Centre de Référence des Infections Ostéo-articulaires Complexes

CRIOAc LYON

Diagnostic rapide des infections de prothèse basés sur les biomarqueurs locaux et circulants : aujourd'hui… et demain?

Camille KOLENDA

Hôpital de la Croix Rousse – Institut des Agents Infectieux (IAI)

CIRI - Equipe « Pathogénie des infections à Staphylocoque » INSERM U1111

6ème journée régionale scientifique de formation et d'échange du CRIOAc LYON

10/04/2017

Hospices Civils de Lyon

CIRI

Infections de prothèse

Le diagnostic c’est pas si facile …

Clin Orthop Relat Res (2011) 469:2992–2994
DOI 10.1007/s11999-011-2102-9

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

SYMPOSIUM: PAPERS PRESENTED AT THE 2010 MEETING OF THE MUSCULOSKELETAL INFECTION SOCIETY

New Definition for Periprosthetic Joint Infection

From the Workgroup of the Musculoskeletal Infection Society

Définition MSIS

Javad Parvizi MD, Benjamin Zmistowski BS, Elie F. Berbari MD, Thomas W. Bauer MD, PhD, Bryan D. Springer MD, Craig J. Della Valle MD, Kevin L. Garvin MD, Michael A. Mont MD, Montri D. Wongworawat MD, Charalampos G. Zalavras MD

CRITERES MAJEURS

1) There is a sinus tract communicating with prosthesis; or — CLINIQUE

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:

CRITERES MINEURS

1) Elevated ESR and serum C-reactive protein (CRP) concentration — MARQUEURS SANGUINS

2) Elevated synovial leukocyte count
3) Elevated synovial neutrophil percentage — CYTOLOGIE

4) Presence of purulence in the affected joint — BACTERIOLOGIE

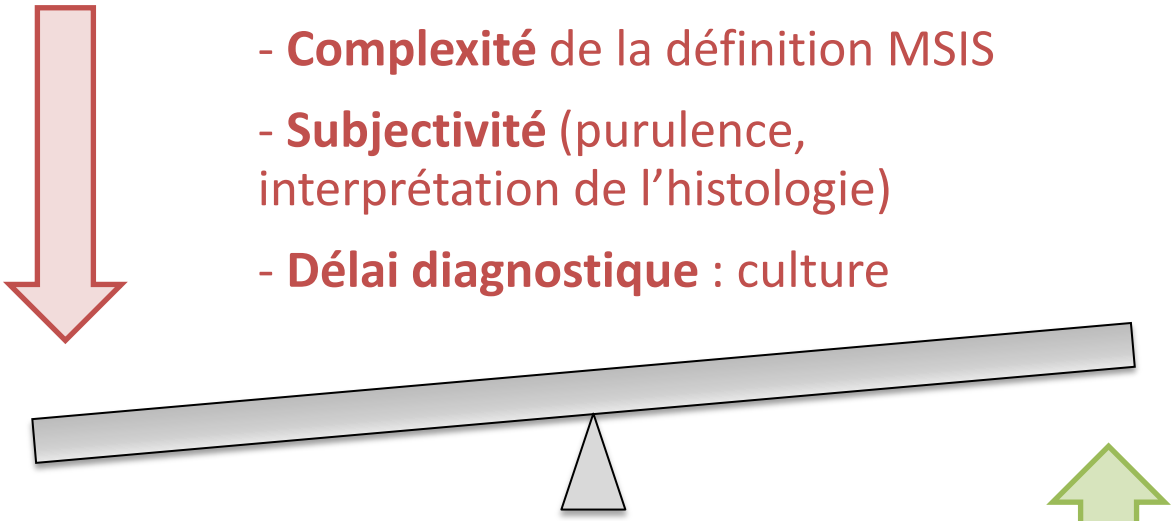
5) Isolation of a microorganism in one culture of periprosthetic tissue or fluid

6) Greater than five neutrophils per high-power field in five high-poweer fields observed from histologic analysis of periprosthetic tissue at x 400 magnification — ANAPATH

Challenge diagnostique

Difficultés cliniques

- Signes cliniques **aspécifiques**
- **Complexité** de la définition MSIS
- **Subjectivité** (purulence, interprétation de l'histologie)
- **Délai diagnostique** : culture



Biomarqueur

- Caractéristique **objectivement** mesurée, indicatrice de **processus biologiques** normaux ou pathologiques, ou de réponses pharmacologiques
- Marqueur idéal : **Exact**, **facile** d'utilisation, **rapide**

Biomarqueur : A quel moment dans la prise en charge ?

- **Préopératoire** : aide à la décision sur le type de chirurgie
- **Peropératoire** : écarter/affirmer rapidement une suspicion d'infection non envisagée avant la chirurgie
- **Postopératoire** : devant une culture négative, trancher entre infection ou contamination

Quels biomarqueurs doser ?

SANG : Marqueurs de l'inflammation

(GB, VS, CRP, PCT, IL-6)

LIQUIDE ARTICULAIRE : GB, CRP, cytokines, enzymes et peptides antimicrobiens

Inflammatory Blood Laboratory Levels as Markers of Prosthetic Joint Infection

A Systematic Review and Meta-Analysis

By Elie Berbari, MD, Tad Mabry, MD, Geoffrey Tsaras, MD, Mark Spangehl, MD, Pat J. Erwin, MLS, Mohammad Hassan Murad, MD, James Steckelberg, MD, and Douglas Osmon, MD

Marqueurs **peu coûteux**, résultat **rapide**

Métaanalyse de 30 études

Marqueur sanguin	Sensibilité	Spécificité
GB	45% (41-49)	87% (85-89)
VS	75% (72-77)	70% (68-72)
CRP	88% (86-90)	74% (71-76)

Les auteurs ne font pas d'analyse des critères de définition de l'infection de prothèse et d'exclusion des différents études

Pas de seuils d'interprétation proposés dans cette revue

- Variations importantes dans la littérature VS : 12-40 mm, CRP: 3-13,5 mg/L
- Variations hanche/genou ? infection précoce/tardive ?
- Définition MSIS : seuils arbitraires (CRP : 10mg/L, VS : 30mm/h)

Clin Orthop Relat Res (2013) 471:3186–3195
DOI 10.1007/s11999-013-3070-z

SYMPOSIUM: 2012 MUSCULOSKELETAL INFECTION SOCIETY

Diagnosis of Periprosthetic Joint Infection

The Threshold for Serological Markers

Pouya Alijanipour MD, Hooman Bakhshi MD,
Javad Parvizi MD, FRCS

Revision Arthroplasty 2000-2009 (2203)

180 patients excluded due to conditions that may affect ESR and CRP levels

Exclusion des patients avec des maladies inflammatoires chroniques

Aseptic Revisions (1689)

PJI Revisions (334)

Hips (1095)

Knees (594)

61 patients excluded due to inadequate MSIS criteria

Hips (108)

Knees (165)

Excluded for subgroup analysis due to unclear date of index surgery (9)

Excluded for subgroup analysis due to unclear date of index surgery (4)

Early-postoperative PJI (42)

Late-chronic PJI (57)

Early-postoperative PJI (42)

Late-chronic PJI (119)

Clin Orthop Relat Res (2013) 471:3186–3195
DOI 10.1007/s11999-013-3070-z

SYMPOSIUM: 2012 MUSCULOSKELETAL INFECTION SOCIETY

Diagnosis of Periprosthetic Joint Infection

The Threshold for Serological Markers

Pouya Alijanipour MD, Hooman Bakhshi MD, Javad Parvizi MD, FRCS

Variable/joint	Value*	Cutoff value	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
ESR									
Hips	80 (50–95)	48.5	0.91	78	90	57	96	7.8	0.24
Knees	90 (61–104)	46.5	0.93	87	87	56	97	6.7	0.15
CRP									
Hips	56 (21–85)	13.5	0.94	90	88	44	99	7.5	0.11
Knees	135 (42–222)	23.5	0.97	92	94	85	96	15.3	0.85
ESR + CRP									
Hips			0.91	75	84	21	98	4.7	0.30
Knees			0.96	89	85	55	97	5.9	0.13
ESR									
Hips and knees (early-postoperative PJI)	80 (51–100)	54.5	0.87	80	93	32	99	11.4	0.21
CRP									
Hips and knees (early-postoperative PJI)	131 (48–226)	23.5	0.95	87	94	41	99	14.5	0.14

Le seuil d'interprétation de la CRP dépend de l'articulation et du délai d'apparition de l'infection

