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Review Article

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.

Introduction

Total joint arthroplasty (TJA) is the current standard of care for moderate to severe osteoarthritis (OA).[1,2] 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.[3–5] Given that TJA numbers are expected to grow in the next 10 years based on the prediction of the United States,[6] 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,[6] 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, while *Streptococci* and *Enterococci* together account for approximately 10% of cases.[8] Fungal PJI is considered atypical and occurs in around 1%–2% of all PJI.[8] After reviewing the literature available on the topic, we retrieved information on over 278 fungal PJI infection cases in the published literature, most of which were collected in case reports/small case series[9–28] and just few in cohort studies with samples of 31 patients.[29,30] Despite being rarely encountered, fungal PJI is still featured by poor prognosis, with some strains resistant to current standard of care, which ultimately lead to arthrodesis, lifelong spacer retention or suppressive medical therapy or even amputation.[30,31] Patients with fungal PJI are believed to be a different type of host with decreased cellular immunity, mostly due to an underlying cause of immunosuppression, such as malignant disease, drug therapies (antineoplastic agents, corticosteroids, or immunosuppressive drugs), overuse or inappropriate use of antibiotics and indwelling catheters (urinary or parenteral hyperalimentation).[13,30,32] Other factors, such as diabetes, tuberculosis, intravenous drug use and acquired immunosuppressive disease are associated with an increased frequency of mycotic infection.[13,30,32] The lack of reliable antifungal medications for systemic and, in particular, local delivery poses a real challenge in pathogen-directed treatment. The aim of this review is to report the most up-to-date evidence on the main organisms' features and the

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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.[29,31] 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.[8,29] 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),[29] and *Candida* parapsilosis being the most frequently isolated species in a single-center experience from Southeast Asia.[31] *Aspergillus* species,[30,33,34] dimorphic fungi,[35,36] pigmented yeast,[29] dematiaceous fungi[29] and other filamentous fungi[37] have all been rarely reported in PJIs, 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.[15]

Understanding the etiology of infections around the globe is recently gaining attention because of their medical and economic burden.[38–40] 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.[15] 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.[15] 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.[15,41,42] Infection surveillance might be a crucial instrument in the medical fight against PJI as was shown in other disease outbreaks[38–40] 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.[32] 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.[43] The universal media for most fungi is Sabouraud dextrose brain heart infusion (BHI) agar or plain BHI agar.[44] 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*.[45] 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).[32]

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.[46–48] 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[49,50] demonstrated a sensitivity of approximately 90%, with a turnaround time of a week, a massive improvement over culture.[51] 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.[52] In recent years, the next-generation sequencing has been utilized to isolate fungal species causing PJI, particularly in culture-negative cases.[53] Serum C-reactive protein and erythrocyte sedimentation rate, joint fluid cell counts and bone scintigraphy have limited value for the diagnosis of fungal PJIs,[54,55] 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 PJIs.

Variables	Bacterial PJIs	Fungal PJIs
Epidemiology	98% of all PJIs	1%–2% of all PJIs
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.
Suggested treatment	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	
Success rate	75.1% at 5 years[a] with two-stage revision[56]	38% at 2 years (THA)
		76% at 2 years (TKA)[b,c,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.
[a] According to Delphi consensus definition.
[b] No consensus on exist on reporting fungal PJI success.
[c] 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).[3,5] Two-stage exchange arthroplasty is the recommended treatment of fungal PJI[32] 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.[32] 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.[32] Antifungal agents may be added to the spacer. The available agents with elution from methylmethcarylate cement include Amphotericn B and voricanazole. The recent International Consensus Meeting on Orthopedic Infections has made some robust recommendations regarding fungal PJI and other orthopedic infections.[32] 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.[32] Since patients with fungal PJI are commonly affected by severe comorbidities and inefficient immune response,[13,30,32] 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.

