Does This Adult Patient Have Septic Arthritis?

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CLINICAL SCENARIO

Case 1

A 48-year-old woman with a history of rheumatoid arthritis who has been treated with long-term, low-dose prednisone presents to the emergency department with a 2-day history of a red, swollen left knee that is painful to touch. She reports no prior knee swelling and no recent trauma or knee surgery, illegal drug use, rash, uveitis, or risky sexual behavior. On examination, she is afebrile and has a left knee effusion. Her peripheral white blood cell (WBC) count is 11 000/μL and her erythrocyte sedimentation rate (ESR) is 55 mm/h. An arthrocentesis is performed and initial laboratory test results show a negative Gram stain, a synovial fluid WBC count of 48 000/μL, and the fluid culture is pending. What is the likelihood of septic arthritis in this patient?

Case 2

An 81-year-old man with diet-controlled diabetes mellitus and hypertension presents to the general medicine clinic with a painful left ankle. He reports difficulty walking for the past 2 days and his left ankle is exquisitely tender to touch. When he had pain in his ankle previously, another physi-

See also Patient Page.

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Context In patients who present with an acutely painful and swollen joint, prompt identification and treatment of septic arthritis can substantially reduce morbidity and mortality.

Objective To review the accuracy and precision of the clinical evaluation for the diagnosis of nongonococcal bacterial arthritis.

Data Sources Structured PubMed and EMBASE searches (1966 through January 2007), limited to human, English-language articles and using the following Medical Subject Headings terms: *arthritis, infectious*, *physical examination*, *medical history taking*, *diagnostic tests*, and *sensitivity and specificity*.

Study Selection Studies were included if they contained original data on the accuracy or precision of historical items, physical examination, serum, or synovial fluid laboratory data for diagnosing septic arthritis.

Data Extraction Three authors independently abstracted data from the included studies.

Data Synthesis Fourteen studies involving 6242 patients, of whom 653 met the gold standard for the diagnosis of septic arthritis, satisfied all inclusion criteria. Two studies examined risk factors and found that age, diabetes mellitus, rheumatoid arthritis, joint surgery, hip or knee prosthesis, skin infection, and human immunodeficiency virus type 1 infection significantly increase the probability of septic arthritis. Joint pain (sensitivity, 85%; 95% confidence interval [CI], 78%-90%), a history of joint swelling (sensitivity, 78%; 95% CI, 71%-85%), and fever (sensitivity, 57%; 95% CI, 52%-62%) are the only findings that occur in more than 50% of patients. Sweats (sensitivity, 27%; 95% CI, 20%-34%) and rigors (sensitivity, 19%; 95% CI, 15%-24%) are less common findings in septic arthritis. Of all laboratory findings readily available to the clinician, the 2 most powerful were the synovial fluid white blood cell (WBC) count and percentage of polymorphonuclear cells from arthrocentesis. The summary likelihood ratio (LR) increased as the synovial fluid WBC count increased (for counts $<$25 000/μL: LR, 0.32; 95% CI, 0.23-0.43; for counts $\geq$25 000/μL: LR, 2.9; 95% CI, 2.5-3.4; for counts $>$50 000/μL: LR, 7.7; 95% CI, 5.7-11.0; and for counts $>$100 000/μL: LR, 28.0; 95% CI, 12.0-66.0). On the same synovial fluid sample, a polymorphonuclear cell count of at least 90% suggests septic arthritis with an LR of 3.4 (95% CI, 2.8-4.2), while a polymorphonuclear cell count of less than 90% lowers the likelihood (LR, 0.34; 95% CI, 0.25-0.47).

Conclusions Clinical findings identify patients with peripheral, monoarticular arthritis who might have septic arthritis. However, the synovial WBC and percentage of polymorphonuclear cells from arthrocentesis are required to assess the likelihood of septic arthritis before the Gram stain and culture test results are known.

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cian told him he had gout. On examination, he has a temperature of 38.2°C. By visual inspection, there is erythema and swelling over the dorsal aspect of the midfoot and ankle. Direct pressure over the ankle confirms extreme tenderness and swelling. What is the yield of arthrocentesis in detecting septic arthritis in this patient with presumptive gout?

WHY IS THE DIAGNOSIS OF SEPTIC ARTHRITIS IMPORTANT?

Infection, crystal-induced disease, osteoarthritis, trauma, and a variety of systemic diseases can create a painful, swollen peripheral joint. Nongonococcal bacterial arthritis is possibly the most dangerous and destructive type of acute arthritis and is the focus of this review. Promptly distinguishing nongonococcal septic arthritis from other causes of monoarthritis is important because septic arthritis can be devastating. Within days of onset, septic arthritis destroys cartilage.[1,2] The mortality rate for in-hospital septic arthritis ranges from 7% to 15%, despite antibiotic use.[3-8] The incidence of bacterial arthritis has been reported in Scandinavia and Australia at 5.7 to 9 per 100 000 person-years and in England at 1 in 49 000 per 100 000 person-years, with increased incidence in patients with rheumatoid arthritis and joint prostheses.[6,9,10] Patients with rheumatoid arthritis or joint prostheses have an increased risk of septic arthritis, but distinguishing infection from underlying arthritides creates diagnostic challenges and a heightened urgency.

Although gonococcal arthritis is the most common strain of infectious arthritis,[11] it creates less morbidity and has a different clinical presentation. With gonococcal arthritis, women are affected 2 to 3 times more frequently than men, and a migratory tenosynovitis often accompanies the arthritis.[12] The Gram stain of the synovial fluid is positive in less than 10% of patients, and the test result of synovial fluid culture is often negative.[13] Because the response to therapy is usually rapid and complete, this form of infectious arthritis is much less destructive than nongonococcal arthritis.[14]

When challenged with a patient who has a painful, swollen joint, a clinician must accurately estimate the probability of septic arthritis. This probability directs the physician in further diagnostic testing and treatment. Our goal is to determine the diagnostic value of the history, physical examination, and routine laboratory testing for identifying patients with septic arthritis. We include routine laboratory test results that are rapidly available because the results must be interpreted in light of the clinical findings.

