**Assessment and diagnosis of the acute hot joint: A systematic review and meta-analysis**

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# Abstract

**Background**

Prompt diagnosis of septic arthritis (SA) in acute native hot joints is essential to reduce unnecessary antibiotics and hospital admissions.

Aim: To evaluate the utility of SF and serum tests in differentiating causes of acute hot joints.

**Methods**

We performed a systematic literature review of diagnostic testing for in acute hot joints. Articles were included if studying ≥1 serum or SF test(s) for an acute hot joint, compared with clinical assessment and SF microscopy and culture. English-language articles only were included, without date restriction. The following were recorded for each test, threshold and diagnosis: sensitivity, specificity, positive/negative predictive values and likelihood ratios.

For directly comparable tests (i.e. identical fluid, test and threshold), bivariate random-effects meta-analysis was used to pool sensitivity, specificity and areas under curve (AUC).

**Results**

8443 articles were identified, 49 ultimately included. Information on 28 distinct markers in SF and serum, differentiating septic from non-septic joints, was extracted. Most had been tested at multiple diagnostic thresholds, yielding a total of 27 serum markers and 156 SF markers.

Due to heterogeneity of study design, outcomes and thresholds, meta-analysis was possible for only eight SF tests, all differentiating septic from non-septic joints. Of these, leukocyte esterase had the highest pooled sensitivity (0.94 [0.70, 0.99]) with good pooled specificity (0.74 [0.67, 0.81]).

**Conclusion**

Our review demonstrates many single tests, individually with diagnostic utility but suboptimal accuracy for exclusion of native joint infection. A combination of several tests +/- stratification score is required to optimise rapid assessment of the hot joint.

Key messages:

1. Rapid exclusion of septic arthritis is required to improve patient outcomes and reduce unnecessary admissions and antibiotic-use.
2. Our review identified many biomarkers with individually good diagnostic utility but suboptimal accuracy to exclude septic arthritis.
3. A panel of synovial fluid and/or serum tests may optimise rapid assessment of hot joints.

# Introduction

The presentation of an acutely hot swollen native joint is common in clinical practice. It can be due to numerous conditions, but it is important to promptly exclude septic arthritis, as it can rapidly destroy cartilage. Acute hot joints commonly arise due to crystal-induced disease (i.e. gout or pseudogout), osteoarthritis, trauma, and a variety of systemic diseases. Relative incidence of each condition varies between populations, but an audit of 137 patients at our centre found 38.7% crystal arthritis (almost equal proportion gout and pseudogout), 19.7% osteoarthritis, 19.7% inflammatory arthritis (including rheumatoid arthritis, psoriatic arthritis), 8.0% septic arthritis, and 13.9% other diagnoses (including traumatic hemarthrosis and osteomyelitis) [1].

All can present with fever, joint swelling, pain and stiffness, mimicking septic arthritis. Crystal arthritis and septic arthritis are particularly difficult to distinguish and may also co-exist. The mortality for in-hospital septic arthritis is 7-15%, despite antibiotic use. The incidence of bacterial arthritis in England is 1 in 49 000/100 000 person-years [2]. Infected joints should be identified and treated in a timely manner.

Early joint aspiration and synovial fluid analysis is essential for diagnosis and management of acute hot joints [3]. Synovial fluid Gram stain, white cell count (WCC), crystal examination and culture should be performed. However, British Society for Rheumatology (BSR) guidelines state “patients with a short history of a hot, swollen and tender joint (or joints) with restriction of movement should be regarded as having septic arthritis until proven otherwise” [4]. Patients are frequently admitted to hospital with antibiotic treatment until results become available. Crystal microscopy, to identify uric acid or calcium pyrophosphate crystals, can be done relatively quickly to aid diagnosis of gout and pseudogout respectively. Ultrasonography is also very efficient and increasingly available to aid diagnosis of crystal arthritis. Both procedures are now routinely part of the hot joint assessment protocol in many units. However, Gram stain and culture results, to exclude septic arthritis, may not be available for hours leading to diagnostic delay. Crystal arthritis and septic arthritis can co-exist, especially as an underlying diagnosis of gout increases the risk of septic arthritis[5].

It is of clinical and financial benefit to seek efficient methods of differentiating septic from non-septic joints. Multiple studies suggest the utility of various biochemical markers in differentiating between a septic and non-septic joint. An increasing number of studies have explored the utility of biochemical markers for the rapid exclusion of prosthetic joint infection (PJI), including synovial fluid alpha-defensin and calprotectin, some now routinely used in clinical practice [6–9]. However, similar tests are lacking for native hot joints [6].

This systematic literature review (SLR) evaluates the use of synovial fluid and serum markers in diagnosing an acute native hot joint, compared to the internationally recognised gold-standard of clinical assessment and synovial fluid analysis (including crystal microscopy and cultures) [3].

# Methods

This SLR was conducted in accordance with the Cochrane Handbook and principles for reviews on diagnostic test accuracy, and reported as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10–12].

The protocol was developed by MD, SD and NG, and registered in the online PROSPERO database of systematic reviews (CRD42018117065) [13]. The search question, framed and structured using the ‘Patients, Intervention, Comparator or Control, Outcome, Type of Study (PICOT)’ format [10], was: What is the utility of testing synovial fluid and serum markers in the presentation of an acute hot joint, compared with current gold-standard practice of clinical assessment combined with synovial fluid aspiration, microscopy and cultures?

Information on scoping searches is available in the supplementary material.

The overall aim of this SLR was to identify tests which are able to identify or exclude septic arthritis in the native acute hot joints. The secondary aim was to identify tests to identify or exclude other common causes of an acute hot joint- crystal arthritis and other inflammatory arthritides.

### Participants

A study was included if participants presented with an acutely swollen hot native joint (i.e. symptoms of under six weeks duration), and were undergoing diagnostic tests, in either the synovial fluid, serum or both, to aid diagnosis and management of the acute hot joint.

### Interventions

Included studies used one or more serum or synovial fluid marker(s) for the diagnosis of an acute hot joint.

Diagnostic tests under study were stratified by the condition intended to be either diagnosed or ruled out by the test. The categories of conditions were: septic arthritis, crystal arthritis and other inflammatory arthritis. These categories were then further sub-classified by whether the test was for serum or synovial fluid.

### Comparator or Control

Clinical assessment and synovial fluid aspiration, with microscopy and culture, was deemed the reference standard [2].

