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# Triggering Receptor Expressed On Myeloid Cells-1 (TREM-1) As A New Marker In Ventilated Children With Pneumonia

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**Pneumonia is the world's leading infectious cause of mortality. This is one of the most common lower respiratory tract infections, which contributes significantly to the burden of antibiotic use. Because of the complexity of the pathophysiology, pneumonia is widely recognized that the clinical diagnosis and prognosis are usually not enough to accurately estimate the severity of the condition. The most difficult task for a doctor is above all the value of risk in patients with community-acquired pneumonia. Early diagnosis is important to reduce hospitalization and death. There are widespread biomarkers, none of which look perfect, and the demand for new biomarkers that maximizes the severity and treatment response for pneumonia has increased lately. Ventilation-related pneumonia (VAP) is a hospital-acquired pneumonia that can occur more than 48 hours after mechanical ventilation. This is a common complication of mechanical ventilation, which has a high mortality rate. VAP can make it difficult for patients to turn off the ventilator and cause longer hospitalizations, which can cause a very large financial burden for patients and the need for large medical resources. The incidence and mortality of VAP have decreased with the progress of prevention strategies in the last few decades. However, VAP is still one of the most common causes of nosocomial infections and a frequent cause of death in intensive care units. Current challenges in VAP treatment include the lack of a gold standard for diagnosis, the lack of effective prevention strategies, and increased antibiotic resistance. Active receptors are expressed on myeloid cells (TREM-1) and are considered to be glycoprotein members of the immunoglobulin family. TREM-1 is an inflammatory receptor that causes inflammation after exposure to extracellular fungi and bacterial pathogens. Elevated TREM-1 levels are a potential marker of lung disease. The aim of this study is to evaluate sTREM-1 levels in the serum of pneumonia patients and their use as new biomarkers, which seem promising for accurate diagnosis, risk and follow-up of VAP, always, however, one of the most common causes is nosocomial infection and one of the leading causes of death most commonly in intensive care units. A comparative study was conducted on children diagnosed with pneumonia admitted to Pediatric Abo El Rish Intensive Care Unit and Abo El Rish Pediatric Hospital, Cairo University, compared to age and sex-matched healthy control group. sTREM-1 level was measured using ELISA technique while CRP by Nephelometry. TREM-1 level was significantly higher in ventilated children with pneumonia compared to the control group. No significant correlation was found between sTREM-1 level and CRP level in the studied children. TREM-1 is not a pulmonary infection marker only but areliable marker for ventilator-associated pneumonia (VAP).**

**Keywords:** Triggering receptor expressed on myeloid cells-1, CRP, pneumonia,Ventilator-Associated Pneumonia.

Pneumonia is one of the most common causes of death among children even with all the recent advancements in diagnosis and management[1]. Clinical signs of pneumonia may be very vague leading to difficulty to establish a rational therapeutic approach[2]. Certainly, the early managing of respiratory tract infection is vital to ensure good prognosis and avoid complications[3].

The epidemiology of pneumonia is complicated. Moreover, the definitions of the different subtypes of pneumonia are vague and this is an add on an obstacle in early management[4].

Pneumonia obtained by the community occurs as a whole, although pneumonia associated with a ventilator (VAP) and acquired pneumonia (HAP) is considered as health-related pneumonia. Aspiration pneumonia is another process that can begin in a general situation but is often unfairly referred to as a health event[5].

Mechanical ventilation is an effective intervention method for critically ill patients to save their lives. This is often used in intensive care units. Ventilation-related pneumonia (VAP) is a nosocomial infection that occurs after more than 48 hours of ventilation. Clinical Guidelines (2016), published by the American Infectious Diseases Society (IDSA) and the American Thoracic Society (ATS), show that VAP mortality in the US is 13%[6]. In Europe, a multicentre prospective study found that the 30-day mortality from VAP was 29.9%. The initial VAP mortality rate was 19.2%, while the late VAP mortality rate was 31.4%[7]. Although the prevalence of VAP has declined in recent years due to the application of therapeutic strategies, it remains one of the most common causes of nosocomial infections and critically ill patients during ICU hospitalization. VAP may make it difficult for some patients to leave the ventilator and stay longer in the hospital, which can be a huge financial burden on patients and a great need for medical resources. Therefore, it is very important to explain VAP risk factors to achieve better VAP prevention and control. Patient characteristics (for example, elderly, male) can increase mechanical ventilation time. Continuous mechanical ventilation, disturbance of consciousness, previous antibiotic therapy, burns, comorbidities, gene polymorphisms, and invasive surgery are internationally recognized risk factors for VAP[8].

