DIPLÔME INTER-UNIVERSITAIRE

Prévention et prise en charge des Infections Ostéo Articulaires

Session 2024-2025

Technologies innovantes : Biologie Moléculaire et biomarqueurs synoviaux

Dr Claudie Lamoureux

Dr Louise Ruffier d'Epenoux

Diagnostic en microbiologie

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

NB de prélèvements

Optimal Periprosthetic Tissue Specimen Number for Diagnosis of Prosthetic Joint Infection

Trisha N. Peel,[a,b] Tim Spelman,[c] Brenda L. Dylla,[a] John G. Hughes,[a] Kerryl E. Greenwood-Quaintance,[a] Allen C. Cheng,[b,d] Jayawant N. Mandrekar,[e] Robin Patel[a,f]

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Milieux de culture (solide, liquide)

How Many Samples and How Many Culture Media To Diagnose a Prosthetic Joint Infection: a Clinical and Microbiological Prospective Multicenter Study

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Délai d'incubation

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RESEARCH ARTICLE

Improved Diagnosis of Prosthetic Joint Infection by Culturing Periprosthetic Tissue Specimens in Blood Culture Bottles

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Diagnostic en microbiologie

Infections ostéo-articulaires sur matériel

Recommandation CRIOGO : 4 prélèvements en changeant les pinces pour chaque prélèvement :

- 1 liquide articulaire (flacon Hémoculture au bloc + flacon stérile)
- 3 prélèvements péri-prothétiques

Recommandations CRIOGO :

• Gélose sang cuit sous CO2	7 jours
• 1 milieu pour bactérie ana liquide ou solide	7 jours
• 1 flacon d'hémoculture anaérobie	14 jours

Diagnostic en microbiologie

Mais :

- Cultures négatives dans 5-30 % des cas de suspicion d'IOAP Corvec *et al.,* 2012 ; Tande et Patel 2014

- Faux négatifs :
  - Antibiothérapie préalable
  - Bactéries à croissance exigeante
  - Biofilm
  - Intra ostéoblastique

Intérêt de la Biologie moléculaire et des Biomarqueurs Synoviaux

Biomarqueurs synoviaux

Biomarqueurs synoviaux

Scores composites

2011 MSIS criteria

(1) There is a sinus tract communicating with the prosthesis; or
(2) A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or
(3) Four of the following six criteria exist:

- (a) Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration,
- (b) Elevated synovial leukocyte count,
- (c) Elevated synovial neutrophil percentage (PMN%),
- (d) Presence of purulence in the affected joint,
- (e) Isolation of a microorganism in one culture of periprosthetic tissue or fluid, or
- (f) Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification.

Parvizi et al., Clin Orthop Relat Res (2011) 469:2992–2994

Biomarqueurs synoviaux

Scores composites

2013 MSIS criteria

Table I. Musculoskeletal Infection Society criteria, reproduced from: **Parvizi J, Gehrke T, Chen AF.** Proceedings of the International Consensus on Periprosthetic Joint Infection. *Bone Joint J* 2013;95-B:1450-1452.

Periprosthetic joint infection is defined as:
Two positive periprosthetic cultures with phenotypically identical organisms, or
A sinus tract communicating with the joint, or
Meeting three of the following minor criteria:
-Elevated serum C-reactive protein AND erythrocyte sedimentation rate
-Elevated synovial fluid white blood cell count OR ++change on leukocyte esterase test strip
-Elevated synovial fluid polymorphonuclear neutrophil percentage
-Positive histological analysis of periprosthetic tissue
-A single positive culture

Table 2. The threshold for the minor diagnostic criteria according to the International Consensus Group

Criterion	Acute PJI (< 90 days)	Chronic PJI (> 90 days)
Erythrocyte sedimentation rate (mm/hr)	Not helpful; no threshold was determined	30
C-reactive protein (mg/L)	100	10
Synovia white blood cell count (cells/μL)	10,000	3,000
Synovial polymorphonuclear percentage (%)	90	80
Leukocyte esterase	+ or ++	+ or ++
Histological analysis of tissue	> 5 neutrophils per high-power field in 5 high-power fields (×400)	Same as acute

Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. Bone Joint J 2013;95-B:1450-1452.

Biomarqueurs synoviaux

Scores composites

Table 1. 2018 ICM criteria for PJI definition.

MAJOR CRITERIA		DECISION
Two positive cultures of the same organism		INFECTED (at least one of the following is present)
Sinus tract evidence of communication to the joint or visualization of the prosthesis		
MINOR CRITERIA	**SCORE**	**DECISION**
Elevated serum CRP or D-dimer	2	≥6, infected 2–5, possibly infected 0–1, not infected
Elevated serum ESR	1	
Elevated synovial WBC count or LE	3	
Positive synovial alpha-defensin	3	
Elevated synovial PMN (%)	2	
Elevated synovial CRP	1	

CRP = C-Reactive Protein; ESR = Erythrocyte Sedimentation Rate; WBC = White Blood Cells; LE = Leucocyte Esterase; PMN = Polymorphonuclear Cells.

- Serum CRP > 1 mg/dL
- D-dimer > 860 ng/mL;
- Erythrocyte sedimentation rate (ESR) > 30 mm/h
- Synovial fluid WBC count >3000 cells/Ml
- Increased synovial fluid alpha-defensin signal-to-cut off ratio > 1
- Synovial fluid leukocyte esterase (++);
- Polymorphonuclear percentage > 80%
- Synovial CRP > 6.9 mg/L.

Biomarqueurs synoviaux

Review

What's New in the Diagnosis of Periprosthetic Joint Infections: Focus on Synovial Fluid Biomarkers

Giuseppe Solarino [1,†], Davide Bizzoca [1,2,*,†], Lorenzo Moretti [1], Giovanni Vicenti [1], Andrea Piazzolla [1,2] and Biagio Moretti [1]

α défensine

Leucocyte estérase

IL-6

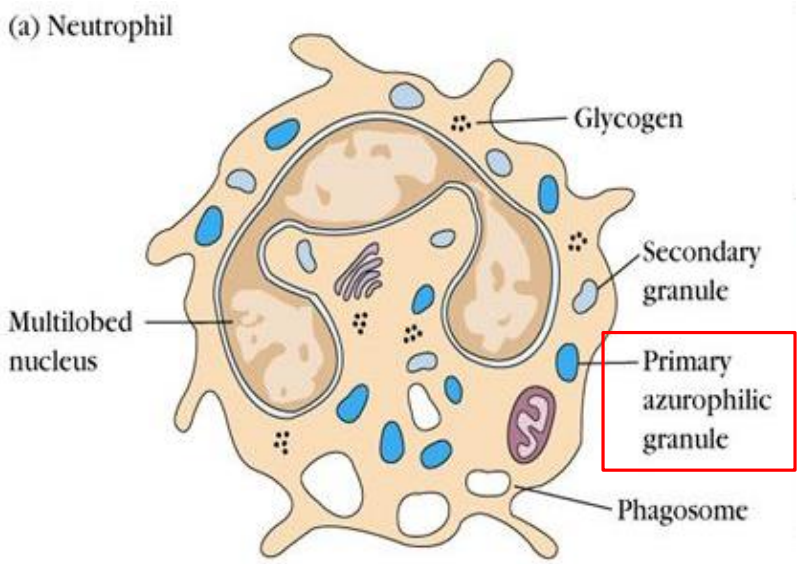
Calprotectine articulaire

CRP articulaire

Biomarqueurs synoviaux

α défensine

Peptide antimicrobien produit par les PNN en réponse à une infection [1]
Action antimicrobienne : interaction avec les membranes microbiennes, formation de pores …



[1] T Tajima *et al*, Journal of UOEH, 2020 ; Selsted ME & Ouellette AJ, Nat Immunol, 2005

Biomarqueurs synoviaux

α défensine

Deux types de test :

- ELISA dosage en série , délai au moins 24h, 800€/plaque

- Test rapide unitaire (Synovasure, Zimmer) , 300€/test, 5 minutes

Biomarqueurs synoviaux

The Journal of Arthroplasty 31 (2016) 456–460

α défensine

α-Defensin Accuracy to Diagnose Periprosthetic Joint Infection—Best Available Test?

Salvatore J. Frangiamore, MD, MS [a], Nicholas D. Gajewski, BS [b], Anas Saleh, MD [a], Mario Farias-Kovac, MD [a], Wael K. Barsoum, MD [a], Carlos A. Higuera, MD [a]

[a] Department of Orthopedic Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio
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- 116 PTH ou PTG
- *Vs* MSIS 2011
- Dosage α-défensine – Synovasure
- CE : QI, métallose coexistante, absence de paramètres de laboratoire nécessaires pour confirmer ou exclure l'IP

Table 2
Laboratory Data Categorized by Infected and Not Infected Cases Using MSIS Criteria for All Patients.

Variable	Total Cases (n = 116)	Noninfected First- and Single-Stage Revision (n = 54)	Infected First- and Single-Stage Revision (n = 24)	Noninfected Second-Stage Revision (n = 35)	Infected Second-Stage Revision (n = 3)	*P*
WBC (serum; k/μL), mean ± SD	7.6 ± 2.6	7.4 ± 2.4	9.09 ± 3.5	7.06 ± 2.2	8.3 ± 0.6	.01[T]
CRP (mg/dL), mean ± SD	2.6 ± 5.6	1.05 ± 2.5	7.02 ± 8.9	1.6 ± 4.1	0.7 ± 0.5	<.0001[T]
ESR (mm/h), mean ± SD	23.8 ± 22.8	16.7 ± 15.2	44.6 ± 30.7	17.6 ± 14.9	19.0 ± 9.5	<.0001[T]
Presence of sinus track, n (%)	4 (3.4)	0	4 (16.7)	0	0	.002[X]
Preoperative culture organism, n (%)	71 (61.2)	18 (33.3)	21 (87.5)	30 (85.7)	2 (66.7)	<.001[X]
CoNS	3 (4.2)	0	3 (14.3)	0	0	
Fungus	3 (4.2)	1 (5.6)	2 (9.5)	0	0	
MRSA	4 (5.6)	0	4 (19)	0	0	
Propionibacterium species	1 (1.4)	0	1 (4.8)	0	0	
Gram-positive bacilli	4 (5.6)	0	4 (19)	0	0	
Gram-negative bacilli	3 (4.2)	0	3 (14.3)	0	0	
Negative	53 (74.6)	17 (94.4)	4 (19)	30 (100)	2 (100)	
Frozen section with acute inflammation, n (%)	13 (11.2)	1 (1.9)	11 (45.8)	0	1 (33.3)	<.001[X]
Introperative culture organism, n (%)	107 (92.2)	46 (85.2)	24 (100)	34 (97.1)	3 (100)	<.001[X]
CoNS	9 (8.4)	0	3 (12.5)	5 (14.7)	1 (33.3)	
Fungus	4 (3.7)	1 (2.2)	2 (8.3)	1 (2.9)	0	
MRSA	1 (0.9)	0	1 (4.2)	0	0	
Propionibacterium species	3 (2.8)	0	2 (8.3)	1 (2.9)	0	
Gram-positive bacilli	7 (6.5)	0	7 (29.1)	0	0	
Gram-negative bacilli	2 (1.9)	0	2 (8.3)	0	0	
Negative	81 (75.7)	45 (97.8)	7 (29.1)	27 (79.4)	2 (66.7)	
α-Defensin	116	54	24	35	3	<.001[X]
Negative	88 (75.9)	53 (98.1)	0	34 (97.1)	1 (33.3)	
Positive	28 (24.1)	1 (1.9)	24 (100)	1 (2.9)	2 (66.7)	

T, Student *t* test; X, χ^2 test for independence; CoNS, coagulase-negative *Staphylococci*.

Biomarqueurs synoviaux

α défensine

The Journal of Arthroplasty 31 (2016) 456–460

α-Defensin Accuracy to Diagnose Periprosthetic Joint Infection—Best Available Test?

Salvatore J. Frangiamore, MD, MS [a], Nicholas D. Gajewski, BS [b], Anas Saleh, MD [a], Mario Farias-Kovac, MD [a], Wael K. Barsoum, MD [a], Carlos A. Higuera, MD [a]

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[b] Lerner College of Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio

Table 3
Diagnostic Parameters of Synovial Fluid α-Defensin Compared With Serum ESR and CRP for First-Stage and Single-Stage Revisions.