### Outcome

The following outcomes from all studies were recorded: sensitivity and specificity for the test(s) under study; positive and negative predictive values; likelihood ratios. Receiver operating characteristic (ROC) curves, e.g. false positive vs true positive rate, were also recorded where reported.

### Type of study

Observational studies of patients with a native acute hot joint presentation, undergoing test(s) to establish the diagnosis, were included. In most cases, this involved testing serum and/or synovial fluid for the exclusion of joint infection, but studies were also included if the test under study was seeking to diagnose or exclude crystal arthritis or inflammatory arthritis, the two main differential diagnoses for septic arthritis.

Reviews, meta-analyses, comments and editorials were excluded. Case series or case studies comprising ten or fewer cases were excluded.

##

The search strategy was developed by MD, SD and NG, and is available in the supplementary material along with database information and inclusion/exclusion criteria.

All identified full-length articles were uploaded into EndNote VX9 (Clarivate Analytics, PA, USA). Duplicates were subsequently removed. Titles and abstracts were screened by two reviewers, to assess eligibility. The full articles which met initial inclusion criteria were subsequently examined in detail by two reviewers. Any disagreements between reviewers were resolved through discussion or with involvement from a third reviewer. Full-text screening was not performed for three articles due to inability to access the article despite contacting a university library and the authors.

## Assessment of risk of bias, data extraction and synthesis

Risk of bias for each included study was assessed using the Quality Assessment of Diagnostic Accuracy Studies version-2 (QUADAS-2) tool [14]. Details of QUADAS-2, with results for each article, are included in the supplementary material. Data extraction was performed by one reviewer with 20% repeated by a second reviewer for validation. Disagreements were discussed until a consensus was agreed.

For each selected article, in addition to basic information, the following information was extracted: level of evidence; study design; sample size; inclusion and exclusion criteria; prevalence of septic arthritis, crystal arthritis and other arthritis; diagnostic marker(s) under study; gold-standard test (comparator). With regards diagnostic values, the following were extracted from each article: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, true and false positive rates, true and false negative rates.

## Meta-analysis

Bivariate random-effects meta-analyses were used to pool sensitivity, specificity and areas under curve (AUC) for biomarkers which were directly comparable, for tests discriminating septic from non-septic arthritis. A test was eligible for meta-analysis if >1 study used the same marker, threshold and fluid (i.e. serum or synovial fluid). Studies testing the same markers at different thresholds and/or in a different fluid were not eligible for meta-analysis if not replicated in a second study. Meta-analyses were conducted in R (version 3.5.3) by fitting a generalized linear mixed model and using the R package lme4.

# Results

A total of 8443 articles were identified through our initial search across the three included databases (Figure 1). Ultimately, 49 articles were included in the review. Five animal studies were also initially identified, but were ultimately excluded due to lack of comparability between the studies and with human studies. Complete concordance was achieved between reviewers at all stages. Figure 1 summarises the article numbers and retrieval process. Table 1 displays basic information on each included study, including diagnoses under study and biomarkers investigated.

Articles in the final SLR included the following study types: prospective cohort (n=25); prospective cross-sectional (n=2); prospective case-control (n=1); retrospective cohort (n=18); retrospective cross-sectional (n=2); retrospective case-control (n=5); mixed retrospective and prospective cohort (n=1). Four studies comprised a partial or complete paediatric cohort.

Conference abstracts (n=782 after deduplication) were screened separately, with 26 meeting eligibility criteria (Supplementary Figure 1). Only one study included as a full-text article was present in the conference abstracts eligible for inclusion.

Risk of bias assessments for included full-text articles are available in Table 2.

## Differentiation of septic from non-septic arthritis

Most included studies focussed on the differentiation of septic arthritis from non-septic causes of a hot joint (usually from inflammatory arthritis or gout). Synovial fluid markers were investigated in 40 studies [15–54]; serum markers were investigated in seven studies [20,25,38,39,51,52,55]. Markers and thresholds are summarised in Supplementary Table 1. Most markers had been tested at multiple potential diagnostic thresholds, yielding a total of 27 serum markers and 156 SF markers.

The following serum markers were studied: pro-calcitonin, ESR, CRP, WBC, uric acid, TIMP-1, CTX-II, calprotectin. Of these, pro-calcitonin, ESR and CRP and uric acid were tested at multiple thresholds in serum. While serum pro-calcitonin was noted to have excellent specificity (up to a value of 1), sensitivity was noted to be poor (0.087-0.727), with an additional study concluding a sensitivity of 0 for procalcitonin at a serum value 10μg/l. CRP and ESR were conversely noted to have good sensitivity at multiple thresholds, with poor specificity. Of the remaining markers, TIMP-1 and CTX-II had high specificity (0.94 and 0.89 respectively) with poor sensitivity (0.57 and 0.61 respectively), with calprotectin having moderately good values for both (sensitivity 0.65, specificity 0.77).

There were a far greater number of synovial fluid than serum markers tested for the differentiation of septic from non-septic arthritis. Due to heterogeneity of study design, outcomes and diagnostic thresholds, meta-analysis was possible for only eight tests in synovial fluid, all differentiating septic from non-septic joints. Results (pooled sensitivity, specificity and AUC) are summarised in Table 3 and Figure 2. All tests were conducted in synovial fluid, with the following markers investigated: glucose, lactate, leukocyte esterase, polymorphonucleocytes (PMNs), pro-calcitonin, tumour necrosis factor-α (TNFα), WCC. Overall, of these tests, leukocyte esterase had the highest pooled sensitivity (0.94 [0.70, 0.99]) with good pooled specificity (0.74 [0.67, 0.81]).

## Differentiation of crystal from non-crystal arthritis

Two studies investigated synovial fluid biomarkers for the exclusion of gout [31,56]. One of these also investigated the exclusion of calcium pyrophosphate disease or pseudogout (CPPD) using the presence or absence of CPPD crystals) [31]. A third study looked at the exclusion of all crystal arthritides (using synovial fluid WCC <1650/mm3) [57]. With regards studies investigating the differentiation of gout from non-gout causes of a hot joint, one studied the utility of a synovial fluid to serum uric acid ratio of ≥1.01 [56], yielding a sensitivity of 0.896 (0.81, 0.95) and specificity of 0.663 (0.56, 0.75). The second study investigated the utility of synovial fluid monosodium urate crystals [31]. For the utility of monosodium urate crystals to distinguish gout from non-gout causes of a hot joint, sensitivity was 0.89 (0.72, 0.98) and specificity 1.00 (0.97, 1.00), as would be expected based on current clinical practice. For CPPD to differentiate between CPPD disease from non-CPPD hot joints, sensitivity was 0.93 (0.80, 0.98) and specificity 0.88 (0.78, 0.94). Results from all studies are summarised in Supplementary Table 1.

