Evaluation of the Role for Synovial Aspiration in the Diagnosis of Aseptic Loosening After Total Knee Arthroplasty

Peter N. Chalmers, MD, David Walton, MD, Scott M. Sporer, MD, and Brett R. Levine, MD, MS

Investigation performed at the Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, Illinois

Background: Aseptic prosthetic loosening is known to be an inflammatory, cellular process. We hypothesized that the synovial cell count would significantly differ among normal controls, patients with aseptic loosening, and patients with other etiologies of aseptic failure after total knee arthroplasty and thus that the cell count would be useful in the diagnosis of aseptic loosening.

Methods: Over a six-year time period, all patients undergoing revision total knee arthroplasties at our institution underwent prospective intraoperative aspiration by the two senior authors. Each patient was assigned to a failure category on the basis of a priori criteria: aseptic loosening, periprosthetic infection, component wear, periprosthetic fracture, component malposition, instability, stiffness, and extensor mechanism failure. Simultaneously, patients with well-functioning total knee replacements underwent aspiration as normal controls. Aspirate characteristics were then compared between groups. Receiver-operating characteristic curves were created to determine optimal white blood-cell cutoffs when periprosthetic infection was compared with each individual failure category.

Results: Thirty normal control patients and 433 patients who underwent revision total knee arthroplasties were included in this study. The synovial white blood-cell count in the normal control group was 558 ± 522 cells/μL, which did not significantly differ ($p = 0.091$) from that taken from patients with aseptic loosening (947 ± 1027 cells/μL). However, normal controls had significantly higher white blood-cell counts than subjects with stiffness (367 ± 392 cells/μL; $p = 0.002$) and significantly lower white blood-cell counts than subjects with periprosthetic fractures (1687 ± 1613 cells/μL; $p = 0.002$). Subjects with aseptic loosening had significantly higher white blood-cell counts than subjects with component malpositioning ($p = 0.002$) or stiffness ($p = 0.001$). When individual aseptic failure categories were compared with periprosthetic infection, the optimal white blood-cell cutoff varied widely, including 2104 cells/μL for component malposition and 4697 cells/μL for periprosthetic fracture, and the optimal differential segmented cell count percentages varied from 47% to 83%.

Conclusions: Although synovial fluid aspirates in patients with aseptic loosening and those with normal total knee arthroplasties did not differ, synovial fluid aspirate characteristics differed among categories of aseptic failure. As a result, the optimal diagnosis of periprosthetic infection on the basis of synovial aspiration results may need to utilize different cutoff values depending on the alternative mode of failure being considered. Large prospective studies will be necessary to validate these threshold values.

Level of Evidence: Diagnostic Level II. See Instructions for Authors for a complete description of levels of evidence.

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Aseptic loosening remains one of the most common reasons for revision after total knee arthroplasty[1,2]. However, the diagnosis may remain challenging until the components are noted to have migrated[3,4]. Radiographs and technetium-labeled bone scintigrams are both relatively insensitive (77% for radiographs[3] and 76% for scintigrams[5]) and nonspecific (72% for radiographs[3] and 75.9% for scintigrams[4]). We are aware of no other diagnostic modalities or data points that differentiate aseptic loosening from other causes of aseptic failure or from extra-articular sources of knee pain such as lumbar radiculopathy. Although aseptic loosening is thought to be associated with an intra-articular inflammatory response[6-9], we are aware of no previous studies that have examined the attributes of synovial fluid in patients with aseptic loosening or have compared these attributes with those of patients with other etiologies of aseptic failure[10,11].

Periprosthetic infection, another common source of failure after total knee arthroplasty, is a process of acute inflammation, and thus the synovial cell count and differential are widely used to diagnose infection with excellent sensitivity and specificity[12-15]. However, previous studies have compared patients with infection with patients with all other causes of aseptic failure grouped together, which does not match the clinical scenario in which this test is used. Clinically, aspiration is often used to rule out infection when a single other diagnosis, such as aseptic loosening, is suspected. Perhaps as a result, past studies examining the use of the white blood-cell count in the diagnosis of periprosthetic infection have suggested an almost fourfold variation in optimal cutoff values from 1100[16] to 4200 cells/μL[13]. In addition, we are not aware of any previous studies that have examined the attributes of synovial fluid in painless, well-functioning total knee replacements. If the results of synovial fluid analysis differ between normal knees and various categories of aseptic failure, synovial fluid analysis may be diagnostically useful in the differential diagnosis of aseptic failure.

