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Grammatico-Guillon, Pascal Astagneau

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Epidemiology of complex bone and joint infections in France using a national registry: the CRIOAc network

Adrien LEMAIGNEN^{1,2}, Louis BERNARD¹, Simon MARMOR³, Tristan FERRY⁴, Leslie

GRAMMATICO-GUILLON ^{5,6}, Pascal ASTAGNEAU ^{2,7}, Scientific Committee for Complex

Bone and Joint Infections Reference Centers (CRIOAc), on behalf of the CRIOAc network

- ¹ CHRU de Tours, Service de Médecine Interne et Maladies Infectieuses, Tours, France
- ² Sorbonne Université, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique, IPLESP,

Paris, France

- ³ Groupe Hospitalier Diaconesses-Croix Saint Simon, CRIOAc, Paris, France
- ⁴ Hospices Civils de Lyon, Service de Maladies Infectieuses et Tropicales, Lyon, France
- ⁵CHRU de Tours, Unité d'Épidémiologie des données cliniques, EpiDcliC, Tours, France
- ⁶ Unité Inserm 1259, Université de tours, Tours, France
- ⁷ Centre d'appui pour la prévention des infections associées aux soins (CPIAS), Paris, France
- * Composition of the study groups detailed in the Acknowledgement section

Corresponding author: Adrien Lemaignen, MD

Service de médecine interne et maladies infectieuses - Hôpital Bretonneau, CHRU de Tours

2, Boulevard Tonnellé, 37044 Tours CEDEX 9, France

Tel: +33 2 47 47 37 14 - Fax: +33 2 47 47 37 31

Mail: adrien.lemaignen@univ-tours.fr

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Introduction

Bone and joint infections (BJI), including septic arthritis and osteomyelitis are becoming of immediate concern because of a significant human and economic burden (1–5). The incidence is estimated to be 70/100,000 patients-year in France, and increases with age (1). Population ageing with a higher prevalence of comorbidities, and increasing arthroplasty procedures could explain partly this trend (6). In parallel, microbiological characteristics as well as clinical management of BJI are evolving for the last decade (7,8).

BJI represent a very heterogenous group of pathology leading to complex medical cares. Device-associated infections, first-line management failure, sometimes due to multidrug resistant or difficult-to-treat micro-organisms, and multiple comorbidities are associated with higher morbidity and costs and require multi-professional competencies (9,10). To face the problem, the French Ministry of Health has created 30 several reference centers located in university hospitals since 2008, so called *Centres de référence des infections ostéoarticulaires complexes* (CRIOAc) (11). These centers are responsible for the organization of multi-professional expertise on the management of BJI in their geographic unit, especially for complex BJIs (cBJI, defined below). This is made through periodic multidisciplinary meeting (MM) hold in the reference center.

A registry for BJI was then set up in 2012 to perform the MM and to collect individual data for patients referred to each reference center, as the decision taken during MM (12). The main objective of this study was to describe the main characteristics and advised management for patients referred to cBJI reference centers in France between 2014 and 2019, and to determine significant temporal trends.

Methods

Study design

This multicentric observational study was a descriptive analysis of the data from the French registry of reference centers for cBJI management.

Patients

All consecutive adult patients presented in MM for a suspected or confirmed BJI and recorded in the registry from January 2014 to December 2019 were included in this study. Data-quality could not be analyzed for 7 centers, therefore patients from these reference centers were not included in the analysis.

Study variables

The definition of complex BJI (cBJI) was based on the presence of at least one of the following criteria determined during a MM: Host criteria (severe comorbidity limiting treatment options, severe drug allergy or intolerance); Microbiological criteria (difficult-to-treat micro-organism(s) with or without multidrug resistance); Surgical criteria (BJI requiring large bone resection and bone and/or soft-tissue reconstruction); Relapse or failure of a previous episode of BJI. The classification as cBJI during MM was under the responsibility of each reference center.

Variables recorded in the registry were previously detailed (12). They include: *i*/ characteristics of the MM (date, localization); *ii*/ demographics (age, sex) and comorbidities; *iii*/ clinical and biological data; *iv*/ characteristics of the infection (localization, rank of infection, device presence or not, microbiological identification and resistance to antibiotics); and *v*/ decision of MM: recommended surgery, proposed antibiotic treatment, definition as a complex BJI or not and criterion for complexity.

