Unnecessary Routine Use of Mycobacterial Cultures in Patients With Periprosthetic Joint Infections

Marjorie Golden,1,2 Anne Spichler Moffarah,1 Christopher Kerantzis,2,3 Lee Rubin,2 and Jane O'Bryan3

1Section of Infectious Diseases, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA; 2Department of Laboratory Medicine, Yale New Haven Hospital, New Haven, Connecticut, USA; 3Section of Department of Orthopedics and Rehabilitation, Center for Musculoskeletal Care, Yale University School of Medicine, Yale New Haven Health, New Haven, Connecticut, USA.

Accurate diagnosis ensures appropriate therapy of periprosthetic joint infection (PJI). Since mycobacterial PJI is rare, routine testing is inappropriate. We reviewed hip and knee PJI at our institution over 28 months. Mycobacterial cultures were routinely sent with rare positivity. Mycobacterial cultures should be sent only when there is clinical suspicion.

Keywords. mycobacterial cultures; prosthetic joint infection.

Practice-based guidelines were developed to address variability in medical diagnosis and treatment [1]. Choosing appropriate tests requires a thorough history and understanding of pretest probability. Compliance with guidelines is not universal [2].

Most cases of periprosthetic joint infection (PJI) are caused by bacteria. Less than 1% are caused by fungi and, rarely, by zoonotic organisms or mycobacteria [3–6]. Culture-negative PJI (CNPJI) accounts for about 15% of cases [3–7]. Guidelines published by the Infectious Diseases Society of America (IDSA) and the American Academy of Orthopedic Surgeons (AAOS) direct workup for patients with possible PJI [8,9], including recommendations for preoperative arthrocentesis and collection of multiple intraoperative specimens for bacterial culture.

Since mycobacterial PJI is unusual, routine mycobacterial cultures are not cost effective [10]. AAOS cites a lack of evidence supporting routine mycobacterial cultures and recommends submitting only bacterial cultures from intraoperative specimens along with bacterial culture of sonicate from explanted hardware [8]. IDSA guidelines do not mention routine tissue culture for mycobacteria but specifically state that culture of sonicate fluid is not validated for mycobacteria and should not be routinely ordered [9].

The aim of this study was to assess the frequency of mycobacterial testing from operating room (OR) specimens of patients with known or suspected PJI.

METHODS

Eligible subjects were identified through the Yale Center for Clinical Investigation Joint Data Analytics Team database using specific International Classification of Diseases, Tenth Revision codes for PJI hips and knees.

We retrospectively reviewed charts of 97 patients admitted to Yale New Haven Hospital from 1 September 2017 through 31 December 2019, and meeting criteria for first PJI of the hip or knee. We reviewed OR cultures from all procedures in patients diagnosed with PJI over the course of the study period. We included patients with evidence of infection after primary or revision arthroplasty. Revision arthroplasty could have been done for management of prosthesis failure or reimplantation of a new joint following appropriate treatment of PJI (second stage of a 2-stage procedure). Patients with prior history of PJI, those with PJI managed exclusively as outpatients, and those who had surgery at another institution were excluded.

Abstracted variables included demographics, surgical procedures, tissue cultures submitted (ie, bacterial, mycobacterial, fungal), and number of intraoperative cultures.

PJI was defined using IDSA criteria [9]. CNPJI was diagnosed based on the following criteria: purulence surrounding the prosthesis at surgery, histopathologic evidence of acute inflammation, or cutaneous sinus tract communicating with the prosthesis with negative aerobic and anaerobic cultures [7].

Costs were calculated using variable supply and variable labor estimates as determined by the Yale New Haven Hospital Microbiology Department (personal communication).

All charts were reviewed by 2 authors. Statistical analyses were conducted using SAS Studio (3.8) software. Demographic and clinical characteristics of the sample were summarized using appropriate descriptive statistics.

Ethical Consideration and Patient Consent Statement

This research was approved by the Yale University Institutional Review Board Human Investigation Committee. No patient consent was required. None of the authors have any relevant disclosures.
### RESULTS

Ninety-seven patients were included in the study, with mean age of 69.0 (± 13.4) years (range, 35–97 years). The sample was divided relatively equally by sex (n = 48 male; n = 49 female). Most subjects were White (79.6%) and non-Hispanic (95.9%). Overall, 256 surgical procedures were performed during the study period, ranging from 1 to 10 procedures per patient (median, 2). Intraoperative specimens were always sent for bacterial culture and routinely for mycobacterial culture. Of 97 patients, 91 (93.4%) had ≥1 OR specimens submitted for mycobacterial culture. Overall, a total of 556 mycobacterial cultures were sent.

Table 1 shows the distribution of mycobacterial cultures. Among 29 patients undergoing revision arthroplasty following hardware removal and culture-directed antibiotics, 21 (72.4%) still had mycobacterial cultures sent at time of reimplantation, even though a causative organism(s) had already been identified, hardware had been removed, and culture-directed antibiotics had been prescribed.