Our goals with this study were to determine the synovial fluid characteristics of patients with a well-functioning total knee replacement, patients with aseptic loosening after a total knee arthroplasty, patients with other modes of aseptic failure, and patients with periprosthetic infection. We hypothesized that the synovial fluid white blood-cell count and differential cell counts would significantly differ among normal controls, patients with aseptic loosening, patients with other sources of aseptic failure after total knee arthroplasty, and patients with periprosthetic infection and thus that these attributes could be diagnostically useful.

Materials and Methods

From April 2008 to September 2014, all patients who underwent revision total knee arthroplasty performed by the two senior authors (B.R.L. and S.M.S.) were evaluated with use of a standardized regimen. Intraoperatively, all patients underwent synovial fluid aspiration after dissection down to the layer of the capsule. These aspirates were analyzed for the cell count and differential and aerobic, anaerobic, and fungal cultures. Intraoperatively, the stability of the prosthesis was tested and this finding was noted in the operative report. In all cases, the etiology of failure was noted in the diagnosis of the operative report and was noted in our surgical database. Exclusion criteria included revision from a partial knee arthroplasty, as it was thought that this could not be easily categorized as a normal or a replaced knee. Similarly, patients who were undergoing revision with removal of an antibiotic spacer placed for a prior infection were excluded. Patients were also excluded if the quantity of fluid was deemed insufficient for analysis by our laboratory, which generally processes all samples with >0.5 mL of fluid. Otherwise, all patients during this period with complete electronic medical records were included (Fig. 1).

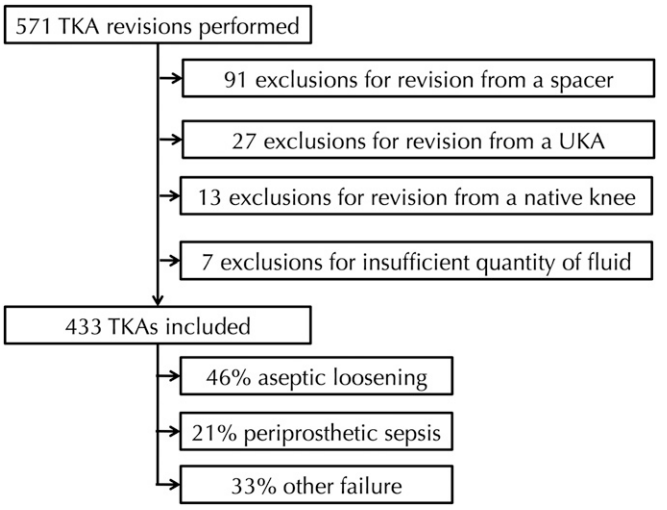

Fig. 1
Flowchart showing the number of patients included and excluded as well as the overall distribution of failure etiologies. TKA = total knee arthroplasty and UKA = unicompartmental knee arthroplasty.

For the normal control cohort, from November 26, 2012, to August 29, 2014, all patients who underwent either primary or revision knee or hip arthroplasty performed by the senior author (B.R.L.) at the hospital for which the study was approved by the institutional review board were screened prospectively by their surgical history. We considered for inclusion those patients who, as part of their surgical history, had undergone a total knee arthroplasty more than six months prior to the time the arthroplasty that caused them to be screened was performed and who had a total knee replacement that was currently painless, stable on clinical examination, and well-functioning. This time cutoff was chosen as the postoperative synovial inflammatory response has been shown to have resolved at six months[10]. Exclusion criteria included patients who, in relation to the total knee arthroplasty, had had any complication or had abnormalities on physical examination or radiographs. Knee Society scores were also collected and patients with scores of <90 points were excluded. All patients who met these criteria were offered participation. In those patients who agreed to participate, synovial fluid from the total knee arthroplasty was aspirated and was analyzed for the cell count and differential.