The registry does not contain outcome data, but some patients are presented several times in MM. We considered several MM as a same infectious episode when the delay between 2 presentations in MM was less than one year in the absence of device, and less than two years

when patients presented device-associated infection. These time intervals are usually retained in the literature for definition of BJI cure (13,14).

Episodes have been classified into 7 different mutually exclusive types, according to the main mechanism of infection: 1/prosthetic joint infections (PJI); 2/osteomyelitis: osteomyelitis with or without contiguous septic arthritis; 3/native arthritis: isolated septic arthritis, without foreign device; 4/septic pseudarthrosis: delayed healing of a fracture-related infection, with or without associated foreign device; 5/vertebral infections; 6/other/undefined: affections involving external fixators, soft tissues (muscle, tendons, skin, abscesses etc.), tumoral processes or other mechanisms not mentioned above ; 6/multiple: several associated mechanisms among the previous ones and several sites of infection.

Analysis

We considered for analysis aggregated data from individual infectious episodes for patient's characteristics, BJI characteristics and MM decision (one patient could be presented for several different infectious episodes). Descriptive statistics included frequency analyses (percentages) for categorical variables and mean (standard deviation [SD]) or median (25th and 75th quantile [Q25-Q75]) for quantitative variables. When necessary, comparisons were made using chi-square test, or student t-test as needed. Linear regression analysis and a non-parametric Mann-Kendall test were used to assess a temporal trend. Significance was assumed for a p-value < 0.05. Missing data were presented in the different tables and figures. Statistical analyses were performed using the R statistical package version 3.6.3 (The R Foundation for Statistical Computing, https://www.R-project.org/).

Ethics

The registry was endorsed by the French National Data Protection Agency in 2012 (CNIL / 2012-220). Non-opposition to the use of the recorded data for research purposes is systematically sought for each patient included in the cohort. Funding of this registry and the reference centers is supported by the French Ministry of Health.

Results

Registry population

From 2014 to 2019, 37,289 patients were recorded in the French registry for cBJI. Data were analyzed for patients from the 23 centers included in this study, representing 27,483 individual patients, corresponding to 28,365 distinct infectious episodes requiring 47,262 presentations in MM (mean number of MM by infectious episode: 1.66 [SD=1.37], max=30). In excluded centers, type of infections, microbiological data, surgical and medical management were comparable to those in included centers, but with a significantly higher amount of missing data, indicating a lower reliability of data. The majority of the BJI presented concerned prosthetic joint infections (PJI), and 16,370 infectious episodes (57.7%) involved foreign device infection (Figure 1). The number of infectious episodes presented each year increased over the study period from 3,711 in 2014 to 6,047 in 2019 (Supplemental files, Appendix 1).

About two-third of the cases were cBJI (Table 1). Considering the type of the BJI classified as complex, multiple infections (445/537: 82.9%) and septic pseudarthrosis (1,039/1,454: 71.5%) had the highest rate of complexity (Figure 1). A comorbid condition was the most prevalent criteria of complexity (9,365 infectious episodes) and BJI were considered as complex with a mean of 1.54 (SD=0.76) criteria of complexity (9,466 infectious episodes with 2 or more criteria). These rates remained stable over years, without significant trend among different criteria.

A microbiological documentation was recorded for 19,574 infectious episodes (69.0%). Microbiology was detailed by type of infection in Figure 2 and in Supplemental files, Appendix 2. Microbiology remained stable over time. *Staphylococcus aureus* was the main pathogen in all types of BJI with 8,596 infectious episodes (45.1% of documented episodes). Polymicrobial infection was reported for 6,140 infectious episodes (32.2%), and was often associated with multiple infections (216/537, 40.2%) or osteomyelitis (2,508/8,384, 29.9%). When polymicrobial, mean number of different species was 2.73 (SD:1.10) ranging from 2 to 15. Resistant microorganisms were involved in 3,977 documented infectious episodes (20.9%), and were significantly associated with foreign device (22.1% vs 17,8%, p<0.001) and multiple infections (37.2% vs 19.9%, p<0.001). Their prevalence remained stable over time.

