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Management of prosthetic joints infection in France: a national audit

Marion Le Maréchal

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Université de Nice Sophia-Antipolis
Faculté de Médecine de Nice

Modalités de prise en charge des infections ostéo- articulaires en France : un audit national

THESE D'EXERCICE DE MEDECINE

Présentée et soutenue publiquement à la Faculté de Médecine de Nice

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Née le 22 septembre 1988 à Fontainebleau

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(Diplôme d'Etat)

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“Wit beyond measure is man’s greatest treasure.”

TABLE DES MATIÈRES

LISTE DES ABRÉVIATIONS	13
PREMIERE PARTIE – RESUME DU TRAVAIL EN LANGUE FRANÇAISE	14
DEUXIEME PARTIE – ARTICLE EN LANGUE ANGLAISE	15
TITLE PAGE	15
INTRODUCTION	17
METHODS	18
Background information	18
Participants	18
Survey tool development	19
Data collection	19
Ethical statement	20
Data analyses	20
RESULTS	21
Baseline characteristics of respondents	21
Prophylaxis	21
Surgical intervention	22
Post-operative antibiotic treatment	22
Oral antibiotic regimen	23
Total antibiotic regimen duration	24
Use of recommendations	24
DISCUSSION	25
Main results	25
Duration of post-operative antibiotic regimen	26
Oral antibiotic prescription	27
Total duration of antibiotic regimen	28
Recommendations	29
Strengths and limitations	30
Conclusion	30
ACKNOWLEDGMENTS	31
FUNDING	31
TRANSPARENCY DECLARATIONS	31
AUTHOR CONTRIBUTION	31
REFERENCES	32
TABLES AND FIGURES	36
TABLE DES ANNEXES	39

LISTE DES ABRÉVIATIONS

BJI: Bone and joint infection

E. faecalis: *Enterococcus faecalis*

MRSA: Methicillin-resistant *Staphylococcus aureus*

MSSA: Methicillin-susceptible *Staphylococcus aureus*

PJI: Prosthetic joint infection

S. aureus: *Staphylococcus aureus*

S. agalactiae: *Streptococcus agalactiae*

Première partie – Résumé du travail en langue française

Introduction – Les infections ostéo-articulaires (IOA) sont parmi les complications les plus sévères des arthroplasties. La prise en charge des IOA nécessite une prise en charge multidisciplinaire entre, au moins, le chirurgien orthopédiste, l'infectiologue et le microbiologiste. En France, en 2008, les hospitalisations pour IOA comptaient pour 0,2% du total des hospitalisations. La prise en charge de ces infections est organisée autour de centres de référence, les CRIOACs. Étant donnée l'hétérogénéité des IOA, et le niveau de preuve bas disponible dans les différentes recommandations, nous avons fait l'hypothèse que les pratiques différaient d'un établissement à l'autre. Notre objectif principal était de réaliser un audit, grâce à une enquête par questionnaire organisé autour de cas cliniques, pour évaluer la prise en charge des IOA par les professionnels de santé concernés.

Méthodes – Les participants éligibles étaient tous les professionnels de santé impliqués dans la prise en charge des IOA, qui étaient inscrits sur les mailings liste dédiées à la prise en charge de ces infections. Les médecins pouvaient répondre individuellement, ou lors de RCP dédiées aux IOA. L'enquête consistait en trois questionnaires, soit un total de six cas cliniques.

Résultats – Le taux de réponses de la part des CRIOACs aux trois questionnaires étaient de 92%, 77%, et 53%. 65%, 58%, et 86% des répondants respectivement avaient répondu individuellement. Pour un patient avec un antécédent d'arthrite septique à *S. aureus* ayant besoin d'une pose de prothèse sur le même genou, 47% préféraient réalisés plus d'exams que la radio fournie, sans différence entre les centres CRIOACs (41%) ou non (51%), $p=0,470$. Dans cette même situation, 32% des répondants n'administrait pas d'antibioprophylaxie per-opératoire, sans différence entre les centres CRIOACs (25%) ou non (36%), $p=0,406$. Pour un patient avec une infection tardive, dont la ponction pré-opératoire est positive à *S. aureus*, 39% n'administrait pas d'antibioprophylaxie, avec une différence entre les CRIOACs (26%) et les autres centres (67%), $p=0,023$. Pour la prise en charge chirurgicale, une large majorité des répondants choisissait une stratégie en un temps, peu importe la situation clinique, sans différence entre les CRIOACs et les autres centres. La rifampicine était utilisée, que ce soit chez un patient présentant une IOA à *S. aureus*, avec (90-92%) ou sans matériel (70%). Elle était également prescrite pour les infections à streptocoques (24-47%). La durée totale d'antibiotiques était variée, allant de six à 12 semaines.

Conclusion – La prise en charge chirurgicale dans notre enquête était assez homogène, avec une large préférence pour la chirurgie en un temps. La prise en charge médicale faisait beaucoup plus débat, avec un éventail large de réponses pour la durée d'antibiothérapie post-opératoire ou la durée totale d'antibiotique. Cette hétérogénéité dans la prise en charge de des IOA reflète l'hétérogénéité des IOA elles-mêmes et la difficulté de réaliser des études permettant de répondre clairement à des situations cliniques aussi variées.

Deuxième partie – Article en langue anglaise

TITLE PAGE

Title: Management of prosthetic joints infection in France: a national audit

Running title: French audit on prosthetic joints infection

Abstract:

Introduction – Prosthetic joint infections (PJI) are one of the most serious complication of arthroplasty. The management of PJI needs a multidisciplinary collaboration between, at least, orthopaedic surgeon, infectious disease specialist and microbiologist. The management of PJI is organized around reference centres named CRIOACs. Considering the heterogeneity of PJI and the global low level of evidence available, our main objective was to perform an audit through a questionnaire survey based on clinical case, to evaluate how French physicians manage in daily care PJI.

Methods – Eligible participants were all physicians involved in care of patients presenting a PJI. Physicians could answer individually, or collectively during a multidisciplinary team meeting dedicated to PJI. The survey consisted as three questionnaires organized in a total of six clinical cases.

