Introduction

Total joint arthroplasty (TJA) is the current standard of care for moderate to severe osteoarthritis (OA).2,7 While the complications are uncommon events, with surgical success between 80% and 100%, periprosthetic joint infection (PJI) is the most difficult and dreadful possible consequence of the surgery.1,9 Given that TJA numbers are expected to grow in the next 10 years based on the prediction of the United States,7 infections will be more commonly seen in orthopaedic clinical practice.7,8 In addition, it is unclear if the incidence per person-joint-years is increasing or not,8 but just the absolute number of PJI predicted to rise, together with the need for specialized and expert management, should be a reason for a major focus of high-quality research on the topic.

Most of the etiological strains, accounting for over 98% of PJI, are bacterial species, with Staphylococcus aureus and Coagulase-negative staphylococci present in between 50% and 60% of all PJIs. Fungi, though rare, can also cause PJI in 1%–2% of cases and can be challenging to manage. The management of this uncommon but complex condition is challenging due to the absence of a consistent algorithm. Diagnosis of fungal PJI is difficult as isolation of the organisms by traditional culture may take a long time, and some of the culture-negative PJI can be caused by fungal organisms. In recent years, the introduction of next-generation sequencing has provided opportunity for isolation of the infective organisms in culture-negative PJI cases. The suggested treatment is based on consensus and includes operative and non-operative measures. Two-stage revision surgery is the most reliable surgical option for chronic PJI caused by fungi. Pharmacological therapy with antifungal agents is required for a long period of time with antibiotics and included to cover superinfections with bacterial species. The aim of this review article is to report the most up-to-date information on the diagnosis and treatment of fungal PJI with the intention of providing clear guidance to clinicians, researchers and surgeons.

Fungal periprosthetic joint infection: Rare but challenging problem

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Abstract

Periprosthetic joint infection (PJI) is the most difficult complication following total joint arthroplasty. Most of the etiological strains, accounting for over 98% of PJI, are bacterial species, with Staphylococcus aureus and Coagulase-negative staphylococci present in between 50% and 60% of all PJIs. Fungi, though rare, can also cause PJI in 1%–2% of cases and can be challenging to manage. The management of this uncommon but complex condition is challenging due to the absence of a consistent algorithm. Diagnosis of fungal PJI is difficult as isolation of the organisms by traditional culture may take a long time, and some of the culture-negative PJI can be caused by fungal organisms. In recent years, the introduction of next-generation sequencing has provided opportunity for isolation of the infective organisms in culture-negative PJI cases. The suggested treatment is based on consensus and includes operative and non-operative measures. Two-stage revision surgery is the most reliable surgical option for chronic PJI caused by fungi. Pharmacological therapy with antifungal agents is required for a long period of time with antibiotics and included to cover superinfections with bacterial species. The aim of this review article is to report the most up-to-date information on the diagnosis and treatment of fungal PJI with the intention of providing clear guidance to clinicians, researchers and surgeons.

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diagnosis and treatment of fungal PJI, focusing on providing clear guidance to clinicians, researchers and surgeons.

Organism profile

Several species of fungi may cause PJI that includes Candida species in about 80% of cases. However, isolation of a fungus as the predominant species causing the infection does not rule out the presence of bacteria also, and in fact, concomitant bacterial infection is shown to occur in 15%–20% of fungal PJI cases. In addition, the fungi isolated might be influenced by geographic differences, with Candida albicans causing the majority of infections in one multicentre American study (Table 1), and Candida parapsilosis being the most frequently isolated species in a single-center experience from Southeast Asia. Aspergillus species, dimorphic fungi, pigmented yeast, and other filamentous fungi have all been rarely reported in PJs, but based on the available evidence, we can expect difference of their spread around the globe. Thus, it was shown how the geographical area, the local and regional policies and the timeframe observed could change not only the organism profile, but also its incidence periods prevalence.

Understanding the etiology of infections around the globe is recently gaining attention because of their medical and economic burden. However, the evidence of this in PJI is still primitive, although two major PJI referral centers (one in Europe and one in the United States) tested this hypothesis and showed how fungal PJI differ from one country to another. It seems that fungal PJI were almost 8 times more prevalent (0.3% vs. 2.3%, p < 0.001) in the United States than in Europe. Although the overall incidence of infecting organisms in PJI has remained somewhat stable over the years and across the globe, small changes in bacterial/fungi resistance and spreading patterns may have a profound impact on the treatment algorithms in the future.

Infection surveillance might be a crucial instrument in the medical fight against PJI as was shown in other disease outbreaks, and should be performed under international consensus and collaboration. Research and policy efforts should focus the organisms that caused PJI, and specifically atypical and multi-resistant organism to better control their spread and modifications in both developed and developing countries.

Diagnosis

Clinical symptoms of fungal PJI are aspecific and usually subtle. Contrary to bacterial PJI, acute presentation is unlikely. Diagnosis still relies on traditional enriched culture isolation. Given that, fungi are notoriously difficult to isolate in culture due to the need for specialized media that might differ when several species of fungi are considered. The universal media for most fungi is Sabouraud dextrose brain heart infusion (BHI) agar or plain BHI agar. A blood-containing media such as BHI agar with 10% sheep blood improves the sensitivity or recovery of dimorphic fungi. Special media are required, such as birdseed agar for Cryptococcus neoformans, chromogenic agar for Candida, dermatophytes’ test medium for dermatophytes, and long-chain fatty acid supplementation for Malassezia furfur. Second, the traditional duration of culture slowly growing fungi requires 4 weeks or longer, which can ultimately lead to a late diagnosis and an untargeted treatment. Given the shortcomings associated with the use of culture, alternative techniques capable of detecting fungi such as molecular techniques may be used as an adjunct (Table 1).

