DE GRUYTER OPEN

Research article

DOI: 10.1515/rrlm-2015-0025

Usefulness of Presepsin (sCD14-ST) in diagnosis of Infective Endocarditis - preliminary results of an observational study

Utilitatea presepsinului (sCD14-ST) în Endocardita Infecțioasă –rezultate preliminare ale unui studiu observațional

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Abstract

***Background**: Soluble CD14 subtype (sCD14-ST), also named presepsin, has been proposed as a novel biomarker for the diagnosis of sepsis. We hypothesized that presepsin value might be helpful in the diagnosis of infective endocarditis (IE). **Material and methods**: In this prospective study a total of 29 patients with clinical suspicion of IE were enrolled. The plasma presepsin samples were collected at the admittance in the same time with blood cultures, CRP (C-reactive protein) and routine blood tests. Data about the antibiotic treatment prior to admittance were recorded. The diagnosis of IE was made using the Duke modified criteria. Receiver operating characteristic (ROC) curves analysis and binary logistic regression were performed using SPSS software, version 18. A p value less than 0.05 is considered statistically significant. **Results**: Patients were divided in two subgroups: 14 patients with definite IE and 8 with IE - rejected according to the modified Duke criteria. 7 patients with final diagnosis of sepsis were excluded. Presepsin levels in patient with definite IE were significantly higher than in those with rejected IE ($p<0.03$). The area under the receiver operating characteristic curve (AUC) was 0.781 (95 % confidence interval (CI) 0.590 - 0.973). The threshold value of presepsin in predicting IE was determined to be 345 pg/ml, of which the clinical sensitivity and specificity were 64% and respectively, 88%. The AUC for CRP was 0.656 (95% CI 0.37-0.88). **Conclusion**: Presepsin might be a useful additional diagnostic marker in patients with suspected IE. These preliminary results needs confirmation by future studies.*

***Keywords**: Presepsin, infective endocarditis, biomarker*

Rezumat

***Introducere**: Presepsinul sau subtipul formei solubile a CD14 (s CD14-ST), a fost propus ca si biomarker nou în diagnosticul sepsisului. Scopul acestui studiu este de a testa utilitatea presepsinului in diagnosticul endocarditei infecțioase (EI). **Material și metodă**: Acest studiu prospectiv a înrolat 29 de pacienți care s-au prezentat în serviciul nostru cu suspiciunea clinică de endocardită infecțioasă. În momentul internării concomitent cu recoltarea*

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probelor de sânge uzuale si a hemoculturilor s-au recoltat si probe de sânge pentru dozarea proteinei C-reactive (CRP) si a presepsinului. Tratamentele antibiotice efectuate anterior internării au fost consemnate împreună cu datele demografice. Diagnosticul final de endocardită infecțioasă s-a stabilit pe baza criteriilor Duke modificate. Prelucrarea statistică a constat în efectuarea regresiei binare si a curbei ROC folosind softul SPSS, versiunea 18. O valoare p mai mică de 0.05 este considerată semnificativă statistic. ***Rezultate****: Pacienții au fost împărțiți în două grupe: 14 pacienți cu EI certă și 8 pacienți cu EI exclusă. 7 pacienți cu diagnosticul final de sepsis au fost excluși din analiza statistică. Nivelele de presepsin la pacienții cu EI certă comparativ cu cei cu EI exclusă au fost semnificativ mai mari (p<0.03). Aria de sub curba ROC (AUC) pentru presepsin a fost 0.781 (95% CI 0.590-0.973). La valoarea presepsinului de 345 pg/ml sensibilitatea a fost de 64%, cu o specificitate de 88%, sugerând capacitatea presepsinului de a confirma EI, atunci când suspiciunea clinică este mare. Pentru CRP AUC a fost 0.656 (95% CI 0.37-0.88).* ***Concluzii****: Presepsin ar putea fi un marker aditional util la pacientii cu suspiciune clinica de endocardita infectioasa. Aceste rezultate preliminare necesita confirmare prin studii viitoare.*

