

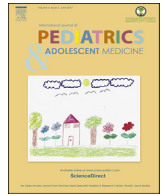
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Original research article

## New diagnostic biomarker in acute diarrhea due to bacterial infection in children

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## ABSTRACT

**Background and objectives:** Diarrhea is a major cause of morbidity and mortality in children, and diarrhea may be due to infection that is bacterial or non-bacterial. Differentiation between diarrhea from a bacterial or non-bacterial infection is not a simple task, and no single method is present to differentiate between these causes of diarrhea.

To evaluate the diagnostic accuracy of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and procalcitonin (PCT) in the diagnosis of acute diarrhea due to bacterial infection.

**Patients and methods:** Case control study of forty children with bacterial infection diarrhea diagnosed by stool culture and CRP, 40 children with acute non-bacterial infection diarrhea and 30 age- and sex-matched healthy controls. Stool cultures, serum CRP, PCT and serum sTREM-1 were measured in all children on admission.

**Results:** Children with acute bacterial infection diarrhea had a significant increase in the serum sTREM-1 and PCT levels on admission compared to patients with nonbacterial infection diarrhea and controls (26.3667 ± 16.8184 ng/ml vs 7.2267 ± 6.4174 ng/ml vs 6.7367 ± 5.6479 ng/ml and 39.9933 ± 22.5260 ng/ml vs 1.8533 ± 1.7123 vs 0.2840 ± 0.1208 ng/ml, respectively;  $P < 0.05$ ). sTREM-1 demonstrated significantly higher sensitivity (93.7%) and specificity (94.3%) in the prediction of bacterial infection as a cause of acute diarrhea in children with an area under the receiver operator characteristic (ROC) curve (95% CI) of 0.94 (0.84–0.99) at a cutoff value of 12.4 ng/ml.

**Conclusions:** Both serum PCT and sTREM-1 are valuable in the early diagnosis of acute bacterial infection-induced diarrhea in children, and there was markedly higher diagnostic discriminatory power for sTREM-1.

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## 1. Introduction

Although it is a preventable disease, acute diarrhea remains a major cause of morbidity and mortality in children worldwide, resulting in more than 1.8 million deaths per year among those younger than five years. Most of these mortalities occur in developing countries [1]. Diarrhea in children is caused by a wide range

of pathogens, including viral, bacterial and protozoal pathogens. These pathogens make overcoming the high disease burden a large challenge [2]. In developed countries, the morbidity and mortality caused by acute diarrhea have become less threatening in recent decades. However, acute diarrhea continues to be an important and frequent cause of hospitalization; it has significant morbidity, especially in young children under 5 years of age in developing countries [3]. The frequency of bacterial and parasitic gastrointestinal infections has declined with improvements in the public health infrastructure (water and sewage management); however, this is not the case with viral gastroenteritis [4]. A rapid, reliable test that predicts bacterial infection is beneficial to improving the outcome through early antibiotic treatment [5]. Markers of bacterial infection include a routine leukocyte count and C-reactive

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protein (CRP) [6]. During the acute phase response, there is an increase in the blood levels of many proteins, including C-reactive protein (CRP) and procalcitonin (PCT). Both showed better performance than other traditionally used markers, such as leukocyte counts, to differentiate between bacterial and viral infections [7–11]. Because they are fast, without requiring time for the bacteriology results, and can rule out bacterial infection, particularly for PCT, they are routinely used in developed countries [12,13]. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is a newly proposed marker [14].

The molecular weight of CRP is 120 kDa, and its gene location is between 1q21 and 1q23. It is an important component of the innate defense system against infections [15]. It recognizes the phosphocholine on the surface of many bacteria; then, it activates the classical complement pathway and facilitates phagocytosis by neutrophils. Because CRP lacks specificity, it is used as an additional marker in combination with more conventional parameters, such as the number of leukocytes in CSF, blood count and protein level, to help the clinician to narrow down the differential diagnosis [16]. PCT protein (the calcitonin precursor propeptide) is synthesized in C cells of the thyroid gland and secreted from leukocytes in the peripheral blood. Its molecular weight is 13 kDa [17], and its gene is located on the short arm of chromosome 11 (11p15.4) [16]. In bacterial infection, the secretion of PCT is increased up to several thousand-fold, but it remains normal or slightly increased in viral infections and inflammatory reactions that are not infectious [18]. The serum PCT level increases within 2–3 h after infection with a peak value at 6–12 h, which normalizes within 2 days. In contrast, the CRP levels increase between 12 and 18 h after bacterial infections [19,20]. PCT is stable in plasma and its plasma half-life is approximately 22 h. Unlike most cytokines, PCT is stable in vitro, which makes it both a promising new marker for early and sensitive identification of infected patients as well as for titration of the response to treatment [21]. However, PCT is not considered an ideal marker because it is elevated in conditions other than infection, and it may remain low in infections [22]. Additionally, the use of PCT is complicated by variation in the choice for the abnormal cutoff value and the diverse age range.