Pathogenesis

Initially, bacteria enter the joint and deposit in the synovial membrane, which leads to an acute inflammatory response. Synovial tissue has no limiting basement membrane; therefore, bacterial organisms can easily enter the synovial fluid and create the characteristic purulent joint. Any microbial pathogen can cause septic arthritis, although staphylococci and streptococci are the most common of the nongonococcal bacterial isolates.[3,5,6,8,15,16] In the majority of cases, septic arthritis is monoarticular and occurs most commonly in large peripheral joints, such as the knee, which accounts for approximately 50% of cases.[17,18] The diagnosis for nongonococcal septic arthritis is confirmed by positive synovial fluid Gram stain or culture.

Clinical Presentation

Many conditions including crystal arthritis and systemic diseases, such as rheumatoid arthritis, can present with fever, joint swelling, pain, and stiffness,[2,12,19-23] mimicking the clinical presentation of septic arthritis. The differential diagnosis of an acute monoarticular arthritis is shown in Box 1. Several historical features, symptoms, and signs have been associated with acute septic arthritis and may be useful as analytical tests; however, the diagnostic values of these tests have not been established. The classic presentation of septic arthritis is an acutely swollen, painful joint with limited range of motion. Chills and fever are common but may be absent. When septic arthritis is suspected, arthrocentesis is mandatory. If an overlying cellulitis is present, the physician should perform the arthrocentesis while attempting to avoid percutaneous puncture of infected skin. Some clinicians favor proceeding with arthrocentesis through a cellulitic area when no other approach is possible. The synovial fluid should be sent for WBC count with differential, Gram stain, and culture to confirm the diagnosis and help guide treatment. Radiographs are usually normal early in the disease or are nonspecific.[24] Even the changes for septic arthritis by magnetic resonance imaging are imprecise and can be observed in noninfectious inflammatory arthropathies.[25]

Box 1. Differential Diagnosis for Acute Monoarthritis*

Infection (bacterial, fungal, mycobacterial, viral, spirochete)
Rheumatoid arthritis
Gout
Pseudogout
Apatite-related arthropathy
Reactive arthritis
Systemic lupus erythematosus
Lyme arthritis
Sickle cell disease
Dialysis-related amyloidosis
Transient synovitis of the hip
Plant thorn synovitis
Metastatic carcinoma
Pigmented villonodular synovitis
Hemarthrosis
Neuropathic arthropathy
Osteoarthritis
Intra-articular injury (fracture, meniscal tear, osteonecrosis)

*Adapted from Klippel et al.[18]

Box 2. Predetermined Criteria for the Quality of Evidence in Primary Studies

Study Quality

Score 1: Study includes consecutive patients with both negative and positive test results. No application of established clinical criteria for septic arthritis exists as an inclusion criterion. Patients require positive synovial fluid culture, Gram stain, blood culture, or clinical response to antibiotics to be classified as having septic arthritis.

Score 2: Study includes consecutive patients with both negative and positive results. Patients are classified based on both the presence of predefined established clinical criteria and positive synovial fluid culture, Gram stain, blood culture, or clinical response to antibiotics.

Score 3: Study of a nonconsecutive sample of patients with both negative and positive test results. Patients require positive synovial fluid culture, Gram stain, blood culture, or clinical response to antibiotics to be classified as having septic arthritis.

Score 4: A series of consecutive patients with septic arthritis proven by synovial culture, Gram stain, or clinical response to antibiotics.

Score 5: A random sample of patients with a clinical diagnosis of septic arthritis. No use of established criteria. Patients require positive synovial fluid culture, Gram stain, blood culture, or clinical response to antibiotics to be classified as having septic arthritis.

Level of Evidence

Level I: Independent, blind comparison of symptoms or signs with a gold standard among a large number (>50) of consecutive patients suspected of having septic arthritis.

Level II: Independent, blind comparison of symptoms or signs with a gold standard among a small number (≤50) of consecutive patients suspected of having septic arthritis.

Level III: Independent, blind comparison of symptoms or signs with a gold standard in nonconsecutive patients OR in patients known to have septic arthritis.

Level IV: Nonindependent comparison of symptoms or signs with a gold standard among samples of patients who obviously have septic arthritis plus, perhaps, healthy individuals.

Level V: Nonindependent comparison of symptoms or signs with a gold standard of uncertain validity (which may even incorporate the sign or symptom result in its definition) among samples of patients plus, perhaps, healthy individuals.

METHODS

Search Strategy and Quality Literature Review

We searched the English-language medical literature from 1966 to January 2007 to identify articles that reported the diagnostic value of the history, physical examination, blood, or synovial fluid laboratory test results for distinguishing septic arthritis from other conditions. The search strategy used the following Medical Subject Headings (MeSH): *arthritis, infectious*, *physical examination*, *medical history taking*, *diagnostic tests*, and *sensitivity and specificity*, combined with the MeSH terms: *arthritis, infectious* or *arthritis, gouty* and *synovial fluid*, and *arthritis, infectious* AND (*risk** [title/abstract] OR *risk** [MeSH:noexp] OR *risk** [MeSH:noexp] OR *cohort studies* [MeSH terms] OR *group** [text word], both limited to human, English-language articles. We also searched EMBASE using similar MeSH terms. Finally, we reviewed the references and citations from these articles to identify other relevant articles. The complete search strategy is available from the authors by request.