Results – Answers from the CRIOACs to the three questionnaires were 92%, 77%, and 53%. Respectively 65%, 58%, and 86% of respondents were answering as individuals. For a patient with a comorbidity of *S. aureus* acute arthritis who needed a prosthesis on the same knee, 47% preferred to perform more exams than the available knee x-ray, with no difference between CRIOACs (41%) and other centres (51%), $p=0.470$. In the same situation, 32% did not administer antibiotic prophylaxis. Concerning surgical strategies, a large majority of respondents preferred 1-stage exchange strategy in all clinical cases, with no difference between CRIOACs and other centres. Concerning the prescription of rifampicin, it was widely used, for *S. aureus* PJI (70-92%). It was also used for *Streptococcus* spp. PJI (24%-47%). There was no consensus for the total antibiotic regimen duration.

Conclusion – Surgical strategy for the management of PJI was homogenous with a preference for one-stage exchange strategy. Medical management was more heterogenous, which reflects the heterogeneity of those infections and difficulties to perform studies with strong conclusions.

Key words (from the MeSH catalogue): (/8)

- Clinical audit
- Joint prosthesis

- Rifampin
- Staphylococcus aureus
- Surveys and Questionnaires

INTRODUCTION

Prosthetic joint infections (PJI) are one of the most serious complication of arthroplasty (1). Those infections are not rare, between 0.8% and 1.9% of PJI after total knee replacement (2–4), and between 0.3 and 1.7% of PJI after total hip replacement (4–6). The management of PJI needs a multidisciplinary collaboration between, at least, orthopaedic surgeon, infectious disease specialist and microbiologist, to decide for exams to perform in the pre-operative evaluation, the type of surgery to choose, and the most suitable antibiotic regimen. There are three main surgical strategies possible: 1) debridement, antibiotics and implant retention (DAIR); 2) one-stage arthroplasty exchange; 3) two-stage arthroplasty exchange. There is no consensus in post-operative antibiotic duration.

Staphylococcus aureus (*S. aureus*) accounts for 27% of the bacteria isolated in all time periods PJI (38% in early period PJI) (7), and is one of the most studied bacteria in PJI (5% of PJI research on PubMed on the 26th of August 2019). One of the main issues in PJI management is the high heterogeneity of clinical situation: one infection can concern a shoulder, a hip, a knee; it can be early (1-3 months after implantation (1)), or delayed; acute, or chronic. Microbiologic samples can isolate, none, one, or several bacteria. Therefore, out of *S. aureus* PJI literature, strength of recommendations and quality of evidence are scarce. For instance, in the recommendations from IDSA concerning the management of PJI, 63.5% of recommendations are based on level III quality of evidence “evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees” (8).

In France, in 2008, hospitalization for PJI accounted for 0.2% of all hospitalization (9). The management of PJI is mainly in public hospitals (83% in 2008, (9)), and organized around reference centres. Considering the heterogeneity of PJI to manage and the global low level of evidence available, we hypothesized that clinical practice was diversified from one hospital to another.

Our main objective was to perform an audit through a questionnaire survey based on clinical case, to evaluate how French physicians manage in daily care PJI.

METHODS

Background information

In France, the follow-up of a patient presenting a PJI is generally led by an orthopaedic surgeon, or an infectious diseases specialist. Management is frequently multidisciplinary, structured as a multidisciplinary team meeting, or as informal advice between the different specialists.

For PJI management, the country is organized, since 2008, in a large specialized network of Reference centres in the management of PJI (*Centre de Référence des Infections Ostéo-Articulaires complexes (CRIOACs)*). This CRIOACs network is divided in nine reference centres, each coordinating at least two of the 21 associated centres. The reference centres missions are 1) to coordinate the local network with the associated centres; 2) to provide their expertise in PJI care, with multidisciplinary team meeting dedicated to PJI; 3) to ensure education of physicians training in PJI care; 4) to promote research in the PJI field; 5) care of patients presenting a PJI. The nine reference centres in France are mainly teaching hospitals: Ambroise Paré teaching hospital (Paris), Bordeaux teaching hospital, Diaconesses Croix Saint-Simon hospital (Paris), Lille teaching hospital and Tourcoing hospital (working together as one reference centre), Lyon teaching hospital, Marseille teaching hospital, Nancy teaching hospital, Rennes teaching hospital, and Tours teaching hospital. Associated centres main mission is patient care. Most of them also have a local multidisciplinary team meeting dedicated to PJI and can ask for expertise to their reference centre.

All physicians and hospitals in France can contact one of the CRIOACs, to ask for a patient management advice, or for a patient transfer to a specialized centre. The list of all CRIOACs is available on the ministry of health website (10).

Participants

Eligible participants were all physicians involved in care of patients presenting a PJI, with no restriction regarding their speciality (clinical care medicine, microbiologists, or surgeons). Regarding the large amount of eligible participants, we restricted the list to the physicians who subscribed to one of those mailing lists: 1) French society of hip and knee (*Société Française de la Hanche et du Genou (SFHG)*), 2) National network of research in infectious diseases (*Réseau National de Recherche Clinique en Infectiologie (RENARCI)*), 3) The CRIOAC centers mailing list. All physicians who subscribed to one (or several) mailing list(s) received an invitation email (sent by JC and TF) including information about the study and a link to the online survey. Total number of physicians who received the invitation email is hard to establish. Therefore, we estimated the response rate over the number of CRIOACs who answered among the total number of CRIOACs in France (N = 30).

Physicians could answer individually, or collectively during a multidisciplinary team meeting dedicated to PJI (one answer per meeting independently of the number of physicians taking part to the meeting).

Survey tool development

The survey consisted as three questionnaires sent one after the other. Each questionnaire was divided in three parts: 1) an introduction to characterize the participant(s); 2) the first clinical case; 3) the second clinical case. They concerned: 1) first questionnaire, first clinical case (Q1C1): a 45 years-old man without any comorbidities, presenting with an acute infectious arthritis of the left knee, associated with a methicillin-susceptible *S. aureus* (MSSA) bacteraemia; 2) first questionnaire, second clinical case (Q1C2): the same patient presents few months after the acute septic arthritis, ipsilateral knee osteoarthritis requiring arthroplasty; 3) second questionnaire, first clinical case (Q2C1): a 70 years-old man presenting a delayed MSSA infection, following a right hip replacement; 4) second questionnaire, second clinical case (Q2C2): a 69 years-old man, presenting a delayed *Enterococcus faecalis* (*E. faecalis*), following a left knee replacement; 5) third questionnaire, first clinical case (Q3C1): a 70 years-old man with a background of Streptococcal hip prosthetic infection five years ago, and with a prosthetic hip replacement (same hip) 21 days ago presenting a febrile wound drainage; 6) third questionnaire, second clinical case (Q3C2): a 65 years-old woman with a background of hip replacement nine months ago presenting a persistent hip pain and a positive hip puncture growing a *Streptococcus agalactiae* (*S. agalactiae*) (Figure 1; Questionnaires are available in “Annexes” part). Thrice questionnaires were developed by JC, MLM, TF, and ZC based on the literature, and on their personal experience.

