CENTRES DE RÉFÉRENCE
POUR LES INFECTIONS OSTÉO-ARTICULAIRES COMPLEXES
DU GRAND OUEST
CRIOGO

Réunion CRIOGO
Octobre 2018

Marqueurs synoviaux pronostiques d'arthrite septique

numecan
nutrition • métabolismes • cancer

Instituts thématiques
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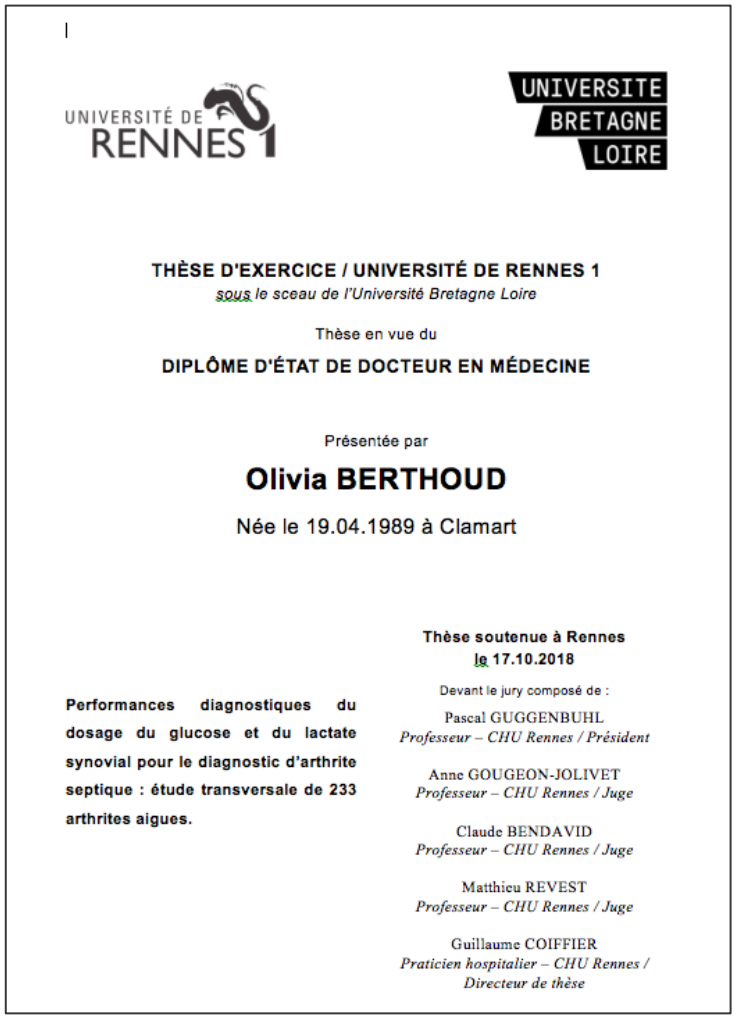

UNIVERSITÉ DE RENNES 1

UNIVERSITE BRETAGNE LOIRE

THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1

sous le sceau de l'Université Bretagne Loire

Thèse en vue du

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Présentée par

Olivia BERTHOUD

Née le 19.04.1989 à Clamart

Performances diagnostiques du dosage du glucose et du lactate synovial pour le diagnostic d'arthrite septique : étude transversale de 233 arthrites aigues.

Thèse soutenue à Rennes
le 17.10.2018

Devant le jury composé de :

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Cohorte Synolactate

Recueil prospectif de ponctions synoviales
Arthrite Aigue (< 30 jours)

Monocentrique
Service de Rhumatologie CHU Rennes
Début en Janvier 2015

Arthrite aigue ≠ Arthrite septique
Importance des diagnostics différentiels

Arthrite aigue = Arthrite < 4-6 semaines

Au CHU de RENNES… 11 à 13 % AA => Septique

Cohorte DNAr16S/Spectrosyno (2006-2008 et 2010-2014)

(arthrite < 6 semaines) (208 liquides, 13%)

Cohorte Synolactate (2015-2018)

(arthrite hyper aigue :moyenne 5 jours) (233 liquides, 11 %)

Quels diagnostics différentiels ?

- 10 % arthrites septiques
- 45 % arthrites métaboliques (Goutte, dépôts de PPC)
- 45 % arthrites « non-non » (PR, SpA, Are, autres)

Culture bactériologique… …problématique du gold-standard

- Critères de Newman

- Pathogène isolé dans le liquide synovial
- Pathogène isolé dans une hémoculture et clinique concordante avec arthrite septique
- Liquide purulent sans germe, sans cristaux, sans diagnostics différentiels d'arthrite septique retrouvé

Preuve bactériologique = 80 à 85% des cas

ED < 40 à 50 %, (16 % dans la cohorte SYNOLACTATE)

Délai moyen de positivité de 3 jours

Cohorte SYNOLACTATE : 18,5 % des patients avaient reçu des antibiotiques avant (< 10 jours) la ponction articulaire

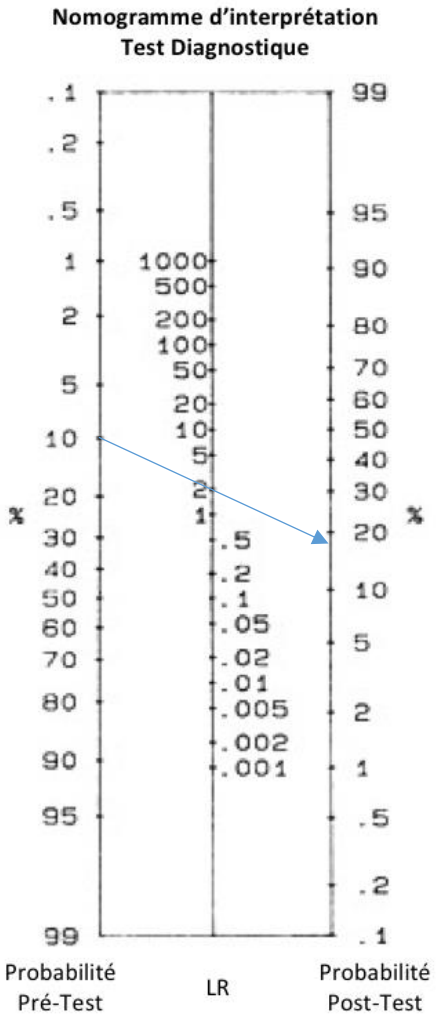
Arthrite aigue fébrile ≠ Arthrite septiques