## Differentiation of inflammatory from non-inflammatory arthritis

The definition of “inflammatory arthritis” varied between studies, but mostly referred to diagnoses including autoimmune inflammatory arthritis, crystal arthritis and septic arthritis. This differentiation of inflammatory vs non-inflammatory arthritis has limited clinical utility due to the widely varying treatment for each of these diagnoses. Four studies focussed on the differentiation of inflammatory from non-inflammatory causes of a hot joint, investigating the utility of eight synovial fluid biomarkers (adenosine deaminase, high-sensitivity C-reactive protein [hs-CRP], WCC, PMNs, glucose, total protein, lactate dehydrogenase [LDH], leukocyte esterase), summarised in Supplementary Table 1 [58–61]. Of the synovial fluid markers tested, adenosine deaminase, CRP, WBC, LDH and leukocyte esterase were noted to have good levels of sensitivity and specificity but results were limited by the fact that studies aimed to differentiate multiple inflammatory arthritides (including septic, crystal and rheumatoid) from non-inflammatory diagnoses such as osteoarthritis, limiting their utility in clinical practice. No studies looked at serum biomarkers in the differentiation of inflammatory from non-inflammatory arthritis in the acute hot joint setting.

Meta-analysis was not possible for studies investigating markers to differentiate crystal from non-crystal arthritis, or inflammatory from non-inflammatory arthritis, due to heterogeneity in study design, markers and thresholds.

# Discussion

This systematic review identified a large number of studies of medium-high quality, highlighting several single tests that may have diagnostic utility for differentiating septic from non-septic arthritis. It is important to promptly exclude joint sepsis in acute settings. Our review demonstrates that based on current evidence, joint aspiration and synovial fluid testing remain necessary to facilitate this. However, our review identifies additional tests to those used in current clinical practice which may facilitate more efficient exclusion of septic arthritis.

Our review demonstrates many single tests with some evidence for diagnostic utility. Individually, all have suboptimal accuracy and sensitivity when compared with the gold-standard, for exclusion of native joint infection. A far greater number of synovial fluid than serum tests were identified. However, not all are readily available or validated for exclusion or diagnosis of septic arthritis e.g. pro-calcitonin (PCT), TNF-alpha. The individual biomarker with greatest sensitivity and specificity was synovial fluid leukocyte esterase, a relatively cost-effective, quick and easy test that could be conducted in acute clinical settings to give early indication of septic arthritis. However, further testing would be required before this could be used in in place of synovial fluid microscopy and culture in routine clinical care.

It is possible that a panel of individual serum and synovial biomarkers may yield better early diagnostic accuracy for 1) diagnosis of septic arthritis, or 2) exclusion of septic arthritis.

A far greater number of markers, tested at multiple threshold for differentiation of septic from non-septic joints, were identified in synovial fluid [15–40,42–54,62–65]. This may reflect the fact that, early in septic arthritis, infection may be confined to the joint space, therefore synovial fluid sampling, including culture, is key to diagnosis. Septic arthritis arises due to bacterial deposits in the synovial membrane, leading to acute inflammation. Bacteria can easily enter the joint space as synovial tissue has no basement membrane [2]. The severity of infection may therefore not be represented by levels of serum markers early in the disease process.

In clinical practice, it is crucial to be able to distinguish reliably between septic and crystal arthritis, which have similar presentations. Synovial fluid microscopy and culture are already able to do this; however, culture results take several hours-days to be processed. In addition, rarer causes of joint infection, such as tuberculosis, Brucella and fungi, will not be identified by usual culture methods. Polarising microscopy to identify CPPD or uric acid crystals can be done relatively quickly, sometimes within the rheumatology unit [66,67]. Ultrasonography is also increasingly available to identify the characteristic double-contour sign of gout as well as presence of CPPD [68]. However, even in the presence of confirmed gout, septic arthritis may co-exist [5].Furthermore, in the emergency setting, such as emergency departments or out of hours, these resources may not always be available. It is necessary to be able to promptly predict a diagnosis of infection accurately, with tests with high sensitivity and good specificity.

Other important causes of an acute hot joint include a flare of inflammatory arthritis and osteoarthritis. We identified seven studies which tested the utility of serum markers to distinguish septic from non-septic joints [20,25,38,39,51,52,55]. Markers included CRP, pro-calcitonin and ESR at multiple thresholds, as well as uric acid and calprotectin. It is important to note that serum uric acid often paradoxically decreases during flares due to increased renal clearance and is therefore not an accurate marker of acute gout [69]. Both specificity and sensitivity of serum CRP and ESR, regardless of threshold were suboptimal. Pro-calcitonin was found to have high specificity, above 0.9, regardless of threshold, for septic arthritis. However, sensitivity was consistently low, (0.35-0.55) [20,38]. This is a limitation, as it is important to reliably exclude septic arthritis when using this test in the acute setting.

Meta-analysis was possible for eight tests (of same marker, fluid and threshold), identifying leukocyte esterase in synovial fluid as the marker with the most optimal pooled sensitivity and specificity for septic arthritis [24,42,48,62]. This is a simple point-of-care “dipstick” test, usually undertaken on urine, making this a potentially cost-effective and quick screening test for joint infection. The evidence for its use in PJI is well-established, where synovial fluid leukocyte esterase may be used as part of the diagnostic work-up [70,71], and sensitivity and specificity for infection is high. However, there are limitations to its precision and readability, and it most likely to be useful as part of a panel of tests.

Another synovial fluid biomarker commonly used in the diagnosis of PJI is alpha-defensin. However, we identified no studies on the use of this marker in native septic arthritis. It may be interesting for future studies to evaluate its use in the native hot joint setting. It is, however, important to note several differences between prosthetic and native joint infections, which may account for the limited use of markers such as alpha-defensin and leukocyte esterase, and the overall lack of research in native joint infection markers [72]. An important difference is in the pathogenesis, crucially the formation of a biofilm in PJI aids the survival and growth of bacteria and, if left to mature, can lead to difficult-to-treat chronic PJI. Another key difference is the feature of blood cultures in the definition for septic arthritis, and its absence from PJI criteria [73,74]. This has led to the development and use of alternative diagnostic tests in PJI, while blood cultures remain key to the diagnosis of septic arthritis, along with physician or clinical assessment.