The Journal of Arthroplasty 31 (2016) S152–S155

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

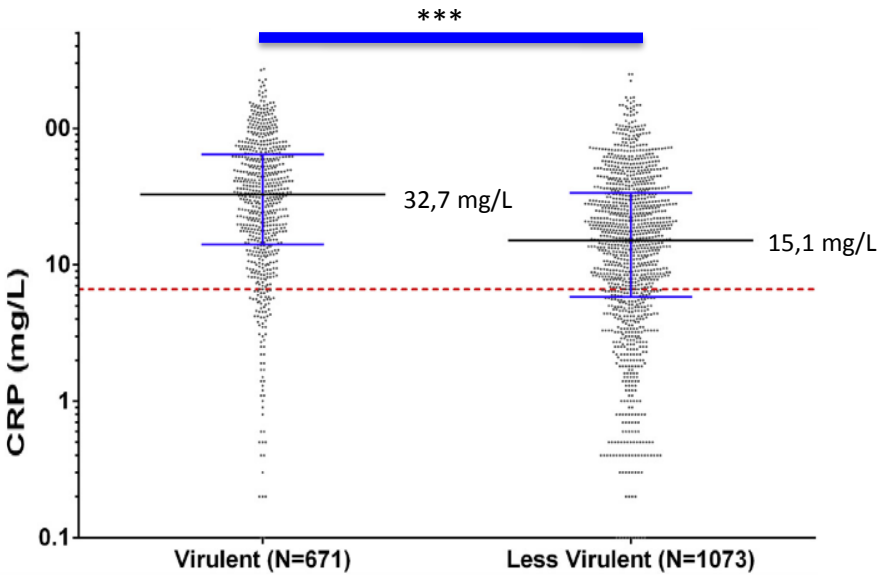
Complications - Infection

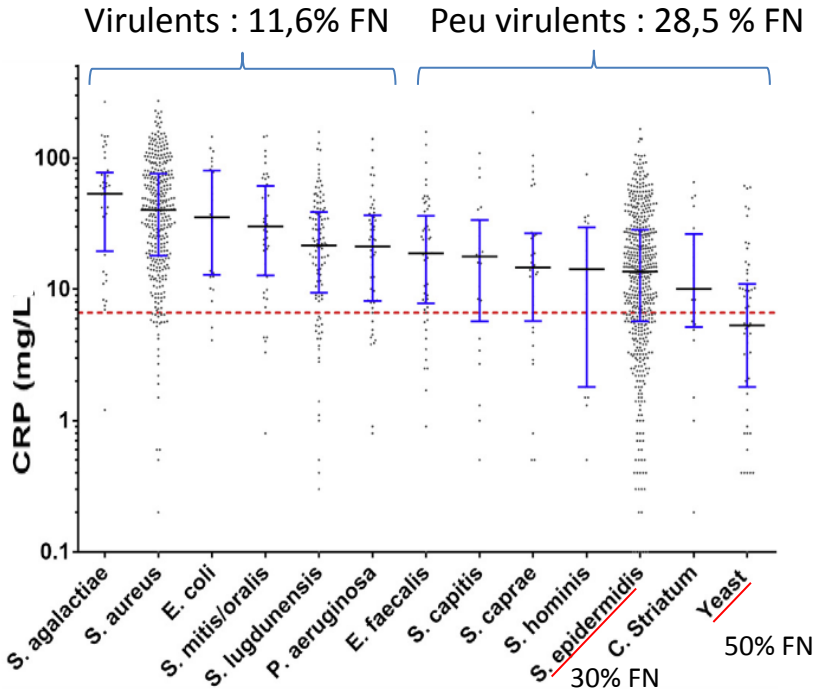
The C-Reactive Protein May Not Detect Infections Caused by Less-Virulent Organisms

Carl A. Deirmengian, MD [a, b, *], Patrick A. Citrano, BS [b], Simmi Gulati, MS [b], Erick R. Kazarian, MD [c], James W. Stave, PhD [b], Keith W. Kardos, PhD [b]

[a] The Rothman Institute, Thomas Jefferson University, The Lankenau Institute for Medical Research, Wynnewood, Pennsylvania
[b] CD Diagnostics, Claymont, Delaware
[c] University of Michigan Medical School, Ann Arbor, Michigan

Etude rétrospective : 1744 patients avec infection de prothèse avec culture du liquide synovial positive (monomicrobienne) et une valeur de CRP disponible





Le seuil d'interprétation de le CRP dépend de la virulence du germe

Clin Orthop Relat Res (2015) 473:2244–2249
DOI 10.1007/s11999-015-4142-z

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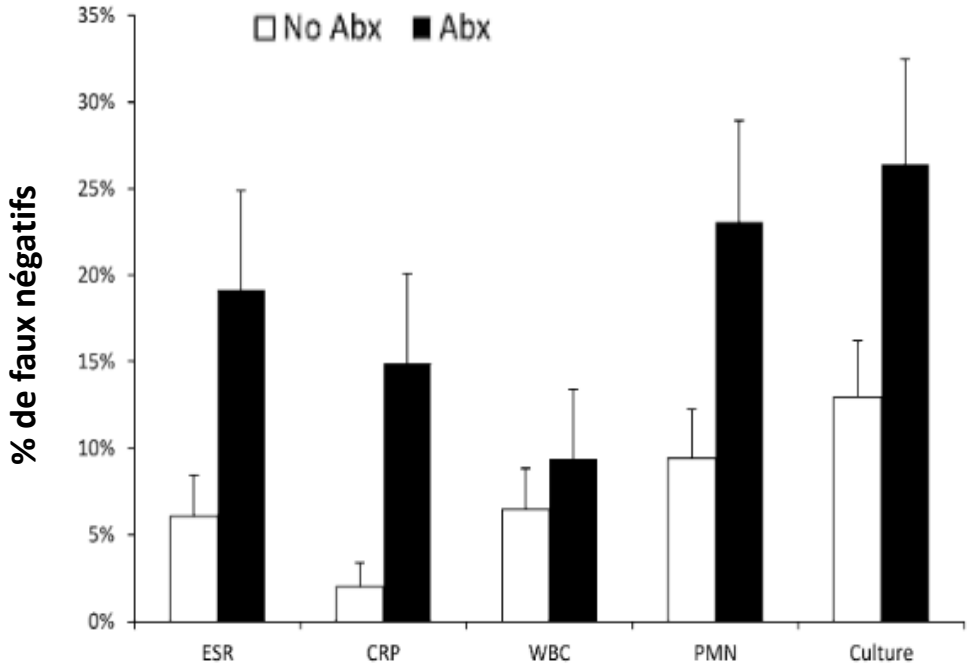
CrossMark

SYMPOSIUM: 2014 MUSCULOSKELETAL INFECTION SOCIETY

Premature Therapeutic Antimicrobial Treatments Can Compromise the Diagnosis of Late Periprosthetic Joint Infection

Alisina Shahi MD, Carl Deirmengian MD, Carlos Higuera MD,
Antonia Chen MD, MBA, Camilo Restrepo MD,
Benjamin Zmistowski MD, Javad Parvizi MD

Etude rétrospective : 182 patients avec infection sur prothèse chronique : 65 patients avec prise d'antibiotiques récente (< 2 semaines)



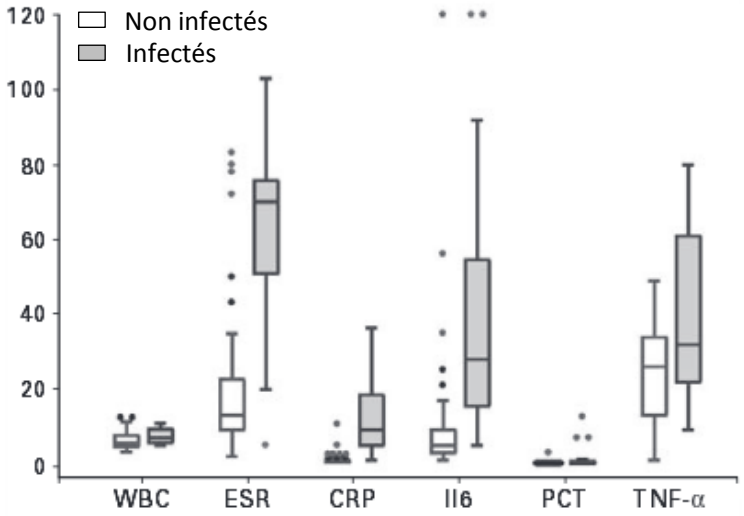
L'interprétation des marqueurs sanguins doit prendre en compte la prise récente d'antibiotiques

F. Bottner,
A. Wegner,
W. Winkelmann,
K. Becker,
M. Erren,
C. Götze

THE JOURNAL OF BONE & JOINT SURGERY (BR)