Cuvinte cheie*: presepsin, endocardita infectioasa, biomarker*

Received: 12th March 2015; Accepted: 27th June 2015; Published: 18th July 2015

Introduction

Infective endocarditis is a very complex disease with an interesting evolution in time. Despite the improvement in diagnosis and treatment, infective endocarditis has a constant morbidity and a high mortality rate. This can be explained by the continuous changing in epidemiological profile of the disease. The majority of cases are now involving older people with degenerative valvulopathies, people with frequent contact with health-care system, with valvular prosthesis or cardiovascular devices or people with i.v. drug abuse. As a consequence, a shift in the etiology has also occured with *Staphylococcus aureus* on first place followed by oral streptococci and enterococci (1).

Modified Duke criteria, which encompasses major and minor criteria, are used for the diagnosis of the infective endocarditis. These criteria integrate clinical, microbiological and echocardiography findings (2). Blood cultures and echocardiographic evidence of endocardial involvment are the cornerstones for the clinical diagnosis of infective endocarditis and the major criteria of Duke scoring system. However, in blood culture negative endocarditis or in prosthetic valve endocarditis, performance of Duke criteria is diminished (3). Multiple studies have tried to identify an inflammatory marker that will improve the diagnosis of infective endocarditis, especially in blood culture negative cases. Ehrythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and procalcitonin have been evaluated, but the results are controversial and so far, only rheumatoid factor has been accepted as a minor criteria of infective endocarditis (2, 4-7).

Recently, a new biomarker has been proposed for the early diagnosis of bacterial infections and sepsis. This biomarker, named soluble CD14 subtype (sCD14-ST) or presepsin, is a soluble fraction of the coreceptor CD14. CD14 (CD-cluster-of-differentiation) is a membrane coreceptor present on the surface of mononuclear cells monocytes/macrofages and other non-hematopoietic cells (e.g. gingival fibroblasts, chondrocytes, keratinocytes). During bacterial infection CD14 binds lypopolysaccharides (LPS) and LPS binding protein (LBP) resulting a complex, which initiates proinflammatory signaling cascade. Thus, CD14 has an important role in initiating the innate immune response. Besides LPS, which is the major wall cell component in Gram negative bacteria, CD14 recognises surface components of Gram positive bacteria, like peptidoglycan. Upon initiating the proinflammatory cascade, CD14-LPS-LBP

complex is internalised into a phagolysosom and released in circulation by shedding of CD14 from cell membrane, resulting soluble CD14 – sCD14 form. Plasma proteases activate the cleavage of sCD14 into a truncated N-terminal 13 kDa fragment, named sCD14 -subtype or Presepsin (8,9).

Presepsin is stable in blood circulation and automated measurements are available, the results being available in less than 20 minutes (10).

In patients with sepsis, presepsin levels are much higher than in healthy persons or in those with non-bacterial inflammation (11). Several studies have shown that presepsin levels could be useful as early diagnostic, risk stratification and a prediction marker in sepsis (8,10, 12,13).

In infective endocarditis (IE) bacteremia is both, a cause and a consequence of the disease. Starting as a localised infection of the heart, infective endocarditis often spreads locally and/ or at distance through septic emboli. Moreover, evolution to severe sepsis or even septic shock is also possible (14). High levels of sCD-14 were corelated with interleukin (IL)-8 levels and poor outcome in sepsis. Experimental results have shown that IL8 local expresion in pigs with IE was high and correlate with the systemic inflammatory response (15). Therefore, based on these findings, we can assume that in infective endocarditis high levels of sCD-14 may be found. In this paper, our main hypothesis is that presepsin could be a helpful additional marker for the diagnosis of infective endocarditis. To the best of our knowledge, none of the existing studies evaluated the potential usefulness of presepsin in infective endocarditis.

Material and methods

Patients

We performed a prospective observational study at the University Hospital of Infectious Diseases, a tertiary care center in Cluj-Napoca.

