The alpha-defensin can rule out septic arthritis in pediatric cases: a first case series study

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Achieving a rapid diagnosis in suspected septic arthritis is challenging as a pathogen is only isolated in 50% of cases, and the necessary investigation takes time and delays treatment. The alpha-defensin lateral flow test (Synovasure) has been shown to effectively and rapidly diagnose prosthetic joint infection, with the benefit of early initiation of treatment. This study tests the hypothesis that the alpha-defensin can diagnose pediatric septic arthritis and differ nonseptic arthritis (NSA) in native joints. A retrospective cohort study analysis was carried out for patients presenting with joint pain and fever with a differential that included septic arthritis. The Synovasure alpha-defensin lateral flow test kit was used to detect alpha-defensin in synovial fluid aspirated from the symptomatic joint. Septic arthritis was defined as present when a causative bacteria was identified in either blood or synovial fluid culture, whereas NSA was recognized when a causative bacteria was not identified, drainage or antibiotic treatment was not implemented, and symptoms improved without joint destruction. Demographic data and culture results were compared between septic arthritis and NSA. Eighteen eligible cases were identified. Of these, six were defined as septic arthritis and 12 as NSA. There were no significant differences in age, body temperature, serum white blood cell count, and C-reactive protein. All cases with confirmed septic arthritis showed a positive alpha-defensin lateral flow test, whereas all of the NSA group showed a negative result. The Synovasure alpha-defensin lateral flow test may be a reliable investigation for rapidly distinguishing septic arthritis from NSA in children. *J Pediatr Orthop B* 34: 515–519

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Introduction

Pediatric septic arthritis is fortunately uncommon, with an incidence of between four and 37 cases/100 000 per year [1–3]. Septic arthritis requires urgent surgical treatment to control the infection and prevent destruction of the afflicted joint, however, the diagnosis is difficult as pediatric nonseptic arthritis (NSA) has similar symptoms and signs [4,5]. Further complicating this is that 29% of patients with suspected septic arthritis treated with antibiotics before confirming a diagnosis, and the responsible pathogen is isolated in only 50% of cases [6].

The Synovasure alpha-defensin lateral flow test kit (one kit: ¥50 000, USD 325; Zimmer Biomet, Warsaw, Indiana, USA) was approved in 2019 for use in the diagnosis of prosthetic joint infection (PJI) through detecting alpha-defensin in aspirated synovial fluid. Alpha-defensin is an antimicrobial peptide produced by the synovium which works to disrupt the membranes of the infecting organism. Importantly, alpha-defensin is absent in the disease-free state, and it is thus a potentially useful marker of native joint infection [7].

The Synovasure alpha-defensin lateral flow test has a reported sensitivity and specificity of 97% in diagnosing PJI [8,9]. Moreover, the results of the investigation are available within 10 min and are not affected by prior antibiotic administration, proinflammatory comorbidities, or the nature of the infecting organism [10–12]. In combination with its ease of use, the bedside investigation is both practical and rapidly informative in guiding ongoing treatment.

This cohort study aimed to confirm this hypothesis by establishing if the alpha-defensin lateral flow test is effective in the diagnosis of septic arthritis in the pediatric population presenting with acute monoarthropathy.

Methods

Institutional research ethics board approval was granted, and informed consent was obtained from all patients and parents. A financial support from Saitama Children's Medical Center covered to meet the cost of purchasing Synovasure alpha-defensin lateral flow tests. A retrospective cohort study analysis was carried out for pediatric patients with a suspected diagnosis of septic arthritis presenting with joint pain and fever in a single

