Culture-proven osteoarticular mycoses: an eight-year single-center descriptive study of fungal distribution and antifungal susceptibility trends

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PII: S1201-9712(26)00349-8
DOI: https://doi.org/10.1016/j.ijid.2026.108714
Reference: IJID 108714

To appear in: *International Journal of Infectious Diseases*

Received date: 25 February 2026
Revised date: 9 April 2026
Accepted date: 15 April 2026

Please cite this article as: Charles Gibert , Olivier Dauwalder , Pauline Tirard-Collet , Damien Dupont , Céline Dupieux , Martine Wallon , Anne Conrad , Florent Valour , Jean Menotti , Tristan Ferry , Lyon BJI Study Group, Culture-proven osteoarticular mycoses: an eight-year single-center descriptive study of fungal distribution and antifungal susceptibility trends, *International Journal of Infectious Diseases* (2026), doi: https://doi.org/10.1016/j.ijid.2026.108714

Highlights

- Osteoarticular fungal infections are rare and difficult to manage.
- The type of fungus involved will depend greatly on the clinical context.
- These chronic infections promote the emergence of resistant strains.
- Non culture-based tools (PCR, serology) should be evaluated in these infections.

Type of Manuscript: Original Article

Title:

Culture-proven osteoarticular mycoses: an eight-year single-center descriptive study of fungal distribution and antifungal susceptibility trends

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Keywords: Osteoarticular mycoses, Invasive fungal infections, Antifungal resistance, Prosthetic joint infection

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Number of References: 36

Number of Tables: 4

Number of Figures: 5

Conflict of interests: None declared

Research Funding: None declared

AUTHOR CONTRIBUTIONS

Conceptualization: CG, JM, TF

Methodology: CG, OD, JM, TF

Investigation: CG, TF

Visualization: CG, JM, TF

Project administration: CG, JM, TF

Supervision: JM, TF

Writing – original draft: CG, JM, TF

Writing – review & editing: CG, OD, PTC, CD, DD, MW, AC, FV, JM, TF

ABSTRACT

Objectives

To describe the mycological profile of culture-proven osteoarticular mycoses (OAM) at a 5400-bed university hospital (2017–2024) according to clinical syndromes and assess antifungal resistance trends.

Methods

Adults with deep osteoarticular specimens (bone, joint fluid, prosthetic material) positive by culture were retrospectively included. Isolations within ±15 days were grouped as a sample

batch (SB). Patients were classified into four categories: 'Traumatic injury infection', 'Infection of prostheses and other materials', 'Craniofacial infection' and 'Other infections'. Antifungal susceptibility testing (AST) was performed using gradient strips.

Results

357 patients yielded 1,993 analyzed specimens and 380 SB. Yeasts predominated outside 'Traumatic injury infection' (range from 88.3–96.2%), mainly *Candida albicans* and *Candida parapsilosis*, whereas 'Traumatic injury infection' was mold-dominant (64.0%), chiefly *Aspergillus* and *Fusarium*. AST was available for 306/357 (85.7%) *Candida* isolates; fluconazole resistance was found in 12/36 (33.3%) *Candida glabrata*, 5/67 (7.5%) *Candida parapsilosis,* and 2/21 (9.5%) *Candida tropicalis*. No *Aspergillus* resistance was detected. Recurrence occurred in 18/357 (5.0%) patients; three developed azole resistance.

Conclusions

OAM shows syndrome-specific fungal profiles, supporting syndrome-adapted diagnostic and therapeutic approaches. Although susceptibility profiles were largely stable, resistant and evolving phenotypes justify repeat culture and susceptibility testing during follow-up of these chronic infections.

INTRODUCTION

Osteoarticular mycoses (OAM) are uncommon infections that are difficult to diagnose and manage [1]. These conditions can affect bones and joints and can occur in native bone or in a periprosthetic implant environment [2,3]. In regions outside endemic areas for dimorphic fungi (particularly Blastomycosis and Coccidioidomycosis), the main fungal etiologies are species from the *Candida* and *Aspergillus* genera, although any fungal species capable of growing at human temperature can cause infection [4]. As with bacterial osteoarticular infections, OAMs can occur in several routes of infection, via hematogenous spread from a primary source

located at variable distances, via contiguity from a superficial site of infection, or via direct inoculation, such as in the case of trauma with an open fracture, with exposure to environmental contamination [5,6]. The colonization of fungi on bone surfaces or abiotic surfaces, such as orthopedic implants, is closely linked to biofilm formation. Biofilm formation involves a dynamic process that can be described in four stages: adhesion, accumulation, maturation, and dispersion [6,7]. The production of biofilm by pathogenic fungi also explains the difficulty in treating these invasive infections, as systemic antifungals are less effective on biofilm than on planktonic cells [8].

It is difficult to target a population of at-risk patients, as these pathologies can affect both immunocompromised and immunocompetent patients [4]. Immunocompromised patients may be at risk of developing primary or secondary osteoarticular forms (through hematogenous dissemination after pulmonary localization, for example) [9,10], while immunocompetent patients may develop severe disease following direct inoculation, particularly in cases of road traffic accidents [11]. Thus, depending on the clinical context, the diagnosis of these infections requires the combination of various elements, including clinical signs, imaging, and laboratory tests. Regarding imaging findings, computed tomography (CT) imaging can be used to visualize bone destruction or joint space narrowing, while magnetic resonance imaging (MRI) can be used to visualize focal or diffuse marrow involvement [12]. Regarding microbiological diagnosis, consensus definitions from international societies have been established to define bone, joint, or periprosthetic infections, but these are primarily focused on bacterial infections [13–15]. However, it could be difficult to apply these approaches to fungal organisms, as culture results are not consistently interpreted in the same way as in bacteriology, particularly for filamentous fungi, where a single colony appearing after several days may still be relevant. Moreover, fungal culture using dedicated media, appropriate incubation temperatures, and longer incubation times than those used for bacteria are not systematically performed. Thus, OAM is considered proven in any patient with a positive culture and/or positive histology from bone tissue, synovial fluid, or prostheses [6]. To aid the interpretation of microbiological

cultures of precious samples (joint fluids, bone biopsies), combining a histopathological examination with culture results may be decisive in diagnosing confirmed OAM [16,17]. Given the rarity of these infections and the difficulty of diagnosing them, it could be challenging to conduct studies on large cohorts unless multicenter studies are performed [18].

Our objective was therefore to conduct a single-center retrospective study to describe culture-proven osteoarticular mycoses occurring between 2017 and 2024 in a 5400-bed university teaching hospital, focusing on microbiological data and analyzing trends in antifungal resistance over time.

METHODS

Study design and participant inclusion

This retrospective study was performed at Lyon University Hospitals, with a data collection period from January 1, 2017, to December 31, 2024. All patients for whom one or more deep osteoarticular samples (bone biopsy, bone, joint fluid, prosthetic material) were collected and sent to the microbiology laboratory were considered. Patients over the age of 18 with fungal isolation by culture in at least one deep osteoarticular sample were included in the subsequent analysis. Pediatric cases were excluded because the pediatric subgroup was too small and clinically heterogeneous to allow for a meaningful stratified analysis. Diagnoses made exclusively by molecular detection (whether targeted or panfungal PCR) were not included. Patients for whom the diagnosis of OAM had been ruled out or for whom there was insufficient information were excluded from the analysis, including laboratory contamination (clearly indicated on patient reports), and lack of standard clinical information. Samples that appeared to be superficial but were mistakenly recorded as deep samples were excluded from the analysis. Regarding infections of prosthetic devices, the sample may have been collected intraoperatively during one of the stages of surgical management of a previous potential prosthetic infection. For patients fulfilling the criteria for proven osteoarticular mycosis [6], each

sample batch (SB) was distinguished as corresponding to the isolation period of fungi in the same batch of samples collected within +/- 15 days from previous or next deep osteoarticular sampling.