Parameter	α-Defensin	Serum ESR	Serum CRP
Cutoff value	5.2 mg/L	30 mm/h	10 mg/L
Sensitivity (%)	100	58	83
Specificity (%)	98	81	79
Positive likelihood ratio[a]	54	3	4
Negative likelihood ratio[b]	0	0.5	0.2

[a] A value greater than 5 is considered useful for ruling-in infection.
[b] A value less than 0.2 is considered useful for ruling out infection.

Table 4
Diagnostic Parameters of Synovial Fluid α-Defensin Compared With Serum ESR and CRP for Second-Stage Revisions.

Parameter	α-Defensin	Serum ESR	Serum CRP
Cutoff value	5.2 mg/L	30 mm/h	10 mg/L
Sensitivity (%)[a]	67 (12-95)	0 (0-70)	33 (5-88)
Specificity (%)[a]	97 (83-99)	84 (67-95)	82 (65-93)
Positive likelihood ratio[a,b]	21 (3-167)	0	1.9 (0.3-11)
Negative likelihood ratio[a,c]	0.3 (0.07-1.7)	1.2 (1-1.4)	0.8 (0.4-1.8)

[a] Values reported with 95% CI.
[b] A value greater than 5 is considered useful for ruling in infection.
[c] A value less than 0.2 is considered useful for ruling out infection.

Biomarqueurs synoviaux

α défensine

Observational Study > Bone Joint J. 2017 Jan;99-B(1):66-72.
doi: 10.1302/0301-620X.99B1.BJJ-2016-0295.R1.

Qualitative α-defensin test (Synovasure) for the diagnosis of periprosthetic infection in revision total joint arthroplasty

I K Sigmund [1], J Holinka [1], J Gamper [1], K Staats [1], C Böhler [1], B Kubista [1], R Windhager [1]

50 patients :

- 30 PTH, 17 PTG, 1 coude, 1 épaule et une arthroplastie totale du fémur.
- *Vs* MSIS 2013
- Dosage α-défensine – Synovasure
- CE : Pb de contamination évidente

13 IOA, 36 non IOA, 1 non concluant

Table II. Measures of diagnostic accuracy of all performed tests (95% confidence intervals). The positive likelihood ratios (LR+) of bacteriology with at least two positive cultures could not be computed because specificity was 100%

	Sensitivity (%)	Specificity (%)	LR+	LR-
Synovasure test	*69* (46 to 92)	*94* (86 to 100)	12.46 (3.09 to 50.27)	0.33 (0.14 to 0.74)
Frozen section	*73* (46 to 100)	*77* (63 to 89)	3.18 (1.57 to 6.46)	0.35 (0.13 to 0.94)
Histology	*69* (46 to 92)	*67* (53 to 81)	2.08 (1.16 to 3.74)	0.46 (0.2 to 1.08)
Bacteriology (≥ 1 positive culture)	*92* (77 to 100)	*94* (86 to 100)	16.61 (4.28 to 64.48)	0.08 (0.01 to 0.54)
Bacteriology (≥ 2 positive cultures)	*85* (62 to 100)	*100* (100 to 100)	-	0.15 (0.04 to 0.55)
Sonication culture	*83* (58 to 100)	*94* (84 to 100)	12.92 (3.3 to 50.53)	0.18 (0.05 to 0.63)
C-reactive protein	*77* (54 to 100)	*78* (64 to 92)	3.46 (1.75 to 6.83)	0.3 (0.11 to 0.81)

Se et LR+ : test qui constitue un complément préop pour le diag des PJI
Sp et LR- : adapté pour exclure une infection articulaire

Biomarqueurs synoviaux

α défensine

156 patients arthroplastie douleure
Hanche ou genou

Vs MSIS 2013

Dosage α-défensine – Synovasure

Clin Orthop Relat Res (2017) 475:408–415
DOI 10.1007/s11999-016-4906-0

Clinical Orthopaedics and Related Research®
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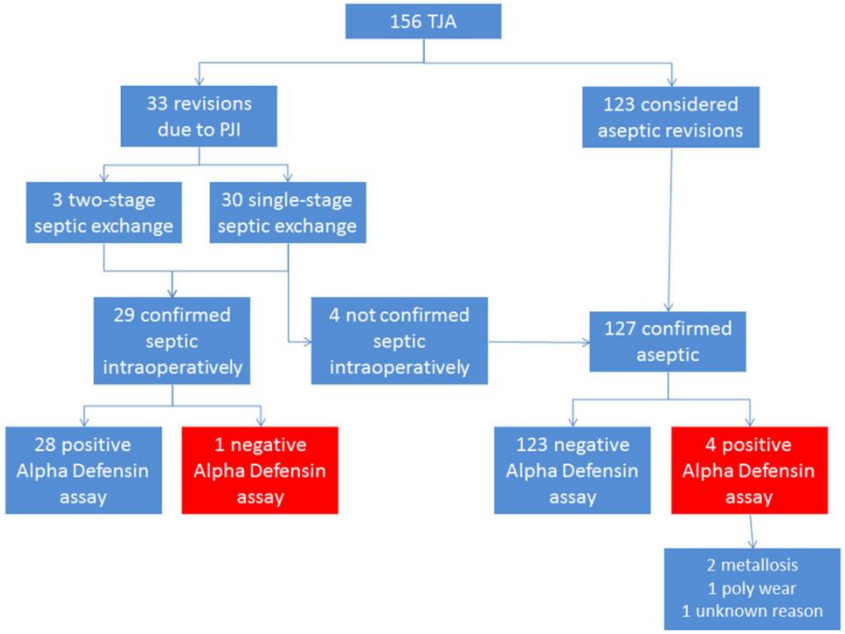
SYMPOSIUM: 2016 HIP SOCIETY PROCEEDING

How Reliable Is the Alpha-defensin Immunoassay Test for Diagnosing Periprosthetic Joint Infection? A Prospective Study

Tommaso Bonanzinga MD, Akos Zahar MD, Michael Dütsch MSc,
Christian Lausmann MD, Daniel Kendoff MD, PhD, Thorsten Gehrke MD



Biomarqueurs synoviaux

Clin Orthop Relat Res (2017) 475:408–415
DOI 10.1007/s11999-016-4906-0

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SYMPOSIUM: 2016 HIP SOCIETY PROCEEDING

α défensine

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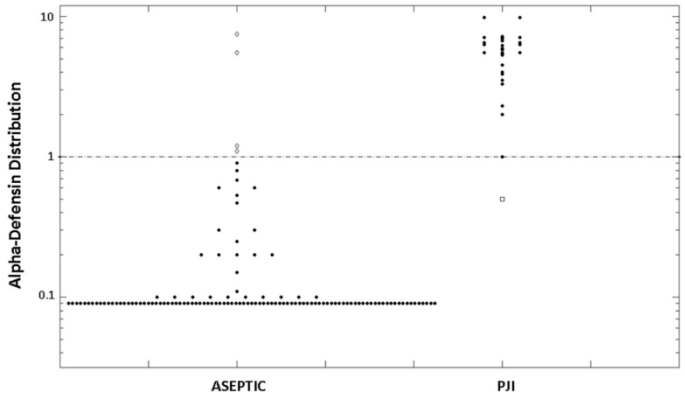


Se = 97%, Sp= 97%, VPP= 88%, VPN = 99%

4FP :

- 2 : métallose
- 1 : usure du polyéthylène

FP avec métallose

Biomarqueurs synoviaux

α défensine

Méta-analyse :

- 10 études Synovasure
- 11 études ELISA
- 2043 patients
- PTH ET PTG (2014-2018)
- USA /UE

Han et al. Journal of Orthopaedic Surgery and Research (2019) 14:274
https://doi.org/10.1186/s13018-019-1320-9

Journal of Orthopaedic Surgery and Research

RESEARCH ARTICLE Open Access

Synovial fluid α-defensin in the diagnosis of periprosthetic joint infection: the lateral flow test is an effective intraoperative detection method

Xuequan Han[1†], Kai Xie[1†], Xu Jiang[1], Liao Wang[1], Haishan Wu[1], Xinhua Qu[2] and Mengning Yan[1*]

Table 1 Characteristics of the 19 studies in meta-analysis for the diagnosis of PJI using α-defensin

Study	Country	Patients number	Mean age (years)	Study design	Excluded antibiotic therapy	Site of arthroplasty	Reference standard	QUADAS
Laboratory-based immunoassay								
Deirmengian et al., 2014 [10]	USA	95	67	Prospective	N	Hip, knee	MSIS (2011)	14
Bingham et al., 2014 [9]	USA	57	64.2	Retrospective	NA	Hip, knee	MSIS (2011)	13
Deirmengian et al., 2014 [10]	USA	149	65	Prospective	N	Hip, knee	MSIS (2011)	13
Deirmengian et al., 2014 [10]	USA	46	65	Prospective	N	Hip, knee	MSIS (2011)	13
Frangiamore et al., 2016 [15]	USA	78	63.3	Prospective	NA	Hip, knee	MSIS (2011)	14
Bonanzinga et al., 2017 [19]	Germany	156	NA	Prospective	N	Hip, knee	MSIS (2013)	14
Gehrke et al., 2018 [23]	Germany	173	NA	Prospective	Y	Hip, knee	MSIS (2013)	14
Kanwar et al., 2018 [24]	USA	70	66	Retrospective	NA	Hip, knee	MSIS (2013)	14
Sigmund et al., 2018 [42]	Germany	71	70	Retrospective	Y	Hip, knee	MSIS (2013)	13
Stone et al., 2018 [43]	USA	183	65.7	Retrospective	Y	Hip, knee	MSIS (2011)	14
Kelly et al., 2018 [39]	USA	32	64	Retrospective	N	Hip, knee	MSIS (2013)	13
Lateral flow test								
Kasparek et al., 2016 [16]	Austria	40	NA	Retrospective	Y	Hip, knee	MSIS (2013)	13
Suda et al., 2017 [21]	Germany	28	67.7	Prospective	N	Hip, knee	MSIS (2013)	13
Balato et al., 2018 [17]	Italy	51	63	Prospective	Y	Knee	MSIS (2013)	12
Berger et al., 2017 [18]	Belgium	121	63.5	Prospective	N	Hip, knee	MSIS (2011)	14
Gehrke et al., 2018 [23]	Germany	191	NA	Prospective	Y	Hip, knee	MSIS (2013)	14
Plate et al., 2018 [26]	Switzerland	109	65	Prospective	Y	Hip, knee	MSIS (2013)	13
de Saint Vincent et al., 2018 [22]	French	39	62	Prospective	N	Hip, knee	MSIS (2013)	12
Riccio et al., 2018 [41]	Italy	71	69	Retrospective	N	Hip, knee	MSIS (2013)	13
Sigmund et al., 2018	Germany	71	70	Retrospective	Y	Hip, knee	MSIS (2013)	13
Renz et al., 2018 [40]	Germany	221	70	Prospective	N	Hip, knee	MSIS (2013)	14

PJI periprosthetic joint infection, *NA* not available, *MSIS* Musculoskeletal Infection Society, *QUADAS* Quality Assessment of Diagnostic Accuracy Studies

Biomarqueurs synoviaux

α défensine

Han et al. Journal of Orthopaedic Surgery and Research (2019) 14:274
https://doi.org/10.1186/s13018-019-1320-9

Journal of Orthopaedic Surgery and Research

RESEARCH ARTICLE Open Access

Synovial fluid α-defensin in the diagnosis of periprosthetic joint infection: the lateral flow test is an effective intraoperative detection method

Xuequan Han[1†], Kai Xie[1†], Xu Jiang[1], Liao Wang[1], Haishan Wu[1], Xinhua Qu[2] and Mengning Yan[1*]

Table 2 Subgroup analysis of laboratory-based immunoassay and lateral flow test for PJI diagnosis