Interleukin-6, procalcitonin and TNF-α

MARKERS OF PERI-PROSTHETIC INFECTION FOLLOWING TOTAL JOINT REPLACEMENT



78 patients dont 21 infections de prothèse

Pas d'apport de la procalcitonine par rapport à la CRP : faible élévation en cas d'infection de prothèse, coût (20 €)

	White blood cells (1000/μl)	ESR within 60 minutes (mm)	CRP (mg/dl)	Interleukin-6 (pg/ml)	CRP (mg/dl) and interleukin-6 (pg/ml)	Procalcitonin (ng/ml)	TNF-α (ng/ml)
Cut-off level	≤ 6.2	≤ 32	≤ 3.2	≤ 12.0	(*)	≤ 0.3	≤ 40.0
Sensitivity	0.70	0.81	0.95	0.95	1.00	0.33	0.43
Specificity	0.60	0.89	0.96	0.87	0.86	0.98	0.94
Positive predictive value	0.40	0.74	0.91	0.74	0.72	0.87	0.75
Negative predictive value	0.86	0.93	0.98	0.98	1.00	0.80	0.85
Accuracy	0.63	0.87	0.96	0.89	0.90	0.81	0.83

Place du dosage des cytokines proinflammatoires : IL6 !??

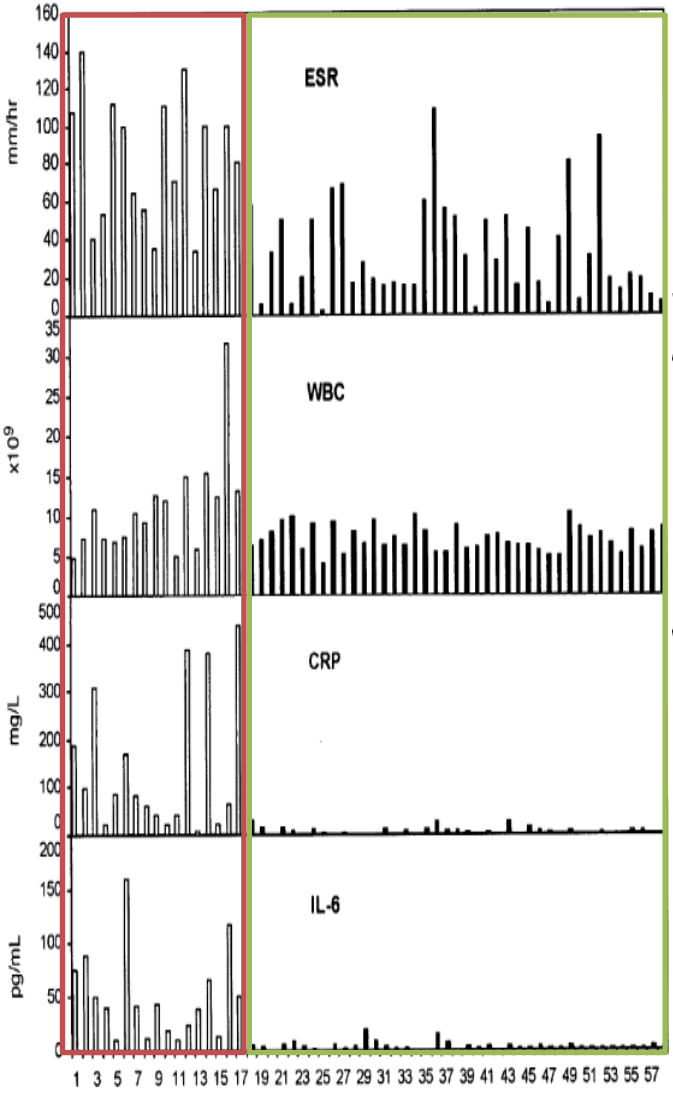
Serum Interleukin-6 as a Marker of Periprosthetic Infection Following Total Hip and Knee Arthroplasty

By Paul E. Di Cesare, MD, Eric Chang, BS, Charles F. Preston, MD, and Chuan-ju Liu, PhD

Investigation performed at the Musculoskeletal Research Center, NYU–Hospital for Joint Diseases, New York, NY

17 patients infectés

51 descellements aseptiques



Test*	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
ESR	1.00	0.56	0.49	1.00	69%
WBC	0.47	1.00	1.00	0.82	84%
CRP	0.94	0.78	0.64	0.97	83%
IL-6	1.00	0.95	0.89	1.00	97%

Exclusion des patients avec maladie inflammatoire chronique, prise récente d'antibiotique

IL-6 : seuil de 10 pg/mL déterminé arbitrairement

Intérêt clair dans cette étude du dosage de l'IL-6 par rapport à la CRP !

Quels biomarqueurs doser ?

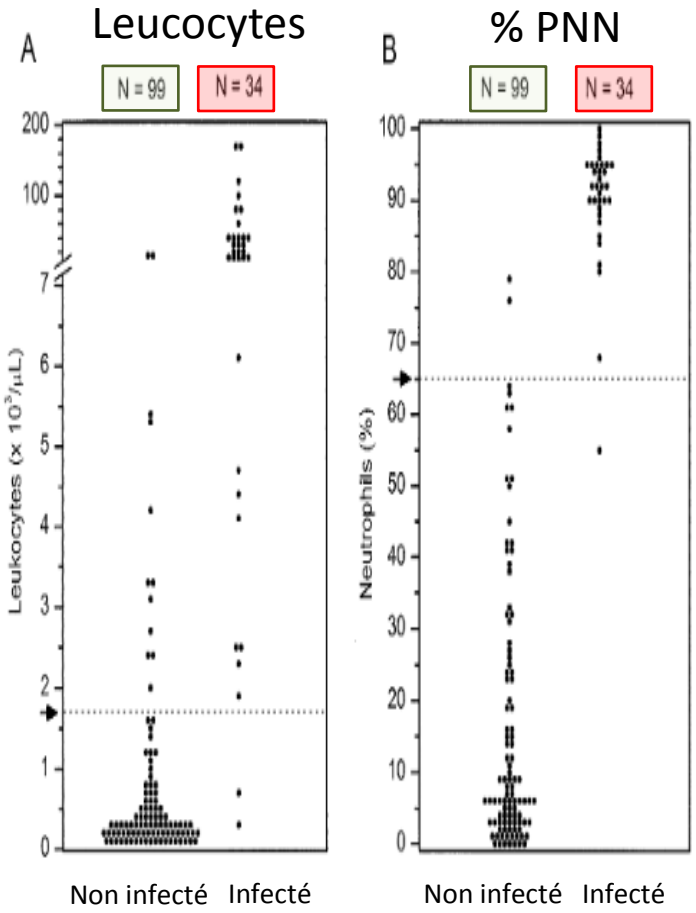
SANG : Marqueurs de l'inflammation

(GB, VS, CRP, PCT, IL-6)

LIQUIDE ARTICULAIRE : GB, CRP, cytokines, enzymes et peptides antimicrobiens

Synovial Fluid Leukocyte Count and Differential for the Diagnosis of Prosthetic Knee Infection

Andrej Trampuz, MD, Arlen D. Hanssen, MD, Douglas R. Osmon, MD, MPH,
Jayawant Mandrekar, PhD, James M. Steckelberg, MD, Robin Patel, MD



Characteristic	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
	Percentage (95% Confidence Interval)					
Cutoffs with optimal combination of sensitivity and specificity for diagnosing prosthetic joint infection in current report						
Leukocytes >1.7 X $10^3/\mu L$	94 (80–99)	88 (80–93)	73 (57–85)	98 (92–100)	8 (5–13)	0.1 (0.0–0.3)
Neutrophils >65%	97 (85–100)	98 (93–100)	94 (81–99)	99 (95–100)	48 (12–190)	0.0 (0.0–0.2)
Cutoffs used for diagnosing inflammatory joint disorders in native joints†						
Leukocytes >2 X $10^3/\mu L$	91 (76–98)	89 (81–94)	74 (58–86)	97 (91–99)	8 (5–15)	0.1 (0.0–0.3)
Neutrophils >75%	94 (80–99)	98 (93–100)	94 (80–99)	98 (93–100)	47 (12–184)	0.1 (0.0–0.2)
Cutoffs used for diagnosing septic arthritis in native joints†						
Leukocytes >50 X $10^3/\mu L$	21 (9–38)	100 (96–100)	100 (59–100)	79 (70–85)	∞	0.8 (0.7–0.9)
Neutrophils >90%	59 (41–75)	100 (96–100)	100 (83–100)	88 (80–93)	∞	0.4 (0.3–0.6)

Leucocytes et polynucléaires :
c'est pas si mal ! …

Clin Orthop Relat Res (2014) 472:3997–4003
DOI 10.1007/s11999-014-3828-y

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CLINICAL RESEARCH

Is Synovial C-reactive Protein a Useful Marker for Periprosthetic Joint Infection?

