**RESEARCH**
Open Access

# Presepsin is a potent biomarker for diagnosing skin wound infection in hemodialysis patients compared to white blood cell count, high-sensitivity C-reactive protein, procalcitonin, and soluble CD14

Jun Shiota[1,2*], Hitoshi Tagawa[2], Norihiko Ohura[3] and Hitoshi Kasahara[2]

## Abstract

**Background:** The production of presepsin has been shown to be strongly related to bacterial phagocytosis. The purpose of the present study is to compare the usefulness of presepsin for diagnosing localized skin wound infection with that of conventional infection biomarkers.

**Methods:** We enrolled 29 hemodialysis (HD) patients with skin wound infections of foot gangrene or decubitus ("localized infection group") and 20 HD patients without infection ("no infection group"). The white blood cell (WBC) count and high-sensitivity C-reactive protein (hsCRP) and presepsin levels were measured using blood samples collected before HD, 2 days after the previous dialysis session. Soluble CD14 (sCD14) and procalcitonin (PCT) levels were also measured in 12 patients with localized infection and 8 patients without infection.

**Results:** The levels of hsCRP and presepsin were significantly higher in the localized infection group ($N = 29$) than in the no infection group ($N = 20$) ($P = 0.0209$ and $0.0000$, respectively). In receiver operating characteristics (ROC) analyses, when the cut-off values of hsCRP and presepsin were set at 1.07 mg/dL and 2080 pg/mL, respectively, the sensitivity was 0.69 and 0.86, and the specificity was 0.70 and 0.80, respectively. The area under the curve (AUC) was calculated as 0.696 for hsCRP and 0.874 for presepsin. The AUC for presepsin was significantly higher than that for hsCRP ($P = 0.0348$). No marked differences were found in the age, gender, WBC, or sCD14 or PCT levels between groups.

**Conclusions:** Presepsin is a potent, useful biomarker for diagnosing skin wound infection in HD patients compared to conventional infection biomarkers.

**Keywords:** Presepsin, Localized infection, Skin wound infection, Hemodialysis, hsCRP, Procalcitonin, Soluble CD 14

## Background

Complex wounds develop rapidly and are refractory to healing in hemodialysis (HD) patients because of persistent bacterial infection due to immune deficiency and ischemic limbs due to peripheral arterial disease [1]. Bacterial phagocytosis by monocytes is required to overcome bacterial proliferation in order to localize the infection focus [2].

Although bacterial infection of skin wound can be diagnosed by physical signs [3], the bacterial burden is occasionally hard to evaluate in the presence of deep localized lesions or myelitis despite apparently mild skin lesions, resulting in overlooking indications for antibiotics therapy and surgical or vascular intervention.

Presepsin is an N-terminal fragment of CD14 on monocytes with a molecular weight of 13 kDa that was discovered in Japan in 2002 as a biomarker for diagnosing sepsis [4, 5]. In contrast to conventional infection biomarkers which are induced by endotoxins or cytokines, the novel production mechanism of presepsin has

* Correspondence: jun.siota@grp.zenjinkai.or.jp
[1]Department of Internal Medicine, Tsunashima Kidney Clinic, 1-10-4 Tsunashima-Higashi, Kohoku-ku, Yokohama 223-0052, Japan
[2]Department of Internal Medicine, Kichijoji Asahi Hospital, Tokyo, Japan
Full list of author information is available at the end of the article

Shiota *et al. Renal Replacement Therapy* (2017) 3:31

Page 2 of 6

been reported to be closely related to phagocytosis by monocytes [6, 7]. We previously reported the usefulness of presepsin for predicting the prognosis of foot gangrene in HD patients (cut-off plasma value 2083 pg/mL) [8]. In the present study, we hypothesized that presepsin might be useful for diagnosing localized infection, and we compared the diagnosing ability of presepsin for skin wound infection in HD patients with that of conventional infection biomarkers: white blood cell count (WBC) and levels of high-sensitivity C-reactive protein (hsCRP), soluble CD14 (sCD14), and procalcitonin (PCT).