Data Abstraction

One of the authors (M.E.M.) initially screened the titles and abstracts of the search results. Three of the authors (J.K., S.B., and M.E.M.) then independently reviewed and abstracted data from articles identified as relevant. Differences in assessment were discussed and resolved by consensus.

Studies were included if they described patients who presented with an acutely painful or swollen joint and contained original data on accuracy and precision of the history and/or physical examination and/or laboratory data in diagnosing septic arthritis. We included laboratory data that were readily available to the bedside physician so that they could be used in clinical decision making. Articles were excluded if they did not include a gold standard measure for the diagnosis of septic arthritis. Although synovial fluid culture is considered the gold standard test for evaluating the presence of septic arthritis, it is an imperfect gold standard with reported sensitivities of only 75% to 95%.[13] Therefore, we also included studies that used gold standard tests of positive Gram stain, positive blood cultures, no organism isolated but macroscopic pus aspirated from joint, or response to antibiotics.

We classified the quality of evidence in each study by 2 separate methods (BOX 2). To evaluate clinical symptoms and signs of septic arthritis, we used criteria that included consecutive vs nonconsecutive samples, inclusion of patients with the diagnosis of only septic arthritis vs other joint disease, and the requirement of positive synovial culture, Gram stain, blood culture, or response to antibiotics for all patients labeled as having nongonococcal septic arthritis.[26] Also, we graded the quality of each study using a classification scheme for levels of evidence used previously for The Rational Clinical Examination series.[27]

Statistical Methods

The primary outcome measures of this study were the likelihood ratios (LRs) for all symptoms or signs used to dis-

tinguish septic arthritis from other causes of an acutely painful or swollen joint. We used data from the identified articles to calculate the sensitivity, specificity, and positive and negative LR, as well as the summary LR. The positive LR is a measure of how strongly a positive result increases the odds of disease, and the negative LR is a measure of how well a negative result decreases the odds of a disease. To calculate summary LRs, we used a random effects model, a conservative summary measure in that it provides broad confidence intervals (CIs) that display the heterogeneity of results. Microsoft Excel 2003 (Microsoft Corp, Redmond, Wash) was used for all statistical analyses. $P<.05$ was considered statistically significant.

Accuracy of Signs and Symptoms

Studies used varying definitions for fever ranging from 37.5°C to 38.0°C and whether fever occurred at either presentation or during hospital course. We defined fever as absent or present based on the individual article definitions. The studies presented used the definition for elevated peripheral WBC count as more than 10 000/μL, elevated ESR as more than 30 mm/h, and markedly elevated C-reactive protein (CRP) as more than 100 mg/L. A reduction in synovial fluid glucose was based on individual article definitions and ranged from a serum/synovial fluid glucose ratio of less than 0.5 or 0.75, a synovial fluid glucose level of less than 1.5 mmol/mL, or both. To convert synovial fluid glucose to g/dL, divide by 0.0555.

RESULTS

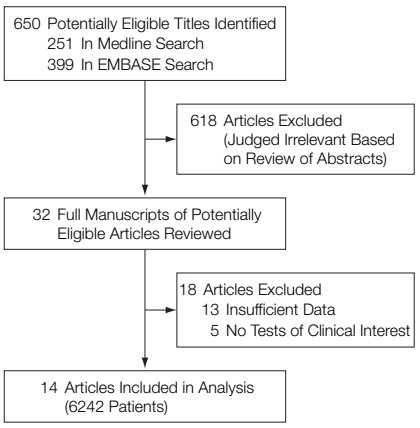
The PubMed searches identified 251 articles and the EMBASE search identified an additional 399 articles for a total of 650 articles (FIGURE). Studies were judged irrelevant if they did not include original data on the accuracy or precision of history, physical examination, and/or routine laboratory test results in diagnosing septic arthritis. Six hundred eighteen articles were excluded based on review of their abstracts, leaving 32 articles for full manuscript review. There were 13 studies that reviewed patients with infected joints but did not provide sufficient data and, therefore, could not be included in our study.[5,7,8,10,28-36] Five studies did not evaluate clinical tests of interest.[37-41] Thus, the final data shown in TABLE 1 are based on 14 studies that met all the inclusion criteria[3,6,15,42-51] and included 6242 patients, of whom 653 were diagnosed with septic arthritis. The studies took place between 1979 and 2003, and ranged in size from 41 to 4889 patients. However, 1 study[42] evaluating risk factors involved the majority of the patients. The other 7 studies[43-48] included a total of 1353 patients, ranging from 41 to 362 patients and assessed symptoms, signs, serum laboratory values, and synovial fluid for the diagnosis of septic arthritis. Although we did not exclude studies of gonococcal arthritis, the difficulty of confirming gonococcal arthritis by Gram stain or culture (gold standard) meant that only a few of these patients were included in the retained studies.

The patients in the 14 studies were all adults and included patients in rheumatology clinics, those patients presenting to the emergency department, or hospitalized patients. The quality scores were relatively low, with only 3 studies attaining a level 1 score. Most studies used an adequate gold standard.

Prevalence of Septic Arthritis Among Patients With Acute Monoarthritis

Two of the studies were prospective studies enrolling patients with acutely swollen, painful joints, and were therefore useful for estimating a pretest probability of septic arthritis. In the prospective study by Shmerling et al,[46] 8 (8%) of 100 consecutive patients evaluated for 1 or more painful, swollen joints between 1987 and 1988 at Beth Israel Hospital in Boston, Mass, had septic arthritis. In the prospective study by Jeng et al,[48] 20 (27%) of 75 patients presenting to the emergency department with acute arthritis between 1993 and 1995 in Taiwan were found to have septic arthritis. Thus, the range of reported prevalence from 2 prospective studies of septic arthritis in patients who presented with an acutely painful and swollen joint is 8% to 27%.[46,48] We report the prevalence estimate as a range rather than a summary because the risks are significantly different (χ^2 test, $P<.001$), and the patient populations were from 2 different clinical settings.

