was positive for *C. acnes* in only 12 patients (46.2%). It should be noted that 2 of the joint punctures were positive for other germs (7.7%) (2 coagulase-negative staphylococci). During revision surgery, the median number of surgical samples was 6, and the median number of positive samples was 4, for an average positivity rate of 69%. The median growth time was 6.5 days, ranging from 3 to 17 days. Penicillin susceptibility was tested 44 times and was found to be sensitive in all cases (100%). Penicillin susceptibility testing has been performed on penicillin G for one centre since 2018, and on amoxicillin since 2012 for the other centre. 1 out of 55 strains was found to be resistant to clindamycin, and 1 out of 54 to rifampicin. For fluoroquinolone susceptibility, 38 of the 44 strains tested were found to be sensitive, and 6 strains were found to be sensitive at high doses ; it should be pointed out that the breakpoint values and the antibiotic tested on the antibiogram for the fluoroquinolones varied greatly over the study period for the study in the 2 centres.

Data on antibiotic treatment are displayed on Table 3. The median duration of antibiotic treatment was 89.5 days (12-13 weeks). It did not differ significantly according to the type of surgery, with a median duration of 86.5 days for DAIR, 89.5 days for 1-stage prosthesis changes, and 83 days for 2-stage changes (p-value= 0.399). The median duration of IV treatment was 10 days, and of oral treatment 76 days (10-11 weeks). 80.4% of patients received a postoperative IV treatment. Regarding oral treatment, 19 patients (33.9%) were treated with a dual antibiotic therapy. 87.5% of patients were treated for at least 7 days with clindamycin, 28.6% with rifampicin, 16.1% with amoxicillin, and 12.5% with a fluoroquinolone (levofloxacin or ofloxacin). More data about rifampicin dual therapy is available in supplementary table 3. The median follow-up time was 442.5 days, and after

excluding 5 patients who had follow-up times of less than 6 months, the median was 468 days.

Table 3 : Antibiotic data of the 56 patients and in function of the joint, Shoulder vs lower limb

Total		All patients 56	Shoulder 27	Hip (19) and Knee (10) 29	P-Value
Antibiotic data :					
Number of IV treatment ^a	n, %	45 (80.4%)	22 (81.5%)	23 (79.3%)	>0.999
IV antibiotics duration	In day (median, IQR)	10 (7 ;15) (N=46)	10 (7 ; 14.5) (N=23)	10 (7.5 ; 15) (N=23)	0.658
PO antibiotics duration	In day (median, IQR)	76 (55.75 ; 90.25)	75 (53.5 ; 90)	77 (61 ; 91)	0.838
Total antibiotics duration	In day (median, IQR)	89.5 (69 ; 99.25)	87 (68 ; 98)	90 (71 ; 100)	0.768
Clindamycin >7 days	n, %	49 (87.5%)	22 (81.5%)	27 (93.1%)	0.244
Rifampicin >7 days	n, %	16 (28.6%)	10 (37.0%)	6 (20.7%)	0.24
Amoxicilin >7 days	n, %	9 (16.1%)	5 (18.5%)	4 (13.8%)	0.725
Fluorouinolone >7 days ^b	n, %	7 (12.5%)	5 (18.5%)	2 (6.9%)	0.244
Dual therapy >7days	n, %	19 (33.9%)	12 (44.4%)	7 (24.1%)	0.159
Follow up time	In day (median, IQR)	442.5 (314.5 ; 925)	369 (233 ; 917)	462 (349 ; 916)	0.512
Follow up time (>6 month) ^c	In day (median, IQR)	468 (346.5 ; 967.0)	458 (333.75 ; 983.75)	468 (357.5 ; 934)	0.699
	N ^d	N=51	N=24	N=27	

Abreviation : IQR, interquartile ratio ; IV, intravenous ; PO, oral

^aNumbers of patients that receive a intravenous antibiotic treatment just after the surgery, other patients receive no treatment (most of the time its due to a diagnosis after the surgery)

^bFluoroquinolone treatment include ofloxacin and levofloxacin

^cpatient with a folow up period for less than 6 month were excluded

^dnumber of patient on witch the analyse was done (5 patients excluded for a folow up of less than 6 month)

Failure analysis

The failure rate was calculated after excluding the 5 patients with less than 6 months follow-up (i.e. in 51 patients). In each case, this lack of follow-up was related to transfer to a different hospital. Overall, there were 15 failures (29.4%). Failure occurred under antibiotic treatment in 5 of the 15 patients (33.3%) and after completion of antibiotic treatment in 10 patients (66.7%). The median time to failure was 153 days (IQR =78; 379.5). Of the 51 patients, 29 (59.2%) had persistent pain at the end of follow-up, including 14 of the 15 failures (93.4%).

Of the failures, 13 (86.6%) were re-operated and had a bacteriology sample. Finally, of the 15 failures, only 4 (26.6%) were relapses (due to *C. acnes*), and 9 (60%) were new infections (due to another germ). In two patients, microbiological samples were negative, but infection was attested by the presence of a fistula. Relapses were all monomicrobial and among new infections, *C. acnes* was never associated with the isolated germs. 8 were monomicrobial and 1 was plurimicrobial (with 3 digestive germs). Bacteriological documentation of failures are available in Supplementary tables 1 and 2.

Table 4 : Failure data of of the 51 patients whith a folow up >6 month and in function of the joint, Shoulder vs lower limb

Total		All patients 51	Shoulder 24	Hip (17) and Knee (10) 27	P-Value
Failure data :					
Overall failure	n, %	15(29.4%)	5 (20.8%)	10 (37.0%)	0.235
Failure during AB treatment	n/N, %	5/15 (33.3%)	0/5(0.0%)	5/10(50.0%)	0.101
Failure after AB treatment stop	n/N, %	10/15 (66.7%)	5/5(100.0%)	5/10(50.0%)	0.101
Relapse	n, %	4 (7.8%)	4 (16.7%)	0 (0.0%)	0.043
New infection	n, %	9 (17.7%)	1 (4.2%)	8 (29.6%)	0.026
Failure without microbiology	n, %	2 (3.9%)	0 (0.0%)	2 (7.4%)	0.492
Time to failure ^a	In day (median, IQR)	153 (78 ; 379.5)N=15	453 (235 ; 518)N=5	114 (49.75 ; 174)N=10	0.075
Pain at the end of folow up	n, %	29 (59.2%)	13 (54.2%)	16 (64.0%)	0.682

Abreviation : IQR, interquartile ratio ; AB, antibiotic.