Matthew W. Tetreault MD, Nathan G. Wetters MD,
Mario Moric MS, Christopher E. Gross MD,
Craig J. Della Valle MD

Etude	Dosage	Technique	AUC	Seuil (mg/L)	Se (%)	Sp (%)	VPP (%)	VPN (%)	LA hémolysé (%)
Parvizi *et al*. 2012	Sang (n=66)	Immuno turbidimétrie (Beckman)	0,88	16,5	76	93	91	82	
	Liq. Art. (n=15/59)	ELISA unique /Mutiplex	**0,84/0,91**	**0,06/3,7**	**70/84**	**100/97**	**100/96**	**63/89**	
Vanderstappen *et al*. 2013	Sang (n=24)	Immuno turbidimétrie (Roche)	0,98	-	-	-	-	-	
	Liq. Art. (n=44)		**0,98**	**1,8/2,8**	**100/91**	**85/94**	**69/83**	**100/97**	45
Tetreault *et al*. 2014	Sang (n=119)	Immuno turbidimétrie (Abbott)	0,9	11,2	97	76	60	99	
	Liq. Art. (n=119)		**0,9**	**6,6**	**88**	**85**	**68**	**95**	15

- Forte corrélation entre la CRP plasmatique et synoviale
- Non réalisable si liquide visqueux, hémorragique

Faible valeur ajoutée de la CRP synoviale versus sang ?

Contents lists available at ScienceDirect

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journal homepage: www.arthroplastyjournal.org

Synovial IL-6 AS Inflammatory Marker in Periprosthetic Joint Infections

Markus Lenski, Cand. med. [a,b], Michael A. Scherer, Dr. med. [a]

[a] Department of Orthopedics and Trauma Surgery, Klinikum Dachau, Academic Teaching Hospital of the Ludwig-Maximilians-University of Munich, 7 Krankenhausstraße 15, 85221 Dachau, Germany

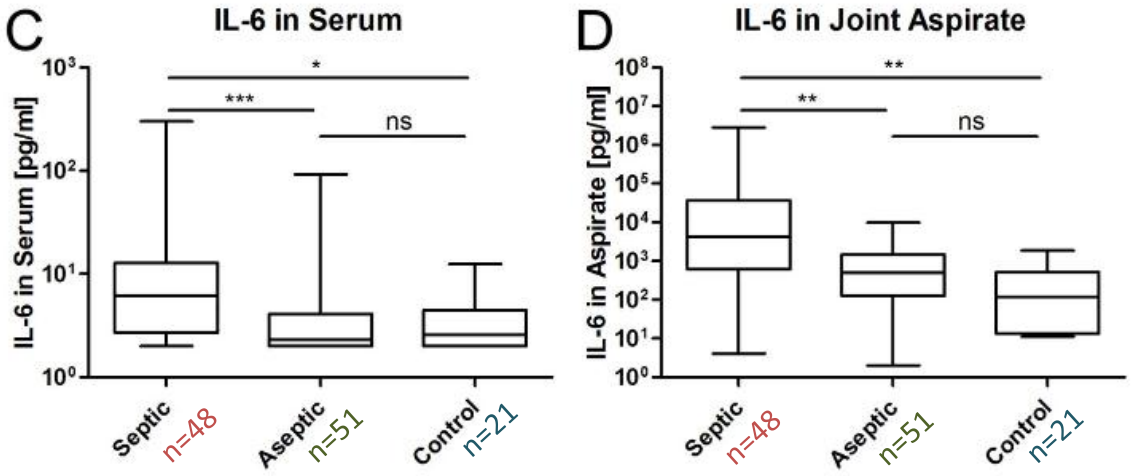
[b] Faculty of Medicine, Technical University of Munich, Munich, Germany

69 patients dont 31 infections de prothèse

	Number	Mean	AUC	Cutoff	SE	SP	+LR	−LR
IL-6 (pg/ml)	n = 22	308,099	0.959	30,750	90.9% (72.2–97.5)	94.7% (75.4–99.1)	17.27 (2.55–116.9)	0.10 (0.03–0.36)
Glucose (mg/dL)	n = 24	30.4	0.829	44.0	79.2% (59.5–90.8)	78.6% (60.5–89.8)	3.69 (1.77–7.73)	0.27 (0.12–0.59)
Lactate (mmol/L)	n = 21	12.8	0.844	8.3	71.4% (50.0–86.2)	88.0% (70.0–95.8)	5.95 (1.99–17.80)	0.33 (0.16–0.65)
SFWBC ($\times 10^3/\mu L$)	n = 25	69.6	0.807	23.0	60.0% (40.7–76.6)	94.3% (81.4–98.4)	10.50 (2.63–41.87)	0.42 (0.26–0.69)
LDH (U/l)	n = 25	4918	0.779	1423	84.0% (65.4–93.6)	62.1% (44.0–7.3)	2.22 (1.35–3.64)	0.26 (0.10–0.66)
CRP_{serum} (mg/dl)	n = 30	13.4	0.768	0.5	93.3% (78.7–98.2)	21.4% (10.2–39.5)	1.19 (0.96–1.47)	0.31 (0.07–1.42)
pWBC ($\times 10^3/\mu L$)	n = 30	11.1	0.676	11.5	40.0% (24.6–57.7)	83.9% (67.4–92.9)	2.48 (0.99–6.19)	0.72 (0.51–1.00)

Interleukin-6 in Serum and in Synovial Fluid Enhances the Differentiation between Periprosthetic Joint Infection and Aseptic Loosening


Thomas M. Randau[1,3], Max J. Friedrich[1,3], Matthias D. Wimmer[1], Ben Reichert[1], Dominik Kuberra[1], Birgit Stoffel-Wagner[2], Andreas Limmer[1], Dieter C. Wirtz[1], Sascha Gravius[1]*



Parameter	AUC (95% CI)	Cut-Off	Sensitivity (95% CI)	Specificity (95% CI)
WBC	0,63 (0,53 to 0,73)	10'300/µl	21,28% (10,70%–35,66%)	94,44% (86,38%–98,47%)
CRP	0,73 (0,64 to 0,83)	>9.1 mg/l	61,70% (46,38%–75,49%)	82,61 (71,59%–90,68%)
PCT	0,65 (0,51 to 0,80)	>46 ng/ml	12,90% (3,630%–29,83%)	100,0% (86,28%–100,0%)
IL-6 Serum	0,72 (0,61 to 0,83)	>2.6 pg/ml	79,49% (63,54%–90,70%)	58,33% (44,88%–70,93%
		>6.6 pg/ml	48,72% (32,42%–65,22%	88,33% (77,43%–95,18%)
IL-6 Joint Aspirate	0,76 (0,64 to 0,88)	>2100 pg/ml	62,50% (43,69%–78,90%)	85,71% (71,46%–94,57%
		>9000 pg/ml	46,88% (29,09%–65,26%)	97,62% (87,43%–99,94%)

Même technique, deux seuils bien différents !

	Number	Mean	AUC	Cutoff	SE	SP
IL-6 (pg/ml)	n = 22	308,099	0.959	30,750	90.9% (72.2–97.5)	94.7% (75.4–99.1)

Faible valeur ajoutée de l'IL6 synoviale versus sang ? ?