Figure. Reason for Exclusion of Studies



Risk Factors for Septic Arthritis

TABLE 2 shows abstracted sensitivity and specificity data and calculated positive and negative LRs for the risk factors, signs, and serum laboratory values to aid the diagnosis of acute septic arthritis. Two studies examined risk factors for diagnosing septic arthritis among patients with an acute inflammatory arthritis. One prospective cohort[42] from the Netherlands found that the likelihood of septic arthritis increases with age older than 80 years (LR, 3.5; 95% CI, 1.8-7.0), diabetes mellitus (LR, 2.7; 95% CI, 1.0-6.9), rheumatoid arthritis (LR, 2.5; 95% CI, 2.0-3.1), recent joint surgery (LR, 6.9; 95% CI, 3.8-12.0), hip or knee prosthesis (LR, 3.1; 95% CI, 2.0-4.9), skin infection (LR, 2.8; 95% CI, 1.7-4.5), and skin infection in combination with joint prosthesis (LR, 15.0; 95% CI, 8.1-28.0). The second study,[43] a case-control study in Rwanda (in which the prevalence of human immu-

nodeficiency virus [HIV] infection is 30%), assessed only the diagnostic value of HIV-1 and found that infection increases the likelihood of septic arthritis minimally (LR, 1.7; 95% CI, 1.0-2.8).

Symptoms of Septic Arthritis

We found only 6 studies[3,6,15,49-51] that tested the sensitivity of symptoms for

Table 1. Studies of the Performance of Clinical Findings in Diagnosing Septic Arthritis

Source	Study Quality/ Level of Evidence	Location	No. of Patients	Mean Age, y	Study Design	Case Selection	Control Selection	Prevalence of Septic Arthritis, %	Clinical Finding
Kaandorp et al,[42] 1995	1/I	The Netherlands	4889 (total) 37 (cases)	65	Prospective cohort from outpatient rheumatology clinics	Blood culture and synovial fluid or strong clinical suspicion*	Control patients were members of cohort who did not develop septic arthritis	0.25†	Various risk factors
Saraux et al,[43] 1997	2/II	Rwanda	24 (cases) 135 (controls)	30	Prospective case-control series	Hospitalized patients with inflammatory joint disease	Hospitalized patients with malaria	0.50 (HIV positive) 0.25 (HIV negative)	HIV-1 antibody test confirmed with immunoassay or Western blot
Söderquist et al,[44] 1998	3/III	Sweden	54 (cases) 34 (controls)	72 (cases) 78 (controls)	Retrospective case-control series	Hospitalized patients with blood culture and synovial fluid	Crystal plus synovial fluid	Not reported	C-reactive protein, synovial WBC count, glucose, TNF-α, granulocyte colony-stimulating factor, IL-6, IL-8
Krey et al,[45] 1979	3/IV	United States	50 (cases) 312 (controls)	Not reported	Case-control series	Blood culture and synovial fluid	Crystal plus synovial fluid or diagnosis of rheumatoid arthritis‡	Not reported	Synovial WBC count, percentage of polymorphonuclear cells
Shmerling et al,[46] 1990	1/I	United States	100 (total) 8 (cases)	Not reported	Prospective case series	Blood culture plus synovial fluid and blood culture indicated probable septic arthritis§	Crystal plus synovial fluid, diagnosis of rheumatoid arthritis,‡ osteoarthritis, trauma, or miscellaneous (sickle cell, SLE, MCTD, hepatitis B positive), no diagnosis	8	Synovial WBC count, percentage of polymorphonuclear cells, glucose, protein, lactate dehydrogenase
Shmerling et al,[46] 1990	4/III	United States	119 (total) 27 (cases)	Not reported	Retrospective and prospective case series	Blood culture plus synovial fluid and blood culture indicated probable septic arthritis§	Crystal plus synovial fluid, diagnosis of rheumatoid arthritis,‡ osteoarthritis, trauma, miscellaneous (sickle cell, SLE, MCTD, hepatitis B positive), no diagnosis	Not reported	Synovial WBC count, percentage of polymorphonuclear cells, glucose, protein, lactate dehydrogenase
Kortekangas et al,[47] 1992	3/III	Finland	28 (cases) 52 (controls)	57 (cases) 36 & 60 (controls)	Retrospective case-control series	Blood culture and synovial fluid	Blood culture indicated arthritis, diagnosis of rheumatoid arthritis‡ or reactive arthritis‖	35	Fever, synovial WBC count, percentage of polymorphonuclear cells
Jeng et al,[48] 1997	1/I	Taiwan	75 (total) 20 (cases)	55	Prospective case series	Patients in emergency department with acute arthritis and positive synovial cultures	Crystal plus synovial fluid, diagnosis of rheumatoid arthritis,‡ osteoarthritis, reactive arthritis,‖ SLE	27	Peripheral WBC count, erythrocyte sedimentation rate, synovial TNF-α, IL-1, IL-6
Gupta et al,[3] 2001	4/III	Scotland	75	63	Prospective cohort from 11 hospitals serving a population of 2.3 million	Patients identified by rheumatologists or orthopedic surgeons with blood culture and synovial fluid	Control patients were members of cohort who did not develop septic arthritis	0.0016†	Symptoms (joint pain, edema, sweats, rigors) and fever

(continued)

Table 1. Studies of the Performance of Clinical Findings in Diagnosing Septic Arthritis (cont)