Data Collection

The following data were collected: demographic characteristics, Charlson Comorbidity Index[17-19], etiology of degeneration (classified as osteoarthritis, inflammatory arthritis, or posttraumatic arthritis), time interval between the index total knee arthroplasty and the revision, whether the serum C-reactive protein (CRP) and serum erythrocyte sedimentation rate (ESR) were considered abnormal on the basis of laboratory normal values, whether the pathologic frozen section was positive for acute inflammation by having a mean of more than five neutrophils per high-power field in the five most cellular fields[20,21], synovial fluid white blood-cell count, synovial fluid red blood-cell count, synovial fluid differential, and whether the final cultures were considered positive or

TABLE I Aspirate Characteristics for Each Failure Category*

Diagnosis	Age (yr)	Body Mass Index (kg/m^2)	Charlson Comorbidity Index	Follow-up Duration† (yr)	White Blood-Cell Count (cells/μL)	Differential (%)		
						Segmented Cell Count	Lymphocytic Cell Count	Monocytic Cell Count
Normal (n = 30)	66 ± 9	36 ± 10	0.4 ± 0.7	3.1 ± 3.3	558 ± 522	14 ± 17	40 ± 25	45 ± 26
Aseptic loosening (n = 201)	64 ± 10	34 ± 7	0.9 ± 1.2	5.4 ± 5.1	947 ± 1027	20 ± 22	39 ± 24	36 ± 25
Infection (n = 93)	65 ± 11	33 ± 10	1.0 ± 1.2	2.4 ± 3.3	62,299 ± 73,376	86 ± 18	6 ± 9	8 ± 12
Instability (n = 39)	63 ± 11	35 ± 10	0.7 ± 1.1	3.1 ± 2.8	730 ± 636	13 ± 17	50 ± 26	35 ± 27
Stiffness (n = 27)	58 ± 11	34 ± 7	0.7 ± 1.0	3.7 ± 3.1	367 ± 392	32 ± 26	34 ± 20	31 ± 27
Extensor mechanism failure (n = 22)	66 ± 11	35 ± 9	1.1 ± 1.3	4.3 ± 3.9	491 ± 461	30 ± 31	37 ± 26	29 ± 24
Component malposition (n = 21)	64 ± 10	35 ± 12	0.5 ± 0.9	3.1 ± 2.2	389 ± 473	22 ± 24	33 ± 22	37 ± 30
Polyethylene wear (n = 15)	74 ± 9	31 ± 6	1.3 ± 1.4	13.8 ± 7.2	909 ± 1019	15 ± 13	35 ± 19	48 ± 28
Periprosthetic fracture (n = 11)	72 ± 8	37 ± 12	0.8 ± 1.3	7.6 ± 6.6	1687 ± 1613	46 ± 35	30 ± 31	25 ± 23

*The values are given as the mean and the standard deviation. †This is the time since the prior arthroplasty was performed.

negative. The upper limit of normal for the reference ranges provided by our laboratory is 200 cells/μL for the synovial white blood-cell count and 25% for the segmented cell differential percentage. Our laboratory does not provide reference ranges for synovial lymphocyte and monocyte differential percentages.

Normal Cohort Characteristics

For the normal control cohort, 883 patients were screened. Of these patients, only fifty-two met the inclusion and exclusion criteria; twenty-two of these patients declined participation, and thirty patients (58%) enrolled. The mean follow-up

TABLE II Diagnostic Value of Synovial White Blood-Cell Count and Segmented Cell Count Differential Percentage When Patients with Infection Were Compared with Each Individual Category of Aseptic Failure*