^aNumber of days between the revision surgery and the diagnosis of failure.

Comparison between upper and lower limb prostheses: (shoulder implant vs. hip implant + knee implant)

Of the 51 patients, 27 had an infection on a shoulder implant (SI), and 29 on a lower limb implant (LLI).

Shoulder infections were more frequent in patients recruited in Montpellier due to the expertise of a surgical team in this hospital. There were no difference in clinical characteristics except for a higher proportion of men in SI infections.

Pain was significantly more frequent in LLI infections. Classification and surgical management of infection were not different according to the affected joints except for a trend to a higher frequency of late PJI when SI was affected. There was no significant difference in bacteriological data. There were non-significant trends for some antibiotic regimens, with more rifampicin in the SI group (37.0% vs. 20.7%), more fluoroquinolones in the SI group (18.5% vs. 6.9%), and more dual therapy in the SI group (44.4% vs. 24.1%).

Globally, failure were less frequent for infections on SI with 5/24 (20.8%) failures versus 10/27 (37.0%) for infections on LLI but this difference was not statistically different (P-value=0.235). Relapses were significantly more frequent in shoulder infections while, reciprocally, new infections were significantly more frequent in lower limb infections.

Factors associated with failure

In bivariable analyses of factors associated with the risk of failure (Table 5 and Figure 1), only acute infections were significantly associated with more failures, with 5/8 (62.5%) versus 10/43 (23.3%) of chronic infections (P-value=0.039). However, some trends should be noticed, especially in terms of clinical characteristics, with less failures when the only symptom presented was pain (13.3% vs. 36.1%), more failures when the prosthesis was inflammatory (50% vs. 21.6%), when a fistula was present (43.8% vs. 22.9%), or when the CRP was >50mg/L (60% vs. 28.5%), but without significance.

There was no difference for infections diagnosed retrospectively. There was a trend for DAIR to be more frequently associated with failure (50% vs. 25.6%). Concerning antibiotic therapy, dual therapy was not significantly associated with the risk of failure, despite a lower number of failures with 17.6% vs. 35.3% (P-Value=0.328). There was no significant difference according to the different antibiotic regimens, with no difference for clindamycin 14/45 (31.1%), rifampicin 3/15 (20%), amoxicillin 1/8 (12.5%) and fluoroquinolones: 1/6. (16.7%).

Table 5 : Factors influencing treatment failure

	Failure rate if true ^a	Failure rate if wrong ^b	ODD-ratio	CI	P-Value
A) General patient information					
Female gender	6/17 (35.3%)	9/34 (26.5%)	1.52	[0.43 ; 5.3]	0.532
Age >65 years	10/28 (35.7%)	5/23 (21.7%)	2	[0.57 ; 7.03]	0.36
Age >75 years	5/12 (41.7%)	10/39 (25.6%)	2.07	[0.53 ; 8.02]	0.302
Renal insufficiency (CrCl <60 mL/min)	3/6 (50.0%)	12/45 (26.7%)	2.75	[0.49 ; 15.53]	0.343
BMI>25 kg/m ²	12/32 (37.5%)	3/19 (15.8%)	3.2	[0.77 ; 13.32]	0.123
BMI>30 kg/m ²	2/7 (28.6%)	13/44 (29.6%)	0.95	[0.16 ; 5.56]	p>0.999
Active smokers	3/8 (37.5%)	12/40 (30.0%)	1.4	[0.29 ; 6.82]	0.692
Active smokers and Former quitters	8/17 (47.1%)	7/31 (22.6%)	3.05	[0.85 ; 10.86]	0.108
Diabetes mellitus	2/8 (25.0%)	13/43 (30.2%)	0.77	[0.14 ; 4.33]	p>0.999
Previous surgery	11/36 (30.7%)	4/15 (29.4%)	1.21	[0.31 ; 4.65]	p>0.999
Previous surgery including prosthesis	7/21 (33.3%)	8/30 (26.7%)	1.38	[0.41 ; 4.64]	0.757
History of cured infection	0/8 (0.0%)	15/43 (34.0%)			0.087
B) Clinical presentation					
Shoulder	5/24 (20.8%)	10/27 (37.0%)	0.45	[0.13 ; 1.57]	p=0.235
Hip	7/17 (41.2%)	8/34 (23.5%)	2.27	[0.65 ; 7.94]	p=0.211
Knee	3/10 (30.0%)	12/41 (29.3%)	1.04	[0.23 ; 4.69]	p>0.999
Acute (vs chronic)	5/8 (62.5%)	10/43 (23.3%)	5.5	[1.11 ; 27.15]	p=0.039
Early (vs late)	11/35 (31.4%)	4/16 (25.0%)	1.38	[0.36 ; 5.24]	p=0.749
Fistula	7/16 (43.8%)	8/35 (22.9%)	2.62	[0.74 ; 9.29]	p=0.187
Inflammatory sign	7/14 (50.0%)	8/37 (21.6%)	3.62	[0.98 ; 13.4]	p=0.083
Pain	14/46 (30.4%)	1/5 (20.0%)	1.75	[0.18 ; 17.1]	p>0.999
Isolated pain	2/15 (13.3%)	13/36 (36.1%)	0.27	[0.053 ; 1.4]	p=0.177
Luxation	1/6 (16.7%)	14/45 (31.1%)	0.44	[0.047 ; 4.15]	p=0.657
Haematoma	1/4 (25.0%)	14/47 (29.8%)	0.79	[0.075 ; 8.22]	p>0.999
CRP >50 mg/L	6/10 (60.0%)	6/21 (28.6%)	3.75	[0.77 ; 18.21]	p=0.127
C) Surgery data					
DAIR (vs explantation surgery)	4/8 (50.0%)	11/43 (25.6%)	2.91	[0.62 ; 13.65]	p=0.213
Not programmed surgery	2/6 (33.3%)	13/45 (28.9%)	1.23	[0.2 ; 7.56]	p>0.999
Diagnosis after surgery	4/15 (26.7%)	11/36 (30.6%)	0.83	[0.22 ; 3.18]	p>0.999
D) Antibiotic data					
Oral antibiotic >6 week	12/44 (27.3%)	3/7 (42.9%)	0.5	[0.097 ; 2.57]	p=0.406
Total antibiotic >12week	9/29 (31.0%)	6/22 (27.3%)	1.2	[0.35 ; 4.08]	p>0.999
Intra-venous antibiotic	12/41 (29.3%)	3/10 (30.0%)	0.97	[0.21 ; 4.37]	p>0.999
Dual therapy	3/17 (17.7%)	12/34 (35.3%)	0.39	[0.094 ; 1.64]	p=0.328
Amoxicilin >7 days	1/8 (12.5%)	14/43 (32.6%)	0.3	[0.033 ; 2.64]	p=0.409
Clindamycin >7 days	14/45 (31.11%)	1/6 (16.7%)	3.07	[0.54 ; 17.37]	p=0.244
Rifampicin >7 days	3/15 (20.0%)	12/36 (33.3%)	0.5	[0.12 ; 2.12]	p=0.503
Fluoroquinolone >7 days	1/6 (16.7%)	14/45 (31.1%)	0.44	[0.047 ; 4.15]	p=0.657

