Systemic Inflammatory Markers and Aspiration Cell Count May Not Differentiate Bacterial From Fungal Prosthetic Infections

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Abstract

Background Fungal periprosthetic joint infections (PJIs) are rare. Fewer than 200 cases have been reported in the literature. The characteristics of systemic inflammatory markers and joint aspirate cell count analysis obtained in patients with fungal PJIs have not been fully assessed. The ability to diagnose involvement of fungal PJI preoperatively may optimize the surgical and medical management of these patients.

Questions/purposes We determined whether preoperative systemic inflammatory markers and total synovial fluid leukocyte count and neutrophil percentage were different between patients with fungal and bacterial PJI.

Methods We reviewed the medical records of 44 patients with culture-positive diagnosed fungal PJIs treated at our institution between January 1, 2002, and December 31,

2011, in this study. This represented 1.2% of the total 3822 PJIs treated at our institution during the study period. The mean values for C-reactive protein, erythrocyte sedimentation rate, leukocyte count, and neutrophil percentage of patients with purely fungal PJIs were compared to those of 59 patients with bacterial PJIs treated by one surgeon during the same time period.

Results The mean erythrocyte sedimentation rate values for fungal and bacterial PJIs were 40 mm/hour (95% CI: 30, 50 mm/hour) and 41 mm/hour (95% CI: 33, 49 mm/hour), respectively ($p = 0.61$). The mean C-reactive protein values for fungal and bacterial PJIs were 42 mg/L (95% CI: 22, 62 mg/L) and 65 mg/L (95% CI: 43, 88 mg/L), respectively ($p = 0.42$). The mean total nucleated leukocyte counts for fungal and bacterial PJIs were 11,928 (95% CI: 3906, 19,950) with 81% (95% CI: 75%, 88%) neutrophils and 36,901 (95% CI: 21,822, 51,921) with 73% (95% CI: 65%, 81%) neutrophils, respectively (leukocyte count: $p = 0.19$; neutrophil percentage: $p = 0.55$).

Conclusions Early detection of fungal PJI is needed, but systemic inflammatory markers and synovial fluid cell count analyses from aspirations do not discriminate whether an infection may be of fungal origin.

Level of Evidence Level IV, diagnostic study. See Instructions for Authors for a complete description of levels of evidence.

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Introduction

Prosthetic joint infections (PJIs) are an extremely costly and detrimental complication of total joint arthroplasty [12]. Optimal management of PJI is dependent on early identification of the offending microorganism(s). Establishing a microbiologic diagnosis of PJI may lead to an

earlier institution of antimicrobial therapy [8, 12]. The vast majority of PJIs are due to a bacterial origin, followed by fungal and mycobacterial. Fungal PJIs represent only 1% of PJIs [4, 5]. Early knowledge of fungus involvement would aid in selecting the appropriate antimicrobial therapy quicker and perhaps yield better treatment outcomes [8].

While synovial fluid leukocyte count, neutrophil percentage, and systemic inflammatory marker levels have been well studied in patients with bacterial PJI, the same have not been established for fungal PJI. Previous reports have established optimal cutoff points for the diagnosis of bacterial PJI of TKAs with a synovial leukocyte count of greater than 1.7×10^3 and a leukocyte differential of greater than 65% neutrophils [8, 10]. While less extensively evaluated, a synovial leukocyte count of 4.2×10^3 has been established as the cutoff for PJI in THAs [8]. Due to the rare nature of fungal PJIs and their propensity for slower culture growth, it would be helpful to be able to identify them based on similar systemic inflammatory marker cutoff points. This would allow the clinician to begin treatment before a formal culture revealed the exact fungus.

We therefore undertook an unmatched case-control study to determine whether preoperative systemic inflammatory markers and joint aspiration leukocyte count and neutrophil percentage were different between patients with fungal and bacterial PJI.

Patients and Methods

After obtaining institutional review board approval, we reviewed the medical records of patients with PJI seen at our institution between January 1, 2002, and December 31, 2011, to identify patients diagnosed with fungal PJI. Three to five cultures were taken in each case and standard culturing technique was used in our microbiology laboratory. We utilized the current Infectious Diseases Society of America guidelines for the definition of a PJI to include only those infections that were deemed not to be contaminants [12].

Forty-four patients were found to have a fungal PJI, which comprised 1.2% of the total PJIs (3822) diagnosed at our institution during the study period. Of these 44 patients, 23 were men. Twenty-three cases involved TKAs and 21 involved THAs. The mean age at the time of diagnosis was 68 years (range, 47–83 years). Of the positive cultures, 32 (73%) were purely fungal and 12 were mixed (bacterial/fungal). There were 10 unique species of fungi cultured. Twenty-two (51%) of the cultures involved the organism *Candida albicans* (Table 1).

Data on preoperative joint aspiration leukocyte count and differential cell count, preoperative systemic inflammatory

Table 1. Cultured microorganisms from 44 cases of fungal prosthetic joint infection

Organism	Number of cases
<i>Candida albicans</i>	22
<i>Candida parapsilosis</i>	10
<i>Candida glabrata</i>	4
<i>Penicillium</i>	2
<i>Candida tropicalis</i>	1
<i>Coccidioides immitis</i>	1
<i>Dematiaceous</i>	1
<i>Paecilomyces</i>	1
<i>Pithomyces</i>	1
<i>Sporothrix schenckii</i>	1

markers, and subsequent surgical management were collected. All 44 of the identified patients had preoperative erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values. Sixteen of the 44 (36%) had a preoperative joint aspiration cell count. Of the 16 patients with a preoperative joint aspiration cell count, 10 had experienced a prior episode of bacterial PJI, 13 had fungal only PJIs, and 12 had infections involving *Candida* species.