Subgroup analyses	No. of studies	No. of patients	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95%CI)	PLR (95%CI)	NLR (95%CI)	DOR (95%CI)
Laboratory-based immunoassay								
Overall studies	11	1110	0.96 (0.90–0.98)	0.97 (0.95–0.99)	0.99 (0.98–1.00)	35.0 (18.5–66.2)	0.04 (0.02–0.11)	811 (220–2990)
Excluded metallosis								
Yes	4	416	0.97 (0.88–0.99)	0.99 (0.96–1.00)	0.99 (0.98–1.00)	80.7 (26.0–251.1)	0.03 (0.01–0.13)	2447 (383–15,647)
No and NA	7	694	0.94 (0.84–0.98)	0.96 (0.94–0.97)	0.98 (0.96–0.99)	23.1 (14.2–37.6)	0.06 (0.02–0.17)	382 (103–1414)
Study design								
Prospective	6	697	0.97 (0.92–0.99)	0.98 (0.96–0.99)	0.99 (0.98–1.00)	42.9 (22.9–80.4)	0.03 (0.01–0.09)	1480 (423–5172)
Retrospective	5	413	0.91 (0.79–0.96)	0.95 (0.90–0.98)	0.98 (0.96–0.99)	19.9 (8.9–44.5)	0.10 (0.04–0.24)	207 (52–830)
Lateral flow test								
Overall studies	10	933	0.86 (0.81–0.91)	0.96 (0.93–0.98)	0.95 (0.93–0.97)	21.2 (11.7–38.5)	0.14 (0.10–0.21)	148 (64–343)
Excluded antibiotic therapy								
Yes	5	462	0.86 (0.77–0.92)	0.97 (0.91–0.99)	0.94 (0.92–0.96)	32.7 (9.3–114.6)	0.15 (0.08–0.25)	225 (46–1099)
No and NA	5	471	0.87 (0.78–0.92)	0.95 (0.91–0.97)	0.97 (0.95–0.98)	17.3 (9.1–33.1)	0.14 (0.08–0.23)	124 (46–336)
Number of patients								
≥ 50	7	826	0.89 (0.84–0.92)	0.97 (0.94–0.99)	0.95 (0.92–0.96)	30.9 (15.4–61.9)	0.12 (0.08–0.17)	263 (109–631)

PLR positive likelihood ratio, *NLR* negative likelihood ratio, *DOR* diagnostic odds ratio, *AUC* area under the curve

Supériorité de la technique ELISA

Pour les 2 techniques :

- FP avec la métallose
- Pas d'influence d'un traitement ATB préalable

ELISA pos 90% probabilité d'être infecté vs 84% pour Test unitaire pos

ELISA neg 1% probabilité d'être infecté vs 3% pour Test unitaire pos

Biomarqueurs synoviaux

α défensine

- Se et Sp ↗
- Rapide
- Facile d'utilisation
- Pas d'influence de l'hémarthrose, la prise d'ATB et maladies inflammatoires chroniques

- Coût ↗ (300 euros/test)
- FP: Métallose
- FN : Germe à croissance lente
- Non disponible en routine
- Délai de positivité après l'implantation de la prothèse?

Biomarqueurs synoviaux

Leucocyte estérase

- Enzyme sécrétée par les leucocytes
- Bandelette
- Seuil = 125/µL (2+) *Salari et al., 2020*

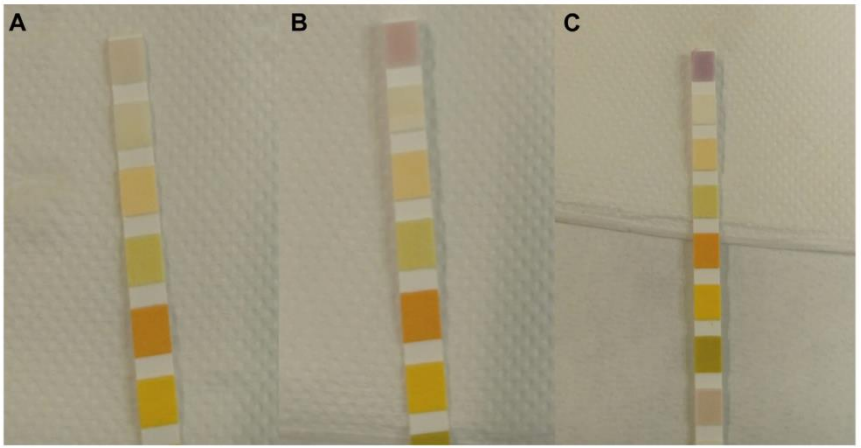


Fig. 2. Leukocyte esterase strip test in synovial fluid samples: (A) negative; (B) positive 1+; and (C) positive 2+.

N. Logoluso et al. / The Journal of Arthroplasty 37 (2022) 565e573

Biomarqueurs synoviaux

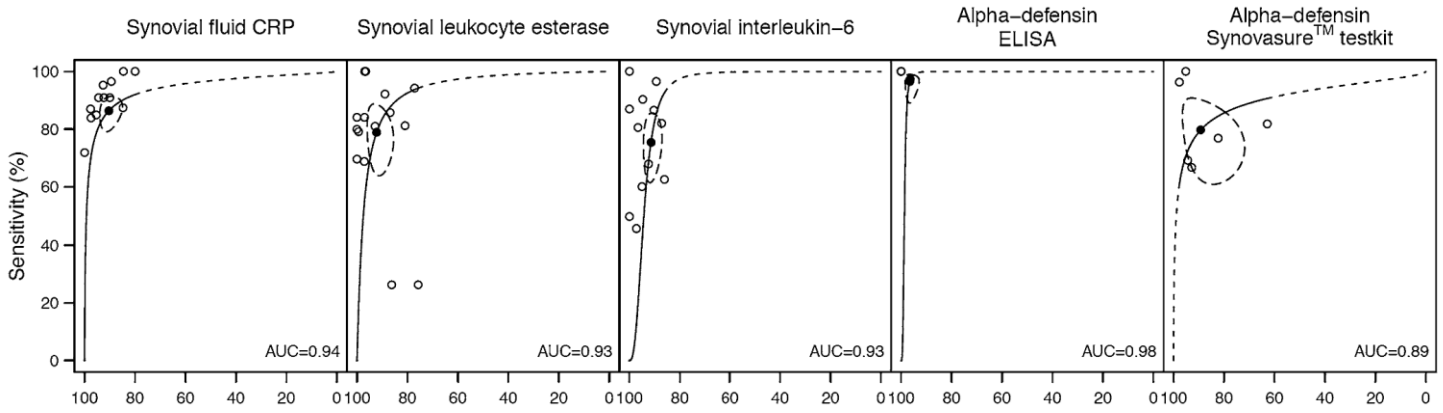
Knee Surgery, Sports Traumatology, Arthroscopy (2018) 26:3039–3047
https://doi.org/10.1007/s00167-018-4904-8

Leucocyte estérase

A meta-analysis of synovial biomarkers in periprosthetic joint infection: Synovasure™ is less effective than the ELISA-based alpha-defensin test

Sufian S. Ahmad[1,7] · Michael T. Hirschmann[2] · Roland Becker[3] · Ahmed Shaker[1] · Atesch Ateschrang[4] · Marius J. B. Keel[1,5] · Christoph E. Albers[1] · Lukas Buetikofer[6] · Sithombo Maqungo[7] · Ulrich Stöckle[4] · Sandro Kohl[1,5]

- Méta analyse : LE (12 publications)



IL-6 et LE bonne précision , mais pas supérieure à celle rapportée numération des globules blancs synoviaux (sWBC) ou la culture bactériologique.

Biomarqueurs synoviaux

Leucocyte estérase

The Journal of Arthroplasty 32 (2017) S232–S235

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Complications - Infection

Diagnosing Periprosthetic Joint Infection: And the Winner Is?

Alisina Shahi, MD, Timothy L. Tan, MD, Michael M. Kheir, MD, Dean D. Tan, Javad Parvizi, MD, FRCS *

The Rothman Institute at Thomas Jefferson University, Philadelphia, Pennsylvania

- Etude rétrospective, monocentrique
- 6015 révisions
- Vs MSIS 2013

Table 1
Diagnostic Measures by Test.

	CRP and ESR	CRP or ESR	CRP	ESR	WBC	LE	PMN
Sensitivity	86.74 ± 1.22%	96.01 ± 0.70%	92.31 ± 0.95%	89.95 ± 1.07%	85.78 ± 1.67%	75.00 ± 4.17%	85.82 ± 1.70%
Specificity	78.81 ± 0.68%	51.47 ± 0.84%	68.13 ± 0.78%	62.05 ± 0.78%	83.00 ± 1.88%	90.93 ± 1.22%	80.84 ± 2.02%
Positive predictive value	47.13 ± 1.32%	30.12 ± 0.92%	38.48 ± 1.12%	32.80 ± 1.00%	84.62 ± 1.72%	61.83 ± 4.24%	83.26 ± 1.79%
Negative predictive value	96.47 ± 0.34%	98.34 ± 0.30%	97.62 ± 0.30%	96.77 ± 0.35%	84.26 ± 1.83%	94.89 ± 0.96%	83.70 ± 1.93%
Diagnostic odds ratio	23.33 ± 0.11	25.52 ± 0.19	25.66 ± 0.14	14.64 ± 0.12	29.45 ± 0.19	30.06 ± 0.27	25.53 ± 0.19
Positive likelihood ratio	4.09	1.98	2.90	2.37	5.05	8.27	4.48
Negative likelihood ratio	0.17	0.08	0.11	0.16	0.17	0.27	0.18

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LE, leukocyte esterase; PMN, polymorphonuclear; WBC, white blood cell.

Parmi les critères diagnostiques mineurs,
→LE est le plus performant

Table 2
True and False Negative and Positives by Diagnostic Tests.

	ESR and CRP	ESR or CRP	CRP	ESR	WBC	LE	PMN
True negative	2811	1836	2461	2399	332	501	308
False negative	103	31	60	80	62	27	60
False positive	756	1731	1151	1467	68	50	73
True positive	674	746	720	716	374	81	363
Total	4344	4344	4392	4662	836	659	804

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LE, leukocyte esterase; PMN, polymorphonuclear; WBC, white blood cell.

Acute PJI : WBC count >10,000 cells per mL and a 90% PMN
Chronic PJI : 3000 cells per mL WBC count and differential >80%

Biomarqueurs synoviaux

Leucocyte estérase

- Simple d'utilisation
- Cout faible (20 centimes)
- Facilement disponible

- Variabilité d'interprétation inter opérateur : lecture subjective
- Interférence (inutilisable sur liquide hémorragique)
- VPN et spécificité faible

Biomarqueurs synoviaux

CRP articulaire

Roche Cobas®

- Protéine synthétisée par le foie
- Protéine libérée en cas d'inflammation aigue

- Seuil = 8,8 mg/L Gallo et al., 2018 6,9 mg/L MSIS 2013

Biomarqueurs synoviaux

Clin Orthop Relat Res (2014) 472:3254–3262
DOI 10.1007/s11999-014-3543-8

SYMPOSIUM: 2013 MUSCULOSKELETAL INFECTION SOCIETY

CRP articulaire

Diagnosing Periprosthetic Joint Infection

Has the Era of the Biomarker Arrived?