Clin Orthop Relat Res (2010) 468:2017–2023
DOI 10.1007/s11999-010-1298-4

SYMPOSIUM: PAPERS PRESENTED AT THE 2009 MEETING OF THE MUSCULOSKELETAL INFECTION SOCIETY

Synovial Fluid Biomarkers for Periprosthetic Infection

Carl Deirmengian MD, Nadim Hallab PhD,
Abdul Tarabishy MD, Craig Della Valle MD,
Joshua J. Jacobs, Jess Lonner MD, Robert E. Booth Jr MD

Approche « multiplex » : Evaluation de 23 marqueurs dans le liquide synovial (51 patients dont 14 infections de prothèse)

Biomarker or variable	Fold-elevation	Cutoff value	Spec.	Sens.	PPV	NPV	ACC
IL-1b	258	112 pg/ml	1.00	1.00	1.00	1.00	1.00
IL-6	27	13350 pg/ml	1.00	1.00	1.00	1.00	1.00
G-CSF	120	35 pg/ml	0.95	1.00	0.88	1.00	0.96
IL-1a	24	1 pg/ml	0.97	0.86	0.92	0.95	0.94
IL-17	112	7.2 pg/ml	0.97	0.86	0.92	0.95	0.94
SKALP	2	1880 pg/ml	0.89	0.79	0.73	0.92	0.86
SF WBC	31	2000 cells/mm^3	0.84	0.93	0.68	0.97	0.86
CRP	13	10 mg/l	0.86	0.71	0.67	0.89	0.82
% Segs	2	65	0.73	1.00	0.58	1.00	0.80
ESR	3	30 mm/hr	0.73	0.86	0.55	0.93	0.76

IFN-g	Interferon ga[illegible]	2.0	0.168
FGF-Basic	Fibroblast gr[illegible]		0.0012*
IL-1ra	Interleukin 1		0.0054
IL-4	Interleukin 4	1.3	0.336
VEGF	Vascular endothelial growth factor	1.3	0.0302
Tpo	Thrombopoietin	1.2	0.1019
MCP-1	Monocyte chemotactic protein 1	0.8	0.3185
Rantes	Regulated upon Activation, Normal T-cell Expressed, and Secreted	0.7	0.4706
SLPI	Secretory leukocyte peptidase inhibitor	0.6	N/A

6 protéines se détachent …

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

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SYMPOSIUM: 2013 MUSCULOSKELETAL INFECTION SOCIETY

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

Evaluation de 43 marqueurs dans le liquide synovial d'un petit groupe de patients,
→ **16 marqueurs préselectionnés**
→ **testés sur 95 patients** (29 infections de prothèse)

Proteins passing screen (n = 16)	Proteins failing screen (n = 27)
Human α-defensin 1-3	Procalcitonin
Interleukin 1α	Transforming growth factor α
Interleukin 1β	Cathelicidin (LL-37)
Interleukin 6	Lipopolysaccharide binding protein
Interleukin 8	Calcitonin gene-related peptide
Interleukin 10	Orsomucoid
Interleukin 17	Nibrin
Granulocyte colony-stimulating factor	Tumor necrosis factor-stimulated gene 6 protein
Vascular endothelial growth factor	Plekstrin
C-reactive protein	Superoxide dismutase 2
Neutrophil elastase 2	Urokinase
Lactoferrin	Migration inhibitory factor
Neutrophil gelatinase-associated lipocalin	Plasminogen activator inhibitor type 1
Resistin	Soluble Fas
Thrombospondin 1	Soluble Fas ligand
Bactericidal/permeability-increasing protein	Soluble intercellular adhesion molecule 1
	Soluble vascular cell adhesion molecule 1
	Granzyme B
	Heat shock protein 70
	Macrophage inflammatory protein 1α
	Macrophage inflammatory protein 1β
	Matrix metalloproteinase 8
	Tumor necrosis factor α
	Interferon-γ inducible protein
	Fibroblast growth factor 2
	α-2 macroglobulin
	Skin-derived antileukoprotease

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

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SYMPOSIUM: 2013 MUSCULOSKELETAL INFECTION SOCIETY

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

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

5 protéines humaines ”anti-bactériennes” avec sensibilité, spécificité = 100% dans cette population

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

Clinical Orthopaedics and Related Research®
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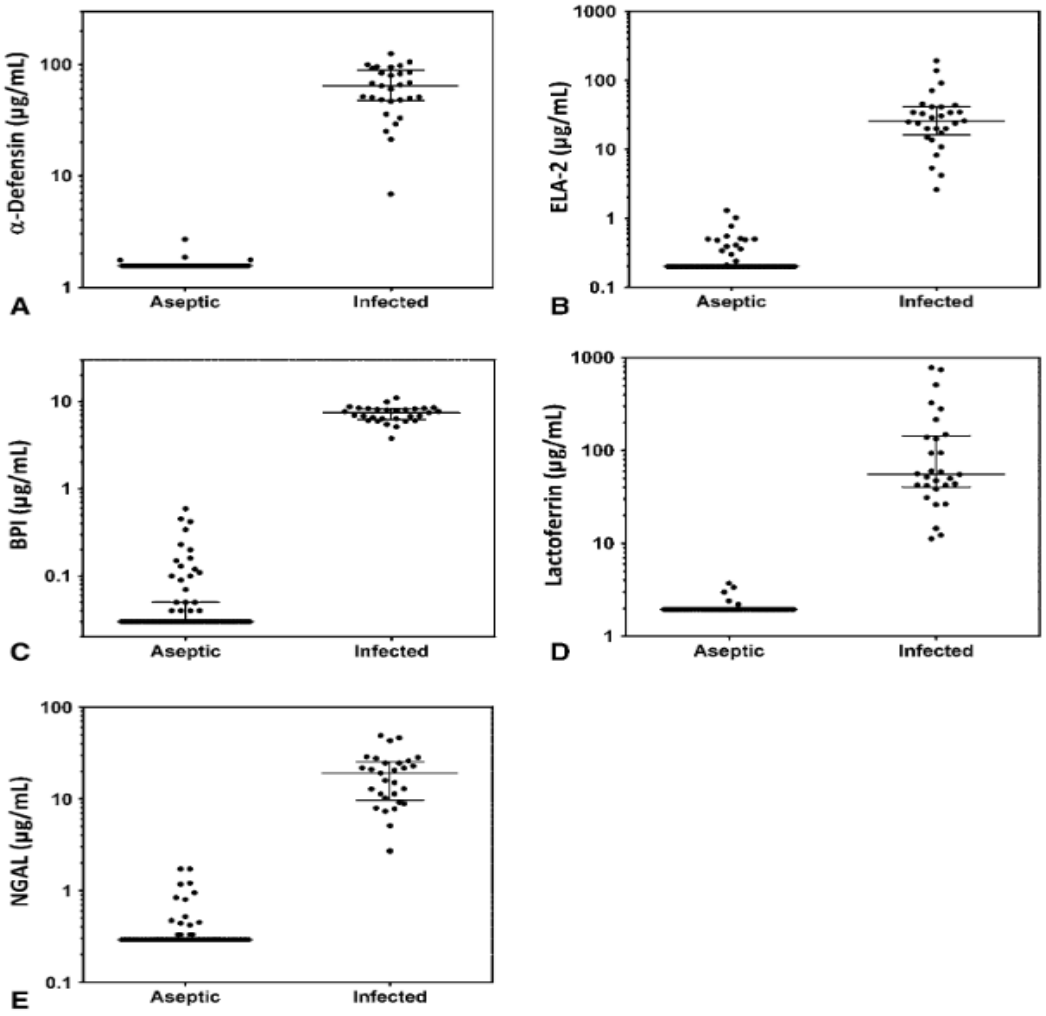


Pas de corrélation entre ces marqueurs et ceux de l'inflammation

mécanisme de régulation différent et indépendant de l'inflammation ?

Alpha-defensine

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]

The Journal of Arthroplasty 31 (2016) 456–460

78 prélèvements dont 24 infections de prothèse.

Sensibilité : 100%, Spécificité : 98%

The Alpha Defensin-1 Biomarker Assay can be Used to Evaluate the Potentially Infected Total Joint Arthroplasty

Joshua Bingham MD, Henry Clarke MD, Mark Spangehl MD, Adam Schwartz MD, Christopher Beauchamp MD, Brynn Goldberg RN

Clin Orthop Relat Res (2014)

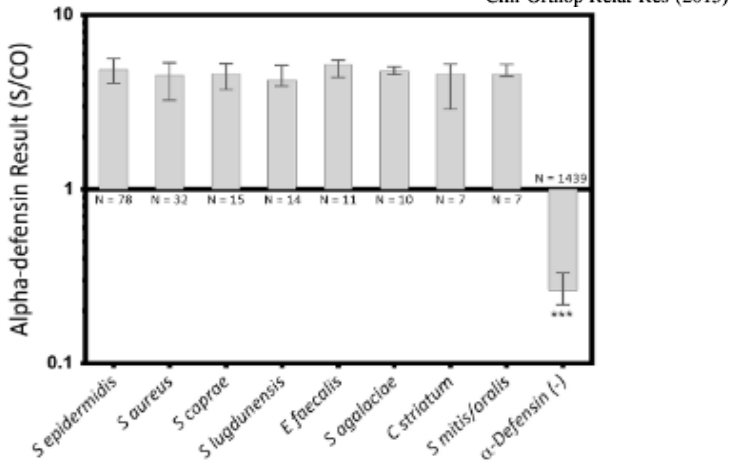
61 prélèvements dont 19 infections de prothèse.

