SOCIÉTÉ DE
RHUMATOLOGIE
DE L'OUEST

Les nouveaux outils de diagnostiques microbiologiques

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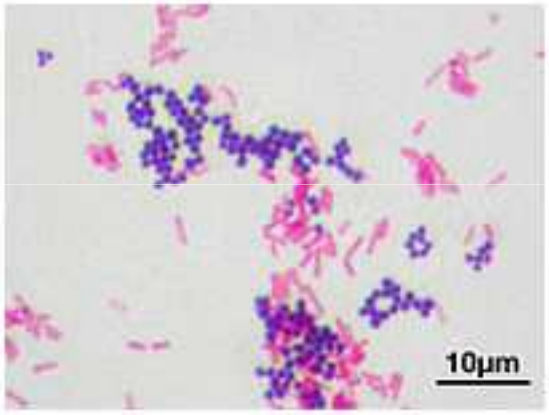
Problème des « anciens » outils diagnostiques microbiologiques

- Examen direct par coloration de Gram



Rapide mais seulement 30 à 40% de positif en cas d'arthrite septique (dépend de l'inoculum)

Ne permet pas la détection des intra-cellulaires (*Chlamydiae, Mycoplasme, Whipple, Spirochètes* (Lyme, Syphilis)…*)*

Ne permet pas la détection des Mycobactéries

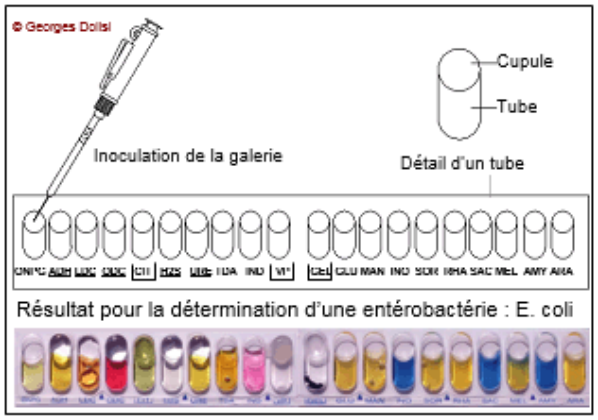
Problème des « anciens » outils diagnostiques microbiologiques

- Cultures sur géloses standards

  Examen de référence pour le diagnostic d'arthrite septique mais

  . Positive dans 85% des arthrites septiques

  (antibiothérapie préalable ou bactéries fastidieuses)



. Temps de positivité variable > 48h

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ORIGINAL ARTICLE

Synovial fluid culture: agar plates vs. blood culture bottles for microbiological identification

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Abstract

Objectives Bacteriological diagnosis of septic arthritis (SA) is complicated. Agar plates are the main culture method and yields 40–60% of positive bacterial detection. Addition of bottled culture broth (Bactec®) as a method for detecting synovial microorganisms is common. The advantages of this method and the combination of both have not been thoroughly investigated. This study evaluates an added value of the Bactec culture broth as a single method or as combined with the agar-plate culture.

Methods All culture aspirates of SA-suspected patients were analyzed. All cases with a positive result by either method were reviewed for background data and clinical diagnosis.

Results Out of 5000 synovial fluid samples, a clinical diagnosis of SA was suspected in 1024 cases. Samples processed by both culture methods were extracted during the same event. Bactec® vials were positive for significant bacterial detection in 113/148 cases (76.4%) while agar-plate cultures were positive in only 96/154 (62.3%) representing higher sensitivity of 0.5 vs. 0.42 and a positive predictive value (PPV) of 0.76 vs. 0.62. Bacterial detection by both methods combined was positive in 137/221 (62%) and did not achieve a significant increment.

Conclusions The Bactec® method has many advantages in bacteriological identification of synovial infection, including a broader identification spectrum, faster response time, and superior qualities of identification although being more expensive. This method has a better yield in detecting septic arthritis and might be considered a single method for synovial fluid culture in cases suspected for SA.

Key Points
- *The Bactec method had improved detection rates.*
- *Culturing by agar plates and Bactec revealed higher sensitivity and lower specificity.*
- *The use of the blood culture bottles (Bactec system) alone will raise the detection rate of septic arthritis with lower false positive rates and at lower costs.*

Keywords Agar · Bactec · Broth · Culture · Synovial fluid

Introduction

Septic arthritis is one of the known medical emergencies, caused by one or more pathogens which invade the joint. This can take place either by direct inoculation or by hematogenous seeding. In a small number of cases, more than one joint is involved. The presence of a pathogen together with the inflammatory response can cause massive damage to the joint, hence the need for immediate medical identification and treatment. This pathology was described centuries ago but is becoming increasingly important and more common due to the increased usage of artificial joints in the recent decades [1, 2]. There are several different diagnostic methods for septic arthritis in

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Table 3 Comparison of statistical qualifiers for both culture methods

	Bactec	Conventional culture	Combined
Sensitivity	.502 (.457–.541)	.427 (.378–.472)	.609 (.556–.658)
Specificity	.956 (.944–.967)	.927 (.914–.940)	.895 (.880–.909)
PPV	.764 (.695–.822)	.623 (.552–.690)	.620 (.566–.658)
NPV	.872 (.861–.882)	.852 (.839–.864)	.890 (.876–.904)
OR	22.023 (14.068–34.603)	9.508 (6.421–14.097)	13.251 (9.197–19.118)
positive LR	22.72	13.69	9.53
negative LR	0.52	0.62	0.43

PPV positive predictive value, *NPV* negative predictive value, *LR* likelihood ratio

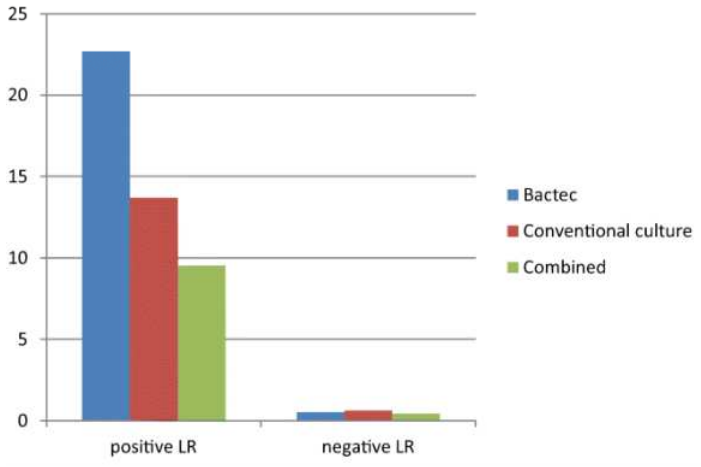


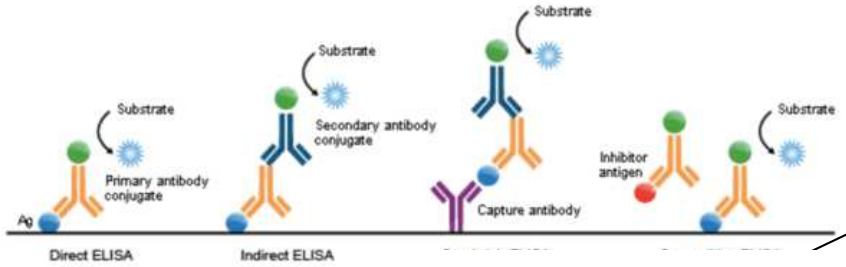
Table 2 Sample Description—positive, negative culture, and clinical scenario

	Sample number	Positive culture	Negative culture
Bactec	1024	148	876
Agar	1024	154	870
Combined	1024	221	803
	SA negative	SA positive	
Bactec positive	35 (23.6%)	113 (76.4%)	
Agar positive	58 (37.7%)	96 (62.3%)	
Combined positive	84 (38.0%)	137 (62.0%)	

SA, septic arthritis

Cohen D. Clin Rheumatol. 2020;39(1):275-279.