Cohorte SYNOLACTATE :

33,7 % des arthrites aigues non septiques sont fébriles

1/3 des arthrites septiques n'avaient pas de fièvre

LR+ = 2.0, Probabilité post-test à 20 %



Quels marqueurs biologiques pronostiques ?

Sanguin

. CRP ?

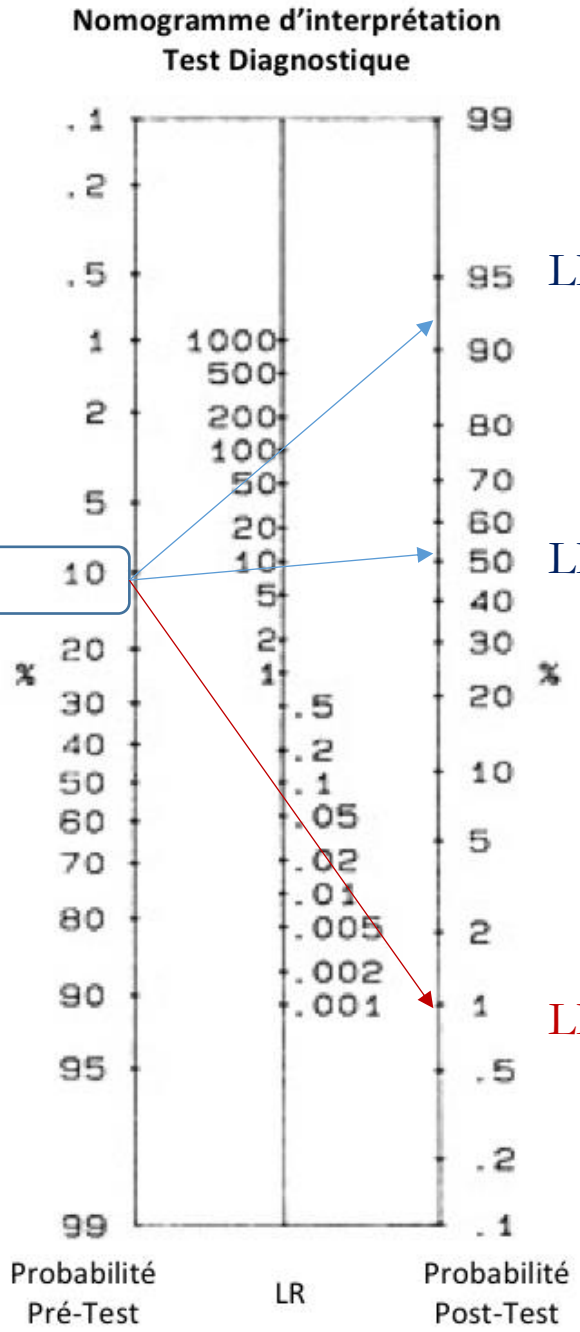
. Procalcitonine ?

Liquide synovial

. Numération leucocytaire ? PNN ?

. Cristaux ?

. Lactate ? Glucose ?



Monoarthrite aigue

LR+ > 100, VPP > 90 %

LR+ > 10, VPP > 50 %

Cliniquement pertinent
pour retenir
l'hypothèse septique
(dans l'attente des résultats bactériologiques)

LR- < 0,1 VPN < 99%

Cliniquement pertinent
pour éliminer
l'hypothèse septique

EVIDENCE-BASED DIAGNOSTICS

CME Evidence-based Diagnostics: Adult Septic Arthritis

Christopher R. Carpenter, MD, MS, Jeremiah D. Schuur, MD, MHS, Worth W. Everett, MD, and Jesse M. Pines, MD, MBA, MSCE

Abstract

Background: Acutely swollen or painful joints are common complaints in the emergency department (ED). Septic arthritis in adults is a challenging diagnosis, but prompt differentiation of a bacterial etiology is crucial to minimize morbidity and mortality.

Objectives: The objective was to perform a systematic review describing the diagnostic characteristics of history, physical examination, and bedside laboratory tests for nongonococcal septic arthritis. A secondary objective was to quantify test and treatment thresholds using derived estimates of sensitivity and specificity, as well as best-evidence diagnostic and treatment risks and anticipated benefits from appropriate therapy.

Methods: Two electronic search engines (PUBMED and EMBASE) were used in conjunction with a selected bibliography and scientific abstract hand search. Inclusion criteria included adult trials of patients presenting with monoarticular complaints if they reported sufficient detail to reconstruct partial or complete 2 × 2 contingency tables for experimental diagnostic test characteristics using an acceptable criterion standard. Evidence was rated by two investigators using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS). When more than one similarly designed trial existed for a diagnostic test, meta-analysis was conducted using a random effects model. Interval likelihood ratios (LRs) were computed when possible. To illustrate one method to quantify theoretical points in the probability of disease whereby clinicians might cease testing altogether and either withhold treatment (test threshold) or initiate definitive therapy in lieu of further diagnostics (treatment threshold), an interactive spreadsheet was designed and sample calculations were provided based on research estimates of diagnostic accuracy, diagnostic risk, and therapeutic risk/benefits.