Between November 2013 - July 2014, a total of 29 consecutive adult patients hospitalised with clinical suspicion of infective endocarditis were enrolled. Clinical suspicion of infective endocarditis was raised based on the recomandation criteria of ESC (European Society of Cardiology) (16). Inclusion criteria were 1) new regurgitant murmur, 2) embolic events of unknown origin, 3) fever and intracardiac prosthetic material; previous history of IE; previous valvular or congenital heart disease; recent intervention associated with bacteremia; congestive heart failure; vascular and imunonologic phenomena (embolic event, splinter haemorrhages, Janeway lesions, Osler 's nodes or 4) fever and no clinical signs of localised infection. The exclusion criterion was fever or hypothermia, with an obvious origin other than endocarditis.

The final diagnosis of infective endocarditis was made according to the modified Duke criteria (2). Our patients were classified in two groups: definite and rejected IE. In the rejected group, we identified 7 patients with final diagnosis sepsis. Sepsis diagnosis was established according to the criteria of the international guidelines for management of severe sepsis and septic shock (17).

Data about empirical antibiotic treatment prior to admittance and also antibiotic treatment in the previous month were recorded. None of the patients were in cardiogenic or septic shock.

We performed serology for *Coxiella burnetii* in all cases of IE with blood culture negative results and in one case we also searched for *Chlamydia psittaci* due to positive epidemiologic risk factors, but without confirmation.

Informed consent was obtained from all patients included in the study. Study was approved by Ethical committee from our University.

Measurement methods

Blood samples for routine analyses were collected. Three sets of blood cultures were taken in the first 24 hours of the admittance and performed by BacT/Alert 3D (Biomerrieux, France). For *Staphylococcus aureus* and coagulase-negative staphylococci minimum two positive blood cultures were accepted to exclude contamination. We have also collected blood samples for routine blood tests and for rheumatoid factor (RF). For presepsin, 2ml of blood samples were collected in endotoxin-free tubes containing ethylenediaminetetraacetate (EDTA), centrifuged a 3,000 g for 10 min and obtained plasma was stored at - 70°C until evaluated. PATHFAST™ automated immunoassay analyzer (Mitshubishi Chemical Europe GmbH) was used to determine presepsin concentration. The test principle of PATHFAST™ presepsin is based on a non-competitive chemiluminescent enzyme immunoassay (CLEIA) combined with Magtration technology®.

Serum CRP was determined by an immunoturbidimetric assay (COBAS c311).

All patients were referred for transthoracic echocardiography and/or transesophageal echocardiography when needed.

Statistical analysis

Data were analysed with the use of SPSS for Windows, version 18. The quantitative variables are expressed as mean ± standard deviation (SD) or median values and ranges. All qualitative variables are expressed in percentage.

Comparison was made using Fisher's exact test for categorical variables, two- sample t-test for normally distributed data and Mann – Whitney U test for non–normally distributed data.

Receiver operating characteristic (ROC) curves analysis was performed. Area under the curve (AUC) was displayed including 95% confidence interval. An area under the ROC curve (AUC) of 0.5 means that the discriminatory ability of test is low and a value of 1 represents the perfect discriminatory ability. A p value less than 0.05 means statistically significant.

Results

This study included 29 patients (19 men and 10 women) with clinical suspicion of infective endocarditis. According to modified Duke criteria final diagnosis was definite IE in 14 cases and rejected IE in 15 cases. In table I, combinations of Duke criteria in IE cases, are presented. In the IE group of patients, pathologic confirmation was available for 9 cases (7 cases from surgery and 2 cases from autopsy). Three cases were initially diagnosed with possible IE and upgraded to definite IE after pathological confirmation obtained from surgery. 7 patients (only 2 with positive blood culture), diagnosed with sepsis and no endocardial involvement were excluded from the final analysis. Usefulness of presepsin in diagnosis of sepsis was already presented and we intended to evaluate the utility for the diagnosis of IE. Final diagnosis in the rejected group was non-infectious disease in 6 cases (rheumatic acute fever n=1 case; degenerative valvular disease in n=4 cases, acute coronary ischemia n=1 case) and acute pneumonia (n=2 cases). Demographic characteristics of patients from IE definite and rejected group are shown in Table II. We have found a similar median age in both groups and no significant differences regarding the presence of comorbidities. Table III summarizes the