Detailed advised surgical procedures are resumed in Appendix 3 (Supplemental files). Surgical procedures were advised for 23,768 infectious episodes (83.8%), mainly cleaning and device removal surgery (9,678/23,768 and 9,818/23,768, respectively). An antibiotic treatment was proposed for 23,984 infectious episodes (84.6%) (Table 2). For the others, several reasons may have conducted to the absence of antimicrobial therapy: 1/advice for cessation (end of treatment, post-second stage of a two-stage exchange, amputation, creation of effective drain fistulae); and 2/ to a lower extent absence of confirmed infection. Among the detailed antibiotic treatment proposals (22,482 infectious episodes), a combination was advised in 19,152 infectious episodes (85.2%). During one infectious episode, patients could have been presented several times in MM with different antibiotic therapies proposed (i.e. for microbiologic adaptation, previous failure etc.). At the MM level, Beta-lactams were the most widely used class of antibiotics with 26,200 prescriptions out of the 39,271 MM with a proposed antibiotic therapy (66.7%). Antibiotics most used were broad spectrum beta-lactams (piperacilline/tazobactam and cefepime, accounting for 17% and 10% of total number of MM, respectively), then amoxicillin (7.7%), ceftriaxone (5.8%), cefazolin (5.3%), amoxicillin/clavulanate (4.2%) and cloxacillin (3.1%). Other main classes were quinolones (12,498 MM), glycopeptides (9,867 MM) and rifampicin (9,269 MM) (Supplemental files, Appendix 4). The class of antibiotics used according to the main micro-organisms was detailed in Supplemental files, Appendix 5. Notably, fluoroquinolones-rifampicin

combination was advised after 5,827 MM, including 3,131 infections due to staphylococci, and 1,786 polymicrobial infections.

Prosthetic joint infections

In total, including multiple sites infections and vertebral prosthesis, 12,125 episodes of PJI were presented, and involved mainly hip (6,458 episodes) and knee (4,840 episodes) (Figure 1). Considering individually every hip or knee PJI, infections were considered as complex in 4,310 (66.7%) and 3,357 episodes (69.3%), due to previous management failure in 2,065 (32.0%) and 1,833 episodes (37.9%), and/or to complex surgery in 1,719 (26.6%), and 1,572 episodes (32.5%), respectively. The acute, chronic or hematogenous character of infection was not recorded in the database. Microbiological documentation was notified in 4,532 hip PJIs (70.2%) and 3,326 knee PJIs (68.7%) episodes with predominance of Staphylococcus aureus (1,698 and 1,276), Coagulase negative staphylococci (1,491 and 1,175) and polymicrobial infections (1,024 and 679). Microbiology was similar between both localizations except for Enterobacteriaceae (853; 13.2% vs 511; 10.6%, p<0.001), anaerobic bacteria (435; 6.7% vs 228; 4.7%, p<0.001), and streptococci (542; 8.4% vs 531; 11.0%, p<0.001). Trends remained stable over time (Figure 3). Medical management was similar between hip or knee PJIs and depended of microbiological findings. During the study period, we noticed a significant rise both in single antibiotic therapies and multiple combinations of antibiotics (3 antibiotics or more), associated with a significant decrease of non-documented treatment (Figure 3). Rifampicin was used in 30.1% of episodes, in association with quinolones in 18.2%. A long-term suppressive antibiotic treatment was advised in 4.6% of episodes, after an initial "standard" 6-to-12 weeks therapy. It was prescribed as a palliative treatment, usually for at least 6 months and often for life, as a single molecule. The main antibiotics advised were cyclins (doxycycline and minocyclin). Other antibiotics used were cotrimoxazole, amoxicillin, pristinamycine, clindamycin, depending on the susceptibility of

micro-organisms. Considering surgical management, DAIR (debridement, antibiotics and implant retention) was proposed for 1,671 (25.9%) and 1,275 (26.3%) episodes, whereas one-stage exchange for 1,979 (30.6%) and 1,383 (28.6%) episodes, and two-stage exchange for 860 (13.3%) and 737 (15.2%) episodes. There was no significant trend for these procedures during the study period (Figure 3). Coverture procedure, arthrodesis, or amputation were proposed mainly for knee PJI (239 vs 20; 174 vs 10; 132 vs 22, respectively, p<0.001), whereas joint resection was mainly advised for hip PJI (117 vs 22, p<0.001). In total, 1.271 patients (11.6%) had several procedures. Among them, when DAIR was the first option (256), one- or two-stage revisions were performed in 151 (59.0%) and 122 patients (47.7%), respectively (both for 17 patients).