Tests such as glucose, pH and WCC levels are easy to conduct, quick and cost-effective. Meta-analysis of glucose and WCC in synovial fluid at same thresholds found high pooled specificity but low sensitivity. However, one study testing the use of a glucometer at a threshold of 1.4mmol/l demonstrated greater sensitivity for joint infection [15]. Similarly, sensitivities for synovial fluid WCC, at various thresholds, were wide-ranging, suggesting further work is required in this area to assess its utility to distinguish joint infection. It is also important to note that smaller joints may have a higher WCC than larger ones in the presence of similar clinical inflammation, which can also be misleading [75]. Lactate is another marker which is easy and cost-effective to test, and at a threshold >10mmol/L in synovial fluid, had best specificity. However, overall results were variable between the included studies. A marker which is less widely-available, but may have diagnostic utility and was investigated by two studies, is synovial fluid PCT [20,38]. PCT in serum has been shown to be a useful early indicator of sepsis [76], and from these initial two studies, it appears to be able to distinguish between an infected and non-infected joints at certain thresholds. This is a biomarker which certainly warrants further research in this area.

Of the included studies, seven aimed to either distinguish crystal from non-crystal, or inflammatory from non-inflammatory arthritis [31,56–61]. It is ultimately most important to distinguish an infected from non-infected joint, perhaps reflected by the small numbers of studies focussing on non-infectious causes of a hot joint. Nonetheless, this raises the question of whether a panel of rapid tests for synovial fluid, each with high sensitivity and specificity for a given diagnosis, may be of greater utility in the acute setting than a single test. This would not simply exclude infection as a cause of the hot joint, but also provide an indication as to the possible cause, while more specific tests are awaited. For example, one included study found sensitivity and specificity of 0.9 or greater for synovial fluid calcium pyrophosphate crystals and monosodium urate crystals for pseudogout and gout respectively [31].

Studies have shown that no single biomarker, in serum or synovial fluid, can diagnose or exclude septic arthritis alone [25]. It requires a combination of clinical findings, physical examination and multiple laboratory investigations, some of which may be feasible at point-of-care to form a panel or score. Scores using multiple biomarkers are reliable in identifying septic arthritis in acute hot joints, comprising synovial fluid lactate, WCC, crystals and glucose tests [77]. Similar criteria or scores are used in other specialties to aid diagnosis, such as in pleural effusions in which Light’s criteria (comprising lactate dehydrogenase and protein levels) to distinguish a transudative from exudative effusion, and the use of pH to distinguish a complicated from uncomplicated parapneumonic effusion [78]. Give the variation in utility of tests identified in this review, it is likely that a panel of multiple tests, rather than a single test, would be of greater benefit and accuracy in the acute setting when assessing hot joints. Based on our results, such a panel may comprise synovial fluid lactate, WCC and leukocyte esterase, along with point-of-care uric acid identification which is already available. However, further work, including validation of such tests is required.

## Strengths and limitations

Our review has several strengths. To our knowledge, this is the first review of this scale undertaken to compare tests used in the setting of an acute hot joint, in a largely understudied area. We identified a large number of papers, enabling comparison of many synovial fluid and serum markers at multiple thresholds and for multiple diagnoses in the acute hot joint setting. We were able to extract a large volume of data to facilitate these comparisons and analyse this topic in depth. However, our study was limited by the fact that many markers were tested at multiple thresholds and meta-analysis is only possible where markers are tested for a given diagnosis at a specified threshold. Therefore, meta-analysis was only possible on a small number of markers. Nonetheless, valuable comparisons were possible even in the absence of meta-analysis for those studies where this was not possible. Additionally, the nature of acute hot joints means that multiple potential diagnoses are possible, which can help as well as hinder comparisons across studies. We stratified studies by septic vs non-septic, crystal vs non-crystal and inflammatory vs non-inflammatory arthritis, to facilitate comparisons between markers testing for the same diagnoses.

## Conclusion

Our review demonstrates the potential of multiple individual tests in synovial fluid and serum which may be able to facilitate prompt exclusion of joint sepsis in the acute setting. Having a reliable score or testing panel to distinguish septic from non-septic arthritis in acute hot joints would ensure antibiotic treatment is delivered promptly where needed, and avoided where there is very low likelihood of infection, avoiding complications such as unnecessary admissions and antimicrobial-use. Further work developing testing panels including serum, urine and synovial panels of tests to facilitate prompt bedside diagnosis is essential. If effective this could be employed in emergency care and even primary care setting to reduce the need for hospital admission and unnecessary antibiotic use.

Data available upon request.

Authors declare no conflicts of interest.

