

Revision Total Knee Arthroplasty: Infection Should Be Ruled Out in All Cases

Mohammad R. Rasouli, MD, Armin Aalami Harandi, MD, Bahar Adeli, BA,
James J. Purtill, MD, and Javad Parvizi, MD, FRCS

Abstract: We hypothesized that some aseptic revision total knee arthroplasty failures are indeed caused by occult infection. This prospective study recruited 65 patients undergoing revision total knee arthroplasty. The mean follow-up period was 19 months. Collected synovial fluid was analyzed by Ibis T5000 biosensor (Abbott Molecular Inc, Ill; a multiplex polymerase chain reaction technology). Cases were considered as infected or aseptic based on the surgeon's judgment and Ibis findings. Based on Ibis biosensor, 17 aseptic cases were indeed infected that had been missed. Of these 17 cases, 2 developed infection after the index revision. A considerable number of so-called aseptic failures seem to be occult infections that were not adequately investigated and/or miscategorized as aseptic failure. We recommend that all patients undergoing revision arthroplasty be investigated for periprosthetic joint infection. **Keywords:** revision knee arthroplasty, aseptic failure, periprosthetic joint infection, Ibis T5000 biosensor, diagnosis.

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Periprosthetic joint infection (PJI) that occurs after 1% to 3% of total knee arthroplasties (TKAs) [1,2] is the most common cause of failure after TKA [3-5]. Diagnosis of PJI continues to pose a challenge to the medical community because of lack of a "gold standard" [6]. It is, however, critical that aseptic cases be distinguished from PJI because treatment of these conditions is vastly different [7,8].

History taking, physical examination, and radiographic findings can be similar in PJI and aseptic loosening and may not allow distinction in most cases [7]. Joint aspiration and serologic tests such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually performed during the workup of a patient with suspected PJI. Although a very high sensitivity has been reported for ESR and CRP, these laboratory tests have their own limitations in the diagnosis of PJI [9]. Even intraoperative culture and pathology have limited sensitivity in diagnosis of PJI, particularly in those receiving antibiotics [10,11]. It has been demonstrated that intraoperative culture yields

false-negative results in 6.6% [12] to 17.7% [13] and false-positive results in 13% of cases [14]. Imaging modalities such as nuclear scans (technetium-99, indium-111, gallium) have also been used in diagnosis of PJI, but these tests are also unable to accurately differentiate between aseptic loosening and septic failure after joint arthroplasty [15-17].

One of the main reasons for the inability to isolate the pathogen relates to the presence of a biofilm [8,18] and/or internalization of organism by osteoblasts [19]. Biofilm is a complex structure comprising microorganisms enveloped in macromolecules of glycocalyx and other protective films [18,20]. As a result, it is probable that some of PJIs to be missed and treated as aseptic failure, which subsequently cause recurrent failure [21].

Using molecular techniques may improve the diagnosis of PJI because these methods have high sensitivity and are culture independent [11]. Polymerase chain reaction (PCR) has been used in several studies to diagnose PJI [22-25]. Using a specific PCR or a broad-range (16S ribosomal DNA) PCR, which are respectively able to detect only a single microorganism or previously unknown organisms, is a limitation of these studies. Compared with the specific PCR, the sensitivity and specificity of the broad-range PCR are lower, need subsequent sequencing for bacterial identification, and fail to detect mixed infections [11]. Recently, the Ibis T5000 universal biosensor (Abbott Molecular Inc, Ill) has been introduced as a sensitive and specific method for identification of bacteria, viruses, fungi, and protozoa. The system operates based on a broad-range PCR

From the Rothman Institute of Orthopaedics at Thomas Jefferson University Hospital, Philadelphia, Pennsylvania.

Supplementary material can be found at www.arthroplastyjournal.org.

Submitted June 5, 2011; accepted January 15, 2012.

The Conflict of Interest associated with this article can be found at [doi:10.1016/j.arth.2011.01.019](https://doi.org/10.1016/j.arth.2011.01.019).

Reprint requests: Javad Parvizi, MD, FRCS, 925 Chestnut St, 2nd Floor, Philadelphia, PA 19107.

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0883-5403/2706-0068\$36.00/0

[doi:10.1016/j.arth.2011.01.019](https://doi.org/10.1016/j.arth.2011.01.019)

and high-performance mass spectrometry and seems to be more accurate than conventional PCR. [26] However, it has not yet been approved by the Food and Drug Administration for routine use in clinical practice.