Discussion

Main results

The CRIOAc network has been set up to provide access to the best care using the specialized multidisciplinary experience of chosen centers for patients presenting with complex BJI across the country (1,11). If the definition of complexity is not widely recognized, it corresponds with higher health costs and complications (1). Due to comorbidities, difficult-to-treat micro-organisms, previous failure or complex surgical management, the recognition of a complex BJI should lead to refer the patient to a specialized multidisciplinary team in order to optimize his care. A detailed description of these infections may permit to improve their surveillance and management.

The nationwide registry from this network recorded a large amount of data for various types of BJI with a mean of 5,726 new infectious episodes each year (SD=870) from 2014 to 2019. Most of them were qualified as complex, due to comorbid conditions, previous treatment failure, need for complex surgical procedures or due to resistant or atypical microorganisms. This definition of complexity has previously shown to be poorly reproducible outside of a multidisciplinary approach (15). A scoring-tool deducted from this registry could be useful to improve the homogeneity of the definition for cBJI.

This cohort was not designed as a surveillance tool for BJI and was mainly dedicated to most complex situations, not permitting an exhaustive record of BJI. However, with 41% of all infectious episodes presented in reference center (14,085 individual episodes from 2014 to 2019 considering the entire database, a mean of 2,711 infectious episodes/year, and 3,716 episodes in 2019), PJI from the registry represented a large proportion of estimated PJI in France during the study period. Indeed, total hip arthroplasties increased from 128,564 in 2009 to 153,128 in 2019 and total knee arthroplasties increased from 71,476 in 2009 to

115,591 in 2019 (16), mostly performed for osteoarthritis (17,18). With an estimated PJI incidence of 2.3% person-year (19), one could expect about 6,000 episodes each year. There is no other longitudinal cohort dedicated to BJI nor PJI in France. Thus, as a prospective multicenter cohort with more than 5,000 new infectious episodes each year, this registry is a unique opportunity to monitor trends in epidemiology and management of BJI and PJI in France. For example, monitoring temporal trends in the rate of complexity for previous failures could be a useful tool to monitor the overall effectiveness of the CRIOAc network in its assignment of training and local networking. Indeed, although it remained stable from 2014 to 2019, a relative decrease of these complex infections for failure could signify a better overall management of primary BJIs.

If the French Society of Orthopedics set up a national cohort of total hip arthroplasties in 2007, this registry does not detail characteristics and management of PJIs (20). Another source of information resides in large population-based epidemiological studies with data extracted from medical information systems (1,19). These studies have a high potential for exhaustivity and permit a good estimation of BJI incidence. For this purpose, they have recently been chosen for semi-automated routine surveillance of hip and knee PJI in France (21). However, some comorbidities, microbiology and detailed management are not well encoded in hospital discharge databases and may not be monitored by this tool (19,22). Thus, the French registry of CRIOACs could complete this surveillance tool providing more detailed data, particularly for most complex cases. Furthermore, the registry provides information on other rare BJIs which are poorly studied elsewhere (septic pseudarthrosis, chronic osteomyelitis, vertebral infections). Due to its size, this cohort can also detect infections due to atypical or rare microorganisms and permits to investigate them more precisely by returning to patient records.