Results: The prevalence of nongonococcal septic arthritis in ED patients with a single acutely painful joint is approximately 27% (95% confidence interval [CI] = 17% to 38%). With the exception of joint surgery (positive likelihood ratio [+LR] = 6.9) or skin infection overlying a prosthetic joint (+LR = 15.0), history, physical examination, and serum tests do not significantly alter posttest probability. Serum inflammatory markers such as white blood cell (WBC) counts, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are not useful acutely. The interval LR for synovial white blood cell (sWBC) counts of 0×10^9–25×10^9/L was 0.33; for 25×10^9–50×10^9/L, 1.06; for 50×10^9–100×10^9/L, 3.59; and exceeding 100×10^9/L, infinity. Synovial lactate may be useful to rule in or rule out the diagnosis of septic arthritis with a +LR ranging from 2.4 to infinity, and negative likelihood ratio (–LR) ranging from 0 to 0.46. Rapid polymerase chain reaction (PCR) of synovial fluid may identify the causative organism within 3 hours. Based on 56% sensitivity and 90% specificity for sWBC counts of $>50 \times 10^9$/L in

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A related commentary appears on page 797.

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CRP ?

CRP	Se	Sp	LR+	LR-
>10 mg/L				
Fottner 2008[55]	87	39	1.4	0.3
Ernst 2010[59]	91	15	1.1	0.6
>100 mg/L				
Söderquist 1998[9]	83	27	1.1	0.6
Martinot 2005[51]	82	70	2.8	0.3
>150 mg/L				
Martinot 2005[51]	73	83	4.5	0.3
> 200 mg/L				
Söderquist 1998[9]	44	85	2.9	0.7

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Diagnostics

Serum procalcitonin levels as a diagnostic marker for septic arthritis: A meta-analysis

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ABSTRACT

Background: The aim of this study was to assess the value of serum procalcitonin (PCT) levels as a diagnostic marker for septic arthritis (SA) via meta-analysis.
Methods: We searched PubMed, Embase and the Cochrane Library, as well as the reference lists of relevant articles, for studies published up to May 21, 2015 and did not impose language restrictions. We selected original studies reporting the usefulness of PCT or C-reactive protein (CRP) as a diagnostic marker for SA. We summarized test performance characteristics with the use of forest plots, hierarchical summary receiver operating characteristic curves, and bivariate random effects models. Prespecified subgroup analyses and meta-regression analyses were also performed.
Results: This meta-analysis comprised 10 studies including 838 patients. The overall sensitivity of serum PCT levels for the diagnosis of SA in these studies was 0.54 (95% CI, 0.41–0.66), and the specificity of PCT was 0.95 (95% CI, 0.87–0.98). The positive likelihood ratio (LR) was 10.97 (95% CI, 4.65–25.89); the negative LR was 0.49 (95% CI, 0.38–0.62); and the area under ROC curve (AUROC) was 0.82 (95% CI, 0.78–0.85). Six studies also examined the usefulness of CRP levels as a marker for the diagnosis of SA. The sensitivity and specificity of CRP were 0.45 (95% CI, 0.35–0.55) and 0.079 (95% CI, 0.0.021–0.25), respectively, and the positive LR, negative LR and AUROC curve were 0.48 (95% CI, 0.39–0.61), 6.79 (95% CI, 2.04–23.81), and 0.30 (95% CI, 0.26–0.34), respectively.
Conclusion: PCT is more valuable than CRP for distinguishing SA from non-SA.

1. Introduction

Septic arthritis (SA) is a disease entity that is commonly associated with disability and is frequently encountered by physicians practicing in the emergency department. SA is an enigmatic condition associated with significant morbidity and mortality that may destroy affected joints within a matter of days if left untreated [1]. The clinical features of SA are similar to those of non-SA. Thus, the two diseases are difficult to distinguish from each other. Currently, SA is diagnosed based on blood culture results or diagnostic puncture culture results. The use of these techniques is associated with several disadvantages. Diagnostic punctures must be performed under aseptic conditions, are time-consuming and can lead to false positive or negative results. The usefulness of traditional inflammatory markers, such as white blood cell (WBC) counts, routine blood tests, erythrocyte sedimentation rates (ESRs), synovial fluid WBC counts and C-reactive protein (CRP) levels, for distinguishing between SA and non-SA is controversial, as the efficacy and applicability of these tests for distinguishing between the above conditions vary [2]. Moreover, many of those biomarkers may be elevated regardless of whether SA is present [2].

Several studies have recently explored the roles of CRP and procalcitonin (PCT) in the diagnosis of SA. CRP is an acute-phase reactant produced primarily by hepatocytes. In contrast, PCT is produced constitutively by the parafollicular cells of the thyroid gland and the neuroendocrine cells of the lung. PCT concentrations are low (<0.11 ng/ml) in the serum of healthy patients and increase rapidly in the serum of patients with severe bacterial or fungal infections but not in the serum of patients with viral infections [3-5]. These properties, as well as a half-life of 22 to 29 h, may make PCT a convenient tool for monitoring serious infections and for differentiating between bacterial infections and non-bacterial infections or non-infectious inflammatory disorders [6]. However, some previous studies have investigated the usefulness of PCT as a diagnostic marker for SA and obtained conflicting

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PCT ?

10 études (9 adultes + 1 enfant)

PCT > 0.5 ng/mL

AUC 0.82 (95% CI, 0.78-0.85)

Se 0.54 (95% CI, 0.41-0.66)

Sp 0.95 (95% CI, 0.87-0.98)

LR+ 10.97 (95% CI, 4.65-25.9)

LR- 0.49 (95% CI, 0.38-0.62)

Zhao J. Am J Emerg Med. 2017;35(8):1166-71.

THE RATIONAL CLINICAL EXAMINATION

CLINICIAN'S CORNER

Does This Adult Patient Have Septic Arthritis?