The hypothesis of this study was that some cases of aseptic failure were indeed due to infection that either had escaped diagnosis using conventional modalities or had not been adequately investigated. This prospective study was set up to examine the postoperative course of a consecutive cohort of patients undergoing revision TKA in whom an intra-articular tissue and/or fluid sample was also sent for analysis by Ibis T5000 biosensor.

Materials and Methods

After approval of the institutional review board of the Thomas Jefferson University, all patients who underwent TKA revision from February 2009 to May 2010 were recruited for this study. The study consists of 65 patients, of whom 33 were men. The mean age of the patients was 65 ± 11 years. All patients underwent appropriate preoperative workup based on the recommendation of the treating surgeon and then categorized as infected or uninfected based on these investigations and surgeon's judgment. In our center, patients who are suspicious for PJI are evaluated by measurement of serum ESR and CRP, intraoperative culture, and synovial fluid analysis. However, frozen section is not used as a part of PJI workup in our institute. Intraoperatively tissue and/or fluid samples were collected and analyzed using the Ibis T5000 biosensor. After discharging from the hospital, patients are followed up based on the protocol used routinely in our institution at 6 weeks, 6 months, and 2 years after the revision surgery. In this study, all patients were followed up for a minimum of 6 months, with a mean follow-up of 19 months (range, 12-26 months). In particular, "aseptic" patients in whom the Ibis T5000 biosensor had detected an infecting pathogen were followed up closely for development of subsequent failure after the index revision.

Preoperative Workup

Detailed history taking, examination, and routine radiographs were performed in all patients in this cohort. It is an institutional policy that all patients undergoing revision arthroplasty at our institution have their preoperative ESR and CRP measured. In addition, and based on the findings of serology, most patients ($n = 57$) underwent joint aspiration with the fluid sent for analysis for neutrophil count, neutrophil differential, and culture. Because this was an observational and not an interventional study, we did not make any changes to the preoperative workup of any patients. Collection of synovial fluid and/or tissue sample for analysis by Ibis T5000 biosensor was a requirement of the study.

Sample Collection and the Ibis T5000 Method

Joint fluid and/or tissues were collected intraoperatively. Joint fluid was aspirated before the arthrotomy and was also sent for white blood cell count (WBC) (if indicated) and culture. Tissue sampling was performed from areas that were considered by the surgeon to be most suggestive of infection. In addition to the Ibis analysis, tissues were sent for histopathologic assessment and culture. The samples were not sent for measurement of inflammatory markers for this study. The samples were then processed appropriately for later analysis by Ibis T5000 in batches. Appropriate cryogenic vials were used to store fluid samples in a Styrofoam container. The vials were transferred in ice bags from the operating room to liquid nitrogen. About 0.5 to 1 mL of the liquid was stored for further analysis in liquid nitrogen. The syringe was changed to minimize possibility of accidental microbial contaminations before synovial fluid was transferred to the labeled vials. These vials were transferred to -140°F freezer where they were stored until they were shipped in batch to the Center for Research and Genomic Studies in Allegheny, Pa.

For DNA extraction, 1 mL of the aspirate was centrifuged at 10 000 rpm for 3 minutes, and 900 μL of supernatant was removed. Then, ATL lysis buffer and proteinase K were added, and the samples were incubated at 56°C until lysis occurred. The Qiagen DNeasy Tissue kit (catalog no. 69506; Qiagen Inc, Valencia, Cal) was used to extract nucleic acid from the lysed sample. After DNA was extracted, 10 μL of the sample was loaded per well into each of 16 wells on the bacterial artificial chromosome (BAC) detection PCR plate that each contained a different primer pair (catalog no. PN 05N13-01; Abbott Molecular). The BAC detection plate is a 96-well, 6-sample plate that contains 16 primers that identify all bacterial organisms, *Candida* species, and determines the presence of several key antibiotic resistance markers such as van-A and van-B (vancomycin resistance) in *Enterococcus* species, *Klebsiella pneumoniae* carbapenemases (KPC) indicating carbapenem resistance in gram-negative bacteria, and mec-A (methicillin resistance) in *Staphylococcus* species. Once PCR was completed, the plate was loaded onto the Ibis T5000 machine. The products from the PCRs were desalted in a 96-well plate format and sequentially electrosprayed into the time-of-flight mass spectrometer. The resultant spectral signals were then processed to determine the masses of each of the PCR products present with sufficient accuracy, in that the base composition of each amplicon could be unambiguously deduced. Using combined base compositions from multiple PCRs, the identities of the pathogens and their relative concentrations in the starting sample were determined.