This study has some limitations. As previously described (12), the registry was not originally designed for epidemiological studies but as an activity audit tool, with consequent heterogeneity in data-filling. However, data-quality analysis showed acceptable parameters. Furthermore, comparison with other cohorts from the literature showed consistent results indicating acceptable reliability. Indeed, considering PJI, comorbidities (23,24) and microbiology (7,25) were comparable to other international cohorts. In our registry hip infections accounted for 53% and knee for 39% of the PJIs, in the opposite direction to some other studies. This is mainly due to the predominance in France of hip arthroplasties compared to knee arthroplasties in a ratio of 2 to 1 (19). As this registry captures approximately 40% of all prosthetic joint infections, it appears to be a good proxy of national epidemiology. As previously reported (12), categorical data for comorbid conditions did not contain missing data because of the type of data-entry in the e-CRF: only positive data were filled without distinction between negative or missing data: considering it as negative offered better consistency of data than considering it as missing. Conversely, continuous variables like precise height and weight, CRP, and creatinine level were not retained for analysis due to a too high amount of missing data. Unfortunately, in addition to missing data in some variables of interest, some information is lacking in the MM report form (i.e. timing of infection, primary arthroplasty indication, precise antimicrobial susceptibilities of microorganisms). However, this information is often detailed in unstructured data and natural language processing could help extracting informative data. In parallel, better homogenizing data filling between centers and monitoring of data quality will facilitate data analysis. A good example is for the methicillin susceptibility of SA: we preferred the notion of "SA with resistance" over "methicillin-resistant SA", because some centers classified as "with resistance" some methicillin-susceptible SA with resistance to oral treatment as quinolones and/or rifampicin. Thus, most of "SA with resistance" are MRSA, but we cannot precise their

exact number. Finally, the lack of systematic follow-up data record prevents tracking of longterm outcome, and only the patients with management failure will be seen again in MM. This introduces recruitment and survival bias which impede proper analysis of outcomes. Currently, a return to patient files is necessary to record these outcome data. The registry facilitates the identification of patients of interest for such retrospective research. But the implementation of systematic follow-up in selected voluntary reference centers could partially resolve this problem in the future.

Conclusion

The French model of structured reference centers for complex BJIs allows optimization of care for BJIs with multidisciplinary management. Introducing the concept of complex BJIs allows to focus on those infections responsible for the most of complications and highest health-costs. The clinical data recorded from these reference centers feed the national registry of CRIOACs, a unique opportunity to draw up a detailed picture of the epidemiology of BJIs in France and to follow on a large scale the trends of these infrequent infections.

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Author's contributions: AL, LB, PA, LGG, SM, TF and the Scientific Committee for Complex Bone and Joint Infections Reference Centers conceived the study protocol. AL, LB, SM, TF, and members of the CRIOAc network included patients in the registry. AL and LGG ensured the statistical analysis. AL, LGG, PA and LB wrote the manuscript. All authors reviewed the final manuscript and proposed significant modifications. *Funding statement:* None of the authors received any industrial grant regarding the current study. The CRIOAC network and the French Registry for cBJI are funded by the *Direction Générale de l'Offre de Soin* (DGOS) / French Ministry of Health. No author has conflict related to the current study.

Members of the Scientific Committee of the CRIOAc network: Pr. Tristan Ferry (Président, Hospices Civils de Lyon, Service de Maladies Infectieuses et Tropicales, Lyon, France), Dr. Simon Marmor (Groupe Hospitalier Diaconesses-Croix Saint Simon, Service d'orthopédie, Paris, France), Pr. Didier Mainard (CHU de Nancy, Service d'Orthopédie, Vandoeuvre-lès-Nancy, France), Pr. Eric Stindel (CHU de Brest, Service d'orthopédie, Brest, France), Pr. Éric Senneville (Hôpital Dron, Service de Maladies Infectieuses et Tropicales, Tourcoing, France), Pr. Andreas Stein (Service de Maladies Infectieuses Tropicales et Infections Chroniques (MITIC), IHU–Méditerranée Infection, Marseille, France), Dr. Pascale Bemer (CHU de Nantes, Service de Bactériologie, Nantes, France), Pr. Véronique Dubois (CHU de Bordeaux, Service de Bactériologie, France)

CRIOAc network collaborators: CRIOAc: Groupe Hospitalier Diaconesses-Croix Saint
Simon, Paris; Dr. Simon Marmor (Orthopedic surgeon, coordinator), Dr. Valérie Zeller
(Infectiologist), Dr. Béate Heym (Microbiologist); AP-HP Hôpital Ambroise-Paré, Boulogne-Billancourt; Dr. Thomas Bauer (Orthopedic surgeon, coordinator), Dr. Aurélien Dinh
(Infectiologist), Dr Anne-Laure Roux (Microbiologist); CHRU de Lille - CH de Tourcoing;
Pr. Éric Senneville (Infectiologist, coordinator), Pr. Henri Migaud (Orthopedic surgeon), Dr.
Caroline Loiez (Microbiologist); CHU de Nancy et Centre Chirurgical Émile Gallé, Nancy;
Pr. Didier Mainard (Orthopedic surgeon, coordinator), Dr Olivier Roche (Orthopedic surgeon), Dr.