Sensibilité : 100%, Spécificité : 95%

The Alpha-defensin Test for Periprosthetic Joint Infection Responds to a Wide Spectrum of Organisms

Carl Deirmengian MD, Keith Kardos PhD, Patrick Kilmartin MS, Simmi Gulati MS, Patrick Citrano BS, Robert E. Booth Jr MD

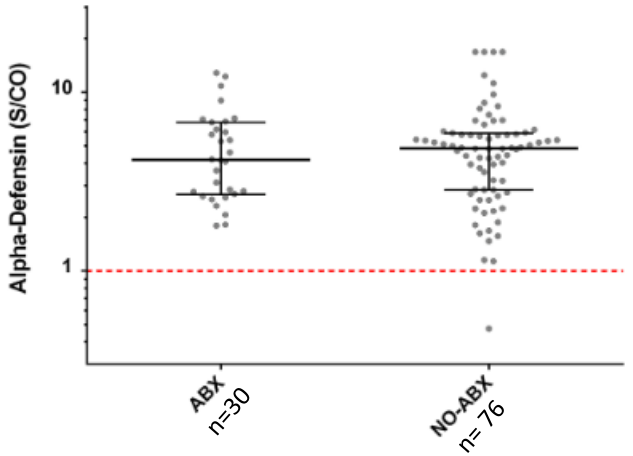
Clin Orthop Relat Res (2015)



The Alpha-defensin Test for Periprosthetic Joint Infections Is Not Affected by Prior Antibiotic Administration

Alisina Shahi MD, Javad Parvizi MD, FRCS, Gregory S. Kazarian AB, Carlos Higuera MD, Salvatore Frangiamore MD, Joshua Bingham MD, Christopher Beauchamp MD, Craig Della Valle MD, Carl Deirmengian MD

Clin Orthop Relat Res (2016)



Alpha-defensine – Test qualitatif

Test rapide, utilisable au bloc ?

Prix du test : 300 €

→ Pour quels patients le proposer ?

THE BONE & JOINT JOURNAL

■ ARTHROPLASTY

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

Sigmund IK et al. Bone Joint J 2017

49 patients (dont 13 infections de prothèse)

Diversité des procédures chirurgicales : dosage avant changement de prothèse, changement spacer, 2ème temps de changement de prothèse

Sensibilité : 69%, Spécificité : 94%

Diagnosis of Periprosthetic Joint Infection: The Utility of a Simple Yet Unappreciated Enzyme

Javad Parvizi, MD, FRCS, Christina Jacovides, BS, Valentin Antoci, MD, PhD, and Elie Ghanem, MD

Investigation performed at the Rothman Institute of Orthopedics at Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Rapide, faible coût, bonne reproductibilité

108 patients dont 30 infections de prothèse

	Knees Undergoing Arthroplasty (N = 108)	
	Positive = ++	Positive = + or ++
Sensitivity	80.6 (61.9-91.9)	93.5 (77.2-98.8)
Specificity	100 (94.5-100)	86.7 (77.1-92.9)
Positive predictive value	100 (83.4-100)	72.5 (55.9-84.9)
Negative predictive value	93.3 (85.4-97.2)	97.3 (89.7-99.5)

*Values are given as percentages, with the 95% confidence interval in parentheses.

Prix du test : 0.2 € !!!

- **-/traces : infection très peu probable ; ++ : infection très probable**
- Mais non utilisable si prélèvement hémorragique, subjectivité de l'interprétation

THE BONE & JOINT JOURNAL

■ SPECIALTY UPDATE: ARTHROPLASTY

Proceedings of the International Consensus on Periprosthetic Joint Infection

Bone Joint J 2013

J. Parvizi,
T. Gehrke,
A. F. Chen

From The Rothman Institute, Philadelphia, Pennsylvania, United States

Vers une indication en routine de ce marqueur ?

International Consensus Group (ICG) on PJI * (2)
One of the following **major criteria** must be met for diagnosis of PJI: 1. Two positive periprosthetic cultures with phenotypically identical organisms, or 2. A sinus tract communicating with the joint, or **Three** of the following **five minor criteria** must be met for the diagnosis of PJI: 1. Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR) 2. Elevated synovial fluid white blood cell (WBC) count OR ++ change on leukocyte esterase test strip 3. Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) 4. Positive histological analysis of periprosthetic tissue 5. A single positive culture

Pèle-mêle

SYNOVIAL CALPROTECTIN: A RAPID TEST TO DIAGNOSE A PROSTHETIC JOINT INFECTION

EBJIS 2016

M. Wouthuyzen-Bakker, J. Ploegmakers, G. Kampinga, P. Jutte, A. Muller Kobold

34 patients : Sensibilité 93% , Spécificité 84%

Lipopolysaccharide-binding protein: A valuable biomarker in the differentiation between periprosthetic joint infection and aseptic loosening?

Max J. Friedrich · Thomas M. Randau · Matthias D. Wimmer · Ben Reichert · Dominik Kuberra · Birgit Stoffel-Wagner · Dieter C. Wirtz · Sascha Gravius

120 patients : Sensibilité 66% , Spécificité 71%

JCM

Toll-Like Receptor 2 in Serum: a Potential Diagnostic Marker of Prosthetic Joint Infection?

Emanuela Galliera,[a,b] Lorenzo Drago,[b,c] Christian Vassena,[b] Carlo Romanò,[b] Monica Gioia Marazzi,[c] Lucia Salcito,[c] Massimiliano M. Corsi Romanelli[c,d]

60 patients

Oppegaard et al. BMC Infectious Diseases 2013, 13:278
http://www.biomedcentral.com/1471-2334/13/278

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

CD64 as a potential biomarker in septic arthritis

Oddvar Oppegaard[1*†], Brita Skodvin[1†], Anne-Kristine Halse[2] and Nina Langeland[3]

90 patients

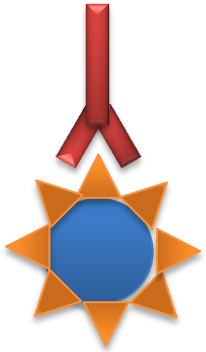
AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Multiplex Antibody Detection for Noninvasive Genus-Level Diagnosis of Prosthetic Joint Infection

Simon Marmor,[a] Thomas Bauer,[b] Nicole Desplaces,[c] Beate Heym,[d,e] Anne-Laure Roux,[d,e] Olivier Sol,[f] Julie Rogé,[f] Florence Mahé,[f] Laurent Désiré,[f] Philippe Aegerter,[g] Idir Ghout,[g] Jacques Ropers,[g] Jean-Louis Gaillard,[d,e] Martin Rottman[e,h]

Service de Chirurgie Orthopédique, Groupe Hospitalier Diaconesses Croix Saint-Simon, Paris, France[a]; Service de Chirurgie Orthopédique et Traumatologie, Hôpital Ambroise Paré (Assistance Publique–Hôpitaux de Paris [AP-HP]), Boulogne-Billancourt, France[b]; Service de Microbiologie, Groupe Hospitalier Diaconesses Croix Saint-Simon, Paris, France[c]; Laboratoire de Microbiologie, Hôpital Ambroise Paré (AP-HP), Boulogne-Billancourt, France[d]; UMR 1173, UFR Simone Veil, Université de Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France[e]; DIAXONHIT, Paris, France[f]; Unité de Recherche Clinique Paris Île-de-France Ouest, Hôpital Ambroise Paré (AP-HP), Boulogne-Billancourt, France[g]; Laboratoire de Microbiologie, Hôpital Raymond Poincaré (AP-HP), Garches, France[h]

Test : 16 antigènes coatés sur des billes pour détecter IgG anti *S. aureus*, *S. epidermidis*, *S. lugdunensis*, *S. agalactiae* et *P. acnes*
455 patients dont 176 infections de prothèse



	All cases	
Organism(s)	Sensitivity	Specificity
Staphylococci targeted	68/94 (72.3) [62.7–80.7]	213/264 (80.7) [75.6–85.1]
S. aureus	36/54 (66.7) [53.4–78.2]	
S. epidermidis	26/35 (74.3) [58–86.7]	
S. lugdunensis	9/9 (100) [71.7–100]	
S. agalactiae	6/8 (75) [38.8–95.6]	250/270 (92.6) [89–95.3]
P. acnes	5/13 (38.5) [15.7–65.9]	235/277 (84.8) [80.2–88.7]

- **40 % des patients de cette étude infectés par des germes non ciblés par ce test**
- **Effectifs réduits pour *S. agalactiae*, *P. acnes***

Vers la combinaison de plusieurs biomarqueurs ?