Each questionnaire, was written in French, formatted in SurveyMonkey® and the first one was pilot tested by four physicians, to check for length and clarity.

For each questionnaires, for questions concerning only antibiotic therapy, a choice was offered to skip the question if the respondents was not concerned.

Data collection

A link to the first questionnaire was sent to participants by e-mail. One month later, a link to the second questionnaire was sent to the participants, also including a reminder and the link to the first questionnaire. The same procedure was performed for the third questionnaire, with a reminder and links to the two first questionnaires.

The first questionnaire was opened on January 2019, the second one on February 2019, and the third one on May 2019. Participation in the survey was voluntary, anonymous and without any financial compensation.

Ethical statement

In accordance with French laws, this survey did not need any ethical approval. Data analysis and reporting preserved respondents' anonymity.

Data analyses

Data from three surveys were extracted from the SurveyMonkey® platform, imported in an Excel® spreadsheet and analysed with the R® software (version 3.5.1). Continuous variables were presented as means (and standard deviations), or as medians (and interquartile ranges) depending on the variable's distribution. Categorical variables were described as absolute numbers and percentages.

Univariate analyses were performed, using Fisher exact test or chi square test where needed.

All answers were considered. If several physicians from the same institution answered individually (and not as a multidisciplinary team meeting), their answers were weighted to overcome the selection bias.

RESULTS

All answers presented in the **Results** section are weighted data (details in **Data analyses** section).

Baseline characteristics of respondents

We sent thrice questionnaires to the three mailing lists detailed in the **Participants** section. Answers from the CRIOACs to the questionnaires were: 1) 27.5/30 to the first questionnaire (Q1) (response rate = 92%); 2) 23/30 to the second questionnaire (Q2) (response rate = 77%); 3) 16/30 to the third questionnaire (Q3) (response rate = 53%).

Questionnaires were available online from: 1) the 18/01/2019 to the 30/06/2019 for Q1; 2) the 06/03/2019 to the 30/06/2019 for Q2; 3) the 15/05/2019 to the 30/06/2019 for Q3.

For Q1, Q2, and Q3, respectively 44% (27.5/63), 46% (23/50), and 29% (16/56) of respondents were part of a CRIOAC, and 83%, 63%, and 78% of them were undertaking at least four multidisciplinary meetings dedicated to PJI every month. Among respondents who were not part of CRIOACs, respectively 30% (10.5/34.5), 34% (8.5/25), and 46% (17.5/38) of them were undertaking multidisciplinary meetings dedicated to PJI in their own hospitals. Respectively 65% (41/63), 58% (29/50), and 86% (48/56) of respondents were answering as individuals (in opposition to an answer during a multidisciplinary meeting), and 78% (32/41), 88% (25.5/29), and 77% (37/48) of those individual respondents were surgeons. For respondents answering during a multidisciplinary meeting, 88% (14/16), 94% (14.5/15.5), and 42% (2.5/6) of those multidisciplinary meetings consisted of at least one microbiologist, one orthopaedic surgeon, and one infectious disease specialist. All respondents' characteristics are available Table 1.

PJI diagnosis

In Q1C2, for a patient with a comorbidity of *S. aureus* acute arthritis who needs a prosthesis on the same knee, 47% (26/55.25) preferred to perform more exams than the available knee x-ray, with no difference between CRIOACs (41%) and other centres (51%), p-value = 0.470. 54% (14/26) performed an MRI, 42% (11/26) a white blood cell scan, 31% (8/26) a bone scintigraphy, and 29% (7.5/26) a CT-scan.

In a case of a suspicion of acute PJI (Q3C1), 63% (33.5/53) perform a needle aspiration before surgery.

Prophylaxis

In a situation with a patient presenting a comorbidity of invasive *S. aureus* infection (acute arthritis associated with an MSSA bacteraemia, Q1C1 and Q1C2), 94% of respondents (50.75/54.25) were not performing a systematic nasal decolonization with mupirocin (without

performing anterior nares swab), and 42% (22.75/54.25) were detecting *S. aureus* from anterior nares swab and treating the carrying patients.

For a patient with a comorbidity of *S. aureus* acute arthritis who needs a prosthesis on the same knee (Q1C2), 32% (17.5/54.25) did not administer antibiotic prophylaxis, with no difference between CRIOACs (25%, 6.5/25.5) and other centres (36%, 10/27.75), p-value = 0.406. For a patient presenting a late PJI with a positive *S. aureus* pre-operative needle puncture, in case of 1-stage exchange strategy, 39% (13.5/34.5) did not administer antibiotic prophylaxis, with a significant difference between CRIOACs (26%, 4.5/17.5), and other centres (67%, 9/13.5), p-value = 0.023.

Surgical intervention

Concerning late PJI (Q2C1, Q2C2, and Q3C1): 1) for Q2C1, 91% (40.5/44.5) preferred a 1-stage exchange strategy; 2) for Q2C2, 75% (30/40) preferred a 1-stage exchange strategy, and 20% preferred a 2-stage exchange strategy (7/40); 3) for Q3C2, 82% (38.5/47) chose a 1-stage exchange strategy, 23% (11/47) chose a debridement with removal of mobile components via an open arthrotomy, and 9% (4/47) chose a 2-stage exchange strategy.

Concerning early PJI (Q3C1), 94% of respondents (48.5/51.5) chose a debridement with removal of mobile components via an open arthrotomy, 4% (2/51.5) chose a 1-stage exchange strategy, 2% (1/51.5) chose a debridement via an arthroscopy without any removal, and none of the respondents chose a 2-stage exchange strategy.