Abreviation : CI, confidence interval ; CrCl, creatinine clearance BMI, body mass index ; CRP, C reactive protein ; DAIR, Debridement, antibiotics and implant retention.

^aThis column includes all patients who satisfy the condition in the corresponding line. Example for the first line : there are 3 failures among the 17 women.

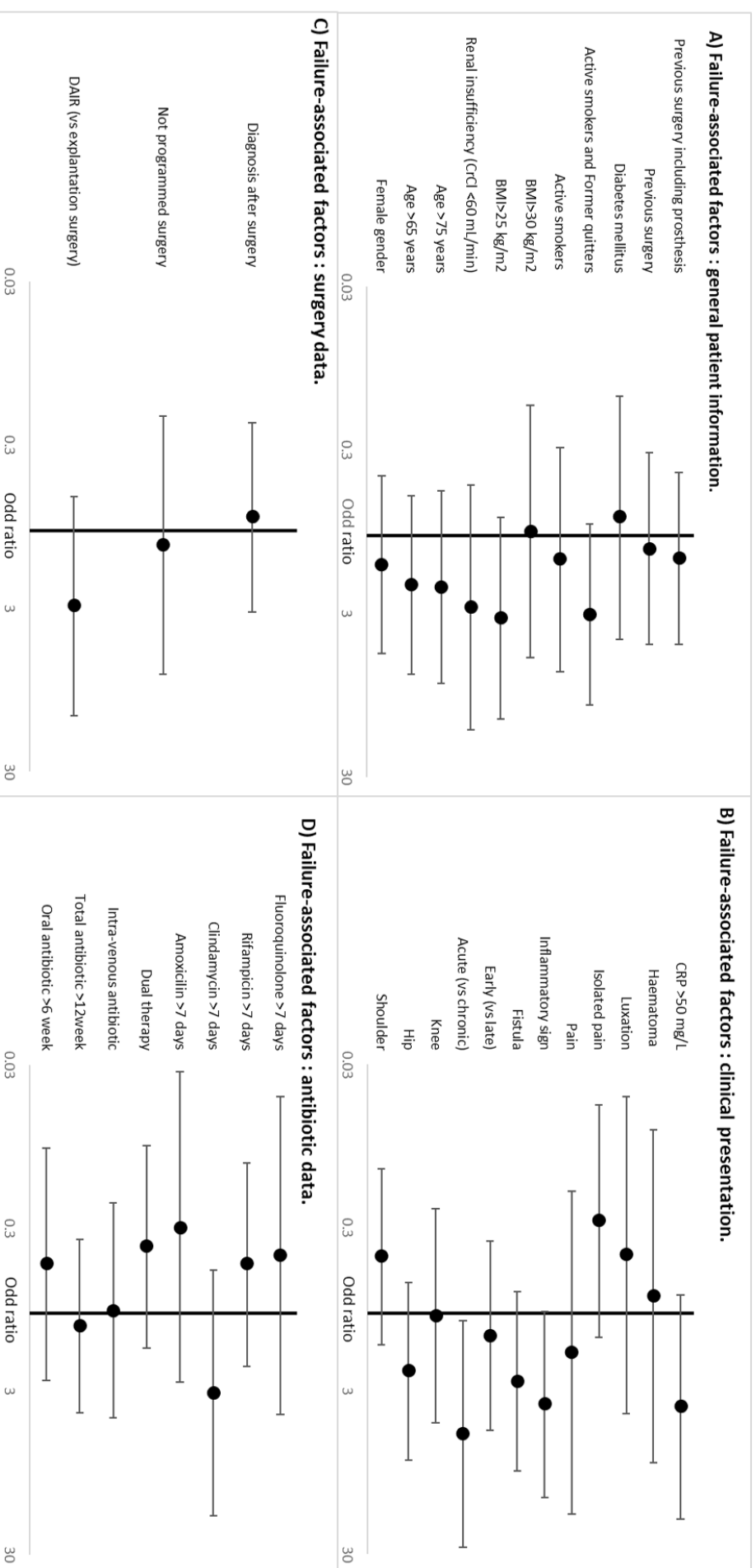
^bThis column includes all patients who do not satisfy the condition in the corresponding line. Example for the first line : there are 9 failures among the 34 men.