On the other hand, TREM-1 is a trans-membrane glycoprotein cell-surface receptor of the immunoglobulin superfamily. TREM-1 acts in cooperation with toll-like receptors (TLRs), and this cooperation is controlled by nuclear factor- $\kappa$ B (NF- $\kappa$ B) [23]. The expression of TREM-1 is up-regulated on phagocytic cells in the presence of bacteria and fungi, triggering the secretion of the pro-inflammatory cytokines that amplify the host response to the microbial agents [24]. Some data have demonstrated that expression of membrane-bound TREM-1 on neutrophils and monocytes/macrophages is strongly altered during bacterial infection, peaking at 6 h. Therefore, the aim of this study was to evaluate the diagnostic utility of these markers (PCT and sTREM1) in acute diarrhea from bacterial infection and their usefulness in differentiating between acute diarrhea from bacterial and non-bacterial infections.

## 2. Patients and methods

**Subjects:** This study was performed on eighty infants and children with acute diarrhea, aged 3–36 months, admitted to the Pediatric Department at Tanta University Hospital, Tanta, Egypt. Another 40 age- and sex-matched, apparently healthy infants and children were enrolled as controls. Diarrhea was defined according to the WHO case definition criteria [1].

**Exclusion criteria:** Patients with chronic diarrhea, malnutrition, other systemic infections, or those who had received antibiotics in the last 14 days before enrollment or had co-existing morbidities were excluded. Informed consent was obtained from the guardians

of the studied infants and children before study participation.

Children with acute diarrhea were further subdivided into the following two groups:

**Group 1: children with acute diarrhea due to bacterial infection (no = 40).** Bacterial infection was diagnosed by the presence of all of the following: fever, toxic manifestation, leukocytosis and positive stool bacterial culture (the isolated bacterial pathogens included the following: *Escherichia coli* in 47%, *Campylobacter jejuni* in 20%, *Shigella* in 17% and *Salmonella* in 16%).

**Group 2: children with acute diarrhea due to non-bacterial infection (no = 40),** including those positive for rotavirus antigen in stool and those with proven protozoal infection (*Entamoeba histolytica* or *Giardia lamblia*) in stool analysis with negative results for stool bacterial cultures.

On admission, the following items were recorded for each patient: age, sex, vital signs and clinical symptoms and signs (fever, vomiting and diarrhea). Acute diarrhea was defined as an increase in the number of loose stools to more than the normal number (i.e., an increase to  $\geq 2$  loose stools per day) for a period of <15 days. History taking included the following: administration of antibiotics, recent travel abroad, date and duration of admission, duration of illness and previous hospitalization or history of diarrhea. Thorough clinical examination was performed with special emphasis on the assessment of dehydration level following the recommendations of the WHO Program for Control of Diarrheal Diseases. The symptoms were regularly evaluated and recorded daily on the follow-up chart along with the diarrheal episode.

### 2.1. Stool samples

A single stool specimen was collected from each child with the help of their parents. The specimens were examined for the color and consistency of the stools. Fresh fecal specimens were examined by light microscopy for the presence of parasitic ova, cysts, blood, mucous, pus cells, fatty drops and white blood cells (WBCs) as well as by the modified acid-fast stain for *Cryptosporidium parvum*. All stool specimens were cultured for *Salmonella*, *Shigella*, *Campylobacter jejuni*, *Vibrio cholerae*, and *Escherichia coli* by standard methods [25]. Stool samples were tested for rotavirus antigen by enzyme immunoassay (EIA) using a kit (RIDASCREEN® Rotavirus test, R-Biopharm AG, Landwehrstr. Darmstadt, Germany) [26].