Carl Deirmengian MD, Keith Kardos PhD, Patrick Kilmartin, Alexander Cameron, Kevin Schiller, Javad Parvizi MD

95 patients, PTH ou PTG: 66
non PJI, 29 PJI
ELISA
Vs MSIS 2011

Seuil 12,2 mg/l :
Sensibilité 90%
Spécificité 97 %

Table 4. Diagnostic characteristics of synovial fluid biomarkers

Biomarker	AUC	Cutoff	Specificity (%)	95% CI (%)	Sensitivity (%)	95% CI (%)
α-Defensin	1.000	4.8 μg/mL	100	95–100	100	88–100
ELA-2	1.000	2.0 μg/mL	100	95–100	100	88–100
BPI	1.000	2.2 μg/mL	100	95–100	100	88–100
NGAL	1.000	2.2 μg/mL	100	95–100	100	88–100
Lactoferrin	1.000	7.5 μg/mL	100	95–100	100	88–100
IL-8	0.992	6.5 ng/mL	95	87–99	100	87–100
SF CRP	0.987	12.2 mg/L	97	90–100	90	73–98
Resistin	0.983	340 ng/mL	100	95–100	97	82–99
Thrombospondin	0.974	1061 ng/mL	97	90–100	90	73–98
IL-1β	0.966	3.1 pg/mL	95	87–99	96	82–100
IL-6	0.950	2.3 ng/mL	97	89–100	89	71–98
IL-10	0.930	32.0 pg/mL	89	79–96	89	72–98
IL-1α	0.922	4.0 pg/mL	91	81–97	82	63–94
IL-17	0.892	3.1 pg/mL	99	92–100	82	63–94
G-CSF	0.859	15.4 pg/mL	92.	82–97	82	62–94
VEGF	0.850	2.3 ng/mL	77	65–87	75	55–89

Biomarqueurs synoviaux

CRP articulaire

The Journal of Arthroplasty 37 (2022) 2437–2443

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Complications - Infection

Synovial C-Reactive Protein is a Useful Adjunct for Diagnosis of Periprosthetic Joint Infection

Colin M. Baker, BS, Graham S. Goh, MD, Saad Tarabichi, MD, Noam Shohat, MD, Javad Parvizi, MD, FRCS *

Rothman Orthopaedic Institute at Thomas Jefferson University, Philadelphia, Pennsylvania

Data prospectifs, Review rétrospectif

621 patients suspicion PJI:

- 394 : pas d'PJI
- 194 : PJI
- 33 : non concluant

Vs 2018 ICM

Seuil 6,9 mg/l

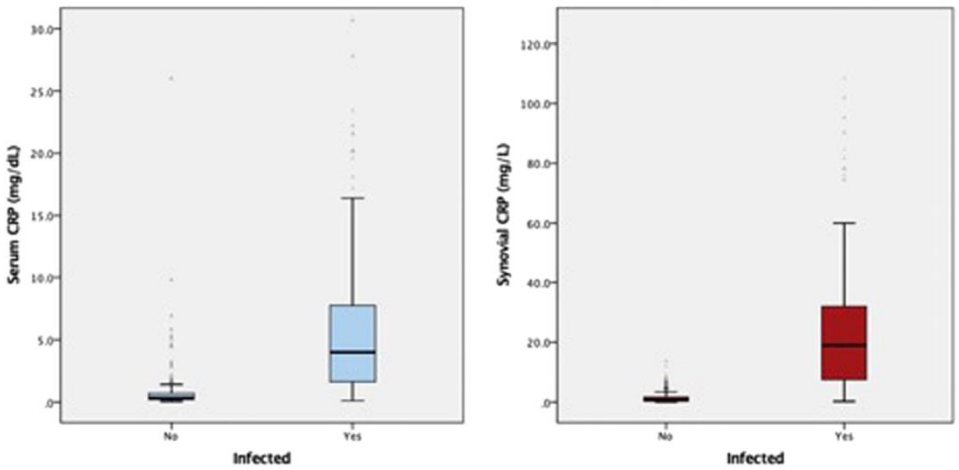


Fig. 1. Box plots of serum and synovial CRP according to infection groups.

Table 3
Receiver Operating Characteristic (ROC) Curve Analysis for Each Biomarker.

Biomarker	AUC	SE	95% CI Lower	95% CI Upper	2018 ICM Cutoff	Sensitivity	Specificity
Synovial CRP	0.951	0.010	0.932	0.970	6.9	0.742	0.980
Serum CRP	0.926	0.018	0.903	0.949	1.0	0.835	0.883
Serum ESR	0.848	0.018	0.813	0.884	30	0.874	0.729
Synovial PMN	0.973	0.009	0.956	0.991	80	0.864	0.992
Synovial WBC	0.978	0.007	0.963	0.992	3,000	0.917	0.987
Alpha-Defensin	0.925	0.013	0.898	0.951	-	0.986	0.869

AUC, area under the curve; SE, standard error; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PMN%, polymorphonuclear leukocyte percentage; WBC, white blood cell count; ICM, International Consensus Meeting.

Biomarqueurs synoviaux

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The Journal of Arthroplasty
journal homepage: www.arthroplastyjournal.org

Complications - Infection

Synovial C-Reactive Protein is a Useful Adjunct for Diagnosis of Periprost

Colin M. Ba
Javad Parvi
Rothman Orthopae

Check for updates

CRP articulaire

Bonne corrélation taux de CRP sérique et synoviale

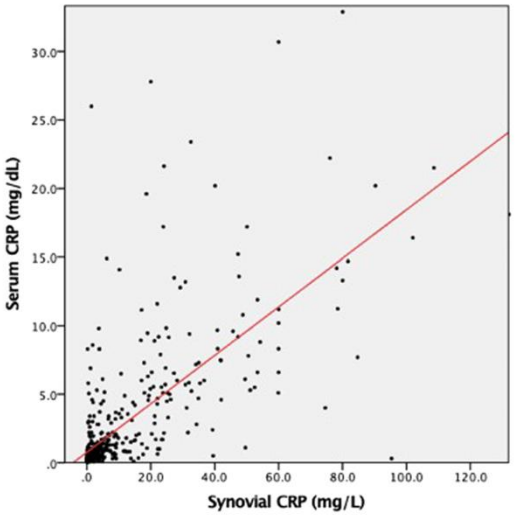


Fig. 2. Relationship between serum and synovial CRP.

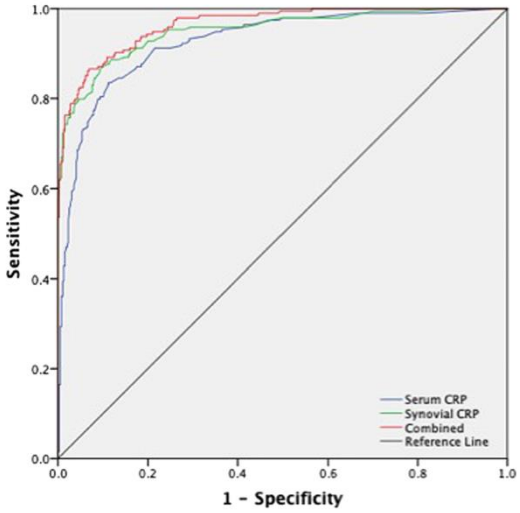


Fig. 3. Receiver operating characteristic curves of serum and synovial CRP.

CRP sérique + synoviale : AUC ↗ CRP sérique seule

Ces résultats soutiennent l'utilisation de la CRP synoviale comme complément dans le bilan de PJI

Valeur ajoutée de la CRP synoviale vs CRP sérique?

Biomarqueurs synoviaux

CRP articulaire

Roche Cobas®

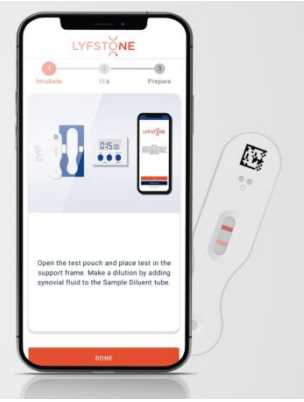
- Coût faible (0,38€HT)
- Facilement disponible
- Intérêt en association avec CRP sérique
- Valeur quantitative

- Faible sensibilité dans les IOAPs chroniques
- Seuil?

Biomarqueurs synoviaux

Calprotectine articulaire

- Protéine pro inflammatoire relarguée par les macrophages et les PNN
- Suivi MICI
- Test ELISA et test Unitaire
- Seuil = 50 mg/L J.A Warren 2022 ; Grassi 2022 ; J, Warren 2021



- 15 minutes
- [Calprotectine] proportionnelle à l'intensité de la couleur et peut donc être calculée par l'application mobile.
- 14 to 300 mg/ml.
- low risk (less than 14 mg/ml)
- moderate risk (14 to 50 mg/ml)
- high risk (more than 50 mg/ml).

https://lyfstone.com/lyfstone-calprotectin/

Biomarqueurs synoviaux

The Journal of Arthroplasty 33 (2018) 1149–1153

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Complications - Infection

Calprotectine articulaire

Synovial Calprotectin: An Inexpensive Biomarker to Exclude a Chronic Prosthetic Joint Infection

Marjan Wouthuyzen-Bakker, MD, PhD [a,*], Joris J.W. Ploegmakers, MD [b], Karsten Ottink, MD [b], Greetje A. Kampinga, MD, PhD [a], Lucie Wagenmakers-Huizenga [c], Paul C. Jutte, MD, PhD [b], Anneke C.M. Kobold, MD, PhD [c]

[a] Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[b] Department of Orthopaedic Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[c] Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

52 patients, chronique (>4 mois) :
15PJI, 37 non PJI

Dosage immunoenzymatique de la calprotectine (BÜHLMANN)

Vs MSIS 2011

Cutt off = 50 mg/L

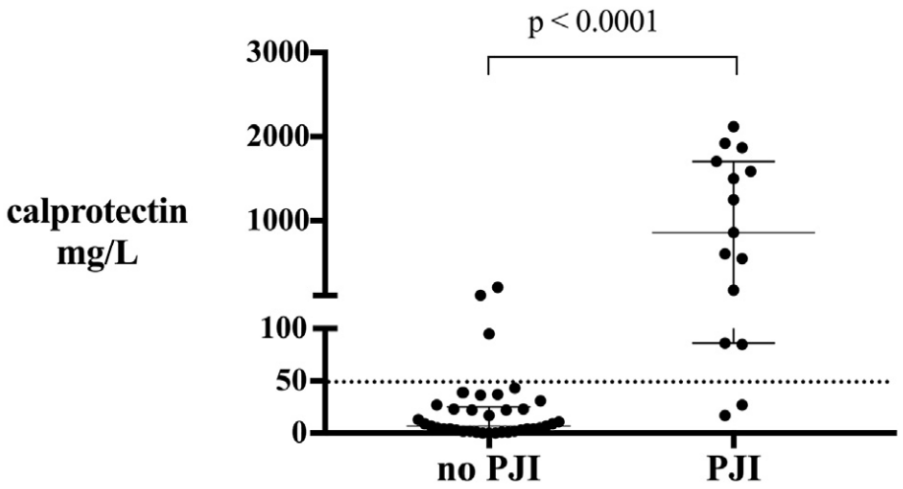


Table 1
Diagnostic Accuracy of Synovial Calprotectin (Cut-Off Value 50 mg/L), Serum CRP (Cut-Off Value 10 mg/L), and ESR (Cut-Off Value 30 mm/h) for Diagnosing a PJI.

	Synovial Calprotectin	Serum CRP	Serum ESR	Serum CRP and ESR
Sensitivity	86.7% (95% CI 59.5-98.3)	66.7% (95% CI 38.8-88.2)	72.7% (95% CI 39.0-93.9)	63.7% (95% CI 30.8-89.1)
Specificity	91.7% (95% CI 78.1-98.3)	70.4% (95% CI 49.8-86.3)	69.6% (95% CI 47.1-86.8)	75.0% (95% CI 50.9-91.3)
PPV	81.3% (95% CI 59.0-92.9)	55.6% (95% CI 38.7-71.2)	53.3% (95% CI 35.8-70.1)	58.3% (95% CI 36.7-77.2)
NPV	94.4% (95% CI 82.3-98.4)	79.2% (95% CI 64.1-89.0)	84.2% (95% CI 66.2-93.6)	80.0% (95% CI 62.3-89.5)
PLR	10.9 (95% CI 3.6-32.2)	2.3 (95% CI 1.1-4.5)	2.4 (95% CI 1.2-4.9)	2.6 (95% CI 1.1-6.1)
NLR	0.14 (95% CI 0.04-0.53)	0.47 (95% CI 0.2-1.0)	0.4 (95% CI 0.1-1.1)	0.5 (95% CI 0.2-1.1)

PPV, positive predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; CI, confidence interval.

Biomarqueurs synoviaux

Calprotectine articulaire

The Journal of Arthroplasty 33 (2018) 1149–1153

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Complications - Infection

Synovial Calprotectin: An Inexpensive Biomarker to Exclude a Chronic Prosthetic Joint Infection

Marjan Wouthuyzen-Bakker, MD, PhD [a,*], Joris J.W. Ploegmakers, MD [b], Karsten Ottink, MD [b], Greetje A. Kampinga, MD, PhD [a], Lucie Wagenmakers-Huizenga [c], Paul C. Jutte, MD, PhD [b], Anneke C.M. Kobold, MD, PhD [c]

[a] Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[b] Department of Orthopaedic Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[c] Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

3FP → pas de discussion

2FN → prise d'antibiotique
→ prise AINS

Table 2
Characteristics of Patients With False Positive and False Negative Values of Synovial Calprotectin (Cut-Off Value 50 mg/L) for Diagnosing or Excluding a PJI.