The vast majority of techniques have focused on the sequencing of the 16S segment, a highly conserved region of bacterial DNA that allows for identification of bacteria at the species level. Thus, many of these techniques are unable to identify fungal organisms. However, sequencing of the internal transcribed spacer segment, a fungal sequence analogous to the 16S segment, demonstrated a sensitivity of approximately 90%, with a turnaround time of a week, a massive improvement over culture. A conventional polymerase chain reaction is performed to amplify the microbial DNA. Forward and reverse primers homologous to the regions flanking the 16S rRNA gene, and the internal transcribed spacer gene are used to identify bacteria and fungi. These two regions are highly conserved regions of the bacterial and fungal genomes, enabling their accurate identification. In recent years, the next-generation sequencing has been utilized to isolate fungal species causing PJI, particularly in culture-negative cases. Serum C-reactive protein and erythrocyte sedimentation rate, joint fluid cell counts and bone scintigraphy have limited value for the diagnosis of fungal PJs, and they provide no information regarding the identity of the infecting organism.

In conclusion, isolation of fungal species causing PJI can be very difficult using the traditional culture. Specialized medium and

### Table 1
Procedures for management of PJs.

| Variables                             | Bacterial PJs                  | Fungal PJs                    |
|---------------------------------------|--------------------------------|--------------------------------|
| Epidemiology                          | 98% of all PJs                 | 1%–2% of all PJs              |
| Most common strain                    | Staphylococcus species         | Candida species               |
| Macroscopic and acute signs of infection (purulence, fistula, etc.) | Commonly present               | Rarely present                |
| Diagnostic approach                   | Culture gold standard          | Targeted culture sensibility <50% |
|                                       | NGS seems to be superior.      | PCR, NGS might be a better option with results up to 90% of sensibility. |
|                                       | Two-stage is the gold standard. | Two-stage plus pre- and post-operation fluconazole/amphotericin B is the SOC by consensus. |
|                                       | DAIR is effective for early acute infection. | Two-stage, single-stage, and antibiotic and antifungal suppression were proved successful in a few cases. |
|                                       | Single-stage is a viable alternative | 75.1% at 5 years with two-stage revision6 |
| Suggested treatment                   |                                 |                                 |
| Success rate                          | 75.1% at 5 years with two-stage revision6 | 78% at 2 years (THA) |
|                                       | 76% at 2 years (TKA)30          |                                 |

**PJI:** periprosthetic joint infections; **PCR:** polymerase chain reaction; **NGS:** next-gen sequencing; **DAIR:** debridement, antibiotics and implant retention; **SOC:** standard of care; **THA:** total hip arthroplasty; **TKA:** total knee arthroplasty.

* According to Delphi consensus definition.

* No consensus on exist on reporting fungal PJI success.

* Free of infection recurrence after treatment. Treatment options vary across the patients.
longer incubation periods are needed to isolate fungi in these circumstances. Thus, in light of the difficulties associated with isolation of fungal organisms, alternative techniques are needed. Techniques capable of detecting fungal organisms, such as next-generation sequencing, may be used as an adjunct in the diagnosis of fungal PJI.

Treatment

The treatment of a confirmed PJI often includes the need for surgical intervention with two-stage exchange arthroplasty being the most preferred mode of the surgical treatment in North America (Table 1). Two-stage exchange arthroplasty is the recommended treatment of fungal PJI and relies on removal of all foreign material and insertion of an antimicrobial-impregnated cement spacer for the purpose of delivering high doses of antimicrobials locally in the interval of time between the resection arthroplasty and subsequent reimplantation. Fluconazole, by both oral and intravenous routes, is currently the treatment of choice for fungal PJI, including those caused by Candida species, which are responsible for the majority of fungal PJI cases. Amphotericin B lipid formulations or echinocandins given intravenously are secondary considerations but may be less well tolerated. Culture data, including antifungal susceptibilities, should be used to guide systemic therapy. Antifungal agents may be added to the spacer. The available agents with elution from methylmethacrylate cement include Amphotericin B and voriconazole. The recent International Consensus Meeting on Orthopedic Infections has made some robust recommendations regarding fungal PJI and other orthopedic infections. It is recommended that systemic treatment should be administered for a minimum of 6 weeks. Following revision, treatment with oral fluconazole 400 mg daily should be continued for 3–6 months, if tolerated. Since patients with fungal PJI are commonly affected by severe comorbidities and inefficient immune response, treatment should be part of a structured and collaborative team approach including internal medicine specialists, infectious disease specialist, clinical microbiologist and the orthopaedic surgeon to lead the efforts.

Conclusions

Fungal PJI is a complex, yet uncommon complication of TJA. Its management should rely on an evidence-based team approach with a joint specialist to lead the diagnostic and the steps of the treatment. Future research should further investigate the features of the main organisms involved, trying to find new approaches to prevent better, diagnose and treat this condition.

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Ethical statement

Not applicable.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Author contributions

Data collection, literature research and original draft preparation were performed by Emanuele Chisari and Feitai Lin. Jun Fei critically revised the draft. The study conception and design is contributed to Javad Parvizi, and the final revision was also made by Javad Parvizi.

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