Table 1. Summary of Mycobacterial Cultures (N = 97)

| Culture | No. (%) |
|---------|---------|
| Mycobacterial cultures sent | 91/97 (93.4) |
| Mycobacteria isolated | 1/91 (1.1) |
| Preoperative evidence of infection | 58/91 (61.5) |
| Pathogenic organism isolated on prior culture | 50/56 (89.3) |
| Presumptive hematogenous seeding of joint | 5/56 (8.9) |
| Positive Synovasure | 1/56 (1.8) |
| Revision arthroplasty (stage 2 of 2) performed | 29/97 (29.9) |
| Mycobacterial cultures sent | 21/29 (72.4) |
| Revision arthroplasty for prosthesis failure performed | 22/97 (22.7) |
| Mycobacterial cultures sent | 16/22 (72.7) |
| Culture-negative PJI | 4/97 (4.1) |
| Mycobacterial cultures sent | 3/4 (75.0) |

The sole positive mycobacterial culture was deemed a contaminant by the treating physicians. Mycobacterial cultures were sent at the time of revision arthroplasty after causative organism(s) had already been identified, hardware had been removed, and culture-directed antibiotics had been prescribed.

Abbreviation: PJI, periprosthetic joint infection.

The table displays the distribution of mycobacterial cultures. A total of 556 mycobacterial cultures were sent among 97 patients. Among these, 91 (93.4%) had ≥1 OR specimen submitted for mycobacterial culture. Preoperative evidence of infection was present in 58/91 (61.5%) patients. Pathogenic organisms were isolated on prior culture in 50/56 (89.3%) cases, and presumptive hematogenous seeding of the joint was observed in 5/56 (8.9%) cases. Positive Synovasure results were obtained for 1/56 (1.8%) patients. Revision arthroplasty was performed in 29/97 (29.9%) patients, with 21/29 (72.4%) having mycobacterial cultures sent. Revision arthroplasty for prosthesis failure was performed in 22/97 (22.7%) patients, with 16/22 (72.7%) having mycobacterial cultures sent. Culture-negative PJI was observed in 4/97 (4.1%) patients, while 3/4 (75.0%) had mycobacterial cultures sent.

### DISCUSSION

Among patients with PJI, mycobacterial cultures should only be sent in select circumstances, such as patients receiving immunosuppressive therapy and those with CNPJII or failure to respond to antibacterial therapy [3, 4, 10, 11]. In addition, patients with PJI and epidemiologic risk factors for tuberculosis should have specimens sent for mycobacterial culture [12]. A history of trauma, corticosteroid injection, and certain environmental exposures (example: hot tub exposures or gardening) may be considered as risk factors for mycobacterial infection. Mycobacterial cultures are also appropriate in patients with evidence of granulomatous inflammation on histology. Last, given the poor sensitivity of mycobacterial culture from synovial fluid, when mycobacterial infection is suspected, molecular diagnostics may be more appropriate than culture, further challenging the role of routine mycobacterial culture [13].

Given the overall rarity of mycobacterial PJI, Wadey et al proposed an algorithm to guide use of mycobacterial cultures, which resulted in an 80% decrease in unnecessary mycobacterial cultures [10]. Routine AFB cultures, especially in patients where a pathogen has already been isolated, is not an appropriate use of limited resources. This is especially true in the midst of the current coronavirus disease 2019 pandemic, where technician time could be better directed. Mycobacterial cultures can take up limited Biosafety Level 3 space and are labor intensive, since solid media plates are held for 6 weeks and are checked manually by the technologist on a weekly basis [14]. A better use of resources is to identify patients at risk for mycobacterial infections and target them for AFB cultures [15, 16].

Assessing the cost of failure to diagnose a mycobacterial PJI is difficult. Romanò et al [17] attempted to address indirect costs of a missed diagnosis, but their analysis was limited by small sample size (20 patients) and was not conducted in the United States, limiting generalizability. Berbari et al [7] reviewed 60 episodes of CNPJII over 10 years and none had mycobacteria...
isolated. In a retrospective study of 2116 episodes of PJI over 22 years by Marculescu et al [15], 0.3% were caused by *M. tuberculosis*. Nontuberculous mycobacteria such as *M. fortuitum*, *M. chelonei*, and *M. avium-intracellulare* complex (MAC) were rarely isolated [4–6, 11] In this review article, 1 case of MAC PJI was described in the setting of advanced human immunodeficiency virus disease and known disseminated mycobacterial infection [18]. Eid at al reviewed all cases of rapidly growing mycobacteria causing PJI at Mayo Clinic over 38 years and found only 9 episodes (8 patients) [5].

We had only 1 positive mycobacterial culture in our study (MAC), which was deemed a contaminant by the treating physicians. In addition, among the 4 patients in our study with CNPJII where mycobacterial cultures would be expected to have the most utility, it was sent in only 3 patients.