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| **Source** | **Study quality/ Level of evidence** | **Country** | **Sample size** | **Median age (y)** | **Study design** | **Inclusion criteria** | **Exclusion criteria** | **Prevalence of septic arthritis (%)** | **Prevalence of crystal arthritis (%)** | **Prevalence of other diagnosis (%)** | **Diagnostic marker** | **Gold-standard** |
| Aliste-Fernández 2020 [57] | 2b | ESP | 205 | 64 (mean) | Prospective cohort | Acute or chronic arthritis with joint effusion. | Nil described | 7.8 | 22 | 70.2 | SF WBC | Diagnosis of gout/pseudogout: Polarized light microscopy to examine all samples for microcrystals |
| Baillet 2019 [35] | 1b | FRA | 74 | SA: 66, PG: 81, RA: 63 | Prospective cohort | Acute monoarthritis with inflammatory synovial fluid (i.e. with white blood cell count >2000/mm3 and >80% neutrophils) consistent with septic arthritis. | Nil described | 35.14 | 37.84 | 27.03 | Calprotectin, alpha-defensin | Positive synovial fluid/blood culture |
| Baran 2014 [21] | 2b | USA | 96 | 47 | Retrospective case-control | Hip or knee symptoms suggestive of septic arthritis requiring arthrocentesis. | Age < 18, inmate in the county jail, at the time of aspiration, synovial fluid analysis done at outside facility, results listed as contaminants, prosthetic joints, repeat aspirate shows negative culture . | 45.83 | N/A | N/A | Percentage polymorphonuclear cells in synovial WBC | Positive synovial culture |
| Berthoud 2020 [45] | 2b | FRA | 233 | 61.8 (mean) | Prospective cross-sectional | Age > 18 years, acute joint effusion on a native joint, atraumatic, evolving for less than 30 days. | Nil described | 10.7 | 44.6 | 44.7 | SF lactate & glucose | Newman's criteria and SF analysis when one of the following present: pathogen was isolated from SF; pathogen isolated from blood culture with typical clinical presentation for septic arthritis; arthrocentesis revealed purulent SF with clinical presentation for septic arthritis, absence of crystals and absence of other suitable diagnoses. |
| Bonilla 2011 [26] | 2b | USA | 63 | N/A | Retrospective cohort | Patients with clinically suspected infection, inflammatory arthritis, or normal joints under evaluation by the rheumatologist. | Not described | 25.4 | 0 | 74.6 (inflammatory and normal) | SF 16S rDNA PCR | SF culture |
| Borzio 2016 [28] | 2b | USA | 458 | 51.7 | Retrospective cohort | Patients undergoing arthrocentesis and septic arthritis of the knee and shoulder. | Incomplete clinical or imaging data, atypical patients, periprosthetic infections, postoperative septic arthritis, and associated proximal femoral osteomyelitis. | 4.8 | N/A | N/A | SF WBC | SF culture |
| Bram 2018 [29] | 2b | USA | 302 | 6.0 (4.5) | Retrospective cohort | All patients with suspected SA who underwent arthrocentesis and subsequent surgical irrigation and debridement. | Patients who underwent foreign body removal, or with contiguous osteomyelitis and/or pyomyositis. | 34 | N/A | 16% had positive Lyme titers | SF Gram stain | SF culture |
| Carpenter 2020 [46] | 2b | USA | 71 | 58 (mean) | Prospective cohort | Acute monoarticular knee symptoms, possible septic arthritis, with at least 10ml SF aspirated. | Failure to obtain consent or use of antibiotics within 72hrs. | 7 | N/A | 93 | SF lactate, SF PCR, SF WBC | SF bacterial growth |
| Cohen 2019 [36] | 2b | ISR | 1024 | 63 | Retrospective cohort | all synovial fluid specimens that were analysed in the microbiology laboratory between 2002 and 2016 of a single general medical centre. | Nil described | 62.3 | N/A | N/A | Bottled culture broth (Bactec) | positive culture on agar or a combination of clinical findings highly supporting the diagnosis with a negative culture |
| Coiffier 2013 [60] | 2b | FRA | 98 | N/A | Prospective cohort | Patients evaluated for joint effusion at a rheumatology department at a single centre over 12 months. | Nil described | 7.1 | 30.6 | 62.3 | Leukocyte esterase | Leukocyte count per mm3, with microbiological cultures for 72 hours; polarized light microscopy |
| Coiffier 2019 [37] | 1b | FRA | 95 | Mean 57.7 | Retrospective cross-sectional | Adults (≥ 18 years old) referred for acute monoarthritis or oligoarthritis (progression < 6 weeks) on native joint and who received a diagnostic joint fluid puncture. | Nil described | 35.9 | N/A | N/A | 16s rDNA PCR | Newman’s criteria, SF direct examination and culture, blood culture |
| Colvin 2015 [24] | 2b | USA | 5 | N/A | Retrospective cohort | Clinical suspicion of septic arthritis. | Patients with insufficient fluid or blood-stained SF. | 20 | N/A | 80 | Leukocyte esterase | Positive synovial fluid culture |
| Couderc 2015 [25] | 1b | FRA | 105 | N/A | Prospective cohort | Patients with suspected septic arthritis. | Prosthetic joint; trauma; <18yrs. | 36.2 | N/A | 63.8 | Serum WBC >10000/mm3 ; ESR> 15 mm; ESR> 50 mm; ESR> 100 mm; CRP>15 mg/L; CRP>100 mg/L; Uric acid> 420 mg/L; SF WBC >10000/μL; SF WBC >10000/μL; SF WBC >50000/μL; SF WBC >100000/μL ; PMNs >90% ; Presence of microcrystals ; Positive Direct Gram Stain  | Synovial fluid culture with clinician assessment and diagnosis |
| Couderc 2019 [39] | 1b | FRA | 39 | Mean 64.5 | Prospective cohort | Patients with suspicion of SA. | Nil described | 53.85 | 28.21 | 12.82 | Serum and SF metalloproteinase MMP-2, MMP-9, tissue inhibitor of MMP (TIMP-1), cartilage oligomeric matrix protein (COMP), C-terminal telopeptide of type II collagen (CTX-II), and calprotectin (CALP) | microorganisms from synovial fluid or blood cultures |
| Cunningham 2014 [19] | 3b | DEU | 273 | N/A | Prospective cohort | Adult patients hospitalised for suspicion of septic arthritis (prosthetic joints included, therefore values for native joints calculated by reviewer). | Nil described | 73 | N/A | 27 | Gram stain | Positive synovial fluid culture |
| Curtis 1983 [30] | 2b | UK | 238 | Not described | Prospective cohort | Specimens that arrived in the laboratory for routine culture, further 38 fluids from patients with non-septic conditions. | Specimens without refrigeration for more than six hours. | 7.98 | 4.20 | Viral arthritis 2.10; acute osteomyelitis 1,68%; osteogenic sarcoma 1.26%; osteoarthrosis 26.05%; recent trauma 15.97%; coagulopathies 1.26%; RA 28.99%; Reiter’s syndrome 3.36%; connective tissue diseases 6.30% | SF lactate | SF culture |
| Ferreyra 2016 [31] | 2b | FRA | 208 | 59.6 +- 18.5 | Retrospective cohort | Patients older than 18 years enrolled in either of two cohorts: SPECTROSYNO cohort of patients with acute or chronic monoarthritis, oligoarthritis, or polyarthritis investigated by joint aspiration; and DNAr16S cohort of patients who underwent joint aspiration for onset of monoarthritis or oligoarthritis within the last 6 weeks. | Incomplete joint fluid data, cytological results expressed semi-quantitatively, septic arthritis due to nonpyogenic organisms, septic arthritis without micro-biological documentation. | 13.46 | Chondrocalcinosis 19.71%; gout 13.46% | RA 15.87%; SpA 14.90%; OA 8.65%; undifferentiated arthritis 13.94% | Absolute leukocyte count, Absolute neutrophil count, Differential neutrophil count, monosodium urate, CPPD | SF/blood culture for septic arthritis. clinical findings, blood and joint fluid test results, and the radiographic appearance for the other diagnosis |
| Foocharoen 2011 [32] | 2b | THA | 40 | 52.3+-17.4 | Retrospective cohort | Patients over 15 years of age with clinically suspected TB arthritis or having an unknown aetiology of their arthritis that were candidates for arthrocentesis. | Not described | 24.2% (all septic arthritis); 16.7% (TB arthritis); 7.5% non-TB bacterial septic arthritis | 0 | RA 20%; miscellaneous 57.5% | SF adenosine deaminase | SF culture for *Mycobacterium tuberculosis* |
| Garg 2018 [61] | 4 (“Use of a non-independent reference standard (where the ‘test’ is included in the ‘reference’, or where the ‘testing’ affects the ‘reference’) implies a level 4 study.”) | IND | 100 | Not described | prospective, observational and cross-sectional | All the patients of any age with one or more joint effusions were included in this study. | Uncontrolled diabetes mellitus, cutaneous soft tissue infections mimicking acute arthritis. | 10% (6% tuberculous arthritis; 4% septic arthritis) | 3 | OA 22%, RA 16%, trauma 3% | WBC | Gross examination, WBC, viscosity, % PMNs, Gram stain, culture, red blood cells presence, crystals presence |
| Gautam 2017 [33] | 2b | IND | 27 | 22.32 +- 19.20 | Prospective cohort | Any age; acute monoarticular disease of major joint; clinical symptoms: acute onset, fever, limping while walking, unable to bear weight on the affected extremity, severe pain even on gentle passive movement, pseudoparalysis in children. | Poor skin condition; presence of sinus; presence of blood in aspirate; known case of haemophilia or any other bleeding disorder; patients who give definite history of antibiotic intake for the same condition; proven case of any other joint pathology. | 77.78 | N/A | N/A | SF Leukocyte esterase; Gram stain; CRP; ESR | SF culture |
| Gbejuade 2019 [47] | 2b | GBR | 830 | N/A | Retrospective cohort | Suspected septic arthritis with SF samples taken. | Results show possible contaminants; patient details duplicated; samples sent for possible TB; culture and Gram stain reports unavailable. | 12 | N/A | 88 | SF Gram stain | SF culture |