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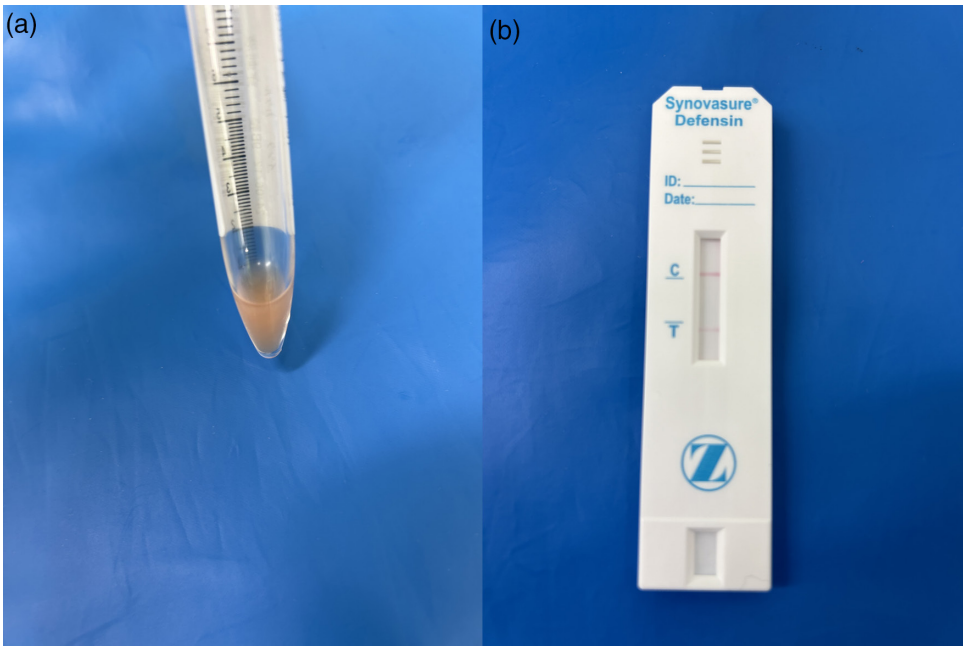
Fig. 1



(a) Synovial fluid suspected septic arthritis. (b) The positive result of the Synovasure alpha-defensin lateral flow test kit.

center between 2023 and 2024. Patients were included if the symptomatic joint was native, the patient was aged under 15 years. Patients were excluded if they were aged over 15 years or if insufficient fluid could be aspirated from the affected joint with ultrasound guidance for the Synovasure test. Septic arthritis was defined as present when a causative bacteria was identified in either blood or synovial fluid culture whereas NSA was defined when the causative bacteria was not identified on culture for at least 1 week following aspiration or surgical lavage, the patient did not undergo drainage or receive antibiotic treatment, and symptoms improved without joint destruction when followed up over 6 months with clinical and radiographic findings.

Synovial fluid was aspirated guided by either surface anatomy or ultrasound while under sedation or local anesthesia. The sample was then applied to the Synovasure alpha-defensin lateral flow test kit following the manufacturer's instructions. The demographic data and clinical history, alongside hematological and microbiological results were recorded and included in the analysis.

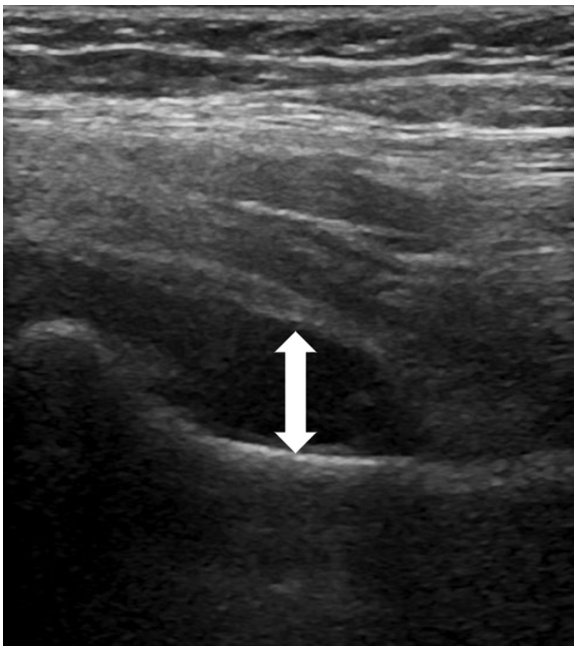
The data were analyzed using R (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria). Variables are presented as means, SD, and ranges. A Shapiro–Wilk test was conducted to assess the distribution of continuous variables, and a Mann–Whitney *U* test was used for all nonparametric variables. The Fisher exact test was used to investigate dichotomous variables. For all statistical tests, a *P* value less than 0.05 was considered significant.