Problème des « anciens » outils diagnostiques microbiologiques



Sérologies

Virales

Polyarthrites aigues

VIH,
VHB, VHC (VHA, VHE)
Parvovirus B19
Chikungunya
Alphavirus (virus Sindbis)

Bactériennes

Sérologies utiles	Bartonella spp., ***(Maladie des griffes du chat)***, Brucella spp., Borrelia spp. ***(Maladie de Lyme)***, Chlamydia pneumonia (Chlamydophila pneumonia), Chlamydia psittaci (Chlamydophila psittaci), Clostridium. Tetani ***(Tétanos)***, Coxiella burnetii ***(Fièvre Q)***, Francisella spp. ***(Tularémie)***, Legionella spp. ***(Légionellose)***, Leptospira spp., Mycoplasma pneumoniae, Rickettsies ***(Fièvre boutonneuse, Typhus des broussailles)***, Treponema pallidum ***(Syphilis)***.
Sérologies utiles selon le contexte médical	Campylobacter spp. (arthrites réactionnelles, syndrome de Guillain-Barré), Chlamydia trachomatis, Corynebacterium diphteriae ***(Diphtérie)***, Haemophilus spp., Helicobacter pylori, Salmonella spp., Streptococcus pneumoniae (Pneumocoque), Streptocoques (ASLO, ASDOR), Yersinia (arthrites réactionnelles, syndrome de Guillain-Barré).
Sérologies inutiles	Bordetella pertussis ***(Coqueluche)***, Klebsiella spp., Listeria spp., Mycoplasmes génitaux (Ureaplasma urealyticum, Mycoplasma hominis, Mycoplasma genitalium), Neisseria gonorrhoeae (Gonocoque), Pasteurella spp., Shigella spp., Staphylocoques, Mycobacterium tuberculosis ***(Tuberculose)***, Pseudomonas aeruginosa.

Ann Rheum Dis 2001;60:337–343 337

Frequency of triggering bacteria in patients with reactive arthritis and undifferentiated oligoarthritis and the relative importance of the tests used for diagnosis

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Abstract

***Objective*—Reactive arthritis (ReA) triggered by *Chlamydia trachomatis* or enteric bacteria such as yersinia, salmonella, *Campylobacter jejuni*, or shigella is an important differential diagnosis in patients presenting with the clinical picture of an undifferentiated oligoarthritis (UOA). This study was undertaken to evaluate the best diagnostic approach.**

***Patients and methods*—52 patients with ReA, defined by arthritis and a symptomatic preceding infection of the gut or the urogenital tract, and 74 patients with possible ReA, defined by oligoarthritis without a preceding symptomatic infection and after exclusion of other diagnoses (UOA), were studied. The following diagnostic tests were applied for the identification of the triggering bacterium: for yersinia induced ReA—stool culture, enzyme immunoassay (EIA), and Widal's agglutination test for detection of antibodies to yersinia; for salmonella or campylobacter induced ReA—stool culture, EIA for the detection of antibodies to salmonella and *Campylobacter jejuni*; for infections with shigella—stool culture; for infections with *Chlamydia trachomatis*—culture of the urogenital tract, microimmunofluorescence and immunoperoxidase assay for the detection of antibodies to *Chlamydia trachomatis*.**

***Results*—A causative pathogen was identified in 29/52 (56%) of all patients with ReA. In 17 (32%) of the patients with enteric ReA one of the enteric bacteria was identified: salmonella in 11/33 (33%) and yersinia in 6/33 (18%). *Chlamydia trachomatis* was the causative pathogen in 12/19 (63%) of the patients with urogenic ReA. In patients with the clinical picture of UOA a specific triggering bacterium was also identified in 35/74 (47%) patients: yersinia in 14/74 (19%), salmonella in 9/74 (12%), and *Chlamydia trachomatis* in 12/74 (16%).**

***Conclusions*—*Chlamydia trachomatis*, yersinia, and salmonella can be identified as the causative pathogen in about 50% of patients with probable or possible ReA if the appropriate tests are used.**

(Ann Rheum Dis 2001;60:337–343)

www.annrheumdis.com

Reactive arthritis (ReA) is a well known complication of enteric infections caused by yersinia, salmonella, shigella, and campylobacter, or of urogenital tract infections caused by *Chlamydia trachomatis*.[1] This form of ReA is regarded as part of the spondyloarthropathies and HLA-B27 is positive in about 50% of these patients.[2] The arthritis has a typical joint pattern, which is also characteristic for the whole group of spondyloarthropathies: an asymmetrical arthritis predominantly of the legs.[3] In most patients an oligoarthritis or monarthritis is present. Patients with such a joint pattern constitute up to 30% of patients in clinics for early arthritis.[4–6] Therefore ReA is an important differential diagnosis.

Despite the clinical relevance there are no established criteria available for the diagnosis of ReA. Earlier criteria relied almost exclusively on clinical indicators of a symptomatic preceding infection, such as urethritis/cervicitis, or on symptoms characteristic for the whole group of spondyloarthropathies.[7–9] However, it is likely that in a substantial proportion of patients with ReA the preceding infection is asymptomatic or associated with only a few symptoms,[10] often labelled as undifferentiated arthritis or undifferentiated oligoarthritis (UOA).[11 12] Better laboratory tests identifying the triggering bacteria are now available[13] and are increasingly used for the diagnosis of ReA,[5 14 15] especially in patients with possible ReA or UOA.

In this study we used all available tests (except polymerase chain reaction (PCR) for the detection of bacteria in the joint) for the identification of the bacteria causing ReA in a large number of patients with ReA (having a symptomatic preceding infection of the gut or the urogenital tract) or possible ReA (UOA with a joint pattern compatible with ReA). We report the frequency of single bacteria in these two subgroups and the relative importance of the different tests used.

Patients and methods

PATIENTS' SELECTION AND CHARACTERISTICS

In this study 126 patients from different rheumatology clinics in Berlin, Germany, with a clinical diagnosis of ReA (n=52) or UOA (n=74) were included. A diagnosis of ReA was made if patients presented with the clinical picture of an asymmetrical arthritis and a preceding symptomatic urethritis or enteritis no longer than four weeks before the onset of arthritis. A diagnosis of UOA was made after

Table 1 Characteristics of all patients, patients with reactive arthritis (ReA), and patients with undifferentiated oligoarthritis (UOA)

	All patients	*ReA*	*UOA*
Number	126	52	74
Age (years*)	36.6	35.8	37.4
Range	18–65	18–60	19–65
Sex (M/F)	66/60	28/24	38/36
Disease duration‡ (weeks†)	14	8	30
Range	1–354	1–260	2–354
HLA-B27+ (%)¶	45.2	57.7	35.1
Patients with monarthritis (%)	42	35	47

*Mean; † median.
‡At time of inclusion into the study.
¶The frequency of HLA-B27 in the Berlin area is 9.3%.[47]

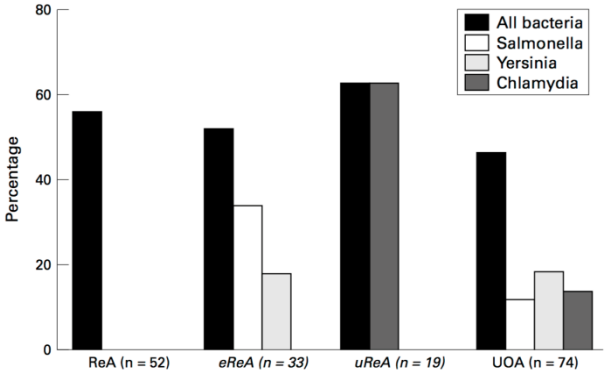
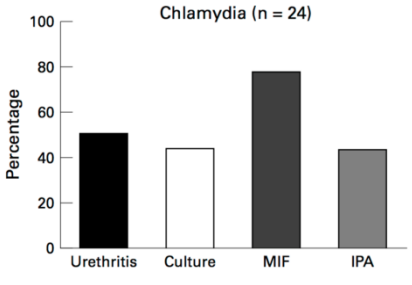
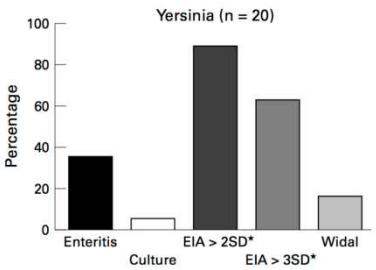
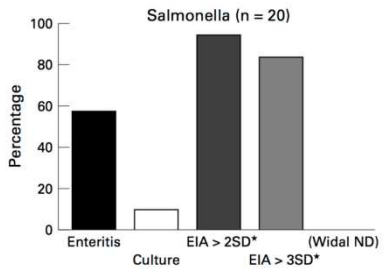


Figure 1 Frequency of all bacteria or single bacteria identified as responsible for enteric reactive arthritis (eReA), urogenic reactive arthritis (uReA), or undifferentiated oligoarthritis (UOA).