For each patient and each SB, clinical and microbiological information was collected. Clinical information was extracted from the minimum data provided to the laboratory when the samples were sent, as well as from the medical summaries prepared upon the patient's admission. These included demographic data, anatomical localization of the infection, and hospitalization context. Diabetes status, immunocompromised status (hematologic malignancies, solid organ transplantation, immunosuppressive therapy, long-term corticosteroid therapy), and intensive care unit admission status at the time of sample collection were also extracted from the patients' medical summaries. When these variables were not explicitly documented, they were treated as unavailable. No systematic full chart review was performed, thus, imaging data, including PET-CT, were not captured. Considering the laboratory-based design of our study, we chose to perform a syndromic classification based on information directly derived from the hospital admission records. Four categories were therefore established: "Traumatic infections," which corresponds to direct inoculations or contiguous extension in case of burn patients, "Infections of prostheses and other materials", corresponding to foreign-body associated infections, which may follow perioperative inoculation or later hematogenous seeding, "Craniofacial infections" and "Other infections", which can reflect contiguous spread from adjacent lesions, whereas episodes without a documented local source were categorized as indeterminate/possibly hematogenous. Microbiological information included the total number of samples performed, the number of samples with fungal growth, and the identification of each fungal species with its antifungal susceptibility test (AST) result, if performed.

Microbiological diagnostic methods

Joint fluid samples were collected in Bact/ALERT blood culture bottles (BIOMERIEUX, Marcy l'Etoile, France), BD Bactec Mycosis fungal blood culture bottles (Becton Dickinson, Franklin Lakes, NJ, USA), or sterile BD Vacutainer tubes. Conventional bottles were incubated in a

Virtuo instrument (BIOMERIEUX) for 14 days. If the bottle was detected positive, a direct examination and Gram staining were performed, then the positive bottle was subcultured onto blood agar (COS, BIOMERIEUX), PolyVitex agar (PVX, BIOMERIEUX), and Schaedler agar (SCS, BIOMERIEUX) plates. If fungal elements were visible during direct examination, CHROM ID Candida agar (CAN2, BIOMERIEUX) was also inoculated. The plates were incubated for 5 days. Mycosis bottles were incubated in a FX2000 incubator (Becton Dickinson) for 14 days. If the bottle was detected positive, a direct examination was performed, then the positive bottle was subcultured onto CAN2 agar and Sabouraud agar for 14 days. Fungal growth was monitored daily.

For all other samples collected in sterile containers (bone biopsies, bones, joint fluids, prosthetic materials), two handling procedures could be performed: one for samples sent to the bacteriology laboratory (systematically), and one if samples were sent to the mycology laboratory (specific request from clinicians). When samples were sent to the bacteriology laboratory, bone samples were crushed into ball containers (Ultra-Turrax, Labelians, Nemours, France). All samples were examined after Gram staining. The samples were then manually inoculated onto COS, PVX, and SCS agars and in Schaedler broth. The incubation period was 2 days for COS agar, 5 days for PVX, and 14 days for SCS agar plates and Schaedler broth. When samples were sent directly to the mycology laboratory, after being cut into small pieces, a direct examination using Calcofluor white (Becton Dickinson) staining was performed, followed by inoculation on CAN2 agar and Sabouraud tube agar, which were then incubated for 14 days. Fungal growth was monitored daily.

In the case of growth on agar, identification was performed using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry on a VITEK MS (BIOMERIEUX) using a combination of VITEK MS (3.2 and 3.3 versions) database and Mass Spectrometry Identification (MSI) 2.0 database [19].

AST was performed using antifungal gradient strips (E-test, BIOMERIEUX), according to manufacturer instructions. Minimal inhibitory concentrations (MIC) were interpreted according

to the breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) v12.0 and the note for guidance on rare yeasts (v2024-06-19), when applicable.

Statistical analysis and ethics approval

The study compied with the Declaration of Helsinki and has been authorized by the Institutional Review Board of the Hospices Civils de Lyon (Scientific and Ethical Committee, authorization no. 25-361)

The demographic and microbiological characteristics of the patients were represented as descriptive statistics. The distributions of fungal species were compared according to clinical syndromes and according to the year of isolation. For fungal/antifungal pairs with at least five MIC results per year, corresponding to a minimum of 40 MIC results over the study period, changes in MIC values for a specific fungal/antifungal combination were evaluated over years using a Kruskal-Wallis test, followed, in case of statistically significant differences, by a Dunn's multiple comparison test. Qualitative values were compared using Fisher's exact test. A *p-value* < 0.05 was considered statistically significant. All analyses were performed using Prism 10.5.0 (GraphPad software, Boston, MA, USA).

RESULTS

Study population

Between January 1, 2017, and December 31, 2024, 78 213 samples of bone biopsies, bones, joint fluids, or osteosynthesis material were received at the microbiology laboratory, corresponding to 16 778 patients. This corresponded to 72 955 (93.3%) samples that were sterile or showed only bacterial growth. Four hundred fifty-one patients over the age of 18 had at least one sample with fungal growth, representing a total of 5 145 samples (with and without fungal growth). Samples showing certified laboratory contamination, those incorrectly recorded

as superficial samples, and samples from patients for whom a lack of clinical information prevented analysis were excluded (746 samples from 94 patients). Of the 4 399 initial samples from 357 patients, 1 993 (with and without fungal growth) were ultimately eligible, corresponding to 380 distinct SB of proven OAM. Three hundred thirty-nine patients had one SB, 14 had two SB, three had three SB, and one had four SB (**Figure 1**).

Clinical groups and main microbiological characteristics

The 'Traumatic injury infection' group consisted of 86 patients (24.1%), corresponding to 91 SB (23.9%). The main clinical contexts were open fractures (59 SB), road traffic accidents (with or without open fractures, 26 SB), bone infections following burn injuries (22 SB), and agricultural injury (with or without open fractures, 8 SB). Of these 91 SB, 29 (31.9%) involved a single yeast species, 3 (3.3%) involved multiple yeast species, 30 (33.0%) involved a single mold species, 14 (15.4%) involved multiple mold species, and 15 (16.5%) involved multiple species of yeast(s) and mold(s). The 'Infection of prostheses and other materials' group consisted of 42 patients (11.8%), corresponding to 45 SB (11.8%). Of these 45 SB, 40 (88.9%) involved a single yeast species, three (6.7%) involved multiple yeast species, two (4.4%) involved a single mold species. The 'Craniofacial infection' group consisted of 71 patients (19.9%), corresponding to 78 SB (20.5%). The main clinical contexts were chemotherapy-related osteonecrosis (16 SB) or osteoradionecrosis (10 SB). Of these 78 SB, 55 (70.5%) involved a single yeast species, 15 (19.2%) involved multiple yeast species, five (6.4%) involved a single mold species, two (2.6%) involved multiple mold species, and one (1.3%) involved multiple species of yeast(s) and mold(s). The 'Other infections' group consisted of 158 patients (44.3%), corresponding to 166 SB (43.7%). The main clinical context was contiguous infection following diabetic foot ulcer (50 SB). Of these 166 SB, 143 (86.1%) involved a single yeast species, 16 (9.6%) involved multiple yeast species, six (3.6%) involved a single mold species, and one (0.6%) involved multiple species of yeast(s) and mold(s) (**Table 1**).

In the ‘Traumatic injury infection’ group (n=86), the main sites of infection were the hand (25, 27.5%), the leg (19, 20.9%), and the foot (13, 14.3%). In the ‘Infection of prostheses and other materials’ group (n=42), the main sites of infection were the knee (21, 46.7%) and the hip (18, 40.0%). In the ‘Craniofacial infection’ group (n=71), the main localization of these infections was the mandible (65, 83.3%). Finally, in the ‘Other infections’ group (n=158), the main sites of these infections were the foot (47, 28.3%), the leg (n=22, 13.3%), and the pelvis (20, 12.0%) (**Figure 2** and **Figure 3**).

Fungal distribution

Yeast isolation (mainly *Candida* spp) was predominant in 'Infection of prostheses and other materials' (95.9%), 'Craniofacial infection' (88.3%), and 'Other infections' (96.2%) groups compared to the 'Traumatic injury infection' group (36.0%) ($p<0.0001$), where most infections were due to molds (n=96, 64.0%). In the 'Traumatic injury infection' group, among the molds, *Aspergillus* was the predominant genus (n=31/96, 32.3%), followed by *Fusarium* (n=23/96, 24.0%), then dematiaceous molds (n=18/96, 18.8%), and Mucorales (n=13/96, 13.5%). In the 'Infection of prostheses and other materials' and 'Other infections' groups, *Candida albicans* was the most common species (36.7% and 42.7%, respectively), followed by *Candida parapsilosis* (32.7% and 22.7%, respectively), while in the 'Craniofacial infection' group, *C. albicans* was also the most common species (43.1%), but was followed by *Candida glabrata* (18.6%). The description of the different fungal species found and the comparison of the distributions of these species between each clinical syndrome are indicated in **Table 2** and **Figure 4**.