## Methods

### Participants

We enrolled 29 HD patients (male, 48.3%) complicated with skin wound infections of foot gangrene or decubitus ("localized infection group") and 20 HD patients (male, 55.0%) without skin wound ("no infection group") who had been admitted to Kichijoji Asahi Hospital between 2014/1/1 and 2015/3/31. All patients were thoroughly examined to confirm the absence of infection of other organs. Patients who had received immunosuppressants were excluded. Patients with chronic hepatitis and liver cirrhosis were excluded because higher presepsin levels have been observed due to the bacterial translocation [9]. The skin wounds were all examined and evaluated by the same plastic surgeon (who is one of the authors). The localized infection group was defined by skin wounds with exudate/pus, friable tissue, or debris, suggesting critical colonization with ongoing bacterial proliferation [3]. A photograph of a localized skin wound infection is shown in Fig. 1.

Blood was collected with heparin as an anticoagulant using an endotoxin-free tube (TERUMO, Tokyo, Japan) before HD, 2 days after the previous dialysis session, and the blood samples were immediately measured or frozen prior to the analysis of the WBC and levels of hsCRP and presepsin (Table 1; shown as "all patients"). sCD14 and PCT levels were measured additionally in the 20 HD patients ($N = 12$, localized infection group; $N = 8$, no infection group) enrolled after 2015/1/1 (Table 1; shown as "patients examined for all biomarkers including sCD14 and PCT").

All of the patients received 4-h dialysis three times per week with a blood flow rate of 180–200 mL/min and a dialysate flow rate of 400 mL/min. We used high-flux membrane dialyzers that were not reused and standard bicarbonate dialysate diluted with ultrapure water. All dialysate samples were negative for bacteria measured in colony-forming units in bacterial culture and had an endotoxin (ET) level ≤0.001 EU/mL as measured by a chromogenic assay (Endospecy ES-24S; Seikagaku Corporation, Tokyo, Japan).

### Measurement of biomarkers

The WBC was measured using an automated analyzer, LH780 (Beckman Coulter, Tokyo, Japan). The hsCRP levels were measured using an automated analyzer, JCA-BM8060 (JEOL, Tokyo, Japan) based on a turbidometeric immunoassay (CRP-latex X2 "Seiken"; Denka Seiken, Tokyo, Japan). The upper reference limit in healthy volunteers was 0.30 mg/dL. The presepsin levels were measured using an automated immunoanalyzer, PATHFAST, based on a non-competitive chemiluminescent enzyme immunoassay (CLEIA), which contained Magtration technology (LSI Medience Corporation, Tokyo, Japan) [10], modified from an enzyme-linked immunosorbent assay (ELISA) [11]. The method was calibrated using heparinized plasma samples that contained a recombinant human presepsin antigen. The reference range in healthy volunteers has not been established yet [12]. The sCD14 levels were measured using a commercially available ELISA kit (sCD14 Quantikine ELISA Kit; R&D Systems, Minneapolis, USA). The levels were measured in duplicate, and the mean value was used. The median value in healthy volunteers without infection has been reported as 1660 ng/mL [13]. The PCT levels were measured using an automated electrochemiluminescence immunoanalyzer based on Elecsys reagent (BRAHMS PCT; Roche Diagnostics, Tokyo, Japan). The median PCT level in healthy volunteers without infection has been reported as 0.034 ng/mL [14].

### Statistical analyses

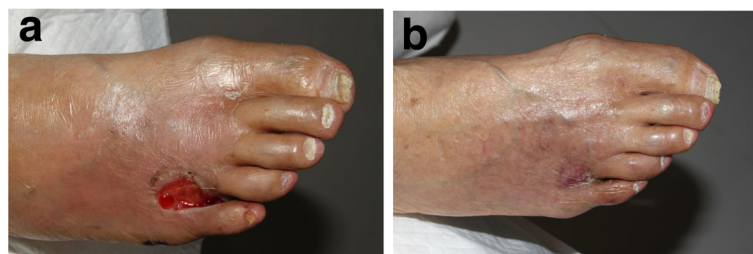The data were presented as the median (interquartile range, IQR). The data were compared between the