Tabel I. Duke criteria in IE group

Combination of Duke criteria	N(%)
2M+3m	2(14.28)
2M+2m	6(42.85)
2M+1m	1(7.14)
1M+3m	2(14.28)
1M+2m	3(21.42)

M=major criterion; m=minor criterion

Table II. Demographic and laboratory parameters of patients in definite and rejected IE

	Definite IE (n=14)	Rejected IE (n=8)	p value
Age (mean±SD)¤	56.41±15.04	56.5±15.04	0.97
Gender Male/Female (n)	6/8	2/6	0.09
Diabetes mellitus	3 (21.4)	1 (7.1)	0.99
Hypertension	5 (35.7)	4 (28.5)	0.06
End- stage kidney disease	0	1 (7.1)	0.36
Whithout known comorbidities	6 (42.8)	2 (14.2)	0.64
*ESR (mm/h) mean±SD	59.07±27.92	67.13±33.54	0.55
**CRP(mg/dl) median (IQR)§	5.28 (9.18)	3.4 (6.58)	0.47
***RF (UI/ml) median (IQR)	20.15 (25.7)	11.85(7.9)	0.03
WBC (nx10^3/µL) mean±SD	10.5±4.68	8.06±3.30	0.19
Creatinine (mg/dl) median (IQR)	0.98(0.37)	0.8(0.3)	0.66
Presepsin (pg/ml) median (IQR)	546 (1077.5)	202(163)	0.03
Antibiotic treatment			
< 2 days	3 (21.4)	2 (25)	0.64
> 2 days	6 (42.8)	2 (25)	
Blood culture			
Positive	9 (64.2)	0	0.73
Negative	5 (35.7)	8(100)	

*ESR =erythrocytes sedimentation rate;** CRP= C-reactive protein;***FR=rheumatoid factor. Categorical variables are presented as number (%).¤SD= standard deviation;§IQR=interquartile range

characteristics and laboratory parameters values of the definite IE group. Blood culture negative endocarditis were found in 5 cases (35,71%) from which 4 cases (80%) had antibiotic treatment prior to admittance. Presepsin levels in the definite IE group were significantly higher than the rejected IE group (p value<0.03). The rheumatoid factor levels were significantly different between those two groups (p<0.03).

The ROC curves were designed including patients with definite IE (see Figure 1). The AUC were 0.615 (95%confidence interval (CI) 0.35-0.88) for CRP and 0.781 (95% CI 0.59-0.97) for presepsin, respectively (Fig.1). Threshold value for presepsin is shown in Table IV with positive predictive value (PPV) and negative predictive value (NPV). A value of 345 pg/ml has sensitivity (Se) of 68% and specificity (Sp) of 88%. At this value, when we compared positive blood culture with negative blood culture patients, in the definite IE group, no significant difference was found (p=0.74).

Discussions

Persistent and positive bacteremia and ecocardiography evidence of endocardial involvement are the main findings in the diagnosis of infective endocarditis. However, blood culture negative endocarditis represents almost 1/3 of cases and it is due to fastidious or intracellular bacteria or to empirical antibiotic treatment before sampling. Echocardiography may not be available in all hospitals or the results can be doubtful or false negative. The routine inflam-

Table III. Characteristics of patients with definite IE

	n (%)
Site of cardiac lesion	
Mitral valve	4 (28.57)
Aortic valve	4 (28.57)
Aortic and mitral valve	2 (14.28)
Prosthetic valve	4 (28.57)
Causative organisms	
Coagulase-negative staphylococci	3 (21.42)
Staphylococcus aureus	1 (7.14)
Viridans streptococococci	2 (14.28)
Streptococcus pneumoniae	1 (7.14)
Aerococcus viridans	1 (7.14)
Enterococcus faecalis	1 (7.14)
Unknown	5 (35.71)
Urgent surgical treatment*	5 (35.71)
Late surgical treatment ¤	2 (14.28)
In hospital mortality	2 (14.28)