The systemic inflammatory values collected on the 32 patients with purely fungal PJI and the joint aspiration data from the 13 patients with purely fungal PJI were compared to 59 patients with bacterial PJI managed by a single surgeon (RS) at the same institution over the same study period. These bacterial PJIs for comparison were all confirmed by multiple intraoperative cultures and consisted of the most commonly cited offending bacteria in the literature, including coagulase-negative *Staphylococcus* species, *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus* species. These were identified using the joint registry database at our institution.

Data were analyzed using the JMP® statistics package (SAS Institute Inc, Cary, NC, USA). A t-test was performed on ESR, CRP, and total nucleated cells to determine whether there was a difference between bacterial and fungal cases. A post hoc power analysis was also calculated to determine the effect of the small sample size. Statistical power was calculated to be 6.5%.

Results

ESR, CRP, and total synovial fluid leukocyte count and neutrophil percentage were not different with the numbers available between patients with fungal PJI and those with bacterial PJI (Table 2). The mean ESR values for fungal and control bacterial PJIs were 40 mm/hour (95% CI: 30, 50 mm/hour) and 41 mm/hour (95% CI: 33, 49 mm/hour),

Table 2. Comparison of systemic inflammatory markers and joint aspiration leukocyte count and neutrophil percentage between fungal and bacterial infections

Variable	Fungal		Bacterial		p value
	Mean	95% CI	Mean	95% CI	
ESR (mm/hour)	40	30, 50	41	33, 49	0.61
CRP (mg/L)	42	22, 62	65	43, 88	0.42
Leukocyte count	11,928	3906, 19,950	36,901	21,822, 51,921	0.19
Neutrophil percentage	81	75, 88	73	65, 81	0.55

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

respectively ($p = 0.61$). The mean CRP values for fungal and bacterial PJIs were 42 mg/L (95% CI: 22, 62 mg/L) and 65 mg/L (95% CI: 43, 88 mg/L), respectively ($p = 0.42$). The mean total synovial fluid leukocyte counts and differential cell counts for the 13 fungal PJIs with joint aspirate leukocyte counts and the bacterial PJIs were 11,928 (95% CI: 3906, 19,950) with 81% (95% CI: 75%, 88%) neutrophils and 36,901 (95% CI: 21,822, 51,921) with 73% (95% CI: 65%, 81%) neutrophils, respectively (leukocyte count: $p = 0.19$, neutrophil percentage: $p = 0.55$).

Discussion

Fungal PJI is rare. It is difficult to differentiate fungal PJI from bacterial PJI based on clinical or epidemiologic factors [5]. The lack of evidence concerning fungal PJI, as well as the lack of diagnostic criteria for detecting fungal PJI in patients with suspected PJI, presents the clinician with a dilemma when presented with a failed prosthetic joint due to a presumed infection [12]. The risk factors include immunocompromise, previous bacterial PJI, and underlying systemic illness, but this is not always the case [1–3, 6, 9]. We therefore determined whether preoperative systemic inflammatory markers and joint aspiration leukocyte count and neutrophil percentage were different between patients with fungal and bacterial PJI.

The limitations of this study stem from the fact that, while it is the largest case series of fungal PJIs reported, it is still a relatively small sample. This is evidenced by the statistical power of 6.5%. While we found no difference in any of the preoperative markers studied, this could be explained as simply having no difference or it could be due to the small sample size, which makes it impossible to detect any difference. Forty percent of the initial cohort had a previously resected knee or hip and therefore were unlikely to be aspirated preoperatively. In addition, a number of infections were diagnosed at the time of surgery through

tissue culture and no aspirate had been performed. Additionally, because 10 of the 16 aspirated cases were in the setting of a previous bacterial PJI, it is impossible to determine whether this finding diluted our ability to detect a difference. Along with this, as with other retrospective studies of this nature, there were many variables, including operating surgeon and antibiotic regimen at the time of culture, which may have biased the results [11]. As this was not analyzed in the present study and would likely have been underpowered, this may warrant further studies into the nature of mixed PJIs and/or subsequent fungal PJIs after an already diagnosed bacterial PJI.

We found that the preoperative systemic inflammatory markers ESR and CRP and the total synovial fluid leukocyte count and neutrophil percentage were not different between fungal and bacterial PJI. The literature supports this difficulty to differentiate bacterial PJI from fungal PJI preoperatively [1–7, 9]. Dutronc et al. [4] pointed out the difficulty in diagnosing a *Candida* PJI due to delay from misidentification as a contaminant. The same authors also noted that standard biologic markers (ESR, CRP) preoperatively provide little information in *Candida* PJI. Lerch et al. [7] reported the specific difficulty of diagnosing *Candida* PJI from a bony specimen. Kuiper et al. [5] recommended that diagnosis of PJI should be based on multiple cultures, and due to the delay in culture growth time, any *Candida* species cultured should be treated as a pathogen.

In conclusion, in this large case series of fungal PJIs, preoperative systemic inflammatory markers and fluid analyses from fungal PJIs were not different from bacterial PJIs or mixed bacterial/fungal PJIs and were unable to differentiate between these infections. Due to the underpowered nature of this study and the rare nature of this type of infection, multicenter collaborations are a possible avenue to further study this question. Therefore, further research is warranted to reveal methods to preoperatively differentiate between fungal and bacterial PJI. When there is a clinical suspicion, fungal and bacterial prosthetic tissue cultures should be obtained in the setting of multiply failed THA or TKA infection.

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