

Synovial fluid biomarkers and the diagnosis of implant related joint infections

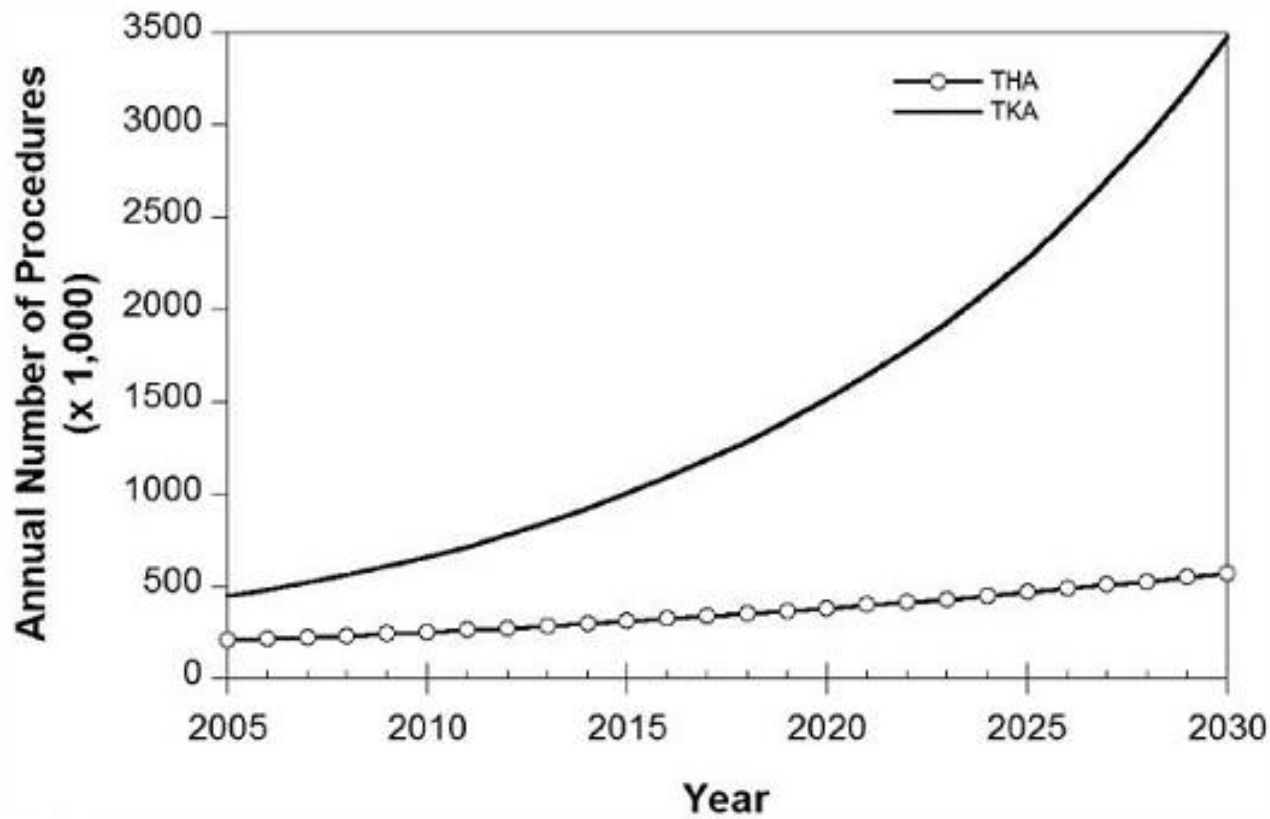
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The projected number of primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures in the United States from 2005 to 2030.

Kurtz SJ. Bone Joint Surg Am 2007;89: 780 -5.

Ambiguous diagnosis of PJI



Measurement of markers in **synovial fluid** probably provide the most accurate reflection of the current status of “arthritis” in any one joint.



Synovial Fluid Biomarkers for periprosthetic infection



- ❑ Prospective
- ❑ 51 revisions: 14 PJI and 37 “non infected”
- ❑ 23 biomarkers were tested by immunoassay

Results

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
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
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
ESR	3	30 mm/hr	0.73	0.86	0.55	0.93	0.76

Serum IL6 5-150 pg/ml

Synovial IL6 1 5k-130k pg/ml 1000x amplified at the local source

* Generally very labile, hence samples need to be tested ideally within 1 hr!!