The isolated microorganism from the Ibis biosensor was considered an "orthopedic pathogen" based on extensive search of the available literature. In other

words, if there was any evidence, as suggested by even a case report, that shows that the isolated microorganism is able to cause bone and/or joint infection, that microorganism was defined as an *orthopedic pathogen*. However, Ibis biosensor results did not change the treatment strategy, and all patients were treated based on results obtained from conventional diagnostic tests and surgeon's judgment.

Results

Based on preoperative investigations and surgeon's judgment, of the 65 patients recruited for this study, 21 were undergoing revision arthroplasty for PJI and the remaining 44 patients had aseptic failure. Among the 21 patients with PJI, synovial culture was negative in 11 cases. In the remaining 10 patients, the isolated organisms were coagulase-negative *Staphylococcus* (5 cases), *Staphylococcus aureus* (3 patients), *Streptococcus mitis* plus *Streptococcus sanguis* (1 case), and *Peptostreptococcus* species (1 case). Ibis identified a pathogen with a confidence level of 0.7 or higher in a total of 36 cases. Ibis T5000 isolated an organism in 19 PJI cases and failed to isolate any organism in 2 cases that were categorized as infected. The isolated organism by Ibis was coagulase-negative *Staphylococcus* in 10 patients and *S aureus* in 4 patients. In the PJI group, comparison of the isolated organisms from the culture and the detected organism by the Ibis T5000 biosensor showed the same pathogens in 9 cases samples, whereas in 11 cases, the Ibis biosensor found an additional pathogen. [Table 1](#) (available online at www.arthroplasty.org) demonstrates comparison between isolated organism by culture and Ibis T5000 results in patients with PJI. On the other hand, the Ibis T5000 found additional nonpathogen organisms in 3 cases in which the Ibis T5000 had also detected an orthopedic pathogen.

All culture results in the aseptic group were negative, whereas in 17 cases, the Ibis T5000 found orthopedic pathogens. In 27 patients, the biosensor failed to find any orthopedic pathogens. [Table 2](#) (available online at www.arthroplasty.org) demonstrates more details on aseptic cases. During the follow-up period, 2 patients failed and needed re-revision who were both initially revised for aseptic failure. The cause of failure in these 2 patients was subsequent PJI with the same organism (coagulase-negative *Staphylococcus*) as the one isolated by the Ibis T5000. At the latest follow-up, which ranged from 12 to 26 months after the index revision, all the remaining patients appear to be doing well with no evidence of infection.

Discussion

Given the completely different management of aseptic loosening and PJI as well as the importance of early diagnosis of PJI for establishment of a more effective treatment, distinguishing between these 2 conditions

needs special attention. The absence of a criterion standard for diagnosis of PJI [27], in addition to various defensive mechanisms of pathogens such as biofilm production [8], makes this differentiation more difficult. The infecting organism that segregate in biofilm evade detection by conventional culture, as the latter relies on isolation of planktonic organisms. As a result, it is suggested that some cases of PJI escape detection and erroneously are categorized as aseptic failures [8]. Although many factors contribute to the development of PJI after revision surgery, the latter point may be considered as one of the contributing factors for the much higher incidence of PJI after revision arthroplasty than that after primary arthroplasty.

The Ibis T5000 universal biosensor is a promising technology that has been used to identify a wide spectrum of pathogens in sepsis [28], and it may cover limitations of the PCR method for diagnosis of PJI. Because of reliance on mass spectrometry and further "purification" of DNA, it is assumed that Ibis does not have the same extreme sensitivity as conventional PCR. Furthermore, because of pan-genomic amplification, Ibis may be able to detect infecting organisms that could be missed by conventional PCR.

This prospective study was designed to examine the possibility of escaping some cases of TKA failures that are assumed to be aseptic from conventional diagnostic tests. These cases may be indeed infections that have escaped diagnosis and have been miscategorized as aseptic failures. The study relied on Ibis T5000 for isolation of organism. Although we did not accept Ibis as the criterion standard for diagnosis of PJI, we were interested to know in what percentage of patients with aseptic failure Ibis T5000 biosensor was able to isolate a pathogen. Furthermore, we sought to examine the correlation between conventional culture and Ibis in terms of their ability for isolation of a pathogen and its resistance profile.