Figure 5 shows the number of isolates obtained for each fungal genus according to the year of isolation. Analysis of the distribution of *Candida* strains showed no significant difference in the proportion of *C. albicans* strains compared to *Candida* non-*albicans* strains over time ($p=0.46$).

Trend in antifungal resistance over time

AST was performed on 306 of the 357 (85.7%) *Candida* and Candida-like strains, on 13 of the 39 (33.3%) *Aspergillus* strains, and on 7 of the 25 (28%) *Fusarium* strains.

For the study of antifungal resistance, data were only sufficient for *C. albicans* and *C. parapsilosis* for fluconazole and micafungin to analyze the trend between 2017 and 2024. For *Candida albicans*, a median of 15 [range 13-31] MIC values for fluconazole and 15 [range 10-30] MIC values for micafungin were available per year between 2017 and 2024, for a total of 142 and 129 MICs analyzed, respectively. For *C. parapsilosis*, a median of 9 [range 4-12] MIC

values for fluconazole and 9 [range 4-12] MIC values for micafungin were available per year between 2017 and 2024, for a total of 67 and 64 MIC values analyzed, respectively. Some MIC comparisons between different years proved statistically significant in *C. albicans*, but without clinical relevance (**Figure 6**).

In our cohort, among *Candida* strains with EUCAST clinical breakpoints, 12 (33.3%) strains of *C. glabrata*, five (7.5%) strains of *C. parapsilosis* (1 in 2019, 1 in 2021, 1 in 2023, and 2 in 2024), and two (9.5%) strains of *Candida tropicalis* were resistant to fluconazole. These two strains of *C. tropicalis* were also resistant to voriconazole. One strain (0.8%) of *C. albicans*, one strain (1.6%) of *C. parapsilosis*, and one strain (5%) of *C. tropicalis* were resistant to micafungin. One strain of *C. krusei* and three strains of *C. parapsilosis* were resistant to amphotericin B (including 1 *C. parapsilosis* strain that was also resistant to fluconazole) (**Table 3**). None of the strains of *Aspergillus fumigatus* or *Aspergillus flavus* were resistant to any antifungal.

Analysis of patients with recurrences

In our cohort, 18 patients (5.04%) experienced microbiologically documented recurrence, with SB collected at least 15 days apart and yielding fungi. Five patients were classified as ‘Traumatic injury infection’, two as ‘Infection of prostheses and other materials’, five as ‘Craniofacial infections’ and six as ‘Other infections’. Among these 18 patients, the same pathogen was found in the first SB and in subsequent SB in 14 (77.8%) of them. AST data were available and exploitable for eight patients (identical pathogens during each SB). For four patients who had two SB and one patient who had three SB, there was no change in susceptibility to antifungal agents over time. For the last three patients, a shift from a susceptible phenotype to a resistant phenotype for azole antifungals was observed between the initial SB and the secondary SB. A *C. parapsilosis* strain that was initially susceptible to fluconazole became resistant seven weeks after the first SB. A *C. tropicalis* strain that was initially susceptible to increased exposure (I) to fluconazole and voriconazole became resistant 41 weeks after the first SB. Finally, a *C. glabrata* strain, which was initially I to fluconazole,

became resistant from the fourth SB onwards, i.e., 63 weeks (14 months) after the first SB (**Table 4**).

DISCUSSION

The present study highlights that culture-proven OAMs are heterogeneous and strongly shaped by clinical context. The most striking finding was the contrast between trauma-associated infections, in which molds predominated, and non-traumatic syndromes, in which yeasts accounted for the vast majority of isolates. This syndrome-specific distribution has direct practical implications for the interpretation of culture results and for the expected fungal spectrum in different osteoarticular settings. In parallel, AST data showed no major shift in MIC distributions over time for the main *Candida* species-agent combinations evaluated, although resistance and within-patient susceptibility changes were documented in a small number of recurrent cases. Overall, these results suggest that osteoarticular mycoses should be approached as a spectrum of clinico-microbiological syndromes rather than as a uniform infectious category.

In the “traumatic injury infections” group, OAMs were primarily caused by molds, which is consistent with previous data on invasive fungal infections secondary to traumatic injuries (civilian or military injuries) [20,21]. However, we observed more infections involving *Aspergillus* or *Fusarium* than Mucorales [22,23]. This lower isolation rate of Mucorales could be due to the fact that, when samples were sent exclusively to the bacteriology laboratory, bone sample were crushed, which may damage the delicate hyphae of Mucorales and limit growth on agar, whereas cutting biopsies is preferable to achieve higher culture sensitivity [24–26]. Furthermore, our study only included cases confirmed by culture on bone samples, whereas PCR methods specifically targeting the main Mucorales species (*Mucor*, *Rhizopus*, *Rhizomucor*, *Lichteimia*) have become more widespread. Given their fast turnaround time and high sensitivity, the systematic use of these PCR tests could be a valuable addition to a screening strategy for these at-risk patients [27]. The overwhelming majority of cases of infection involving prostheses and other osteosynthesis devices involved yeasts of the

Candida genus, as classically reported in the literature [28]. The most commonly involved species were *C. albicans*, *C. parapsilosis*, and *C. glabrata* (*N. glabratus*), respectively. This distribution was similar in recent multicenter studies and systematic reviews [18,3]. Although *Candida* prosthetic joint infections (CPJI) are difficult to treat and exhibit high failure or recurrence rates (ranging from 0% to 53% across studies [28]), we identified only two patients (4.8%) with recurrence during our eight-year longitudinal follow-up. In one of these patients, the *C. parapsilosis* strain became resistant to fluconazole between the first and second SB, complicating its management, given the occurrence of a second recurrence (three SB in total). Therefore, in the context of these chronic or recurrent infections, it is essential to perform mycological culture whenever new samples are collected, to avoid missing a relapse or the emergence of antifungal resistance. In this regard, the sensitivity of molecular tools (targeted PCR or metagenomics) warrants further evaluation. Interpreting results from these highly sensitive techniques can be challenging due to the potential risk of contamination (particularly from skin flora), but could enable the detection of a resistant population [29,30]. A significant proportion of cases (20.5%) correspond to craniofacial infections, most of which involve the mandible. Fungal infections of the head and neck are rarely reported in the literature; however, when they involve the mandible, *Candida* is usually implicated and these infections often complicate osteoradionecrosis, consistent with our findings [31–33]. Previous studies have also reported increased susceptibility to candidiasis in patients following head and neck radiotherapy, related to alteration in oral flora and an increase in the fungal population [34]. Other localizations (sinuses, orbital roof, etc.) more frequently involve molds (*Aspergillus* and Mucorales) and typically affect immunocompromised patients [35].

The antifungal resistance trend data did not indicate significant change in MICs over time for fluconazole and micafungin in *C. albicans* and *C. parapsilosis* isolates. Moreover, the rate of fluconazole resistance remained low among strains that are usually susceptible (i.e., excluding *C. glabrata/N. glabratus*). The proportion of fluconazole-resistant *C. parapsilosis* in our cohort was 7.5%. One strain was isolated in 2019, one in 2021, one in 2023, and two in 2024. This

population therefore appears to have been spared from the emergence of this resistant subpopulation [36], which is also in line with national data from France (data from the National Reference Center for Invasive Fungal Infections and Antifungals) [37].