Deirmengian *et al.* Clin Orthop Relat Res. 2010; 468: 2017-2023

THE FEDERATION OF INFECTION SOCIETIES ANNUAL CONFERENCE 2013

Molecular diagnostics in periprosthetic joint infection

- ❑ Prospective
- ❑ 74 revision T H/K R (31 PJI and 43 non-infected)
- ❑ 46 protein were tested from each synovial fluid

Parvizi *et al.* International Journal of Artificial Organs 2011;34: 847-855



AUC ANALYSIS OF MOLECULAR MARKERS IN SYNOVIAL FLUID

AUC between 0.7-0.79	AUC between 0.80-0.89	AUC between 0.9-0.99
<ul style="list-style-type: none"> · interleukin (IL)-1 receptor antagonist · IL-1β · IL-5 · tumor necrosis factor (TNF)-α · TNF receptor-like 2 · Macrophage inflammatory protein-1β · β-2 microglobulin · Vascular cell adhesion molecule-1 	<ul style="list-style-type: none"> · interferon-γ · TNF-β · von Willebrand factor · matrix metalloproteinase-3 · tissue inhibitor of metalloproteinase-1 	<ul style="list-style-type: none"> · IL-6 (AUC = 0.95) · IL-8 (AUC = 0.94) · CRP (AUC = 0.92) · α-2 macroglobulin (AUC = 0.92) · Vascular Endothelial Growth Factor (VEG-F) (AUC = 0.90)

46 Proteins tested

5 Proteins with AUC > 0.9

IL-6, IL-8, α 2-macroglobulin, CRP, VEGF



Leukocyte esterase

- Using a simple colorimetric strip test, prior to arthrotomy

SUBJECTIVE



Leukocyte esterase strip test showing negative, trace, +, and ++ readings.

Ability of Leukocyte Esterase to Diagnose Periprosthetic Joint Infection Intraoperatively and in the Clinic Setting*

30 PJI & 78 aseptic loosening (r TKA) (N = 108)

Knees Evaluated in the Clinic (N = 17)

	Positive = ++	Positive = + or ++	Positive = ++	Positive = + or ++
Sensitivity	80.6 (61.9-91.9)	93.5 (77.2-98.8)	80.0 (29.9-98.9)	100 (46.3-100)
Specificity	100 (94.5-100)	86.7 (77.1-92.9)	100 (69.9-100)	41.7 (16.5-71.4)
Positive predictive value	100 (83.4-100)	72.5 (55.9-84.9)	100 (39.6-100)	41.7 (16.5-71.4)
Negative predictive value	93.3 (85.4-97.2)	97.3 (89.7-99.5)	92.3 (62.1-99.6)	100 (46.3-100)

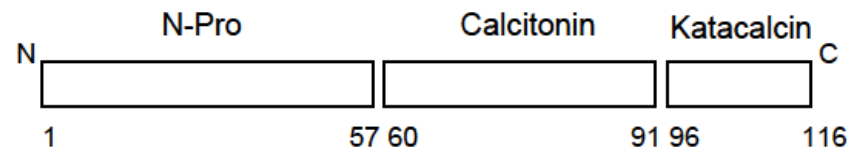
*Values are given as percentages, with the 95% confidence interval in parentheses.