Our cost calculations are likely underestimates, given that none of these variables account for compounded opportunity costs in lost technologist effort toward onboarding new technologies, validating new assays, and training staff, all of which can bring additional revenue and improve patient care. Given the current national shortage of microbiology technologists [19], many hospital laboratories are understaffed, and it would be helpful to reallocate technologist effort for other laboratory testing. Some hospital microbiology laboratories cannot perform AFB testing in-house, and send-out testing may carry additional costs that we have not included in our analysis. Wadey et al estimated a cost to their healthcare system of more than $66,000 to identify 1 patient with mycobacterial PJI [10].

In summary, we found that routine cultures for mycobacteria in patients with PJI are routinely sent, which does not reflect high-value care. This practice may be cultural within the OR environment rather than representing best practice guidelines of major societies, so reeducation of surgeons, OR nurses, and staff will be needed to modify this practice. Use of an algorithm to guide selection of cultures is recommended.

### Notes

**Author contributions.** M. G. and A. S. M. abstracted data from charts and contributed substantially to writing of the manuscript. C. K. contributed substantially to preparation of the manuscript, specifically writing sections about cost benefit analysis as related to the microbiology laboratory. L. R. served as the orthopedic consultant and contributed substantially to writing of the manuscript. J. O. performed statistical analysis and contributed substantially to writing of the manuscript.

**Potential conflicts of interests.** M. G. has received consulting fees from Iterum Pharmaceuticals. L. R. has received consulting fees from DePuySynthes and ConvaTEC, as well as publishing royalties from SLACK Inc and Johns Hopkins University Press. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

### REFERENCES

1. National Academies of Sciences, Engineering and Medicine. Improving diagnosis in health care. Washington, DC: The National Academic Press; 2015.
2. Pronovost PJ. Enhancing physicians’ use of clinical guidelines. JAMA 2013; 310:2501–2.
3. Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev 2014; 27:302–45.
4. Berbari EF, Hanssen AD, Duffy MC, et al. Prosthetic joint infection due to *Mycobacterium tuberculosis*: a case series and review of the literature. Am J Orthop 1998; 27:219–27.
5. Eid AJ, Berbari EF, Sia IG, et al. Prosthetic joint infection due to rapidly growing mycobacteria: report of 8 cases and review of the literature. Clin Infect Dis 2007; 45:687–94.
6. Ramanathan M, Ayoade FA. A case of *Mycobacterium fortuitum* prosthetic joint infection successfully treated medically without prosthesis explantation or joint debridement. BMJ Case Rep 2021; 14:e243675.
7. Berbari EF, Marculescu C, Sia I, et al. Culture-negative prosthetic joint infection. Clin Infect Dis 2007; 45:1113–9.
8. Tubb CC, Polkowksi GG, Krause B. Diagnosis and prevention of periprosthetic joint infections. J Am Acad Orthop Surg 2020; 28:e340–8.
9. Osmon DR, Berbari EF, Berendt AR, et al. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013; 56:1–10.
10. Wadey VM, Huddleston JI, Goodman SB, et al. Use and cost-effectiveness of intraoperative acid-fast bacilli and fungal cultures in assessing infection of joint arthroplasties. J Arthroplasty 2010; 25:1231–4.
11. Henry MW, Miller AO, Kahn B, et al. Prosthetic joint infections secondary to rapidly growing mycobacteria: two case reports and a review of the literature. Infect Dis 2016; 48:453–60.
12. Lo CKL, Chen L, Wood GCA, et al. Management of *Mycobacterium tuberculosis* prosthetic joint infection: 2 cases and literature review. Open Forum Infect Dis 2021; 8:ofab451.
13. Cook VJ, Turenne CY, Wolfe J, et al. Conventional methods versus 16S ribosomal DNA sequencing for identification of nontuberculous mycobacteria: cost analysis. J Clin Microbiol 2003; 41:1010–5.
14. Martín I, Pfiffer GE, Parrish N. *Mycobacterium*: general characteristics, laboratory detection, and staining procedures. In: Manual of Clinical Microbiology, 12th ed. Washington, DC: ASM Press, 562–8; 2019.
15. Marculescu CE, Berbari EF, Cockerill FR III, Osmon DR. Fungi, mycobacteria, zoonotic and other organisms in prosthetic joint infection. Clin Orthop Relat Res 2006; 451:64–72.
16. Yoon HK, Cho SH, Lee DY, et al. A review of the literature on culture-negative periprosthetic joint infection: epidemiology, diagnosis and treatment. Knee Surg Relat Res 2017; 29:155–64.
17. Romanò CL, Trentinaglia MT, De Vecchi E, et al. Cost-benefit analysis of antifilm microbiological techniques for peri-prosthetic joint infection diagnosis. BMC Infect Dis 2018; 18:154.
18. McLaughlin JR, Tierney M, Harris WH. *Mycobacterium avium intracellulare* infection of hip arthroplasties in an AIDS patient. J Bone Joint Surg 1994; 76:498–9.
19. Kaplan RL, Burgess TE. The impending crisis. J Microbiol Biol Educ 2010; 11:140–3.