References

1. Price AJ, Alvand A, Troelsen A, et al. Knee replacement. *Lancet*. 2018;392:1672–1682. https://doi.org/10.1016/S0140-6736(18)32344-4.
2. Ferguson RJ, Palmer AJ, Taylor A, et al. Hip replacement. *Lancet*. 2018;392:1662–1671. https://doi.org/10.1016/S0140-6736(18)31777-X.
3. Kapadia BH, Berg RA, Daley JA, et al. Periprosthetic joint infection. *Lancet*. 2016;387:386–394. https://doi.org/10.1016/S0140-6736(14)61798-0.
4. Parvizi J, Tan TL, Goswami K, et al. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. *J Arthroplasty*. 2018;33:1309–1314. https://doi.org/10.1016/j.arth.2018.02.078.
5. Pulido L, Ghanem E, Joshi A, et al. Periprosthetic joint infection: the incidence, timing, and predisposing factors. *Clin Orthop Relat Res*. 2008;466:1710–1715. https://doi.org/10.1007/s11999-008-0209-4.
6. Sloan M, Premkumar A, Sheth NP. Projected volume of primary total joint arthroplasty in the U.S., 2014 to 2030. *J Bone Joint Surg Am*. 2018;100:1455–1460. https://doi.org/10.2106/JBJS.17.01617.
7. Lenguerrand E, Whitehouse MR, Beswick AD, et al. Description of the rates, trends and surgical burden associated with revision for prosthetic joint infection following primary and revision knee replacements in England and Wales: an analysis of the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. *BMJ Open*. 2017;7, e014056. https://doi.org/10.1136/bmjopen-2016-014056.
8. Tande AJ, Patel R. Prosthetic joint infection. *Clin Microbiol Rev*. 2014;27:302–345. https://doi.org/10.1128/CMR.00111-13.
9. Wiwattanawarang N. Fungal periprosthetic joint infection after total knee arthroplasty. *J Med Assoc Thail*. 2014;97:1358–1363.
10. Wu MH, Hsu KY. Candidal arthritis in revision knee arthroplasty successfully treated with sequential parenteral-oral fluconazole and amphotericin B-loaded cement spacer. *Knee Surg Sports Traumatol Arthrosc*. 2011;19:273–276. https://doi.org/10.1007/s00167-010-1211-4.
11. Phelan DM, Osmon DR, Keating MR, et al. Delayed reimplantation arthroplasty for candidal prosthetic joint infection: a report of 4 cases and review of the literature. *Clin Infect Dis*. 2002;34:930–938. https://doi.org/10.1086/339212.
12. Fukasawa N, Shirakura K. Candida arthritis after total knee arthroplasty - a case of successful treatment without prosthesis removal. *Acta Orthop Scand*. 1997;68:306–307. https://doi.org/10.3109/17453679708996709.
13. Ueng SWN, Lee CY, Hu CC, et al. What is the success of treatment of hip and knee candidal periprosthetic joint infection? *Clin Orthop Relat Res*. 2013;471:3002–3009. https://doi.org/10.1007/s11999-013-3007-6.
14. Gaston G, Ogden J. Candida glabrata periprosthetic infection : a case report and literature review. *J Arthroplasty*. 2004;19:927–930. https://doi.org/10.1016/j.arth.2004.04.012.
15. Aggarwal VK, Bakhshi H, Ecker NU, et al. Organism profile in periprosthetic joint infection: pathogens differ at two arthroplasty infection referral centers in Europe and in the United States. *J Knee Surg*. 2014;27:399–406. https://doi.org/10.1055/s-0033-1364102.
16. Yang SH, Pao JL, Hang YS. Staged reimplantation of total knee arthroplasty after Candida infection. *J Arthroplasty*. 2001;16:529–532. https://doi.org/10.1054/arth.2001.21458.
17. Açikgöz ZC, Şayli U, Avci S, et al. An Extremely uncommon infection: Candida glabrata arthritis after total knee arthroplasty. *Scand J Infect Dis*. 2002;34:394–396. https://doi.org/10.1080/00365540110080232.
18. Graw B, Woolson S, Huddleston J. Candida infection in total knee arthroplasty with successful reimplantation. *J Knee Surg*. 2010;23:169–174. https://doi.org/10.1055/s-0030-1267470.
19. Simonian PT, Brause BD, Wickiewicz TL. Candida infection after total knee arthroplasty. *J Arthroplasty*. 1997;12:825–829. https://doi.org/10.1016/S0883-5403(97)90015-2.
20. Merrer J, Dupont B, Nieszkowska A, et al. Candida albicans prosthetic arthritis treated with fluconazole alone. *J Infect*. 2001;42:208–209. https://doi.org/10.1053/jinf.2001.0819.
21. Hennessy MJ. Infection of a total knee arthroplasty by Candida parapsilosis. A case report of successful treatment by joint reimplantation with a literature review. *Am J Knee Surg*. 1996;9:133–136.
22. Gaston G, Ogden J. Candida glabrata periprosthetic infection: a case report and literature review. *J Arthroplasty*. 2004;19:927–930. https://doi.org/10.1016/j.arth.2004.04.012.
23. Levine M, Rehm SJ, Wilde AH. Infection with Candida albicans of a total knee arthroplasty. Case report and review of the literature. *Clin Orthop Relat Res*. 1988;226:235–239. https://doi.org/10.1097/00003086-198801000-00031.
24. Lim EV, Stern PJ. Candida infection after implant arthroplasty. A case report. *J Bone Joint Surg Am*. 1986;68:143–145. https://doi.org/10.2106/00004623-198668010-00020.
25. Ramamohan N, Zeineh N, Grigoris P, et al. Candida glabrata infection after total hip arthroplasty. *J Infect*. 2001;42:74–76. https://doi.org/10.1053/jinf.2000.0763.