| Gratacos 1995 [34] | 3b | ESP | 17 patients (20 samples) with proven septic arthritis | N/A | Retrospective case-control | Unclear – collected over 3-year period, non-consecutive. | Nil described | 16.81 | 21.84 | 61.34 | Synovial D-lactic acid, %PMN, WBC, gram stains. | Included patients already had diagnosis by synovial culture |
| Hassas Yeganeh 2020 [48] | 3b | IRN | 68 | N/A | Retrospective case-control | Suspected JIA or septic arthritis. | Nil described | 50 | N/A | 50 | SF leukocyte esterase | JIA: ILAR criteria; SF culture and SF WBC >50000/ml |
| Jeng 1997 [18] | 2b | TWN | 75 | N/A | Prospective cohort | Patients with suspected bacterial arthritis. | Nil described | 27 | 27 | 46 | SF TNFα | Positive SF bacterial culture |
| Kim 2010 [17] | 3b | KOR | 80 | N/A | Prospective cohort | Patients with suspected septic arthritis. | Nil described | 34 | N/A | 66 | Multiplex PCR | Positive SF bacterial culture and clinician assessment |
| Kinugasa 2019 [40] | 1b | JPN | 30 | Mean 4.5 | Prospective cohort | clinical features of SA; laboratory data suggesting inflammatory disease (≥38.0°C, WBC count>12 000 cells/mm3, or a serum CRP level of 2.0 mg/ dl); increased SF on USS or MRI. Paediatric cohort. | Nil described | 56.67 | N/A | 43.33 | SF glucose; Serum CRP; SF WCC | SF culture positive |
| Kunnamo 1986 [54] | 3b | FIN | 129 | N/A | Mixed retrospective and prospective cohort | Patients undergoing joint aspiration for suspected septic arthritis or for therapeutic aspiration for intra-articular steroid. | Nil described | 10 | N/A | 90 | SF WBC | Positive SF bacterial culture |
| Lenski 2014 (1) [52] | 2b | DEU | 82 | N/A | Retrospective cohort | All patients with culture-verified septic arthritis and gout arthritis, presenting during study period. | Nil described | 53 | 29 | 18 | Serum WBC; Serum CRP; Serum uric acid; SF lactate; SF glucose; SF uric acid; SF LDH; SF WBC; SF total protein; SF IL6 | SF culture, SF crystal microscopy |
| Lenski 2014 (2) [53] | 4 | DEU | 119 | N/A | Retrospective case-control | All patients requiring arthrocentesis for suspected native septic arthritis, based on 3/5 of following: pain, redness, swelling, heat, impaired ROM. | Peri-prosthetic infections | 53 | N/A | 47 | SF IL6; SF total protein; SF glucose; SF lactate; SF WBC | Positive bacterial culture |
| Li 2007 [51] | 2b | USA | 156 (13% paeds) | 53 | Retrospective cohort | Adults and children undergoing arthrocentesis during study period. | Dry taps | 10 | 38 | 52 | Serum WBC; Serum ESR; SF WBC; Combination of WBC/ESR/SF WBC | SF culture positive; Intraoperative findings consistent with septic arthritis |
| Logters 2009 [50] | 2b | DEU | 42 | N/A | Prospective cohort | Acutely inflamed joints | Dry taps | 21.4 | N/A | 78.6 | SF cf-DNA; SF IL6; SF TNFa; SF IL1 beta; SF MPO | SF culture positive; Intraoperative findings consistent with septic arthritis |
| Logters 2010 [49] | 1b | DEU | 41 | N/A | Prospective cohort | Acutely inflamed joints | Dry taps | 30 | N/A | 70 | SF tryptophan; SF kynurenine; Kyn/trpt ratio | SF culture positive; Intraoperative findings consistent with septic arthritis |
| Lu 2019 [79] | 1b | CHI | 70 |  | Prospective cohort | Gouty arthritis, RA and OA involving the knee and knee swelling with effusions by examination. | Patients developing more than one joint disease. Use of warfarin or antiplatelet therapy. Presence of infection. | N/A | 28.6 | 71.4 | serum/ SF urate ratio | Gouty arthritis was defined as presence of MSU in SF determined by compensated polarized light microscopy previously or currently |
| Martinot 2005 [38] | 1b | FRA | 42 | 66.6 | Prospective cohort | Patients hospitalised for acute arthritis, with: bacterial arthritis, crystal arthritis, rheumatoid arthritis. | Patients without one of the 3 described conditions. | 26.1 | 31 | 42.9 | Serum PCT; SF PCT | SF/serum culture; SF microscopy |
| McGillicuddy 2007 [27] | 2b | USA | 49 | 63 | Retrospective cohort | >16yrs; diagnosed by septic arthritis by SF culture. | Nil described | 100 | N/A | N/A | SF WBC | SF culture |
| Mico 2015 [16] | 3b | ESP | 7 | N/A | Prospective cohort | Joint fluid samples with higher probability of positive outcome. | Nil described | 85.7 | N/A | 14.3 | SF FilmArray blood culture identification (PCR) | SF culture |
| Morgenstern 2018 [65] | 2b | GER | 57 | 62 | Prospective cohort | >18yrs, with acute inflammatory native hip or knee. | SF volume <5ml aspirated | 38.6 | N/A | 61.4 | PCR, microcalorimetry | SF/synovial tissue culture positive, or local inflammation, increased SF leukocytes, absence of non-infectious arthritis |
| Mortazavi 2019 [42] | 2b | IRN | 25 | 2.8 (mean) | Prospective cohort | Suspected hip or knee SA undergoing arthrocentesis in children 18yrs or younger. | Findings suggestive of any other diagnosis; insufficient SF; rheum disorders; immunodeficiencies; autoimmune disease; renal failure. | 76 | N/A | 24 | Leukocyte esterase strip  | 1 or more of the following: (1) positive SF culture, (2) positive bacterial smear, (3) WBC count in the SF > 50×103 plus positive blood culture, (4) purulent SF |
| Omar 2014 [62] | 2b | DEU | 146 | 59 | Prospective cohort | Atraumatic joint effusion of shoulder/ elbow/ hip/ knee. | Nil described | 13 | 31.5 | 55.5 | SF leukocyte esterase; SF leukocyte esterase + glucose | SF crystal analysis; Newman criteria- One of following: SF/serum culture positive; Purulent SF, no crystals |
| Omar 2017 [15] | 2b | DEU | 102 | 61 | Prospective cohort | Atraumatic joint effusion of shoulder/ elbow/ wrist/ hip/ knee/ ankle. | Patients with joint arthroplasty | 14.7 | N/A | 85.3 | SF glucose via glucometer | One of the following: Newman criteria; SF/serum culture positive; Purulent SF in absence of crystals; Negative micro, but SF WBC >50000/mm3 and %PMN >75%, no crystals |
| Shmerling 1990 [59] | 2b | USA | 100 | N/A | Prospective cohort | All synovial fluid samples received at haematology or chemistry lab at Beth Israel Hospital November 87 – October 88. | Samples sent only to microbiology; Bursal fluid specimens; Repeated aspiration from same patient. | 8 | 25 | 66% (26% no diagnosis, 40% other diagnosis) | Protein, glucose, LDH, lactate, WBC, % PMN | Septic arthritis – synovial culture. Crystal arthritis – microscopy for intracellular crystals. RA – ACR criteria. |
| Shu 2019 [43] | 2b | USA | 40 | 51 (mean) | Prospective cohort | Arthrocentesis for a swollen or painful joint, with at least 1ml extra SF obtained. | Nil described | 27.50 | 22.50 | 50 | SF lactate, cloudy SF, warmth/erythema, WBC (50000 or 100000), PMN, Gram stain, micromotion tenderness | (1) SF culture positive or (2) septic arthritis diagnosed by orthopedists with surgical intervention and IV antibiotics given during the hospital stay, even if cultures negative |
| Sigmund 2019 [44] | 2b | AUT | 72 | 64 (mean) | Prospective cohort | Suspected septic arthritis | Insufficient data or SF | 58.30 | N/A | 41.70 | Automated multiplex PCR; SF culture; combination | Pathogenic organism in affected joint; pathogenic organism from another source, e.g. blood in the context of a hot, red joint suspicious of sepsis; typical clinical features and turbid joint fluid in the presence of previous antibiotic treatment; post-mortem or pathological features of septic arthritis; and leucocyte count > 50 000/µl or PMN> 90% in synovial fluid. |
| Thornton 2019 [55] | 2b | GBR | 190 | 63 | Retrospective cohort | Patients requiring native joint aspiration. | Recent surgery or joint injection; prosthetic joints; paediatric patients; overlying cellulitis. | 78.9 | 9.5 | 82.6 | Serum CRP | Consultant clinician overall interpretation of investigations and clinical presentation. Ix include SF WBC, crystals, extended culture, peripheral WBC, CRP |
| Vaidya 2018 [56] | 2b | NPL | 181 | 51.5 | Retrospective cross-sectional | Pain and swelling in one or multiple joints onset ≤1 day. | Chronic joint pain (>14 days), known RA/SpA/gout on treatment DMARDs/ urate lowering therapy, those not willing to give consent. | 0 | 52.50 | 47.50 | Synovial fluid to serum uric acid ratio ≥1.01 (diagnosis of gout) | Gout - ACR/EULAR 2015 criteria. RA - ACR/EULAR 2010 criteria. SpA – ASAS criteria. AnkSpA - modified New York criteria. Pseudogout - chondrocalcinosis by Xray or SF aspirate. |
| Wang 2014 [76] | 2b | China | 95 | N/A | Retrospective cohort | Patients from outpatient clinic Jan 12 – June 13. | Arthritis other than SA, RA, OA or GA. Artificial joints. Patients with SA excluded if culture negative; RA, OA and GA patients excluded if culture positive. | 24.20 | 11.60 | 64.20 | Serum procalcitonin, SF procalcitonin | ACR criteria and bacterial culture of SF |
| Wiener 2008 [23] | 2b | Switzerland | 30 | N/A; Mean = 58 | Retrospective cohort | Referrals by orthopaedic surgeons of suspected septic arthritis July 1 2004 - June 2007. | Aspirate <10ml | 33.33 | N/A | N/A | Lactate concentration and T2 relaxation time in MR (synovial fluid)  | Positive synovial culture |
| Yang 2008 [22] | 2b | USA | 121 | N/A | Retrospective cohort | Suspected acute septic arthritis in ED, ortho clinic or rheum clinic July 06-07. | Nil described | 17.40 | N/A | N/A | PCR assay 16S rRNA gene | Synovial culture |
| Zamani 2012 [58] | 2b | IRN | 75 | N/A | Retrospective cohort | Knee monoarthritis; Joint effusion requiring arthrocentesis. | Nil described | 4 | 17.3 | 78.7 | SF adenosine deaminase; SF hs-CRP | SF/serum culture; SF crystal microscopy |