Hospices Civils de Lyon, Lyon; Pr. Tristan Ferry (Infectiologist, coordinator), Pr. Sébastien Lustig (Orthopedic surgeon), Pr. Frédéric Laurent (Microbiologist); Assistance Publique des Hôpitaux de Marseille, Marseille; Pr. Andreas Stein (Infectiologist, coordinator), Pr. Jean Noël Argenson (Orthopedic surgeon), Pr. Pierre-Edouard Fournier (Microbiologist); CHU de Tours, Chambray-Lès-Tours; Pr. Louis Bernard (Infectiologist, coordinator), Pr. Philippe Rosset (Orthopedic surgeon), Dr. Anne-Sophie Valentin (Microbiologist); CHU de Rennes, Rennes; Dr. Cédric Arvieux (Infectiologist, coordinator), Pr. Hervé Thomazeau (Orthopedic surgeon), Pr. Anne Jolivet-Gougeon (Microbiologist); CHU de Bordeaux, Bordeaux; Dr Frédéric-Antoine Dauchy (infectiologist, coordinator), Pr Thierry Fabre (orthopedist surgeon), Pr Michel Dupon (infectiologist), Pr Véronique Dubois (microbiologist). Corresponding Centers: CHU de Toulouse, Toulouse; Pr. Jean-Michel Laffosse (Orthopedic surgeon), Pr. Pierre Delobel (Infectiologist, coordinator), Dr. Marion Grare (Microbiologist); Centre Hospitalier de Versailles André Mignot, Le Chesnay; Dr. Philippe Boisrenoult (Orthopedic surgeon, coordinator), Dr. Audrey Therby (Infectiologist), Dr. Béatrice Pangon (Microbiologist); AP-HP Hôpital Lariboisière, Paris; Pr Anne-Claude Crémieux (infectiologist, coordinator), Pr Pascal Bizot (Orthopedic surgeon), Dr. Anne-Lise Munier (Infectiologist), Dr. Hervé Jacquier (Microbiologist); AP-HP Hôpital Pitié-Salpetrière, Paris; Dr Alexandre Bleibtreu (infectiologist, coordinator), Dr Eric Fourniols (orthopedic surgeon), Pr Véronique Aubry (microbiologist) ; AP-HP Hôpital Cochin, Paris; Pr Yannick Allanore (orthopedist surgeon, coordinator), Pr Dominique Salmon (infectiologist), Pr Philippe Anract (orthopedist surgeon), Dr Philippe Morand (microbiologist); CHU Amiens Picardie, Amiens; Dr. Benoit Brunschweiler (Orthopedic surgeon, coordinator), Dr. Cédric Joseph (Infectiologist), Dr. Florence Rousseau (Microbiologist); CHU de Caen, Caen; Dr. Goulven Rochcongar (Orthopedic surgeon), Dr. Jocelyn Michon (Infectiologist, coordinator), Dr. Francois Guerin (Microbiologist); CHU de Rouen, Rouen ; Pr Manuel Etienne (infectiologist,