**Blood samples** were used for routine laboratory investigations, including CRP, leukocyte count, PCT, and sTREM-1 measurements. After 72 h of antibiotic treatment for cases with evidence of acute diarrhea due to bacterial infection, the CRP, serum PCT and sTREM-1 levels were re-estimated.

**Serum analysis:** Serum was separated from blood samples collected on admission from all patients and after 3 days from patients who received antibiotic treatment for acute bacterial diarrhea. The serum was then stored at  $-20^{\circ}\text{C}$ .

**C-reactive protein (CRP):** A nephelometric assay (Dade-Behring, France) was used to measure CRP with a detection limit of 0.2 mg/l and intra-assay coefficients of variation at low and high concentrations of 3.3% and 2%, respectively, using the normal value of 6 mg/l [27].

**Procalcitonin (PCT):** A specific immunoluminometric assay (LUMItest®, Brahms Diagnostica GmbH, Germany) was used to measure the PCT in duplicate. Luminescence was automatically measured on a Berilux Analyzer 250 (Behring Diagnostics, Germany). The detection limit was 0.08 ng/ml, and the intra-assay coefficients of variation at low and high concentrations were 12% and 5%, respectively. The normal serum PCT for this assay is  $< 0.5$  ng/ml [28].

**Soluble triggering receptor expressed on myeloid cell-1 ELISA:** According to the manufacturer's instructions (Quantikine

Human TREM-1 Immunoassay, R&D Systems, USA), TREM-1 was measured with a commercially available human ELISA kit using a murine monoclonal antibody specific for human TREM-1 coating on a 96-well plate, 50  $\mu$ l of recombinant human TREM-1 standards and/or samples, 200  $\mu$ l of polyclonal antibody against TREM-1 conjugated to horseradish peroxidase and 200  $\mu$ l of TMB solution containing tetramethylbenzidine as a substrate. The color was developed in proportion to the level of bound TREM-1, which changed from blue to yellow by the stop solution, and the intensity was measured at 450 nm. The concentration of sTREM-1 was then obtained from the standard curve. The mean minimum detectable dose was 13.8 pg/ml with intra-assay variability of 3–7% and inter-assay variability of 6–8% when measured in duplicate [29].

### 3. Statistical analysis

Data were expressed as the range and mean  $\pm$  standard deviation (SD) for quantitative data or numbers and percentages for qualitative data. Statistical analysis was performed using SPSS for Windows, version 16. The level of significance was adopted at  $P < .05$ . Receiver operator characteristic (ROC) plots were performed using MedCalc software to determine the areas under the curve (AUCs) with 95% confidence intervals for the three markers to detect acute bacterial diarrhea.

### 4. Results

Our study showed that there was no significant difference between all studied groups regarding the age or sex. Similarly, the

mean values for the serum sodium, serum potassium and hemoglobin were not significantly different between the studied groups. The mean body temperature values were significantly higher in children with bacterial diarrhea than in those with non-bacterial diarrhea or in controls, and they were significantly higher in the non-bacterial diarrhea group compared to the control group. With respect to the total and differential leucocyte counts, children with acute bacterial diarrhea had significantly higher levels of both the total leucocyte count and segmented neutrophil percentages than those with non-bacterial diarrhea and controls. On the other hand, the lymphocyte percentages were significantly higher in those with non-bacterial diarrhea than in controls and higher in the former two groups than in those with bacterial diarrhea, as shown in Table 1.

Children with bacterial diarrhea had blood, mucous and pus in their stool. Significantly more patients in the bacterial diarrhea group had more RBCs and pus on stool examination than in those with non-bacterial diarrhea, as seen in Table 2.

Serum C reactive protein was significantly higher in children with acute bacterial diarrhea than in children with non-bacterial diarrhea and controls. For both serum procalcitonin and serum TREM 1, the mean levels were significantly higher in children with acute bacterial diarrhea than in children with non-bacterial diarrhea and controls, but no significant differences were found on comparison between children with non-bacterial diarrhea and controls.