**Fig. 1 a** An exudative skin wound indicating a bacterial burden. Presepsin level 4480 pg/mL; **b** healed skin wound (the same case)

Shiota *et al. Renal Replacement Therapy* (2017) 3:31

Page 3 of 6

**Table 1** Comparison of characteristics and infection biomarkers between the localized infection group and the no infection group

| Group | All patients | | Patients examined for all biomarkers including sCD14 and PCT | |
|---|---|---|---|---|
| | Localized infection | No infection | Localized infection | No infection |
| Number | 29 | 20 | 12 | 8 |
| Age, years | 72 (66–77) | 78 (74–83) | 73 (65–78) | 78 (72–84) |
| Male, % | 48.3 | 55.0 | 66.7 | 62.5 |
| WBC, μL | 5700 (4333–7100) | 5250 (4475–6000) | 5800 (4675–6735) | 5450 (4475–5750) |
| hsCRP, mg/dL | 1.26 (0.71–2.24)* | 0.23 (0.10–1.22) | 1.30 (0.50–2.16) | 0.17 (0.11–0.74) |
| Presepsin, pg/mL | 3370 (2240–4480)** | 1510 (1205–1810) | 3330 (2515–3990)* | 1560 (1488–1973) |
| sCD14, ng/mL | | | 2278 (1969–2906) | 2417 (2226–2732) |
| PCT, ng/mL | | | 0.23 (0.20–0.27) | 0.25 (0.21–0.28) |

Data were presented as the median (interquartile range, IQR). Statistics were analyzed using the Mann-Whitney $U$ test. A blood analysis was performed to determine the WBC count, and the hsCRP and presepsin levels of 49 HD patients who were enrolled in 2014/1/1–2015/3/31 (shown as "all patients"). sCD14 and PCT were also measured in the 20 HD patients enrolled after 2015/1/1 (shown as "patients examined for all biomarkers including sCD14 and PCT")
*$P < 0.05$, **$P < 0.01$ vs. the no infection group

localized infection group and the no infection group using Fisher's exact test or the Mann-Whitney $U$ test. A receiver operating characteristic (ROC) analysis was performed to determine the area under the curve (AUC), sensitivity and specificity. Diagnostic AUCs were compared using DeLong's test [15]. The calculations were performed using R 3.3.1, which is open to the public. All analyses set a $P$ value of 0.05 (two-tailed) to indicate significance.

## Results

### Comparison between two groups for all patients ($N = 49$)

The levels of hsCRP and presepsin were significantly higher in the localized infection group ($N = 29$) than in the no infection group ($N = 20$) ($P = 0.0209$ and $0.0000$, respectively), although no marked differences were found in the age, gender, or WBC (Table 1). In ROC analyses (Fig. 2), when the cut-off values of hsCRP and presepsin were set at 1.07 mg/dL and 2080 pg/mL, respectively, the sensitivity was 0.69 and 0.86, and the specificity was 0.70 and 0.80, respectively. The AUC was calculated as 0.696 for hsCRP and 0.874 for presepsin. The AUC for presepsin was significantly higher than that for hsCRP ($P = 0.0348$) (Fig. 2).

### Comparison between two groups for the patients examined additionally for sCD14 and PCT ($N = 20$)

The levels of presepsin were significantly higher in the localized infection group ($N = 12$) than in the no infection group ($N = 8$) ($P = 0.0206$), although no marked differences were found in the age, gender, WBC, hsCRP, sCD14, or PCT levels (Table 1, Fig. 3).

