TABLE E-1

Organisms in Infected Knees (n=45)	# of Knees	Antibiotic Sensitivity
Staphylococcus aureus	16	Sensitive to methicillin, oxacillin
Staphylococcus epidermidis	10	Sensitive to methicillin, oxacillin
Staphylococcus epidermidis	7	Sensitive to vancomycin
Streptococcus viridans	5	Sensitive to penicillin
Staphylococcus aureus (MRSA)	4	Sensitive to vancomycin
Enterococcus faecalis	2	Sensitive to ampicillin, vancomycin
Serratia marcescens	2	Sensitive to ceftriaxone, ciprofloxacin
Enterobacter cloacae	1	Sensitive to gentamicin, ciprofloxacin
Corynebacterium afermentans	1	Sensitive to cloxacillin, vancomycin
>1 organism grown	3	

Appendix

Interpretation of Diagnostic Tests

Sensitivity is determined by identifying the proportion of patients with infection for whom the test result was positive. High sensitivity is desired for diagnostic tests that screen for disease. Specificity is determined by identifying the proportion of patients without infection for whom the test result was negative. High specificity is desired for tests that are done to confirm the absence of a disease. The likelihood ratio incorporates both the sensitivity and the specificity and describes the relative odds of an outcome, such as infection, given a particular test result[11]. A positive likelihood ratio and a negative likelihood ratio indicate the likelihood of a positive or negative test occurring for a patient with an infection in comparison with the likelihood for a patient without an infection.

Likelihood ratios may be used by the clinician to estimate the posttest probability of the patient having a disease compared with the pretest probability of the patient having a disease based on clinical judgment. Previous literature suggests that likelihood ratios of >10 or <0.1 generate large and often conclusive changes from pretest to posttest probability, ratios of 5 to 10 and 0.1 to 0.2 generate moderate shifts in probability, ratios of 2 to 5 and 0.2 to 0.5 generate small (but sometimes important) changes in probability, and ratios of 1 to 2 and 0.5 to 1 alter probability to a very small (and rarely important) degree[14].

The receiver-operating-characteristic curve is a representation of the trade-offs between sensitivity and specificity (as one increases, the other decreases) over the continuum of possible cut-points for the diagnostic test. It is important to recognize that both the traditional positivity criteria and our proposed criteria represent distinct cut-points on the same receiver-operating-characteristic curve for the respective diagnostic tests. Therefore, additional comparative analysis to demonstrate superiority of one cut-point over another is not meaningful. Rather, the clinician should employ the information derived with use of different cut-points on the receiver-operating-characteristic curve according to the requirements of the clinical scenario at hand (Figs. 3 and 4). In most situations, our proposed threshold of 22.5 mm/hr for the erythrocyte sedimentation rate and 13.5 mg/L for the C-reactive protein level should be accepted if the clinician desires a cut-point that optimizes both the sensitivity and the specificity of the respective tests. However, the clinician may choose to deviate from these proposed thresholds and use either the traditional cut-points, or alternate cut-points that are not at the apex of the receiver-operating-characteristic curve, in order to increase the sensitivity or specificity of any single test. The receiver-operating-characteristic curves demonstrate that, as the criteria for a positive test are made more stringent, the cut-point on the curve moves to the left and down (high specificity, low sensitivity). If the purpose of the test is to confirm a strong clinical suspicion, these stringent criteria are ideal. If high specificity is desired in order to maximize the confirmatory behavior of the test, then a cut-point that is left and down (that is, an erythrocyte sedimentation rate of 30 mm/hr instead of 22.5 mm/hr) is selected. Conversely, as the criteria for a positive test are made more liberal, the cut-point on the curve moves to the right and up (greater sensitivity, lower specificity). If the purpose of the test is to exclude (rule out) infection, without overdiagnosing it, then the more liberal criterion that optimizes sensitivity and specificity (that is, an erythrocyte sedimentation rate of 22.5 mm/hr instead of 30 mm/hr) is appropriate.