The levels of the three studied markers, serum C reactive protein, serum procalcitonin and serum TREM1, were significantly decreased in children with acute bacterial diarrhea on re-

**Table 1**  
Characteristics and laboratory data of the studied groups at presentation.

Parameter	Bacterial diarrhea (culture positive) (n = 40)		Non-bacterial diarrhea (culture negative) (n = 40)		Controls (n = 30)		F	P-value
Age (months)	15.53	$\pm$ 9.209	14.03	$\pm$ 9.212	15.10	$\pm$ 8.372	0.224	.800 .793 <sup>a</sup> .981 <sup>b</sup> .889 <sup>c</sup>
Temperature (°C)	38.610	$\pm$ 0.6429	38.047	$\pm$ 0.7587	37.237	$\pm$ 0.3211	39.275	.000* .001* <sup>a</sup> .000* <sup>b</sup> .000* <sup>c</sup>
serum Na (mEq/l)	137.96	$\pm$ 3.189	137.89	$\pm$ 5.662	140.05	$\pm$ 3.009	2.656	.076 .998 <sup>a</sup> .127 <sup>b</sup> .112 <sup>c</sup>
serum K (mEq/l)	3.8577	$\pm$ 0.2672	3.9150	$\pm$ 0.46066	3.9057	$\pm$ 0.26859	0.239	.788 .796 <sup>a</sup> .852 <sup>b</sup> .994 <sup>c</sup>
Hb (gm/dL)	10.403	$\pm$ 0.7185	10.667	$\pm$ 1.2254	10.810	$\pm$ 1.0018	1.267	.287 .569 <sup>a</sup> .264 <sup>b</sup> .845 <sup>c</sup>
WBCs (x 10 <sup>3</sup> /mm <sup>3</sup> )	12520.0	$\pm$ 4441.9	8066.67	$\pm$ 2731.22	9986.7	$\pm$ 2620.44	13.185	.000* .000* <sup>a</sup> .013* <sup>b</sup> .076 <sup>c</sup>
Lymphocytes %	27.27	$\pm$ 6.198	55.03	$\pm$ 18.757	42.73	$\pm$ 7.320	39.256	.000* .000* <sup>a</sup> .000* <sup>b</sup> .001* <sup>c</sup>
Neutrophils seg. %	59.57	$\pm$ 7.509	41.73	$\pm$ 19.210	36.93	$\pm$ 5.595	28.026	.000* .000* <sup>a</sup> .000* <sup>b</sup> .293 <sup>c</sup>

\* $P = .000$  means  $P < .0005$ .

<sup>a</sup> Bacterial group vs non-bacterial group.

<sup>b</sup> Bacterial group vs control group.

<sup>c</sup> Non-bacterial group vs control group.

**Table 2**  
The stool characteristics of the studied groups.

Variable	Group	Group				Chi-square	
		Bacterial diarrhea (culture positive) (n = 40)		Non-bacterial diarrhea (culture negative) (n = 40)		X <sup>2</sup>	P-value
		N	%	N	%		
Stool mucus	Positive	26	65	35	87.5	4.490	.072
	Negative	14	35	5	12.5		
Stool RBCs	Positive	33	83.3	16	40	12.466	.001*
	Negative	7	16.7	24	60		
Stool pus	Positive	20	50	6	15	12.21	.002*
	Negative	20	50	34	85		

\*P = .000 means P < .0005.

assessment at 72 h after starting antibiotic treatment, as shown in Tables 3 and 4.

In our study, the ROC curve analysis showed that sTREM1, at a cutoff value of >14.5 ng/ml, had a higher sensitivity (93.33%) and specificity (93.33%) than procalcitonin (66.7% and 80%, respectively, at a cutoff value of >4.95 ng/ml), but C reactive protein showed the highest sensitivity (100%) and had specificity similar to procalcitonin. The highest sensitivity was for CRP (100%), while sTREM-1 had the highest specificity (93.33%), as shown in Table 5. The area under the curve was 0.99 for CRP, 0.95 for sTREM-1 and 0.88 for PCT (Fig. 1).