coordinator), Pr Xavier Roussignol (orthopedist surgeon), Dr Elise Fiaux (infectiologist), Dr Noélie Frebourg (microbiologist); CHU de Besancon, Besancon; Pr. Catherine Chirouze (Infectiologist), Dr. Grégoire Leclerc (Orthopedic surgeon, coordinator), Dr. Isabelle Patry (Microbiologist); Hôpitaux Universitaires de Strasbourg, Illkirch Graffenstaden; Dr Cécile Ronde-Oustau (coordinator), Dr. Jeannot Gaudias (Infectiologist), Pr. Jean-Yves Jenny (Orthopedic surgeon); Dr. Philippe Riegel (Microbiologist); CHU de Reims, Reims; Pr Firouzé Bani-Sadr (infectiologist, coordinator), Dr Saidou Diallo (orthopedic surgeon), Dr Véronique Vernet-Garnier (microbiologist) ; CHU de Grenoble, Grenoble; Dr Patricia Pavese (Infectiologist, coordinator), Pr. Jerôme Tonetti (Orthopedic surgeon), Dr. Sandrine Boisset (Microbiologist); CHU de Clermont-Ferrand, Clermont-Ferrand; Pr. Olivier Lesens (Infectiologist, coordinator), Pr. Stéphane Descamps (Orthopedic surgeon), Dr. Frédéric Robin (Microbiologist); CHU de Nice, Nice; Pr. Christophe Trojani (Orthopedic surgeon, coordinator), Dr Régis Bernard de Dompsure (orthopedist surgeon), Dr. Johan Courjon (Infectiologist), Pr. Raymond Ruimy (Microbiologist); CHU de Nîmes, Nîmes ; Pr Albert Sotto (infectiologist, coordinator), Pr Pascal Kouyoumdjian (orthopedist surgeon), Dr Catherine Lechiche (infectiologist), Pr Jean-Philippe Lavigne (microbiologist) ; CHU de Limoges, Limoges; Dr. Fabrice Fiorenza (Orthopedic surgeon, coordinator), Dr. Hélène Durox (Infectiologist), Dr. Christian Martin (Microbiologist); CHU de Brest, Brest; Pr. Eric Stindel (Orthopedic surgeon, coordinator), Pr. Séverine Ansart (Infectiologist), Dr. Didier Tande (Microbiologist); CHU d'Angers, Angers; Dr. Pierre Abgueguen (Infectiologist, coordinator), Dr Florian Ducellier (Orthopedic surgeon), Dr. Carole Lemarie (Microbiologist); CHU de Poitiers, Poitiers; Pr. France Roblot-Cazenave (Infectiologist, coordinator), Pr. Louis Etienne Gayet (Orthopedic surgeon), Dr. Chloé Plouzeau-Jayle (Microbiologist); CHU de Nantes, Nantes; Dr. Sophie Touchay (Orthopedic surgeon, coordinator), Dr. Nathalie Asseray (Infectiologist), Dr. Pascale Bemer (Microbiologist).

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Table 1: Characteristics of patients

Variables	5	47.00							
		17 328 (61.1 %)		10 998 (38.8 %)			28 365		NA
Age	med [Q25-Q75]	66	[53-77]	64	[50-75]	<0.001	65	[52-76]	0 (0%)
Number of MM	mean [SD]	2.09	[1.81]	1.33	[0.77]	<0.001	1.79	[1.54]	0 (0%)
Number of different sites	mean [SD]	1.15	[0.44]	1.05	[0.24]	<0.001	1.11	[0.38]	0 (0%)
Weight	med [Q25-Q75]	78	[65-90]	77	[65-90]	<0.001	77.2	[65-90]	9080 (32%)
BMI	med [Q25-Q75]	26.8	[23.2-31.2]	26.5	[23.1-30.5]	<0.001	26.7	[23.2-30.9]	11629 (41%)
ASA score	mean [SD]	2.16	[0.85]	2.00	[0.78]	<0.001	2.10	[0.83]	12566 (44.3%)
Male sex	n/%	10 748	62%	6 762	61.5%	0.8	17 534	61.8%	0 (0%)
Multiple comorbidities	n/%	5 728	33.1%	2 448	22.3%	<0.001	8 183	28.9%	0 (0%)
Number of comorbidities	mean [SD]	1.00	[1.16]	0.72	[0.97]	<0.001	0.89	[1.10]	0 (0%)
Diabetes	n/%	3 487	20.1%	1 701	15.5%	<0.001	5 194	18.3%	0 (0%)
Obesity	n/%	4 099	23.7%	2 239	20.4%	0.06	6 345	22.4%	0 (0%)
Горассо	n/%	1 817	10.5%	945	8.6%	0.002	2 763	9.7%	0 (0%)
Alcohol	n/%	778	4.5%	451	4.1%	0.004	1 228	4.3%	0 (0%)
mmunodeficiency	n/%	1 114	6.4%	344	3.1%	<0.001	1 459	5.1%	0 (0%)
Inflammatory disease	n/%	751	4.3%	342	3.1%	0.001	1 093	3.9%	0 (0%)
Paraplegia	n/%	568	3.3%	242	2.2%	0.3	812	2.9%	0 (0%)
Anticoagulation	n/%	1 394	8%	701	6.4%	<0.001	2 095	7.4%	0 (0%)
Neoplasm	n/%	508	2.9%	182	1.7%	<0.001	691	2.4%	0 (0%)
Heart failure	n/%	1 766	10.2%	579	5.3%	<0.001	2 345	8.3%	0 (0%)
Kidney failure	n/%	1 758	10.1%	610	5.5%	<0.001	2 370	8.4%	0 (0%)
Liver disease	n/%	512	3%	163	1.5%	<0.001	674	2.4%	0 (0%)
Dementia	n/%	289	1.7%	203	1.8%	0.2	491	1.7%	0 (0%)
Intracardiac device	n/%	335	1.9%	175	1.6%	0.03	510	1.8%	0 (0%)
Drug intolerance	n/%	1 481	8.5%	635	5.8%	<0.001	2 118	7.5%	0 (0%)
Complex infection	n/%	-	-	-	-		17 328	61.1%	39 (0.1%)