Fendler C. Ann Rheum Dis. 2001;60:337-343.

EXPERIMENTAL AND THERAPEUTIC MEDICINE 17: 3465-3476, 2019

Usefulness of complex bacteriological and serological analysis in patients with spondyloarthritis

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Abstract. Spondyloarthritis (SpA) is a group of associated chronic systemic inflammatory immune-mediated rheumatic diseases affecting axial and peripheral joints and entheses. The aim of the present study was to identify what parameters are useful to determine in order to better understand the correlation between the disease activity/severity and the microbiological results/immune status against intestinal and/or urogenital pathogens. Microorganisms known to trigger SpA, including *Klebsiella spp.*, *Yersinia spp.*, *Salmonella spp.*, *Campylobacter spp.* and *Chlamydia spp.*, were analyzed in various specimens (stool, urine, synovial fluid and serum) collected from 27 randomly selected SpA patients and 26 healthy controls using a combined direct and indirect approach relying on conventional culture technique and nucleic acid-based assays together with serological testing by ELISA. Although *Escherichia coli* derived from phylogroup A prevailed in the gut microflora of the patients and controls, differences were observed regarding the representatives of the other phylogroups with a higher prevalence of *E.coli* members of phylogenetic group B1 in the stool specimens of patients. Antibodies against the targeted species were detected in SpA patients and controls, and the seroligical profiles of the former were more diverse and complex. In conclusion, the detection of anti-bacterial antibodies combined with other specific laboratory investigations should be more extensively used to monitor SpA patients in association with their symptoms and in order to determine and administer more effective therapeutics.

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Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ATG, anti-thyroglobulin antibodies; ATPO, anti-thyroid peroxidase; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; HLA, human leukocyte antigen; IL, interleukin; PCR, polymerasechainreaction; ReA, reactive arthritis; SpA, spondyloarthritis; TNF, tumournecrosis factor; VTEC, verocytotoxigenic *Escherichia coli*; uSpA, undifferentiated spondyloarthritis

Key words: spondyloarthritis, bacteriology, serology

Introduction

According to the Assessment of SpondyloArthritis (SpA) International Society (ASAS) and the European League against Rheumatism (1,2), SpA is a group of associated chronic systemic inflammatory immune-mediated rheumatic diseases affecting axial and peripheral joints and entheses. SpA includes different disease phenotypes: Ankylosing spondylitis (AS), reactive arthritis (ReA), arthritis/spondylitis with inflammatory bowel disease, psoriatic arthritis and undifferentiated (u)SpA (1,2). Extensive progress has been achieved in the understanding of SpA pathogenesis in the last two decades, including the complex interaction between environmental, immune, genetic and epigenetic factors (3-8). Furthermore, the gut and/or urogenital microbiota, representing one of the most important environmental factors,was revealed to have a much more complex configuration than previously thought, when studied by using modern high-throughput techniques, including genomic and metagenomic approaches (9-11). Infections with pathogens including *Yersinia* spp., *Salmonella* spp., *Campylobacter* spp., *Shigella* spp. and *Chlamydia trachomatis* have been reported at increasing rates worldwide (12,13), with a subsequent increase in the number of patients at risk

Table I. Clinico-pathological characteristics of the control and SpA groups.

Paramete	SpA (n=27)	Controls (n=26)	P-value
Age (years)	46.07±14.37 (34-68)	60.9±7.69 (54-77)	<0.001[a]
Male sex	24 (88.9)	12 (46.2)	0.002[b]
HLA-B27	24 (88.9)	2 (7.7)	<0.001[b]
Disease duration (years)	5.77±6.58 (1-33)	-	-
CRP (mg/l)	12.52±10.24 (1.8-32)	-	-
BASDAI	3.35±1.7 (1.1-7.0)	-	-
BASFI	3.3±1.96 (1.0-7.2)	-	-
$ASDAS_{CRP}$	2.18±1.27 (0.9-5.2)	-	-

[a]P-value determined by the Mann-Whitney U-test or [b]χ^2 test. The upper limit of normal for CRP is 5 mg/l. Values are expressed as the mean ± standard deviation (range) or n (%). $ASDAS_{CRP}$, Ankylosing Spondylitis Disease Activity Score using CRP; CRP, C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; HLA, human leukocyte antigen; SpA, spondyloarthritis.

Table III. Distribution by bacterial trigger specificity and class of Ig of anti-microbial antibodies detected in sera of SpA patients and control subjects.

Target pathogen/antibody type	SpA group (n=27)	Controls (n=26)	P-value
Klebsiella	11 (40.7)	21 (80.8)	0.003[a]
Anti-K21	4 (11.1)	14 (80.8)	
Anti-K36	1 (3.7)	0	
Anti-K50	6 (22.2)	0	
Yersinia	22 (81.5)	11 (42.3)	0.006[a]
IgA	15 (55.6)	5 (19.2)	
IgG	7 (25.9)	6 (23.1)	
Salmonella	8 (29.6)	5 (19.2)	0.296[a]
IgA	5 (18.5)	3 (11.5)	
IgG	3 (11.1)	2 (7.7)	
Campylobacter	7 (25.9)	1 (3.9)	0.024[b]
IgA	4 (14.8)	1 (3.9)	
IgG	3 (11.1)	0 (0.0)	
Chlamydia	5 (18.5)	2 (7.7)	0.248[b]
IgA	2 (7.4)	1 (3.9)	
IgG	3 (11.1)	1 (3.9)	

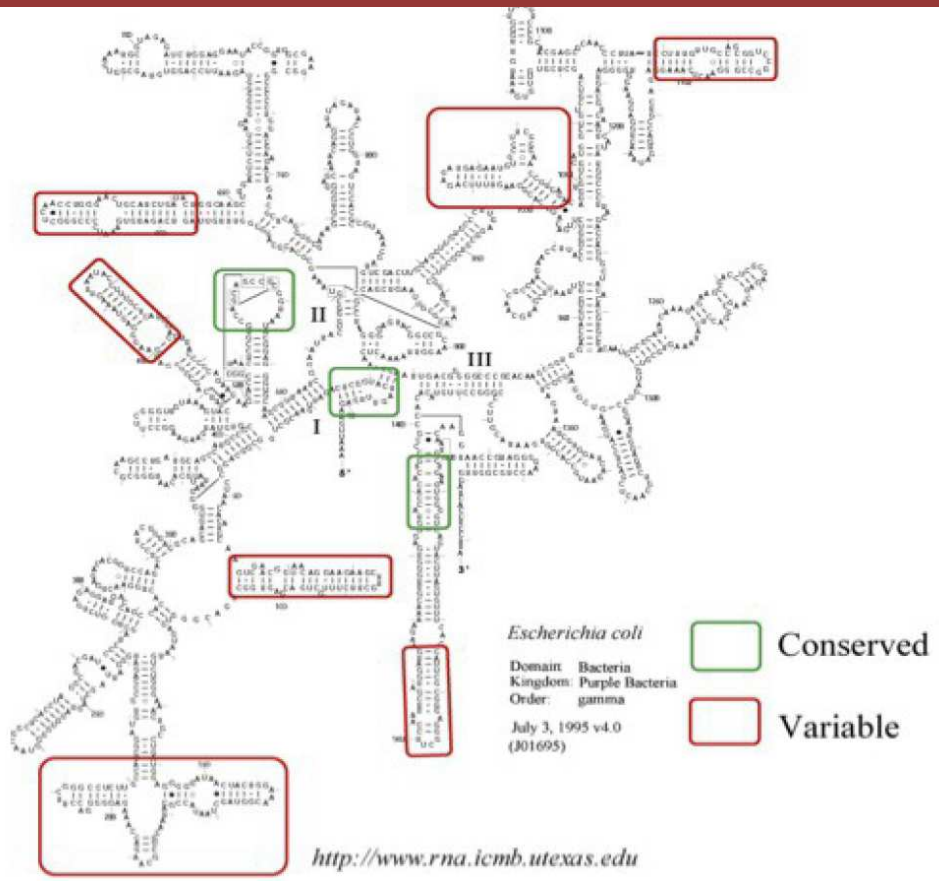
[a]P-value determined by the χ^2 test or [b]Fisher's exact test. Values are expressed as n (%). SpA, spondyloarthritis; IgG, immunoglobulin G.