F. Bottner,
A. Wegner,
W. Winkelmann,
K. Becker,
M. Erren,
C. Götze

THE JOURNAL OF BONE & JOINT SURGERY (BR)

Interleukin-6, procalcitonin and TNF-α

MARKERS OF PERI-PROSTHETIC INFECTION FOLLOWING TOTAL JOINT REPLACEMENT

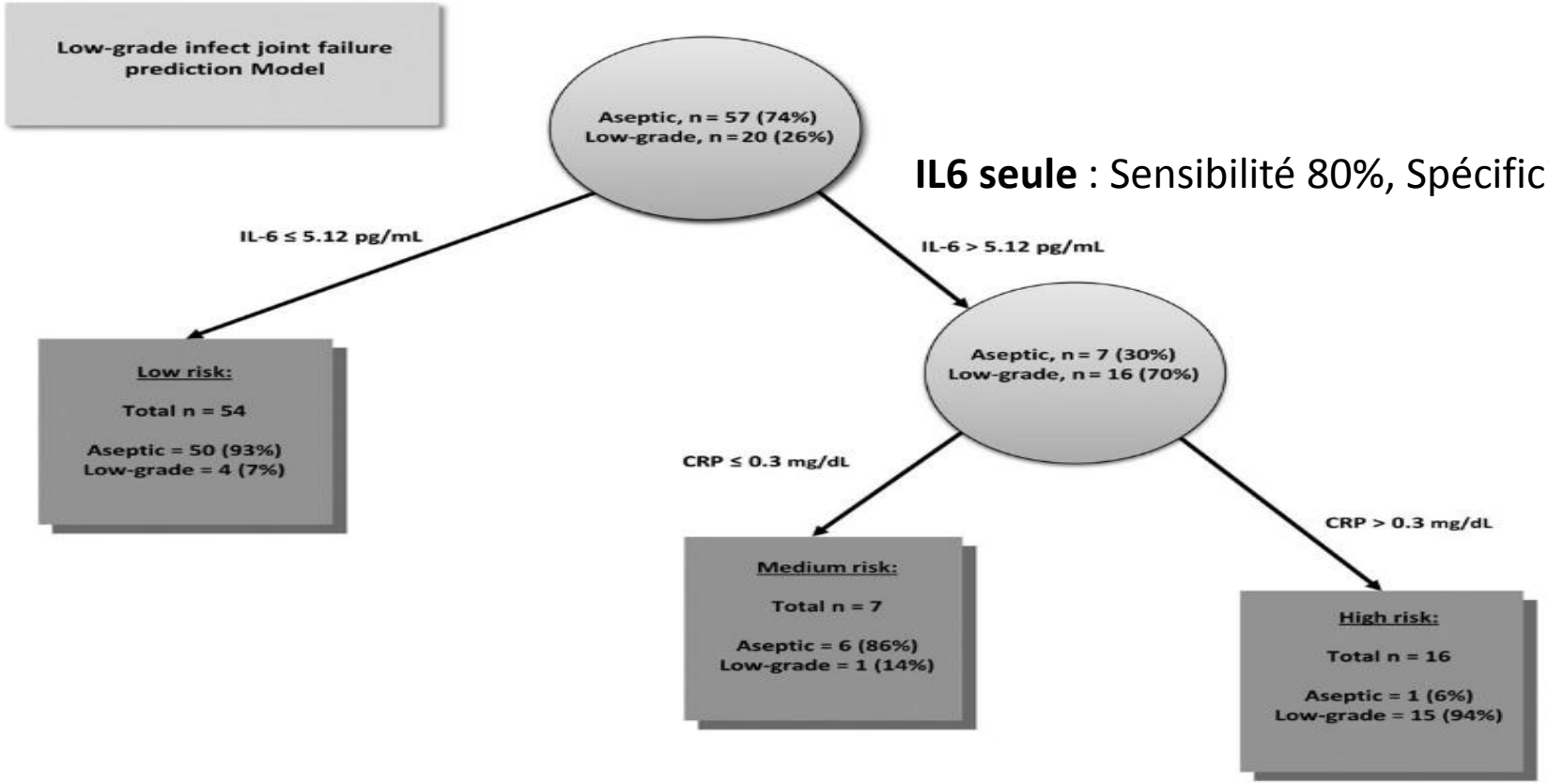
	White blood cells (1000/μl)	ESR within 60 minutes (mm)	CRP (mg/dl)	Interleukin-6 (pg/ml)	CRP (mg/dl) and interleukin-6 (pg/ml)	Procalcitonin (ng/ml)	TNF-α (ng/ml)
Cut-off level	≤ 6.2	≤ 32	≤ 3.2	≤ 12.0	(*)	≤ 0.3	≤ 40.0
Sensitivity	0.70	0.81	0.95	0.95	1.00	0.33	0.43
Specificity	0.60	0.89	0.96	0.87	0.86	0.98	0.94
Positive predictive value	0.40	0.74	0.91	0.74	0.72	0.87	0.75
Negative predictive value	0.86	0.93	0.98	0.98	1.00	0.80	0.85
Accuracy	0.63	0.87	0.96	0.89	0.90	0.81	0.83

MAJOR ARTICLE

Circulating Biomarkers for Discrimination Between Aseptic Joint Failure, Low-Grade Infection, and High-Grade Septic Failure

Max Ettinger,[1] Tilman Calliess,[1] Jan T. Kielstein,[2] Jasmin Sibai,[1] Thomas Brückner,[1] Ralf Lichtinghagen,[3] Henning Windhagen,[1] and Alexander Lukasz[2,4]

[1]Department of Orthopaedic Surgery, [2]Department of Nephrology and Hypertension, [3]Department of Laboratory Medicine, Hannover Medical School, and [4]Department of Medicine D, Division of General Internal Medicine, Nephrology, and Rheumatology, University Hospital Münster, Germany

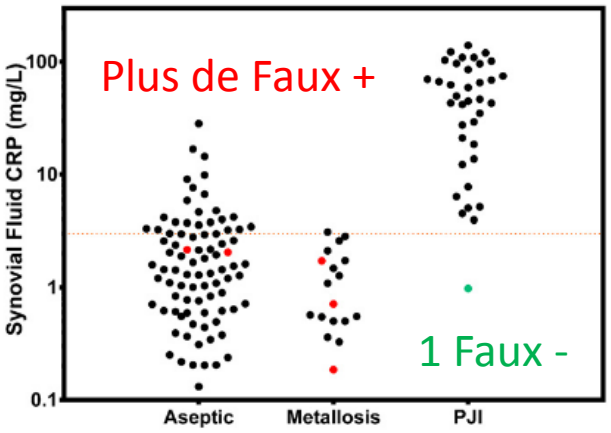


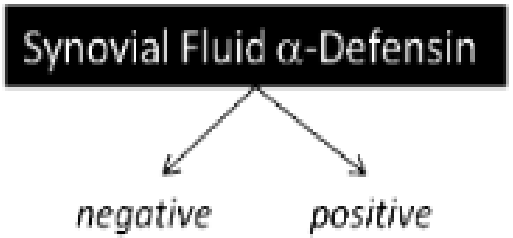
IL6 seule : Sensibilité 80%, Spécificité 87,7 %

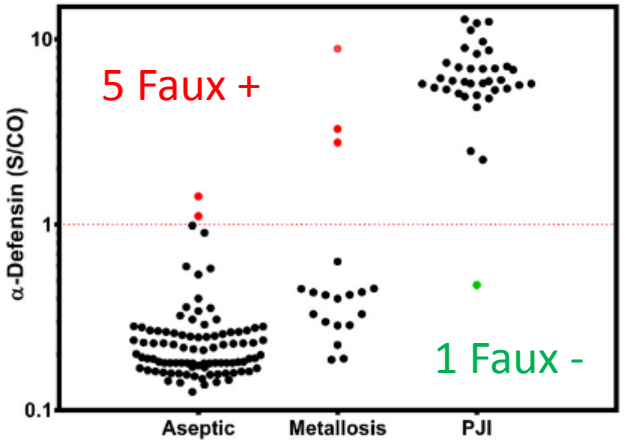
IL6 > 5,12 pg/mL + CRP > 3 mg/L :
Sensibilité 75%, Spécificité 98,2 %

Combined Measurement of Synovial Fluid α-Defensin and C-Reactive Protein Levels: Highly Accurate for Diagnosing Periprosthetic Joint Infection

Carl Deirmengian, MD, Keith Kardos, PhD, Patrick Kilmartin, MSc, Alexander Cameron, BS, Kevin Schiller, BS, and Javad Parvizi, MD, FRCS