* Surgical treatment during acute phase of IE. ¤ Surgical valve replacement at the end of antibiotic treatment. Data are expressed in numbers (percentages).

matory markers like CRP or ESR are not useful due to the low specificity. In some cases, clinical manifestation of IE may be discrete or atypical. Therefore, early and accurate diagnosis of IE may not be always achievable. Having a reliable marker to confirm the presence of bacterial infection in IE is highly desirable.

Presepsin is a newly emerging marker which has proved to be highly specific for the early diagnosis of sepsis. According to the PATHFAST point - of- care manufacturer, measuring range for presepsin is very large 20-20,000 pg/ml and in 127 healthy volunteers, presepsin concentrations ranged from 92.7-398 pg/ml. Upper normal reference limit proposed by the same manufacturer is 320 pg/ml (10). A recent study reported new interval reference for presepsin, between 55-184 pg/ml (18). In sepsis, different cut-off limits have been reported: in a prospective study involving 41 patients and 128 healthy volunteers, a value of presepsin of 415 pg/ml revealed

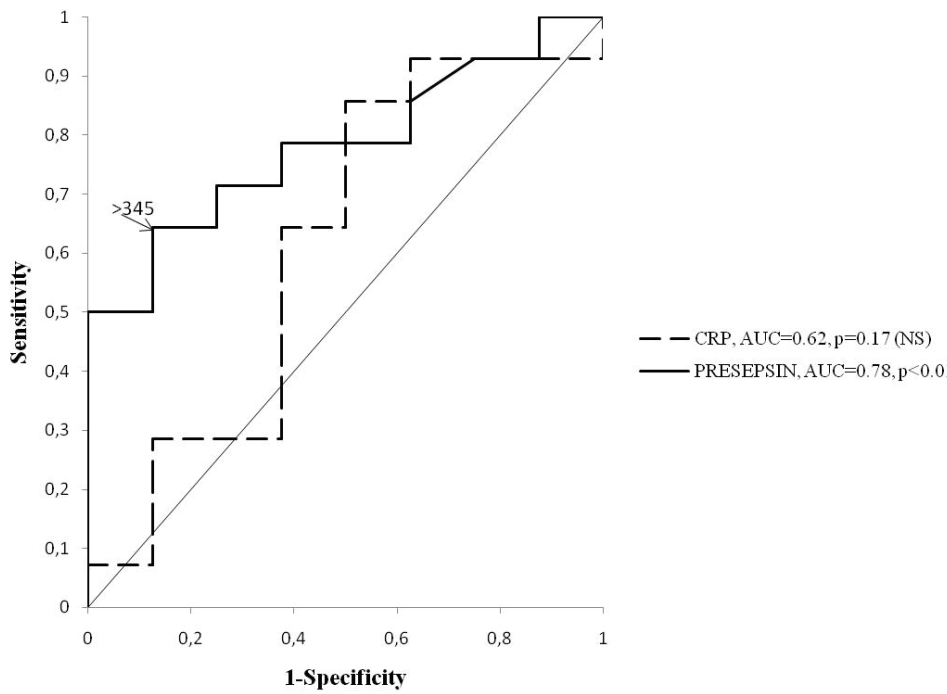

Fig. 1 ROC curve for the values of Presepsin and CRP in patients with infective endocarditis

Table IV. Cut-off value of Presepsin and CRP, with Sensitivity, Specificity , NPV and PPV

	AUC 95% (CI)	Cut-off value	Se (%)	NPV (%)	Sp (%)	PPV (%)
Presepsin	0.781 (0.59-0.97)	>345 pg/ml	64	58.3	88	90
CRP	0.656 (0.37-0.86)	44.50 mg/L	64	72	63	62.5