There was no difference between survival distributions according to the affected joint (SI vs ILM) (p=0.163). At 2 years, the global failure-free survival was 79.2% (95% CI: 57.0-90.8) for shoulder PJI and 66.7% (95% CI: 45.7-81.1) for lower limb PJI. (Figure 2A)

There was no difference between survival distributions according to the affected joint (shoulder, knee, and hip (p=0.275). At 2 years, the global failure-free survival was 79.2% (95% CI: 57.0-90.8) for shoulder, 70.0% (95% CI: 32.9-89.2) for knee and 58.2% (95% CI: 31.7-77.5) for hip. (Figure 2B)

There was no difference between survival distributions according to surgical strategy (explantation vs DAIR) (p=0.106). At 2 years, the global failure-free survival was 76.7% (95% CI: 61.1-86.7) for explantation and 50.0% (95% CI: 15.2-77.5) for DAIR. (Figure 2C)

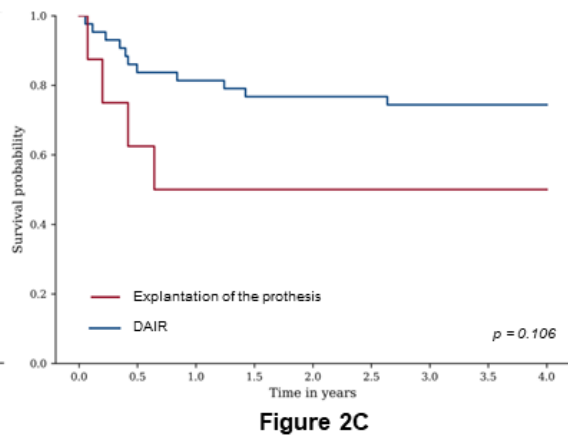
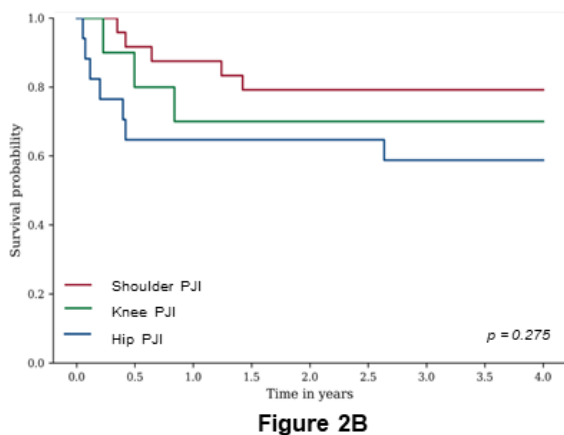
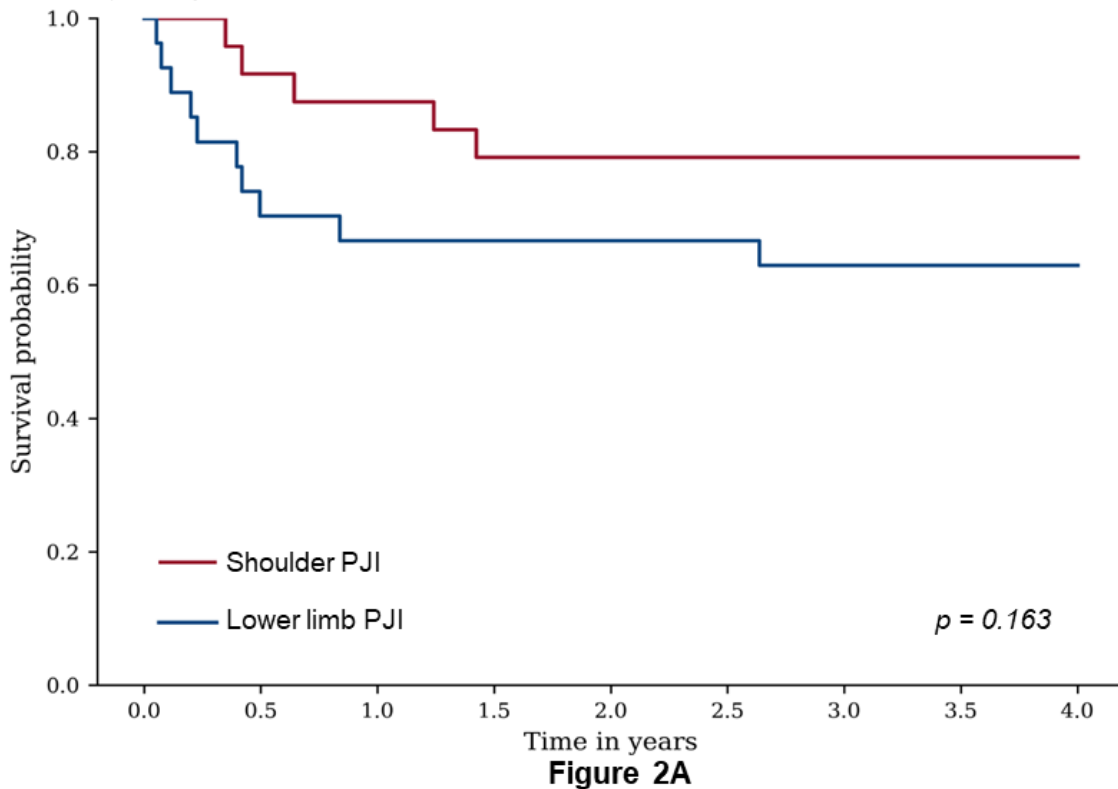
Figure 1 : factors associated with overall failure : Odds-ratios with confidence interval presented in forest plot models.



Abbreviation : BMI, body mass index ; CrCl, creatinine clearance ; DAIR, Debridement, antibiotic and implant retention.

Figure 2 : Time to treatment failure according joint the surgical strategy : Kaplan-Meier curve of patients between shoulder and lower limb (2A), Each joint (2B) and surgical strategy (2C).