The ideal biomarker for pulmonary infection must allow rapid diagnosis and prognostic value and facilitate therapeutic decision making[9].

The trigger receptors expressed on myeloid cells (TREM-1) are glycoproteins and a member of the immunoglobulin family. TREM-1 acts as an important receptor for the inflammatory response that is regulated by neutrophils and monocytes during inflammation[10]. When it comes to pneumonia, TREM-1 has great promise[11].

Its expression is upregulated with the presence of extracellular bacteria and fungi and in some noninfectious inflammatory conditions[12]. TREM-1 may be measured in body fluids only in response to infection as it is not detectable in healthy individuals[12]. TREM-1 is a good predictor of VAP[13]; however,[14] claimed that TREM-1 may be found elevated in the bronchoalveolar lavage (BAL) fluid in patients with and without confirmed VAP.

Activated phagocytes release soluble forms of TREM-1 (sTREM-1) and are found in all body fluids[15]. This soluble form is closely related to infection. There are many studies on sTREM-1 in adults that show elevated serum levels of sTREM-1 in body fluid samples for various diseases and conditions[15-19].

It has been found that sTREM-1 levels increase in bronchoalveolar lavage fluid in patients with pneumonia, in exhaled breath condensation in patients with VAP and in the plasma of septic patients[19]. sTREM-1 acts as a biomarker of known infectious diseases[20].

The study and cultivation of lung tissue is the gold standard for diagnostic confirmation of VAP[21,22] because intervention procedures are indispensable for obtaining a lung biopsy and therefore clinical relevance is limited[22]. The trigger receptors expressed on myeloid cell-1 (TREM-1) are members of the immunoglobulin superfamily and are secreted by neutrophils, macrophages, and monocytes. It increases the inflammatory response after exposure to bacterial and fungal cells[23]. Soluble forms of TREM-1 (sTREM-1) are planned as new biomarkers and have been tested in patients with acute infections and have different diagnostic and prognostic results[23-25]. Increased levels of sTREM-1 in bronchoalveolar lavage (BALF), serum, and ventilatory condensate (EVC) fluids have been reported in patients with VAP [26,27].

Identification of vulnerability sites associated with pneumonia in life and childhood. They also postulated that this locus showed evidence of an association with genetic variants related to lung function, immune response, COPD, lung development, and asthma[28].

In patients with pneumonia, no nucleotide polymorphism has reached the importance of the genome, although it identifies potential areas of interest. In the analysis of pediatric pneumonia with variants of NGR1 ($P = 6.3 \times 10^{-8}$), PAK6 ($P = 3.3 \times 10^{-7}$) and around MATN1 ($P = 2.8 \times 10^{-7}$). In a lifetime analysis of lung inflammation containing variants in LOC339862 ($P = 8.7 \times 10^{-7}$), RAPGEF2 ($P = 8.4 \times 10^{-7}$),

PHACTR1 ($P = 6.1 \times 10^{-7}$) near PRR27 ($P = 4.3 \times 10^{-7}$) and near MCPH 1 ($P = 2.7 \times 10^{-7}$). Analysis of childhood lung inflammatory gene tissue including upper tissue development, WNT signaling, DNA damage, apoptosis, inflammation, blood vessel morphogenesis, muscle contraction, and immune response ($P \leq 0.05$). We have identified genes that might be associated with pneumonia risk[29].

The aim of this research was to determine the level of TREM-1 in ventilated and non-ventilated children with confirmed pneumonia diagnosis compared to an age and sex-matched control group.

## METHODOLOGY

A comparative study included 43 children selected from those admitted to Pediatric Abo El Rish ICU and Abo El Rish Pediatric Hospital, Cairo University. Another 18 age and sex-matched apparently healthy children were enrolled as control group.