Regarding the limitations of our study, we have already mentioned the unfeasibility of formally classifying cases based on the route of infection (direct inoculation, hematogenous spread, spread by contiguity) due to the laboratory-based design of our study. However, our four-category syndromic approach allows us to infer the relevant route of infection, thereby limiting the bias associated with a formal classification of the route, which would be prone to error without exhaustive chart review of each patient's medical record, and maintaining a clinically relevant approach. In addition, the host factors (diabetes, immunocompromised status, and ICU admission) should be interpreted as targeted clinical proxies rather than as a comprehensive phenotypic characterization of the cohort. Furthermore, our study only considered culture results to define infections, in accordance with proven OAM definitions [6]. Given the diversity of clinical manifestations, other diagnostic tools could be evaluated. Although molecular methods have been discussed, no study has yet assessed the measurement of β-D-glucans or galactomannan antigen in joint fluids. Such biomarkers could potentially be useful to rule out the diagnosis (given the high negative predictive value of β-D-glucans) or to provide additional evidence in strongly suspected but culture-negative cases. Histological data and direct microscopic examination of samples were not included in this study but may also be valuable in characterizing infections caused by uncommon fungi. Despite the abundance of our laboratory data on MICs, particularly for *Candida* cases, the design of our study does not allow us to link clinical outcomes to antifungal resistance. Furthermore, in the case of patients with prosthetic infections, it is likely that the complex clinical history plays a significant role in the outcome, requiring a more complex statistical analysis to identify antifungal resistance as a risk factor for poor outcomes in these cases. Finally, due to laboratory workflow constraints, sample processing in the bacteriology laboratory may not be optimal for OAM diagnosis, owing to the shorter agar storage time and the pre-treatment steps

mentioned above. This may have led to an underestimation of the proportion of positive samples per SB, or even of the total number of diagnosed patients.

This project provides a foundation for future research involving a more in-depth analysis of each clinical syndrome, with the aim of identifying risk factors within each population, particularly the impact of bacterial co-infections, and evaluating the influence of antifungal and surgical treatments on patient outcomes. Molecular data on the strains involved in recurrent infections could help determine whether recurrence results from the persistence of the original strain or from infection by a new strain, and to explore potential evolutionary adaptations in pathways related to virulence, biofilm formation, or immune evasion.

In conclusion, this study represents one of the largest single-center cohorts of culture-proven osteoarticular mycoses, highlights strong syndrome-specific fungal distributions, and supports repeated culture and antifungal susceptibility testing in chronic or recurrent infections. Although single center, the relatively large cohort and the inclusion of cases diagnosed through different routine laboratory workflows may enhance the transferability of the main microbiological findings. Further clinically detailed analyses within each syndrome are now needed to refine diagnosis and management.

ACKNOWLEDGEMENTS

Lyon Bone and Joint Study Group (list of collaborators participating to multidisciplinary meetings):

Coordinator: Tristan Ferry. ***Infectious Diseases Specialists***: Tristan Ferry, Florent Valour, Claire Triffault-Filit, Agathe Becker, Anne Conrad, Evelyne Braun, Florence Ader, Isabelle Eberl, Joanna-Isabelle Kurban Bessa Lippman, Lorena Van-Den-Bogaart, Marie Simon, Olivier Bahuaud, Pierre Chauvelot, Sandrine Roux, Sarah Soueges, Sophie Landre, Thomas Perpoint, Clément Javaux, Marie Wan. ***Surgeons***: Cécile Batailler, Sébastien Lustig, Elvire Servien, Gerald Delfosse, Guillaume Mesnard, Jean Baltzer, Julien Erard, Nicolas Cance, Sébastien Martres, Franck Trouillet, Stanislas Gunst, Alexandre Couraudon, Anthony Viste, Fabien Ewald, Jean-Luc Besse, Matthieu Cotte, Philippe Chaudier, Thomas Cuinet, Vianney Derreveaux, Antoine Bertani, Antoine Colas, Frédéric Rongieras, Jean-Baptiste Masson, Léonard Vézole, Maxime Rarchaert, Vincent Pibarot, Aram Gazarian, Arnaud Walch, Christophe Gaillard, Gaetan Vanpoulle, Louis Ducharne, Lyliane Ly, Nael Ben-Hadid, Selma Lahlali, Thibault Druel, Victor Rutka, Alain-Ali Mojallal, Abdulrahman Hashim, Guillaume Henry, Hélène Person, Mathilde Lherm. ***Anesthesiologists***: Audrey Chevreau-Ciliberti, Caroline Macabéo, Frédéric Aubrun, Kaissar Rouhana, Mikhail Dziadzko. ***Microbiologists***: Céline Dupieux, Tiphaine Roussel-Gaillard, Laetitia Beraud, Matthieu CurtilDit-Galin, Ani Horikian, Anne-Lise Maucotel, Camille

Kolenda, Jean-Philippe Rasigade. ***Pathologist***: Alexis Trecourt. ***Imaging***: David Gicquel, Grégoire Vervust, Isabelle Morelec, Jean-Baptiste Pialat, Joris Lavigne, Nicolas Stacoffe. ***Pharmacists & PK/PD specialists***: Agnes Henry, Noémie Vieux, Romain Garreau, Thomas Briot, Sylvain Goutelle. ***Clinical research assistant and database manage***r: Johanna Boulant.

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Table captions

	Traumatic injury infection	Infection of prostheses and other materials	Craniofacial infection	Other infections	Total
Patients	86 (24.1)	42 (11.8)	71 (19.9)	158 (44.3)	357
Age, years, mean ± sd	45.5 ± 20.7	68.2 ±12.7	61.2 ±15.4	60.9 ± 16.5	58.2 ± 18.5
Female	17 (19.8)	19 (45.2)	28 (39.4)	40 (25.3)	104 (29.1)
Clinical characteristics at admission					
Diabetes mellitus	6 (7.0)	14 (33.3)	9 (12.7)	77 (48.7)	106 (29.7)
Immunocompromised[1]	2 (2.3)	4 (9.5)	7 (9.9)	18 (11.4)	31 (8.7)
Intensive care unit admission	40 (46.5)	0	2 (2.8)	26 (16.5)	68 (19.0)
Presumed route of infection					
Direct inoculation	64 (74.4)	0		0	64 (17.9)
Contiguous extension[2]	22 (25.6)	0	71 (100)	63 (39.9)	156 (43.7)
Foreign body associated		42 (100)		0	42 (11.8)
Indeterminate, possible hematogenous		0		95 (60.1)	95 (26.6)
SB	91 (23.9)	45 (11.8)	78 (20.5)	166 (43.7)	380
Number of SB / patients, median (range)	1 (1-2)	1 (1-3)	1 (1-4)	1 (1-3)	1 (1-4)
Road traffic accident	26 (28.6)				26 (6.8)
Burn injury	22 (24.2)				22 (5.8)
Agricultural injury	8 (8.8)				8 (2.1)
Open fracture	59 (64.8)				59 (15.5)
Amputation	12 (13.2)			40 (25.3)	52 (13.7)
Diabetic foot ulcer or vascular necrosis				50 (30.1)	50 (13.2)
Sacral pressure ulcer				20 (12.0)	20 (5.3)
Osteoradionecrosis			10 (12.8)		10 (2.6)
Chemotherapy-related osteonecrosis			16 (20.5)		16 (4.2)
Microbiological findings					
Number of samples per SB, median (range)	6 (1-31)	5 (1-23)	4 (1-10)	3 (1-22)	4 (1-31)

Number of samples with fungal growth per SB, median (range)	2 (1-19)	2 (1-11)	2 (1-8)	2 (1-7)	2 (1-19)
Rate of sample with fungal growth / total samples, median percentage (interquartile range)	33.3 (20-63.3)	62.5 (10.0-100.0)	77.5 (33.3-100.0)	66.7 (33.3-100.0)	55.6 (28.9-100.0)
Single yeast	29 (31.9)	40 (95.2)	55 (70.5)	143 (86.1)	267 (70.3)
Multiple yeasts	3 (3.3)	3 (6.7)	15 (19.2)	16 (9.6)	37 (9.7)
Single mold	30 (33.0)	2 (4.4)	5 (6.4)	6 (3.6)	43 (11.3)
Multiple molds	14 (15.4)	0	2 (2.6)	0	16 (4.2)
Multiple yeasts and molds	15 (16.5)	0	1 (1.3)	1 (0.6)	17 (4.5)

Results are presented as n (%) unless otherwise specified.