Diagnosis (Compared with Infection)	Cutoff†	Sensitivity	Specificity	PPV‡	NPV§	Accuracy	AUC#
White blood-cell count							
Component malposition	2104	0.95	1.00	1.00	0.99	0.99	0.992 (0.980 to 1.000)
Stiffness	2176	0.95	1.00	1.00	0.99	0.99	0.991 (0.979 to 1.000)
Normal controls	2386	0.95	1.00	1.00	0.99	0.99	0.988 (0.972 to 1.000)
Extensor mechanism failure	1970	0.95	1.00	1.00	0.99	0.99	0.987 (0.971 to 1.000)
Instability	2550	0.94	1.00	1.00	0.99	0.99	0.982 (0.962 to 1.000)
All aseptic failures	4450	0.90	0.99	1.00	0.98	0.97	0.977 (0.961 to 0.998)
Aseptic loosening	4418	0.90	1.00	1.00	0.98	0.98	0.976 (0.955 to 0.997)
Fracture	4697	0.89	1.00	1.00	0.98	0.98	0.956 (0.917 to 0.994)
Segmented cell count							
Instability	47	0.96	0.95	0.99	0.99	0.95	0.988 (0.975 to 1.000)
Normal controls	68	0.89	1.00	1.00	0.98	0.98	0.986 (0.972 to 1.000)
Aseptic loosening	71	0.89	0.96	0.99	0.98	0.95	0.972 (0.955 to 0.990)
Component malposition	73	0.89	0.94	0.98	0.98	0.92	0.971 (0.943 to 0.998)
All aseptic failures	73	0.89	0.94	0.98	0.98	0.93	0.958 (0.937 to 0.979)
Stiffness	61	0.90	0.89	0.97	0.98	0.89	0.947 (0.908 to 0.986)
Extensor mechanism failure	69	0.89	0.86	0.97	0.97	0.87	0.923 (0.851 to 0.995)
Fracture	83	0.81	0.82	0.95	0.95	0.82	0.873 (0.767 to 0.979)

*Data are presented in descending order based on the area under the ROC curve (AUC). The cutoff values and diagnostic performance statistics are presented after maximizing the Youden J statistic. †The values are given as the cells/μL for the white blood-cell count and the differential percentage for the segmented cell count. ‡PPV = positive predictive value. §NPV = negative predictive value. #The values are given as the AUC, with the 95% confidence interval in parentheses.

duration (and standard deviation) after the primary total knee arthroplasty for these subjects was 3.1 ± 3.3 years (range, 0.5 to 13.0 years). The mean Knee Society score among the normal cohort was 95 ± 3 points (range, 90 to 100 points).

Modes of Failure

The prospectively documented causes of failure in the surgical databases were confirmed at the completion of the study with use of the radiographs, preoperative consultation notes, and operative reports for all patients. These data were used in combination to select a single failure mode with use of the following a priori criteria. In cases in which the preoperative and intraoperative diagnoses conflicted, the intraoperative diagnosis took precedence.

The criteria for the various modes of failure were as follows. For aseptic loosening, the criteria were revision for migration on preoperative radiographs or gross intraoperative implant movement with surgical manipulation prior to any attempts to disrupt the bone or the cement mantle in the absence of infection. For periprosthetic infection, the criteria were revision for bacterial growth from aspirate cultures, the presence of a sinus tract, intraoperative purulence, or a combination of at least three of four laboratory values (abnormal ESR, abnormal CRP, synovial fluid white blood-cell count of >3000 cells/μL, or abnormal intraoperative frozen section[22]). In cases in which the attending surgeon perioperatively documented a positive culture as a contaminant because of growth of a single common skin bacterium in a single broth culture without confirmation on any solid cultures, the cultures were considered negative. For component wear, the criteria were revision for preoperative radiographic and intraoperative evidence of polyethylene wear that produced contact or perceived impending contact between the tibial tray and the femoral component in the absence of aseptic loosening or infection. For periprosthetic fracture, the criteria were revision for a radiographically documented fracture in the absence of aseptic loosening or infection. For component malposition, the criteria were revision for component internal rotation of >5° demonstrated on CT (computed tomography) or patient subjective reports of symptomatic tibial or femoral component overhang reproducible by the surgeon on examination and apparent intraoperatively in the absence of aseptic loosening or infection. For instability, the criteria were revision for radiographically documented dislocation of the tibiofemoral or patellofemoral joints, >10° of varus or valgus instability in full extension, or hyperextension due to a neurologic condition, in the absence of aseptic loosening or infection. For stiffness, the criteria were revision for limitation of flexion or extension with <90° arc of motion in the absence of aseptic loosening or infection. For extensor mechanism failure, criteria were revision for inability to extend the knee due to damage to the patellar tendon, patella, or quadriceps tendon in the absence of aseptic loosening or infection.