In case of a 2-stage exchange surgery for a late knee prosthesis infection with a positive *E. faecalis* pre-operative needle puncture (Q2C2), 88% of respondents chose to use an antibiotic impregnated bone cement (gentamicin associated or not to vancomycin), for 1-stage (26.5/30), or 2-stage exchange strategy (7/8). For a late hip prosthesis infection with a positive *S. agalactiae* pre-operative needle puncture (Q3C2), 42% (16.5/38.5) of respondents who chose a 1-stage exchange strategy used an antibiotic impregnated bone cement (gentamicin associated or not to clindamycin or vancomycin).

There was no difference between CRIOACs and other centres to choose between a 1-stage or a 2-stage exchange strategy (Q2C2: 22% (4/18.5) of 2-stage exchange strategy for non CRIOACs vs. 21% (4/19.5) for CRIOACs, p-value = 1; Q3C2: 5% (1.5/27.5) vs. 22% (2.5/11.5), p-value = 0.562).

Post-operative antibiotic treatment

Concerning MSSA bone and joint infection (BJI)/PJI (Q1C1, Q2C1, and Q3C1): 1) after a debridement via an open arthrotomy for an acute arthritis associated with a bacteraemia (Q1C1), 99% (36.5/36.75) of respondents decided to start an IV treatment directly after surgery, during 3-5 days (25%, 9/35.5) or during 6-14 days (64%, 23.5/36.5). All were using a

beta-lactam therapy effective against *S. aureus* (100%, 36.5/36.5). 2) for a late chronic PJI, after a positive *S. aureus* pre-operative needle puncture, 22% (10/44.5) of respondents did not consider this positive puncture to choose post-operative antibiotic therapy. For an early PJI, 21 days after 1-stage hip replacement (Q3C1), before microbiologic documentation, 69% (14.5/21) were using piperacillin-tazobactam as an anti-Gram negative therapy, and 48% (10/21) and 38% (8/21) were respectively using daptomycin and vancomycin as an anti-Gram positive therapy. With microbiological results being available at day three, duration of IV regimen was five days or less (43%, 9.5/22), five to eight days (34%, 7.5/22), or more than eight days (23%, 5/22). Only one respondent chose to administer an anti-Gram positive therapy without an anti-Gram negative therapy.

Concerning *Streptococcus* spp. PJI (*E. faecalis* for Q2C2 and *S. agalactiae* for Q3C2): 1) for a late *E. faecalis* PJI, after the first stage of a 2-stage exchange strategy, 56% (17.5/31) were using IV amoxicillin, until availability of antibiotic susceptibility testing (26%, 8/30.5), until seven days after surgery (23%, 7/30.5), until 14 days after surgery (33%, 10/30.5), or until the second stage of the 2-stage strategy (15%, 4.5/30.5). Finally, with microbiological results, 45% (14/31), were using a broad-spectrum antibiotic therapy, and 60% (18.5/31) used a two antibiotics regimen therapy. 2) for a late *S. agalactiae* PJI, 12% (5.5/46) started an antibiotic therapy before surgery. After a 1-stage exchange strategy, 56% (22.5/40.5) were using IV amoxicillin (27%, 6/22.5 as a single therapy), until five days after surgery (37%, 16.5/44.5), from five to eight days after surgery (24%, 10.5/44.5), or more than eight days after surgery (39%, 17.5/44.5). Finally, 47% (19/40.5) used an anti-methicillin-resistant *S. aureus* (MRSA) empirical antibiotic therapy, even with a *S. agalactiae* documentation.

Oral antibiotic regimen

Concerning the prescription of rifampicin for *S. aureus* BJI/PJI (Q1C1, Q2C1, and Q3C1): 1) in a situation without any prosthesis (Q1C1), respondents were giving priority to a regimen associating fluoroquinolone and rifampicin (70%, 28/40). 2) in situations with prosthesis (Q2C1 and Q3C1), respondents were giving priority to a regimen associating fluoroquinolone and rifampicin in 92% (33.5/36.5) and 90% (19/21) of cases.

Concerning the prescription of rifampicin for *Streptococcus* spp. PJI (*E. faecalis* for Q2C2 and *S. agalactiae* for Q3C2): 1) for an *E. faecalis* infection, oral regimen was containing rifampicin in 24% of cases (9.5/39.5). 2) for a *S. agalactiae* PJI, oral regimen was containing rifampicin in 47% of cases (18.5/39.5). For an 85kg patient (Q3C1), 62% of respondents (13/21) used a dosage of 900mg once a day.

In case of a Gram positive infection, priority for a fluoroquinolone was given to levofloxacin (90%, 18/20 for *Staphylococcus* spp., and 89% (16.5/18.5) for a *Streptococcus* spp. infection).

For an enterobacteria infection, respondents did not have any preference between levofloxacin (38%, 7/18.5), ofloxacin (32%, 6/18.5), and ciprofloxacin (24%, 4.5/18.5).

For *S. aureus* PJI (Q2C1), clindamycin was a frequent choice if fluoroquinolone or rifampicin were not available (64%, 23.5/36.5), but the MLS_B inducible phenotype was considered (23%, 8.5/36.5 of clindamycin in case of a MLS_B inducible phenotype).

Total antibiotic regimen duration

Concerning total antibiotic regimen duration: 1) After a 1-stage exchange surgery, total antibiotic regimen duration was for Q2C1: 4-6 weeks (16%, 6/36.5), 6-8 weeks (49%, 18/36.5), 8-12 weeks (33%, 12/36.5), or six months (1%, 0.5/36.5); and for Q3C2: six weeks (37%, 16.5/45), eight weeks (4%, 2/45), or 12 weeks (59%, 26.5/45).

2) After a 2-stage exchange surgery (Q2C2), total antibiotic regimen duration was eight weeks (six weeks between explantation and implantation, and two weeks after implantation) (45%, 19/42), 10 weeks (5%, 2/42), or 12 weeks (six weeks between explantation and implantation, and six weeks after implantation) (24%, 10/42).

3) After a debridement via an arthroscopy without any removal (Q3C1), total antibiotic regimen duration was six weeks (26%, 6/23.5), three months (68%, 16/23.5), or suspensive (4%, 1/23.5). After a debridement via an arthroscopy without any prosthesis (Q1C1), total antibiotic regimen duration was three weeks (6%, 2/36), four weeks (35%, 12.5/36), six weeks (53%, 19/36), eight weeks (1%, 0.5/36), or 12 weeks (3%, 1/36).

