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Title page

THE UTILITY OF BEDSIDE LEUCOCYTE ESTERASE TESTING TO RULE OUT SEPTIC ARTHRITIS

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Disclosures

We do not wish to make the article available for open access.

* Section 1: What is already known on this subject

- Studies have shown Leucocyte esterase (dip stick) to have high sensitivity and specificity during the investigation of suspected prosthetic joint infection, and to be a quick and reliable test in the evaluation of pleural and peritoneal aspirates.
- Few studies have established the usefulness of leucocyte esterase in the investigation and exclusion of a native joint infection and those that exist have looked at predominantly paediatric or young adult populations, or mixed ages. Septic arthritis is more common in children.

* Section 2: What this study adds
- In this prospective observational study of adults in 3 emergency departments in England, leucocyte esterase had a high negative predictive value when evaluating joint fluid for suspected infection.
- While it cannot distinguish crystal arthropathy from septic joints, this test may help to decrease diagnostic uncertainty and improve adult patient management, safe discharge and flow in the emergency setting. Larger studies are needed.

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Abstract

Introduction

Suspected septic arthritis is a common presentation to Emergency Departments. The underlying diagnosis is often non-infective pathology. Differentiating between aetiologies is difficult. A bedside test with high negative predictive value (NPV) may allow safe discharge of patients, reduce the time in the Emergency Department, hospital admission and associated costs. This study aims to evaluate the NPV of bedside leucocyte esterase in the assessment of these patients.

Methods

A prospective multi-centre observational study of Emergency department adult patients referred to Orthopaedics with suspected native joint septic arthritis between October 2015 and April 2016. At three hospital sites in the Bristol region the results of the leucocyte esterase test (LE) exposed to aspirated synovial fluid were recorded along with Gram stain, culture, haematinics and length of stay. A positive LE test was considered 2+ or 3+ leucocytes based on the test strip colour. Data were analysed to establish sensitivity, specificity, negative predictive value and positive predictive value against the gold standard 48-hour culture. We determined the potential number of inpatient bed-days that might be avoided using this bedside test.

Results

Eighty patients underwent joint aspiration. Five cases had positive 48-hour culture. All (5/5) infected cases showed ≥2+ LE, sensitivity of 100% (95% CI 47.8-100%) while the Gram stain was positive in only one case (sensitivity 20%, 95% CI 0.51% - 71.6%). Twenty-three LE were read negative or 1+, all with negative 48-hour culture results resulting in a NPV of 100% (95% CI 82.1- 1.00%) for a negative LE test. Specificity of a positive LE test was 30.7% (95% CI 20.5-42.45) with PPV of 8.77% (95% CI 7.64-10.1%). It was calculated that 57 orthopaedic

bed-days could have potentially been saved by immediately discharging those with a negative LE test.

Conclusions

LE point of care testing for suspected septic arthritis of native joints has a high NPV. Implementation of LE may facilitate more rapid discharge of patients with negative results. This test has the potential to reduce diagnostic uncertainty and costs to the healthcare system.

Introduction

Bacterial septic arthritis is an orthopaedic emergency. In the adult population referrals to the orthopaedic team for suspected native joint infection (NJI) are common; however incidence is low, 7.8 per 100,000 in the UK (1). The detection rate for NJI varies between published studies with a range of 8-27% (2-4). Risk factors for septic arthritis include: extremes of age, diabetes mellitus, intravenous drug use, rheumatoid arthritis, osteoarthritis, joint surgery, haemodialysis, human immunodeficiency virus (HIV) and immunosuppression (4, 5).

Proteolytic enzymes which are released by bacteria destroy articular cartilage (6). This can occur as early as 1-2 days if left untreated (7). A delay to or suboptimal treatment can result in significant long-term morbidity or death (8, 9). Differentiating NJI from other causes of a red, hot, swollen joint can be extremely challenging. Similar presentations are seen with a variety of aetiologies including reactive arthritis, crystalloid arthropathies, haemarthrosis, osteoarthritis, rheumatoid arthritis, lupus, bursitis and trauma. Research by Freed et al. suggested that it commonly takes up to 3 days to confirm the aetiology on history, examination and synovial examination (10).