Results

Twenty-seven patients presented with either suspected septic arthritis or NSA during the study period. Seven cases were excluded because of a failure to collect enough synovial fluid for the alpha-defensin lateral flow test. Twenty cases were tested using the Synovasure lateral flow test. Eight cases were categorized as a positive alpha-defensin test (Fig. 1a and b), and 12 as a negative alpha-defensin test. All 12 cases with a negative alpha-defensin test were later classified as NSA by the above criteria and finally diagnosed with transient synovitis or reactive arthritis. Two positive alpha-defensin test cases diagnosed with clinically suspected septic arthritis were excluded because no responsible pathogen was identified at any time (Fig. 1a and b).

Patients in the septic arthritis group showed a mean age of 5.7 ± 3.8 years. Patients in the NSA group were aged 5.8 ± 4.1 years ($P = 0.85$). The mean patient temperature at admission was 38.3 ± 0.4 °C in the septic arthritis group and 38.4 ± 1.2 °C in the NSA group ($P = 0.96$). One shoulder, two hips (Fig. 2), one knee, and one sacroiliac joint were afflicted in the septic arthritis group; one elbow, three hips, seven knees, and one ankle were symptomatic in the NSA group (Table 1). A single case of septic sacroiliac joint was treated with aspiration and drainage to dryness. All other septic arthritis cases were

Fig. 2



A 5-year-old girl with septic arthritis of the hip. Ultrasound of the femoral neck showing synovial fluid (white arrow).

Table 1 Patients demographics

	SA ($N = 6$)	NSA ($N = 12$)	P value
Mean of age (years)	5.7 ± 3.8 (range: 0.1–11.0)	5.8 ± 4.1 (range: 1.2–12.3)	0.85
Sex			0.054
Male	0	6	
Female	6	6	
Affected joint	Shoulder: 1 Hip: 3 Knee: 1 Sacroiliac: 1	Elbow: 1 Hip: 3 Knee: 7 Ankle: 1	–
Body temperature (° C)	38.3 ± 0.4 (range: 38.0–39.0)	38.4 ± 1.2 (range: 37.5–40.0)	0.96

NSA, nonseptic arthritis; SA, septic arthritis.

treated with aspiration and surgical lavage whereas the NSA cases with only aspiration.

Table 2 shows the hematological, microbiological, and alpha-defensin lateral flow test results observed in each group. The serum white blood cell counts and C-reactive protein (CRP) were not significantly different across the two groups. All cases in the septic arthritis group showed a positive alpha-defensin lateral flow test, whereas every case in the NSA group showed a negative result.

Two cases were excluded despite showing a positive alpha-defensin lateral flow test and undergoing joint lavage, as neither showed any evidence of causative bacteria. Nonetheless, each was treated on the clinical diagnosis of septic arthritis. Both cases improved without evidence of joint destruction at 1 year.

Discussion

This report describes a pragmatic experience of using an alpha-defensin lateral flow test and suggests that it has utility in excluding septic arthritis in the pediatric population.

The existing literature tells the story of the challenges in differentiating septic arthritis and NSA in the pediatric population. It is a critical distinction; whereas transient synovitis is a self-limiting disorder that is managed nonoperatively, septic arthritis requires urgent diagnosis and intervention, including intravenous antibiotics, operative irrigation, and debridement to avoid a potentially devastating and disabling outcome [6,13,14].

At present, there is a low success rate in detecting septic arthritis in children, as many receive antibiotics at the earliest suspicion of the diagnosis, which prevents meaningful culture of aspirated synovial fluid [6]. Moreover, the presenting symptoms of each condition are very similar, particularly when one accounts for communication with younger children.