Use of recommendations

Local guidelines were available for empirical antibiotic regimen after surgery for a PJI in 82% of centres (18/22).

Concerning national guidelines from the French infectious disease society (SPILF, 2009 (11)), and from the National public health society (HAS, 2014 (12)), 57% (32/56) and 75% (42/56) of respondents knew the existence of these recommendations, and 78% (25/32) and 96% (40.5/42) of them had read the recommendations.

Concerning international guidelines from the American infectious disease society (IDSA, 2013 (1)), the Spanish infectious disease society (SEIMC, 2017 (13)), and the Philadelphia international recommendations (2018 (14)), 33% (18.5/56), 2% (1/56), and 26% (14.5/56) of the respondents knew the existence of these recommendations, and 86% (16/18.5), 50% (0.5/1), and 59% (8.5/14.5) of them had read the recommendations.

There were differences between CRIOACs and other centres for the French infectious disease society guidelines, (69% (11/16) vs. 34% (13/38), p-value = 0.020), the American infectious disease society guidelines (53% (8.5/16) vs. 17% (6.5/38), p-value = 0.016), and the Philadelphia international recommendations (41% (6.5/16) vs. 5% (2/38), p-value = 0.006).

DISCUSSION

Main results

Between 32 and 39% of respondents did not administer antibiotic prophylaxis despite positive *S. aureus* pre-operative documentation. One-stage exchange strategy was widely preferred in all clinical cases. Rifampicin was prescribed for *S. aureus* PJI, in a situation with (90-92%) or without any prosthesis (70%). It was also used for *Streptococcus* spp. PJI (24%-47%). There was no consensus for the total antibiotic regimen duration, with prescriptions from six to 12 weeks for a majority of respondents.

IV antibiotic therapy

In a case of a suspicion of acute PJI (Q3C1), 63% perform a needle aspiration before surgery. However, in case of a positive *S. aureus* pre-operative needle puncture (Q2C1), 22% of respondents did not consider this positive result to choose the post-operative antibiotic therapy. For a late *S. agalactiae* PJI, 12% started an antibiotic therapy before surgery, based on the pre-operative needle puncture. Even with the pre-operative identification of a bacteria (*E. faecalis* in Q2C2, or *S. agalactiae* in Q3C2), 45% and 47% of respondents, added an antibiotic therapy against MRSA to the penicillin therapy. Few studies have compared the microbiologic concordance between pre-operative and per-operative samples. In a Goulenok *et al.* study, only presented in congress, concordance between both exams was 85% (15), and in a Matter-Parrat *et al.* work, concordance was 74% (16). In Goulenok's work, they also checked the match between immediate antibiotic therapy and per-operative microbiological samples results. A discrepancy was found in 6% of cases. The choice, whether to start or not an antibiotic regimen before surgery, and therefore before per-operative microbiological samples probably needs to be decided depending on the isolated bacteria, the delay to surgery, the positivity of blood cultures, or, as suggested by the Spanish recommendations, in case of a skin and soft tissue infection, an antibiotic therapy can be started for few days, in order to allow the surgical approach (13).

Without any pre-operative microbiological indication (Q3C1), almost all respondents chose to prescribe an anti-Gram positive and an anti-Gram negative antibiotic therapy as an empirical treatment, and 49% of respondents continued this broad-spectrum antibiotic therapy 48 hours after surgery. In a recent work, with first results published in congress, Deroche *et al.* found that before five days after surgery, 97% of microbiological results were definitive (17). Bacteria growing after day five were mainly *Cutibacterium acnes* and coagulase-negative staphylococci. Majority of our respondents (77%) tend to stop empirical antibiotic therapy before day eight (with microbiological results at day five) (Q3C1).

In two clinical cases (Q1C2 and Q2C1), questions on antibiotic prophylaxis showed that respectively 32% and 39% of respondents did not prescribe antibiotic prophylaxis. The main reason is probably the risk to sterilise microbiological samples. A literature review from Wouthuyzen-Bakker *et al.* pooled all studies comparing patient with and without antibiotic prophylaxis (18). In the antibiotic prophylaxis group, 88% of cultures were positive, vs. 95% in the no antibiotic prophylaxis group (p-value = 0.004). However, several works showed that after a PJI treatment, a failure can be with the same bacteria, or with another one, which enhance the importance of all infections prevention. For instance, Renz *et al.*, showed that after *Streptococcus* spp. PJI treatment, 11/27 failure were due to another bacteria as a *Streptococcus* spp. (19). First results of the DATIPO study showed that in both groups (6 weeks or 12 weeks of treatment), 27% and 61% of failure were due to another bacteria than the first identified (20).

Duration of post-operative antibiotic regimen

In our survey, after a 1-stage exchange surgery, total antibiotic regimen duration was from 6-8 weeks (49%, Q2C1), or 12 weeks (59%, Q3C2). After a 2-stage exchange surgery, total antibiotic regimen duration was eight weeks (including 2 weeks after reimplantation) (45%, Q2C2). After a debridement via an arthroscopy without mobile components exchange (Q3C1) three months (68%, Q3C1). After a debridement via an arthroscopy without any prosthesis (Q1C1), total antibiotic regimen duration was four weeks (35%), or six weeks (53%). A recent literature review by Yen *et al.*, in 2019 analysed 10 studies that compared short-course (four to eight weeks) versus long-course (four weeks to six months) antibiotic regimen (21). It included 856 patients from 1987 to 2013. They did not find any difference between both groups (RR = 0.87, 95% confidence interval (CI) [0.62–1.22]). A recent study published after our survey, by Li *et al.*, evaluated outcome of BJI/PJI, one year after treatment with intravenous or oral antibiotics (22). The study found a -1.4 percentage point in the intention-to-treat population, with a 90%CI [-4.9 to 2.2] meeting non inferiority criteria (7.5 percentage-point margin). For *S. aureus* PJI, after a 1-stage exchange surgery, American recommendations suggest a total duration of antibiotic regimen of three months (1); Spanish recommendations are more moderate (and more recent), and suggest a total antibiotic regimen going from four to eight weeks (13), based on a literature review over 28 studies, but with a low level of evidence (B-II). Finally, French recommendations of 2014 recommend a total antibiotic regimen of six weeks to three months, with a very low level of evidence (expert opinion) (12). The total antibiotic duration is a balance between the risk of failure and the risk of antibiotic adverse effect. This low level of evidence is reflected in the heterogenous answers in our survey.