Sensibilité : 97,3% , Spécificité 95,5%

Algorithme : Analyse de la sCRP
si αdefensine +

Sensibilité : 97,3% , **Spécificité 100%**

Limites de ces études

- La **définition d'une infection de prothèse** parait facile … pourtant sans gold standard
- Populations **hétérogènes** :
  - Critères de définition de l'infection de prothèse
  - Articulation
  - Infection précoce/tardive
  - Critères d'exclusion (maladie inflammatoire chronique, traitement antibiotique antérieur etc.)
- **Peu d'études multicentriques**
- **Techniques** différentes, **seuils** différents
- Nombre de patients limité, avec données manquantes

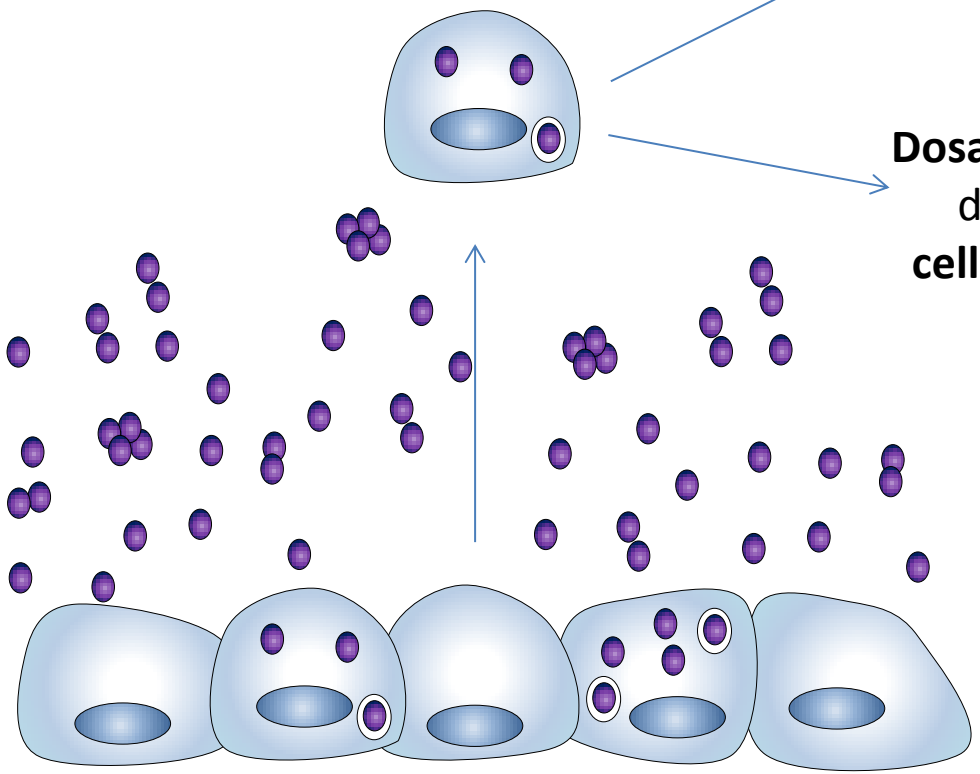
Place en routine des marqueurs synoviaux ?

- Coût (bandelette ”urinaire” : 0.2€, CRP : 2.4€, IL6 : 38€, alpha-défensine : 300€)
- Quand ? Quel délai pour le résultat ?
  - Préopératoire : nécessité de prélever le liquide synovial, résultat doit être obtenu rapidement
  - Peropératoire : test directement au bloc ?
  - Postopératoire : conservation de l’échantillon, stabilité du biomarqueur
- Pas chez tous les patients !

Recherche de nouveaux biomarqueurs *in vitro*

Biomarqueurs de la composante intracellulaire

Sélection des cellules infectées



Ostéoblastes en culture

ARNm

Etude de l'expression des ARNm (RNAseq) des cellules infectées/non infectées

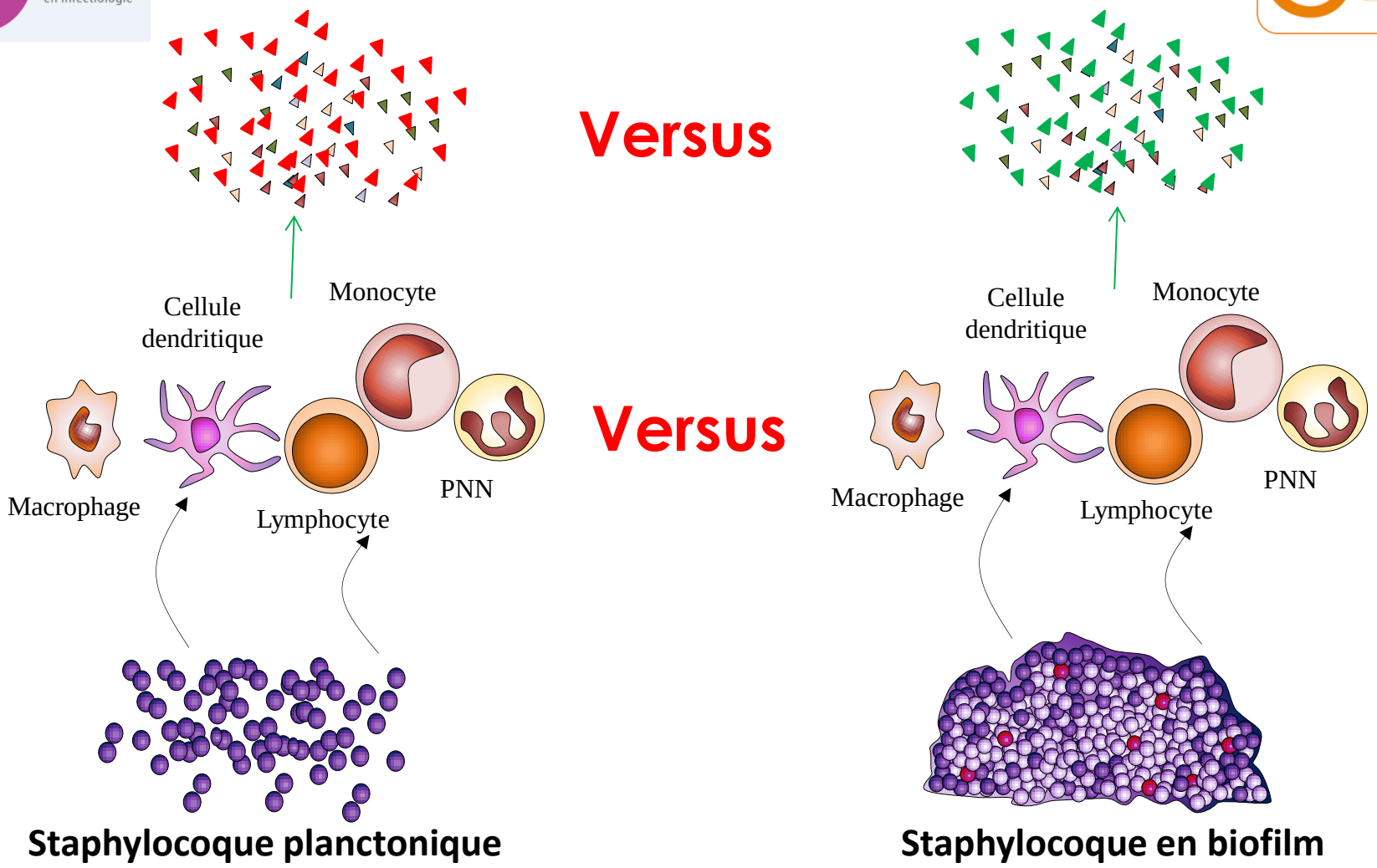
Dosage des protéines correspondant aux ARNm d'intérêt dans les **surnageants de culture cellulaire** (*in vitro*), **liquide articulaire** (*in vivo*)

Recherche de nouveaux biomarqueurs *in vitro*

Centre International de Recherche en Infectiologie

CRIOAc LYON

Biomarqueurs d'activation immunitaire / cellulaire



Conclusion

- Des biomarqueurs **prometteurs** : leucocyte estérase, alphadéfensine …
  - Peu invasifs
  - Rapides
- **Manque d'études bien conduites**
- Biomarqueurs encore à évaluer dans le cadre d'**études multicentriques**
- Evaluation de la place de **combinaison de biomarqueurs** : algorithmes décisionnels/mathématiques
- **Nouvelles approches** : transcriptomique, protéomique

Elément central du diagnostique reste pour l'instant la **clinique** …

sans négliger la **microbiologie** (60-70% de documentation, obtenir l'antibiogramme)

MERCI POUR VOTRE ATTENTION