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Presepsin : a new biomarker of prosthetic joint infection ?



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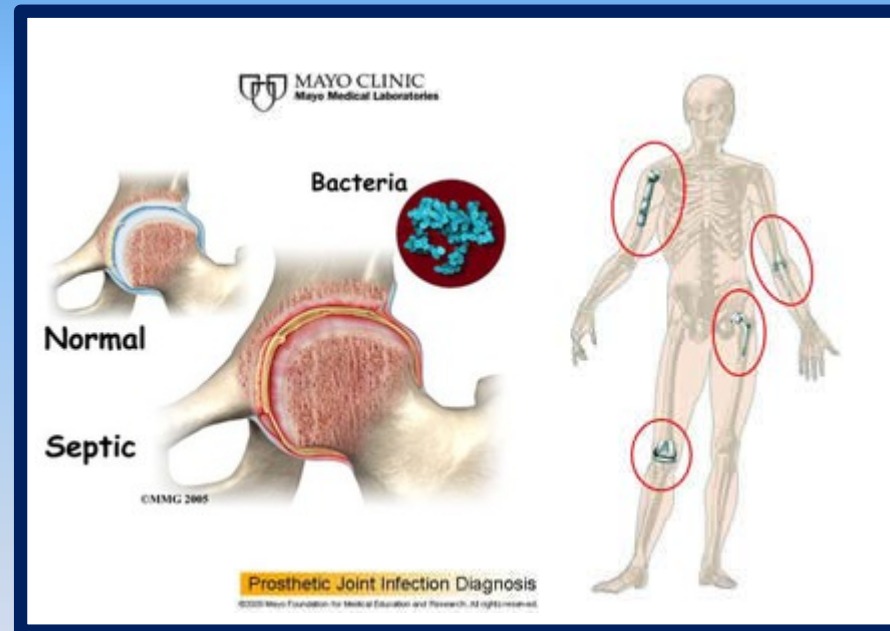


Prosthetic joint infection

Prosthetic joint infection (PJI) is the most common cause of failure of total joint arthroplasty, requiring revision surgery

It is extremely important to identify PJI as early as possible, in order to

- promptly start antibiotic treatment
- in the worse case, plan surgical revision arthroplasty



Prosthetic joint infection diagnosis

Based on the proposed criteria, a definite PJI exists when:

the following major criterium is present

“ A pathogen is isolated by culture from 2 or more separate tissue or fluid samples obtained from the affected prosthetic joint”

Or 4 of the following minor criteria are present :

- (1) Elevated serum ESR and serum CRP concentration
- (2) Elevated synovial WBC count
- (3) Elevated synovial PMN%
- (4) Presence of purulence in the affected joint
- (5) Isolation of a microorganism in 1 culture of periprosthetic tissue or fluid
- (6) 5 neutrophils/high-power field in 5 high-power fields observed from histological analysis of periprosthetic tissue at 9400 magnification

PJI=periprosthetic joint infection;
ESR=erythrocyte sedimentation rate;
CRP=C-reactive protein;
WBC=white blood cell;
PMN%=polymorphonuclear percentage

Prosthetic joint infection diagnosis

Diagnosis is difficult because of



Clinical presentation variability
Lack of gold standard

Currently based on :

- Clinical presentation
- Microbiological test
- histopathology
- imaging

but

- Invasive test
- False negative to microbial culture test

Inflammatory markers:

- Procalcitonin (PCT)
- C reactive protein (CRP)
- IL-6

but

IL-6 and CRP are useful in the diagnosis of PJI, while Procalcitonin had not a great diagnostic value PJI

Drago L, Vassena C, Dozio E, et al. Procalcitonin, C-reactive protein, interleukin-6, and soluble intercellular adhesion molecule-1 as markers of postoperative orthopaedic joint prosthesis infections. (2011)Int J Immunopathol Pharmacol;24:433-440.