PJI : prosthetic joint infection



There was no significant difference between survival distributions according to the presence or not of a fistula ($p=0.109$) but a trend to a higher risk of failure when a fistula was present. At 2 years, the global failure-free survival was 62.5% (95% CI: 34.9-81.1) when a fistula was present and 77.1% (95% CI: 59.5-87.9) when not. (Figure 3A)

There was a significant difference between survival distributions according to the presence or not of local inflammatory signs ($p=0.0338$). At 2 years, the global failure-free survival was 50.0% (95% CI: 22.9-72.2) when inflammatory signs were present and 81.1% (95% CI: 64.4-90.5) when not. (Figure 3B)

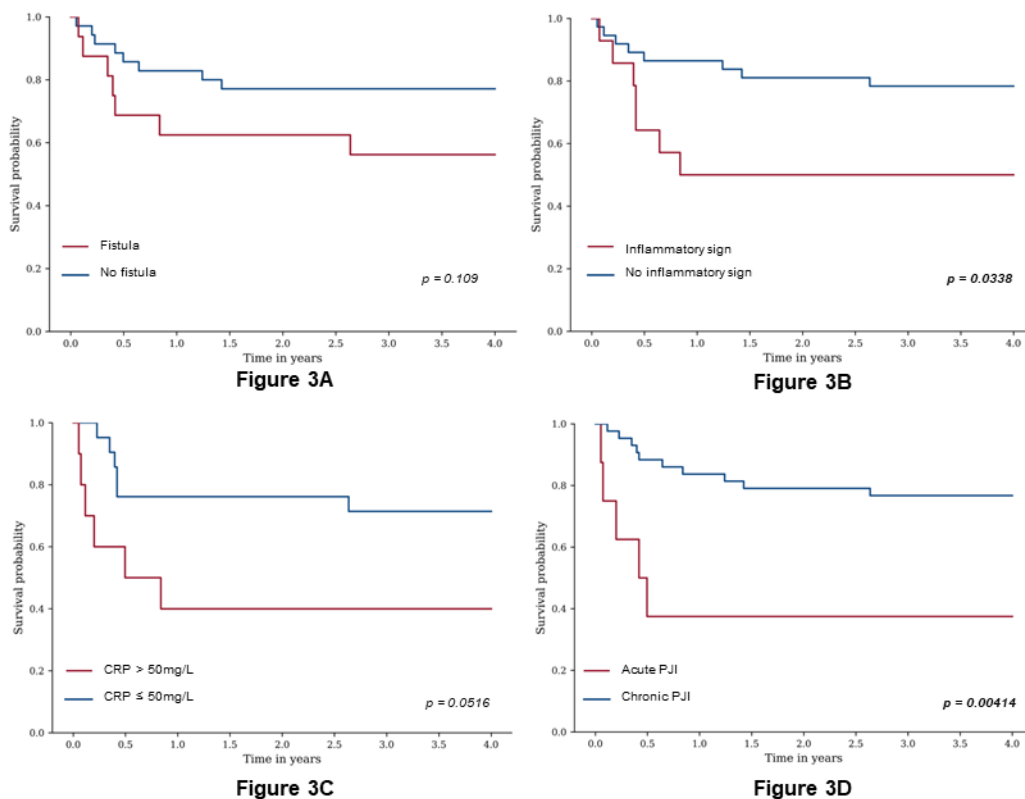
There was no significant difference between survival distributions according to the CRP level (with a cut off of 50mg/L) ($p=0.0516$) but a trend to a higher risk of failure when CRP

was high. At 2 years, the global failure-free survival was 40.0% (95% CI: 12.3-67.0) when CRP was > 50mg/L and 76.2% (95% CI: 51.9-89.3) when CRP was ≤ 50mg/L. (Figure 3C)

There was a significant difference between survival distributions according to the duration of infection (Acute vs Chronic) ($p=0.00415$). At 2 years, the global failure-free survival was 42.9% (95% CI: 9.8-73.4) for acute infection and 79.1% (95% CI: 63.6-88.5) for chronic Infection (Figure 3D)

Figure 3 : Time to treatment failure according to clinical presentation: Kaplan-Meier curve of patients according to clinical presentation with : fistula (3A), Inflammatory sign (3B), CRP level (3C), and type of infection (3D)

PJI : prosthetic joint infection, CRP : C reactive protein.



There was no difference between survival distributions according to the use of rifampicin or not ($p=0.355$). At 2 years, the global failure-free survival was 80.0% (95% CI: 50.0-93.1) when treated by rifampicin and 69.4% (95% CI: 51.7-81.8) when not treated by rifampicin. (Figure 4A)

There was no difference between survival distributions according to the use of amoxicillin or not ($p=0.31$). At 2 years, the global failure-free survival was 87.5% (95% CI: 38.7-98.1) when treated by amoxicillin and 65.7% (95% CI: 48.4-78.4) when not treated by amoxicillin. (Figure 4B)

There was no difference between survival distributions according to the use of a fluoroquinolone or not ($p=0.452$). At years, the global failure-free survival was 83.3%

(95% CI: 27.3-97.5) when treated by fluoroquinolone and 71.1% (95% CI: 55.5-82.1) when not treated by fluoroquinolone. (Figure 4C)

There was no difference between survival distributions according to the use of clindamycin or not ($p=0.531$). At 2 years, the global failure-free survival was 75.6% (95% CI: 60.2-85.6) when treated by clindamycin and 83.3% (95% CI: 27.3-97.5) when not treated by clindamycin. (Figure 4D)

Figure 4: Time to treatment failure according to antibiotic regimen: Kaplan-Meier curve of patients according to antibiotic regimen : rifampicin (4A), amoxicillin (4B), Fluoroquinolone (4C), Clindamycin (4D). Only antibiotics used for more than 7 days were included.