Mary E. Margaretten, MD
Jeffrey Kohlwes, MD, MPH
Dan Moore, PhD
Stephen Bent, MD

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.

CME available online at www.jama.com

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 ≥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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Cytologie ?

	Source	Septic Arthritis: Sensitivity, %	Specificity, %	Likelihood Ratio (95% CI): Positive	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.

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Original article

Combining cytology and microcrystal detection in nonpurulent joint fluid benefits the diagnosis of septic arthritis

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ABSTRACT

Objective: To evaluate the performance of combined cytology and microcrystal detection in joint fluid for diagnosing septic arthritis.

Methods: Retrospective single-center study of joint fluid samples from patients with manifestations suggesting acute or chronic arthritis. The absolute leukocyte count (/mm³) was recorded, as well as the differential counts, particularly of neutrophils (%). Microcrystals were sought and bacteriological cultures performed. Septic arthritis was defined as positive cultures of joint fluid or blood samples. Diagnostic performance was assessed based on sensitivity, specificity, the receiver-operating characteristics (ROC) curve with the area under the curve (AUC), and the positive and negative likelihood ratios (LR+ and LR−).

Results: Two hundred and eight joint fluid samples were included. The diagnoses were septic arthritis (n = 28), chondrocalcinosis (n = 41), gout (n = 28), rheumatoid arthritis (n = 33), spondyloarthritis (n = 31), osteoarthritis (n = 18), and undifferentiated arthritis (n = 29). Among cytological parameters, those having the best diagnostic performance were the neutrophil count (cutoff, > 50,000/mm³), the leukocyte count (cutoff, > 50,000/mm³), and the percentage of neutrophils (cutoff, > 95%); corresponding LR+ values were 8.93, 5.76, and 4.55, respectively. Neutrophil percentages lower than 80% had an LR− value of 0.07. Combining these cytological variables with the absence of crystals improved the diagnostic performance, yielding LR− values of 11.36, 10.94, and 10.82 for neutrophils > 95%, neutrophils > 50,000/mm³, and leukocytes > 50,000/mm³, respectively.

Conclusion: Combining cytological characteristics of joint fluid with the absence of crystals benefits the diagnosis of septic arthritis.

1. Introduction

Septic arthritis is a diagnostic emergency, as only prompt and effective antibiotic treatment can lessen the high risk of life-threatening sepsis and function-threatening joint destruction [1–3]. Although rare, septic arthritis accounts for 25% of all cases of monoarthritis seen at emergency departments. The annual incidence is about 5.7/100,000 population overall and is increased by joint replacement surgery and rheumatoid arthritis (RA) [4–6]. Despite the importance of rapid antibiotic therapy, samples must be collected first, to ensure identification of the organism. The definite diagnosis of septic arthritis rests on identification of a bacterial or fungal pathogen in a joint fluid specimen. Smears are positive in less than half the cases, often due to a small bacterial inoculum, whereas cultures are positive in about 80% of cases. In about 20% of cases, all microbiological specimens remain negative [7–9]. These false-negative results may be ascribable to the inappropriate administration of antibiotics before sample collection or to the fastidious nature of the causative organism.

Although the diagnosis is urgent, the mean time to diagnosis in patients presenting with arthritis is about 3 days [10]. Obtaining diagnostic orientation before the microbiological results are available is therefore extremely useful. Information can be obtained from the medical history, clinical findings, and results of initial blood and joint fluid tests. Nevertheless, several studies indicate that this information fails to contribute significantly to the diagnosis of septic arthritis in a patient presenting with acute arthritis.

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Table 2
Performance of cytological markers alone or combined with microcrystal detection for diagnosing septic arthritis.

	Se (%)	Sp (%)	LR+	LR−
Leukocyte count (/mm³)				
> 50,000	53.60	91.70	5.76	–
> 70,000	39.30	95.60	8.93	–
< 20,000	92.30	70.60	–	0.11
Percentage of neutrophils				
> 90	71.40	79.70	3.52	–
> 95	50.00	89.00	4.55	–
< 80	96.20	56.90	–	0.07
Neutrophil count (/mm³)				
> 50,000	50.00	94.40	8.93	–
< 15,000	92.30	77.00	–	0.1
Combinations of criteria				
> 50,000/mm³ leukocytes and no Cry	53.60	95.10	10.94	–
> 90% Nph and no Cry	67.90	92.80	8.28	–
> 95% Nph and no Cry	50.00	95.60	11.36	–
> 50,000/mm³ Nph and no Cry	35.70	96.70	10.82	–

Se: sensitivity; Sp: specificity; LR+: positive likelihood ratio; LR−: negative likelihood ratio; Nph: neutrophils; Cry: microcrystals.

EN > 50000/mm³ ou PNN > 95% sans cristaux
LR+ 11,0

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THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1

sous le sceau de l'Université Bretagne Loire

Thèse en vue du

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Présentée par

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Née le 19.04.1989 à Clamart

Performances diagnostiques du dosage du glucose et du lactate synovial pour le diagnostic d'arthrite septique : étude transversale de 233 arthrites aigues.

Thèse soutenue à Rennes
le 17.10.2018

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Table 2. Performance of glucose, lactates and lactates/glucose ratio in synovial fluid for diagnosis of septic arthritis.