Figure 1: Flow chart of infectious episodes by type of infection

* 80 patients were seen in several reference centers; ** refers to multiple mechanisms and multiple sites; PJI: Prosthetic joint infections; LLE: lower limb extremity, i.e. foot and ankle; SSTI: Skin and soft tissue infection; BJI: bone and joint infections

Figure 2: Microbiology of bone and joint infections presented in multidisciplinary meetings PJI: Prosthetic Joint Infection; H & K PJI: PJI of hip and knee; FD: foreign device; VI: vertebral infections; MSSA: Multi-susceptible *Staphylococcus aureus*; SA-R: *Staphylococcus aureus* with resistance; MS-CoNS: Multi-susceptible Coagulase-negative staphylococci; CoNS-R: Coagulasenegative staphylococci with resistance; EB: Enterobacteriaceae; MREB: EB with resistance; nfNGB: non-fermentative Gram negative bacilli

Table 2: Medical treatment advised

Type of antibiotic treatment advised by type of bone and joint infections, considering individual episodes presented in multidisciplinary meetings. PJI: prosthetic joint infections. Antibiotics not specified: post-operative antibiotic treatment advised, but without precision on which drug should be used.

Antibiotic treatment	Total	PJI	Osteomyelitis	Arthritis	Septic pseudarthrosis	Vertebral infection	Others	Multiple
Number of episodes	28 365	11 812	8 384	1 649	1 454	923	3 606	537
No treatment	3 649 12,9%	1 334 11,3%	1 074 12,8%	215 13,0%	175 12,0%	196 21,2%	612 17,0%	43 8,0%
Antibiotics not specified	1 502 5,3%	638 5,4%	435 5,2%	71 4,3%	68 4,7%	69 7,5%	197 5,5%	24 4,5%
1 antibiotics	3 330 11,7%	1 239 10,5%	920 11,0%	310 18,8%	80 5,5%	101 10,9%	648 18,0%	32 6,0%
2 antibiotics	7 184 25,3%	2 911 24,6%	2 186 26,1%	458 27,8%	358 24,6%	269 29,1%	926 25,7%	76 14,2%
3 antibiotics or more	11 968 42,2%	5 419 45,9%	3 531 42,1%	539 32,7%	753 51,8%	242 26,2%	1 132 31,4%	352 65,5%
Non available	732 2,6%	271 2,3%	238 2,8%	56 3,4%	20 1,4%	46 5,0%	91 2,5%	10 1,9%

Figure 3: Main trends in the management of prosthetic joint infections from 2014 to 2019

Scatterplots of monthly percentages of episodes presenting with the selected variables among prosthetic joint infection episodes. Solid lines correspond to the fitted trend regression analysis; β : coefficients of the regression analysis; P: p-value of the corresponding Mann-Kendall test, p<0.05 are considered as significant.

A: Microbiological documentation: Percentage of episodes due to *Staphylococcus aureus*, to polymicrobial infections and to resistant micro-organisms.

B: Medical treatment advised for each episode: Single therapy, multiple combination therapy (3 antibiotics or more) and unspecified treatments.

C: Surgical procedures advised: Debridement and antibiotic with implant retention (DAIR), one-stage revision and two-stage revision.