At our institution, since 2006, we have been using an algorithmic approach for workup of patients with failed arthroplasty, which includes determination of ESR and CRP before revision arthroplasty and selective aspiration of the failed joint in those with abnormal serology or high index of suspicion for PJI [7]. In addition, intraoperative culture is performed for all cases undergoing revision arthroplasty. Despite the use of such a comprehensive and strict approach, the present study revealed that a few PJIs cannot be detectable by using routine diagnostic tools. It appears that reliance on conventional investigations is likely to miss occult PJI at least in 30% of patients (13/44 if *Enterococcus faecalis* cases were considered as contamination). The 2 patients who were originally assumed to have aseptic failure developed infection shortly after the index revision by organisms that had been isolated by the Ibis T5000 but failed to be detected by

conventional culture. The infecting organism in 1 case was low-virulence but a recognized pathogen [29,30], namely, *Staphylococcus caprae*. Although these patients did not receive any treatment for isolated additional pathogens from the Ibis biosensor, our findings may indirectly indicate the clinical importance of isolated pathogens from the Ibis biosensor. However, we are not able to make a statement about the effect of the treatment on the outcome of these patients with negative culture in whom the Ibis biosensor isolates additional pathogens. It is possible that the conventional culture may have identified these organisms if supplemented culture was used or if the culture was kept for an extended period.

Polymerase chain reaction has been used previously for the purpose of isolating organism in cases of suspected PJI [22,23,31]. However, PCR methods have several limitations, most important of which is the high incidence of false-positive results [11]. The technique is so sensitive that it may amplify contaminating and noninfecting organism such as those residing on the skin that may have been picked up by an aspirating needle [25]. Ibis T5000 is a multiplex PCR technology that was designed to overcome some of the limitations of conventional PCR.

Compared with conventional PCR, the Ibis T5000 uses a pan-genomic amplifier that is capable of isolating atypical bacteria and even nonbacterial pathogens such as fungi. Unlike conventional PCR, Ibis does not rely on universal primers for amplification of DNA, which may detect contaminating organism. Instead, Ibis T5000 biosensor uses multiple pairs of species-specific primers to amplify regions of an organism's genome. This process is followed by the identification of that region's base composition using mass spectrometry, the results of which are compared with a database that matches it to the closest microorganism [26]. The Ibis T5000 universal biosensor technology combines nucleic acid amplification to high-performance electrospray ionization mass spectrometry and base-composition analysis. The system can identify and quantify all known bacteria, all major groups of pathogenic fungi, and the major families of pathogen viruses in humans and animals. Moreover, the system is capable of detecting virulence factors and antibiotic resistance markers [26].

Despite its appeal, Ibis T5000 may still be a victim of high sensitivity. Ibis isolated a "pathogen" in 17 cases (38%) of aseptic cases. Of the latter, 2 patients have failed so far due to infection, which we believe was missed during the index revision arthroplasty. It is possible that occult PJI may have been present in a few more cases that were either eradicated during index revision arthroplasty, effectively with the patient undergoing a 1-stage exchange arthroplasty, or are likely to manifest a failure with further follow-up. It is unlikely

that the isolated organism by Ibis in all 17 aseptic cases represents a true pathogen. Thus, this technology, despite its appeal, should be reserved for patients in whom high index of suspicion or PJI exists, but no organism can be isolated. In other words, the indication for use of Ibis, in our opinion, is for cases of culture-negative PJI.

The study have a few limitations. Perhaps, the most important limitation of this study is the relatively short follow-up. As mentioned previously, it is possible that with longer surveillance, we are likely to encounter more patients who may fail. Although plausible, the latter is unlikely to alter the message of this study. The study highlights the importance of routine preoperative workup using conventional serology for all and selected aspiration for some, in line with the recent American Academy of Orthopedic Surgeons guidelines for diagnosis of PJI [6,32]. It also highlights the fact that a sophisticated technology is available for use by orthopedic surgeons to isolate the infecting organism in cases of culture-negative PJI. Another limitation of the study relates to lack of a "standard" definition for PJI. It is possible that using a different set of diagnostic criteria, some of the PJI cases in our cohort may have been considered as uninfected and vice versa. The latter is, unfortunately, a limitation inherent to any studies related to the topic of PJI because various definitions for PJI exist, and depending on the definition used, the percent of infected vs uninfected cases in a given cohort may change. It is hoped that orthopedic societies in collaboration with other organizations may be able to address this shortfall in the future.