	AUC (CI95%)	Cut-off	Se (CI95%)	Sp (CI95%)	LR+ (CI95%)	LR- (CI95%)
Glucose *(mmol/L)*	0.833 (0.735-0.931)	≤ 1.0	32 % (0.17-0.52)	99.0% (0.97-1.0)	33.3 (7.5-148)	0.69 (0.53-0.90)
		≤ 1.8	44 % (0.27-0.63)	95.2% (0.91-0.97)	15.6 (5.6-43)	0.59 (0.42-0.83)
Lactates *(mmol/L)*	0.795 (0.681-0.910)	≥ 11.0	36.0% (0.20-0.55)	99.5% (0.97-1.00)	74.9 (9.9-566)	0.64 (0.48-0.86)
		≥ 10.0	40.0% (0.23-0.59)	99.0% (0.97-1.00)	41.6 (9.7-179)	0.61 (0.44-0.84)
		≥ 9.5	48 % (0.30-0.67)	98.1% (0.95-0.99)	25.0 (8.7-71)	0.53 (0.36-0.77)
		≥ 8.5	60 % (0.41-0.77)	96.6% (0.93-0.98)	17.8 (9.9-63)	0.41 (0.25-0.66)
		< 4.3	76 % (0.57-0.89)	59.6% (0.53-0.66)	1.9 (1.4-2.5)	0.40 (0.20-0.82)
Ratio L/Glc	0.859 (0.772-0.945)	≥ 5.0	52 % (0.34-0.70)	98.1% (0.95-0.99)	27.0 (9.5-76)	0.49 (0.33-0.74)
		< 1	80 % (0.61-0.91)	71.6% (0.65-0.77)	2.8 (2.1-3.8)	0.28 (0.13-0.61)

Table 3. Performance of CRP, Synovial white cells count or percentage of synovial polynuclear cells, synovial crystals detection, Gram stain or bacteriological culture in synovial fluid for diagnosis of septic arthritis.

	AUC (CI95%)	Cut-off	Se (CI95%)	Sp (CI95%)	LR+ (CI95%)	LR- (CI95%)
CRP	0.705 (0.581-0.830)					
SWBC (/mm^3)	0.737 (0.595-0.880)	≥ 50000	72.2% (0.49-0.88)	80.0% (0.74-0.85)	3.6 (2.4-5.4)	0.35 (0.16-0.73)
		*	55.6% (0.34-0.75)	90.1% (0.85-0.93)	5.6 (3.1-10)	0.49 (0.29-0.83)
PMN (%)	0.616 (0.498-0.735)	≥ 90 %	59.1% (0.39-0.77)	64.4% (0.57-0.71)	1.7 (1.1-2.5)	0.64 (0.38-1.06)
		*	45.5% (0.27-0.65)	85.9% (0.80-0.90)	3.2 (1.8-5.7)	0.64 (0.43-0.93)
Examen direct	0.556 (0.404-0.707)	-	16.7% (0.07-0.36)	95.9% (0.92-0.98)	4.0 (1.3-12)	0.87 (0.73-1.04)
SJF culture	0.841 (0.716-0.967)	-	80.0% (0.61-0.91)	95.7% (0.92-0.98)	18.5 (9.5-36)	0.21 (0.10-0.46)
Blood culture	0.591 (0.438-0.745)	-	28.0% (0.14-0.48)	95.3% (0.91-0.98)	6.0 (2.4-15)	0.76 0.59-0.97)

**With no crystal (15)*

Figure 2. Comparison of synovial lactates levels (Fig.2A), glucose levels (Fig.2B) and lactate/glucose ratio (Fig.2C) between septic arthritis, crystals associated-arthritis and non-septic non crystals associated-arthritis ("no-no" arthritis).

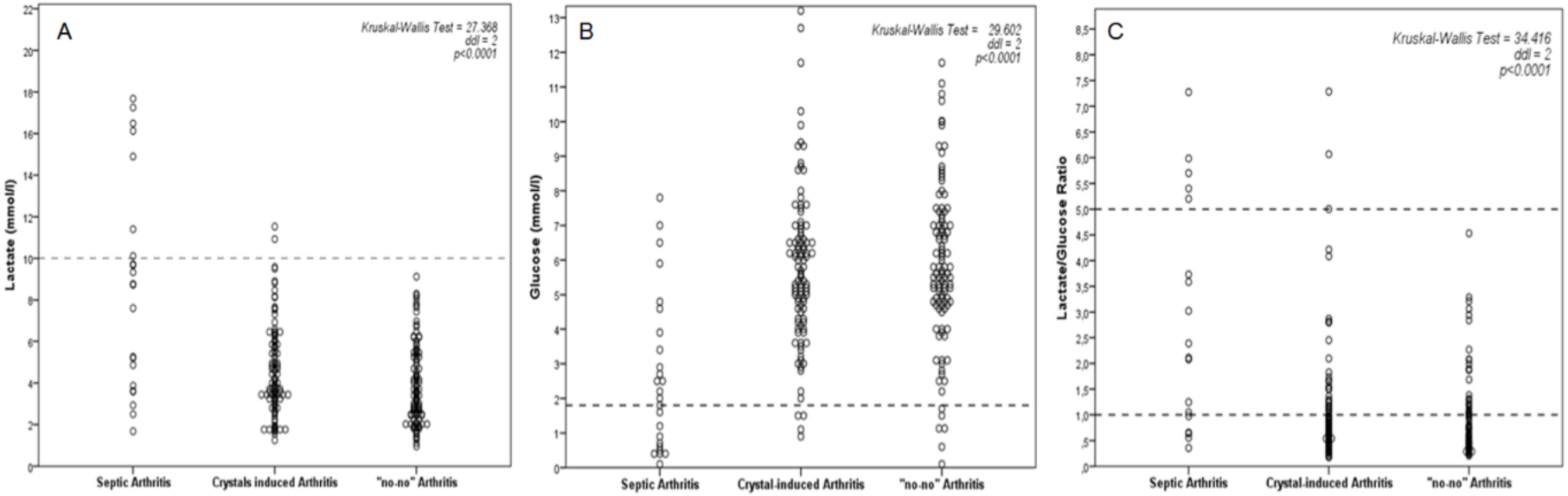
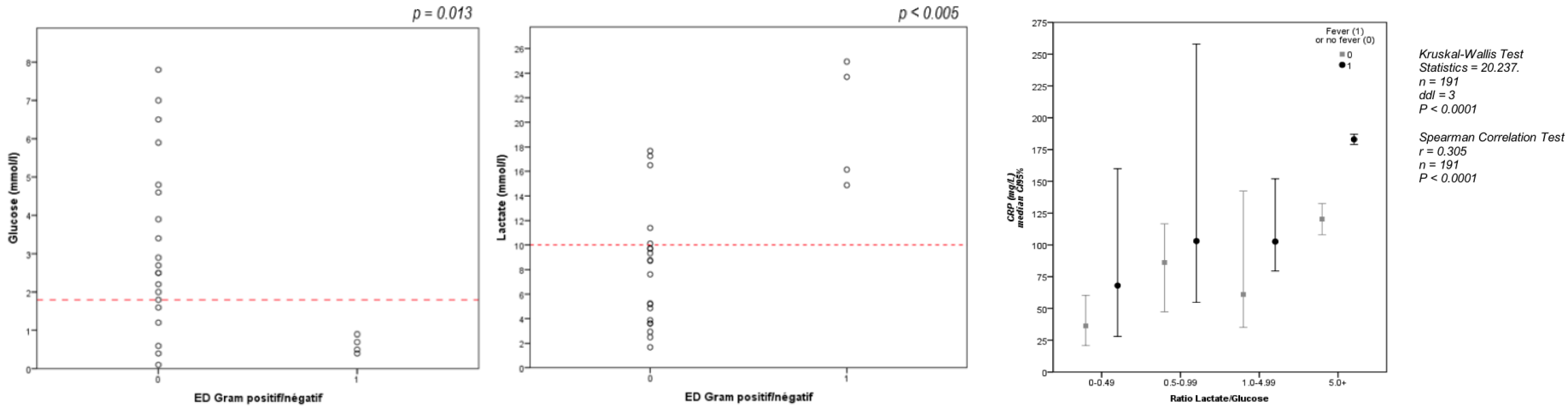