Parvizi *et al.* *J Bone Joint Surg Am* 2011;93:2242-8

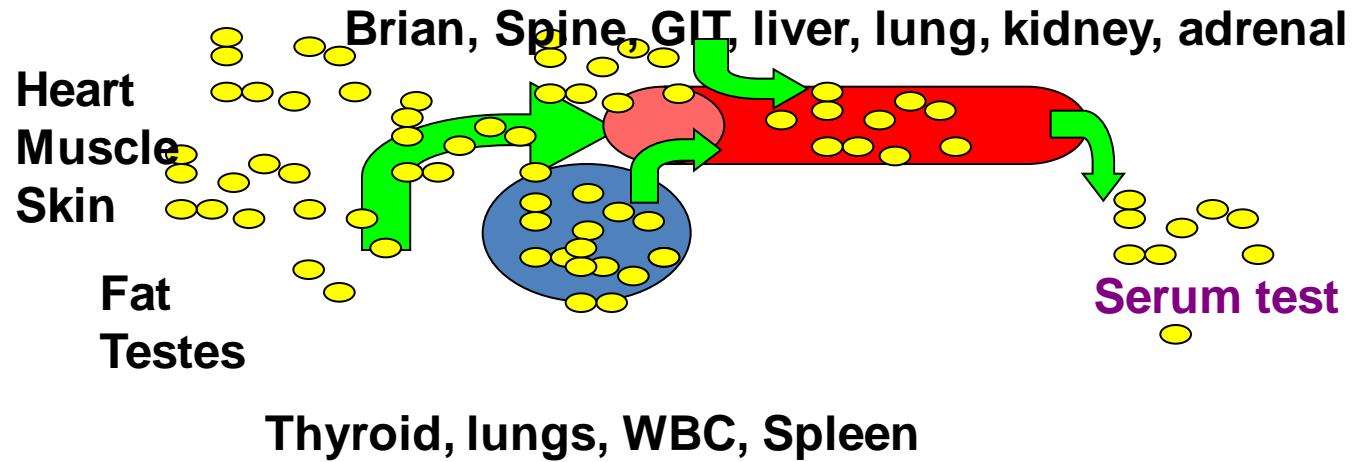


Synovial fluid procalcitonin (PCT) levels!?

- ❑ Procalcitonin is a 116 aa peptide - Precursor of the hormone Calcitonin
- ❑ Synthesis in healthy persons in the C-Cells of the thyroid
- ❑ PCT is enzymatically converted



Procalcitonin

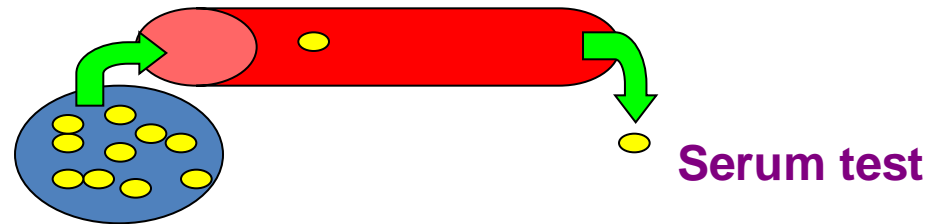
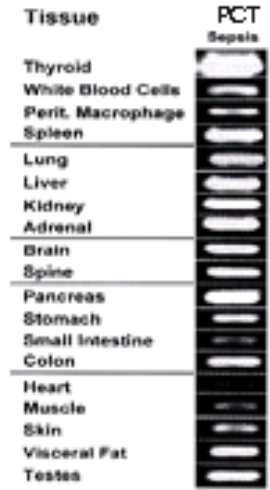
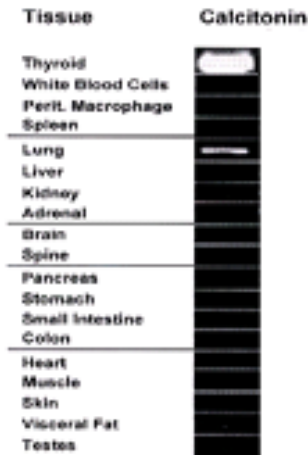


Systemic infection

Origin of PCT

- Bacterial toxins & cytokines stimulate production of PCT in all parenchymal tissues

- Calcitonin in healthy persons



Localised infection

This process can be blocked during viral infection by IFNs

Synovial PCT: Main objectives

- Can procalcitonin (PCT) be measured from synovial fluid (reproducibility)?
- To evaluate the usefulness of measuring **SYNOVIAL** PCT in differentiating septic arthritis from other forms of arthritis including PJI.
- To calculate the sensitivity, specificity, and predictive values for various synovial fluid PCT concentrations and the impact in clinical practice.

Saeed K et al. Infection. 2013; 28: 201-206.



Methods:

- Non-interventional comparative study
- Standard quantitative mini VIDAS Enzyme immuno assay ((BRAHMS UK Limited and BioMérieux, Basingstoke, UK)
- Synovial PCT level was measured retrospectively in 76 adult patients with predefined diagnosis:
 - 26 cases with septic arthritis (Infected)
 - 50 cases with non-septic arthritis (Non infected)
- SPSS Statistics version 20 (IBM) to compare the mean synovial fluid PCT scores of the two groups, as well as determining the sensitivity, specificity, and predictive values for various synovial fluid PCT concentrations



Results

	Infected *	Non infected
Median age in years (range)	78.7 (43-88)	66.5 (30-90)
Diagnosis (Numbers)	- Prosthetic Joint Infection (PJI) (8) - Native joint septic arthritis (18)	- Aseptic loosening (6) - Crystal arthropathy (20) - Osteoarthritis, rheumatoid arthritis, psoriatic arthritis and other inflammatory (24)
Total number of cases (male: female)	26 (15:11)	50 (33:17)