In order to optimize the diagnostic process, infection biomarkers with fast response and high sensitivity and specificity for infection are needed

Use of biomarkers in PJI

Challenges with biomarkers

An ideal sepsis marker should:

- 1. Identify the presence or absence of sepsis.**
- 2. Aid in risk stratification and/or identify those patients that will benefit from a specific therapeutic intervention.**
- 3. Monitor the response to an intervention and/or aid in titrating the intervention.**

Use of biomarkers in PJI

Challenges with biomarkers

The assay used to measure the ideal sepsis marker should:

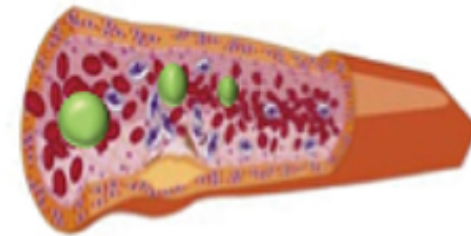
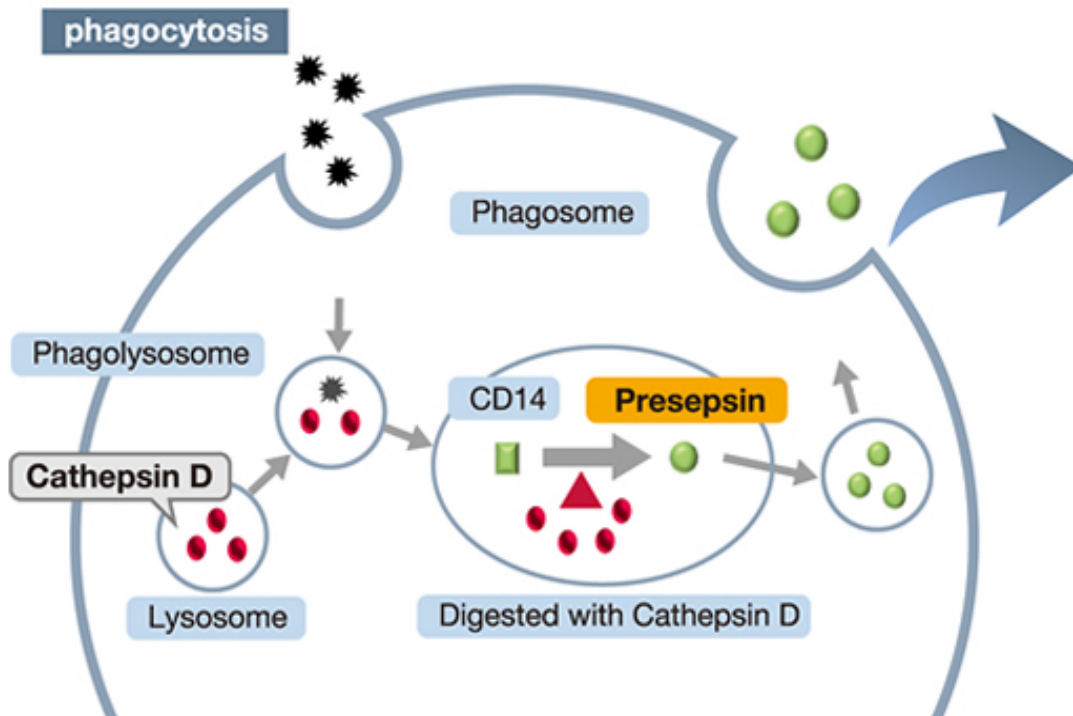
- 1. Be reliable and reproducible in different settings.**
- 2. Provide information from a sample that can be obtained easily.**
- 3. Provide rapid information.**

Use of biomarkers in PJI

Challenges with biomarkers

- No single biomarker can assist the physician at the bedside in sepsis detection or risk stratification.
- Biomarker panels (including RNA's) may be more discriminative.
- Rapid point-of-care tests are needed to implement the use of biomarkers in clinical practice.