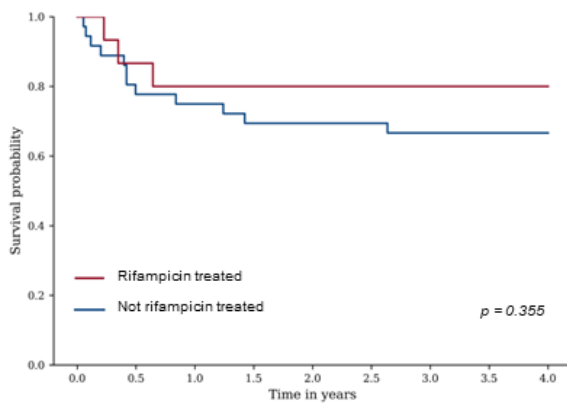


Figure 4A

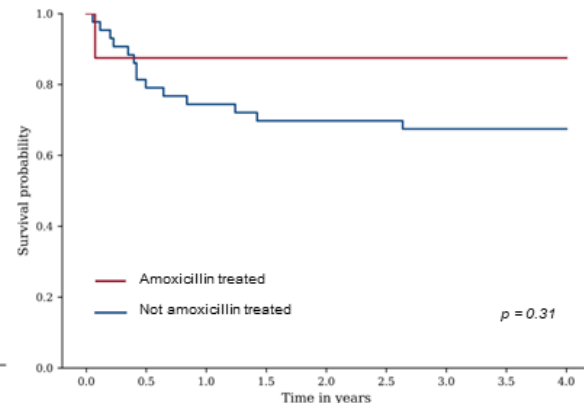


Figure 4B

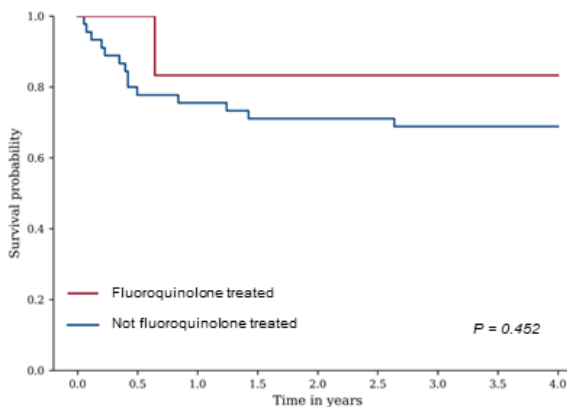


Figure 4C

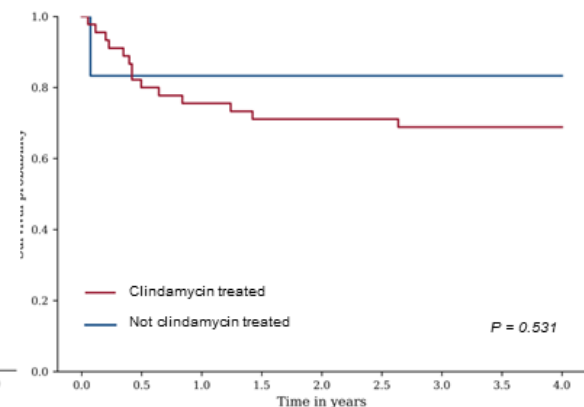


Figure 4D

Safety of antibiotic treatment

There were 11 adverse events (AE) for 58 lines of different antibiotic treatment (Table 6). There was no statistical difference between each antibiotic regimen. Most of AE were digestive. 8 were grade 1 or 2 and 3 were grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. There was 3 cases of antibiotic change for adverse events.

Table 6 : Antibiotic-related adverse events (AE)

	Number of AE	P-value	AE grade 1 ou 2	AE grade 3	change for AE ^a
All treatment	11/58 (18.9%)	-	8/58 (13.8%)	3/58 (5.2%)	3/58 (5.2%)
Clindamycin based regimen	8/45 (17.8%)	0.696	5/45 (11.1%)	3/45 (6.6%)	2/45 (4.4%)
Fluoroquinolone based regimen ^b	2/6 (33.3%)	0.318	2/6 (33.3%)	0/6 (0%)	1/6 (16.7%)
Amoxicillin based regimen	1/8 (12.5%)	>0.999	1/8 (12.5%)	0/8 (0%)	0/8 (0.0%)
Rifampicin based regimen	5/14 (35.71%)	0.112	4/14 (28.6%)	1/14 (7.1%)	1/14 (7.14%)

^aChange for adverse effect : change of antibiotic treatment motivated by a adverse effect with the first line of antibiotic.

^bAll fluoroquinolone regimen were associated with rifampicin.

Discussion

Despite the small number of patients, our study points out that the clinical presentation and outcome of shoulder PJI and lower limb *C. acnes* PJI seem to be different. ILM PJI seem to occur earlier, more painfully with more acute presentations. SI infections occur more frequently in men, are more frequently late infections and are more frequently associated with relapses. Failures tend to be more frequent in ILM infections and are more frequently new infections. Globally, the rate of failure in PJI infections is high, almost 30%, and is associated with presence of a fistula and local and general inflammation and with DAIR but not with antibiotic treatment.

An observational study based on NHS data in England that included more than 50 000 primary shoulder replacement noticed that 72% of the patients were women [20], this study showed a global higher risk of implant revision, septic or not, in men. The main reason may be a stronger colonization of the shoulder by *C. acnes* in men compared to women [4].

The diagnosis of *C. acnes* infection is not easy. The time to make the diagnosis tended to be longer in the lower limb PJI despite having more acute presentation, possibly because *C. acnes* infection is less suspected in lower limb. In some cases of our series, *C. acnes* was already isolated in prior surgery and considered as a contaminant. This led to a diagnosis more than two years after the first symptoms for some patients. To avoid such delays, it is important to take systematic bacteriological samples and ensure that they are negative at 15 days. Also, histopathological samples should be performed : histopathological definition of bone and joint infection (BJI) is based on Mirra's criterion (≥ 5 polymorphonuclears per field in 5 high power fields) [21] but more recently, a study show that the Plasma Cell Infiltration should be also considered for the diagnosis of *C.acnes* PJI [22]. We did not include histopathological samples in our study because they were rarely performed.