	No PJI (n = 37)		PJI (n = 15)	
	True Negative (n = 34)	False Positive (n = 3)	True Positive (n = 13)	False Negative (n = 2)
Joint				
Hip	21	3	8	0
Knee	12	0	3	2
Shoulder	1	0	2	0
Rheumatoid arthritis	2	0	2	0
Malignancy bone	4	1	0	0
Use of antibiotics	0	0	2	1
Use of immunosuppressive drugs	3	0	2	0
Fistula	0	0	1	1
Onset of symptoms				
Early (<3 mo after arthroplasty)	4	0	2	0
Delayed (3-24 mo after arthroplasty)	6	0	3	1
Late (>24 mo after arthroplasty)	24	3	8	1
Microorganism causing the infection				
Staphylococcus aureus			0	0
Coagulase-negative staphylococci			4	1
Gram negatives			2	0
Streptococcus species			1	0
Enterococcus species			0	1
Propionibacterium acnes			2	0
Corynebacterium species			0	0
Polymicrobial			3	0
Culture negative			1	0
Alternative diagnosis				
Aseptic loosening	15	3		
Metallosis	7	0		
Luxation	3	0		
Fracture	3	0		
Patella problem	2	0		
Other/unknown	4	0		

Biomarqueurs synoviaux

Calprotectine articulaire

The Journal of Arthroplasty 33 (2018) 1149–1153

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Synovial Calprotectin: An Inexpensive Biomarker to Exclude a Chronic Prosthetic Joint Infection

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[a] Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[b] Department of Orthopaedic Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[c] Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

En + Analyse supplémentaire, 12 patients, 2ème T

- Chez 2 des 12 patients (17%), 2 cultures tissulaires peropératoires ou plus étaient positives→ infection persistante ou une réinfection.
- Chez ces deux patients : CRP, ESR, histologie et calprotectine : NEG.
- Pas de prise Immunosuppresseurs

Faibles inocula de bactéries → la calprotectine pas assez sensible

Biomarqueurs synoviaux

Calprotectine articulaire

International Orthopaedics (2022) 46:1473–1479
https://doi.org/10.1007/s00264-022-05421-1

ORIGINAL PAPER

Synovial calprotectin is a reliable biomarker for periprosthetic joint infections in acute-phase inflammation — a prospective cohort study

Igor Lazic[1] · Peter Prodinger[2] · Maximilian Stephan[1] · Alexander T. Haug[1] · Florian Pohlig[1] · Severin Langer[1] · Rüdiger von Eisenhart-Rothe[1] · Christian Suren[1]

33 patients pour une révision genou ou hanche avec cause d'inflammation :

- 17 patients en phase postopératoire précoce
- 11 patient après luxation
- 5 patients pour rupture d'implant

17PJI, 16 non PJI

Test cassette

Vs 2021 EBJIS

Table 1 Performance of CRP, WBC, PMN and calprotectin lateral-flow-test. The modified EBJIS 2021 definition served as the gold standard. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; EBJIS 2021, European Bone and Joint Infection society definition of periprosthetic joint infection published in 2021

	CRP	WBC	PMN	Calprotectin
Sensivity (95% *CI*)	0.41 (0.18, 0.67)	0.41 (0.18, 0.67)	0.71 (0.44, 0.90)	0.88 (0.64, 0.99)
Specificity (95% *CI*)	0.81 (0.54, 0.96)	1.00 (0.79, 1.00)	1.00 (0.79, 1.00)	0.81 (0.54, 0.96)
PPV (95% *CI*)	0.70 (0.35, 0.93)	1.00 (0.59, 1.00)	1.00 (0.74, 1.00)	0.83 (0.59, 0.96)
NPV (95% *CI*)	0.57 (0.35, 0.77)	0.62 (0.41, 0.80)	0.77 (0.53, 0.92)	0.87 (0.60, 0.98)
Accuracy	0.6	0.7	0.85	0.85

3FP : 2/3 : rupture d'implant de la mégaprothèse

Même en présence d'une inflammation locale due à d'autres causes non infectieuses, la calprotectine est un paramètre diagnostique fiable pour la détection d'une PJI dans les THA et TKA primaires et de révision.

Biomarqueurs synoviaux

Calprotectine articulaire

The Journal of Arthroplasty 35 (2020) 534–537

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Complications - Infection

Synovial Fluid Calprotectin for the Preoperative Diagnosis of Chronic Periprosthetic Joint Infection

Paolo Salari, MD [a,*], Marco Grassi, MD [a], Barbara Cinti, BS [b], Nicoletta Onori, BS [b], Antonio Gigante, MD [a]

[a] Department of Clinical and Molecular Science, Clinical Orthopedics, School of Medicine, Università Politecnica delle Marche, Ancona, Italy
[b] Laboratory of Clinical Pathology and Microbiology, General Service Department, Azienda Ospedaliera Universitaria "Ospedali Riuniti", Ancona, Italy

Etude prospective observationnelle

Ponction préop sur PTG uniquement

Vs ICM 2018

76 patients inclus (37%PJI)

CE : infection aigue, ATB moins de 2sem, maladies inflammatoires chroniques

ELISA

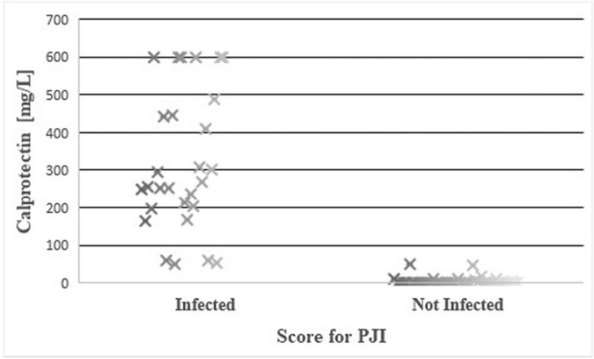


Fig. 1. Dosage of synovial calprotectin in infected and non-infected patients.

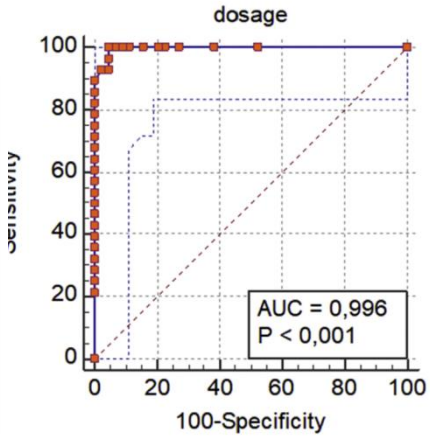


Fig. 2. AUC of synovial calprotectin test.

Se=100%; Sp = 95%

Résultats :
- Aucun FN, 2 FP (53 et 58 mg/l) avec seuil > 50 mg/L
- taux moyen positif = 320 mg/L

Biomarqueurs synoviaux

Optilite®

Calprotectine articulaire

- Coût faible (10,60€ HT)
- Facilement disponible
- Valeur quantitative

- Non utilisable chez les patients maladie inflammatoire systémique (Polyarthrite rhumatoïde, Spondylarthrite ankylosante, Maladie inflammatoire chronique de l'intestin (MICI))
- Influence d'un traitement Immunosuppresseur ? [1]

1: Whouthuyzen et al., 2018

Biomarqueurs synoviaux

Conclusion

↗ d'études

Aide au diagnostic, intégrés dans les scores

Peu utilisés encore dans les différents CRIOAC → 2020 : 67% centres du CRIOAC utilisent aucun marqueurs synoviaux (Plouzeau, JNI Poitiers, 2020)

Biologie Moléculaire

(PCR ciblée, multiplexe/syndromique, NGS)

APPORT DE LA BIOLOGIE MOLÉCULAIRE (BM)

✓ Sensibilité très souvent plus faible que la culture :
- IOA : très peu d'ADN bactérien mais beaucoup d'ADN humain
- Biopsies osseuses/tissulaires = milieu complexe → extraction ADN bactérien difficile

→ Positionnement des techniques BM : en seconde ligne en cas de négativité des cultures malgré une forte suspicion clinique d'infection

✓ Intérêt +++ quand traitement antibiotique administré avant la réalisation des prélèvements per-opératoires

✓ Apport des techniques de BM : rapidité du résultat pour une adaptation rapide du traitement probabiliste

Techniques de BM:

-PCR ciblées

- PCR multiplexes/syndromiques
- Séquençage de nouvelle génération (NGS)

PCR ciblée

Cible 1 gène bactérien

→ **Universelle à toutes les bactéries**

Exemple : gène *rrl* (gène ribosomique ARNr 16S)

✓ Patients sous ATB ++ (persistance ADN bactérien viable/non viable avec traitement ATB)

✗ PCR non adaptée aux infections plurimicrobiennes

Délai de rendu de résultats (1-3 jours)

Contamination

Sensibilité < culture (Bémer *et al.,* 2014)

Evaluation performances pour diagnostic des IOAP :

Etude sur 299 patients

192 IOAP confirmées par culture bactérienne positive

→ 143 PCR ARNr 16S positives

Sensibilité PCR ARNr 16s = 73,3% , Spécificité = 95,5%

Research Article | October 2014

Evaluation of 16S rRNA Gene PCR Sensitivity and Specificity for Diagnosis of Prosthetic Joint Infection: a Prospective Multicenter Cross-Sectional Study

Authors: Pascale Bémer, Chloé Plouzeau, Didier Tande, Julie Léger, Bruno Giraudeau, Anne Sophie Valentin, Anne Jolivet-Gougeon, SHOW ALL (21 AUTHORS) the Centre de Référence des Infections Ostéo-articulaires du Grand Ouest (CRIOGO) Study Team | AUTHORS INFO & AFFILIATIONS

PCR ciblée | Cible 1 gène bactérien

→ **Spécifique d'une bactérie**

PCR *Staphylococcus aureus* : gène spécifique bactérie +/- gène de résistance aux béta-lactamines

Exemple kit commercial : **Xpert® MRSA/SA SSTI (Cepheid)**
(protéine A, gène *spa* + PLP2A, gène *mec*A)

✓ Résultat rapide (72 minutes)

✗ Kit validé sur les prélèvements de peau et de tissu mou uniquement

PCR ciblée | Cible 1 gène bactérien

→ Spécifique d'une bactérie

PCR *Staphylococcus aureus* : gène spécifique bactérie +/- gène de résistance aux béta-lactamines

Exemple kit commercial : **Xpert® MRSA/SA SSTI (Cepheid)**

(protéine A, gène *spa* + PLP2A, gène *mec*A)

Evaluation performances - IOA :

Détection de *S. aureus* : sensibilité entre 85,4% et 100%

Détection des SARM : sensibilité entre 81,8% et 100%

Détection des Staphylocoques coagulase négative résistants : sensibilité entre 36% et 100%

Challenging Methicillin Resistance Detection in Bone and Joint Infections: Focus on the MRSA/SA SSTI® Strategy

Marie Titécat[1,2,3], Caroline Loïez[1,3], François Demaeght[3,4], Jean-Thomas Leclerc[3,5,6], Théo Martin[3,5], Hervé Dezèque[3,5], Henri Migaud[2,3,5] and Eric Senneville[2,3,4]*

Evaluation performances - infections d'ostéosynthèse, d'arthrodèses et pseudarthroses :

Sensibilité = 42,9%

Spécificité = 96,8%

VPP = 60%

VPN = 93,8%

Orthopaedics & Traumatology: Surgery & Research

Volume 110, Issue 6, October 2024, 103820

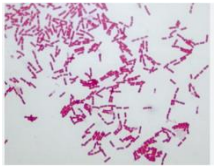
Original article

Accuracy of the GeneXpert® MRSA/SA SSTI test to diagnose methicillin-resistant *Staphylococcus* spp. infection in bone fixation and fusion and management of infected non-unions

Théo Martin [a b c], Pierre Martinot [d], Jean-Thomas Leclerc [a b c e], Marie Titécat [b c f], Caroline Loïez [b c f], Julien Dartus [a b c], Alain Duhamel [b g], Henri Migaud [a b c], Christophe Chantelot [b c h], Barthélémy Lafon Desmurs [b c j], Thomas Amouyel [a b c], Eric Senneville [b c j]

PCR ciblée | Cible 1 gène bactérien

→ Spécifique d'une bactérie



PCR *Kingella kingae* : ostéo-arthrite ou ostéo-myélite de l'enfant (6 mois – 4 ans)
Bactérie à croissance lente (1-5 jours) / culture difficile (faible sensibilité)
PCR maison, cibles différentes (toxine RTX *rtx*A/*rtx*B, chaperonnine 60 *cpn*60, …)

Sensibilité PCR sur liquide articulaire 5 à 10 fois > à celle de la culture (dépend du gène ciblé par les PCR et de l'utilisation de flacon d'hémoculture pour la culture)

Performances PCR *vs* culture :