AUC=area under de curve; 95% CI= 95% confidence interval; Se=sensitivity; NPV= negative predictive value; Sp= Specificity; PPV=positive predictive value

a clinical Se of 80.1% and a Sp of 81% for diagnosis of sepsis. In the same study, the mean level of presepsin in the control group was 190 pg/ml (8). Higher optimal cut-off values of presepsin for diagnosis of sepsis have been reported by other studies: 600 pg/ml was confirmed by Ulla et al., 700 pg/ml was reported in an emergency department population (19,20). Another interesting feature of presepsin seems to be the ability to predict outcome in sepsis and also in acute pneumonia (21,22). Future issues remain to be solved concerning presepsin as a new biomarker, such as: influence of age and different medical conditions (e.g renal or hepatic dysfunctions), optimal cut off values in specific types of infections (20, 23).

In this study, we evaluated the presepsin levels in 14 patients with confirmed IE compared to 8 patients with rejected IE. We have confirmed the diagnosis of IE using the gold standard method for this disease: modified Duke criteria. Demographic and clinical features of our patients with definite IE, were similar to those related by a prospective international cohort study (24).

Almost one third of the IE cases in our study were blood culture negative. In other study, proportion of blood culture negative IE was almost 50% (25). We have found that in 80% of blood culture negative endocarditis were due to previous antibiotic treatment. These data were much higher than those reported in previous study (3).

Similar with other study, none of the inflammatory parameters that we routinely use in clinical practice (ESR, CRP, WBC) have shown significant levels in definite IE patients (5). One of the minor Duke criteria is rheumatoid factor (2). In our study, we found significant level for RF in definite IE patients versus rejected IE. Without having this RF increased, final clinical diagnosis of definite IE in blood culture negative patients would not have been possible in two from five cases. These results suggest the importance of routinely searching for rheumatoid factors in all clinical suspicions of IE.

Another finding of our study is that presepsin levels are significantly higher in patients with definite IE than in those with rejected IE. A value of 345 pg/ml had a modest sensitivity but with good specificity and positive predictive value. High specificity of a test means low rate of false positive results, thus being a demanding feature of a diagnostic test (26).

It could be possible that, in clinical situations of high IE suspicion, a positive value of presepsin could sustain the diagnosis before obtaining the blood culture results.

However, this result must be interpreted with caution due to the limitations of our study. First limitation, and the most important one, is the small number of patients due to the low incidence of IE and short period of time**.** Another limit of our study is the lack of a control group with positive blood culture and thus, we could not evaluate the ability of presepsin in predicting bacteremia in IE.

Further research is needed in the area, so as to confirm these preliminary results and also, the role of the presepsin in predicting bacteremia and outcome in IE. The short turnaround time and the easy manipulation of the small size PATHFAST analyzer make it very useful in every hospital. High specificity value of presepsin in identifying bacterial infection could be used as a tool for avoiding overuse of antibiotics in this era of emerging drug resistant microorganisms.

Conclusion

We conclude that presepsin could be a valuable marker not only for sepsis but also for infective endocarditis, both with positive or negative blood cultures. Larger studies are necessary to confirm this finding.

Conflicting interests

The authors declare that they have no conflict of interest.

Acknowledgments

The abstract of this paper has been presented at the 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Copenhagen, Denmark, 25-28 April, 2015.

List of abbreviations

AUC= area under the curve
CD14=cluster of differentiation
CLEIA= chemiluminescent enzyme immunoassay
CRP= C-reactive proteine
EDTA= ethylenediaminetetraacetate
ESC= European Society of Cardiology
ESR= erythrocyte sedimentation rate
ICE-PCS=International Collaboration on Endocarditis - Prospective Cohort Study
IE= infective endocarditis
IL8= interleukin 8
LBP= lypopolysaccharides binding proteine
LPS= lypopolysaccharides
NPV= negative predictive value
PPV= positive predictive value
RF= rheumatoid factor
ROC= receiver operating characteristic
SD=standard deviation
sCD14-ST= soluble cluster of differentiation 14-subtype
Se=Sensitivity
Sp=Specificity
WBC=white blood cells

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