Despite the aforementioned limitations, the present study demonstrated that some aseptic loosening cases are not "truly" aseptic and are low-grade PJIs that remain undiagnosed using conventional modalities. Some of these cases may fail early for a subsequent infection. This may explain the relatively high incidence of infection after revision, compared with primary, arthroplasty, and also the high rate of early failure of revision cases. It is, thus, recommended that all patients undergoing revision for failed arthroplasty be subjected to routine conventional workup, which includes routine serology (ESR and CRP) and joint aspiration in patients with abnormal serology tests and high index of suspicion for PJI. With further refinements of molecular techniques such as multiplex PCR, the true nature of some of these so-called aseptic failures is likely to be revealed.

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Table 1. Comparison Between Culture and Ibis T5000 Biosensor Results in Patients With Diagnosis of PJI

Culture	Ibis T5000 *	Synovial Fluid WBC (PMN)	ESR (mm/h)	CRP (mg/dL)	Type of Surgery	Secondary Failure
Coagulase-negative <i>Staphylococcus</i>	<i>Staphylococcus warneri</i>	15 600 (92%)	59	3.4	2-Stage exchange arthroplasty	No
Coagulase-negative <i>Staphylococcus</i>	<i>Staphylococcus epidermidis</i>	–	118	4.3	2-Stage exchange arthroplasty	No
Negative	<i>E faecalis</i>	–	94	0.7	Failed 2-stage exchange arthroplasty, AK amputation due to leg ischemia	No
<i>Peptostreptococcus magnus</i> , <i>Peptostreptococcus</i> <i>asaccharolyticus</i> , <i>Corynebacterium striatum</i>	<i>Streptococcus sanguinis</i> , <i>E faecalis</i>	5850 (88%)	27	1.8	Failed 2-stage exchange arthroplasty, AK amputation	No
<i>S aureus</i>	<i>S aureus</i>	53 000 (97%)	101	29.5	2-Stage exchange arthroplasty	No
<i>S aureus</i>	<i>S aureus</i>	20 959 (92%)	107	9	2-Stage exchange arthroplasty	No
Negative	<i>Staphylococcus capitis</i> , <i>S caprae</i> , <i>Candida</i> sp	10 751 (97%)	88	2.5	2-Stage exchange arthroplasty	No
Negative	<i>Candida</i> sp	6317 (92%)	103	7.3	2-Stage exchange arthroplasty	No
Coagulase-negative <i>Staphylococcus</i> , <i>Coryneform</i> species not <i>Corynebacterium</i> J-K	<i>S epidermidis</i>	18 718 (94%)	82	18.2	I&D with exchange of modular polyethylene	No
Negative	<i>Streptococcus</i> sp	44 134 (92%)	79	22.6	2-Stage exchange arthroplasty	No
Negative	<i>S epidermidis</i>	11 482 (89%)	94	12.9	2-Stage exchange arthroplasty	No
Coagulase-negative <i>Staphylococcus</i>	<i>S epidermidis</i>	10 755 (91%)	116	7	2-Stage exchange arthroplasty	No
<i>S mitis</i> , <i>S sanguis</i>	<i>S sanguinis</i>	2303 (93%)	120	14.6	2-Stage exchange arthroplasty	No
Coagulase-negative <i>Staphylococcus</i>	<i>S epidermidis</i>	50 732 (90%)	86	10.7	2-Stage exchange arthroplasty	No
Negative	<i>Streptococcus mutans</i>	30 636 (86%)	70	6.2	I&D with exchange of modular parts	No
<i>S aureus</i>	<i>S aureus</i>	22 913 (91%)	74	7.3	2-Stage exchange arthroplasty	No
Negative	<i>Staphylococcus lugdunensis</i> , <i>S epidermidis</i>	95 939 (90%)	45	<0.05	2-Stage exchange arthroplasty	No
Negative	<i>S epidermidis</i>	514 (50%)	33	<0.05	2-Stage exchange arthroplasty	No
Negative	<i>S aureus</i> , <i>Staphylococcus simulans</i>	10 384 (74%)	53	4.6	2-Stage exchange arthroplasty	No
Negative	Negative	82 412 (94%)	73	5.8	2-Stage exchange arthroplasty	No
Negative	Negative	1534 (89%)	24	4.99	1-Stage exchange arthroplasty	No

In all patients, fungal and *Mycobacterium tuberculosis* cultures were negative. At our institution, reference ranges for ESR and CRP are 0 to 30 mm/h and 0 to 0.8 mg/dL, respectively. PMN indicates polymorphonuclear; AK, above knee; I&D, irrigation and debridement.