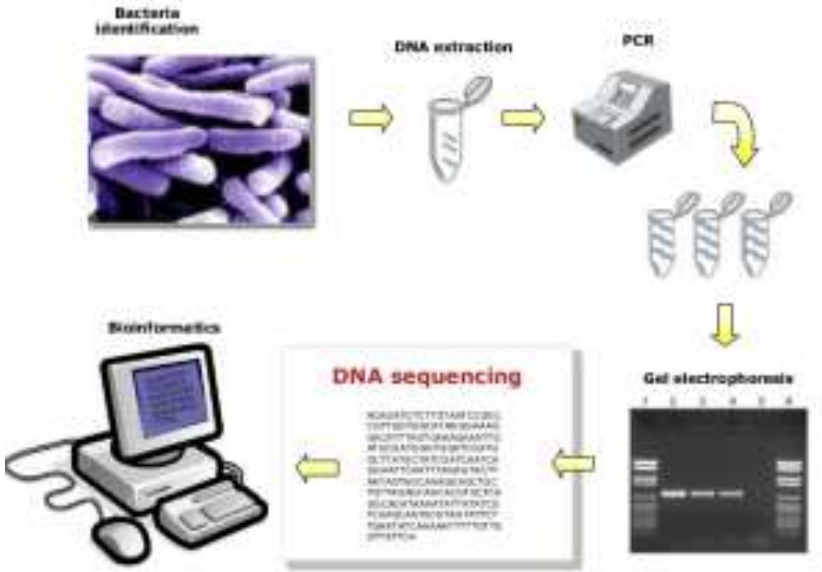
Cristea D. Exp Ther Med. 2019;17(5):3465-76.

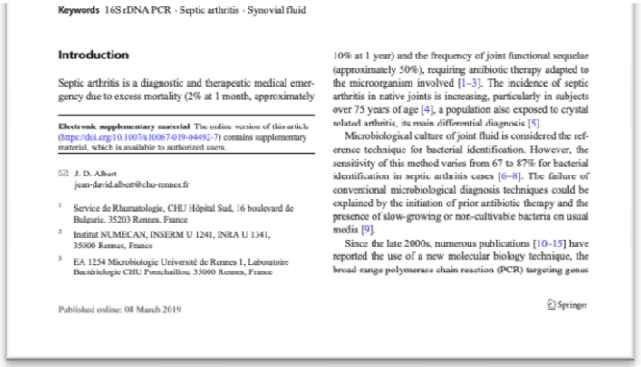
Quels sont les nouveaux outils diagnostiques microbiologiques ?

- PCR DNA ribosomal 16S
- PCR spécifique
- MALDI-TOF

PCR DNA ribosomal 16S (universelle)







Keywords 16S rDNA PCR · Septic arthritis · Synovial fluid

Introduction

Septic arthritis is a diagnostic and therapeutic medical emergency due to excess mortality (2% at 1 month, approximately 10% at 1 year) and the frequency of joint functional sequelae (approximately 50%), requiring antibiotic therapy adapted to the microorganism involved [1–3]. The incidence of septic arthritis in native joints is increasing, particularly in subjects over 75 years of age [4], a population also exposed to crystal related arthritis, the main differential diagnosis [5].

Microbiological culture of joint fluid is considered the reference technique for bacterial identification. However, the sensitivity of this method varies from 67 to 87% for bacterial identification in septic arthritis cases [6–8]. The failure of conventional microbiological diagnosis techniques could be explained by the initiation of prior antibiotic therapy and the presence of slow-growing or non-cultivable bacteria on usual media [9].

Since the late 2000s, numerous publications [10–15] have reported the use of a new molecular biology technique, the broad range polymerase chain reaction (PCR) targeting genes

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	AUC	Sensitivity	Specificity	LR+	LR −
Direct examination	0.691 (0.570–0.812)	0.38 (0.24–0.55)	1.00 (0.94–1.00)	+∞	0.62
Synovial fluid culture	0.925 (0.856–0.994)	0.88 (0.73–0.95)	0.97 (0.89–0.99)	26.9	0.12
16S rDNA PCR	0.618 (0.493–0.742)	0.24 (0.12–0.40)	1.00 (0.94–1.00)	+∞	0.77
Blood culture	0.727 (0.610–0.844)	0.47 (0.31–0.63)	0.98 (0.91–0.99)	28.7	0.54

Coiffier G. Clin Rheumatol. 2019;38(7):1985-1992.

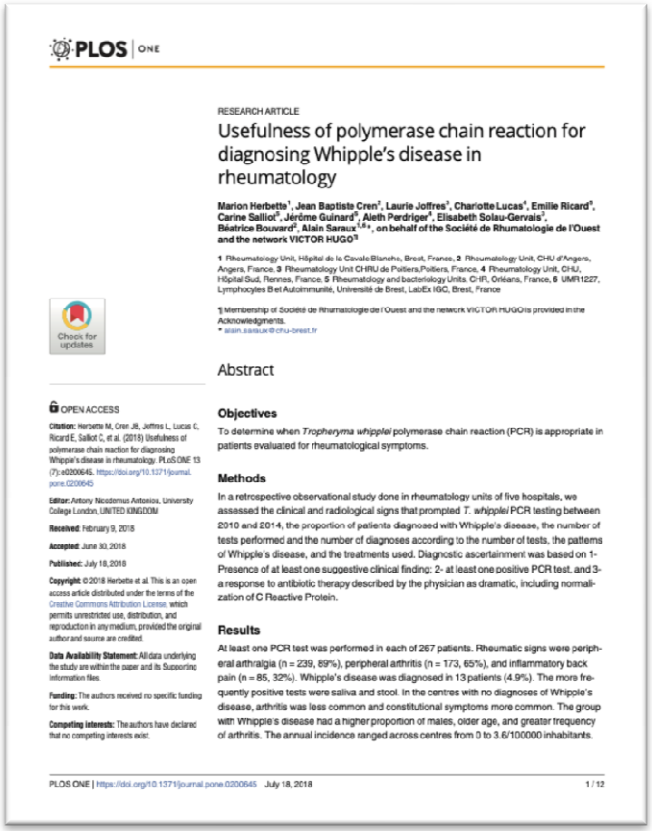
PCR Spécifique

Arthrites Septiques

- PCR *S. pneumoniae* (gène de la pneumolysine (*ply*) et gène de l'autolysine (*lytA*)
- PCR *N. gonorrhoeae*
- PCR *Kingella kingae (enfant < 2 ans)*
- PCR *M. tuberculosis*

Autres Arthrites

- PCR *Borreliella* (LS + 40%)
- PCR *C. trachomatis* (urine 35%, ReA post-uréthrite LS + 30%)
- PCR *T. whippleii*



PLOS ONE

RESEARCH ARTICLE

Usefulness of polymerase chain reaction for diagnosing Whipple's disease in rheumatology

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Abstract

Objectives

To determine when *Tropheryma whipplei* polymerase chain reaction (PCR) is appropriate in patients evaluated for rheumatological symptoms.

Methods

In a retrospective observational study done in rheumatology units of five hospitals, we assessed the clinical and radiological signs that prompted *T. whipplei* PCR testing between 2010 and 2014, the proportion of patients diagnosed with Whipple's disease, the number of tests performed and the number of diagnoses according to the number of tests, the patterns of Whipple's disease, and the treatments used. Diagnostic ascertainment was based on 1- Presence of at least one suggestive clinical finding; 2- at least one positive PCR test, and 3- a response to antibiotic therapy described by the physician as dramatic, including normalization of C Reactive Protein.