[1]Immunocompromised patients included those with hematologic malignancies, patients who had undergone solid organ transplantation, immunosuppressive therapy, as well as patients on long-term, high-dose corticosteroid therapy.

[2]In the traumatic injury group, cases classified as contiguous extension corresponded to burn-related infections

Abbreviations: SB, sample batch

Table 1. Demographics characteristics and main microbiological findings, according to clinical groups of osteoarticular mycoses.

Results are presented as n (%) unless otherwise specified.

[1]Immunocompromised patients included those with hematologic malignancies, patients who had undergone solid organ transplantation, immunosuppressive therapy, as well as patients on long-term, high-dose corticosteroid therapy.

[2]In the traumatic injury group, cases classified as contiguous extension corresponded to burn-related infections

Abbreviations: SB, sample batch

	Traumatic injury infection	Infection of prostheses and other materials	Craniofacial infection	Other infections	p-value	Total
Yeast	54 (36.0)	47 (95.9)	91 (89.2)	178 (96.2)	<0.0001	370 (76.1)
Candida and *Candida-like* species	50 (33.3)	47 (95.9)	89 (87.3)	171 (92.4)	<0.0001	357 (73.5)
Candida albicans	25 (16.7)	18 (36.7)	44 (43.1)	79 (42.7)	<0.0001	166 (34.2)
Candida bracarensis (*Nakaseomyces bracarensis*)	1 (0.7)					1 (0.2)
Candida catenulata (*Diutina catenulata*)				1 (0.5)		1 (0.2)
Candida ciferii (*Trichomonascus ciferrii*)				1 (0.5)		1 (0.2)
Candida dubliniensis	1 (0.7)	1 (2.0)	1 (0.9)	3 (1.6)		6 (1.2)
Candida fermentati				1 (0.5)		1 (0.2)
Candida glabrata (*Nakaseomyces glabratus*)	2 (1.3)	4 (8.2)	19 (18.6)	14 (7.6)	<0.0001	39 (8.0)
Candida inconspicua (*Pichia inconspicua*)		1 (2.0)				1 (0.2)
Candida kefyr (*Kluyveromyces marxianus*)		1 (2.0)	2 (2.0)	4 (2.2)		7 (1.4)
Candida krusei			9 (8.8)	3 (1.6)		12 (2.5)

(*Pichia kudriavzevii*)						
Candida lipolytica (*Yarrowia lipolytica*)				1 (0.5)		1 (0.2)
Candida lusitaniae (*Clavispora lusitaniae*)	4 (2.7)	2 (4.1)	1 (0.9)	2 (1.1)		9 (1.9)
Candida metapsilosis		1 (2.0)	1 (0.9)			2 (0.4)
Candida orthopsilosis		1 (2.0)		1 (0.5)		2 (0.4)
Candida pararugosa (*Wickerhamiella pararugosa*)				1 (0.5)		1 (0.2)
Candida parapsilosis	15 (10.0)	16 (32.7)	5 (4.9)	42 (22.7)	<0.0001	78 (16.0)
Candida spherica (*Kluyveromyces lactis*)			1 (0.9)			1 (0.2)
Candida tropicalis	2 (1.3)	2 (4.1)	6 (5.9)	18 (9.7)	0.02	28 (5.8)
Cryptococcus neoformans				2 (1.1)		2 (0.4)
Geotrichum candidum	1 (0.7)		2 (1.9)	2 (1.1)		5 (1.0)
Malassezia sympodialis				1 (0.5)		1 (0.2)
Malassezia furfur				1 (0.5)		1 (0.2)
Rhodotorula mucilaginosa	1 (0.7)					1 (0.2)
Saccharomyces cerevisiae	1 (0.7)					1 (0.2)
Trichosporon asahii				1 (0.5)		1 (0.2)
Trichosporon dermatis	1 (0.7)					1 (0.2)
Mold	96 (64.0)	2 (4.1)	11 (10.8)	7 (3.8)	<0.0001	116 (23.9)
Aspergillus spp	31 (20.7)	1 (2.0)	5 (4.9)	2 (1.1)	<0.0001	39 (8.0)
Aspergillus calidoustus	2 (1.3)					2 (0.4)
Aspergillus flavus	4 (2.7)		1 (0.9)	1 (0.5)		6 (1.2)
Aspergillus fumigatus	12 (8.0)	1 (2.0)	3 (2.9)	1 (0.5)		17 (3.5)
Aspergillus niger	3 (2.0)					3 (0.6)
Aspergillus terreus	2 (1.3)		1 (0.9)			3 (0.6)
Aspergillus tubingensis	5 (3.3)					5 (1.0)
Aspergillus udagawae	2 (1.3)					2 (0.4)
Aspergillus sp	1 (0.7)					1 (0.2)
Fusarium spp	23 (15.3)		1 (0.9)	1 (0.5)	<0.0001	25 (5.1)
Fusarium falciforme (*Neocosmospora falciformis*)	1 (0.7)			1 (0.5)		2 (0.4)
Fusarium incarnatum-equiseti	2 (1.3)					2 (0.4)
Fusarium keratoplasticum (*Neocosmospora keratoplastica*)	1 (0.7)					1 (0.2)
Fusarium oxysporum complex	4 (2.7)					4 (0.8)
Fusarium solani complex	9 (6.0)		1 (0.9)			10 (2.1)
Fusarium sporothricioides	1 (0.7)					1 (0.2)
Fusarium thapsinum	1 (0.7)					1 (0.2)
Fusarium sp	4 (2.7)					4 (0.8)
Mucorales	13 (8.7)		2 (2.0)	1 (0.5)	0.001	16 (3.3)
Lichteimia corymbifera	2 (1.3)		1 (0.9)			3 (0.6)
Lichteimia spp	1 (0.7)					1 (0.2)
Mucor circinelloides	8 (5.3)					8 (1.6)
Mucor sp	1 (0.7)					1 (0.2)
Rhizopus arrhizus	1 (0.7)		1 (0.9)	1 (0.5)		3 (0.6)
Dematiaceous molds	18 (8.0)				<0.0001	18 (3.7)
Alternaria sp	11 (7.3)					11 (2.3)
Curvularia sp	7 (4.7)					7 (1.4)
Other molds	11 (7.3)	1 (2.0)	3 (2.9)	3 (1.6)	0.093	18 (3.7)
Acremonium sp	1 (0.7)					1 (0.2)
Penicillium sp	2 (1.3)		2 (2.0)			4 (0.8)
Purpureocilium lilacinum	1 (0.7)					1 (0.2)
Scedosporium apiospermum	2 (1.3)			1 (0.5)		3 (0.6)
Scedosporium aurantiacum	1 (0.7)					1 (0.2)
Scedosporium boydii		1 (2.0)	1 (0.9)			2 (0.4)
Talaromyces spp	1 (0.7)					1 (0.2)
Thermoascus sp	1 (0.7)					1 (0.2)
Trichoderma longibrachium	1 (0.7)					1 (0.2)
Trichoderma simmonsi	1 (0.7)					1 (0.2)
Trichophyton interdigitale				1 (0.5)		1 (0.2)
Trichophyton rubrum				1 (0.5)		1 (0.2)
Total	150 (30.9)	49 (10.1)	102 (21.0)	185 (38.1)		486

Results are presented as n (% of column total).

Table 2. Distribution of involved fungal species, according to the clinical classification of osteoarticular mycoses.

Results are presented as n (%).

Table 3. Distribution of antifungal susceptibility patterns among *Candida* species in the cohort

	Fluconazole				Voriconazole			Micafungin			Amphotericin B		
Yeasts	N	S	I	R	N	S	R	N	S	R	N	S	R
Candida albicans	142	142	0	0	51	51		129	128	1	45	45	0
Candida dubliniensis	4	4	0	0	1	1	0	4	4	0	1	1	0
Candida kefyr	5	5	0	0	2	1	1				2	2	0
Candida krusei											3	2	1
Candida glabrata	36	0	24	12				30	30	0	9	9	0
Candida parapsilosis	67	61	1	5	30	30	0	64	63	1	21	18	3
Candida tropicalis	21	18	1	2	10	8	2	20	19	1	8	8	0

Abbreviations: N, number of strains; S: Susceptible; I: susceptible to increased exposure; R: Resistance

Interpretations of minimal inhibitory concentrations were performed using European Committee on Antimicrobial Susceptibility Testing breakpoints v12.0.