Serum white cell count (WCC) and C-reactive protein (CRP) along with temperature are useful in the assessment of a patient but these measures lack specificity (4, 8, 11). Currently investigation relies on joint aspiration, visual inspection for pus and analysis with Gram stain whilst awaiting 48-hour culture if no organisms are seen on initial microscopy. Gram stain remains the best first line test at our disposal with 100% specificity for septic arthritis however, it is labour intensive and shows a sensitivity of only 45% (12). As part of laboratory analysis a Synovial WCC can also be performed. This can be a useful adjunct to gram staining in differentiating septic from inflammatory conditions, however this is not performed in all laboratories(4). Depending on laboratory reference levels synovial WCC can carry a higher sensitivity than gram stain but this comes at the cost of specificity (4). Unfortunately, with both gram staining and synovial fluid white cell count being laboratory-based investigations the time period from patient presentation to aspiration to results can be lengthy. In emergency departments worldwide, with time pressure on management decisions, these laboratory tests often present a barrier to patient flow. In current practice, in the absence of a reliable test, immediate patient management needs to be a clinical decision.

Leucocyte esterase is an enzyme released by activated leucocytes. Parvizi et al. analysed its use in investigating prosthetic joint infections, with a positive (≥2+) leucocyte esterase

strip reading yielding a 80.6% sensitivity and 100% specificity (13). The utility of leucocyte esterase test strips has also been reported for the analysis of pleural fluid, peritoneal fluid and cerebrospinal fluid to help differentiate between septic and aseptic fluid (14-16).

The aim of this multi-centre prospective study was to assess the usefulness of leucocyte esterase strip testing in the bedside evaluation of a patient referred with suspected septic arthritis. We hypothesised that leucocyte esterase strip testing (LE test) of the native joint aspirate could provide a useful adjunct to exclude bacterial septic arthritis and thus allow safe, timely discharge of patients from the Emergency Department.

Methods

A prospective collaborative multi-centre observational methodology was used to study the utility of LE in ruling out septic arthritis in three Emergency departments across the Bristol region. The use of this bedside test has been adopted as part of our regional protocol for the assessment of native joint fluid. We performed LE testing on all native joint synovial aspirates in adults (>18 years old) referred to the Orthopaedic team from the Emergency department, with suspected septic arthritis at three hospital sites (North Bristol NHS trust, Royal United Hospital NHS foundation trust and Great Western Hospitals NHS foundation trust) between October 2015 and April 2016. At two sites patient demographics were collected allowing retrospective analysis of blood parameters and admission data. Age, gender, joint, WCC, CRP, duration of symptoms, leucocyte esterase, Gram stain, presence of crystals, 48-hour cultures along with surgical treatment and length of stay were recorded for each case. We excluded any cases of suspected prosthetic joint infection, insufficient aspirate to perform the test and haemarthrosis or blood contamination making the LE result unreadable without further processing.

Joints were aspirated by the on-call Orthopaedic doctor under an aseptic technique. Joint aspirates were sent to the microbiology laboratory in a sterile specimen pot for Gram stain, crystals and culture. At the bedside one drop of the remaining aspirate was then applied to the leucocyte esterase pad on the testing strip, (Combur 7 chemical test strip *Roche diagnostics Ltd. CH-6343 Rotkreuz. Switzerland*). Results were recorded after 60 seconds as either neg (*white*), + (*Slightly purple*), ++ (*light purple*) or +++ (*dark purple*) according to the colour chart on the packaging of the test strips as per the manufacturer's instructions. The result of the leucocyte esterase was recorded but was not taken into account in subsequent patient management regarding antibiotics, admission or surgery. A LE test of neg or + (*white or slightly purple*) was used as a negative indicator. This has previously been

shown to have good correlation in the assessment of suspected prosthetic joint infections by *Parvizi et al*. (13).

Sensitivity, specificity, positive predictive value and negative predictive value with associated 95% confidence intervals (CI) were calculated for both LE test and Gram stain using the 48-hour culture results as the gold standard for infection. For the LE test, positive likelihood ratio and negative likelihood ratio were also calculated. No a priori sample size was estimated; the sample size was dependent on the number of patients referred during this time.

Through correlation of admission data with LE and culture results we estimated the potential cost benefit for a negative LE test result in this study. For this calculation we used the Department of Health's estimated cost of an acute bed as £303 per day (17).

Patient and public involvement

No patients were involved. Leucocyte esterase strip testing formed part of our routine clinical practice prior to conducting this study. In the analysis of the usefulness of LE there was no change or impact on patient care or management therefore ethical approval was not required. This was confirmed using the HRA decision tool.