Figure 5. Comparison of synovial lactates and glucose levels between positive or negative Gram bacteria in septic arthritis with positive culture.



Kruskal-Wallis Test
Statistics = 20.237.
n = 191
ddl = 3
P < 0.0001

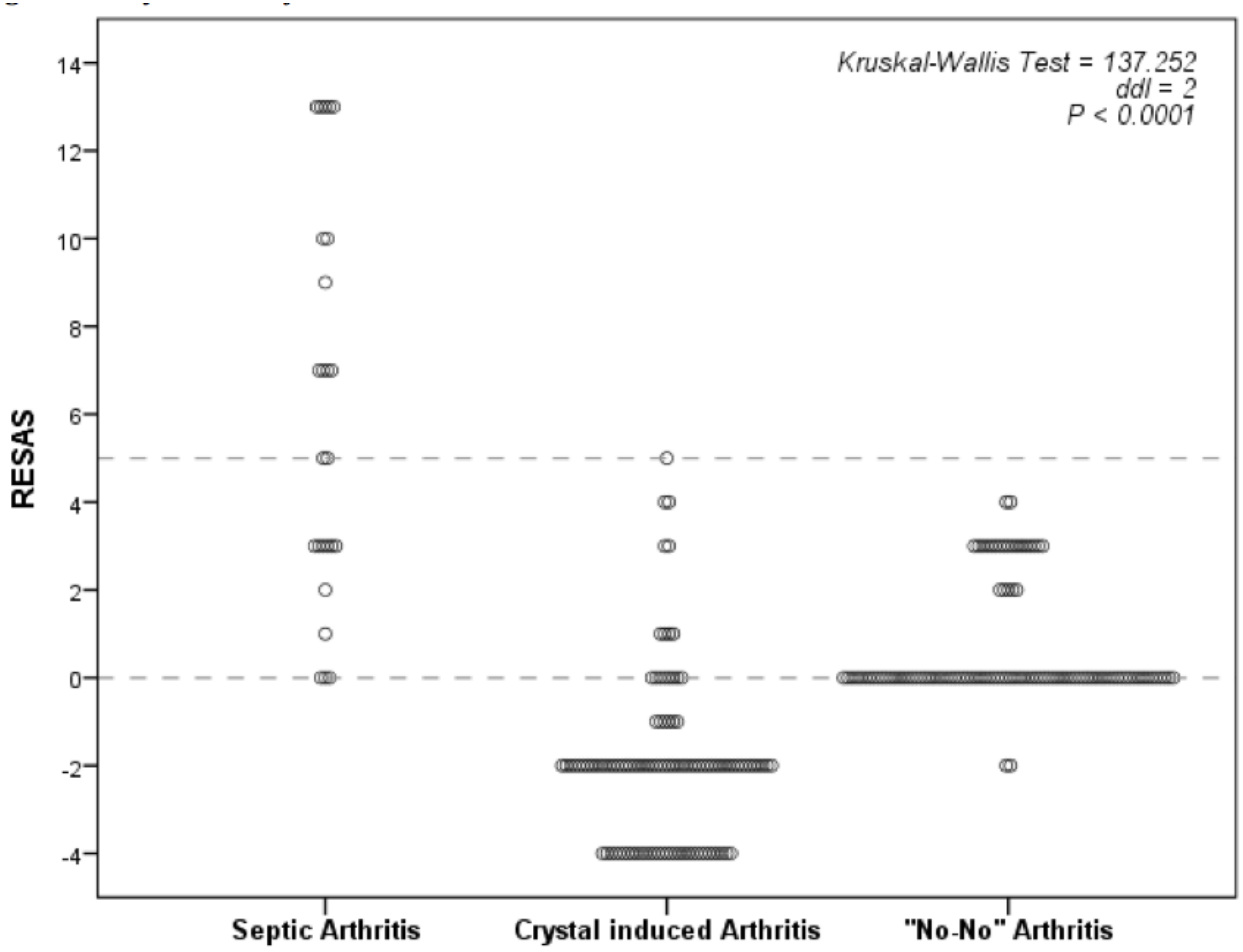
Spearman Correlation Test
r = 0.305
n = 191
P < 0.0001