## Discussion

Chronic wound infection is categorized into four stages: "contamination," "colonization," "critical colonization," and "infection". In the "critical colonization" stage,

bacterial proliferation has exceeded the phagocytosis potential of macrophages [2]. Sibbald et al. [16] created an assessment model using the mnemonic NERDS (exudate/ pus, friable tissue, debris, nonhealing and smell) to predict critical colonization. Woo et al. [3] devised a semi-quantitative bacterial culture system using wound swabs, in which the bacterial burden of the wound is classified as "scant," "light," "moderate," or "heavy" for bacterial growth; scant to light bacterial growth was considered to reflect critical colonization. The odds ratios for individual
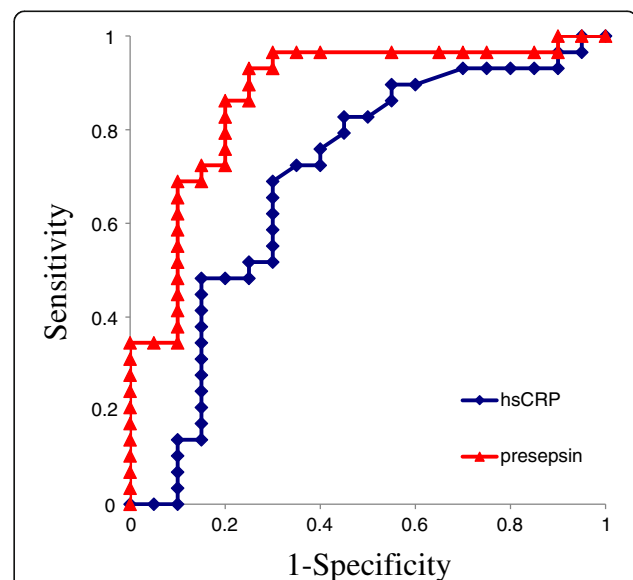
**Fig. 2** Receiver operating characteristic (ROC) curves of presepsin and hsCRP for discriminating the localized infection group ($N = 29$) and the no infection group ($N = 20$). When the cut-off value of presepsin and hsCRP were set at 2080 pg/mL and 1.07 mg/dL, respectively, the sensitivity was 0.86 and 0.69, and the specificity was 0.80 and 0.70, respectively. The AUC was calculated as 0.874 for presepsin and 0.696 for hsCRP, and the AUC for presepsin was significantly higher than that for hsCRP ($P = 0.0348$)
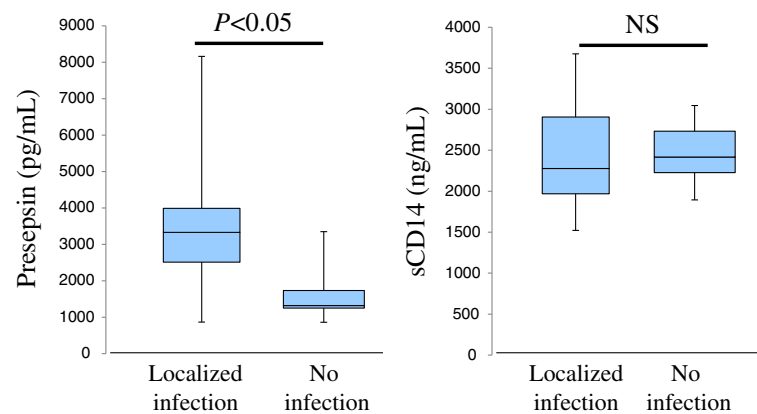
Shiota *et al. Renal Replacement Therapy* (2017) 3:31

Page 4 of 6



**Fig. 3** Comparison of presepsin and sCD14 levels between the localized infection group and the no infection group

NERDS variables and scant/light bacterial growth were calculated and wounds were found to be five times more likely to have a scant/light bacterial growth in the presence of exudate/pus, friable tissue, or debris. In the present study, localized infection was defined as a state of critical colonization, which was diagnosed based on the presence of exudate/pus, friable tissue, or debris.

Presepsin and hsCRP were recognized as useful biomarkers in the present study but the WBC and the sCD14 and PCT levels were not useful for diagnosing localized skin wound infection. ROC analyses showed that the AUC of presepsin was significantly higher than that of hsCRP (0.874 vs. 0.696, $P = 0.0348$) and the sensitivity and specificity of presepsin were 0.86 and 0.80 respectively when the cut-off value was set at 2080 pg/mL. The AUC of presepsin was higher than the evaluation criterion of 0.75 required for the diagnostic ability of biomarkers [17]. The AUC, sensitivity, and specificity for localized infection in the present study were comparable to those for sepsis in meta-analyses (0.874, 0.86, 0.80 vs. 0.89, 0.83, 0.81) [18]. Therefore, presepsin may have the most reliable diagnostic ability among infection biomarkers for diagnosing localized infection.