Any child was admitted to Pediatric Intensive Care Unit and Abo El Rish Pediatric Hospital, Cairo University presented by clinical symptoms (eg cough, fever, pleurisy) and with an infiltrate seen on chest radiography can be considered eligible as a confirmed pneumonia case[30]. Then the selected children were divided into 2 groups according to associated mechanical ventilation or no.

Any children were receiving immunosuppressive therapy, started antibiotic therapy, children with chronic lung diseases and patients who were unwilling to participate in this study were excluded from the study.

**Ethical Considerations**

This study follows the guidelines of the ethics committee of the National Research Centre, Egypt for Medical Research, approval number:16/381. Informed consent was collected from legal child parents/guardians prior to participation and Confidentiality of all data was ensured.

**Data collection**

Data were collected include demographic data, clinical features (cough, fever, pleuritic chestpain) and positive findings of lung imaging, the need for hospitalization in pediatric ward versus intensive care unit admission using mechanical ventilation and associated comorbidities (cardiac abnormalities, convulsion and or dehydration).

**Laboratory analysis**

Three ml of blood samples were drawn from the admitted child under complete aseptic conditions and were collected in plain vacutainers. Samples were left to agglomerate for 30 minutes before centrifugation at around 1000 x g for 15 minutes. Serum separated and stored at -20!. Laboratory blood tests are done in Immunogenetics Laboratory at Excellence centre, National Research Centre (NRC).

**Determination of serum TREM-1**

Samples were analyzed for TREM-1 using the commercially available ELIA EIAab kit. Catalog number: E0213h. In principle, the microtiter plates provided in this kit are pre-prepared with TREM-1 specific antibodies. The standard or sample is then added to the well corresponding to the microtiter plate with the biotin-specific TREM-1 conjugated polyclonal antibody preparation, and the radish conjugated peroxidase conjugate (HRP) radish is added to each microtiter plate well and incubated. Then the TMB substrate solution is added. Only wells containing TREM-1 that are conjugated with biotin antibodies and conjugated with the avidin enzyme show color changes. The enzyme-substrate reaction is ended by adding sulfuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The TREM-1 concentration in the sample is then determined by comparing the O.D. from sample to standard curve.

**Determination of serum C-reactive protein (CRP)**

Measurement of human C-reactive protein (CRP) in serum is done nephelometrically. Product code: ZK044.L.R, Minineph ™, The Binding Site Ltd., PO Box 11712, Birmingham, B14 4ZB, UK. The determination of dissolved antigen concentrations by the nephelometric method involves reactions with antibodies that are bound to latex particles to form insoluble complexes. When light passes through the formed slurry, a portion of the light is scattered and detected by a photodiode. The amount of light scattered is directly proportional to the concentration of specific proteins in the test sample. Concentrations are calculated automatically using a calibration curve that is stored in the instrument.

**Statistical method**

Data is coded and entered using the SPSS statistical package (Statistical Package for Social Sciences), version 23. Data is collected using the mean, standard deviation in quantitative data, and using frequency (number) and relative frequency (percent). Taking into account the level of sTREM-1, the ANOVA method was used to test the difference in significance between the

**Table 1.** Demographic and clinical data of the studied cases

| | Ventilated Pneumonia (n=20) | Non-ventilated Pneumonia (n=23) | Control Group (n=18) |
|---|---|---|---|
| Age (months) | 12.60±11.821 | 32.20±26.411 | 22.47±10.002 |
| Gender: | | | |
| Male | 12(60.0%) | 12(52.2%) | 13 (72.2%) |
| Female | 8(40.0%) | 11(47.8%) | 5 (28.8%) |
| Fever | 20 (100%) | 23 (100 %) | 0 |
| History of cough | 20 (100%) | 23 (100 %) | 0 |
| Associated comorbidity | 5 (25%) | 0 | 0 |

**Table 2.** TREM-1 and CRP level in the studied cases

| | Group | Mean | SD | *p*- value |
|---|---|---|---|---|
| TREM -1 (ng/ml) | Control(n= 18) | 0.56761 | 0.739702 | 0.064 |
| | Pneumonia cases(n=43) | 2.20722 | 3.636479 | |
| C-Reactive Protein(CRP)(mg/dl) | Control(n=18) | 1.5122 | 1.85927 | 0.002* |
| | Pneumonia cases(n=43) | 22.0889 | 26.55067 | |

Independent Samples Test **p*-value

TREM-1in theControl Group with mean 0.56761±0.739702 has a nonsignificant difference from Pneumonia cases with mean 2.20722±3.636479 (*p*-value0.064).