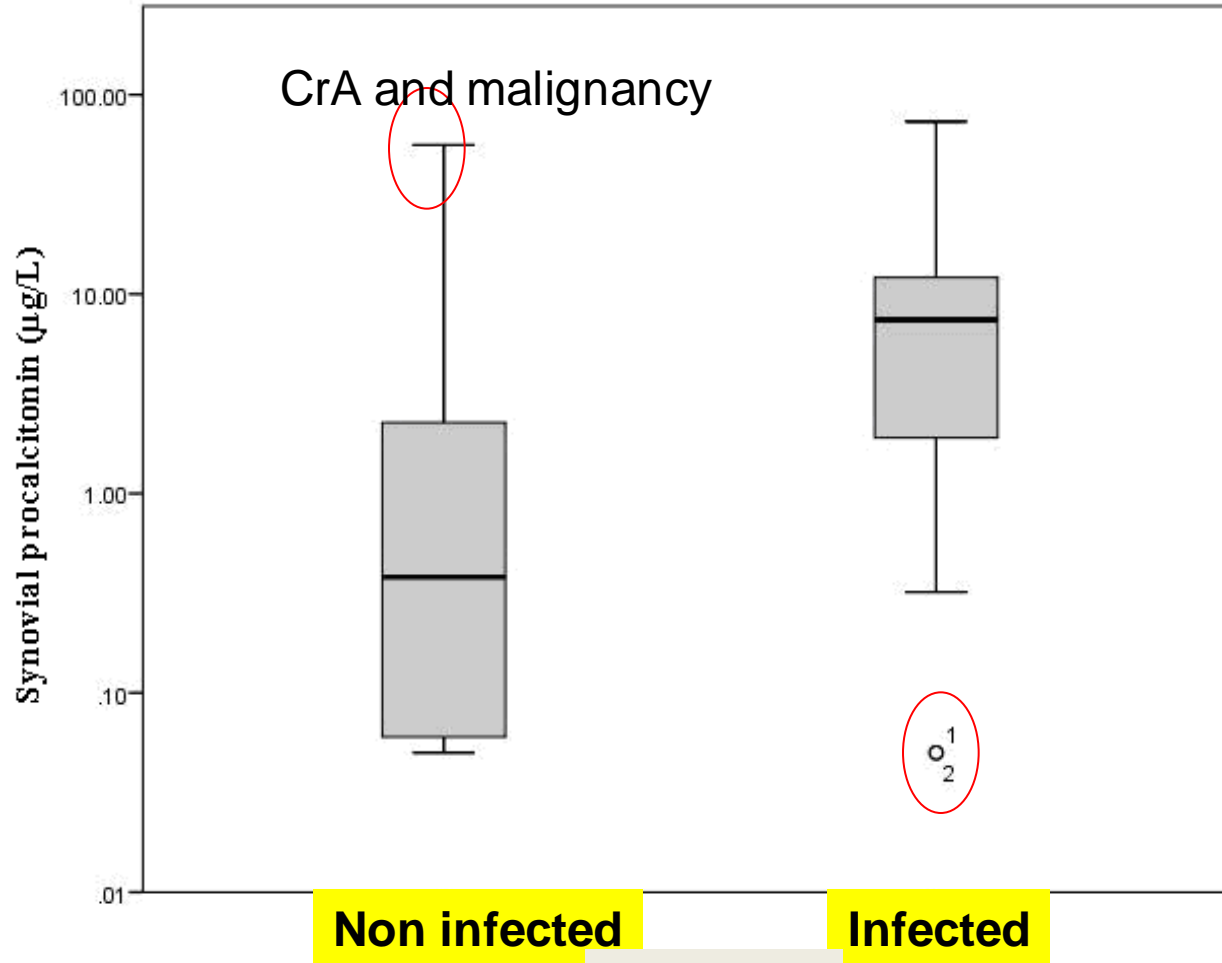
*MSSA 12 cases, other Staphylococci spp. 4 cases,

β -haem strept 3 cases, pneumococci 1 case, enterococci 1 case

Escherichia coli, *Proteus* spp. and other coliforms in the remaining 5 cases.