Oral antibiotic prescription

Rifampicin was preferred in all situation with a *S. aureus* PJI (Q2C1 and Q3C1), with respectively 92% and 90% of respondents who were giving priority to an oral regimen associating fluoroquinolone and rifampicin. Rifampicin as an efficient antibiotic for *S. aureus* PJI has been demonstrated in mouse model (23), and later in in vivo study. For instance the 1998 study of Zimmerli *et al.* showed a higher rate of remission in the rifampicin group than in the placebo group (100% vs. 58%, p-value = 0.02) (24); in the publication of Senneville *et al.* in 2011, where different surgical strategies were used (42% DAIR, 14% 1-stage exchange strategy, 27% 2-stage exchange strategy, 9% arthroplastic resection, and 8% arthrodesis), remission was higher in the group with a rifampicin regimen (75% vs. 48%, p-value = 0.002), and also in the group with a fluoroquinolone and rifampicin regimen (48% vs. 10%, p-value = 0.001) (25). Recommendations on this regimen for *S. aureus* are clear with a high level of evidence (A-I) (1,13). However, in a case without any prosthesis (Q1C1), combination of fluoroquinolone and rifampicin is still preferred (70%). A combination therapy seems to be the most common practice on *S. aureus*. A single therapy could probably be used, as long as the chosen antibiotic has a high biodisponibility (26). Clindamycin is a widely used antibiotic against *S. aureus* infections (27). It was used in our survey as a second choice on *S. aureus* (if fluoroquinolone or rifampicin were not available) (64% of prescription), but the MLS_B inducible phenotype was considered (23% of clindamycin prescription in case of a MLS_B inducible phenotype). Debate is ongoing to know whether or not clindamycin can be used in the case of an MLS_B inducible phenotype. A literature review compiled 11 published clinical cases of induced resistance to clindamycin (28), but this resistance emergence seems to be a rare phenomenon.

In *S. aureus* infections, in our survey, rifampicin was used at a 10 mg/kg regimen (Q3C1), which is the French recommendation (12).

In *Enterococcus* spp. invasive infections, a regimen containing amoxicillin is superior to other regimens (29), but its efficiency in PJI is not demonstrated. For instance, in Tornero *et al.*, there was a difference between remission and failure in patients with amoxicillin (67% vs. 33%), but not significant (p-value = 0.490) (30). In our survey, penicillin was widely used as an empirical antibiotic therapy in the *E. faecalis* clinical case, with 56% of respondents using amoxicillin, and 27% piperacillin (in association with tazobactam). Rifampicin as a companion drug was also used in this clinical case, since 24% of respondents would use it in such situation. Superiority of rifampicin in *Enterococcus* spp. infection is not well established. A study, conducted by Holmberg *et al.*, analysed susceptibility of 15 *E. faecalis* strains derived from knee or hip prosthesis infection to ciprofloxacin, ampicillin, linezolid and vancomycin, associated or not to rifampicin (31). The combination of ciprofloxacin, and linezolid with

rifampicin, was the most effective in reducing the number of bacteria. In vivo, the study of Tornero *et al.* showed a small difference when using rifampicin between the remission group (60%) and the failure group (40%), p-value = 0.049 for early PJI (<30 days), but the difference was no longer significant for late PJI (>30 days) (p-value = 0.310) (30).

Finally, for *Streptococcus* spp. PJI, in our work, respondents used rifampicin in 47% of cases. In a large international study, the outcome of 389 *Streptococcus* spp. PJI was evaluated (32). The use of rifampicin was associated with a better outcome, but with a confidence interval close to 1 (aHR = 0.98 95%CI [0.96-0.998], p-value = 0.030). An in vitro study showed that a combination of gentamicin and rifampicin exerted a synergistic effect against biofilms produced by streptococci strains (33). However, in another study, *Streptococcus* spp. treated with or without rifampicin did not show any difference in outcome (p-value = 0.175) (34).

Total duration of antibiotic regimen

In our first clinical case (Q1C1) on an acute arthritis without any prosthesis, total duration of antibiotic regimen was between three weeks (6%, 2/36), four weeks (35%, 12.5/36), and six weeks (53%, 19/36). Literature suggest that total antibiotic regimen could be shortened on native joints. For instance, a study compared a two-weeks with a four-weeks antibiotic regimen in native joint arthritis (35), and the intention to treat analysis did not find an inferiority in the two-weeks treatment (-0.7 percentage points 90%CI [-8.5% to 7.0%]). However, this study mainly included small joints (only one hip and 14 knee infections). A clinical trial is ongoing, to compare three weeks vs. six weeks in native joints acute arthritis (36). The total duration on a native joint infection will probably evolve to shorter regimen.

For PJI, total duration of antibiotic regimen was different depending on the chosen exchange strategy. In case of a DAIR without change of mobile components, 68% of respondents chose a three months antibiotic regimen therapy. To leave the mobile components is a known risk factor of failure (37). An ongoing French work, DATIPO published its first results (20). They compared 6 weeks vs. 12 weeks antibiotic therapy for PJI. They did not show non-inferiority in the six weeks group, with 22% vs. 14% of failure (8.2 90%CI [0.7-15.7]).

For 1-stage exchange strategy clinical cases (Q2C1 and Q3C1), duration of antibiotic regimen were long, with 49% for 6-8 weeks and 33% for 8-12 weeks for Q2C1, and 59% for 12 weeks in Q3C2. However, for 2-stage exchange strategy (Q2C2), a majority of respondents chose an eight weeks duration (six weeks between explantation and implantation, and two weeks after implantation) (45%). In Q2C1, respondents declared at 84%, that the surgical strategy would not change the duration of antibiotic therapy duration. The discrepancy between those two answers can be explain by a social desirability bias, where respondents declare that the surgical strategy will not influence their choice, but in front of a practical case, a 2-stage exchange strategy is perceived as a less “at-risk” strategy.