Statistical Analysis

To compare categories, Kruskal-Wallis and analysis of variance (ANOVA) tests were performed. Continuous variables for individual failure categories were then compared with use of Mann-Whitney U and Student t tests. The following comparative tests were planned a priori: normal compared with each individual failure category and aseptic loosening compared with each other individual failure category. Similar comparisons were made for categorical values with use of chi-square tests, substituted with Fisher exact tests as appropriate. Post hoc Pearson correlation coefficients between white blood-cell count and time between the prior total knee arthroplasty and the aspiration were calculated. As we defined eight failure categories and one normal category, eight comparisons were performed for each variable and thus p values were Bonferroni-adjusted to a level of significance of 0.00625.

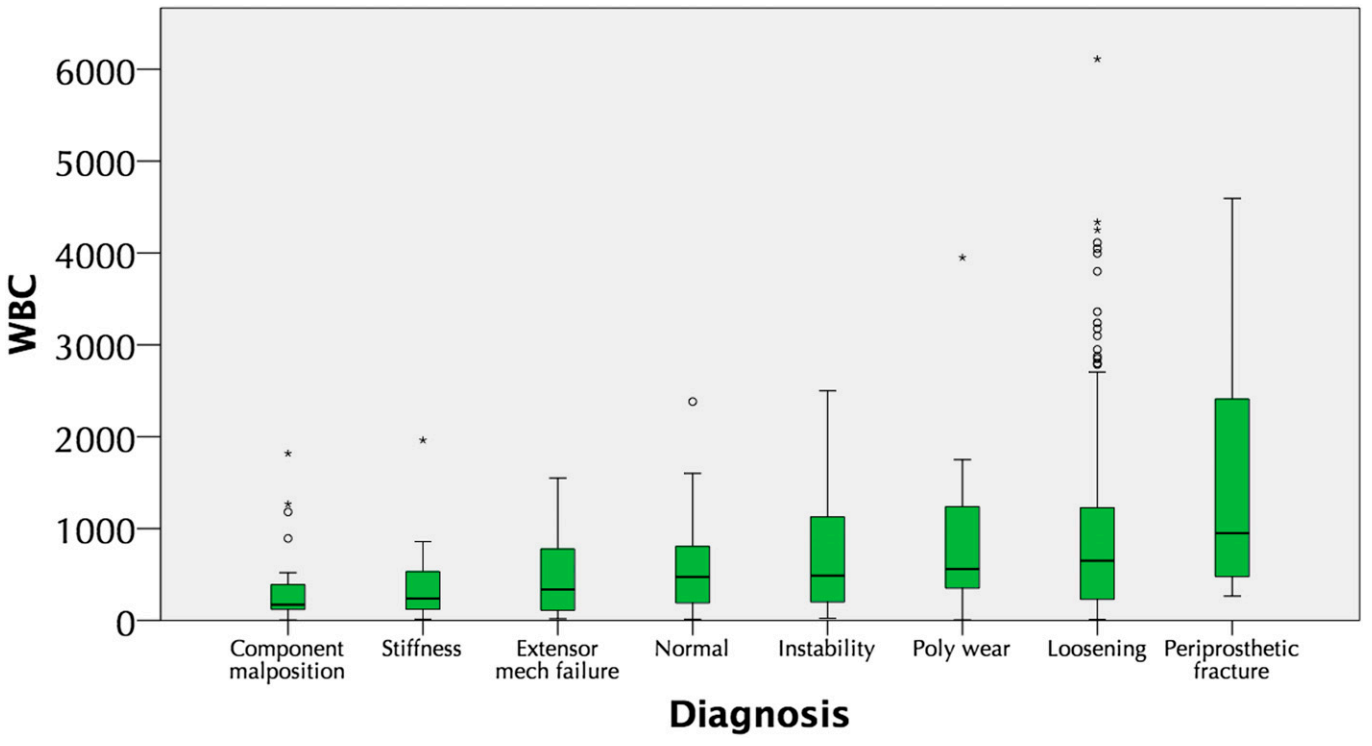

Fig. 2

Box plots displaying the synovial white blood-cell (WBC) count (cells/μL) for each diagnosis. Boxes represent the interquartile range, with the central line representing the median. Whiskers represent the furthest non-outlier, non-extreme value. Outliers, those values between 1.5 and 3 box lengths from either end of the box, are denoted with circles. Extreme values, those values more than three box lengths from either end of the box, are denoted with asterisks. Mech = mechanism and poly = polyethylene.

Receiver-operating characteristic (ROC) curve analyses were performed to compare periprosthetic infection with each individual aseptic failure category, with threshold values determined by maximizing the Youden J statistic[23].

Source of Funding
This study did not receive any external funding.

Results

For normal subjects, the mean value (and standard deviation) was 558 ± 522 cells/μL (range, 13 to 2382 cells/μL) for the synovial fluid white blood-cell count, 14% ± 17% (range, 0% to 63%) for the differential segmented cell percentage, 40% ± 25% (range, 6% to 92%) for the differential lymphocytic cell percentage, and 45% ± 26% (range, 2% to 83%) for the differential monocytic cell percentage (Table I). Synovial fluid characteristics differed significantly when normal controls