In response to these difficulties, Kocher *et al.* [5] and Caird *et al.* [6] described criteria for diagnosing septic arthritis in the hip in children. These criteria include the patient's body temperature, serum white blood cell count, erythrocyte sedimentation rate, ability to bear weight, and CRP. If three out of five factors meet the defined thresholds, the probability of septic arthritis is estimated at greater than 80%, reducing to 40% if only two criteria are met [5,6]. An importantly caveat to these 'Kocher criteria' is that these findings have only been shown to be relevant in the hip, and their application in other joints has not been validated. In using the alpha-defensin lateral flow test across a variety of large joints, this report could broaden the ability of a clinician to make a sound and reliable critical treatment decision early in a patient's course.

Deirmengian *et al.* [9,15] described measuring alpha-defensin in synovial fluid as a novel diagnostic investigation for PJI in 2014. The authors go on to report that all cases with PJI were correctly diagnosed despite synovial cultures being negative. Mason *et al.* [16] expanded on this further, reporting that testing for alpha-defensin is a promising tool for diagnosing PJI in their systematic review and meta-analysis.

In contrast, Kleeman-Forsthuber *et al.* [17] described that testing for alpha-defensin in synovial fluid was beneficial in some cases where laboratory values are otherwise equivocal; however, their results did not support its routine use for the diagnosis of PJI. Furthermore, Cooper *et al.* reported that the alpha-defensin lateral flow test has a high-false-positive rate when used to distinguish septic and inflammatory or crystalline arthropathy in the adult native knee joint [18].

Table 2 Patients laboratory results

	SA ($N = 6$)	NSA ($N = 12$)	
White blood cell count in serum (cells $\times 10^9$ /L)	12.0 ± 3.4 (range: 7.0–17.7)	15.0 ± 3.9 (range: 8.7–21.7)	0.15
CRP (mg/dl)	10.7 ± 9.3 (range: 5.2–30.3)	5.6 ± 4.6 (range: 0.2–16.9)	0.30
Alpha-defensin positive	6	0	<0.01[a]
Positive culture results	6	0	<0.01[a]
	Staphylococcus aureus: 3 *Streptococcus pneumoniae*: 1 *Streptococcus pyogens*:1 *Moraxella lacunata*: 1		

CRP, C-reactive protein; NSA, nonseptic arthritis; SA, septic arthritis.
[a]Significant difference.

Previous reports have observed an association between a positive alpha-defensin finding and Crohn's disease [19], rotavirus infection [20], *Helicobacter pylori* [21], and urinary tract infection in children [22]. This suggests that the test may be vulnerable to systemic inflammatory conditions outside of the joint; therefore, it is possible that the false positive rate may be increased in inflammatory diseases in children if their immune functions vary sufficiently. Further study is needed to explore this phenomenon and to understand the influence of systemic illness of the reliability of this investigation.

In the present study, two cases were alpha-defensin positive but were excluded as the causative pathogen was not detected. In these cases, the clinical suspicion of septic arthritis was sufficient to prompt treatment, because the detection rate of the causative pathogen is low and the consequence of a missed diagnosis was deemed to be sufficiently severe. This is an important limitation; however, excluding these enabled the most accurate association between septic arthritis and the alpha-defensin lateral flow test to be identified. Furthermore, the small number of cases renders the analysis unable to determine sensitivity and specificity. Ongoing studies should seek to increase the number of cases and make allowances to include both true and clinical septic arthritis.

Conclusion

The Synovasure alpha-defensin lateral flow test can diagnose septic arthritis and differentiate NSA in children. This analysis suggests a low potential risk for false negative results in identifying septic arthritis, critical because of the devastating consequences of failing to treat the condition. Future studies should seek to clarify the sensitivity and specificity of alpha-defensin for pediatric septic arthritis through expanding the study sample size and taking into account both microbiologically confirmed and clinically identified septic arthritis.

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Conflicts of interest

The lead author has received financial support from Saitama Children's Medical Center to meet the cost of purchasing Synovasure alpha-defensin lateral flow tests.

M.M. has received financial conflicts of interest from Saitama Children's Medical Center. For the remaining authors, there are no conflicts of interest.

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