**Table 1: Details of studies included in systematic review.** SA= septic arthritis. SF=synovial fluid. ROM=range of movement. JIA=juvenile idiopathic arthritis. WBC=white blood cells. PCR=polymerase chain reaction.

|  |  |  |
| --- | --- | --- |
| **STUDY** | **RISK OF BIAS** | **APPLICABILITY CONCERNS** |
| **PATIENT SELECTION** | **INDEX TEST** | **REFERENCE STANDARD** | **FLOW AND TIMING** | **PATIENT SELECTION** | **INDEX TEST** | **REFERENCE STANDARD** |
| Aliste-Fernández 2020 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Baillet 2019 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Baran 2014 | ? | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Berthoud 2020 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Bonilla 2011 | ☺ | ? | ☺ | ? | ☺ | ☺ | ☺ |
| Borzio 2016 | ☹ | ☹ | ☺ | ? | ☺ | ☺ | ☺ |
| Bram 2018 | ☺ | ? | ? | ☺ | ☹ | ☺ | ☺ |
| Carpenter 2020 | ☺ | ☺ | ☺ | ? | ☺ | ☺ | ☺ |
| Cohen 2019 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Coiffier 2013 | ☺ | ? | ☺ | ☺ | ☺ | ☺ | ☺ |
| Coiffier 2019 | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ | ☺ |
| Colvin 2015 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Couderc 2015 | ☺ | ☺ | ☺ | ☹ | ☺ | ☺ | ☺ |
| Couderc 2019 | ? | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Cunningham 2014 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Curtis 1983 | ? | ☹ | ☺ | ? | ? | ☺ | ☺ |
| Ferreyra 2016 | ? | ☹ | ? | ☺ | ☹ | ☺ | ☺ |
| Foocharoen 2011 | ☺ | ☹ | ☹ | ☹ | ☹ | ☹ | ☹ |
| Garg 2018 | ☺ | ☺ | ☺ | ☹ | ☹ | ☺ | ☺ |
| Gautam 2017 | ☺ | ☺ | ☺ | ☺ | ☹ | ☺ | ☺ |
| Gbejuade 2019 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Gratacos 1995 | ☹ | ? | ☺ | ? | ☺ | ☺ | ☺ |
| Hassas Yeganeh 2020 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Jeng 1997 | ☺ | ? | ☺ | ☺ | ☺ | ☺ | ☺ |
| Kim 2010 | ? | ? | ? | ☺ | ☺ | ☺ | ☺ |
| Kinugasa 2019 | ☺ | ☺ | ? | ? | ☺ | ☺ | ☺ |
| Kunnamo 1986 | ☹ | ☹ | ? | ☹ | ☺ | ☺ | ☺ |
| Lenski 2014 (1) | ? | ☹ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Lenski 2014 (2) | ☹ | ☹ | ☺ | ? | ☺ | ☺ | ☺ |
| Li 2007 | ☺ | ☹ | ? | ? | ☺ | ☺ | ☺ |
| Logters 2009 | ☺ | ☹ | ☺ | ? | ☺ | ☺ | ☺ |
| Logters 2010 | ☺ | ☹ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Lu 2019 | ☹ | ? | ☺ | ☺ | ☹ | ☺ | ☺ |
| Martinot 2005 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| McGillicuddy 2007 | ☹ | ? | ☺ | ☺ | ☺ | ☺ | ☺ |
| Mico 2015 | ☹ | ? | ☺ | ☺ | ☺ | ☺ | ☺ |
| Morgenstern 2018 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Mortazavi 2019 | ☹ | ☺ | ☺ | ? | ? | ☺ | ☺ |
| Omar 2014 | ☺ | ☹ | ? | ☹ | ☺ | ☺ | ☺ |
| Omar 2017 | ☺ | ? | ? | ? | ☺ | ☺ | ☺ |
| Proot 2015 | ☹ | ☹ | ☺ | ? | ? | ☺ | ☺ |
| Robinson 2017 | ☹ | ? | ? | ? | ☺ | ☺ | ? |
| Rohde 2000 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Scharf 2015 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Shmerling 1990 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Shu 2019 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Sigmund 2019 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Thornton 2019 | ? | ☺ | ☹ | ? | ? | ? | ☹ |
| Vaidya 2018 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Wang 2014 | ? | ? | ? | ☺ | ☺ | ☺ | ☺ |
| Wauters 2013 | ☹ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Wiener 2008 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Yang 2008 | ? | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ |
| Zamani 2012 | ☺ | ? | ☺ | ☺ | ☺ | ☺ | ☺ |