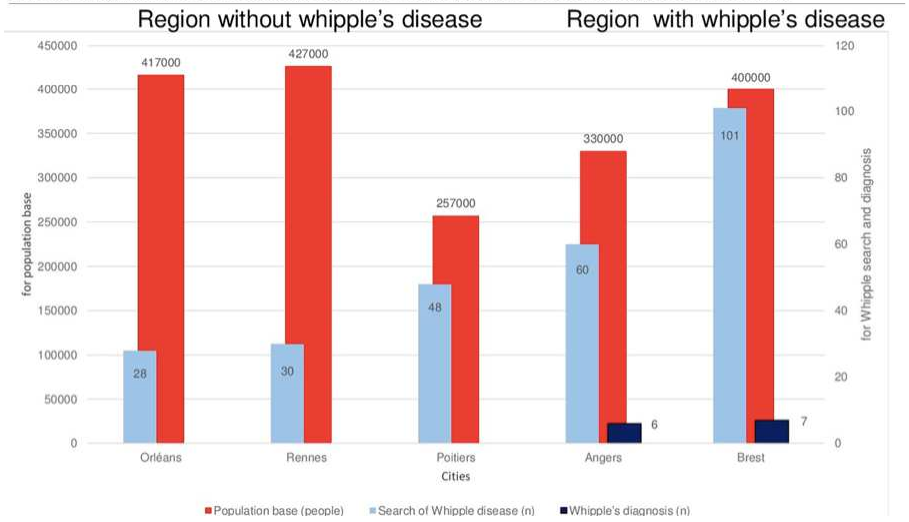
Results

At least one PCR test was performed in each of 267 patients. Rheumatic signs were peripheral arthralgia (n = 239, 89%), peripheral arthritis (n = 173, 65%), and inflammatory back pain (n = 85, 32%). Whipple's disease was diagnosed in 13 patients (4.9%). The more frequently positive tests were saliva and stool. In the centres with no diagnoses of Whipple's disease, arthritis was less common and constitutional symptoms more common. The group with Whipple's disease had a higher proportion of males, older age, and greater frequency of arthritis. The annual incidence ranged across centres from 0 to 3.6/100000 inhabitants.

Table 1. Tests that confirmed the diagnosis of Whipple's disease (13 patients).

CASE	PAS on duodenal biopsy	PCR on stool	PCR on saliva	PCR on duodenal biopsy	PCR on joint fluid	PCR on blood	Pattern of Whipple disease
BREST							
1	negative	**positive**	**positive**	negative	not made	not made	CTWAA
2	negative	**positive**	**positive**	negative	not made	negative	CTWAA
3	negative	**positive**	**positive**	negative	**positive**	negative	FWD
4	**positive**	**positive**	**positive**	**positive**	not made	negative	CWD
5	negative	negative	negative	negative	**positive**	negative	FWD
6	negative	**positive**	negative	negative	not made	negative	CTWAA
7	negative	**positive**	**positive**	**positive**	not made	negative	CTWAA
ANGERS							
8	negative	**positive**	**positive**	**positive**	not made	negative	CWD
9	**positive**	**positive**	**positive**	**positive**	not made	**positive**	CWD
10	negative	**positive**	**positive**	not made	not made	negative	CTWAA
11	negative	**positive**	**positive**	not made	not made	negative	CTWAA
12	negative	**positive**	negative	negative	negative	negative	CTWAA
13	negative	**positive**	**positive**	**positive**	negative	negative	CWD

PAS, periodic acid-Schiff stain; PCR, polymerase chain reaction test for *Tropheryma whipplei*; CTWAA, chronic *Tropheryma whipplei*-associated arthritis; FWD, focal Whipple's disease defined as joint fluid positive by PCR with duodenal biopsy negative by PAS and/or immunohistochemistry; CWD, classic Whipple's disease defined as duodenal biopsy positive by PAS and/or immunohistochemistry or as stool and saliva positive by PCR plus skin biopsy or blood positive by PCR



Herbette M. PLoS One. 2018;13(7):e0200645.

Open Forum Infectious Diseases

MAJOR ARTICLE

Diagnostic Approach for Classic Compared With Localized Whipple Disease

Nicholas R. Crews,[1] Kelly A. Cawcutt,[2] Bobbi S. Pritt,[3,4] Robin Patel,[3,4] and Abinash Virk[1]

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Background. Whipple disease (WD), a rare systemic infection caused by *Tropheryma whipplei*, can be a diagnostic challenge due to its variable presentation. The role of *T. whipplei* polymerase chain reaction (PCR) is unclear as small bowel biopsy with Periodic acid-Schiff (PAS) staining remains the diagnostic gold standard. Individualized diagnostic approaches based on variable clinical manifestations are underutilized. We investigated the methodologies employed at our institution to diagnose WD.

Methods. We retrospectively collected all cases of WD diagnosed from 1994 to 2016. Microbiology laboratory and anatomic pathology databases were queried. Case characteristics and disease clinical phenotypes (classical, localized WD arthritis, and localized central nervous system [CNS] disease) were described. The diagnostic approach and testing yield were analyzed and reported.

Results. Thirty-three cases of WD were diagnosed (18 classic WD [CWD], 9 localized WD arthritis [LWD], 6 CNS WD). Misdiagnosis and delay in diagnosis were frequent. Diagnostic approach and test yield differed by classical vs localized WD involvement. Small bowel tissue biopsy PAS stain/PCR was overwhelmingly positive (86%/92%) in CWD, yet seldom positive (12%/42%) in LWD ($P < .001$). Affected joint synovial fluid PCR was frequently positive in both CWD (100%, 3/3) and LWD (85%, 6/7).

Conclusions. These results support the role of small bowel biopsy PAS stain/PCR in the diagnosis of CW, though this approach may be of limited utility in LWD or CNS WD without gastrointestinal symptoms. Affected joint synovial fluid or cerebrospinal fluid PCR was frequently positive in both CWD and LWD, supporting its diagnostic usefulness.

Keywords. diagnostics; PAS; PCR; *Tropheryma whipplei*; Whipple disease.

Whipple disease (WD) is a chronic infection caused by *Tropheryma whipplei* [1]. In 1949, Black-Schaffer first described the classic WD (CWD) histologic finding of Periodic acid-Schiff (PAS)–positive macrophages within the intestinal mucosa and lymph nodes, which was later correlated with the presence of *T. whipplei* bacilli within the macrophage cytoplasm [2, 3]. Subsequently, PAS staining of formalin-fixed paraffin-embedded (FFPE) small bowel (SB) tissue became the standard WD diagnostic test and is commonly followed by amylase or diastase treatment (ie, PAS–D) to remove glycogen to aid in detection of *T. whipplei* bacilli. Since the identification of *T. whipplei* in 1992, polymerase chain reaction (PCR) assays targeting *T. whipplei* have been developed with excellent sensitivity [4–8]. Additional methods include organism cell culture and immunohistochemical staining, although neither is practical or commonly available [9, 10]. Despite these advances, WD remains a diagnostic challenge due to its rarity and variable presentation, resulting in delayed or missed diagnosis [1, 11, 12].

Fewer than 2000 WD cases have been reported in the literature since WD was first described [13]. The majority were classified as CWD, in which nonspecific gastrointestinal manifestations predominate after a period of prodromal joint involvement and constitutional symptoms [1, 11]. CWD frequently involves the nervous system, with 10%–46% of patients developing neurologic symptoms, and less commonly affects the endocardium, uvea, lymphatic system, pulmonary parenchyma, and pleural cavities [13–15]. In contrast, localized WD (LWD) without classic gastrointestinal involvement (including isolated *T. whipplei* endocarditis, polyarticular inflammatory arthritis, or localized neurologic infection) is becoming increasingly recognized, particularly since the advent of *T. whipplei* PCR, which can be performed on a variety of tissues and body fluids [1, 16–20].

The role of PCR in the WD diagnostic paradigm remains unclear. Intestinal tissue PCR has been traditionally ordered as a confirmatory test after PAS staining in CWD cases [11]. Some have recommended PCR in parallel to PAS staining [8, 21]. Individualized diagnostic approaches for localized *T. whipplei* infection have not been fully investigated and thus are likely underutilized. Recent series report SB PAS stain and PCR positivity in only 39%–48% and 55%–93% of CWD cases without typical gastrointestinal symptoms, respectively [11, 16]. *T. whipplei* synovial fluid PCR has been proposed as the

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Open Forum Infectious Diseases®

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Table 1. Differences in Clinical Data for 33 WD Patients by Whipple Disease Type: Classic vs Localized

Characteristics	Classic WD (n = 18)	Localized WD Arthritis (n = 9)	Localized CNS WD (n = 6)
Male, No. (%)	17 (94)	7 (78%)	4 (67)
Mean age (SD), y	52 (13)	46 (15)	56 (9.3)
Median time from initial symptoms to diagnosis (IQ1,3), y	5.4 (2.6, 6.8)	5.8 (1.4, 6.3)	2.7 (1.5, 3.5)
Previously immunosuppressed, No. (%)	7 (39)	6 (67)	2 (33)
General systemic involvement, No. (%)	18 (100)	4 (44)	5 (83)
GI involvement, No. (%)	16 (89)	0 (0)	1 (16)
Joint involvement, No. (%)	17 (94)	9 (100)	1 (16)
Cardiac involvement, No. (%)	3 (17)	0 (0)	0 (0)
CNS involvement, No. (%)	1 (11)	2 (22)	6 (100)
Anemia, No. (%)	17 (94)	3 (33)	4 (67)
Elevated inflammatory markers, No. (%)	15 (93)	4 (44)	1 (25)
Fat soluble vitamin deficiencies, No. (%)	7 (58)	0 (0)	1 (33)