	Culture			Nucleic Acid Amplification Tests			
	Normally Sterile Body Fluids (Blood, Aspirates, and Exudates)		Oropharyngeal Specimens	Universal Primers	*Kingella kingae*-Specific Primers		
Features	Solid media	Blood culture vial	BAV medium	16S rRNA	*rtx*	*cpn60*	*mdh*
Sensitivity	±	+	+	++	+++	+++	+++
Specificity	+++	+++	+++	+++	++ [b]	+++	+++
Time-to-positivity	1–4 days	1–4 days	2–5 days	1–2 days [a]		hours	

		Culture		Nucleic Acid Amplification Tests	
		Normally Sterile Body Fluids (Blood, Aspirates, and Exudates)	Oropharyngeal Specimens	Universal Primers	*Kingella kingae*-Specific Primers
Enables	Antibiotic susceptibility testing	Yes		no	
	Typing	Yes		no	
	Colonization studies	N/A [c]	Yes	yes	
	Transmission studies	N/A [c]	Yes	no	
	Outbreak investigation	N/A [c]	Yes	yes	
	Whole-genome sequencing	Yes		no	
	Study of virulence factors	Yes		no	

diagnostics MDPI

Review

The Past, Present, and Future of *Kingella kingae* Detection in Pediatric Osteoarthritis

Pablo Yagupsky

PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

Plusieurs panels commercialisés : détection de bactéries et de gènes de résistance

- Kit Biofire® Joint Infection (JI) Panel – BioMérieux (France)

- Kit Implant and Tissue infection (ITI) Unyvero – Curetis (Allemagne)

- Prove-it® bone and joint (Mobidiag, Finlande)

- SeptiFast® Test M^{grade} (Roche, Suisse)

Objectifs :

Diminution des délais avant mise en place d'une antibiothérapie optimisée

Diminution de l'utilisation des antibiotiques à large spectre

PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

Kit Biofire® Joint Infection (JI) Panel – BioMérieux

39 cibles (bactéries + levures + gènes de résistance)

Résultats en 1heure

Sensibilité = 91,7% / Spécificité = 99,8% (données fournisseur)

BACTERIES A GRAM POSITIF	BACTERIES A GRAM NEGATIF	GENES DE RESISTANCE
Aérobies	***Aérobies***	**Résistance à la méticilline**
Staphylococcus aureus	*Kingella kingae*	*mecA/C* et MREJ
Staphylococcus lugdunensis	*Escherichia coli*	
Streptococcus spp.	*Proteus spp.*	**Résistance à la vancomycine**
Streptococcus agalactiae	*Salmonella spp.*	*vanA/B*
Streptococcus pneumoniae	Groupe *Klebsiella pneumoniae*	
Streptococcus pyogenes	*Klebsiella aerogenes*	**BLSE**
Enterococcus faecalis	*Citrobacter*	CTX-M
Enterococcus faecium	Complexe *Enterobacter cloacae*	
	Serratia marcescens	**Carbapénémases**
Anaérobies	*Morganella morganii*	OXA48-like
Anaerococcus prevotii/vaginalis	*Haemophilus influenzae*	KPC
Clostridium perfringens	*Neisseria gonorrhoeae*	NDM
Cutibacterium avidum/granulosum	*Pseudomonas aeruginosa*	VIM
Finegoldia magna		IMP
Parvimonas micra	***Anaérobies***	
Peptoniphilus	*Bacteroides fragilis*	
Peptostreptococcus anaerobius		

LEVURES
Candida spp. *Candida albicans*

Note : les résultats des gènes de résistance aux antibiotiques ne sont pas rapportés à moins qu'une bactérie concernée du panel soit également détectée.

Indications :

-Arthrite septique sur articulation native communautaire chez l'adulte

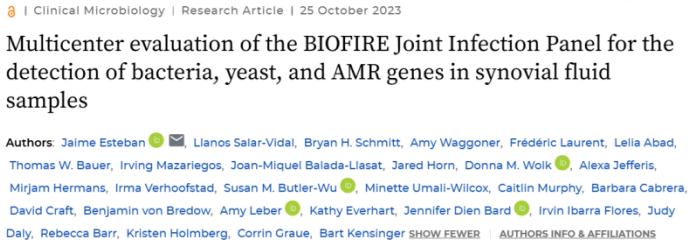
- IOA sur prothèse post-opératoire aigüe, hématogène (hanche et genou)

PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

Kit Biofire® Joint Infection (JI) Panel – BioMérieux

Etude prospective – évaluation kit Biofire® *vs* culture



Clinical Microbiology | Research Article | 25 October 2023

Multicenter evaluation of the BIOFIRE Joint Infection Panel for the detection of bacteria, yeast, and AMR genes in synovial fluid samples

Authors: Jaime Esteban, Llanos Salar-Vidal, Bryan H. Schmitt, Amy Waggoner, Frédéric Laurent, Lelia Abad, Thomas W. Bauer, Irving Mazariegos, Joan-Miquel Balada-Llasat, Jared Horn, Donna M. Wolk, Alexa Jefferis, Mirjam Hermans, Irma Verhoofstad, Susan M. Butler-Wu, Minette Umali-Wilcox, Caitlin Murphy, Barbara Cabrera, David Craft, Benjamin von Bredow, Amy Leber, Kathy Everhart, Jennifer Dien Bard, Irvin Ibarra Flores, Judy Daly, Rebecca Barr, Kristen Holmberg, Corrin Graue, Bart Kensinger SHOW FEWER | AUTHORS INFO & AFFILIATIONS

1544 patients suspects d'IOA/IOAP
202 prélèvements positifs en culture (à une bactérie du panel)
242 prélèvements positifs en PCR

Sensibilité = 90,5% / Spécificité = 99,6%

PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

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Bactéries du panel :
20 faux négatifs (Pvts + en culture/ - en PCR)
70% (14/20) FN confirmés par PCR spécifiques

Result and analyte	No. of results	No. of investigations: Comparator result confirmed	No. of investigations: BIOFIRE JI result confirmed	No. of investigations: Inconclusive
BIOFIRE JI Panel FN				
Parvimonas micra	1	1	0	0
Staphylococcus aureus	7	5	1[a]	1
Streptococcus spp.	6	4	0	2
Streptococcus agalactiae	1	1	0	0
Streptococcus pyogenes	1	0	0	1
Enterobacter cloacae complex	2	1	1[b]	0
Klebsiella pneumoniae group	1	1	0	0
Candida	3	2	0	1
Candida albicans	2	1	0	1
Total	20	14	2	4
% of total FN results		70.0%	10.0%	20.0%

PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

Kit Biofire® Joint Infection (JI) Panel – BioMérieux

Etude prospective – évaluation kit Biofire® *vs* culture

| Clinical Microbiology | Research Article | 25 October 2023

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Bactéries hors panel :
75 faux négatifs (Pvts + en culture/ - en PCR)

Off–Panel organism identified	Number identified
Staphylococcus epidermidis	38
Cutibacterium acnes	8
Staphylococcus capitis	5
Corynebacterium striatum	3
Staphylococcus hominis	3
Corynebacterium amycolatum	2
Staphylococcus caprae	2
Acinetobacter baumannii complex	1
Arthrobacter cumminsii	1
Bacillus licheniformis	1
Capnocytophaga canimorsus	1
Clostridium symbiosum	1
Enterococcus gallinarum	1
Enterococcus hirae	1
Klebsiella oxytoca	1
Granulicatella adiacens	1
Pasteurella multocida	1
Prevotella intermedia	1
Staphylococcus haemolyticus	1
Staphylococcus saccharolyticus	1
Staphylococcus warneri	1
Total	75

PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

Kit Biofire® Joint Infection (JI) Panel – BioMérieux

Etude prospective – évaluation kit Biofire® *vs* culture

Clinical Microbiology | Research Article | 25 October 2023

Multicenter evaluation of the BIOFIRE Joint Infection Panel for the detection of bacteria, yeast, and AMR genes in synovial fluid samples

Authors: Jaime Esteban, Llanos Salar-Vidal, Bryan H. Schmitt, Amy Waggoner, Frédéric Laurent, Lelia Abad, Thomas W. Bauer, Irving Mazariegos, Joan-Miquel Balada-Llasat, Jared Horn, Donna M. Wolk, Alexa Jefferis, Mirjam Hermans, Irma Verhoofstad, Susan M. Butler-Wu, Minette Umali-Wilcox, Caitlin Murphy, Barbara Cabrera, David Craft, Benjamin von Bredow, Amy Leber, Kathy Everhart, Jennifer Dien Bard, Irvin Ibarra Flores, Judy Daly, Rebecca Barr, Kristen Holmberg, Corrin Graue, Bart Kensinger SHOW FEWER | AUTHORS INFO & AFFILIATIONS

Bactéries du panel :
79 faux positifs? (Pvts - en culture/ + en PCR)

96,2% (76/79) confirmés comme positifs
++ *S. aureus/K. kingae/Streptococcus sp*

Result and analyte	No. of results	No. of investigations: Comparator result confirmed	BIOFIRE JI result confirmed	Inconclusive
BIOFIRE JI Panel FP				
Enterococcus faecalis	5	0	5	0
Enterococcus faecium	2	0	2	0
Finegoldia magna	1	0	1	0
Peptoniphilus	1	0	1	0
Peptostreptococcus anaerobius	3	0	3	0
Staphylococcus aureus	22	0	19	3
Staphylococcus lugdunensis	3	0	3	0
Streptococcus spp.	12	0	12	0
Streptococcus agalactiae	1	0	1	0
Bacteroides fragilis	1	0	1	0
Enterobacter cloacae complex	2	0	2	0
Escherichia coli	1	0	1	0
Haemophilus influenzae	1	0	1	0
Kingella kingae	6	0	6	0
Klebsiella pneumoniae group	1	0	1	0
Morganella morganii	2	0	2	0
Neisseria gonorrhoeae	3	0	3	0
Proteus spp.	4	0	4	0
Pseudomonas aeruginosa	3	0	3	0
Serratia marcescens	1	0	1	0
Candida	1	0	1	0
mecA/C and MREJ (MRSA)	4	0	4	0
Total	79	0	76	3
% of total FP results		0%	96.2%	3.8%

PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

Kit Biofire® Joint Infection (JI) Panel – BioMérieux

Impact clinique diagnostic IOA kit Biofire® *vs* culture

Performance and Hypothetical Impact on Joint Infection Management of the BioFire Joint Infection Panel: a Retrospective Analysis

Benjamin Berinson,[a] Laura Spenke,[a] Lukas Krivec,[b] Konstantin Tanida,[a] Anna Both,[a] Johannes Keller,[b] Tim Rolvien,[b] Martin Christner,[a] Marc Lütgehetmann,[a] Martin Aepfelbacher,[a] Till Orla Klatte,[b] Holger Rohde[a]

Etude rétrospective – IOA/IOAP

Identification espèce bactérienne : -49h *vs* culture (temps médian 50,29h)
Rendu de la sensibilité aux antibiotiques : - 99h *vs* culture (temps médian 100,56h)

			Result of:		
Case no.	Joint type	Classification[a]	Gram staining	SOC	BJA[c]
1	Prosthetic	PJI	Negative	*Staphylococcus epidermidis*	None
5	Native	NJI	Negative	*Staphylococcus aureus*	*Staphylococcus aureus*
9	Native	NJI	Negative	*Staphylococcus lugdunensis*	*Staphylococcus lugdunensis*
10	Native	NJI	Negative	*Staphylococcus epidermidis*	None
14	Prosthetic	Noninflammatory, noninfectious	Negative	*Staphylococcus epidermidis*	None
15	Prosthetic	PJI	Negative	*Enterococcus faecalis*	*Enterococcus faecalis*
29	Prosthetic	PJI	Negative	*Staphylococcus epidermidis*	None
32	Prosthetic	PJI	Negative	*Cutibacterium acnes*	None
35	Native	NJI	Gram-positive cocci	*Streptococcus pyogenes*	*Streptococcus pyogenes*
38	Native	NJI	Negative	Sterile	*Bacteroides fragilis*
43	Native	NJI[a]	Negative	*Micrococcus luteus*	None
69	Native	NJI	Negative	Sterile	*Bacteroides fragilis*
70	Prosthetic	PJI	Gram-positive cocci	*Staphylococcus aureus*	*Staphylococcus aureus*
80	Prosthetic	PJI	Negative	Sterile	*Streptococcus pneumoniae*
84	Prosthetic	PJI	Negative	*Escherichia coli*	*Escherichia coli*
103	Prosthetic	Noninflammatory, noninfectious	Negative	Sterile	*Staphylococcus aureus*
104	Prosthetic	PJI	Negative	*Candida albicans*	*Candida albicans*
114	Native	NJI	Negative	*Streptococcus pyogenes*	*Streptococcus pyogenes*
119	Native	NJI	Negative	*Enterobacter cloacae* complex	*Enterobacter cloacae* complex

PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

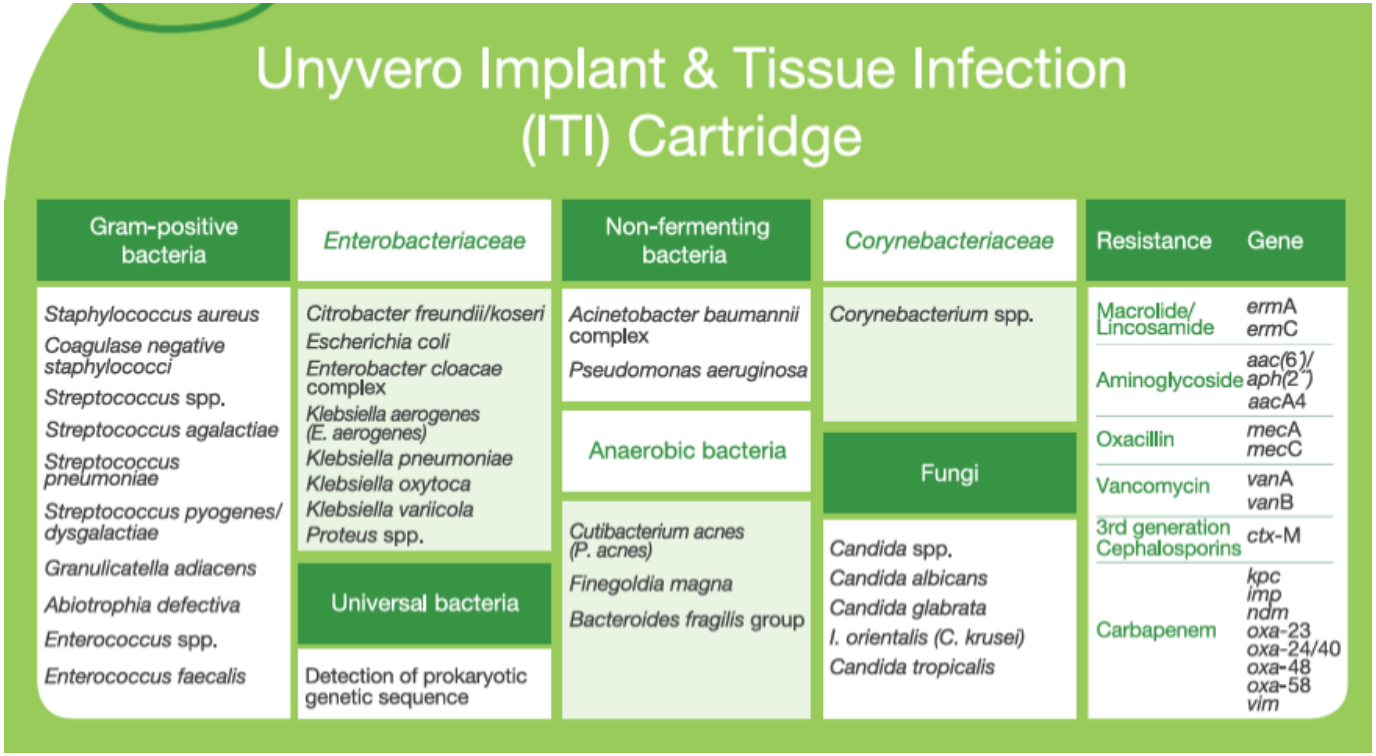
Kit Implant and Tissue infection (ITI) Unyvero® – Curetis

46 cibles (bactéries + levures + gènes de résistance)

Résultats en 5 heures

IOA aigüe : Sensibilité = 85,7% / Spécificité = 100% (données fournisseur)

IOA chronique: Sensibilité = 76,9% / Spécificité = 100% (données fournisseur)



PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

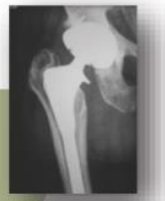
Kit Implant and Tissue infection (ITI) Unyvero® – Curetis

Etude rétrospective – évaluation kit ITI® *vs* culture

Research Article

Diagnostic Performances and Therapeutic Impact of the Unyvero Implant and Tissue Infection Multiplex PCR in Periprosthetic Joint Infections

Claire Richarme, Patricia Pavese, Brice Rubens-Duval, Olivier Seurat, Marion Le Marechal & Sandrine Boisset



Patients with suspected prosthetic joint infection
Joint fluids (n = 33)

Conventional culture

Unyvero ITI mPCR

Analysis of the diagnostic performances

- Rate of concordance = 74%
- Sensitivity$_{PCR}$ = 59%; specificity$_{PCR}$ = 90%
- Median time to results = 21 h for mPCR and 20 days for culture

Analysis of the therapeutic impact

A posteriori evaluation by a panel of experts

- Clinicians would have started an appropriate treatment sooner for 22% of the patients (from 2 to 22 days earlier)

PCR multiplexe / syndromique

Cible un panel de bactéries potentiellement responsables d'IOA

Kit Biofire® Joint Infection (JI) Panel – BioMérieux
Kit Implant and Tissue infection (ITI) Unyvero® – Curetis

✓ Rapidité
Diagnostic malgré antibiothérapie préalable
Bactéries à croissance fastidieuse (anaérobies)

✗ Non exhaustif
Défaut de sensibilité sur certaines espèces
Coût
Intérêt questionnable dans les infections chroniques selon le panel bactérien détecté

NGS

Séquençage de tous les ADN/ARN d'un prélèvement

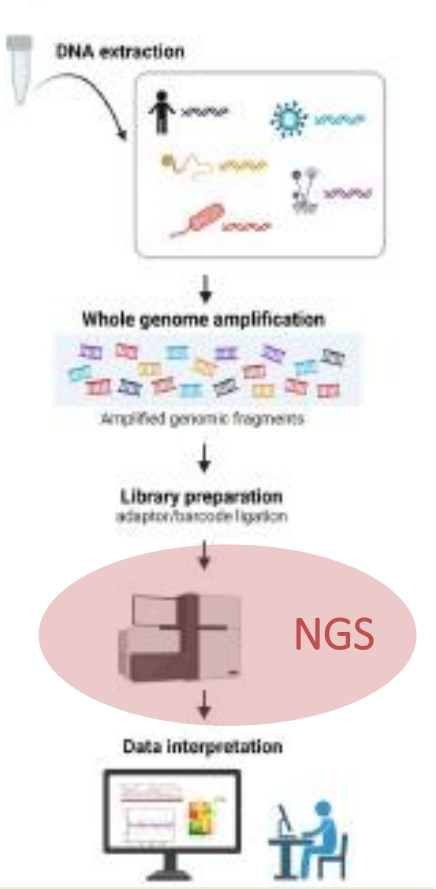
Métagénomique *shotgun*

Amplification de tous les ADN/ARN d'un échantillon

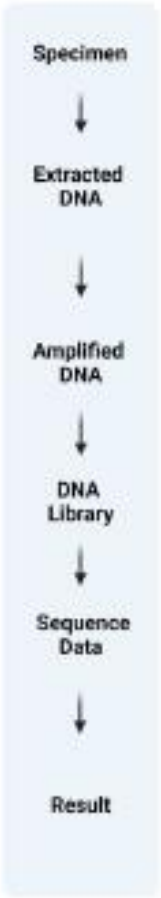
Cible bactéries, virus, champignons, levures,…

Identification à l'espèce

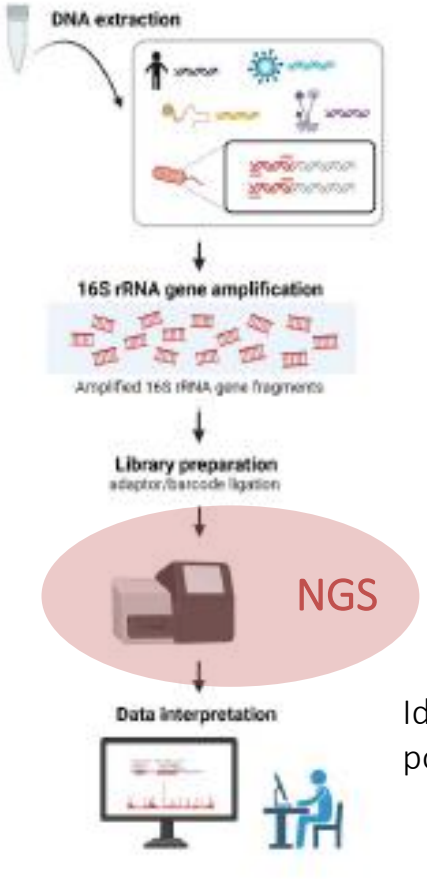
Gènes de résistance / gènes de virulence



>99% de séquences humaines
<1% de séquences microbiennes



16S NGS = métagénomique ciblée



Amplification du gène de l'ARNr 16S

Cible uniquement les bactéries

Identification à l'espèce possible (si longs reads)

D'après Hong H. L., Flurin L., Thoendel M. J., *et al.* (2023). Targeted Versus Shotgun Metagenomic Sequencing-based Detection of Microorganisms in Sonicate Fluid for Periprosthetic Joint Infection Diagnosis. *Clinical infectious diseases. 76*(3), e1456–e1462.

NGS

Séquençage de tous les ADN/ARN d'un prélèvement

Sensibilité de la métagénomique *shotgun* variable selon les études :

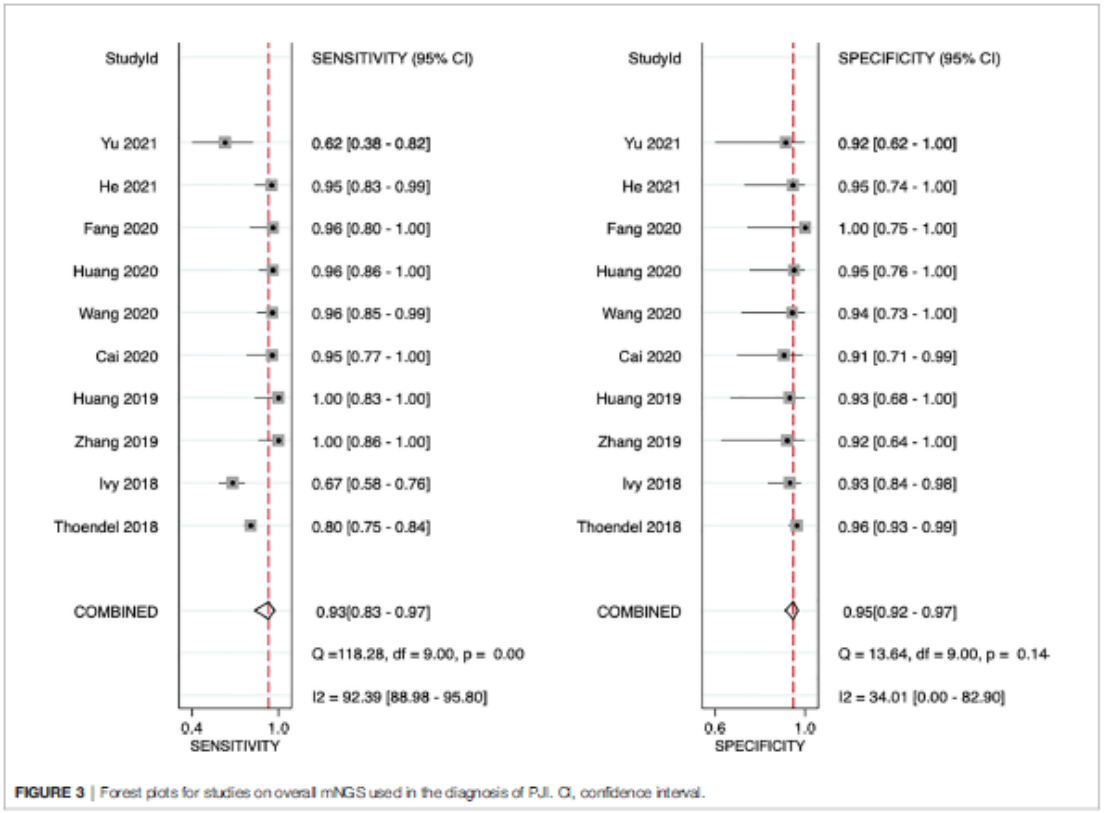


FIGURE 3 | Forest plots for studies on overall mNGS used in the diagnosis of PJI. CI, confidence interval.