While the CRP level was highly significant higher in the studied pneumonia cases with mean 22.0889 ±26.55067 than the control group with the mean 1.5122±1.85927 (*p*-value 0.002).

**Table 3.** Comparison between TREM-1level in the studied groups according to an associated ventilator or no

| | Ventilated pneumonia (Group 1) | Non-ventilated pneumonia (Group 2) | Control Group (Group 3) | *p(*1vs3) | *p (*1vs2) | *p* (2vs3) |
|---|---|---|---|---|---|---|
| TREM-1(ng/ml) | 3.20±3.66 | 1.43±3.50 | 0.57±0.74 | 0.022 | 0.329 | 0.586 |

By comparing the TREM-1 Level according to pneumonia with and without a ventilator, a significant difference was found between the control group and the ventilated pneumonia cases (*p* 0.022).

three groups, and the Dunnett test was used to test the difference in significance for each of the two groups.

## RESULTS

The clinical presentation and demographic data of the studied groups are illustrated in table (1). Twinty Four children were female (39.3%) and 37were males(60.6%). As regards the need of mechanical ventilation 20 case (46.5%) needed mechanical ventilation. Only 5 cases (25%) of them suffered from co-morbidity.

**Table 4.** Correlation between TREM-1 Level and CRP in the studied cases

| | N | Pearson Correlation 1 | Sig. (2-tailed) |
|---|---|---|---|
| CRPvssTREM-1 | 43 | 0.024 | 0.883 |

There was no significant correlation between TREM-1 level and CRP level in the studied cases.

## DISCUSSION

VAP is a leading cause of morbidity and mortality associated with cardiac surgery worldwide, especially in children[31]. Despite advances in diagnosis, early diagnosis of VAP remains difficult, and etiology and therapy are also observed[32]. Because VAP and systemic inflammatory response syndromes have similar characteristics in early development but patients are being treated for VAP, excessive and unnecessary antibiotic treatment is needed in patients with systemic inflammatory response syndrome[33]. This excessive and unnecessary use of antibiotics can lead to increased bacterial resistance and increased costs, emphasizing the importance of early and accurate diagnosis of VAP [34]. In this study, markers of biological infections such as sTREM-1 are being studied to improve the accuracy of VAP diagnoses.

Trigger receptors expressed on myeloid cells (TREM-1) are considered innate inflammatory transmembrane receptors[35]. TREM-1 is expressed on neutrophils, mature monocytes, and macrophages and is related to immunoglobulin superfamily receptors[36]. TREM-1 amplifies inflammation after exposure to extracellular bacterial and fungal pathogen. Therefore, it was initially proposed as the early marker of infection[37]. TREM-1 expression is increased in peritoneal neutrophils of septic shock patients[38].

Later, the expression has also been founded on various non-immune cells like bronchial epithelium and endothelial cells and[39, 40]. A soluble form of TREM-1 (sTREM-1) is present in high concentrations in bronchoalveolar lavage in patients with pneumonia[41].

Many recent studies demonstrated the role of sTREM-1 as a potential biomarker of bacterial infections either to differentiate between types of infections or as an early marker[39-42].

In the current study, the level of sTREM 1 was higher in children with pneumonia in comparison to the control group but without a significant statistical difference.

This is in contrast with the results of a meta-analysisstudy which concluded that sTREM-1 was a reliable biological marker in bacterial infection[43]. On the other hand, another metanalysis study concluded that thoughs TREM-1 is a useful marker for bacterial infections, it is not that accurate in some types of infection as urinary tract infection[44].

The difference between different types of pneumonia especially in ICU patients is not easy.VAP is defined as pneumonia that occurs more than 48 hours after patient intubation and after mechanical ventilation. The diagnosis of VAP requires a high level of clinical suspicion by X-ray examination, nocturnal examination, and microbiological analysis of respiratory secretions[45].

TREM-1 has a significant diagnostic value when it comes to lung diseases as it has been studied in the diagnosis of ventilator-associated pneumonia (VAP) for ICU patients[46]. sTREM-1 had a good diagnostic performance to differentiate patients with and without VAP[47].