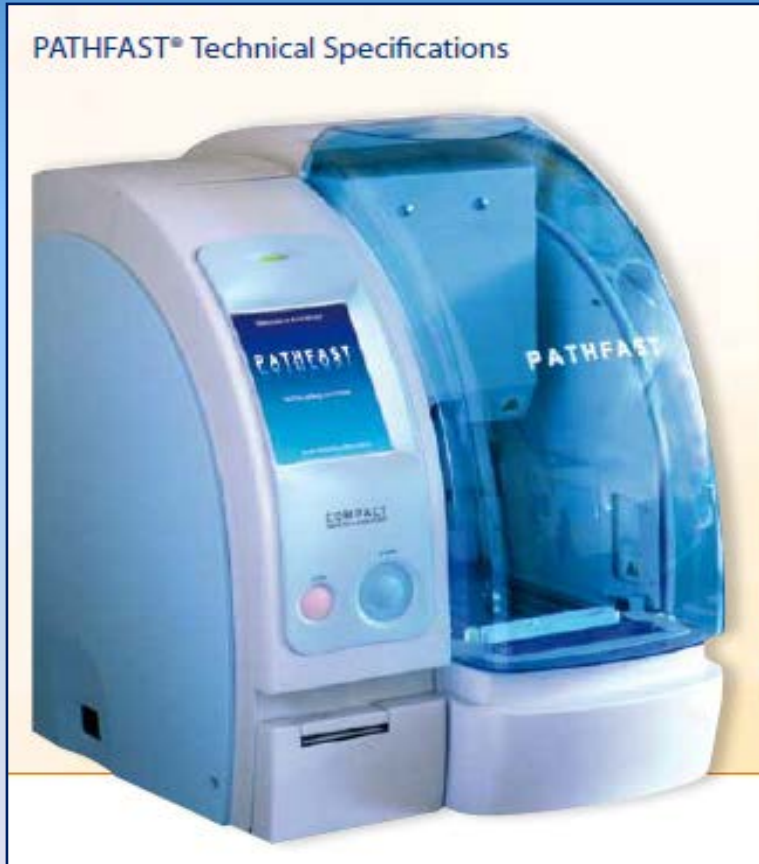
Soluble CD14 : Presepsin



Presepsin elevation is caused by bacterial phagocytosis.

The new sepsis marker, sCD14-ST (PRESEPSIN), induction mechanism in the rabbit sepsis models

Clinical use of PATHFAST Presepsin



- Early diagnosis and prognosis of sepsis
- Prognosis at first presentation
- Current use : emergency and intensive care unit

Aim of the study

Examine the diagnostic value of Presepsin in post operative prosthetic joint infection

Correlate circulating levels of Presepsin with inflammatory markers currently used in clinical detection of post operative prosthetic joint infection

Explore the possible application of this new biomarker in the early diagnosis of operative prosthetic joint infection

Study population

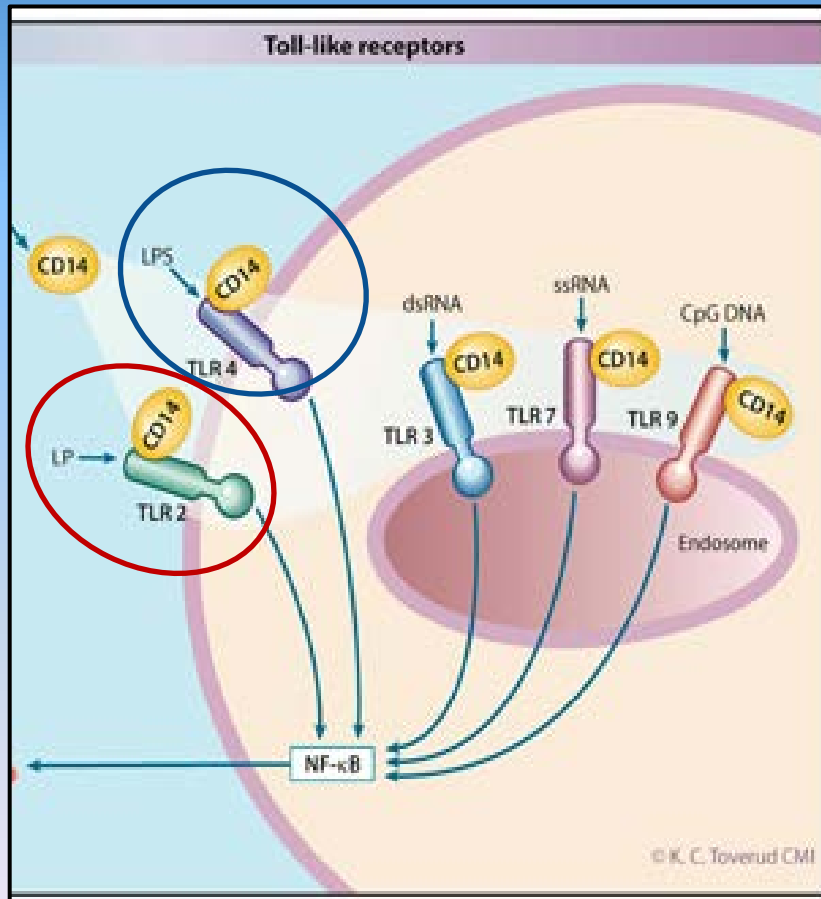
The population of 50 selected undergoing revision surgery patients have been enrolled and subdivided into two groups

- 30 patients having bacterial infection (confirmed by positive culture test)
- 20 patient with no infection, (control group) .

Blood drawings have been performed from all patients for plasma separation and -20°C storage.