## 5. Discussion

Diagnosis of the cause of acute diarrhea, whether bacterial or not, is considered a cornerstone in diarrhea management. Appropriate diagnosis would prevent unnecessary antibiotic administration and hospital admission, on the one hand, and serious negative outcomes results, including death, on the other hand. Recent strategies in the management of diarrhea have been directed toward the use of a combination of clinical and laboratory information, such as the CBC, neutrophil count, and CRP concentrations; however, there is a possibility of overlap between bacterial infection and non-bacterial infection in up to 40% of cases [30]. New accurate, rapid, and reliable diagnostic methods to differentiate between bacterial and non-bacterial diarrhea have been intensively researched and performed with varying degrees of success. Only a few of these methods have been reported [31]. Therefore, this work

aimed to evaluate the use of sTREM compared to PCT and CRP in the early diagnosis and differentiation between acute bacterial and non-bacterial causes of infectious diarrhea in children. Initially, **Assicot et al.** described procalcitonin as a potential marker of bacterial diseases [32]. PCT was assumed to be a protein of the acute phase of inflammation with kinetics faster than that of CRP. Indeed, this marker has gained a solid scientific basis as many studies have demonstrated that quantitative evaluation of PCT is superior to the other biomarkers. Our results showed that children with acute diarrhea due to bacterial infection had a significantly higher mean level of procalcitonin than those with non-bacterial infectious diarrhea and controls. Our study supported the role of serum PCT measurement in distinguishing between acute bacterial diarrhea and acute non-bacterial diarrhea with a 66.7% sensitivity and 80% specificity on admission at a cut off value of >4.95 ng/ml. The rapid kinetics and higher specificity of PCT make it superior to CRP in predicting bacterial infection [10], although the performances of both PCT and CRP were similar. It is important to note that the increase in the PCT and CRP in bacterial infection is due to extra-cellular multiplication in the bloodstream, which induces a strong systemic inflammatory response. In the study by **Ibrahim et al.** [33], the serum PCT levels were significantly higher in bacterial meningitis than in non-bacterial meningitis. This was supported by an African study reported by **Carrol et al.** [14] who concluded that PCT is the best diagnostic and prognostic marker of severe bacterial sepsis in Malawian children, including those with septic meningitis. Therefore, serum PCT is considered to have a better diagnostic and prognostic value for differentiating between bacterial and non-bacterial infections. PCT is also a good indicator of the treatment efficacy for bacterial infection [34]. The specific involvement of TREM-1 in cases of bacterial infection has led researchers to investigate the diagnostic value of the plasma sTREM-1 assay in distinguishing infectious from severe systemic non-infectious inflammation among newly admitted critically ill patients with suspected bacterial infection. Although the baseline plasma levels of CRP, PCT and sTREM-1 were higher in septic patients than in patients with systemic inflammatory response syndrome, only the serum sTREM-1 levels appeared to be the most helpful parameter in differentiating between them [35]. A comparative study of the accuracy of five markers in the diagnosis of serious bacterial infections (SBI), including meningitis, concluded that PCT and not sTREM-1 was the best diagnostic marker [36]. Unfortunately, little is known about the role of sTREM in bacterial diarrhea. Therefore, one of our main goals in this study was to evaluate the role of measuring serum sTREM-1 levels in differentiating between acute

**Table 3**  
CRP, PCT and sTREM serum levels on admission in the studied groups.

Parameter	Bacterial diarrhea (culture positive) (n = 40)		Non-bacterial diarrhea (culture negative) (n = 40)		Controls (n = 30)		F	P-value			
	Mean	SD	Mean	SD	Mean	SD					
TREM 1st day (ng/ml)	26.3667	±	16.81847	7.2267	±	6.41748	6.7367	±	5.64798	31.687	.000* .000 <sup>a</sup> .000 <sup>b</sup> .983 <sup>c</sup>
Procalcitonin 1st day (ng/ml)	39.9933	±	22.52609	1.8533	±	1.71238	0.2840	±	0.12082	89.169	.000* .000 <sup>a</sup> .000 <sup>b</sup> .887 <sup>c</sup>
CRP 1st day (mg/L)	104.5000	±	25.59061	29.567	±	20.35154	3.6400	±	1.18047	230.648	.000* .000 <sup>a</sup> .000 <sup>b</sup> .000 <sup>c</sup>

\*P = .000 means P < .0005.

<sup>a</sup> Bacterial group vs non-bacterial group.