Score composite d'arthrite septique : RESAS

	LR+ (CI95%)	Univariate analysis		Multivariate analysis	
		OR (CI95%)	*p*	OR (CI95%)	*p*
Male sex	1.27 (1.02-1.59)	0.43 (0.15-1.18)	*0.09*	0.72 (0.16-3.25)	*0.66*
Absence of RIC	2.09 (0.82-5.37)	2.27 (0.81-6.25)	*0.11*	1.24 (0.32-3.98)	*0.76*
Fiever	2.00 (1.44-2.78)	4.13 (1.70-10.0)	*0.001*	1.10 (0.30-4.86)	*0.89*
CRP > 50 mg/L	1.44 (1.20-1.73)	4.64 (1.34-16.0)	*0.009*	4.99 (0.82-30.3)	*0.08*
Pus or SFWBC≥ 75000/mm^3	4.51 (3.07-6.63)	17.9 (6.18-51.6)	< *0.001*	13.8 (3.39-56.0)	< *0.001*
Absence of crystals	1.67 (1.34-2.08)	4.90 (1.63-14.7)	*0.002*	4.20 (0.95-18.5)	*0.058*
Lactates ≥ 10 mmol/L	41.6 (9.7-179)	68.7 (13.8-342)	< *0.001*	37.3 (2.63-529)	*0.008*
Glucose < 1.8 mmol/L	15.6 (5.6-42.9)	15.6 (5.65-42.9)	< *0.001*	2.33 (0.42-13.1)	*0.34*

items of the Resas	**Cut-off**	**Points**
SFWBC	≥ 75000/mm^3	+3
Presence of crystals	Calcium Pyrophosphate Crystal	-2
	Urate Crystal	-4
Lactate (mmol/L)	≥ 11.5	+6
	10-11.4	+4
	8.5-9.9	+2
Glucose (mmol/L)	< 1	+4
	1-1.8	+2

Score composite d'arthrite septique : RESAS



AUC = 0.928 (0.877-0.980)

RESAS ≥ 5
Se = 56% , Sp = 99.5%, LR+ 116.5

RESAS ≤ 0
Se = 100% Sp = 42.8% LR- < 0.001

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Letter to the Editor

Comparison of several biomarkers (MMP-2, MMP-9, the MMP-9 inhibitor TIMP-1, CTX-II, calprotectin, and COMP) in the synovial fluid and serum of patients with and without septic arthritis

ARTICLE INFO

Keywords:
Septic arthritis
Diagnosis
Biomarkers
Metalloprotease
CTX

It is critical to diagnosis septic arthritis (SA) in a timely fashion in order to reduce the risk of irreversible cartilage damage, which has important functional sequelae [1,2]. However, direct Gram stain of synovial fluid is positive in only 25 to 50% of SA cases, and the bacteriological results remain negative in approximately 20% of SA cases [3]. Therefore, readily available and specific biomarkers are needed to help clinicians to decide for hospitalization and antibiotic treatment. This study assessed whether the following serum and synovial biomarkers could distinguish between patients with SA versus non-SA: 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).

Serum samples and aspirated synovial fluid samples were prospectively collected from 21 patients with SA. SA was defined as the identification of microorganisms from synovial fluid or blood cultures: *Staphylococcus aureus*, $n = 13$; *Streptococcus*, $n = 4$; *Enterobacteria*, $n = 3$; and coagulase-negative *Staphylococcus*, $n = 1$. We also collected samples from 18 patients with a suspicion of SA who had acutely swollen joints due to other causes: chondrocalcinosis, $n = 9$; gout, $n = 2$; rheumatoid arthritis, $n = 2$; spondyloarthritis, $n = 1$; osteoarthritis, $n = 3$; and hemarthrosis, $n = 1$. TIMP-1, MMP-2, MMP-9, CTX-II, CALP, and COMP levels were measured in synovial fluid and serum using commercial enzyme-linked immunosorbent assay (ELISA) kits and compared between the groups.

The characteristics of the study population are shown in Table 1. Univariate analysis showed that the following were significantly higher in the SA group versus the non-SA group (Table 2): serum TIMP-1 ($P < 0.01$), synovial MMP-9 ($P < 0.01$); serum ($P < 0.05$) and synovial CTX-II ($P < 0.01$); and serum ($P < 0.05$) and synovial CALP ($P < 0.05$). The AUCs for diagnosing SA based on synovial MMP-9, serum TIMP-1, synovial CTX-II, and serum and synovial CALP were 0.84, 0.79, 0.81, 0.7, and 0.72, respectively. When serum TIMP-1 and synovial CTX-II were combined and thresholds of 286.5 ng/mL and 873 ng/mL were used, respectively, the sensitivity was 75% and the specificity was 94% for diagnosing SA. This combination correctly classified patients in 86% of cases. Synovial MMP-9 substantially correlated with C-reactive protein ($r = 0.61$), whole blood white blood cell count [WBC] ($r = 0.46$), synovial WBC ($r = 0.66$) and the polymorphonuclear cell percentage ($r = 0.51$) in synovial fluid. Serum TIMP-1 and synovial CTX-II did not correlate with each other ($r = 0.1$) or with CRP ($r = 0.4$ and $r = 0.25$, respectively) or synovial WBC ($r = -0.04$ and $r = 0.27$, respectively).