26. Gebauer M, Frommelt L, Achan P, et al. Management of fungal or atypical periprosthetic joint infections. *J J Arthroplasty*. 2014;29:112–114. https://doi.org/10.1016/j.arth.2013.09.049.
27. Brooks DH, Pupparo F. Successful salvage of a primary total knee arthroplasty infected with Candida parapsilosis. *J Arthroplasty*. 1998;13:707–712. https://doi.org/10.1016/S0883-5403(98)80017-X.
28. Anagnostakos K, Kelm J, Schmitt E, et al. Fungal periprosthetic hip and knee joint infections. *J Arthroplasty*. 2012;27:293–298. https://doi.org/10.1016/j.arth.2011.04.044.
29. Azzam K, Parvizi J, Jungkind D, et al. Microbiological, clinical, and surgical features of fungal prosthetic joint infections: a multi-institutional experience. *J Bone Joint Surg Am*. 2009;91:142–149. https://doi.org/10.2106/JBJS.I.00574.
30. Brown TS, Petis SM, Osmon DR, et al. Periprosthetic joint infection with fungal pathogens. *J Arthroplasty*. 2018;33:2605–2612. https://doi.org/10.1016/j.arth.2018.03.003.
31. Hwang BH, Yoon JY, Nam CH, et al. Fungal peri-prosthetic joint infection after primary total knee replacement. *J Bone Joint Surg Br*. 2012;94:656–659. https://doi.org/10.1302/0301-620X.94B5.28125.
32. Belden K, Cao L, Chen J, et al. Hip and knee section, fungal periprosthetic joint infection, diagnosis and treatment: proceedings of international consensus on orthopedic infections. *J Arthroplasty*. 2019;34:387–391. https://doi.org/10.1016/j.arth.2018.09.023.
33. Sidhu MS, Cooper G, Jenkins N, et al. Prosthetic fungal infections. *Bone Joint Lett J*. 2019;101:582–588. https://doi.org/10.1302/0301-620X.101B5.BJJ-2018-1202.R1.
34. Ji B, Zhang X, Xu BY, et al. Single-stage revision for chronic fungal peri-prosthetic joint infection: an average of 5 years of follow-up. *J Arthroplasty*. 2017;32:2523–2530. https://doi.org/10.1016/j.arth.2017.03.030.
35. Koëter S, Jackson RW. Successful total knee arthroplasty in the presence of sporotrichal arthritis. *Knee*. 2006;13:236–237. https://doi.org/10.1016/j.knee.2006.02.004.
36. Austen S, van der Weegen W, Verduin CM, et al. Coccidioidomycosis infection of a total knee arthroplasty in a nonendemic region. *J Arthroplasty*. 2013;28:375. https://doi.org/10.1016/j.arth.2012.05.006.
37. Lackner M, de Man FH, Eygendaal D, et al. Severe prosthetic joint infection in an immunocompetent male patient due to a therapy refractory Pseudallescheria apiosperma. *Mycoses*. 2011;54:22–27. https://doi.org/10.1111/j.1439-0507.2011.02107.x.
38. Ling ML, Apisarnthanarak A, Madriaga G. The burden of healthcare-associated infections in southeast Asia: a systematic literature review and meta-analysis. *Clin Infect Dis*. 2015;60:1690–1699. https://doi.org/10.1093/cid/civ095.
39. Allegranzi B, Kilpatrick C, Storr J, et al. Global infection prevention and control priorities 2018-22: a call for action. *Lancet Global Health*. 2017;5:1178–1180. https://doi.org/10.1016/S2214-109X(17)30427-8.
40. Cassini A, Plachouras D, Eckmanns T, et al. Burden of six healthcare-associated infections on European population health: estimating incidence-based disability-adjusted life years through a population prevalence-based modelling study. *PLoS Med*. 2016;13:1002150. https://doi.org/10.1371/journal.pmed.1002150.