- C Reactive protein was measured by immunoturbidimetry
- IL-6 was measured by commercially available ELISA kit
- the level of Presepsin have been measured in, according to PATHFAST[®] Immunoassay protocol (Mitsubishi , Japan) protocol

sCD14 and TLR2



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Biochemical and Biophysical Research Communications 328 (2005) 173–176

BBRC

www.elsevier.com/locate/ybbrc

The CD14 region spanning amino acids 57–64 is critical for interaction with the extracellular Toll-like receptor 2 domain[☆]

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GLIA 55:473–482 (2007)

Identification of Soluble CD14 as an Endogenous Agonist for Toll-Like Receptor 2 on Human Astrocytes by Genome-Scale Functional Screening of Glial Cell Derived Proteins

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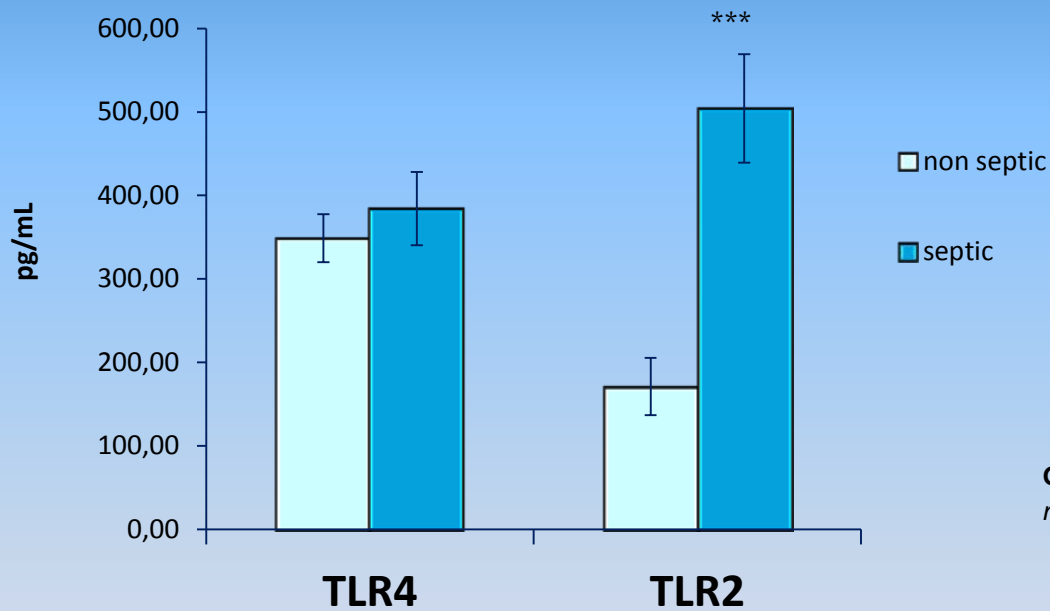
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sTLR2 and sTLR4 in PJI



➤ In PJI patients, compared to not infected controls, we observed a significant increase of sTLR2

➤ sTLR4 displayed no significant differences (87,5 % Gram positive infected)

Galliera E. et AL , *Toll-like receptor 2 in serum: a potential diagnostic marker of prosthetic joint infection?* J Clin Microbiol. 2014

sTLR2 and sCD14 (Presepsin) cooperate in the immune response against bacterial infection

Together they can be considered a useful panel of PJI diagnostic markers

Future perspectives

Evaluation not only DIAGNOSTIC , but also the PROGNOSTIC value of Presepsin in PJI :

- Analysis of different time points pre-post prosthetic surgery
- Comparison with other infection markers



Presepsin : new marker in clinical monitoring/routine follow up of primary prosthetic surgery (?)

Conclusions

There is a need to improve diagnostic methods for the early detection of PJI

- the analysis of a panel of inflammatory biomarkers (CRP and inflammatory cytokines) can be very useful in the diagnosis of prosthesis joint infection, but they still need to be improved, because they still lack a reliable cut off value .
- This study provides a clear indication of the diagnostic potential of Presepsin in the diagnosis of PJI (significant increase and high ROC AUC in PJI patients)
- This molecule could represent a useful diagnostic tool to improve prosthesis joint infection diagnosis , where a clear detection of the infection is still lacking, in addition to routine inflammatory parameters such as CRP and IL-6, and new prosthetic joint infection markers such as TLR2.

Aknowledgement

Prof Massimiliano M. Corsi Romanelli
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