This supports our findings because significant differences have been identified between ventilated cases and control groups and this can be explained by that the ventilation is an add on factor for rising sTREM-1 level with the bacterial infection.

This is in agreement with results of many recent studies which assessed the TREM level either in bronchoalveolar lavage or serum in ICU patient.It was concluded that sTREM-1 is present at a high concentration in patients' lungs with bacterial infections.which can be used as a reliable early marker for VAP and can accurately discriminate VAP from non-pulmonary infection[48-52] Moreover , A study by Baker *et al* used TREM to diagnose VAP for trauma patients as trauma itself can make a proinflammatory state mimicking infection, sos TREM-1 was used to facilitate rapid and accurate diagnosis of VAP in trauma[53]

C-reactive protein (CRP) is a protein of an acute phase and it acts as a well-known biomarker of inflammation[54]. The diagnostic value of CRP was investigated by many researchers. It was compared to many different markers to assess its sensitivity. Since it is an "indirect" marker of infection, the sensitivity and specificity is not 100% and vary[55-58]. Our study shows high significant differencewith CRP in the pneumonia cases than the control group $p$=0.002*

The diagnostic role of CRP and sTREM-1 as biomarkers was investigated recently and Moreover, sTREM-1 has shown it to be more specific and sensitive than C-reactive protein (CRP)[15, 59]. In our study there was no significant correlation between TREM-1 level and CRP level in the studied children.

## CONCLUSION

TREM-1 is a superior pulmonary infection biomarker moreover, it can be used to discriminate between types of pneumonia as VAP.

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## REFERENCES

1. Gupta, G.R., Tackling pneumonia and diarrhoea: the deadliest diseases for the world's poorest children. *Lancet,* **379**(9832): p. 2123-4 (2012).
2. Chen, Y.S., *et al*., [Etiological analysis and establishment of a discriminant model for lower respiratory tract infections in hospitalized patients]. Zhonghua Jie He He Hu Xi Za Zhi, **40**(12): p. 909-914 (2017).
3. Thomas M, B.P. Upper Respiratory Tract Infection. . 2018 [Updated 2018 Nov 23]. Jan 2019]; Treasure Island (FL)::[Available from: https://www.ncbi.nlm.nih.gov/books/NBK532961.
4. DeAntonio, R., *et al*., Epidemiology of community-acquired pneumonia and implications for vaccination of children living in developing and newly industrialized countries: A systematic literature review. *Hum Vaccin Immunother,* **12**(9): p. 2422-40 (2016).
5. Ottosen, J. and H. Evans, Pneumonia: challenges in the definition, diagnosis, and management of disease. *Surg Clin North Am,* **94**(6): p. 1305-17 (2014).
6. Kalil A. C., Metersky M. L., Klompas M., Muscedere J., Sweeney D. A., Palmer L. B., *et al*. (2016). Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of america and the american thoracic society. *Clin. Infect.* Dis. 63 e61–e111. 10.1093/cid/ciw353.
7. Martin-Loeches I., Rodriguez A. H., Torres A. New guidelines for hospital-acquired pneumonia/ventilator-associated pneumonia. *Curr. Opin. Crit. Care* **24**: 347–352 (2018). 10.1097/mcc.0000000000000535.
8. Ding C., Zhang Y., Yang Z., Wang J., Jin A., Wang W., *et al*. Incidence, temporal trend and factors associated with ventilator-associated pneumonia in mainland China: a systematic review and meta-analysis. *BMC Infect. Dis*. **17**: 468 (2017). 10.1186/s12879-017-2566-2567.
9. Rigo, I., *et al*., Induction of triggering receptor expressed on myeloid cells (TREM-1) in airway epithelial cells by 1,25(OH)(2) vitamin D(3). *Innate Immun,* **18**(2): p. 250-7 (2012).
10. Tammaro, A., *et al*., TREM-1 and its potential ligands in non-infectious diseases: from biology to clinical perspectives. *Pharmacol Ther,* **177**: p. 81-95 (2017).