An in vitro study showed that the stimulation of whole blood (including monocytes) from healthy volunteers by lipopolysaccharide (LPS) induced a significant increase in the plasma IL-6 levels, with no significant increase in presepsin levels [19]. CRP seemed to be stimulated by IL-6 released from monocytes in a localized infection group [20], but presepsin might be produced by different mechanisms. The relationship between presepsin production and bacterial phagocytosis by monocytes has been previously demonstrated. It has been shown that presepsin levels increased in a rabbit model of cecal ligation and puncture sepsis but not in a rabbit ET shock model and that presepsin production from peritoneal granulocyte was stimulated by *Escherichia coli* and suppressed by the inhibition of phagocytosis [7]. In vitro

presepsin production by peripheral mononuclear cells was increased by *Escherichia coli*, *Staphylococcus epidermidis*, and sterile monosodium urate crystals and suppressed by an inhibitor of phagocytosis, whereas presepsin production was not induced by peptidoglycan or LPS [6]. Taking into account a report that presepsin levels were not markedly different between systemic bacterial infection patients (positive blood culture) and localized bacterial infection patients (positive culture except blood) [21], presepsin produced by bacterial phagocytosis at a localized infection site might increase the presepsin levels in circulating blood.

CD14 is a pattern-recognition receptor that plays an immunomodulatory role in secreting pro-inflammatory humoral factors in response to not only ET but also lipoteichoic acid (LTA), which is a major constituent of Gram-positive bacteria [22]. sCD14 is a fragment of CD14, and its levels are increased by ET (LPS) stimulation in vitro [23]. In HD patients, sCD14 levels are increased compared with healthy volunteers, probably because of inevitable exposure to ET (LPS) due to contaminated dialysate, intestinal bacterial translocation, and an impaired liver macrophage function [24, 25]. As no marked differences in the sCD14 levels were observed between the localized infection group and the no infection group in the present study, a significant ET (LPS) load from skin wound infection site is unlikely to be observed. Therefore, sCD14 is not appropriate as a biomarker for diagnosing localized skin wound infection, in contrast to presepsin, which is also a fragment of CD14 (Fig. 3). Although both sCD14 and presepsin are released by proteolysis with protease from monocytes, the mechanism is likely to be different. In contrast to sCD14, which was reported to be produced from cell-surface CD14 of activated monocytes [26, 27], presepsin is reported to be produced from monocytes that are activated in the event of phagocytosis [6].

PCT is a polypeptide with a molecular weight of 13 kDa that was first described in 1993 as a biomarker for the diagnosis of sepsis. PCT is mainly produced by

Shiota *et al. Renal Replacement Therapy* (2017) 3:31

Page 5 of 6

monocytes in circulating blood [28], and iatrogenic ET (LPS) load into circulating blood was reported to increase the PCT levels [29]. PCT is ubiquitously produced in response to ET (LPS) in HD patients. The PCT levels in HD patients without infection were reported to be about eight times as high as those in healthy volunteers without infection (median 0.260 vs. 0.034 ng/mL) [14]. In the present study, PCT was not useful for detecting localized skin wound infection, because the PCT levels were not elevated in the localized infection group compared with the no infection group (median 0.23 vs 0.25 ng/mL). The PCT values within a range of 0.13–0.30 ng/mL in the localized infection group of the present study were obviously lower than the cut-off value of 0.5 ng/mL reported in the HD patients with pneumonia and sepsis [30], suggesting that the bacterial load into the circulating blood from the skin wound infection was unlikely.