Results

80 patients were eligible for inclusion (74% male, 26% female). The cohort had a mean age of 71 years (range 27 to 96). Following data normality testing, mean serum WCC, median CRP were reported for both culture positive and culture negative patients (Table 1). Leucocyte esterase test was read as *neg* for nine patients (11%), + for 14 (18%), ++ for 24 (30%) and +++ for 33 patients (41%). Organisms were seen on one gram stain. Five patients had a positive 48-hour culture (Table 1) with pathogens shown in Table 2. Infections were seen at all three hospital sites. The five patients were all managed with surgical washout. Of the 52 patients positive for LE but negative on culture, 34 patients were diagnosed with a crystal arthropathy, 17 with a presumed arthritic flare and one with no identified cause.

Table1. Leucocyte esterase and gram stain result in relation to the 48 hour culture result

		48 hour Culture		Total
		Positive	Negative	
Leucocyte esterase testing	Positive	5	52	57
	Negative	0	23	23
Total		5	75	80
Gram Stain	Positive	1	0	1
	Negative	4	75	79
Total		5	75	80

Table 2. Organisms found in positive cultures

Culture-Positive Organism	No. Patients identified with Organism
Staphlococcus Aureus	1
Pseudomonas aeruginosa	1
Beta Haemolytic Streptococcus Group C	1
Beta Haemolytic Streptococcus Group G	1
Beta Haemolytic Streptococcus Group B	1

A positive LE result had a sensitivity of 100% (95% CI 47.8-100%), specificity 30.7% (95% CI 20.5-42.4%), positive predictive value 8.77% (95% 7.64-10.1%) and positive likelihood ratio 1.44 (95% CI 1.00-1.76) for infection. (Table 1) A negative LE test had a NPV of 100% (95% CI 82.1-100%), and negative likelihood ratio 0.00 (95% CI (0.00-3.93) in ruling out infection. There was a 1 in 11 chance of a patient with an LE reading of 2+ or 3+ having an NJI but there were no incidences of a patient with an NJI having a negative or 1+ LE result. In comparison, Gram stain had a sensitivity of 20% (0.51-71.6%), specificity 100% (95.2-100%), positive predictive value 100% (54.6-100%), negative predictive value of 94.9% (92.4-96.7%) and negative likelihood ratio 0.80 (0.52-1.24).

Table 3. Sensitivity, specificity, PPV and NPV of leucocyte esterase and Gram stain

Measurement Outcome	Result	95% Confidence Interval
Leucocyte esterase		
Sensitivity (%)	100%	47.8-100
Specificity (%)	30.7%	20.5-42.4
PPV (%)	8.77%	7.64-10.1
NPV (%)	100%	82.1-100
Gram stain		
Sensitivity (%)	20%	0.51-71.6
Specificity (%)	100%	95.2-100
PPV (%)	100%	54.6-100
NPV (%)	94.9%	92.4-96.7

Clinical and demographic data was collected for 53 patients at two EDs (Table 2). Of these, 34 were admitted. A final diagnosis of non-infective pathology was made in 30 of these admissions. Admissions for culture negative patients accounted for 311 bed days with a median stay of 6 days (range 1-72 days). The large range related to two admissions where non-orthopaedic infections (urosepsis and pneumonia) were diagnosed and treated during their in hospital stay. Of the 311 bed days, 57 days were made up of patients who had a negative LE test result on admission. If admission could have been prevented on the basis of a negative bedside LE test, potential savings of £17,271 could have been achieved across these two trusts.

Table 4. Comparing the demography, LE results, WCC, CRP, and incidence of crystal arthropathy for patients at two hospitals with culture positive and culture negative results.

	Cohort – Hospital sites one and two N=53	
	Culture positive	Culture negative

Number patients	4	49
Number Male	2 (50%)	37 (75%)
Age	81 (75-85)	67.4 (27-96)
Admissions	4/4 (100%)	30/49 (61.2%)
WCC (10⁹/L) Mean (SD)	11.4 (2.18)	11.5 (3.80)
CRP (mg/L) Median (IQR)	165 (91-434)	71 (43-126)
Crystal Arthropathy	0	34

Discussion

Acute presentations of adult patients with a hot, inflamed native joint to the ED are frequent, however, the majority of atraumatic swellings are secondary to non-infective causes (1). Currently there is no ideal, widely accepted immediate bedside test or marker to differentiate infectious from non-infectious joint swellings. Among current diagnostics peripheral white cell counts are raised in only 50% of cases with sensitivity ranging from 23-75% (4, 8). CRP and ESR are acute phase reactants that respond to both infection and inflammation; specificity is low despite their high sensitivity. Literature suggests an ESR >30mm/hour carries a sensitivity of 76 to 97%, however specificity is only 29% for NJI in adults (11). Similarly, CRP values of >100 mg/litre have a reported sensitivity around 80% but specificity ranging from 27 to 70% (11). Laboratory gram stains are universally performed due to their high specificity but sensitivity remains low. A recent study of 830 native joint aspirates for suspected NJI demonstrated of sensitivity of 17% (95% confidence interval: 10.2% to 25.8%) (18). doi: 10.4081/or.2019.8156.