IPOA

Review > Front Cell Infect Microbiol. 2022 Jun 10:12:875822. doi: 10.3389/fcimb.2022.875822. eCollection 2022.

The Effectiveness of Metagenomic Next-Generation Sequencing in the Diagnosis of Prosthetic Joint Infection: A Systematic Review and Meta-Analysis

Jun Tan [1], Yang Liu [2], Sabrina Ehnert [3], Andreas K Nüssler [3], Yang Yu [1], Jianzhong Xu [1], Tao Chen [1]

Méta-analyse :
10 études

De 62% à 100%
(combinée = 93%)

NGS

Séquençage de tous les ADN/ARN d'un prélèvement

Gain de sensibilité de la métagénomique *shotgun* pour la documentation microbiologique :

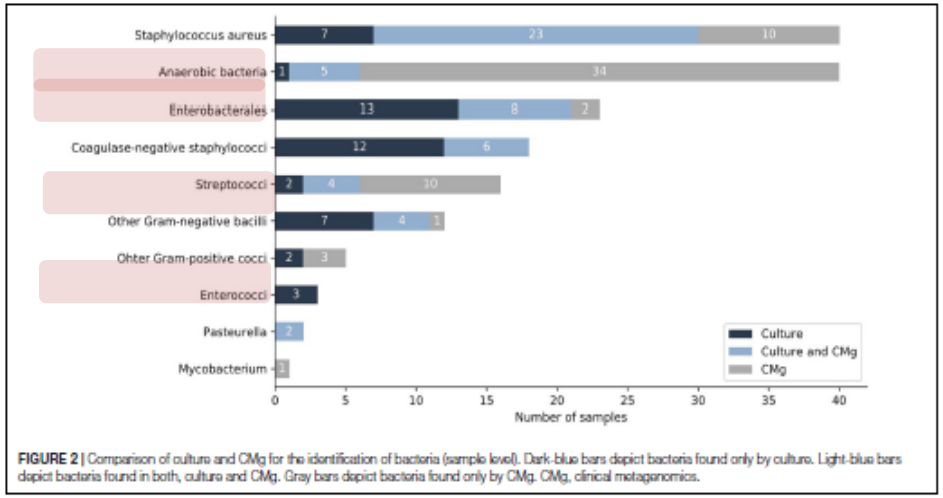


FIGURE 2 | Comparison of culture and CMg for the identification of bacteria (sample level). Dark-blue bars depict bacteria found only by culture. Light-blue bars depict bacteria found in both, culture and CMg. Gray bars depict bacteria found only by CMg. CMg, clinical metagenomics.

IOA

› Front Microbiol. 2022 Apr 21:13:863777. doi: 10.3389/fmicb.2022.863777. eCollection 2022.

Contribution of Clinical Metagenomics to the Diagnosis of Bone and Joint Infections

Camille d'Humières [1 2], Nadia Gaïa [3], Signara Gueye [1], Victoire de Lastours [2 4], Véronique Leflon-Guibout [5], Naouale Maataoui [5], Marion Duprilot [5], Marie Lecronier [4], Marc-Antoine Rousseau [6], Naura Gamany [4], François-Xavier Lescure [2 7], Olivia Senard [7], Laurène Deconinck [7], Marion Dollat [7], Valentina Isernia [7], Anne-Claire Le Hur [1], Marie Petitjean [2], Anissa Nazimoudine [1], Sylvie Le Gac [8], Solaya Chalal [8], Stéphanie Ferreira [9], Vladimir Lazarevic [3], Ghislaine Guigon [10], Gaspard Gervasi [10], Laurence Armand-Lefèvre [1 2], Jacques Schrenzel [3], Etienne Ruppé [1 2]

IPOA

› Bone Joint Res. 2020 Aug 19;9(7):440-449. doi: 10.1302/2046-3758.97.BJR-2019-0325.R2. eCollection 2020 Jul.

Metagenomic next-generation sequencing of synovial fluid demonstrates high accuracy in prosthetic joint infection diagnostics: mNGS for diagnosing PJI

Zida Huang [1], Wenbo Li [1], Gwo-Chin Lee [1 2], Xinyu Fang [1], Li Xing [3], Bin Yang [4], Jianhua Lin [1], Wenming Zhang [1]

Microorganism	No. of isolates from synovial fluid culture	No. of isolates from periprosthetic tissue	No. of isolates from comprehensive culture	No. of identifications from synovial fluid by mNGS
Coagulase-negative staphylococci	10	10	13	13
Staphylococcus aureus	7	8	8	8
Anaerobe*	2	2	2	5
Streptococci	5	5	5	6
Gram-negative bacilli	3	3	4	5
Mycoplasma†	0	0	0	4
Enterococcus faecalis	3	3	5	3
Candida‡	3	5	5	4
Mycobacterium	0	1	1	2
Other organisms§	1	2	2	3
Total	34	39	45	53

NGS

Séquençage de tous les ADN/ARN d'un prélèvement

Gain de sensibilité de la métagénomique *shotgun* pour la documentation microbiologique <u>en cas d'antibiothérapie préalable</u> :

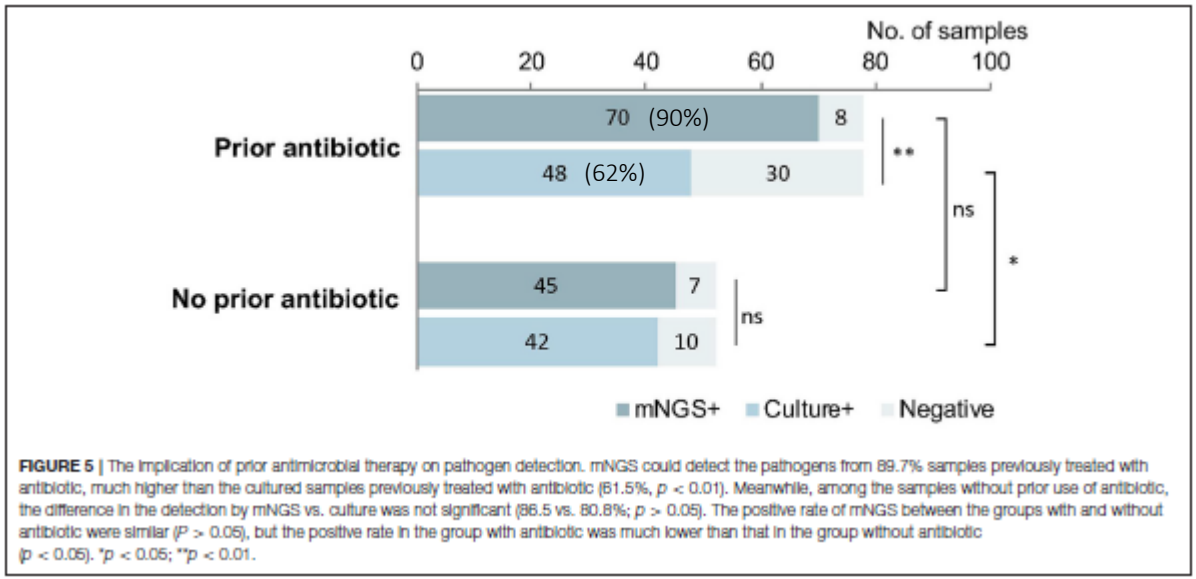


FIGURE 5 | The implication of prior antimicrobial therapy on pathogen detection. mNGS could detect the pathogens from 89.7% samples previously treated with antibiotic, much higher than the cultured samples previously treated with antibiotic (61.5%, $p < 0.01$). Meanwhile, among the samples without prior use of antibiotic, the difference in the detection by mNGS vs. culture was not significant (86.5 vs. 80.8%; $p > 0.05$). The positive rate of mNGS between the groups with and without antibiotic were similar ($P > 0.05$), but the positive rate in the group with antibiotic was much lower than that in the group without antibiotic ($p < 0.05$). *$p < 0.05$; **$p < 0.01$.

IOA

› Front Cell Infect Microbiol. 2020 Sep 17:10:471. doi: 10.3389/fcimb.2020.00471. eCollection 2020.

Pathogenic Detection by Metagenomic Next-Generation Sequencing in Osteoarticular Infections

Zi-da Huang [1], Zi-Jie Zhang [1], Bin Yang [2], Wen-Bo Li [1], Chong-Jing Zhang [1], Xin-Yu Fang [1], Chao-Fan Zhang [1], Wen-Ming Zhang [1], Jian-Hua Lin [1]

Specimen Type	Cases	Culture		mNGS		P value
		Positive Cases	Positive Rate	Positive Cases	Positive Rate	
Antibiotic use	13	3	23.1%	9	69.5%	0.000
Without antibiotic use	18	11	61.1%	10	55.6%	0.766

IPOA

› Infect Drug Resist. 2023 Feb 28:16:1193-1201. doi: 10.2147/IDR.S397260. eCollection 2023.

Diagnostic Performance of Metagenomic Next-Generation Sequencing in the Diagnosis of Prosthetic Joint Infection Using Tissue Specimens

Yali Yu [# 1], Shaohua Wang [# 2], Guixiang Dong [1], Yanli Niu [3]

NGS

Séquençage de tous les ADN/ARN d'un prélèvement

Performances métagénomique *shotgun* selon la nature des prélèvements :

› Bone Joint J. 2021 May;103-B(5):923-930. doi: 10.1302/0301-620X.103B5.BJJ-2020-0745.R1.

Better choice of the type of specimen used for untargeted metagenomic sequencing in the diagnosis of periprosthetic joint infections

Renke He [1], Qiaojie Wang [1], Jin Wang [1], Jin Tang [2], Hao Shen [1], Xianlong Zhang [1]

Etude prospective
59 patients / 40 IPOA (critères MSIS)

	IPOA	
	Sensibilité	**Spécificité**
Tissu péri-prothétique	65%	100%
Liquide articulaire	87,5%	94,7%
Liquide de sonication	92,5%	94,7%

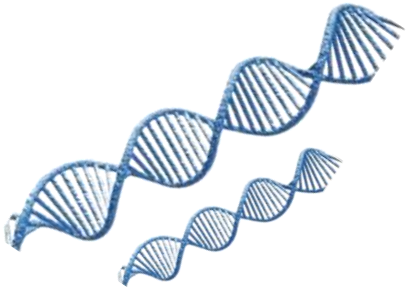
NGS

Séquençage de tous les ADN/ARN d'un prélèvement

Métagénomique *shotgun* : technique de diagnostic microbiologique de dernière ligne

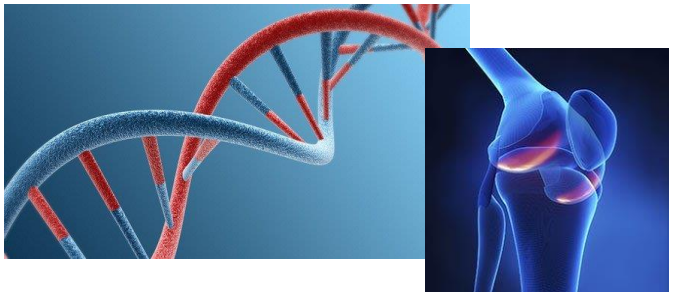
✓ Exhaustif : détection bactéries, virus, champignons, … → Technique à interpréter par concertation pluridisciplinaire
Technique réalisable sur toutes les natures de prélèvements

✗ Contamination : seuils à définir
Coût / Technique longue (5-10 jours)
Data management fastidieux : expertise en bioinformatique indispensable
Harmonisation des pratiques et des critères d'interprétation à encadrer par des recommandations d'experts pour le diagnostic des IOA → études en cours



BM

Place des techniques de BM pour le diagnostic des IOA/IOAP ?



- 2ème ligne après la culture (reste le *gold standard* en terme de sensibilité*)*
- Connaître les performances diagnostiques de chaque technique ainsi que les risques de FP/FN → discussion clinico-biologique
- Intérêt +++ en cas d'antibiothérapie préalable / d'infections à bactéries à croissance lente ou difficile
- Délai de rendu des résultats intéressant en fonction des techniques
- Augmentation du nombre de techniques → à évaluer en fonction des contextes cliniques (infections chroniques, sur prothèse, …)