To our knowledge, this is the first study to assess the performance of numerous potentially useful markers in synovial fluid and serum samples of patients with suspected SA. Synovial CTX-II is especially interesting because it appears to add new information

Table 1
Clinical characteristics and laboratory data of the study population.

	SA group $n = 21$	Non-SA group $n = 18$	*P*-value
Age, years, mean ± SD	64.5 ± 21.1	64.8 ± 12.6	Ns
Male gender, *n* (%)	12 (57.1)	8 (44.4)	Ns
Diabetes, *n* (%)	5 (23.8)	2 (11.1)	Ns
Joint affected			
Knee, *n* (%)	14 (66.7)	15 (83.3)	Ns
Shoulder, *n* (%)	4 (19)	2 (11.1)	
Hip, *n* (%)	3 (14.3)	0 (0)	
Elbow, *n* (%)	0 (0)	1 (5.6)	
Max. temperature, °C, mean ± SD	38.3 ± 0.7	38.1 ± 0.7	Ns
Chills, *n* (%)	7/18 (38.9)	4/18 (22.2)	Ns
Presence of an entry site for infection, *n* (%)	15/20 (75)	8/18 (44)	Ns
Whole blood			
WBC count, /mm³, median [Q1–Q3]	10,770 [8250–13,260]	8230 [4900–11,400]	<0.05*
CRP, mg/L, median [Q1–Q3]	209 [122–256]	90 [35–184]	Ns
Positive Blood culture, *n* (%)	11/20 (55)	0	
Radiological signs of SA, *n* (%)	7/18 (38.9)	1/17 (5.9)	<0.05*
Synovial fluid			
Turbid, *n* (%)	13/19 (68.4)	2/17 (11.8)	<0.01*
WBC count > 50 000/mm³, *n* (%)	7/16 (43.7)	3/18 (16.7)	Ns
PMN, %, median [Q1–Q3]	90 [89–93]	89 [84–90]	Ns
Direct gram stain positive, *n* (%)	8/21 (38.1)	0	
Culture positive, *n* (%)	20/21 (95)	0	

Values are expressed as mean ± standard deviation (SD) or median [Q1–Q3] for continuous variables and *n* (%) for categorical variables. SA: septic arthritis; CRP: C-reactive protein; WBC: white blood cell; PMN: polymorphonuclear cell.
* $P < 0.05$.

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Calprotectine ?

Measurement and performances of the biomarkers according to diagnosis (septic or non-septic arthritis).

Marker level	Septic arthritis ($n = 21$)	Non-septic arthritis ($n = 18$)	*P*-value	AUC [CI 95%]	Threshold	Se % [CI 95%]	Spe % [CI 95%]	LR+ [CI 95%]	LR– [CI95%]
MMP-2 serum, ng/mL	90 ± 35.6	77.1 ± 26.5	Ns						
MMP-2 synovial fluid, ng/mL	248.5 ± 131	241.8 ± 109.4	Ns						
MMP-9 serum, ng/mL	2856 ± 1997	2190 ± 1920	Ns						
MMP-9 synovial fluid, µg/L	49.6 ± 26.3	20.7 ± 16.5	<0.01*	0.84 [0.68–0.99]	32.4	85 [55–98]	82 [57–96]	4.8 [1.7–13.7]	0.19 [0.05–0.68]
TIMP-1 serum, ng/mL	320.6 ± 169	170.8 ± 69.2	<0.01*	0.79 [0.64–0.94]	286.5	57 [34–78]	94 [71–100]	9.7 [1.4–67.4]	0.46 [0.27–0.76]
TIMP-1 synovial fluid, ng/mL	947 ± 315	948.1 ± 377.1	Ns						
CTX-II serum, ng/mL	1036.9 ± 549.2	653.5 ± 268	<0.05*	0.72 [0.54–0.89]	870	61 [36–83]	89 [65–99]	5.5 [1.4–21.4]	0.44 [0.24–0.80]
CTX-II synovial fluid, ng/mL	1069.9 ± 540.3	673.5 ± 335.5	<0.01*	0.81 [0.6–1]	873	83 [52–98]	89 [65–99]	7.5 [2–28.4]	0.19 [0.05–0.67]
COMP serum, ng/mL	304.4 ± 216.1	271.4 ± 157.3	Ns						
COMP synovial fluid, ng/mL	4210 ± 3523	6098 ± 4161	Ns						
CALP serum, mg/mL	2.5 ± 1.4	1.6 ± 1	<0.05*	0.7 [0.52–0.88]	2.11	65 [41–85]	77 [50–93]	2.8 [1.1–6.9]	0.46 [0.24–88]
CALP synovial fluid, mean ± SD, µg/mL	1270.9 ± 605.3	798.1 ± 604.8	<0.05*	0.72 [0.54–0.90]	854	73 [45–92]	67 [41–87]	2.2 [1.1–4.5]	0.4 [0.16–0.98]

Markers levels are expressed as mean and standard deviation. Ns: non significant; AUC: area under the curve; CI: confidence interval; MMP: metalloproteinase; TIMP: metalloproteinase inhibitor; CTX: C-terminal telopeptide of collagen; COMP: cartilage oligomeric matrix protein; Se: sensitivity; Spe: specificity; LR: likelihood ratio; CI: confidence interval.
* P-value < 0.05.

Couderc M. Joint Bone Spine. 2018 May 19.

Conclusion

. Arthrite aigue même fébrile ≠ Arthrite septique

…prévalence < 15 %

. Ponction articulaire avant toute antibiothérapie

…sauf sepsis sévère !

. Culture bactériologique reste le *gold-standard*

…mais c'est long !

. Recherche de cristaux +++

…principal diagnostic différentiel !

. Intérêt de la biochimie (lactate et glucose) pour calcul du score pronostic RESAS pour guider une antibiothérapie probabiliste.

…besoin d'une validation externe !