An accurate rapid diagnosis of NJI is only possible with a positive Gram stain or aspiration of pus. Otherwise, patients presenting with a suspected NJI may be obliged to wait for extended periods in the Emergency Department or be admitted for observation or empirical treatment. An audit by *Butt el al*. of 60 patients presenting with atraumatic knee effusions reported 24 admissions for empirical antibiotic therapy following aspiration. Only four cases

were confirmed septic arthritis. Median stay for all admissions were four days (range 2-14 days) with seven medical complications during admission (19).

In our study we identified a total of 57 Orthopaedic bed days occupied by patients where NJI was excluded by a negative LE test. Discharging these patients could have achieved potential savings of £17,271 across two of the trusts in this cohort (17). However we appreciate that some of the LE negative patients may have had concomitant medical or social factors that necessitate admission. The ability to exclude septic arthritis at the point of access could enable earlier assessment, management or admission under the appropriate speciality for the patient's care needs.

LE dipstick testing is a widely adopted, cheap and readily available test as part of the assessment of joint fluid in suspected prosthetic joint infections. To date the evidence surrounding its use in the assessment of native joint fluid is limited. In this study LE showed excellent sensitivity with a NPV of 100% (82.1-100). These results are in keeping with two recent papers both reporting a 100% NPV for LE (20, 21). However we found specificity was poor with specificity of 30% a PPV of only 8.77%. *Colvin et al*. analysed synovial fluid from 5 patients with suspected native joint infection reporting similarly low specificity and PPV of 50% and 33% respectively (20). In contrast, *Gautam et al*. reported high specificity, 83%, and PPV, 95% (21). The higher specificity and PPV reported by *Gautam et al*. may be explained by the predominantly paediatric cohort of patients in their study, over 75% of the patients under 20 years old. One would expect a different performance of the LE test due to the higher incidence of septic arthritis and rare occurrence of crystal arthropathy in this population group. This increased specificity and PPV of LE for septic arthritis in a paediatric cohort has also been demonstrated by *Mortazavi et al*. *(22)*.

The inflammatory response seen with crystal arthropathies means that a positive LE test alone cannot differentiate between NJI and crystal arthropathy. *Omar et al*. hypothesised that when dipstick synovial glucose readings were taken alongside the LE test this would increase the ability of the dip stick to detect septic arthritis (23). Preliminary results have shown sensitivity 89.5%, specificity 99.2%, PPV 94.4% and NPV 98.4% for a positive LE test (++ or +++) with negative glucose reading for the diagnosis of septic arthritis (23). Combining the results of LE and glucose dipstick testing, may allow distinction of inflammatory arthropathy from NJI, adding to the usefulness of bedside LE testing.

We acknowledge several limitations of this present study. Although data was collected across three centres, the low incidence of NJI in the adult population and low prevalence in patients referred with a possible NJI meant we had few cases of true NJI. The low prevalence of this disease has the potential to impact on the accuracy of predictive values; increasing the observed NPV and decreasing the PPV. As a multi-centre study there were several doctors performing and interpreting the result of the LE. These doctors were not blinded to the patients' history, examination findings or admission bloods which may have introduced an element of bias. Although this study was performed in a solely adult population, the applicability of a LE to the paediatric population have been demonstrated by *Mortazavi et al*. and *Gautam et al*. (21, 22)

We would recommend further multi-centre investigation to increase numbers and corroborate these results. Using the data from this study as pilot data, assuming a prevalence of NJI of 6.25% (95% CI 2.7-13.8%), to test the assumption that the sensitivity of LE testing for detecting NJI is 95% +/-5%, a sample size of 1138 would be required (24)..

This study supports the use of bedside leucocyte esterase testing of synovial fluid aspirate in cases of suspected native joint septic arthritis. The test has a high negative predictive value and can act as an adjunct in the decision-making process to help support safe discharge of patients with negative results. These discharged patients may then be followed up with formal laboratory culture results in an outpatient, telephone or primary care setting at 48 – 72 hours. The LE test can reduce both diagnostic uncertainty and costs to the healthcare system.

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Footnotes

Data sharing – All data relevant to the study are included in the article or uploaded as supplementary information