11. Summah, H. and J.M. Qu, Biomarkers: a definite plus in pneumonia. *Mediators Inflamm*, 2009: p. 675753 (2009).
12. Salluh J.I.F., Souza-Dantas V.C., Povoa P. The current status of biomarkers for the diagnosis of nosocomial pneumonias. *Curr. Opin. Crit. Care.* **23**:391–397 (2017). doi: 10.1097/MCC.0000000000000442.
13. Grover V., Pantelidis P., Soni N., Takata M., Shah P.L., Wells A.U., Henderson D.C., Kelleher P., Singh S. A biomarker panel (Bioscore) incorporating monocytic surface and soluble TREM-1 has high discriminative value for ventilator-associated pneumonia: A prospective observational study. *PLoS ONE.*; **9**: e109686 (2014). doi: 10.1371/journal.pone.0109686.
14. Palazzo S.J., Simpson T.A., Simmons J.M., Schnapp L.M. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) as a diagnostic marker of ventilator-associated pneumonia. *Respir. Care.;* **57**: 2052–2058 (2012).
15. Gibot, S., *et al*., Plasma level of a triggering receptor expressed on myeloid cells-1: its diagnostic accuracy in patients with suspected sepsis. *Ann Intern Med,* **141**(1): p. 9-15 (2004).
16. Chan, M.C., *et al*., Evaluation of a new inflammatory molecule (triggering receptor expressed on myeloid cells-1) in the diagnosis of pleural effusion. *Respirology,* **12**(3): p. 333-8 (2007).
17. Anand, N.J., *et al*., Diagnostic implications of soluble triggering receptor expressed on myeloid cells-1 in BAL fluid of patients with pulmonary infiltrates in the ICU. *Chest,* **135**(3): p. 641-647 (2009).
18. Su, L.X., *et al*., Diagnostic value of urine sTREM-1 for sepsis and relevant acute kidney injuries: a prospective study. *Crit Care,* **15**(5): p. R250 (2011).
19. Determann, R.M., *et al*., Soluble triggering receptor expressed on myeloid cells 1: a biomarker for bacterial meningitis. *Intensive Care Med,* **32**(8): p. 1243-7 (2006).
20. Cao, C., J. Gu, and J. Zhang, Soluble triggering receptor expressed on myeloid cell-1 (sTREM-1): a potential biomarker for the diagnosis of infectious diseases. *Front Med,* **11**(2): p. 169-177 (2017).
21. Venkatachalam V, Hendley JO, Willson DF. The diagnostic dilemma of ventilator-associated pneumonia in critically ill children. *Pediatr Crit Care Med.;* **12**:286–296 (2011). doi: 10.1097/PCC.0b013e3181fe2ffb.
22. Fabregas N, Ewig S, Torres A, El-Ebiary M, Ramirez J, de La Bellacasa JP, Bauer T, Cabello H. Clinical diagnosis of ventilator associated pneumonia revisited: Comparative validation using immediate post-mortem lung biopsies. *Thorax.;* **54**:867–873 (1999). doi: 10.1136/thx.54.10.867.
23. Pontrelli G, De Crescenzo F, Buzzetti R, Calò Carducci F, Jenkner A, Amodio D, De Luca M, Chiurchiu S, Davies EH, Simonetti A, *et al*. Diagnostic value of soluble triggering receptor expressed on myeloid cells in paediatric sepsis: A systematic review. *Ital J Pediatr.*; **42**: 44 (2016). doi: 10.1186/s13052-016-0242-y.
24. Mazzucchelli I, Garofoli F, Ciardelli L, Borghesi A, Tzialla C, Di Comite A, Angelini M, Tinelli C, Merlini G, Stronati M. Diagnostic performance of triggering receptor expressed on myeloid cells-1 and CD64 index as markers of sepsis in preterm newborns. *Pediatr Crit Care Med.;* **14**:178–182 (2013). doi: 10.1097/PCC.0b013e31826e726d.
25. Palazzo SJ, Simpson T, Schnapp LM. Triggering receptor expressed on myeloid cells type 1 as a potential therapeutic target in sepsis. *Dimens Crit Care Nurs.;* **31**: 1–6 (2012). doi: 10.1097/DCC.0b013e31823a5298.
26. Determann RM, Millo JL, Gibot S, Korevaar JC, Vroom MB, van der Poll T, Garrard CS, Schultz MJ. Serial changes in soluble triggering receptor expressed on myeloid cells in the lung during development of ventilator-associated pneumonia. *Intensive Care Med.;* **31**: 1495–1500 (2005). doi: 10.1007/s00134-005-2818-7.
27. Matsuno AK, Carlotti AP. Role of soluble triggering receptor expressed on myeloid cells-1 for diagnosing ventilator-associated pneumonia after cardiac surgery: An observational study. *BMC Cardiovasc Disord.*; **13**: 107 (2013). doi: 10.1186/1471-2261-13-107
28. Hayden LP, Cho MH, McDonald MN, Crapo JD, Beaty TH, Silverman EK, Hersh CP COPDGene Investigators. Susceptibility to childhood pneumonia: A genome wide analysis [abstract] *Am J Respir Crit Care Med*.; **191**: A3374 (2015).
29. Lystra P. Hayden,[1,2] Michael H. Cho,[2,3] Merry-Lynn N. McDonald,[2] James D. Crapo,[4] Terri H. Beaty,[5] Edwin K. Silverman,[2,3] and Craig P. Hersh[2,3], on behalf of the COPDGene Investigators[*] Susceptibility to Childhood Pneumonia: A Genome-Wide Analysis. *Am J Respir Cell Mol Biol.* **56**(1): 20–28 (2017).
30. WHO, Technical bases for the WHO recommendations on the management of pneumonia in children at first-level health facilities: , in Programme for the Control of Acute Respiratory Infection, Geneva: World Health Organization, Editor. 1991, WHO.

31. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, Hanisch EW, Klarin B, Koeman M, Krueger WA, *et al*. Attributable mortality of ventilator-associated pneumonia: A meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis.;* **13**:665–671 (2013). doi: 10.1016/S1473-3099(13)70326-8.
32. Bassetti M, Taramasso L, Giacobbe DR, Pelosi P. Management of ventilator-associated pneumonia: Epidemiology, diagnosis and antimicrobial therapy. *Expert Rev Anti Infect Ther.*; **10**: 585–596 (2012). doi: 10.1586/eri.12.36.
33. Salehifar E, TavakolianArjmand S, Aliyali M, Abedi S, Sharifpour A, Alipour A, Ala S, Eslami G, Bozorgi F, Mahdavi MR, Walley KR. Role of C-reactive protein and tumor necrosis factor-alpha in differentiating between ventilator-associated pneumonia and systemic inflammatory response syndrome without infectious etiology. *Tanaffos.;* **15**: 205–212 (2016).
34. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, Lee G, Magill SS, Maragakis LL, Priebe GP, Speck K, *et al*. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol.;* **35**(Suppl 2):S133–S154 (2014). doi: 10.1086/677144.
35. Pelham, C.J. and D.K. Agrawal, Emerging roles for triggering receptor expressed on myeloid cells receptor family signaling in inflammatory diseases. *Expert Rev Clin Immunol,* **10**(2): p. 243-56 (2014).
36. Anaya-Prado, R., *et al*., Expression of TREM-1 in maternal leukocytes in preterm, prelabour rupture of the membranes. *J Obstet Gynaecol,* **37**(2): p. 162-169 (2017).
37. Palazzo, S.J., T. Simpson, and L.M. Schnapp, Triggering receptor expressed on myeloid cells type 1 as a potential therapeutic target in sepsis. *Dimens Crit Care Nurs,* **31**(1): p. 1-6 (2012).
38. Sigalov, A.B., A novel ligand-independent peptide inhibitor of TREM-1 suppresses tumor growth in human lung cancer xenografts and prolongs survival of mice with lipopolysaccharide-induced septic shock. *Int Immunopharmacol,* **21**(1): p. 208-19 (2014).
39. Jedynak, M., *et al*., Soluble TREM-1 Serum Level can Early Predict Mortality of Patients with Sepsis, Severe Sepsis and Septic Shock. *Arch Immunol Ther Exp (Warsz),* **66**(4): p. 299-306 (2018).
40. Piroozmand, A., *et al*., Comparison of gastric juice soluble triggering receptor expressed on myeloid cells and C-reactive protein for detection of Helicobacter pylori infection. *Electron Physician,* **9**(12): p. 6111-6119 (2017).
41. Ye, W., *et al*., Diagnostic value of the soluble triggering receptor expressed on myeloid cells-1 in lower respiratory tract infections: a meta-analysis. *Respirology,* **19**(4): p. 501-7 (2014).
42. Sierra-Diaz, E., *et al*., Urine TREM-1 as a marker of urinary tract infection in children. *J Int Med Res,* **45**(2): p. 631-638 (2017).
43. Shi, J.X., *et al*., Diagnostic value of sTREM-1 in bronchoalveolar lavage fluid in ICU patients with bacterial lung infections: a bivariate meta-analysis. *PLoS One,* **8**(5): p. e65436 (2013).
44. Jiyong, J., *et al*., Diagnostic value of the soluble triggering receptor expressed on myeloid cells-1 in bacterial infection: a meta-analysis. *Intensive Care Med,* **35**(4): p. 587-95 (2009).
45. Waters, B. and J. Muscedere, A 2015 Update on Ventilator-Associated Pneumonia: New Insights on Its Prevention, Diagnosis, and Treatment. *Curr Infect Dis Rep,* **17**(8): p. 496 (2015).
46. Yu, Y., *et al*., Diagnostic Performance of Soluble Triggering Receptor Expressed on Myeloid Cells-1 in Ventilator-Associated Pneumonia of Patients with Ischemic Stroke. *Can J Infect Dis Med Microbiol,* **2017**: p. 9513690 (2017).
47. Yu, Y., *et al*., Diagnostic Performance of Soluble Triggering Receptor Expressed on Myeloid Cells-1 in Ventilator-Associated Pneumonia of Patients with Ischemic Stroke. The Canadian journal of infectious diseases & medical microbiology = Journal canadien des maladies infectieuses et de la microbiologie medicale, 2017. **2017**: p. 9513690-9513690.
48. Siranovic, M., *et al*., Human soluble TREM-1: lung and serum levels in patients with bacterial ventilator associated pneumonia. *Acta Clin Croat,* **50**(3): p. 345-9 (2011).
49. Isguder, R., *et al*., New parameters for childhood ventilator associated pneumonia diagnosis. *Pediatr Pulmonol,* **52**(1): p. 119-128 (2017).
50. Grover, V., *et al*., A biomarker panel (Bioscore) incorporating monocytic surface and soluble TREM-1 has high discriminative value for ventilator-associated pneumonia: a prospective observational study. *PLoS One,* **9**(10): p. e109686 (2014).
51. Palazzo, S.J., *et al*., Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) as a diagnostic marker of ventilator-associated pneumonia. *Respir Care,* **57**(12): p. 2052-8 (2012).
52. Determann, R.M., *et al*., Serial changes in soluble triggering receptor expressed on myeloid cells in the lung during development of ventilator-