Source	Study Quality/ Level of Evidence	Location	No. of Patients	Mean Age, y	Study Design	Case Selection	Control Selection	Prevalence of Septic Arthritis, %	Clinical Finding
Gupta et al,[6] 2003	4/IV	Scotland	82	67	Prospective case series	Patients identified by rheumatologists, orthopedic surgeons, or bacteriologists with blood culture plus synovial fluid or blood culture alone indicated probable septic arthritis§	NA	NA	Symptoms (joint pain, edema, sweats, rigors) and fever
McCutchan et al,[15] 1990	4/IV	United States	41	47	Retrospective case series	Hospitalized patients with blood culture and synovial fluid	NA	NA	Fever
Schlapbach et al,[49] 1990	5/IV	Switzerland	43	57	Retrospective case series	Hospitalized patients with blood culture and synovial fluid	NA	NA	Rigors and fever
Rosenthal et al,[50] 1980	5/IV	United States	63	36	Retrospective case series	Hospitalized patients with a diagnosis of septic arthritis and blood culture plus synovial fluid or positive blood cultures	NA	NA	Fever
Deesomchok et al,[51] 1990	5/IV	Thailand	101	Not reported	Retrospective case series	Hospitalized patients with a diagnosis of septic arthritis and blood culture plus synovial fluid or positive blood cultures	NA	NA	Rigors and fever

Abbreviations: HIV, human immunodeficiency virus; IL, interleukin; MCTD, mixed connective tissue disease; NA, not applicable; SLE, systemic lupus erythematosus; TNF-α, tumor necrosis factor α; WBC, white blood cell.
*Positive culture or direct identification of microorganisms in synovial fluid or tissue, or macroscopic pus produced by arthrocentesis or a clinical presentation of synovitis with rapidly progressive joint destruction without alternative explanation.
†Annual incidence (disease frequency in the study population over 1 year).
‡All patients with rheumatoid arthritis fulfilled the American College of Rheumatology criteria for classic or definite rheumatoid arthritis.
§Probable septic arthritis includes patients partially treated with antibiotics, positive blood cultures, or clinical response to antibiotics.
||All patients with reactive arthritis had purulent joint effusion with negative synovial cultures, but positive serology or bacteriology for *Yersinia* or *Salmonella* gastrointestinal infections, or *Chlamydia* urogenital infections.

diagnosing septic arthritis, and none that evaluated specificity (TABLE 3). Pain in the affected joint is present in 85% (95% CI, 78%-90%) of cases and a history of swelling is present in 78% (95% CI, 71%-85%) of cases. Other symptoms, such as sweats and rigors, are poorly sensitive at 27% (95% CI, 20%-34%) and 19% (95% CI, 15%-24%), respectively.

Signs of Septic Arthritis

Seven studies[3,6,15,47,49-51] show that fever occurs in more than 50% of patients (sensitivity, 57%; 95% CI, 52%-62%). One case-control study[47] of 80 patients evaluated fever as a physical examination finding in patients with either septic arthritis or other acute joint disease; 46% of patients with culture-positive bacterial arthritis had a fever (temperature >37.5°C. In the only study[47] that assessed the LR of fever, septic arthritis was less likely when the patient was febrile (LR, 0.67; 95% CI, 0.43-1.00). We found no additional studies that assessed other examination findings, such as tenderness to palpation, edema, or range of motion of the affected joint.

Serum Laboratory Values

An abnormal peripheral WBC count, ESR, and CRP were found to have limited diagnostic power for changing the pretest probability of septic arthritis, mostly due to their low specificity. In a prospective study[48] of 75 patients presenting to the emergency department with an acute monoarthritis, a peripheral WBC count of more than 10 000/μL increased the likelihood of septic arthritis minimally (LR, 1.4; 95% CI, 1.1-1.8). The same study showed that an ESR of more than 30 mm/h also increased the likelihood of septic arthritis minimally (LR, 1.3; 95% CI, 1.1-1.8).[48] Similarly, a retrospective case-control series demonstrated that a markedly elevated CRP of more than 100 mg/L increased the likelihood of septic arthritis slightly (LR, 1.6; 95% CI, 1.1-2.5).[44]

Synovial WBC Counts and Polymorphonuclear Cells

Progressively higher synovial WBC counts increase the likelihood of septic arthritis (for synovial WBC count <25 000/μL: LR, 0.32; 95% CI, 0.23-0.43; for synovial WBC counts

Table 2. Likelihood Ratios for Risk Factors, Signs, and Serum Laboratory Values

	Source	Sensitivity, %	Specificity, %	Relative Risk	Likelihood Ratio (95% CI)	
					Positive	Negative
Risk factors						
Age >80 y	Kaandorp et al,[42] 1995	19	95	4.1	3.5 (1.8-7.0)	0.86 (0.73-1.00)
Diabetes mellitus	Kaandorp et al,[42] 1995	12	96	2.8	2.7 (1.0-6.9)	0.93 (0.83-1.00)
Rheumatoid arthritis	Kaandorp et al,[42] 1995	68	73	5.4	2.5 (2.0-3.1)	0.45 (0.32-0.72)
Recent joint surgery	Kaandorp et al,[42] 1995	24	96	8.4	6.9 (3.8-12.0)	0.78 (0.64-0.94)
Hip or knee prosthesis	Kaandorp et al,[42] 1995	35	89	4.1	3.1 (2.0-4.9)	0.73 (0.57-0.93)
Skin infection	Kaandorp et al,[42] 1995	32	88	3.6	2.8 (1.7-4.5)	0.76 (0.60-0.96)
Hip or knee prosthesis and skin infection	Kaandorp et al,[42] 1995	24	98	18	15.0 (8.1-28.0)	0.77 (0.64-0.93)
HIV-1 infection	Saraux et al,[43] 1997	79	50	3.2	1.7 (1.0-2.8)	0.47 (0.25-0.90)
Physical examination						
Fever	Kortekangas et al,[47] 1992	46	31	NA	0.67 (0.43-1.00)	1.7 (1.0-3.0)
Serum laboratory values*						
Abnormal peripheral WBC count	Jeng et al,[48] 1997	90	36	NA	1.4 (1.1-1.8)	0.28 (0.07-1.10)
Erythrocyte sedimentation rate	Jeng et al,[48] 1997	95	29	NA	1.3 (1.1-1.8)	0.17 (0.20-1.30)
C-reactive protein	Söderquist et al,[44] 1998	77	53	NA	1.6 (1.1-2.5)	0.44 (0.24-0.82)

