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Plasmatic presepsin (sCD14-ST) concentrations in acute pyelonephritis in adult patients

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ABSTRACT

Introduction: Presepsin (sCD14-ST) is an emerging biomarker for infection. We hypothesized that presepsin could specifically increase during acute pyelonephritis and correlate with severity.
Methods: We compared presepsin values in patients with acute pyelonephritis and controls, and we assessed its capacity to predict bacteraemia and admission in patients.
Results: In 312 patients with acute pyelonephritis (median age 33 years), presepsin concentrations were higher than in controls (476 vs 200 ng/L, $p < 0.001$). ROC curve indicated an AUC at 0.90 [for presepsin (vs. 0.99 and 0.98 for CRP and PCT, respectively; $p < 0.05$) and an optimal threshold at 340 ng/L (74% sensitivity, 94% specificity). Presepsin concentrations increased in acute pyelonephritis patients with bacteraemia (614 vs. 461 ng/L, p,=0.001) and in those requiring admission (614 ng/L vs. 320 ng/L, $p < 0.001$). Performance of presepsin to predict bacteraemia [AUC = 0.63, 95%CI: 0.55–0.72] was similar to CRP (AUC = 0.64, $p = 0.87$) and less accurate than PCT (AUC = 0.78, $p < 0.001$). AUC for presepsin to detect the need for admission was 0.67, and comparable to CRP ($p = 0.26$) and PCT ($p = 0.18$).
Conclusion: Presepsin is a valuable biomarker to detect patients with acute pyelonephritis. However, it presents mild performance to predict bacteraemia and the need for admission, and offers no advantage as compared to CRP and PCT.

1. Introduction

Innate immunity is the first barrier to fight off microorganisms responsible for infection. It mostly relies on the activity of monocytes, macrophages and granulocytes. These cells recognize pathogen-associated molecular patterns that activate downstream pathways and participate to bacteria clearance [1]. Recognition of microorganisms partly

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depends on membrane expression of CD14. This co-receptor conducts immediate response against endotoxin (lipopolysaccharide, LPS), a component present at the membrane of Gram-negative bacteria. After binding of LPS to CD14 through the LPS-binding protein (LBP), a subtype of soluble CD14 (sCD14-ST, or presepsin) is released to the blood flow. Presepsin increases in patients developing infections in a severity-dependent manner [2,3].

Acute pyelonephritis is a common infection that corresponds to bacterial invasion of the upper urinary tract [4]. Bacteraemia is recorded in 7.5–30% [5,6] and patients often experience systemic signs and symptoms of toxemia [4]. Paradoxically, this mild condition frequently leads to admission. Acute pyelonephritis represents a valuable clinical model of LPS-related sepsis. Indeed, *Escherichia coli* and other Gram-negative enterobacteriacae strains, whose membrane contains endotoxin, are mainly responsible for the infection. In this setting, CD14 is obviously engaged. Therefore, presepsin is likely to be released during these Gram-negative infections and concentrations may depend on the burden of the infection.

Based on previous evidences, we aimed to measure circulating presepsin values in a previously studied population of patients with acute pyelonephritis, and to compare results to a reference population. We further evaluated the accuracy of presepsin to predict bacteraemia, and to predict admission in the pyelonephritis population, in comparison to C-reactive protein (CRP) and procalcitonin (PCT).

2. Methods

We retrospectively analyzed blood samples and data from a multicentric, prospective, observational study conducted in 12 French EDs (2004–2007), entitled 'The Biomarkers In Sepsis (BIS) Study'. Methods have been reported previously in details [7,8]. In addition, we prospectively enrolled a population of 47 healthy volunteers to define reference values.

The study protocol and procedures complied with the principles of the Declaration of Helsinki. The review board for the protection of patients of our institution (Comité pour la Protection des Personnes Paris Centre, Paris, France) approved the study protocol and informed consent procedures to patients. Patients enrolled in the study provided written informed consent for participation.

2.1. Participants

For the purpose of the present study, analyses were restricted to patients from the BIS study with acute pyelonephritis for which of at least one blood microbiological cultures was collected, as previously described [9], and to the reference population.