The fact that in our series the type of failure (relapse vs new infection) is significantly different between upper and lower limb is very interesting. This difference is not due to the surgical strategy, as it was very similar between the 2 groups with the same proportion of DAIR. This difference may be due to the type of infection, with more early and acute infection in the lower limb PJI. Another explanation may be the more frequent occurrence of PJI on replacement implants in lower limb PJI. In our series the PJI occurred on SI replacement in 25.9% of the case, and on LLI replacement in 51.7%. There seems to be more fistula in the lower limb failure also.

A potential cause of new infection is the inoculation of the new bacteria during the revision surgery as a super-infection but this would not explain the difference between SI and LLI. Another hypothesis to explicate this high number of new infections in lower limb in our series is that those presumed new germs were already there and were not identified during the revision surgery. This hypothesis is carried by the fact that a lot of the new infections occurred during the antibiotic treatment and occurred on joints with multiple prior surgery, and most of the time more symptomatic PJI. Given this hypothesis and the high number of new infections in the lower limb (29.63%), and the low number (4.16%) in shoulder, the question is : should we focus the targeted antibiotic treatment only on *C. acnes* when it is the solo microorganism identified in lower limb PJI ? Those data are too

weak to make a conclusion, but more research should be done especially about the incidence of new infection and relapse between those different joints.

The use of rifampicin has been identified as a possible protective factor against the occurrence of failure, notably for its antibiofilm effect [11,14]. In our study, we did not find any difference of rate of failure according to antibiotic regimens but numbers were low and treatment heterogeneous.

Some studies only take relapses into account in the causes of failure [10], which does not necessarily correspond to what is observed in current practice. It is not uncommon for new germs to be identified during failure, whatever the first germ involved. This can lead to wrong conclusion about the best antibiotic regimen. Differences in type of failure should thus be taken in consideration when analysing retrospective studies that include different joints. The biggest retrospective study that tried to identify the best regimen for *C. acnes* PJI didn't stratify the analyses in function of the joints [14], despite the higher number of shoulder PJI in the rifampicin group. This points out the difficulty for retrospective studies to identify the best antibiotic regimen in regard of all the biases that need to be taken in consideration. Of note, a prospective study will soon take place in France studying the addition of rifampicin in shoulder *C. acnes* PJI.

Despite the small number of patients treated with amoxicillin in our study, it appears that this treatment is a good option with a trend to a higher efficacy compared to clindamycin. Unlike rifampicin, there are no studies looking at this particular treatment, which is used by a lot of centres in France. Further studies are needed.

For the fluoroquinolones, in our study, they were always used in combination with rifampicin, which complicates the analysis of the effect of each treatment. Moreover, half of the patient in the fluoroquinolone group also received clindamycin before or after.

Concerning clindamycin in our study, more than half of the patients treated with other therapy than clindamycin, also received clindamycin for more than 7 days at a moment (before, with, or after), and therefore, we only have 6 patients who never received clindamycin.

With those data, it's impossible to conclude which antibiotic is the best to cure *C. acnes* PJI mostly because there was not enough patient in fluoroquinolone and amoxicillin to make a strong analysis.

We report also a higher global rate of failure than most of other study [9, 10, 11, 14, 23]. It is possibly linked to the fact that most of those study didn't include LLI. But therefore it's not the case of the biggest one [14] that include more LLI than SI and still had a lower rate of global failure (around 20%). Also this study did not report the same important rate of new infection despite including a lot of LLI. It's possibly related to a higher rate of "possible relapse without microbiology data" than can be new infection, but still, it did not explain alone the difference. This difference on LLI rate and cause of failure in our study can then just be random, further study is needed to confirm or infirm this data.

The main limitation of our study is thus a lack of power due to the low number of patients and the heterogeneity of situations which preclude any solid conclusion except for the type of failure. Moreover, due to the low number of patients, we had to analyse PJI of the

knee and the hip together, which can lead to wrong conclusion as there are obviously not the same joint.

Another limitation of our study is that we only excluded patients with a follow up of less than 6 month and not 1 year for the failure analysis. We did not choose a cut-off of 1 year for the follow-up, because a large number of patients, whose prostheses were progressing very well, were not seen again by their surgeons. They were then instructed to see their surgeons again if there were any problems. Many of them then had a follow-up very close to 1 year, between 10 and 11 months. excluding these patients did not seem relevant to us.

Another limitation of our study that should be considered is that there is a significant difference of origin of recruitment between shoulder and lower limb PJI that can influence greatly the outcome. In fact, it is possible that the risk of failure is influenced by the experience of different surgeons, which are moreover not the same for upper and lower limbs.

Conclusion

We enlighten the fact that *C. acnes* is not only a germ responsible of shoulder PJI, but this microorganism should also be considered in pauci-symptomatic infections of the lower limb. The type of antibiotic regimen does not seem to influence the outcome.

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Supplementary table 1 : Infection characteristics of all failure cases with microbiological data (N=13) : New infection