<sup>b</sup> Bacterial group vs control group.

<sup>c</sup> Non-bacterial group vs control group.



**Table 4**

Comparison of the CRP, PCT and sTREM serum levels on admission and after 72 h in the bacterial diarrhea group.

Bacterial diarrhea (culture positive)	Mean	±	SD	F	Sig.
CRP 1st day (mg/L)	104.5000	±	25.59061	94.069	0.000*
CRP 72 h	34.0333	±	7.96321		
TREM 1st day (ng/ml)	26.3667	±	16.81847	168.417	0.000*
TREM 72 h	13.0200	±	12.80677		
Procalcitonin 1st day (ng/ml)	39.9933	±	22.52609	457.172	0.000*
Procalcitonin 72 h	7.5167	±	4.25328		

\*P = .000 means P &lt; .0005.

**Table 5**

Sensitivity, specificity and positive and negative predictive values (%) of baseline the CRP, PCT and sTREM values for the acute bacterial diarrhea (culture positive) group.

Marker	Cutoff >	Sensitivity %	Specificity %	PV +	PV –
TREM (ng/ml)	14.5	93.33	93.33	0.9921	0.6086
Procalcitonin (ng/ml)	4.95	66.7	80	0.9677	0.2105
CRP (mg/L)	46.00	100	80	0.9783	1.0000

responsiveness and death [37].

In conclusion, both serum PCT and sTREM are valuable in distinguishing bacterial diarrhea from non-bacterial diarrhea in children, but sTREM-1 had markedly higher diagnostic discriminatory power. However, these findings remain to be confirmed in larger populations. Additionally, further studies are needed to evaluate the prognostic value of sTREM-1 in acute bacterial diarrhea.

### Compliance with ethical statement

- 1 Ethical approval: the study was approved by the ethical committee of Tanta Faculty of Medicine
- 2 Informed consent: Informed consent was obtained from all individual participants included in the study.

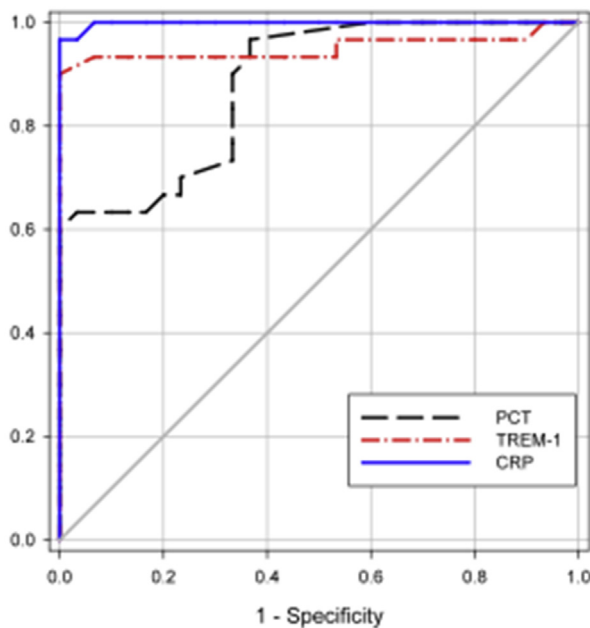
### Conflict of interest

All authors do not have any conflicts of interest to disclose.

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### ROC Curves



**Figure 1.** Receiver operating characteristic (ROC) curves comparing the baseline C-reactive protein (CRP), procalcitonin (PCT) and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1).

diarrhea due to bacterial infections and diarrhea due to non-bacterial infections. As with PCT, but with markedly higher diagnostic discriminatory power, the serum sTREM-1 showed significantly higher concentrations in early acute diarrhea due to bacterial infection compared to non-bacterial diarrhea. After 72 h of treatment, patients with acute bacterial diarrhea still had a high serum soluble TREM-1 level, which was significantly decreased compared with the admission levels. Interestingly, the mechanism by which sTREM modulates the immune response remains unclear. However, the Japanese study by *Oku et al.*, performed using a mouse model, showed that blocked sTREM-1 signaling reduced, but did not abolish, NF- $\kappa$ B activation and cytokine production through competing with the natural ligand of TREM-1 and/or impairing TREM-1 dimerization, protecting septic animals from hyper-

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