Abbreviations: CI, confidence interval; HIV-1, human immunodeficiency virus type 1; NA, not applicable; WBC, white blood cell.
*Defined as abnormal peripheral WBC count of more than 10 000/μL, elevated erythrocyte sedimentation rate of more than 30 mm/h, and elevated C-reactive protein of more than 100 mg/L.

Table 3. Sensitivity of Symptoms and Signs*

Variable	No. of Studies	Sensitivity, % (95% CI)
Joint pain	2	85 (78-90)
History of joint edema	2	78 (71-85)
Fever	7	57 (52-62)
Sweats	2	27 (20-34)
Rigors	4	19 (15-24)

Abbreviation: CI, confidence interval.
*With the exception of the study by Kortekangas et al,[47] the studies reviewed only included patients with septic arthritis, which permits calculation of only sensitivity and not specificity or likelihood ratios.

≥25 000/μL: LR, 2.9; 95% CI, 2.5-3.4; for synovial WBC counts >50 000/μL: LR, 7.7; 95% CI, 5.7-11.0; and for synovial WBC counts >100 000/μL: LR, 28.0; 95% CI, 12.0-66.0) (TABLE 4). Four studies show that polymorphonuclear cells of at least 90% is associated with septic arthritis.[45-47] When the percentage of polymorphonuclear cells is at least 90%, the likelihood of septic arthritis is increased (LR, 3.4; 95% CI, 2.8-4.2); and for polymorphonuclear cells less than 90%, the likelihood decreased (LR, 0.34; 95% CI, 0.25-0.47).

Other Serum and Synovial Markers of Inflammation

TABLE 5 shows abstracted sensitivity and specificity data and calculated positive and negative LRs for other synovial laboratory test results and markers of inflammation. Synovial glucose and protein were evaluated by Söderquist et al[44] in a retrospective case series and by Shmerling et al[46] in a prospective and combined prospective and retrospective case series. A low synovial fluid glucose was not sensitive in the 3 studies (64%, 38%, and 44%, respectively), and specificity was 85% for all 3 studies. Synovial fluid protein levels were determined in only 6 cases in each group, and no differences were found in the study by Söderquist et al. Similarly, elevated protein levels (>3.0 g/dL) were neither sensitive nor specific in the studies by Shmerling et al. The studies by Shmerling et al also looked at lactate dehydrogenase, which was 100% sensitive for septic arthritis but had poor specificity with only half the cases being septic arthritis, resulting in many false-positive test results.

COMMENT

Our systematic review of the literature shows that the quality of evidence describing risk factors, history, and physical examination for the diagnosis of septic arthritis is limited. Only 2 studies, a prospective cohort from outpatient clinics[9] and a case-control series of patients who were hospitalized,[43] assessed risk factors and identified age older than 80 years, diabetes mellitus, rheumatoid arthritis, recent joint surgery, hip or knee prosthesis and/or skin infection, and HIV-1 infection as important risk factors. Most of these risk factors were only useful when present (increasing the likelihood of septic arthritis) and did not substantially lower the likelihood of bacterial infection when they were absent.

Two studies show that joint pain and a history of joint swelling are reasonably sensitive for septic arthritis, but there are no studies addressing the specificity of these symptoms (Table 3). In clinical practice, it is well known that many monoarticular arthritides can present in such a manner. However, these 2 symptoms describe the relevant population in whom septic arthritis should be considered. The sensitivity of fever as a diagnostic test for nongonococcal bacterial arthritis was only 57%, indicating that almost half of patients with septic arthritis will not present with fever, and the absence of fever clearly does not rule out infection. Furthermore, given its poor specificity, the presence of fever does not help the clinician rule in septic