Microbiology	Type of infection	City of recruitment	Joint	Prior joint replacement	Symptoms	Surgical strategy	Moment of diagnosis	Moment of failure	Time to failure diagnosis ^a	Antibiotic regimen
<i>Staphylococcus epidermidis</i>	Chronic and late	Montpellier	Shoulder	NO	Pain and fistula	1-stage exchange of prosthesis	Before the surgery	After antibiotic treatment	127	Clindamycin + rifampicin
<i>Escherichia coli</i>	Chronic and early	Nîmes	Hip	NO	Pain, inflammatory sign and fistula	2-stage exchange of prosthesis	Before the surgery	After antibiotic treatment	153	Clindamycin
<i>Staphylococcus capitis</i>	Acute and early	Nîmes	Knee	NO	Pain	1-stage exchange of prosthesis	Before the surgery	After antibiotic treatment	181	Clindamycin
<i>Streptococcus mitis</i>	Chronic and early	Nîmes	Knee	YES	Pain, inflammatory sign and fistula	2-stage exchange of prosthesis	Before the surgery	After antibiotic treatment	306	Clindamycin
<i>Staphylococcus epidermidis</i>	Acute and early	Nîmes	Hip	YES	Pain, inflammatory sign	DAR	Before the surgery	During antibiotic treatment	73	Clindamycin
<i>Escherichia coli</i> <i>Enterococcus faecalis</i> <i>Proteus mirabilis</i>	Acute and early	Nîmes	Hip	YES	Pain, luxation	1-stage exchange of prosthesis	After the surgery	During antibiotic treatment	19	Clindamycin
<i>Staphylococcus epidermidis</i>	Chronic and early	Nîmes	Hip	YES	Pain, inflammatory sign and fistula	2-stage exchange of prosthesis	Before the surgery	After antibiotic treatment	145	Clindamycin
<i>Staphylococcus epidermidis</i>	Chronic and late	Montpellier	Knee	YES	Pain	1-stage exchange of prosthesis	After the surgery	During antibiotic treatment	83	Clindamycin
<i>Klebsiella pneumoniae</i>	Chronic and late	Montpellier	Hip	YES	Pain and fistula	2-stage exchange of prosthesis	Before the surgery	During antibiotic treatment	42	Clindamycin

^atime to failure diagnosis : time (in day) between the revision surgery and the diagnosis of failure.

Supplementary table 2 : Infection characteristics of all failure cases with microbiological data (N=13) : Relapse and unknown germs

Microbiology	Type of infection	City of recruitment	Joint	Prior joint replacement	Symptoms	Surgical strategy	Moment of diagnosis	Moment of failure	Time to failure diagnosis	Antibiotic regimen
<i>Cutibacterium acnes</i>	Chronic and late	Montpellier	Shoulder	NO	Pain and inflammatory sign	DAR	Before the surgery	After antibiotic treatment	235	Levofloxacin + rifampicin switched for clindamycin
<i>Cutibacterium acnes</i>	Chronic and early	Montpellier	Shoulder	NO	Pain	1-stage exchange of prosthesis	Before the surgery	After antibiotic treatment	453	Clindamycin
<i>Cutibacterium acnes</i>	Acute and early	Montpellier	Shoulder	NO	Pain and inflammatory sign	DAR	During the surgery	After antibiotic treatment	518	Clindamycin
<i>Cutibacterium acnes</i>	Chronic and early	Nîmes	Shoulder	NO	No clinical sign	1-stage exchange of prosthesis	After the surgery	After antibiotic treatment	520	Clindamycin
Unknown	Acute and early	Nîmes	Hip	NO	Pain, inflammatory sign and fistula	DAR	Before the surgery	During antibiotic treatment	27	Amoxicillin
Unknown	Chronic and early	Montpellier	Hip	YES	Pain and fistula	1-stage exchange of prosthesis	After the surgery	After antibiotic treatment	963	Clindamycin

^atime to failure diagnosis : time (in day) between the revision surgery and the diagnosis of failure.

Annexes

Supplementary table 3 : Antibiotic regimen in patient treated with and without rifampicin^a

	<u>Rifampicin treated</u>	<u>Not Rifampicin treated</u>	<u>p value</u>
Clindamycin	11/45 (24.4%)	34/45 (75.6%)	0.054
Fluoroquinolone	6/6 (100%)	0/6 (0%)	<0.001
Amoxiciline	2/8 (25%)	6/8 (75%)	>0.999

N=19^b

^aThe treatment could be taken with or at a another moment than the rifampicin.

^b4 patients in clindamycin group receive also a fluoroquinolone associated with rifampicin : including 3 primary treated by a fluoroquinolone (before the clindamycin) and 1 secondary (after the clindamycin)

Serment

- En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Être suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.
- Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.
- Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.
- Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.
- Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.

Résumé

Contexte : l'infection de prothèse a *Cutibacterium acnes* est une infection survenant majoritairement au membre supérieur, mais pas uniquement. Il n'existe pas ou peu de données dans la littérature qui comparent les données cliniques et le taux d'échecs entre les prothèses d'épaules (PE) et les prothèses du membre inférieur (PMI).

Méthode : Il s'agit d'une étude comparative rétrospective et multicentrique portant sur les infections de prothèses articulaires monomicrobienne à *Cutibacterium acnes* de l'épaule, du genou, et de la hanche survenue entre 2012 et 2022 au CHU de Montpellier et de Nîmes. Nous avons comparé les données cliniques et les taux d'échecs entre les PE et les PMI. Nous avons aussi mené une analyse à la recherche de facteurs prédictifs d'échecs notamment en fonction de l'antibiothérapie choisie.

Résultat : Nous avons inclus 56 patients, la douleur est significativement plus souvent rapporté sur les PMI, il n'y avait pas de différence sur la stratégie chirurgicale. Il y avait une tendance à utiliser plus de bithérapies pour traiter les PE (37.0%). Nous rapportons un taux élevé d'échec et plus important pour les PMI 10/27 (37.0%) contre 5/24 (20.8%) pour les PE, mais de façon non-significative (P-value=0.235). Les raisons de l'échecs semble différente avec significativement plus de rechute au même germe pour les PE (16.7% vs 0.0% P=0.043), et plus de nouvelles infections pour les PMI (29.6% vs 4.2% P=0.026). Pour l'analyse des facteurs prédictifs d'échecs : un tableau d'infection aigu est significativement associé à plus d'échecs. Nous manquons de données pour conclure sur l'antibiothérapie.

Conclusion : La symptomatologie semble plus marquée sur les PMI. Il semblerait que les échecs soient dus à des rechutes pour les PE et des infections à de nouveaux germes pour les PMI.

Spécialité : Maladies infectieuses et tropicales

Mots clefs : Infection ostéoarticulaire, *Cutibacterium acnes*, prothèses articulaire.