Surgical management

The 2-stage exchange strategy is commonly used in the USA and is considered as the gold standard for prosthesis replacement (1,14). An European survey (EBJIS survey) also found that 2-stage exchange strategy was the most common philosophy regarding treatment of chronic PJI (38). However, when prosthesis replacement was clearly indicated for chronic infections in our study, 1-stage exchange strategy was chosen more frequently (without any significant difference between CRIOACs and other centres). Our clinical cases presented PJI without sinus tract or inadequate soft tissue coverage, no systemic manifestation of infection and with identified organisms prior to surgery; none of the usual criteria for a 2-stage exchange strategy were present (39). More recently, a better functional outcome of 1-stage exchange strategy has been suggested in total knee arthroplasty (40,41). Those results need to be confirmed but they highlight another crucial outcome criteria which has to be considered beside the microbiological cure.

Recommendations

Some choices in our survey's answer were not guided by literature or recommendations. For instance, in Q1C1, 26% of respondents chose a needle aspiration via an arthroscopy instead of a surgery. In literature, several studies compared the outcome of patients presenting a native joint infection, but results were not unanimous. For instance Goldenberg *et al.* compared the favourable outcome between needle aspiration group (37/46, 80%) and surgery group (8/17, 47%) in septic arthritis (42). Ravindran *et al.* compared favourable outcome of patients with a native joint infection who benefited from a medical treatment (69% of complete recovery) and a surgical treatment (53% of complete recovery), p-value = 0.240 (43). In sub-group analysis for knee joint infections, difference was statistically significant (71% vs. 38%, p-value = 0.050). A more recent work in 2017 by McConnell *et al.* compared native joints infection medically managed (10/20, 50% of full recovery at three months), or surgically managed (8/41, 20%) (p-value = 0.002) (44). Concerning shoulder infections without any prosthesis, outcome seemed different, since the outcome was better in the arthrotomy group (18% of reinfection) than in the arthroscopy group (52% of reinfection) (p-value = 0.007) (45).

In Q1C2, a lot of respondents (47%) would ask for more exams than the available x-ray. Those supplementary exams are not recommended before implantation of a prosthesis, mainly because their interpretation is uncertain. A study showed a very good outcome after arthroplasty following septic arthritis, with a success rate between 87% and 95% (46). The main risk might not be the previously infected joint, but the risk factor of *S. aureus* infection. For instance, *S. aureus* nasal carriage can be detected with nasal swab. In our survey, in a situation with a patient presenting a comorbidity of invasive *S. aureus* infection (acute arthritis

associated with a bacteraemia, Q1C1 and Q1C2), 94% of respondents were not performing a systematic nasal decolonization with mupirocin, and 42% were detecting *S. aureus* from nasal swab and treating the carrying patients. In the International consensus meeting in Philadelphia 2018, there are no clear recommendation on *S. aureus* nasal carriage (14).

Strengths and limitations

Our study is a pilot study. It is original, since it was dedicated to all physicians involved in the management of PJI, and because we distinguished CRIOACs in the management of PJI with other centres, and individual answers with answers during a multidisciplinary meeting dedicated to PJI. It is a multicentred national study (with the participation of one physician in the United Kingdom, and one in Switzerland). The survey was sent through three different mailing lists and therefore touched the utmost concerned physicians. The data were weighted to overcome the selection bias and to avoid large centres to be over-represented.

Our work also has some limitations. First, the response rate is hard to evaluate since we do not know precisely how many physicians received the invitation emails. The response rate from the CRIOACs decreased during time (92%, 77% and 53%). This is probably due weariness, since our survey was spread over few months. Then, the characteristics of the respondents to the third questionnaire were very different to those in the first and second questionnaires. More respondents were answering as individuals, and less respondents were part of CRIOACs.

Conclusion

Surgical strategy for the management of PJI was homogenous with a preference for one-stage strategy. Medical management was more heterogenous with a wide range of duration of post-operative antibiotic duration, or total antibiotic duration. This heterogeneity in medical PJI management reflects the heterogeneity of those infections and difficulties to perform studies with strong conclusions, and therefore to publish high level of evidence recommendations. However, a recent, but very large study, published in the New England journal of Medicine, despite including various patients, with different infected joints, with or without prosthesis, with different identified bacteria, and with different surgical strategies, conclude to an interesting message, with external validity (22). Finally, all studies discussed in this work have in common the microbiological criteria to define the outcome of patients, where a better outcome should be the joint functional status.

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None to declare.

AUTHOR CONTRIBUTION

J.C. and T.F. initiated the study. J.C., M.L.M., T.F. and Z.C. contributed to the study design.

J.C., M.L.M., and T.F. contributed to the implementation and supervision of the study. M.L.M.

analysed the data and takes responsibility for the accuracy of the data analysis. J.C., M.L.M.,

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TABLES AND FIGURES

Table 1: Characteristics of respondents (weighted data)

	First questionnaire n/N	%	Second questionnaire n/N	%	Third questionnaire n/N	%
The hospital is a CRIOAC in the management of PJI?						
Yes	27.5/63	43.7	23/50	46.0	16/56	28.6
No	34.5/63	54.8	25/50	50.0	38/56	67.9
If the hospital is one of the CRIOAC in the management of PJI, how many multidisciplinary meetings dedicated to PJI are organized (per month)?						
< 4	5.5/27.5	20.0	7.5/23	32.6	1.5/16	9.4
4	17.75/27.5	64.5	10.5/23	45.7	8/16	50.0
> 4	5/27.5	18.2	4/23	17.4	4.5/16	28.1
If the hospital is not one of the CRIOAC in the management of PJI, do you have a multidisciplinary meeting dedicated to PJI?						
Yes	10.5/34.5	30.4	8.5/25	34.0	17.5/38	46.1
No	22/34.5	63.8	15.5/25	62.0	20.5/38	53.9
For the hospital that are not one of the CRIOAC in the management of PJI, how many multidisciplinary meetings dedicated to PJI are organized (per month)?						
< 4	5.5/10.5	52.4	5/8.5	58.8	10.5/17.5	60.0
4	2/10.5	19.0	2/8.5	23.5	5/17.5	28.6
Other	1/10.5	9.5	1.5/8.5	17.6	1/17.5	5.7
For the hospital that are not one of the CRIOAC in the management of PJI, do you ask for expertise to a CRIOAC?						
Yes	22.5/34.5	65.2	16/25	64.0	27.5/38	72.4
No	7/34.5	20.3	8/25	32.0	10.5/38	27.6
Do you answer as an individual person or during a multidisciplinary meeting dedicated to PJI?						