Table 3. Diagnostic Test Yields Differ by Classic vs Localized Whipple Disease

	Classic WD (n = 18), No. Positive/ No. Tested (%)	Localized WD Arthritis (n = 9), No. Positive/No. Tested (%)	Localized CNS WD (n = 6), No. Positive/No. Tested (%)	*P* Value
Small bowel biopsy PAS stain[a]	13/15 (86)	1/8 (12)	1/6 (17)	<.001*
Small bowel biopsy PCR	12/13 (92)	3/7 (42)	2/5 (40)	.018*
Synovial fluid PCR	3/3 (100)	6/7 (85)	0/0 (0)	.35
Cerebrospinal fluid PCR	1/4 (25)	0/2 (0)	5/5 (100)	.009*
Blood PCR	7/12 (58)	2/6 (33)	1/2 (50)	.69
Other PCR[a]	4/5 (80)	0/0 (0)	1/1 (100)	.52

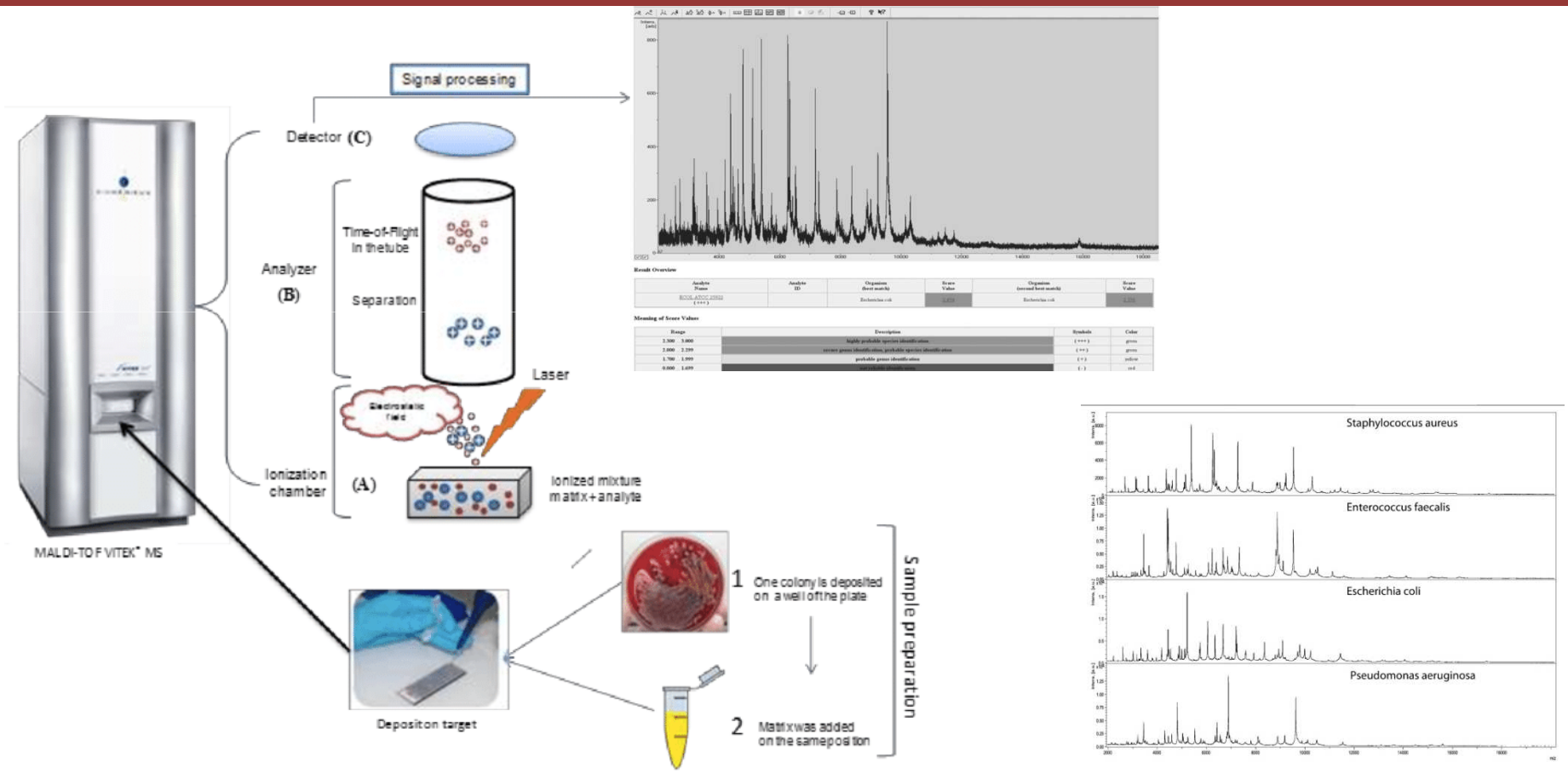
Abbreviations: CNS, central nervous system; PAS, Periodic acid-Schiff; PCR, polymerase chain reaction; WD, Whipple disease.

*P value considered significant if <.05.

[a]Other PCR included 2 vitreous aqueous humor fluid PCRs (1 negative and 1 positive), 1 lymph node tissue specimen PCR (positive), and 1 arterial thrombus surgical pathology specimen PCR (positive).

Crews NR. Open Forum Infect Dis. 2018;5(7):ofy136.

MALDI-TOF


Signal processing
Detector (C)
Analyzer
(B)
Time-of-Flight
In the tube
Separation
Laser
Electrostatic
field
Ionization
chamber
(A)
Ionized mixture
matrix + analyte
MALDI-TOF VITEK® MS
Deposit on target
1 One colony is deposited
on a well of the plate
2 Matrix was added
on the same position
Sample preparation
Staphylococcus aureus
Enterococcus faecalis
Escherichia coli
Pseudomonas aeruginosa

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Research in Microbiology 168 (2017) 122–129

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Original Article

Use of MALDI-TOF mass spectrometry after liquid enrichment (BD Bactec™) for rapid diagnosis of bone and joint infections

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Available online 24 September 2016

Abstract

Advantages of MALDI-TOF MS (MS) were evaluated for diagnosis of bone and joint infections after enrichment of synovial fluid (SF) or crushed osteoarticular samples (CSs). MS was performed after enrichment of SF or crushed osteoarticular samples CS (n = 108) in both aerobic and anaerobic vials. Extraction was performed on 113 vials (SF: n = 47; CS: n = 66), using the Sepsityper® kit prior identification by MS. The performances of MS, score and reproducibility results on bacterial colonies from blood agar and on pellets after enrichment in vials, were compared. MS analysis of the vial resulted in correct identification of bacteria at a species and genus level (80.5% and 92% of cases, respectively). The reproducibility was superior for aerobic Gram-positive bacteria (*Staphylococci* and Gram-positive bacilli: 100% colonies), as compared to aerobic Gram-negative bacilli (89.7%), anaerobes (83.3%) and *Streptococcus/Enterococcus* (58.8%). MS performance was significantly better for staphylococci than for streptococci on all identification parameters. For polymicrobial cultures, identification (score>1.3) of two species by MS was acceptable in 92.8% of cases. Use of MS on enrichment pellets of bone samples is an accurate, rapid and robust method for bacterial identification of clinical isolates from osteoarticular infections, except for streptococci, whose identification to species level remains difficult.

Keywords: MALDI-TOF mass spectrometry; Osteoarticular infection; Sepsityper® kit; Time of detection; Beadmill processing; Polymicrobial samples

1. Introduction

Direct examination is an unreliable method for the diagnosis of bone infections [1], with a sensitivity threshold assessed at an inoculum of approximately 10^4 UFC/mL. Achieving an enrichment step in a liquid medium with prolonged incubation of at least 14 days is essential [2] for correct diagnosis. This time is required to observe the growth of "small colony variants" or fastidious bacteria and to dilute any antibiotic potentially present in the synovial fluid (SF) or crushed bone samples (CSs). A biopsy beadmill processing step [3,4] or a step of sonication [5] on prosthetic samples provides improvement of culture performances. This is particularly true in the case of bacterial biofilms [6], chronic or complicated infections associated with prosthetic material.