The presepsin levels of HD patients are higher than those of healthy volunteers [31], and the reference range of presepsin levels, even in healthy volunteers, has not been established yet [32]. It has been reported that the presepsin levels are inversely correlated with the glomerular filtration rate (GFR) and that they significantly decrease after an HD session [31]. As presepsin (a 13-kDa protein) is freely filtered through the glomeruli and is almost completely reabsorbed and catabolized within the proximal tubular cells [33], the increased levels in the patients with a decreased GFR might be caused by the decreased filtration and catabolism in the kidney. In addition, the increased presepsin levels in HD patients might also be caused by inevitable exposure to ET (LPS), due to the contamination of the dialysate, intestinal bacterial translocation, and an impaired liver macrophage function [24, 25].

Our results showed that the usefulness of presepsin in HD patients for diagnosing skin wound infection was comparable to that for sepsis and superior to the conventional infection biomarkers (WBC, hsCRP, sCD14, and PCT). The cut-off value (2080 pg/mL) for diagnosing skin wound infection was close to that (2083 pg/mL) for predicting the prognosis of foot gangrene [8].

To our knowledge, the present study is the first to address the potential value of presepsin for diagnosing localized infection in HD patients; however, further verification of the usefulness of presepsin for diagnosing localized infection using a larger number of HD patients is necessary before application in clinical practice. In addition, the usefulness of presepsin for diagnosing infection of various organs must also be verified.

## Conclusions

Presepsin is a potent, useful infection biomarker for diagnosing skin wound infection in HD patients compared to conventional infection biomarkers.

## Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## Author details
[1]Department of Internal Medicine, Tsunashima Kidney Clinic, 1-10-4 Tsunashima-Higashi, Kohoku-ku, Yokohama 223-0052, Japan. [2]Department of Internal Medicine, Kichijoji Asahi Hospital, Tokyo, Japan. [3]Department of Plastic, Reconstructive and Aesthetic Surgery, Kyorin University School of Medicine, Tokyo, Japan.

## References
1. Fujioka M, Oka K, Kitamura R, Yakabe A. Complex wounds tend to develop more rapidly in patients receiving hemodialysis because of diabetes mellitus. Hemodial Int. 2009;13:168–71.
2. Kingsley A. The wound infection continuum and its application to clinical practice. Ostomy Wound Manag. 2003;49(7A Suppl):1–7.
3. Woo KY, Sibbald RG. A cross-sectional validation study of using NERDS and STONEES to assess bacterial burden. Ostomy Wound Manag. 2009;55:40–8.
4. Yaegashi Y, Shirakawa K, Sato N, et al. Evaluation of a newly identified soluble CD14 subtype as a marker for sepsis. J Infect Chemother. 2005;11:234–8.
5. Shozushima T, Takahashi G, Matsumoto N, Kojika M, Okamura Y, Endo S. Usefulness of presepsin (sCD14-ST) measurements as a marker for the diagnosis and severity of sepsis that satisfied diagnostic criteria of systemic inflammatory response syndrome. J Infect Chemother. 2011;17:764–9.
6. Arai Y, Mizugishi K, Nonomura K, Naitoh K, Takaori-Kondo A, Yamashita K. Phagocytosis by human monocytes is required for the secretion of presepsin. J Infect Chemothr. 2015;21:564–9.
7. Naitoh K, Shirakawa K, Hirose J, Nakamura M, et al. The new sepsis marker, sCD14-ST (PRESEPSIN), induction mechanism in the rabbit sepsis models. Crit Care. 2010;14 Suppl 2:19.
8. Shiota J, Ohura N, Higashikawa S, et al. Presepsin as a predictor of critical colonization in CLI hemodialysis patients. Wound Rep Reg. 2016;24:189–94.
9. Papp M, Tornai T, Vitalis Z, Tornai I, Tornai D, Dinya T, et al. Presepsin teardown-pitfalls of biomarkers in the diagnosis and prognosis of bacterial infection in cirrhosis. World J Gastroenterol. 2016;22:9172–85.
10. Okamura Y, Yokoi H. Development of a point-of-care assay system for measurement of presepsin (sCD14-ST). Clin Chim Acta. 2011;412:2157–61.

Shiota *et al. Renal Replacement Therapy* (2017) 3:31

Page 6 of 6

11. Shirakawa K, Naitoh K, Hirose J, Takahashi T, Furusako S. Presepsin (sCD14-ST): development and evaluation of one-step ELISA with a new standard that is similar to the form of presepsin in septic patients. Clin Chem Lab Med. 2011;49:937–9.