Table 3. Distribution of antifungal susceptibility patterns among *Candida* species in the cohort.

Abbreviations: N, number of strains; S: Susceptible; I: susceptible to high doses; R: Resistance Interpretations of minimal inhibitory concentrations were performed using European Committee on Antimicrobial Susceptibility Testing breakpoints v12.0.

Patient	Clinical group	Context	SB 1	1 to 2, delay (weeks)	SB 2	2 to 3, delay (weeks)	SB 3	3 to 4, delay (weeks)	SB 4	Change in AST results ?
1	Traumatic injury infection	Burn injury	*C. albicans* + *A. tubingensis*	3	*C. albicans* + *A. flavus*					No data
2	Other infections	Diabetic foot ulcer	*C. parapsilosis*	10	*F. falciforme*					NA
3	Traumatic injury infection	Burn injury	*A. niger* + *Curvularia sp*	4	*C. albicans*					NA
4	Craniofacial	Post-dental extraction ulcer	*Penicillium sp*	14	*C. glabrata*					NA
5	Other infections	Hematogenous arthritis	*C. tropicalis*	10	*C. tropicalis*					No change
6	Craniofacial	Osteoradionecrosis	*C. albicans* + *C. kefyr*	25	*C. albicans*					No change
7	Traumatic injury infection	Road traffic accident	*M. circinelloides* + *A. fumigatus*	4	*M. circinelloides*					NA
8	Other infections	No data	*C. albicans*	6	*C. albicans*					No data
9	Other infections	Sternum biopsy after cardiac surgery	*C. krusei*	4	*C. krusei*					No change
10	Other infections	Sternum biopsy after cardiac surgery	*C. albicans*	17	*C. albicans*					No change
11	Prosthesis	Total knee prosthesis	*C. parapsilosis*	7	*C. parapsilosis*	5	*C. parapsilosis*			#1: FLC-S #2: FLC-R #3: FLC-R
12	Traumatic injury infection	Road traffic accident	*A. alternata* + *F. solani complex* + *Aspergillus sp*	16	*C. albicans*					NA
13	Other infections	Post-candidemia hematogenous arthritis	*C. tropicalis*	41	*C. tropicalis*	12	*C. tropicalis*			#1: FLC-I / VRC-I #2: FLC-R / VRC-R #3: FLC-R / VRC-R
14	Craniofacial	Osteoradionecrosis	*C. tropicalis*	7	*C. tropicalis*					No data
15	Craniofacial	Osteoradionecrosis	*C. glabrata* + *C. albicans*	24	*C. glabrata*	26	*C. glabrata*	13	*C. glabrata*	For *C. glabrata* #1: FLC-I

									#2: No data #3: FLC-I #4: FLC-R
16	Traumatic injury infection	Open fracture	*S. apiospermum + A. terreus*	11	*S. apiospermum*				No data
17	Craniofacial	Osteoradionecrosis	*C. albicans*	84	*C. albicans* + *C. glabrata* + *C. krusei*				No data
18	Prosthesis	Total hip prosthesis	*C. albicans*	12	*C. albicans*	9	*C. albicans*		No change

Abbreviations: SB: sample batch; NA: not applicable; FLC: Fluconazole; VRC: Voriconazole; S: Susceptible; I: susceptible to high doses; R: Resistance

Table 4. Clinical classification and microbiological characteristics of patients who presented multiple sample batch during the study period.

Abbreviations: SB: sample batch; NA: not applicable; FLC: Fluconazole; VRC: Voriconazole; S: Susceptible; I: susceptible to high doses; R: Resistance

Figure captions

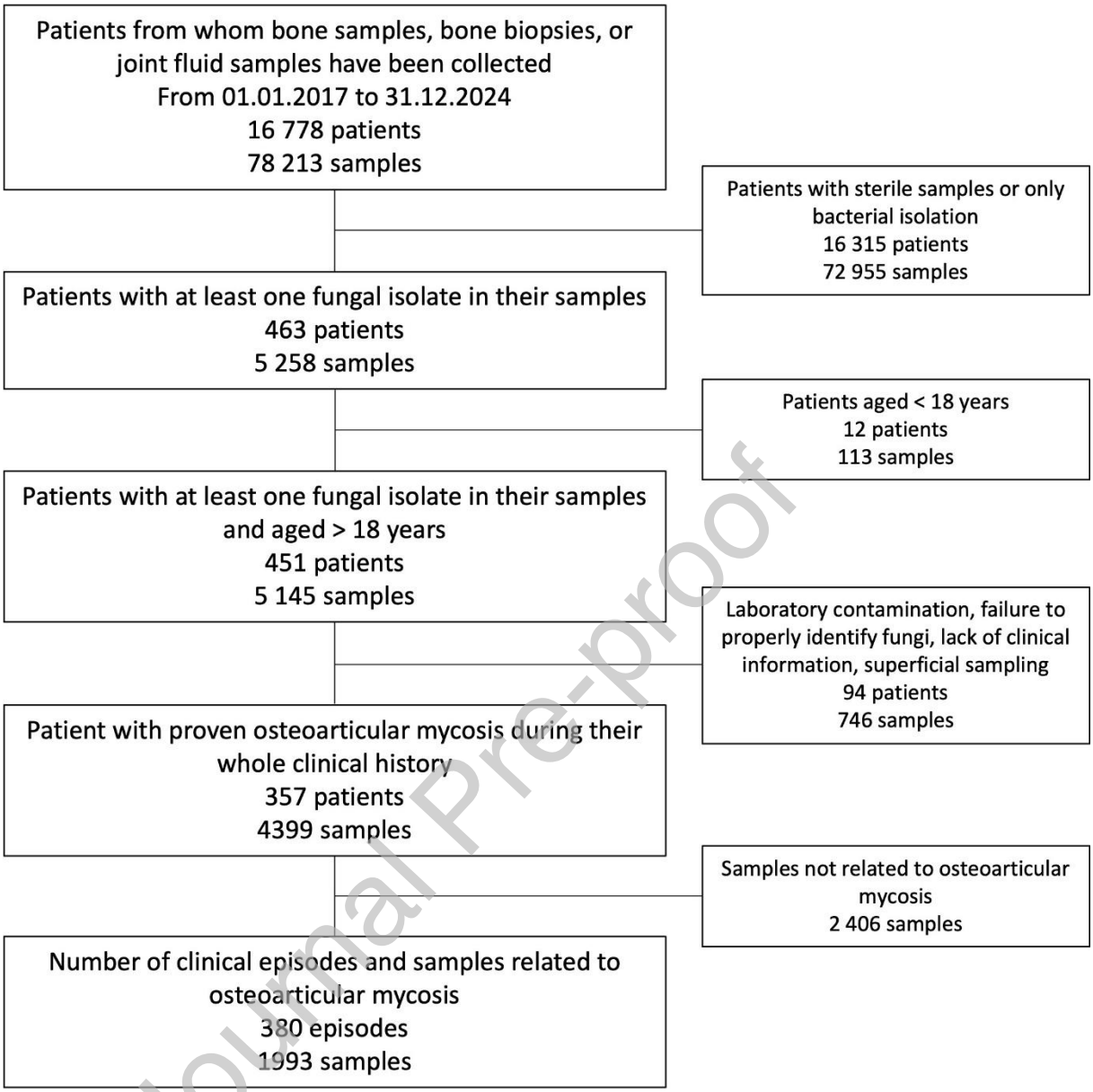

Figure 1. Flowchart of the study.