<i>Individual answer</i>	41/63	65.1	29/50	58.0	48/56	85.7
<i>Multidisciplinary meeting</i>	16/63	25.4	15.5/50	31.0	6/56	10.7
For individual respondents, what is your speciality?						
<i>Surgeon</i>	32/41	78.0	25.5/29	87.9	37/48	77.1
<i>Infectious disease specialist</i>	5.5/41	13.4	4.5/29	15.5	10/48	20.8
<i>Other</i>	3.5/41	8.5	1/29	3.4	1/48	2.1

If you are answering during a multidisciplinary team meeting, who are the specialist participating to the meeting?

<i>Only surgeon, infectious disease specialist, and microbiologist</i>	7/16	43.8	5.5/15.5	35.5	1.5/6	25.0
<i>More than surgeon, infectious disease specialist and microbiologist</i>	7/16	43.8	9/15.5	58.1	1/6	16.6
<i>Other</i>	2/16	12.5	1/15.5	6.5	3.5/6	58.3

How many PJI do you manage?

<i>Less than one a month</i>	24/63	38.1	20/50	40.0	8.5/56	15.2
<i>1 to 5 a month</i>	8/63	12.7	4/50	8.0	12/56	21.4
<i>1 to 5 a week</i>	7.75/63	12.3	6.5/50	13.0	5.5/56	9.8
<i>More than 5 a week</i>	16.75/63	26.6	15/50	30.0	26.5/56	47.3

CRIOAC: Reference centre in the management of PJI; PJI: Prosthetic joint infection

QUESTIONNAIRE 1

CASE 1

A 45 years-old man presenting an acute knee arthritis, with a *Staphylococcus aureus* in blood cultures and in pre-operative knee puncture.

QUESTIONNAIRE 2

CASE 1

A 70 years-old man who received a total hip replacement four months ago is presenting a late PJI with a *Staphylococcus aureus* pre-operative hip puncture.

QUESTIONNAIRE 3

CASE 1

A 70 years-old patient who presented five years ago a Streptococcus PJI on a hip prosthesis with a 2-stage exchange surgery has received 21 days ago a new prosthesis. He presents an early acute PJI.

CASE 2

The same patient is presenting 12 months after the acute knee arthritis, for an arthrosis on the same knee that requires a prosthesis.

CASE 2

A 69 years-old man who received 2 years ago a total knee replacement is presenting a late infection with an *Enterococcus faecalis* pre-operative knee puncture.

CASE 2

A 65 years-old woman received 9 months ago a total hip replacement. She has a persistent pain ever since. Pre-operative hip puncture finds a *Streptococcus agalactiae*.

PJI: Prosthetic joint infection

Figure 1 : Summary of the six clinical cases

TABLE DES ANNEXES

Annexe 1 : Questionnaire 1.....40
Annexe 2 : Questionnaire 2.....53
Annexe 3 : Questionnaire 3.....74

Introduction – Les infections ostéo-articulaires (IOA) sont parmi les complications les plus sévères des arthroplasties. La prise en charge des IOA nécessite une prise en charge multidisciplinaire entre, au moins, le chirurgien orthopédiste, l'infectiologue et le microbiologiste. En France, en 2008, les hospitalisations pour IOA comptaient pour 0,2% du total des hospitalisations. La prise en charge de ces infections est organisée autour de centres de référence, les CRIOACs. Étant donnée l'hétérogénéité des IOA, et le niveau de preuve bas disponible dans les différentes recommandations, nous avons fait l'hypothèse que les pratiques différaient d'un établissement à l'autre. Notre objectif principal était de réaliser un audit, grâce à une enquête par questionnaire organisé autour de cas cliniques, pour évaluer la prise en charge des IOA par les professionnels de santé concernés.

Méthodes – Les participants éligibles étaient tous les professionnels de santé impliqués dans la prise en charge des IOA, qui étaient inscrits sur les mailings liste dédiées à la prise en charge de ces infections. Les médecins pouvaient répondre individuellement, ou lors de RCP dédiées aux IOA. L'enquête consistait en trois questionnaires, soit un total de six cas cliniques.

Résultats – Le taux de réponses de la part des CRIOACs aux trois questionnaires étaient de 92%, 77%, et 53%. 65%, 58%, et 86% des répondants respectivement avaient répondu individuellement. Pour un patient avec un antécédent d'arthrite septique à *S. aureus* ayant besoin d'une pose de prothèse sur le même genou, 47% préféraient réalisés plus d'exams que la radio fournie, sans différence entre les centres CRIOACs (41%) ou non (51%), $p=0,470$. Dans cette même situation, 32% des répondants n'administrait pas d'antibioprophylaxie per-opératoire, sans différence entre les centres CRIOACs (25%) ou non (36%), $p=0,406$. Pour un patient avec une infection tardive, dont la ponction pré-opératoire est positive à *S. aureus*, 39% n'administrait pas d'antibioprophylaxie, avec une différence entre les CRIOACs (26%) et les autres centres (67%), $p=0,023$. Pour la prise en charge chirurgicale, une large majorité des répondants choisissait une stratégie en un temps, peu importe la situation clinique, sans différence entre les CRIOACs et les autres centres. La rifampicine était utilisée, que ce soit chez un patient présentant une IOA à *S. aureus*, avec (90-92%) ou sans matériel (70%). Elle était également prescrite pour les infections à streptocoques (24-47%). La durée totale d'antibiotiques était variée, allant de six à 12 semaines.

Conclusion – La prise en charge chirurgicale dans notre enquête était assez homogène, avec une large préférence pour la chirurgie en un temps. La prise en charge médicale faisait beaucoup plus débat, avec un éventail large de réponses pour la durée d'antibiothérapie post-opératoire ou la durée totale d'antibiotique. Cette hétérogénéité dans la prise en charge de des IOA reflète l'hétérogénéité des IOA elles-mêmes et la difficulté de réaliser des études permettant de répondre clairement à des situations cliniques aussi variées.