Acute pyelonephritis was defined using standard criteria: acute onset of at least one of the following signs or symptoms: dysuria, nausea, flank pain, costovertebral angle tenderness, body temperature above 38.5 °C, and positive urinalysis with a white blood cells count exceeding 10^9 per liter. Patients with the following conditions were not included: 1) History of manual or instrumental urological examination within 1 month before ED presentation; 2) History of previous antibiotic treatment, defined as antibiotic use for at least 3 days during the past month; 3) Presence of an indwelling urinary catheter; 4) Presence of previous structural or functional abnormalities (including bladder diverticula, cystocoeles, urethral strictures, congenital abnormalities, and renal cysts, as well as functional abnormalities, such as neurogenic bladder and vesicoureteral reflux, kidney failure defined as a creatinine level > 130 μmol/L); 4) Lumbar or abdominal tenderness; i.e. tenderness to pressure either on the lumbar region or on the abdomen; 5) comorbid conditions that interfere with admission decision (pregnancy; human immunodeficiency virus infection or alternative immunocompromising conditions [active neoplasm, immunosuppressive therapy, prednisone > 15 mg/day or equivalent]); 6) septic shock [10]; 7) palliative care (precluding admission to an ICU); 8) anticipated barriers to complete follow-up.

Baseline data consisted of demographic data (age, gender), coexisting illnesses, symptoms, clinical findings and available laboratory tests (white blood cell count, haematocrit, blood urea nitrogen, glucose, and sodium).

Reference population was recruited prospectively. Heparinate-blood sample was collected from 47 healthy young participants, including 34 (72%) women, with median age 27 years [IQR 24–31]), free from significant underlying disorders, and without presumed acute infectious disorder within 3 weeks before blood collection. Plasma samples were frozen at −40 °C during 1 month before analysis.

2.2. Blood sample analysis

Blood cultures were processed using an automated colorimetric detection system in each participating center. We defined pyelonephritis related bacteraemia by identification of the same bacterial strain in blood culture and urinalysis within 36 h of culture. Positive samples were stained for Gram coloration and subcultured for identification. All bacterial strains were considered pathogenic but *Staphyloccocus saprophyticus* was considered as contaminant.

Procedure to test biomarkers has been published elsewhere [9]. Briefly, blood samples were collected in sodium heparin-treated tubes, centrifuged, and stored at −40 °C in a central laboratory until completion of the study. The laboratory measurement process complied with French quality standards for medical laboratories.

CRP concentrations were measured using the Tina-quant CRP-Gen3 immunoturbidimetric assay, on a Modular PP analyzer (Roche Diagnostics Meylan, France). Procalcitonin (PCT) concentrations were analyzed using a sandwich immunoassay based on Time Resolved Amplified Cryptate Emission (TRACE) measurement (Kryptor analyzer; B.R.A.H.M.S. ThermoFischer, Germany). In our laboratory, coefficients of variation (CV) for PCT were found to be <10% at 0.280 and 10.8 μg/L. The upper reference limit (URL) announced by the manufacturer was 0.046 μg/L.

Presepsin concentrations were measured using a chemiluminescent enzyme immunoassay (PATHFAST™ Presepsin), performed on the PATHFAST point-of-care analyzer (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Measuring range is 20–20,000 ng/L; manufacturer's URL (95th percentile) is 320 ng/L. Our laboratory CVs for Presepsin were <5% at 860 and 2500 ng/L, during the study period. Correlation between heparinized and EDTA plasma was $Y = 1.00\times + 1.53$ ($r = 0.999$, $n = 23$) [11].

2.3. Statistical analysis

Baseline and follow-up characteristics were described by means and standard deviations (SD) or by median and interquartile range (IQR) for continuous variables, as appropriate, and by percentages for categorical variables. We performed Chi2 statistics or Fisher's exact tests when appropriate for qualitative variables, and the Wilcoxon/Mann–Whitney test for continuous variables with skewed distributions to compare baseline patient characteristics and study outcomes.

We referred to the STAndards for the Reporting of Diagnostic Accuracy (STARD) recommendations for analysis of the results [12]. We used the area under receiver–operator characteristic curves (AUC) to assess the overall discriminatory power of CRP, PCT and presepsin in detecting pyelonephritis or bacteraemia or admission. The AUC and its 95% CIs were estimated for each biomarker and compared by a non-parametric method [13]. Accuracy of biomarkers was calculated for the total population.

Sensitivity, specificity, positive and negative predictive values were calculated for each cut-off value of biomarkers. The threshold value with maximized Youden index (sensitivity + specificity − 1) was reported. We also calculated likelihood ratios (LR) as a measure of the