were compared with patients with infections ($p < 0.001$ for white blood-cell count, segmented cell percentage, lymphocytic cell percentage, and monocytic cell percentage). In addition, there were significant differences in the differential segmented cell percentages between normal controls and patients with periprosthetic fractures and patients with stiffness ($p = 0.002$ in both cases). Otherwise, there were no significant differences in synovial fluid characteristics between normal controls and patients with any other aseptic cause of failure ($p > 0.006$ in all cases) (Figs. 2 and 3). In particular, the synovial white blood-cell count did not differ between normal controls and patients with aseptic loosening ($p = 0.091$).

When patients with aseptic loosening were compared with patients in each of the other failure categories, several significant differences were noted. Patients with aseptic loosening had significantly lower white blood-cell counts than patients with periprosthetic infection and had significantly higher white blood-cell counts than patients with stiffness or component malposition ($p \leq 0.002$ in all cases). When synovial fluid characteristics in patients with periprosthetic infection were compared with those in patients in each aseptic failure category, there were several notable differences (Table II). In the overall cohort, the Youden J statistic was maximized when white blood-cell counts of >4450 cells/μL were considered to indicate infection, which yielded a sensitivity of 90.4% and a specificity of 98.5%, and when differential segmented cell percentages of >73% were considered to indicate infection, which yielded a sensitivity of 89.4% and a specificity of 93.6%. However, optimal cutoffs for both white blood-cell count and segmented cell percentage varied depending on the aseptic failure category being compared with infection; for instance, when comparing two competing diagnoses of component malposition and infection, the optimal white blood-cell cutoff was 2104 cells/μL, with a sensitivity of 95% and a specificity of 100%, but when comparing two competing diagnoses of periprosthetic fracture and infection, the optimal white blood-cell cutoff was 4697 cells/μL, which yielded a sensitivity of