associated pneumonia. *Intensive Care Med,* **31**(11): p. 1495-500 (2005).
53. Baker JJ, V.C., Conley B, Desjardins S, Grindlinger GA., Soluble triggering receptor expressed on myeloid cells-1 (s-TREM1) is increased in trauma patients with ventilator associated pneumonia (VAP). *Chest Meeting,* **134**: p. S9004 (2008).
54. Lai, W., *et al*., C-reactive protein promotes acute kidney injury via Smad3-dependent inhibition of CDK2/cyclin E. *Kidney Int,* **90**(3): p. 610-26 (2016).
55. Mitaka, C., Clinical laboratory differentiation of infectious versus non-infectious systemic inflammatory response syndrome. *Clin Chim Acta,* **351**(1-2): p. 17-29 (2005).
56. Kibe, S., K. Adams, and G. Barlow, Diagnostic and prognostic biomarkers of sepsis in critical care. *J Antimicrob Chemother,* **66 Suppl 2**: p. ii33-40 (2011).
57. Stubljar, D. and M. Skvarc, Effective Strategies for Diagnosis of Systemic Inflammatory Response Syndrome (SIRS) due to Bacterial Infection in Surgical Patients. *Infect Disord Drug Targets,* **15**(1): p. 53-6 (2015).
58. Standage, S.W. and H.R. Wong, Biomarkers for pediatric sepsis and septic shock. *Expert Rev Anti Infect Ther,* **9**(1): p. 71-9 (2011).
59. Ventetuolo, C.E. and M.M. Levy, Biomarkers: diagnosis and risk assessment in sepsis. *Clin Chest Med,* **29**(4): p. 591-603, vii (2008).