Table 4. Test Characteristics of Synovial Fluid Studies

	Source	Septic Arthritis			
		Sensitivity, %	Specificity, %	Likelihood Ratio (95% CI) Positive	Likelihood Ratio (95% CI) Negative
WBCs >100 000/μL					
	Söderquist et al,[44] 1998	30	93	4.7 (1.1-20.0)	0.75 (0.59-0.96)
	Krey et al,[45] 1979	40	99	42.0 (13.0-138.0)	0.61 (0.49-0.77)
	Shmerling et al,[46] 1990 (prospective)	13	100	31.0 (1.1-914.0)	0.84 (0.64-1.10)
	Shmerling et al,[46] 1990 (retrospective and prospective)	19	100	37.0 (2.0-687.0)	0.81 (0.68-0.97)
	Kortekangas et al,[47] 1992	25	98	12.0 (1.5-97.0)	0.77 (0.61-1.00)
	Summary	29	99	28.0 (12.0-66.0)	0.71 (0.64-0.79)
WBCs >50 000/μL					
	Söderquist et al,[44] 1998	58	74	2.2 (1.1-4.4)	0.57 (0.36-0.90)
	Krey et al,[45] 1979	70	92	8.7 (5.7-13.0)	0.33 (0.22-0.51)
	Shmerling et al,[46] 1990 (prospective)	50	97	15.0 (4.0-58.0)	0.52 (0.26-1.10)
	Shmerling et al,[46] 1990 (retrospective and prospective)	63	97	19.0 (6.0-62.0)	0.38 (0.23-0.63)
	Kortekangas et al,[47] 1992	53	86	3.8 (1.8-8.4)	0.54 (0.40-0.80)
	Summary	62	92	7.7 (5.7-11.0)	0.42 (0.34-0.51)
WBCs >25 000/μL					
	Söderquist et al,[44] 1998	73	58	1.7 (1.1-3.0)	0.47 (0.25-0.90)
	Krey et al,[45] 1979	88	71	3.1 (2.5-3.8)	0.17 (0.08-0.36)
	Shmerling et al,[46] 1990 (prospective)	63	83	3.6 (1.8-7.3)	0.45 (0.17-1.10)
	Shmerling et al,[46] 1990 (retrospective and prospective)	70	83	4.0 (2.4-6.8)	0.36 (0.20-0.66)
	Kortekangas et al,[47] 1992	71	62	1.9 (1.2-2.9)	0.46 (0.24-0.87)
	Summary	77	73	2.9 (2.5-3.4)	0.32 (0.23-0.43)
Polymorphonuclear cells ≥90%					
	Söderquist et al,[44] 1998	92	78	4.2 (3.3-5.3)	0.10 (0.04-0.26)
	Krey et al,[45] 1979	63	82	3.4 (1.7-6.4)	0.46 (0.18-1.20)
	Shmerling et al,[46] 1990 (prospective)	58	83	3.3 (1.9-5.9)	0.51 (0.32-0.82)
	Shmerling et al,[46] 1990 (retrospective and prospective)	57	68	1.8 (1.0-3.0)	0.63 (0.39-1.00)
	Summary	73	79	3.4 (2.8-4.2)	0.34 (0.25-0.47)

Abbreviations: CI, confidence interval; WBC, white blood cell.

Table 5. Other Synovial Fluid Laboratory Test Results

	Source	Sensitivity, %	Specificity, %	Likelihood Ratio (95% CI) Positive	Likelihood Ratio (95% CI) Negative
Low glucose*					
	Söderquist et al,[44] 1998	64	85	4.2 (1.4-13.0)	0.43 (0.24-0.78)
	Shmerling et al,[46] 1990 (prospective)	38	85	2.5 (0.87-6.90)	0.74 (0.43-1.30)
	Shmerling et al,[46] 1990 (retrospective and prospective)	44	85	2.9 (1.5-5.6)	0.66 (0.46-0.94)
	Summary	51	85	3.4 (2.2-5.1)	0.58 (0.44-0.76)
Protein >3.0 g/dL					
	Shmerling et al,[46] 1990 (prospective)	50	46	0.93 (0.45-1.90)	1.10 (0.53-2.20)
	Shmerling et al,[46] 1990 (retrospective and prospective)	48	46	0.89 (0.55-1.40)	1.10 (0.68-1.80)
	Summary	48	46	0.90 (0.61-1.30)	1.10 (0.76-1.60)
LDH >250 U/L					
	Shmerling et al,[46] 1990 (prospective)	100	51	1.9 (1.5-2.5)	0.11 (0.01-1.70)
	Shmerling et al,[46] 1990 (retrospective and prospective)	100	50	1.9 (1.5-2.5)	0.09 (0.01-1.40)
	Summary	100	51	1.9 (1.5-2.5)	0.10 (0.00-1.60)

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase.
*Defined in the different studies as serum/synovial fluid glucose ratio of less than 0.5 or 0.75, synovial fluid glucose level of less than 1.5 mmol/mL, or both. To convert synovial fluid glucose to g/dL, divide by 0.0555.

arthritis (LR, 0.67; 95% CI, 0.43-1.00).[47] Other physical examination findings, such as rigors and sweats, have even lower sensitivity and were not assessed for specificity (Table 3). Similarly, laboratory test results, such as peripheral WBC count, ESR, and CRP, had high sensitivity but very poor specificity.

The history and physical examination are not able to substantially change the pretest probability of septic arthritis in patients with an acutely painful, swollen joint. In most cases, the pretest probability for septic arthritis (range, 8%-27%) is neither sufficiently low nor high enough to direct treatment with confidence. Therefore, arthrocentesis with synovial fluid analysis for WBC count and percentage of polymorphonuclear cells is the best diagnostic tool available for detecting bacterial arthritis while waiting for synovial culture test results.

Synovial fluid glucose, protein, and lactate dehydrogenase are not informative. Other inflammatory markers have been studied but are not readily available to the clinician and therefore were not a focus of our literature search. Assays for cytokines, tumor necrosis factor α (TNF-α), granulocyte colony-stimulating factor, interleukin (IL) 8, IL-6, and IL-1β were examined to see if these markers could differentiate septic arthritis from crystal-associated arthritis, rheumatoid arthritis, reactive arthritis, and lupus. Sensitivity was high with synovial IL-6 and IL-1β performing the best at 100%, but specificity was quite poor for these inflammatory markers, ranging from 3% to 53%. Interestingly, one exception was synovial TNF-α. In the prospective case study by Jeng et al[48] of 75 patients presenting to the emergency department with acute arthritis, synovial TNF-α was 95% sensitive and 71% specific for septic arthritis, with an LR of 3.3 (95% CI, 2.1-5.0). Although synovial TNF-α may be helpful in distinguishing between septic arthritis and other inflammatory arthropathies, it cannot be currently recommended without further evidence, and it would need to be readily available.

The reproducibility of the diagnostic value of synovial fluid WBC counts from 4 studies in markedly different clinical environments suggests that the test is simple and generalizable. Results of the arthrocentesis have the potential to change the clinician's management of patients (ie, starting antibiotics). Arthrocentesis is a relatively benign procedure and complications are rare.[12,18,52-54] Patients are likely to achieve substantial benefit from the test, assuming that joint destruction and morbidity can be avoided with early identification of septic arthritis and appropriate treatment.