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0923-2508/

Results of identification scores obtained with the MALDI-TOF MS technique on each bacterial group, i.e. from bacterial colonies (on agar plates obtained from direct spreading of samples or transplanting from enrichment vials) and from pellets after enrichment in blood vials (aerobic and anaerobic). *Vials were extracted with the Sepsityper® Kit before MS identification.

Results of MALDI TOF MS identification	Blood vials (both) (n = 113)	Blood agar (n = 104)	*Staphylococcus* (n = 39)	*Streptococcus Enterococcus* (n = 17)	Gram negative bacilli (n = 29)	Gram positive bacilli (n = 4)	Anaerobes (n = 12)
	No of isolates (%)						
High degree of identification to species *Score >2.3*	62 (54.9)	42 (40.4)	15 (38.5)	3 (17.6)	20 (69)	1 (25)	3 (25)
Identification to species *Score >2*	91 (80.5)	83 (79.8)	35 (89.7)	10 (58.8)	29 (100)	2 (50)	7 (58.3)
Identification to genus *Score >1.7*	104 (92)	94 (90.4)	39 (100)	12 (70.6)	29 (100)	4 (100)	10 (83.3)
Identification to genus with modified threshold *Score >1.5*	107 (94.7)	94 (90.4)	39 (100)	12 (70.6)	29 (100)	4 (100)	10 (83.3)
Unacceptable identification *Score <1.7*	2 (1.8)	2 (1.9)	0	0	0	0	2 (16.7)
Incorrect identification	2 (1.8)	5 (4.8)	0	5 (29.4)	0	0	0
No identification	4 (3.5)	0	0	0	0	0	0
Acceptable reproducibility	99 (87.6)	89 (85.6)	39 (100)	10 (58.8)	26 (89.7)	4 (100)	10 (83.3)

Lallemand E. Res Microbiol. 2017;168(2):122-129.

Eur J Clin Microbiol Infect Dis (2016) 35:857–866
DOI 10.1007/s10096-016-2608-x

ORIGINAL ARTICLE

MALDI-TOF MS performance compared to direct examination, culture, and 16S rDNA PCR for the rapid diagnosis of bone and joint infections

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Abstract The rapid identification of bacterial species involved in bone and joint infections (BJI) is an important element to optimize the diagnosis and care of patients. The aim of this study was to evaluate the usefulness of matrix-assisted laser desorption ionization mass spectrometry (MALDI-TOF MS) for the rapid diagnosis of bone infections, directly on synovial fluid (SF) or on crushed osteoarticular samples (CS). From January to October 2013, we prospectively analyzed 111 osteoarticular samples (bone and joint samples, BJS) from 78 patients in care at the University Hospital of Rennes, France. The diagnosis procedure leading to the sample collection was linked to a suspicion of infection, inflammatory disease, arthritis, or for any bone or joint abnormalities. Standard bacteriological diagnosis and molecular biology analysis [16S rRNA polymerase chain reaction (PCR) and sequencing] were conducted. In addition, analysis by MALDI-TOF MS was performed directly on the osteoarticular samples, as soon as the amount allowed. Culture, which remains the gold standard for the diagnosis of BJI, has the highest sensitivity (85.9 %) and remains necessary to test antimicrobial susceptibility. The 16S rDNA PCR results were positive in the group with positive BJI (28.6 %) and negative in the group without infection. Direct examination remains insensitive (31.7 %) but more effective than MALDI-TOF MS directly on the sample (6.3 %). The specificity was 100 % in all cases, except for culture (74.5 %). Bacterial culture remains the gold standard, especially enrichment in blood bottles. Direct analysis of bone samples with MALDI-TOF MS is not useful, possibly due to the low inoculum of BJS.

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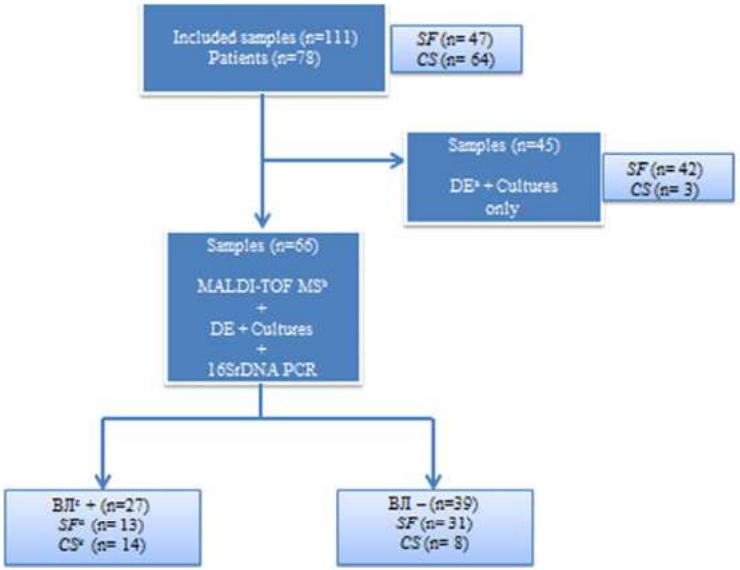
Introduction

Bone infections are composed of several pathologies, like septic arthritis, osteomyelitis, spondylodiscitis, diabetic foot, or prosthetic infection, that can gradually evolve into complex bone and joint infections (BJI), with important mortality and morbidity [1–3]. The diagnosis of bone infections based on clinical, bacteriological, radiological, and histological arguments and its interpretation is facilitated by the publication of guidelines, such as the recommendations of the Société de Pathologie Infectieuse de Langue Française (SPILF) [4] or the Infectious Diseases Society of America (IDSA) [5].

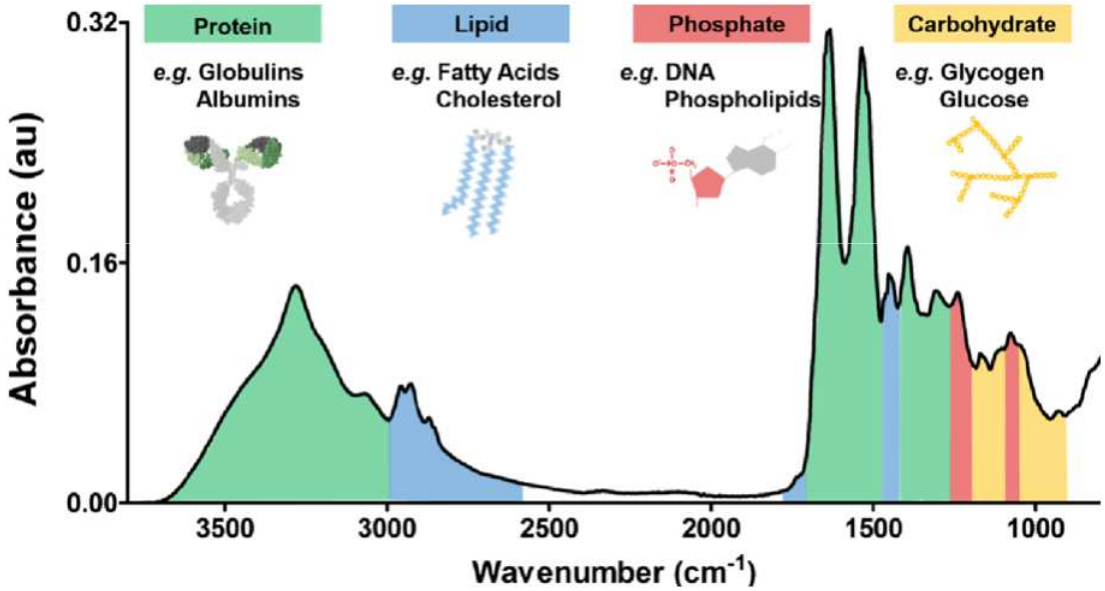
The role of the bacteriology laboratory in the management of samples from patients with BJI is important. For surgical specimens, it is recommended to collect five samples (less than five causes difficulties of interpretation and more than five increases the risk of contamination without improving the sensitivity) [4, 6]. The probability of infection increases



	Culture	Direct examination (Gram staining)	16S rDNA PCR on sample	MALDI-TOF MS on sample
Sensitivity	85.9	31.3	29.6	7.4
Specificity	74.5	100	100	100
PPV	82.1	100	100	100
NPV	79.5	51.6	67.2	60.9
AUC	0.849	0.593	0.648	0.532
Number of samples	111	111	66	66

Lallemand E. Eur J Clin Microbiol Infect Dis. 2016;35(5):857-66.