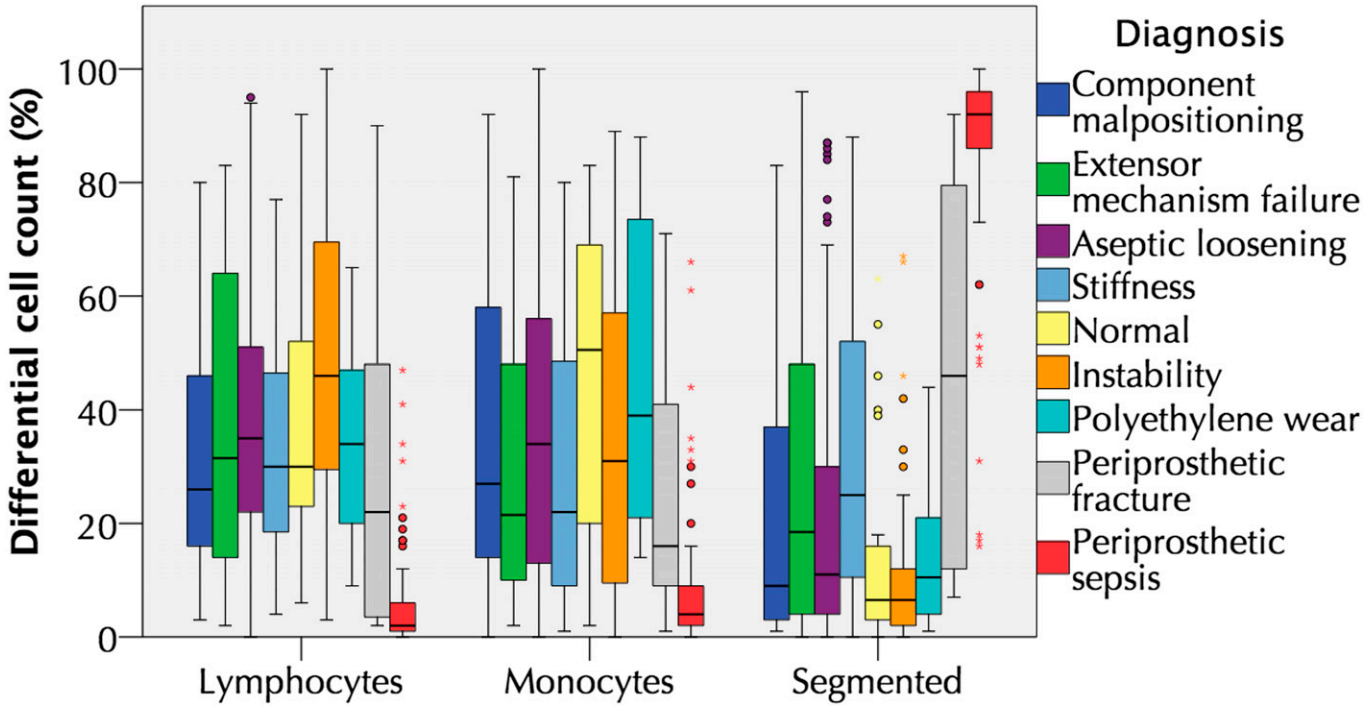

Fig. 3

Box plots displaying the differential cell count, including percent segmented cells, percent lymphocytic cells, and percent monocytic cells, for each diagnosis. Boxes represent the interquartile range, with the central line representing the median. Whiskers represent the furthest non-outlier, non-extreme value. Outliers, those values between 1.5 and 3 box lengths from either end of the box, are denoted with circles. Extreme values, those values more than three box lengths from either end of the box, are denoted with asterisks.

89% and a specificity of 100%. Optimal segmented cell count percentages also varied from 47% to 83% depending on the diagnostic categories being compared (Table II).

Discussion

We had hypothesized that the synovial fluid white blood-cell count would differ among patients with aseptic loosening, normal controls, patients with other causes of aseptic failure, and patients with septic failure after total knee arthroplasty. There were no differences in synovial fluid cell count and differential attributes between patients with aseptic loosening and normal controls. However, several secondary differences were found between the white blood-cell count in patients with aseptic loosening and those with stiffness ($p = 0.001$) and component malposition ($p = 0.002$). This study also provides documentation of the most common etiologies of failure leading to revision total knee arthroplasty, 46% of which were for aseptic loosening, 21% of which were for periprosthetic infection, and 33% of which were for other causes of aseptic failure.

To the best of our knowledge, this is the first description of the characteristics of synovial fluid in a well-functioning, painless, normal total joint replacement. Within our cohort of normal total knee arthroplasties, there was a mean of 558 white blood cells/μL, 14% segmented cells, 40% lymphocytic cells, and 45% monocytic cells. White blood-cell counts in normal total joint arthroplasties were as high as 2382/μL, which is greater than the current American Academy of Orthopaedic Surgery Clinical Practice Guidelines' (AAOS CPG) cutoff for infection of 1700 white blood cells/μL[14]. Historically, normal synovial fluid has been cited as having <200 white blood cells/μL with <25% segmented cells, and synovial fluid in degenerative joint disease has been cited as having 1000 white blood cells/μL, again with <25% segmented cells, although no modern studies have examined these values[24]. After arthroplasty, the normal cell count appears to lie somewhere between these two values.