Results



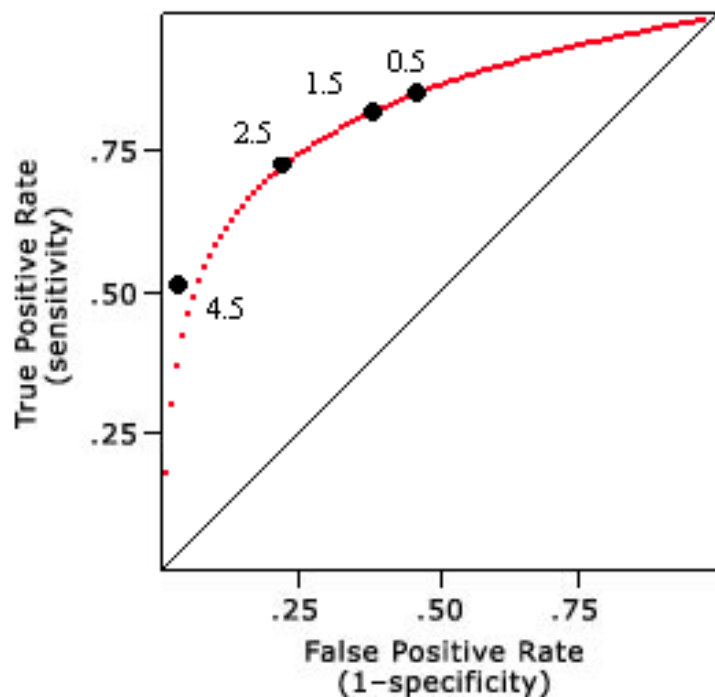
(Mean **2.61**, SD 8.22)

$p = 0.020$

(Mean **10.37**, SD14.95)



ROC Curve for $y = 0.18\ln(x) + 1$
 Area under curve = 0.824



Cut-off µg/L	Sensitivity (95% Confidence Interval)	Specificity (95% Confidence Interval)	PPV (95% Confidence Interval)	NPV (95% Confidence Interval)
0.5	0.88 (0.69-0.97)	0.57 (0.42-0.71)	0.52 (0.37-0.67)	0.90 (0.73-0.97)
1.5	0.85 (0.64-0.95)	0.62 (0.55-0.81)	0.59 (0.42-0.75)	0.89 (0.74-0.96)
2.5	0.69 (0.49-0.85)	0.78 (0.63-0.88)	0.62 (0.42-0.79)	0.83 (0.68-0.92)
4.5	0.54 (0.34-0.73)	0.94 (0.82-0.98)	0.82 (0.56-0.95)	0.79 (0.66-0.88)



So far 17 cases with implants

PJI cases and organisms		Synovial PCT	Aseptic loosening	Synovial PCT
Case 1	MSSA	18.33	Case 1	0.05
Case 2	MSSA	14.51	Case 2	0.2
Case 3	MSSA	7.13	Case 3	0.06
Case 4	MSSA	2.71	Case 4	0.05
Case 5	MSSA	1.87	Case 5	0.05
Case 6	Enterococcus	3.54	Case 6	0.05
Case 7	E coli	1.9	Case 7	0.06
Case 8	CoNS	0.05	Case 8	0.18
			Case 9	0.08

Median synovial PCT in the PJI group was **3.15 µg/L** vs. **0.05µg/L** in the aseptic loosening.

Only two cases with PJIs had concomitant positive blood cultures, Highest synovial PCT levels were seen in *Staphylococcus aureus* infections regardless of presence of concomitant positive blood cultures.



Discussion

LIMITATIONS

- Mostly retrospective,
- No concomitant serum PCT assays
- No concomitant synovial CRP assays
- Small number of patients
- Not full clinical info in e.g. steroid therapy, immunomodulators etc.



Discussion

- Septic arthritis had significantly higher mean synovial PCT values
- Synovial fluid PCT $<0.5 \mu\text{g/L}$ \rightarrow NPV of 0.90
- Higher synovial PCT levels among “Non infected” patients were observed in cases with confirmed crystal arthritis, particularly where there was a concomitant malignancy



PCT and PJI

Serum PCT lacks sensitivity in the diagnosis of PJI [1-4].

Synovial PCT: Our observations:

Cases of PJI, Synovial PCT > cases of aseptic loosening (apart CoNS one case)

Synovial PCT warrant further evaluation in cases of early/ delayed PJI and/ or loosening.

1. Soöderquist B et al. Scand J Infect Dis 1998;30:591–6.
2. Bottner F et al. J Bone Joint Surg Br. 2007;89:94–9.
3. Worthington T et al. Br J Biomed Sci. 2010;67:71–6.
4. Randau T et al. Eur Cells Mater. 2011;21:36.



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