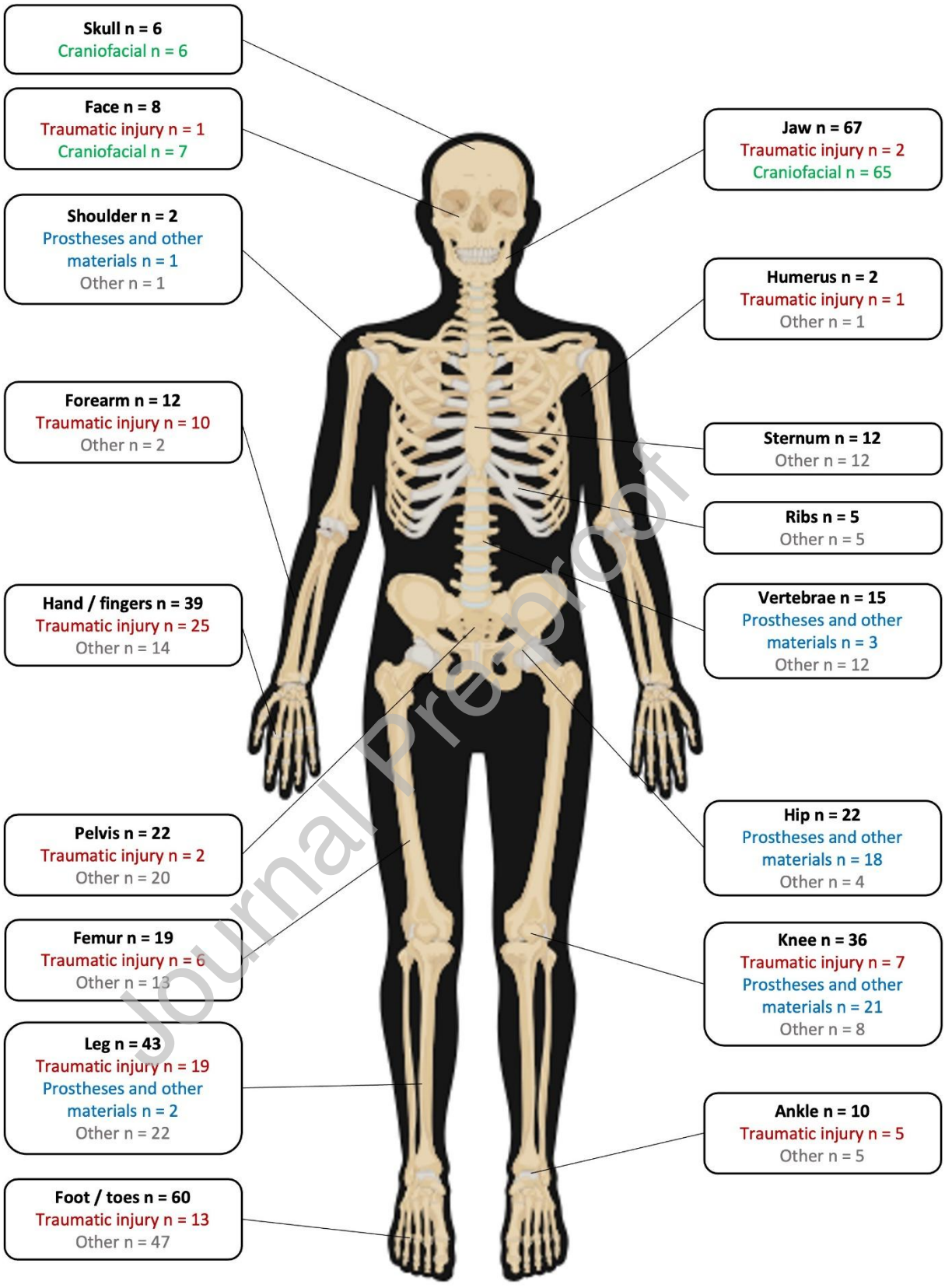

Figure 2. Distribution of infection localizations, according to the clinical classification of osteoarticular mycoses.

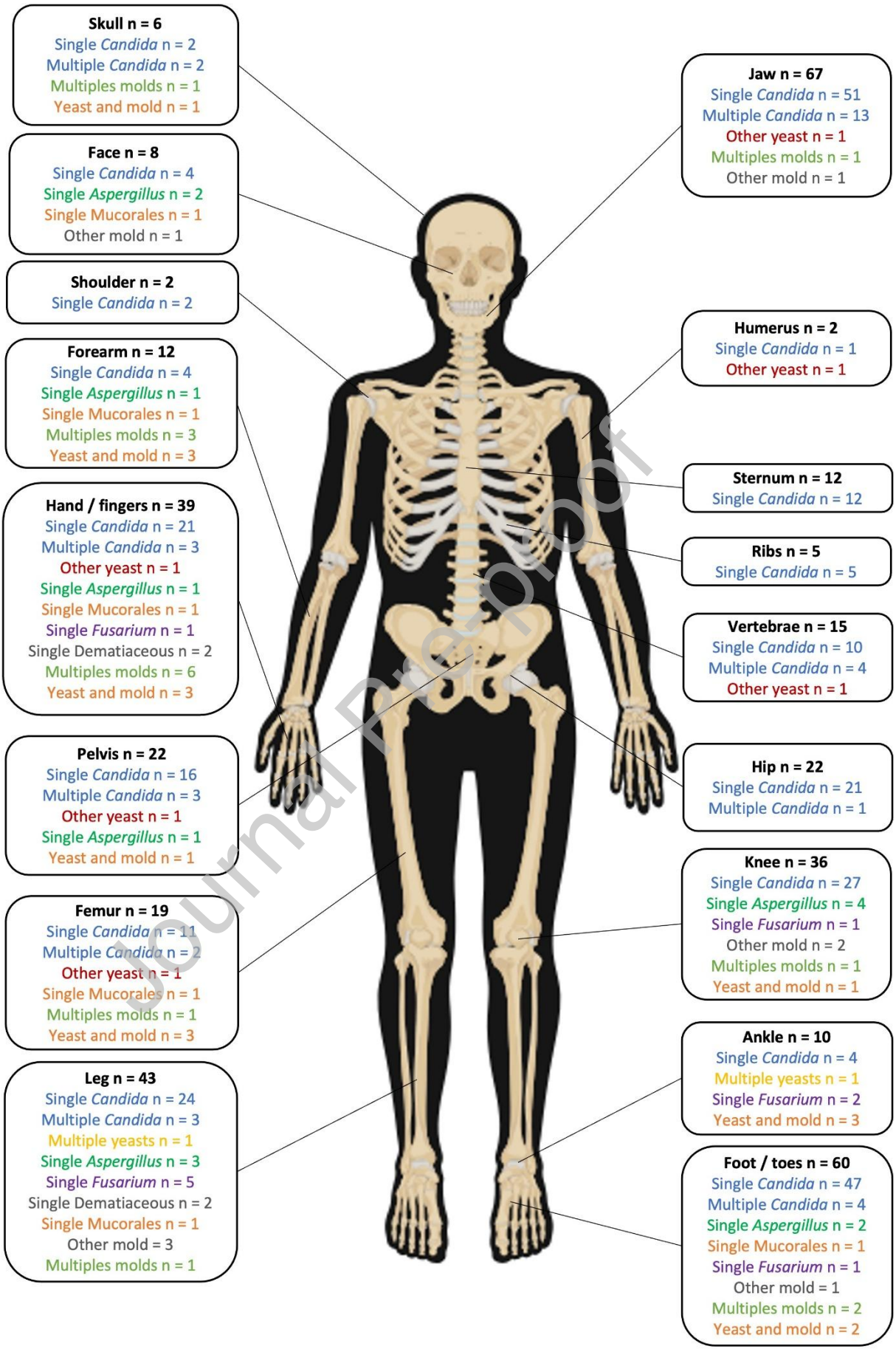

Figure 3. Distribution of infection localizations, according to the type of fungi involved in the

osteoarticular mycoses.