41. Laffer RR, Graber P, Ochsner PE, et al. Outcome of prosthetic knee-associated infection: evaluation of 40 consecutive episodes at a single centre. *Clin Microbiol Infect*. 2006;12:433–439. https://doi.org/10.1111/j.1469-0691.2006.01378.x.
42. Fulkerson E, Della Valle CJ, Wise B, et al. Antibiotic susceptibility of bacteria infecting total joint arthroplasty sites. *J Bone Joint Surg Am*. 2006;88:1231–1237. https://doi.org/10.2106/JBJS.E.00004.
43. Basu S, Bose C, Ojha N, et al. Evolution of bacterial and fungal growth media. *Bioinformation*. 2015;11:182–184. https://doi.org/10.6026/97320630011182.
44. Bosshard PP. Incubation of fungal cultures: how long is long enough? *Mycoses*. 2011;54:539–545. https://doi.org/10.1111/j.1439-0507.2010.01977.x.
45. Williamson MA, Snyder LM, Wallach JB. *Wallach's Interpretation of Diagnostic Tests : Pathways to Arriving at a Clinical Diagnosis*. Philadelphia, PA: Wolters; 2011.
46. Marín M, Garcia-Lechuz JM, Alonso P, et al. Role of universal 16S rRNA gene PCR and sequencing in diagnosis of prosthetic joint infection. *J Clin Microbiol*. 2012;50:583–589. https://doi.org/10.1128/JCM.00170-11.
47. Fihman V, Hannouche D, Bousson V, et al. Improved diagnosis specificity in bone and joint infections using molecular techniques. *J Infect*. 2007;55:510–517. https://doi.org/10.1016/j.jinf.2007.09.001.
48. Gomez E, Cazanave C, Cunningham SA, et al. Prosthetic joint infection diagnosis using broad-range PCR of biofilms dislodged from knee and hip arthroplasty surfaces using sonication. *J Clin Microbiol*. 2012;50:3501–3508. https://doi.org/10.1128/JCM.00834-12.
49. Khot PD, Ko DL, Fredricks DN. Sequencing and analysis of fungal rRNA operons for development of broad-range fungal PCR assays. *Appl Environ Microbiol*. 2009;75:1559–1565. https://doi.org/10.1128/AEM.02383-08.
50. Clarridge JE. Impact of 16S rRNA gene sequence analysis for identification of bacteria on clinical microbiology and infectious diseases. *Clin Microbiol Rev*. 2004;17:840–862. https://doi.org/10.1128/CMR.17.4.840-862.2004.
51. Tarabichi M, Shohat N, Goswami K, et al. Diagnosis of periprosthetic joint infection: the potential of next-generation sequencing. *J Bone Jt Surg Am*. 2018;100:147–154. https://doi.org/10.2106/JBJS.17.00434.
52. Tarabichi M, Shohat N, Goswami K, et al. Can next generation sequencing play a role in detecting pathogens in synovial fluid? *Bone Jt J*. 2018;100:127–133. https://doi.org/10.1302/0301-620X.100B2.BJJ-2017-0531. R2.
53. Goswami K, Parvizi J. Culture-negative periprosthetic joint infection: is there a diagnostic role for next-generation sequencing? *Expert Rev Mol Diagn*. 2020;20:269–272. https://doi.org/10.1080/14737159.2020.1707080.
54. Anagnostakos K, Kelm J, Schmitt E, et al. Fungal periprosthetic hip and knee joint infections. Clinical experience with a 2-stage treatment protocol. *J Arthroplasty*. 2012;27:293–298. https://doi.org/10.1016/j.arth.2011.04.044.
55. Paul J, White SH, Nicholls KM, et al. Prosthetic joint infection due to Candida parapsilosis in the UK: case report and literature review. *Eur J Clin Microbiol Infect Dis*. 1992;11:847–849. https://doi.org/10.1007/BF01960889.
56. Ma CY, Lu YD, Bell KL, et al. Predictors of treatment failure after 2-stage reimplantation for infected total knee arthroplasty: a 2- to 10-year follow-up. *J Arthroplasty*. 2018;33:2234–2239. https://doi.org/10.1016/j.arth.2018.02.007.