**Table 2: Risk of bias assessment using the Newcastle-Ottawa Scale.**

☺Low Risk ☹High Risk ? Unclear Risk

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Synovial fluid test** | **Number of articles in meta-analysis** | **Sensitivity (95% CI)** | **Specificity (95% CI)** | **AUC** |
| Glucose (40mg/dL) | 2 | 0.59 (0.48, 0.69) | 0.86 (0.75, 0.92) | 0.593 |
| Lactate (≥5mmol/L) | 2 | 0.56 (0.32, 0.78) | 0.77 (0.67, 0.84) | 0.768 |
| Lactate (≥10mmol/L) | 2 | 0.36 (0.22, 0.53) | 0.99 (0.96, 1.00) | 0.852 |
| Leukocyte esterase (++ or +++) | 4 | 0.94 (0.70, 0.99) | 0.74 (0.67, 0.81) | 0.784 |
| PMNs (>90%) | 2 | 0.69 (0.41, 0.88) | 0.65 (0.53, 0.75) | 0.665 |
| Pro-calcitonin (0.5μg/L) | 2 | 0.67 (0.26, 0.92) | 0.93 (0.84, 0.97) | 0.931 |
| TNFα (36pg/mL) | 2 | 0.86 (0.49, 0.97) | 0.88 (0.54, 0.98) | 0.931 |
| WBC (50,000/mm3) | 5 | 0.56 (0.42, 0.69) | 0.90 (0.87, 0.92) | 0.895 |

**Table 3:** Sensitivity, specificity and AUCs for SF tests included in the meta-analysis. PMN=polymorphonuclear cells. TNFα=tumour necrosis factor α. WBC=white blood cells.

A test was eligible for meta-analysis if >1 study used the same marker, threshold and fluid. Studies

testing markers at other thresholds and/or in serum were not eligible for meta-analysis

if not replicated in a second study.

**Figure legends**

**Figure 1:** PRISMA flowchart of included papers.

**Figure 2**: Pooled sensitivity, specificity and areas under curve (AUCs) for eligible synovial fluid tests included in meta-analyses, to differentiate septic from non-septic arthritis. PMNs= polymorphonuclear leukocytes. WBC= white blood cells. TNFα= tumour necrosis factor α.

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