Past studies examining the use of the synovial fluid white blood-cell count in the diagnosis of periprosthetic infection encountered greater than six weeks postoperatively have suggested a variety of optimal cutoff values including 1700 white blood cells/μL in the AAOS CPG[14], with other sources suggesting 1100[16], 3000[22], 3450[24], and 4200 white blood cells/μL[13]. Within our own data set, when all aseptic failures were considered together as the non-septic group, the optimal white blood-cell cutoff was 4450 cells/μL, with a sensitivity of 90% and a specificity of 99%. However, the optimal cutoff may vary depending on the clinical scenario. Clinically, the surgeon is usually considering two alternate diagnoses (periprosthetic infection and one cause of aseptic failure) when aspirates are obtained. For example, after considering the history, examination, and radiographs, if aseptic loosening is suspected because of start-up pain, tenderness at the tibial component, and a radiolucent line, an aspiration is often first obtained to exclude infection. Because synovial fluid characteristics differ among various etiologies of aseptic failure, synovial aspiration may be more accurate for assessing infection if individual alternative failure mechanisms were compared with infection. For instance, within our data set, if there was radiographic evidence of component malposition but the surgeon suspected periprosthetic infection, then the optimal white blood-cell cutoff based on our study would be 2104 cells/μL. Alternatively, within our data set, if the patient presented with a periprosthetic fracture but the surgeon suspected that this fracture may have occurred as a consequence of septic loosening, then the optimal white blood-cell cutoff would be 4697 cells/μL. The results of this study are descriptive and not prescriptive and large prospective studies will be necessary to validate these specific threshold values prior to clinical use. However, to maximize the diagnostic accuracy of synovial aspiration, different cutoffs may need to be employed depending on the clinical scenario and the alternative diagnosis being considered. The variation within the optimal white blood-cell cutoffs for infection suggested by the previous literature[13,14,16,22,24] may have arisen from differences in the distribution of failure etiologies within the control groups of these studies. In addition, research into more specific biochemical markers such as interleukins[25-28], cathepsins[28,29], or growth factors may be useful[26,30].

Our study had several limitations. The main limitation is the use of retrospective data collection, especially with regard to determination of failure categories. Failure mechanisms can be complex; for instance, polyethylene wear can lead to aseptic loosening with subsequent periprosthetic fracture. Septic and aseptic failure mechanisms may also be coexistent. We attempted to limit this issue by rigorously defining aseptic loosening as gross implant movement intraoperatively. Some failure mechanisms, such as component malposition and instability, remain controversial in their definitions, partially because they differ in symptom presentation from patient to patient. Although this study involves a large cohort and all revision total knee arthroplasties were performed over a large time period by two high-volume arthroplasty surgeons, some diagnoses, such as polyethylene wear and component malposition, remain relatively uncommon and thus our study may have been underpowered for these categories. The use of the Knee Society score to define normal was another limitation, as this score may not be sufficiently sensitive, but it has been used extensively in the literature to define successful outcomes.

In conclusion, although synovial fluid in patients with aseptic loosening and those with well-functioning, painless total knee replacements did not differ, synovial aspirate characteristics differed among categories of aseptic failure. As a result, optimal diagnosis of periprosthetic infection with use of synovial fluid may need to utilize different cutoff values depending on the alternative aseptic failure diagnosis being considered. Large prospective studies will be necessary to validate specific threshold values. ■

Peter N. Chalmers, MD
David Walton, MD
Scott M. Sporer, MD

Brett R. Levine, MD, MS
Department of Orthopaedic Surgery,
Rush University Medical Center,
1611 West Harrison Street, Suite 300,
Chicago, IL 60612.
E-mail address for P.N. Chalmers: p.n.chalmers@gmail.com

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