Clinical Relevance

Knowledge of test characteristics is important when deciding which test to select for a given purpose. If a number of different tests are available for the diagnosis of infection, the one with the highest sensitivity (that is, combined measurements of the erythrocyte sedimentation rate and C-reactive protein level with at least one positive result indicating infection [sensitivity, 0.95]) should generally be selected if it is important to rule out infection. Conversely, the test(s) with the highest specificity (that is, combined measurements of the erythrocyte sedimentation rate and C-reactive protein level with infection indicated only when both tests are positive [specificity, 0.93]) should be selected if it is most important to confirm the presence of infection. Examining the likelihood ratios of tests can also help one decide which of competing tests to use. Generally, when the clinician wants to rule out infection, the test with the smallest negative likelihood ratio (that is, the combined test with infection indicated by at least one positive test) is preferred, and when he or she wants to confirm an infection, the test with the largest positive likelihood ratio (that is, the combined test with infection indicated if both tests are positive) is preferred. It is important to understand that knowledge of these test operating characteristics cannot determine the presence or absence of infection unless the test result is always positive when infection is present (that is, when sensitivity is 100%) or is always negative when the infection is absent (that is, when specificity is 100%). In order to determine the likelihood of infection when the test is positive or when the test is negative, knowledge of test characteristics must be coupled with the clinician's estimate of the probability of the infection before the test result was obtained.

Our study demonstrates that the erythrocyte sedimentation rate and C-reactive protein level are both very useful and exhibit favorable test characteristics. Therefore, we recommend that both the erythrocyte sedimentation rate and C-reactive protein level be measured as part of the clinical evaluation when a surgeon encounters a patient with pain at the site of a total knee arthroplasty. These test results should be considered together as a screening test for infection; therefore, if one or the other is positive the clinician should consider this together with the history and the results of the physical examination and then consider making arrangements for a highly specific confirmatory test such as a knee aspiration followed by culture. If the erythrocyte-sedimentation-rate and C-reactive-protein tests are negative, and clinical suspicion of infection is low, then the probability of infection as a

cause of the symptoms (posttest probability) is very low (0.03 in our cohort), and an additional invasive test such as aspiration or synovial biopsy followed by culture are probably not warranted.

The erythrocyte sedimentation rate and C-reactive protein level appear to maintain their operating characteristics even if antibiotics were administered prior to referral for clinical consultation. During the time-period of this study, eleven patients with an apparent infection at the site of a knee arthroplasty who were already being treated, or recently had been treated, with antibiotics presented to our clinic. All eleven patients were excluded from our primary data set as they did not meet our criterion of having an established "gold standard" diagnosis of infection based on a positive culture at our institution. Bacteria did not grow on culture of the preoperative aspiration or intraoperative specimens obtained from any of these patients while they were at our institution. (These were likely false-negative results due to current or recent antibiotic usage.) All eleven patients were treated for infection because of a very high clinical suspicion of infection, and all had a final histopathological diagnosis of infection[19]. We included these patients in a secondary data set to evaluate the performance and reliability of measurements of the erythrocyte sedimentation rate and C-reactive protein level in patients being treated with antibiotics (Fig. 2, Table IV). In all patients, the erythrocyte sedimentation rate and C-reactive protein level were elevated above normal levels and remained in agreement with the clinical presentation and final histopathological diagnosis of infection. Evaluation of the test characteristics in Figure 1 (for patients not being treated with antibiotics) and Figure 2 (which included patients being treated with antibiotics) suggests that the presence of antibiotics or recent antibiotic treatment does not substantially affect the performance of the erythrocyte-sedimentation-rate and C-reactive-protein tests. Therefore, it appears that measurements of the erythrocyte sedimentation rate and C-reactive protein level may remain a useful screening or confirmatory diagnostic test for patients who present with symptoms related to a knee arthroplasty and have begun treatment, or have been treated, with antibiotics.

However, if the patient has a systemic disease or inflammatory arthropathy that may result in a falsely elevated erythrocyte sedimentation rate or C-reactive protein level, the clinician should consider alternative testing strategies such as the knee aspiration followed by culture or a serial bone-indium scan[32,33] if the patient had treated with antibiotics.

Additional Tests for Diagnosis of Infection Not Addressed in This Study

In this study, we did not evaluate the white blood-cell count in the synovial fluid in the knee joint aspirate, and we did not obtain intraoperative frozen sections. Therefore, we cannot comment on these tests on the basis of the data in this study.