SPECTROMETRIE INFRAROUGE



RHEUMATOLOGY

Original article

Ruling out septic arthritis risk in a few minutes using mid-infrared spectroscopy in synovial fluids

Jean-David Albert[1,2], Maëna Le Corvec[3], Olivia Berthoud[1], Claire David[4], Xavier Guennoc[5], Emmanuel Hoppe[6], Sandrine Jousse-Joulin[7], Benoît Le Goff[8], Hugues Tariel[3], Olivier Gire[9], Anne Jolivet-Gougeon[2], Guillaume Coiffier[1,2] and Olivier Loréal[2]

Abstract

Objectives. The aim of this study was to show the usefulness of a mid-infrared fibre evanescent wave spectroscopy point of care device in the identification of septic arthritis patients in a multicentre cohort, and to apply this technology to clinical practice among physicians.

Methods. SF samples from 402 patients enrolled in a multicentre cohort were frozen for analysis by mid-infrared fibre evanescent wave spectroscopy. The calibration cohort was divided into two groups of patients (septic arthritis and non-septic arthritis) and relevant spectral variables were used for logistic regression model. Model performances were tested on an independent set of 86 freshly obtained SF samples from patients enrolled in a single-centre acute arthritis cohort and spectroscopic analyses performed at the patient's bedside.

Results. The model set-up, using frozen-thawed SFs, provided good performances, with area under the curve 0.95, sensitivity 0.90, specificity 0.90, positive predictive value 0.41 and negative predictive value 0.99. Performances obtained in the validation cohort were area under the curve 0.90, sensitivity 0.92, specificity 0.81, positive predictive value 0.46 and negative predictive value 0.98. The septic arthritis probability has been translated into a risk score from 0 to 4 according to septic risk. For a risk score of 0, the probability of identifying a septic patient is very low (negative predictive value of 1), whereas a risk score of 4 indicates very high risk of septic arthritis (positive predictive value of 1).

Conclusion. Mid-infrared fibre evanescent wave spectroscopy could distinguish septic from non-septic synovial arthritis fluids with good performances, and showed particular usefulness in ruling out septic arthritis. Our data supports the possibility of technology transfer.

Trial registration. ClinicalTrials.gov, http://clinicaltrials.gov, NCT02260271.

Key words: septic arthritis, biomarker, synovial fluid, mid infra red spectroscopy

Rheumatology key messages

- Septic arthritis diagnosis is a therapeutic emergency implying rapid treatment with antibiotics and hospitalization.
- The study performed in a sizeable multicentre cohort showed that mid-infrared spectroscopy was useful.
- The SynoFAST test could help to better monitor acute arthritis and permit prompter return home.

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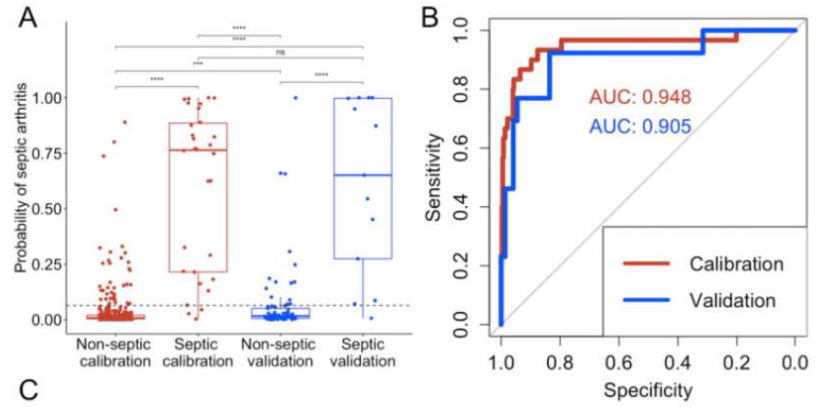
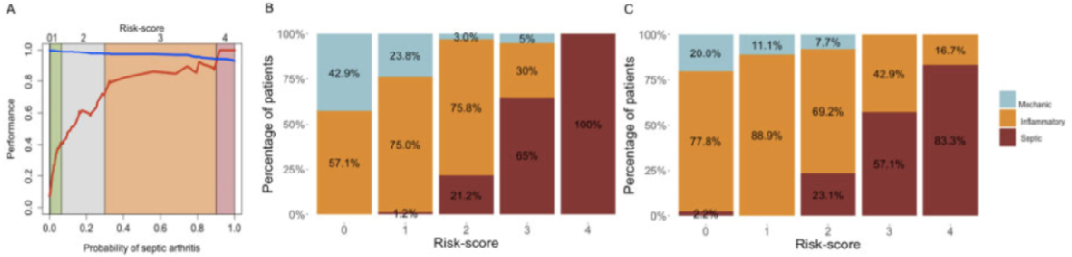
CLINICAL SCIENCE

	Mechanical disease	Inflammatory disease	Septic arthritis	$P^{M/I}$	$P^{I/S}$	$P^{M/S}$
	(*n* = 88)	(*n* = 255)	(*n* = 30)			
Gender (M/F), %	41/59	55/45	67/33	*	NS	*
Age, years	63 (51.25–74)	60 (45.5–72.5)	68 (64.5–76.5)	NS	**	*
Skin temperature, °C	37 (36.7–37.15)	37.1 (36.9–37.6)	37.6 (37–38)	***	**	***
Fever[a], %	7	15	30	NS	NS	**
Duration of arthritis, days	15 (7–60)	7 (3–20)	6 (3–8)	***	NS	***
Gout, %	9	20	15	*	NS	NS
PPCD disease, %	8	8	5	NS	NS	NS
RA, %	28	20	20	NS	NS	NS
SpA, %	5	12	0	NS	NS	NS
OA, %	36	6	23	***	*	NS
Other comorbidities, %	32	34	60	NS	**	**
Diabetes, %	16	15	33	NS	NS	NS
Cirrhosis, %	2	4	19	NS	*	*
SF						
Positive direct examination, *n*	0	1	11	NA	NA	NA
Culture (negative/positive), *n*	NA	NA	3/27	NA	NA	NA
Presence of crystals, %	17	34	8	**	**	NS
Type of crystals[b], %	67/33/0/0	57/41/0/2	100/0/0/0	NS	NS	NS
Leucocyte count, *n*	350 (150–700)	13 000 (6835–28 000)	60 000 (14 400–117 000)	***	***	***
Polymorphonuclear leukocytes, %	22.5 (7.75–63.25)	83 (69–90)	94 (90–97)	***	***	***



C

	AUC	Threshold	Se	Sp	PPV	NPV	WCR	LR+	LR-
Calibration	0.95 (0.89-1)	0.064	0.90 (0.8-1)	0.90 (0.86-0.93)	0.41 (0.34-0.5)	0.99 (0.98-1)	0.90 (0.87-0.92)	9	0.11
Validation	0.90 (0.80-1)		0.92 (0.77-1)	0.81 (0.71-0.89)	0.46 (0.35-0.62)	0.98 (0.95-1)	0.82 (0.74-0.91)	4.8	0.10



CONCLUSION (1)

- ***Arthrite Septique***

- **Spectométrie IR :** utile pour éliminer le diagnostic (mais, FP et ne donne pas l'identification du pathogène)
- **Examen direct et ARN16S :** n'a de valeur que si positif (30%)
- **Milieu liquide (BACTEC) :** augmente de 10-15% le taux de positivité et diminue le temps de pousse
- **MALDI-TOF :** améliore l'identification bactérienne et diminue le temps de résultat à partir de culture positive
- **PCR spécifique :** au cas pas cas…

CONCLUSION (2)

- ***Cas particuliers***

- **Monoarthrite du genou :** Sérologie de Lyme

- **Oligoarthrite masculine > 40 ans :** PCR Whipple (LS)

- **Oligoarthrite non septique non métabolique :** PCR Chlamydiae 1er jet d'urines, Sérologie Yersinia (systématique ?), Campylobacter (si diarrhée banale)

- **Polyarthrite/arthlagies aigue fébrile :** Sérologie hépatite alphabétique, Parvovirus B19, Arbo/Alphavirose (retour zone endémie)