12. Chenevier-Gobeaux C, Borderie D, Weiss N, Mallet-Coste T, Claessens YE. Presepsin (sCD14-ST), an innate immune response marker in sepsis. Clin Chim Acta. 2015;450:97–103.

13. Sandler NG, Koh C, Roque A, et al. Host response to translocated microbial products predicts outcomes of patients with HBV or HCV infection. Gastroenterology. 2011;141:1220–30.

14. Trimarchi H, Dicugno M, Muryan A, et al. Pro-calcitonin and inflammation in chronic hemodialysis. Medicina. 2013;73:411–6.

15. DeLong ER, DeLong DM, Clarke-Peason DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics. 1988;44:837–45.

16. Sibbald RG, Woo K, Ayello EA. Increased bacterial burden and infection: the story of NERDS and STONES. Adv Skin Wound Care. 2006;19:447–61.

17. Behnes M, Bertsch T, Lepiorz D, et al. Diagnostic and prognostic utility of soluble CD14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. Crit Care. 2014;18:507.

18. Tong X, Cao Y, Yu M, Han C. Presepsin as a diagnostic marker for sepsis: evidence from a bivariate meta-analysis. Ther Clin Risk Manag. 2015;11:1027–33.

19. Chenvier-Gobeaux C, Bardet V, Poupet H, Poyart C, Borderie D, Claessens YE. Presepsin (sCD14-ST) secretion and kinetics by peripheral blood mononuclear cells and monocytic THP-1 cell line. Ann Biol Clin. 2016;74:93–7.

20. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111:1805–12.

21. Endo S, Suzuki Y, Takahashi G, et al. Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study. J Infect Chemothr. 2012;18:891–7.

22. Miyake K. Innate recognition of lipopolysaccharide by Toll-like receptor 4-MD-2. Trends Microbiol. 2004;12:186–92.

23. Marcos V, Latzin P, Hector A, et al. Expression, regulation and clinical significance of soluble and membrane CD14 receptors in pediatric inflammatory lung diseases. Respir Res. 2010;11:32.

24. Navarro-Gonzalez JF, Mora-Femandez C, Muros de Fuentes M, Donate-Correa J, Cazana-Perez V, Garcia-Perez J. Effect of phosphate binders on serum inflammatory profile, soluble CD14, and endotoxin levels in hemodialysis patients. Clin J Am Soc Nephrol. 2011;6:2272–9.

25. Seabra VF, Thomas G, Jaber BL. Soluble CD14 and endotoxin levels in hemodialysis patients: A tale of 2 molecules. Am J Kidney Dis. 2009;54:990–2.

26. Nockher WA, Scherberich JE. Monocyte cell-surface CD14 expression and soluble CD14 antigen in hemodialysis: evidence for chronic exposure to LPS. Kidney Int. 1995;48:1469–76.

27. Bazil V, Strominger JL. Shedding as a mechanism of down-modulation of CD14 on stimulated human monocytes. J Immunol. 1991;147:1567–74.

28. Oberhoffer M, Stonans I, Russwurm S, et al. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro. J Lab Clin Med. 1999;134:49–55.

29. Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis. Intensive Care Med. 1998;24:888–9.

30. Grace E, Tutner RM. Use of procalcitonin in patients with various degrees of chronic kidney disease including renal replacement therapy. Clin Infect Dis. 2014;59:1761–7.

31. Nagata T, Yasuda Y, Ando M, et al. Clinical impact of kidney function on presepsin levels. PloS one. 2015;10:e0129159. doi:10.1371/journal.pone.0129159.

32. Giavarina D, Carta M. Determination of reference interval for presepsin, an early marker for sepsis. Biochem Med. 2015;25:64–8.

33. Chenevier-Gobeaux C, Trabattoni E, Roelens M, Borderie D, Claessens Y-E. Presepsin (sCD14-ST) in emergency department: The need for adapted threshold values? Clin Chim Acta. 2014;427:34–6.