The main limitations of our study were the lack of high-quality studies among the included studies and the difficulty in establishing an ideal gold standard. Only 3 of 8 studies were rated as level 1 evidence.[42,46,48] The limited quality of these studies can affect the reported estimates of diagnostic accuracy in either direction. Also, the use of Gram stain and culture as a gold standard test is problematic because prior studies suggest that the sensitivity of Gram stain is only 29% to 50%,[15,30,44,45,47] and the sensitivity of culture may only be 82%.[45] An inadequate gold standard can lead to misclassification of patients with overestimation or underestimation of reported LRs. Currently, the best solution to this problem is to use a combination of Gram stain, culture, and clinical follow-up to detect patients missed by Gram stain and culture alone.

Another significant limitation is the inability to stratify various patient populations within the studies to determine if diagnostic tests operate differently in certain subsets of patients. For example, we were unable to determine if an increased synovial WBC count generates a different LR in patients with septic arthritis who are otherwise well vs patients with chronic rheumatic disease, patients with prosthetic joints, or immunocompromised patients. However, 2 studies did contribute information that these populations are at increased risk. We believe that it is critically important to ask about these risk factors because their presence will increase the clinician's pretest probability for septic arthritis and therefore generate a different posttest probability.

Although the focus of our study was nongonococcal bacterial arthritis, 3 of the included studies included small numbers of patients with *Neisseria gonorrhoeae* infectious arthritis (24 of 6242 patients). We recognize that gonococcal arthritis may have different test characteristics than nongonococcal arthritis. However, we do not believe that the inclusion of this small number of patients with *N gonorrhoeae* infectious arthritis markedly affects the summary LRs that we generated. We do believe it is important for all clinicians to take a detailed sexual history in a patient with an acutely swollen monoarthritis, and to treat for possible *N gonorrhoeae* in patients with known risk factors.

SCENARIO RESOLUTION

Case 1

The individual presented in the first clinical scenario comes to the emergency department with a monoarticular arthritis of the knee. The differential diagnosis includes septic arthritis vs a flare of her rheumatoid arthritis. The prevalence of septic arthritis in the general population presenting to the emergency department with an acutely swollen and tender joint is approximately 18% (midpoint of the range of prevalence estimates, 8%-27%). Because she has rheumatoid arthritis, she is at increased risk for infection (LR, 2.5; 95% CI, 2.0-3.1) and the prior probability of septic arthritis can be revised to 38%.

There are no physical examination findings or maneuvers, such as range of motion or degree of swelling, that have been studied that can help the clinician discriminate between etiologies of the monoarthritis. Her lack of fever is not reassuring given the poor sensitivity and specificity for septic arthritis. Her peripheral WBC count and ESR are both elevated; however, this

may be due to either bacterial arthritis or rheumatoid arthritis.

The synovial WBC count of 48 000/μL has an LR of 2.9 (95% CI, 2.5-3.4) for septic arthritis. Importantly, our review confirms that a low synovial WBC count cannot rule out septic arthritis. A differential for the synovial WBC count should be ordered because if the percentage of polymorphonuclear cells is more than 90%, this will strengthen the clinician's suspicion of bacterial arthritis with an LR of 3.4 (95% CI, 2.8-4.2). Although we do not know if the percentage of polymorphonuclear cells is independently useful when the synovial WBC count is high, her synovial WBC count of 48 000/μL increases the probability from 38% to 64%. The probability of septic arthritis seems high enough and the consequences severe enough that the working diagnosis is septic arthritis, pending the culture test results.

Case 2

The patient's risk factors of age older than 80 years (LR, 3.5; 95% CI, 1.8-7.0) and the presence of diabetes mellitus (LR, 2.7; 95% CI, 1.0-6.9) means the probability of septic arthritis is at least 40% if we start with a prior probability of 18%. However, this patient is unlike the general population in that he has a prior clinical diagnosis of gout, and gout is much more common than septic arthritis.[18] When a diagnosis of gout seems likely, most clinicians would start with a lower prior probability for septic arthritis.

Fever is a nonspecific sign that can be observed in many other diseases, such as gout flares. Because there can be concomitant gout and infection,[28,55,56] clinicians must use their judgment to either treat empirically for gout or to obtain synovial fluid to evaluate for septic arthritis, crystalline disease, or both. Many clinicians would recommend performing an arthrocentesis given that establishing a diagnosis of gout in this patient would be helpful for future presentations, and that the consequences of not treating an infected joint can be devastating.

BOTTOM LINE

When evaluating a patient with a painful, peripheral, swollen joint, the underlying pathology of a monoarthritis may be difficult to diagnose by clinical history and examination alone due to nonspecific symptoms and signs. Identifiable risk factors and the arthrocentesis are most helpful in predicting septic arthritis. In particular, synovial WBC count and percentage of polymorphonuclear cells provide the best utility in identifying septic arthritis while waiting for Gram stain and culture test results. There is no evidence that a patient's symptoms or the physical examination are useful for predicting nongonoccal bacterial arthritis. Future studies should carefully examine the test characteristics of the history, physical examination, and novel synovial fluid laboratory test results to determine if there are any investigative strategies that can provide clinically important benefits for patients with suspected septic arthritis.

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Study concept and design: Margaretten, Kohlwes, Bent.
Acquisition of data: Margaretten.
Analysis and interpretation of data: Margaretten, Kohlwes, Moore, Bent.
Drafting of the manuscript: Margaretten.
Critical revision of the manuscript for important intellectual content: Margaretten, Kohlwes, Moore, Bent.
Statistical analysis: Margaretten, Moore, Bent.
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