* Only pathogens detected with confidence levels of 0.7 or higher were considered.

Table 2. Comparison Between Culture and Ibis T5000 Biosensor Results in Patients With Diagnosis of Aseptic Failure

Culture	Ibis T5000 [†]	Synovial Fluid WBC (PMN)	ESR (mm/h)	CRP (mg/dL)	Secondary Failure
Negative	<i>S epidermidis</i>	2000 (96%)	63	0.6	Yes
Negative	<i>Acinetobacter johnsonii</i>	—	37	—	No
Negative	Negative	1320 (86%)	31	1.7	No
Negative	<i>Coccidioides immitis</i>	—	18	0.5	No
Negative	<i>S sanguinis</i> , <i>E faecalis</i>	1988 (78%)	36	1	No
Negative	Negative	1022 (4%)	36	<0.5	No
Negative	Negative *	139 (12%)	24	0.6	No
Negative	Negative *	215 (36%)	58	<0.5	No
Negative	<i>E faecalis</i>	66 (14%)	7	<.05	No
Negative	Negative	—	34	1.5	No
Negative	<i>Streptococcus</i> sp, <i>Acinetobacter</i> sp	475 (40%)	—	—	No
Negative	Negative *	179 (8%)	25	0.5	No
Negative	Negative *	63 (18%)	21	0.6	No
Negative	<i>E faecalis</i>	45 (59%)	32	0.7	No
Negative	<i>Pseudomonas</i> sp	301 (36%)	25	0.7	No
Negative	<i>Candida</i> sp	699 (12%)	7	0.6	No
Negative	Negative	462 (13%)	24	0.8	No
Negative	<i>Candida</i> sp, <i>Pseudomonas</i> sp	135 (18%)	13	0.5	No
Negative	<i>S epidermidis</i>	733 (42%)	10	0.5	No
Negative	Negative	77 (13%)	34	1.5	No
Negative	Negative	104 (6%)	21	—	No
Negative	Negative *	—	40	—	No
Negative	Negative	92 (49%)	13	0.9	No
Negative	Negative	1389 (31%)	12	0.5	No
Negative	Negative *	1043 (46%)	20	1.5	No
Negative	Negative *	1389 (31%)	16	0.5	No
Negative	<i>E faecalis</i>	68 (38%)	14	1.5	No
Negative	Negative	122 (2%)	—	—	No
Negative	<i>E faecalis</i>	7941 (37%)	44	5.2	No
Negative	Negative	238 (6%)	16	0.9	No
Negative	Negative *	404 (53%)	5	0.5	No
Negative	Negative	—	10	—	No
Negative	<i>S sanguinis</i>	462 (45%)	—	—	No
Negative	Negative	16 503 (88%)	24	1	No
Negative	Negative	1225 (1%)	10	0.5	No
Negative	Negative	991 (5%)	10	<0.5	No
Negative	<i>S capitis/caprae</i>	844 (1%)	10	<0.5	No
Negative	Negative	634 (3%)	14	<0.5	No
Negative	Negative	212 (11%)	59	0.9	No
Negative	Negative	53 (16%)	73	3.1	No
Negative	Negative *	1886 (57%)	70	1	No
Negative	Negative	186 (14%)	14	<0.5	No
Negative	<i>A johnsonii</i> , <i>S caprae</i>	—	25	0.6	Yes
Negative	<i>Acinetobacter baumannii</i>	521 (96%)	—	—	No

In all patients, results of fungal and *M tuberculosis* cultures were negative. At our institution, reference ranges for ESR and CRP are 0 to 30 mm/h and 0 to 0.8 mg/dL, respectively. PMN indicates polymorphonuclear.

* Ibis T5000 found nonorthopedic pathogens.

[†] Only pathogens detected with confidence levels of 0.7 or greater were considered.