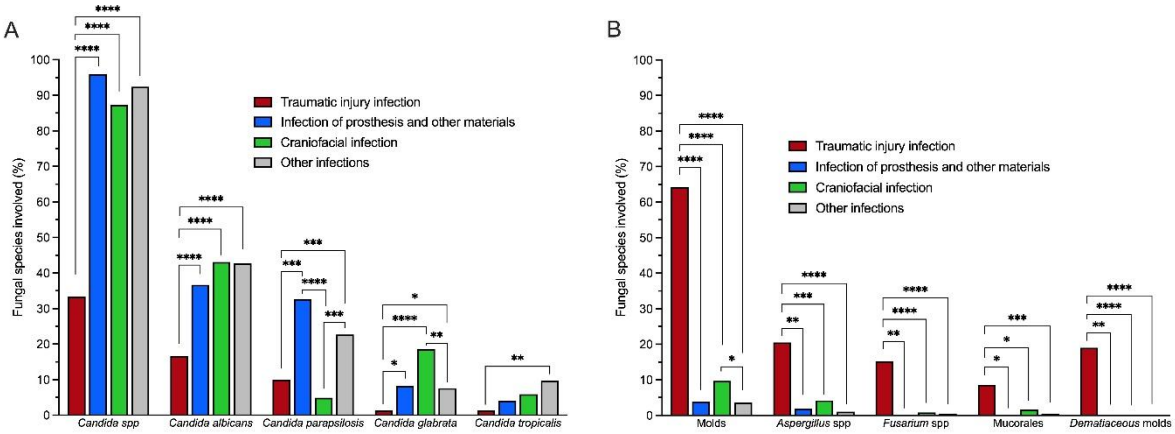

Figure 4. Comparison of isolated fungal species, according to the clinical classification of osteoarticular mycoses, for A/ *Candida* species, B/ Mold species.

*Only statistically significant comparisons were represented. *: p<0.05; ** p<0.01; ***: p<0.001; ****: p<0.0001*

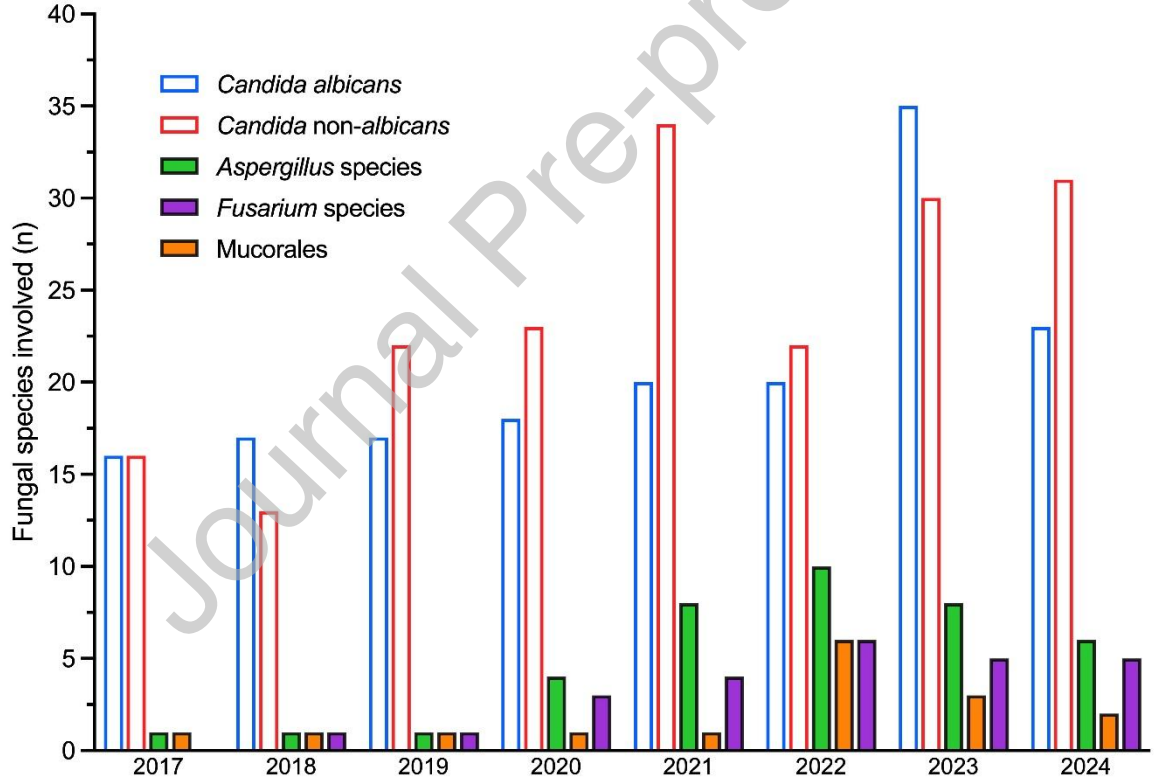

Figure 5. Distribution of the main fungal genera isolated, according to the year of isolation.

Fisher's exact test revealed no significant differences in the distribution of Candida albicans vs Candida non-albicans species over years.

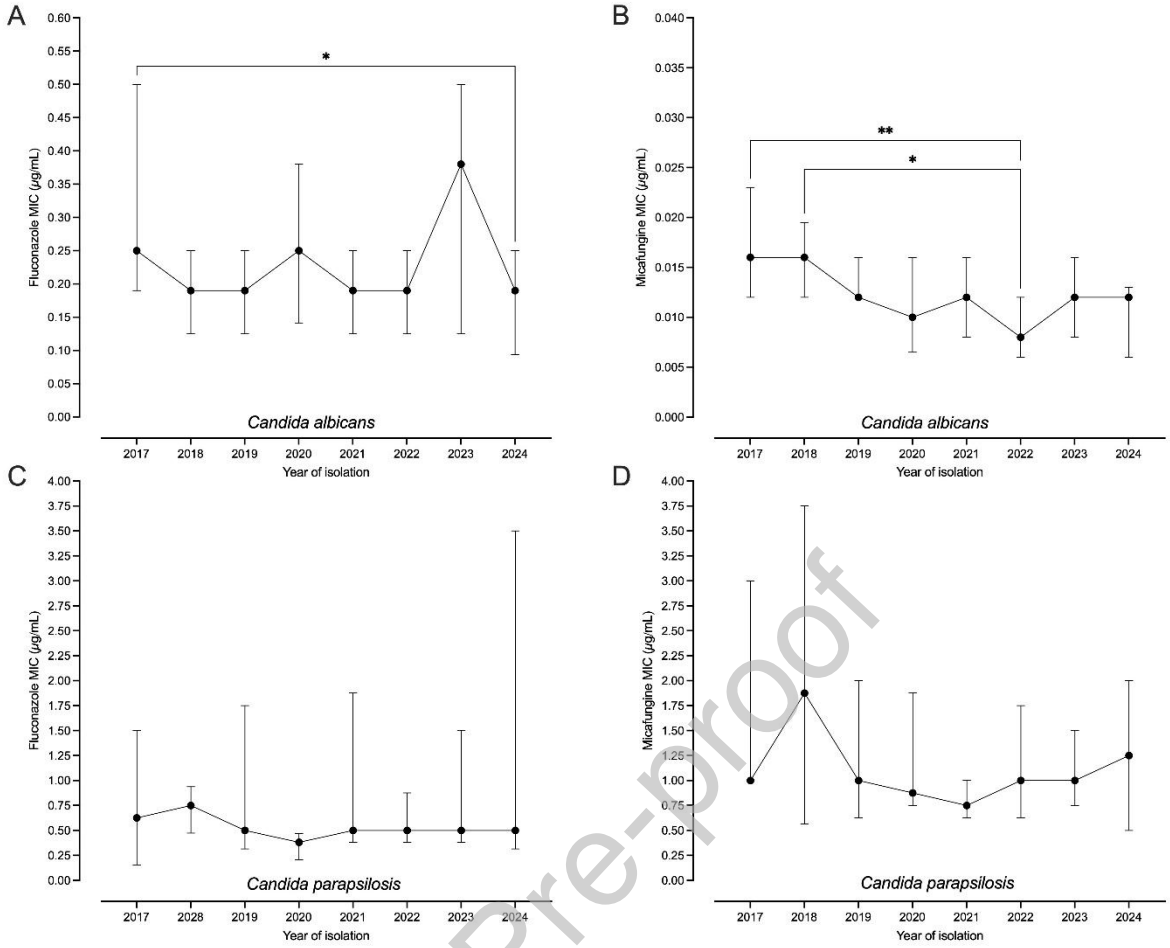

Figure 6. Trends in fluconazole and micafungin minimal inhibitory concentrations (MIC) distribution over years for (A,B) *Candida albicans* and (C,D) *Candida parapsilosis.*

Values are represented as median and their interquartile range.
*Only statistically significant comparison were represented. *: p<0.05; ** p<0.01; ***: p<0.001; ****: p<0.0001*

Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: