

ORIGINAL ARTICLE

Soluble Triggering Receptor Expressed on Myeloid Cells and the Diagnosis of Pneumonia

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ABSTRACT

BACKGROUND

The diagnosis and treatment of bacterial pneumonia in patients who are receiving mechanical ventilation remain a difficult challenge. The triggering receptor expressed on myeloid cells (TREM-1) is a member of the immunoglobulin superfamily, and its expression on phagocytes is specifically up-regulated by microbial products. The presence of soluble TREM-1 (sTREM-1) in bronchoalveolar-lavage fluid from patients receiving mechanical ventilation may be an indicator of pneumonia.

METHODS

We conducted a prospective study of 148 patients receiving mechanical ventilation in whom infectious pneumonia was suspected. A rapid immunoblot technique was used to measure sTREM-1 in bronchoalveolar-lavage fluid. Two independent intensivists who were unaware of the results of the sTREM-1 assay determined whether community-acquired pneumonia and ventilator-associated pneumonia were present or absent.

RESULTS

The final diagnosis was community-acquired pneumonia in 38 patients, ventilator-associated pneumonia in 46 patients, and no pneumonia in 64 patients. The presence of sTREM-1 by itself was more accurate than any clinical findings or laboratory values in identifying the presence of bacterial or fungal pneumonia (likelihood ratio, 10.38; sensitivity, 98 percent; specificity, 90 percent). In multiple logistic-regression analysis, the presence of sTREM-1 was the strongest independent predictor of pneumonia (odds ratio, 41.5).

CONCLUSIONS

In patients receiving mechanical ventilation, rapid detection of sTREM-1 in bronchoalveolar-lavage fluid may be useful in establishing or excluding the diagnosis of bacterial or fungal pneumonia.

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THE DIAGNOSIS AND TREATMENT OF infectious pneumonia in patients who are receiving mechanical ventilation remain a major challenge for clinicians.^{1,2} A presumptive clinical diagnosis of pneumonia is often made when a new radiographic infiltrate develops in a patient with fever, leukocytosis, and purulent tracheal secretions and when microorganisms are isolated from the airways. Unfortunately, many noninfectious processes may be responsible for fever and new pulmonary infiltrates in patients who are receiving mechanical ventilation, and clinical approaches lead to an overestimation of the incidence of pneumonia.³⁻⁵ Moreover, whatever the microbiologic diagnostic procedure chosen,⁵⁻⁹ further laboratory processing and delays of 24 to 48 hours are required for definitive quantitative microbial culture results. Meanwhile, clinicians often feel uncomfortable about the diagnosis and may administer unneeded antibiotics while awaiting laboratory results. Therefore, many biologic markers have been studied in an effort to improve the diagnostic procedure but with disappointing results.¹⁰⁻¹⁶

The triggering receptor expressed on myeloid cells (TREM-1) is a member of the immunoglobulin superfamily¹⁷ whose expression on phagocytes is up-regulated by exposure to bacteria and fungi. TREM-1 mediates the acute inflammatory response to microbial products.¹⁸ Human tissues infected with bacteria are infiltrated with neutrophils and monocytes that express high levels of TREM-1.¹⁸ Conversely, TREM-1 is only weakly expressed in samples from patients with noninfectious inflammatory disorders.¹⁸ TREM-1 is also shed by the membrane of activated phagocytes and can be found in a soluble form in body fluids. We evaluated whether the presence of soluble TREM-1 (sTREM-1) in bronchoalveolar-lavage fluid from patients who are receiving mechanical ventilation is a good indicator of infectious pneumonia.

METHODS

STUDY POPULATION

The institutional review board approved the study, and patients or their relatives provided written informed consent before enrollment. All patients 18 years of age or older who were hospitalized in our medical intensive care unit (ICU) were prospectively enrolled in the study if they required mechanical ventilation and there was a clinical suspicion of infectious pneumonia, defined by a new and persistent infiltrate on chest radiography associated with

at least one of the following¹⁹: purulent tracheal secretions, a body temperature of at least 38.3°C, and leukocytosis (more than 10,000 leukocytes per cubic millimeter) or leukopenia (fewer than 4000 leukocytes per cubic millimeter). Ventilator-associated pneumonia was defined by acquisition of the disease after 48 hours of mechanical ventilation.

The following items were recorded for each patient on admission into the ICU: age, sex, severity of underlying medical condition stratified according to the criteria of McCabe and Jackson,²⁰ the Simplified Acute Physiology Score II (SAPS II) (scores can range from 0 to 163, with higher scores indicating a higher risk of death),²¹ the Sepsis-related Organ Failure Assessment score (the total score can range from 0 to 24; with scores for each organ system [respiration, coagulation, liver, cardiovascular, central nervous system, and kidney] ranging from 0 [normal] to 4 [most abnormal]),²² and the reason for admission to the ICU.

The following base-line variables were also recorded at enrollment: SAPS II score; the Sepsis-related Organ Failure score; body temperature; leukocyte count; ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO₂:FiO₂); serum levels of C-reactive protein and procalcitonin; presence of shock, defined by a systolic arterial pressure below 90 mm Hg with signs of peripheral hypoperfusion or the need for a continuous infusion of vasopressor or inotropic agents²³; duration of mechanical ventilation; and previous use of antimicrobial therapy. A clinical pulmonary infection score was calculated as previously described.¹⁹ The duration of mechanical ventilation and the length and the outcome (death or discharge) of stay in the ICU were also recorded.

CONFIRMATION OF THE DIAGNOSIS

Mini-bronchoalveolar lavage and processing of microbiologic specimens were performed as described in detail elsewhere.^{8,10} Briefly, mini-bronchoalveolar lavage was performed with the use of the Combicath, a single-sheathed, 50-cm, sterile, plugged, telescopic catheter (Plastimed). The recovered fluid (about two thirds of the 20 ml of saline [0.9 percent sodium chloride] that had been instilled) was divided into two samples: one was used for direct microscopical examination and quantitative culture; the other was centrifuged at 10,000 revolutions per minute for 30 minutes, and the supernatant was frozen at -80°C until used for sTREM-1 and cytokine measurements. The concentration of microorganisms considered clinically

significant for the potential diagnosis of pneumonia was more than 10^3 colony-forming units per milliliter of bronchoalveolar-lavage fluid.⁸

A post hoc diagnosis of pneumonia was made on the basis of a combination of already mentioned clinical criteria with microbiologic evidence of microbial infection. These criteria were similar to those used for ventilator-associated pneumonia by Pugin and coworkers.¹⁹ Pneumonia was considered to be absent when an alternative cause for pulmonary infiltrate was established and there was nonsignificant bacterial growth in culture of bronchoalveolar-lavage fluid in association with full recovery from fever, infiltrate, and leukocytosis without antimicrobial therapy. Two intensivists reviewed all medical records pertaining to the patient and independently classified the diagnosis as community-acquired pneumonia, ventilator-associated pneumonia, or no pneumonia. A consensus concerning the diagnosis was achieved in all cases. Both intensivists were unaware of the results of sTREM-1 and cytokine measurements.

sTREM-1 AND CYTOKINE ASSAYS

Levels of sTREM-1 in samples of bronchoalveolar-lavage fluid were measured with the use of an immunoblot technique with 21C7, a monoclonal murine IgG1 directed against human TREM-1 (kindly provided by Dr. M. Colonna; also available from R&D Systems). Briefly, 100 μ l of each supernatant of bronchoalveolar-lavage fluid was dotted onto a nitrocellulose membrane, dried, and coated with phosphate-buffered saline supplemented with 3 percent bovine serum albumin. The nitrocellulose sheet was then incubated for 60 minutes in the presence of 21C7 (dilution, 1:2000). After thorough rinsing, the sheet was incubated for another 60 minutes with goat antimouse immunoglobulins (dilution, 1:1000; Dako), washed in phosphate-buffered saline supplemented with 20 percent dimethylsulfoxide, and incubated for 30 minutes with horseradish peroxidase-conjugated streptavidin (dilution, 1:1000; Bio-Rad). The enzyme substrate chromogen Opti-4CN (Bio-Rad) was then added, and the intensity of staining was in proportion to the amount of sTREM-1 bound to the membrane. Each sheet also contained calibration samples of a known concentration of sTREM-1 (0 to 200 pg per milliliter).

Colorimetric determination was achieved by means of a reflectance scanner and Quantity One Quantitation Software (Bio-Rad). The level of sTREM-1 in each sample was determined by comparing the optical densities of the samples with that

of the standard curve. All measurements were performed in duplicate, and the results are expressed as the mean level in picograms per milliliter of bronchoalveolar-lavage fluid. The sensitivity of this technique allows the detection of sTREM-1 levels as low as 5 pg per milliliter (see Supplementary Appendix 1, available with the full text of this article at www.nejm.org), and the entire procedure takes less than three hours. The coefficient of variation of the assay was lower than 5 percent.

Tumor necrosis factor α and interleukin- 1β were measured in bronchoalveolar-lavage fluid by a solid-phase enzyme-linked immunosorbent assay according to the recommendations of the manufacturer (BD Biosciences). The sensitivity of the technique allows the detection of levels as low as 2 pg per milliliter in the case of tumor necrosis factor α and of 3.9 pg per milliliter in the case of interleukin- 1β .

STATISTICAL ANALYSIS

Descriptive results of continuous variables were expressed as means \pm SD. The sTREM-1 and cytokine levels in bronchoalveolar-lavage fluid were expressed as means \pm SD. Variables were evaluated for an association with the diagnosis with the use of the Pearson χ^2 test for categorical data and the Mann-Whitney U test for numerical data. The groups were compared with the use of the Mann-Whitney U test (or the non-parametric Kruskal-Wallis test when appropriate) for numerical data and the Pearson χ^2 test for categorical data. The relations between sTREM-1 and clinical or biologic features were assessed with the use of Spearman's correlation test. To evaluate the diagnostic value of the presence of sTREM-1 in bronchoalveolar-lavage fluid, we used a multiple stepwise logistic-regression model in which a P value of 0.05 or less was used as a criterion for entry into the model. The predictors included clinical and laboratory findings along with information on the presence of sTREM-1 in bronchoalveolar-lavage fluid. Receiver-operating-characteristic (ROC) curves were constructed to illustrate various cutoff values of sTREM-1, tumor necrosis factor α , and interleukin- 1β . Analysis was completed with Statview software (Abacus Concepts), and a two-tailed P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From July 2001 to December 2002, 1097 patients were admitted to our ICU. All 148 patients fulfilling

the inclusion criteria were enrolled. The characteristics of the overall study group are shown in Table 1. Most of the patients had an associated condition, and 39 (26 percent) had a history of chronic obstructive pulmonary disease. The mean SAPS II score was 52±17, and the mean Sepsis-related Organ Failure score was 7.8±3.9. The ICU mortality rate of 34 percent was in agreement with the predicted risk of death based on the SAPS II score.²¹ The diagnosis was community-acquired pneumonia in 38 patients (26 percent), ventilator-associated pneumonia in 46 patients (31 percent), and no pneumonia in 64 patients (43 percent). Among the group without pneumonia, the diagnoses were as follows: acute exacerbation of chronic obstructive pulmonary disease in 11 patients, acute respiratory distress syndrome of extrapulmonary origin in 29 (abdominal or urogenital sepsis in 19, pancreatitis in 6, and other origins in 4), acute respiratory distress syndrome of pulmonary origin in 2 (near-drowning in 1 and smoke inhalation in 1), cardiogenic shock in 12, and unknown in 10.

The clinical characteristics of the three groups did not differ significantly at entry (Table 1). Patients with community-acquired pneumonia were more likely to be referred to the ICU for acute respiratory failure than were the other groups of patients (P=0.002). As expected, the duration of mechanical ventilation and the length of stay in the ICU were longest among patients with ventilator-associated pneumonia (P<0.001 for both). The mortality rate did not differ significantly among the three groups. A clinical pulmonary infection score of more than 6 was more frequent among patients with community-acquired or ventilator-associated pneumonia than among patients without pneumonia (P=0.02) (Table 2). Body temperature, leukocyte count, the PaO₂:FiO₂, serum C-reactive protein level, and procalcitonin level did not differ among the three groups (Table 2). Microbial species grew to a clinically significant concentration (more than 10³ colony-forming units per milliliter) in specimens of bronchoalveolar-lavage fluid from all but two patients with community-acquired pneumonia, who

Table 1. Characteristics of the Study Population.*

| Characteristic | All Patients (N=148) | Community-Acquired | | No Pneumonia (N=64) | P Value |
|---|-------------------------|---------------------|--|------------------------|---------|
| | | Pneumonia (N=38) | Ventilator-Associated Pneumonia (N=46) | | |
| Age — yr | 60±15 | 58±17 | 59±14 | 62±14 | 0.53 |
| Sex — no. (%) | | | | | 0.97 |
| Male | 95 (64) | 24 (63) | 29 (63) | 42 (66) | |
| Female | 53 (36) | 14 (37) | 17 (37) | 22 (34) | |
| McCabe score at entry† | 1.85±0.95 | 1.77±0.92 | 1.81±0.92 | 1.88±0.91 | 0.79 |
| History of COPD — no. (%) | 39 (26) | 9 (24) | 12 (26) | 18 (28) | 0.93 |
| SAPS II at entry‡ | 52±17 | 53±20 | 50±15 | 53±17 | 0.76 |
| SOFA score at entry§ | 7.8±3.9 | 8.5±4.4 | 7.0±3.5 | 8.1±4.0 | 0.43 |
| Reason for admission — no. (%) | | | | | |
| Acute respiratory failure | 42 (28) | 23 (61) | 4 (9) | 15 (23) | 0.002 |
| Neurologic abnormalities | 41 (28) | 7 (18) | 15 (33) | 19 (30) | 0.45 |
| Shock | 37 (25) | 6 (16) | 16 (35) | 15 (23) | 0.18 |
| Miscellaneous | 28 (19) | 2 (5) | 11 (24) | 15 (23) | 0.08 |
| Duration of mechanical ventilation — days | 14±12 | 8±7 | 21±19 | 11±9 | <0.001 |
| Length of ICU stay — days | 18±15 | 11±8 | 26±21 | 15±9 | <0.001 |
| Death in ICU — no. (%) | 50 (34) | 11 (29) | 19 (41) | 20 (31) | 0.58 |

* Plus–minus values are means ±SD. P values are for the comparisons among the three subgroups. COPD denotes chronic obstructive pulmonary disease.

† The McCabe score can range from 0 to 3, with higher scores indicating more severe underlying conditions.

‡ The Simplified Acute Physiologic Score II (SAPS II) can range from 0 to 163, with higher scores indicating a higher risk of death.

§ The Sepsis-related Organ Failure Assessment (SOFA) score can range from 0 to 24, with higher scores indicating more abnormal organ function.

were infected with *Legionella pneumophila*, and all patients with ventilator-associated pneumonia (see Supplementary Appendix 2, available with the full text of this article at www.nejm.org).

sTREM-1, TUMOR NECROSIS FACTOR α , AND INTERLEUKIN-1 β LEVELS

The levels of sTREM-1 were higher in bronchoalveolar-lavage fluid from patients with community-acquired pneumonia and those with ventilator-associated pneumonia than from patients without pneumonia ($P < 0.001$ for both), but the levels did not differ significantly between the two groups of patients with pneumonia (Fig. 1). Levels of tumor necrosis factor α and interleukin-1 β showed the same trend ($P < 0.001$) but with a large overlap of values. Among patients with pneumonia, there was a trend ($P = 0.07$) toward higher sTREM-1 levels in those who died than in survivors (31.2 ± 5.7 vs. 24.9 ± 3.0 pg per milliliter). There was no correlation between sTREM-1 levels and a history of chronic obstructive pulmonary disease, the amount of inflammatory cells in bronchoalveolar-lavage fluid, the type of microbial species, or any other clinical and biologic features.

DIAGNOSTIC VALUE OF sTREM-1 ASSAY

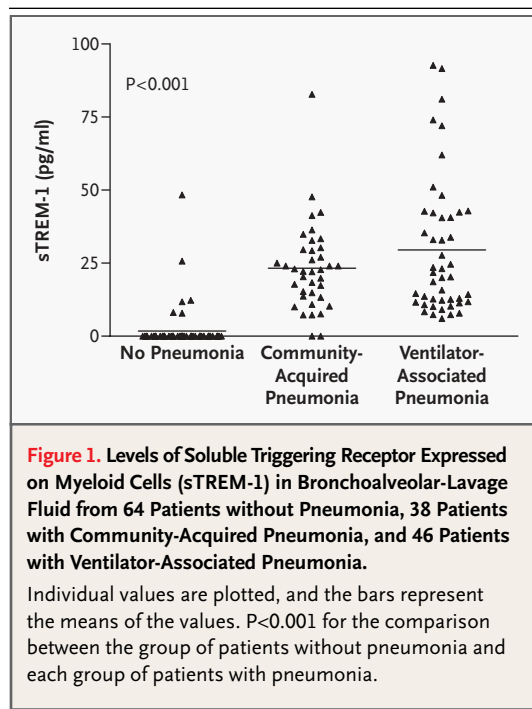
We next determined whether the presence of sTREM-1 in bronchoalveolar-lavage fluid could discriminate between the presence and the absence of pneumonia. Since there was no difference between patients with community-acquired pneumonia and patients with ventilator-associated pneumonia in the following analyses, pooled data are presented. At a level of 5 pg per milliliter or above, sTREM-1 was detected in bronchoalveolar-lavage fluid from 36 of 38 patients with community-acquired pneumonia (sensitivity, 95 percent; 2 false negative results), 46 of 46 ventilator-associated pneumonia patients (sensitivity, 100 percent), and 6 of 64 patients without pneumonia (6 false positive results). Thus, among the whole population of patients, the presence of sTREM-1 in bronchoalveolar-lavage fluid was associated with a likelihood ratio of 10.38.

The capacity of sTREM-1 to differentiate the presence from the absence of pneumonia was assessed with a receiver-operating-characteristic curve analysis (Fig. 2). The area under the receiver-operating-characteristic curve when sTREM-1 was used to differentiate the presence from the absence of pneumonia was 0.93 (95 percent confidence interval,

Table 2. Characteristics of the Three Groups of Patients at Enrollment.*

| Characteristic | Community-Acquired Pneumonia (N=38) | Ventilator-Associated Pneumonia (N=46) | No Pneumonia (N=64) | P Value |
|--|-------------------------------------|--|---------------------|---------|
| Duration of mechanical ventilation before study entry — days | 0.4 \pm 0.2 | 6.4 \pm 8.5 | 2.1 \pm 4.8 | <0.001 |
| Previous antimicrobial therapy — no. (%) | 33 (87) | 19 (41) | 30 (47) | <0.001 |
| Shock — no. (%) | 18 (47) | 19 (41) | 30 (47) | 0.49 |
| Body temperature — °C | 37.9 \pm 2.0 | 38.1 \pm 0.9 | 37.7 \pm 1.1 | 0.82 |
| Leukocyte count — cells/mm ³ | 12,800 \pm 7900 | 13,400 \pm 8500 | 12,500 \pm 5800 | 0.99 |
| PaO ₂ :FiO ₂ | 181 \pm 80 | 203 \pm 67 | 206 \pm 91 | 0.51 |
| Clinical pulmonary infection score >6 — no. (%) | 23 (61) | 28 (61) | 22 (34) | 0.02 |
| Procalcitonin — ng/ml | 3.7 \pm 1.9 | 2.6 \pm 0.8 | 2.5 \pm 1.2 | 0.58 |
| C-reactive protein — mg/liter | 197 \pm 128 | 184 \pm 108 | 141 \pm 110 | 0.34 |
| BAL fluid — pg/ml | | | | |
| Tumor necrosis factor α | 298.2 \pm 47.7 | 290.5 \pm 39.7 | 147.2 \pm 25.1 | <0.001 |
| Interleukin-1 β | 92.5 \pm 22.5 | 95.1 \pm 29.4 | 41.5 \pm 12.5 | <0.001 |
| sTREM-1 | 23.2 \pm 2.8 | 33.6 \pm 5.1 | 1.8 \pm 0.9 | <0.001 |

* Plus-minus values are means \pm SD. PaO₂:FiO₂ denotes the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, BAL bronchoalveolar lavage, and sTREM-1 soluble triggering receptor expressed on myeloid cells.



0.92 to 0.95; $P < 0.001$). A sTREM-1 cutoff value of 5 pg per milliliter (which represented the technique's threshold of detection) had a sensitivity of 98 percent (95 percent confidence interval, 95 to 100) and a specificity of 90 percent (95 percent confidence interval, 84 to 96). In a multiple logistic-regression analysis, we determined that the presence of sTREM-1 in bronchoalveolar-lavage fluid was the strongest independent predictor of pneumonia, with an odds ratio of 41.5 (95 percent confidence interval, 20.9 to 77.6) (Table 3). The best clinical predictor of pneumonia was a clinical pulmonary infection score of more than 6 (odds ratio, 3.0).

DISCUSSION

Our findings are evidence of the value and accuracy of a rapid test for sTREM-1 in the bronchoalveolar-lavage fluid of patients receiving mechanical ventilation to diagnose bacterial or fungal pneumonia. Many noninfectious processes lead to fever and new pulmonary infiltrates in such patients, rendering the diagnosis of pneumonia (and especially ventilator-associated pneumonia) very challenging. The systemic signs of infection, such as fever, tachycardia, and leukocytosis, are nonspecific findings and can be caused by any condition that releases cytokines.

Pugin et al. combined body temperature, the white-cell count, the volume and appearance of tracheal secretions, the $\text{PaO}_2\text{:FiO}_2$, findings on chest radiography, and the results of cultures of tracheal aspirates into a clinical pulmonary infection score and reported that a score of more than 6 was associated with a high likelihood of pneumonia.¹⁹ This finding was confirmed in our study, since a clinical pulmonary infection score of more than 6 was the best clinical predictor of pneumonia, with an odds ratio of 3.0. However, the diagnostic accuracy of this score remains to be confirmed.

In terms of clinical decision making in patients in whom pneumonia is suspected, the main problem with the use of microbiologic diagnostic procedures that require culture is the delay in diagnosis of 24 to 48 hours. The uncertainty often leads to the prescription of unneeded antibiotics. However, the empirical use of broad-spectrum antibiotics in patients without infection is potentially harmful, facilitating colonization and superinfection with multiresistant bacteria,²⁴ and is correlated with an increased length of hospitalization and, therefore, increased hospital costs.²⁵ In addition, overuse of antibiotics in such critically ill patients delays the proper diagnosis and possible treatment of the true cause of fever and pulmonary infiltrates.^{5,7}

Many biologic markers have been studied in an effort to improve the rapidity and performance of the diagnostic procedure. Among critically ill patients, measurements of serum C-reactive protein and procalcitonin have proved disappointing.^{10,11} We obtained similar results: there were no significant differences in the levels of these proteins between patients with pulmonary infections and those without pulmonary infections.

When anatomical and mechanical defense mechanisms that prevent microorganisms from reaching alveoli are overwhelmed, a complex host response develops. Microbial products activate alveolar macrophages, which release multiple endogenous mediators locally. Among these mediators, tumor necrosis factor α , interleukin- 1β , and other cytokines are increased in various types of pulmonary infections¹²⁻¹⁵ and thus have potential prognostic implications.^{14,16} However, in agreement with other studies,^{14,15} we were unable to identify any cutoff value for such mediators that could be used to diagnose pneumonia.

Like other similar cell-surface receptors, TREM-1 has a short intracellular domain and, when bound to its still unidentified ligand, it associates with a

signal-transduction molecule called DAP12 and triggers the secretion of inflammatory cytokines, amplifying the host response to bacterial stimuli. Bouchon and coworkers have shown that the expression of TREM-1 is greatly up-regulated in the presence of bacteria such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* or fungi such as *Aspergillus fumigatus*, both in cell culture and in peritoneal-lavage fluid and tissue samples from patients infected with these microorganisms.¹⁸ In contrast, TREM-1 was not up-regulated in samples from patients with noninfectious inflammatory disorders, such as psoriasis, indicating the specific involvement of this receptor only in the case of infection.^{18,26,27} Using a simple immunoblot technique, we were able to demonstrate that sTREM-1 is released into the bronchoalveolar-lavage fluid from patients with pneumonia and that this marker has a sensitivity of 98 percent. In striking contrast, sTREM-1 was detected in only 6 of 64 patients without pneumonia. The levels of sTREM-1 in bronchoalveolar-lavage fluid were not correlated with any of the other clinical or biologic variables tested and stood as an independent predictor of high specificity. In a multiple logistic-regression analysis, the presence of sTREM-1 in bronchoalveolar-lavage fluid was the best predictor of pneumonia.

A potential limitation of this study may come from the criteria we used to diagnose pneumonia, although these criteria have been widely used.^{5,7,19} Microbiologic documentation of infection was obtained in all cases of community-acquired and ventilator-associated pneumonia. When pneumonia was considered to be absent, either a noninfectious alternative cause of pulmonary infiltrates was established or the criterion of full recovery from fever, infiltrates, and leukocytosis without antimicrobial therapy was used. However, we could not exclude the possibility that some patients with true ventilator-associated pneumonia were misclassified as not having pneumonia and recovered spontaneously. This mistake could have artificially lowered the specificity of the test and may have been responsible for some of the six false positive results in the group without pneumonia. Finally, none of the patients tested presented with viral pneumonia, and thus, our results are not generalizable to viral infections.

Our results demonstrate that rapid detection of sTREM-1 in bronchoalveolar-lavage fluid may improve the ability of clinicians to differentiate patients with bacterial or fungal pneumonia from those with-

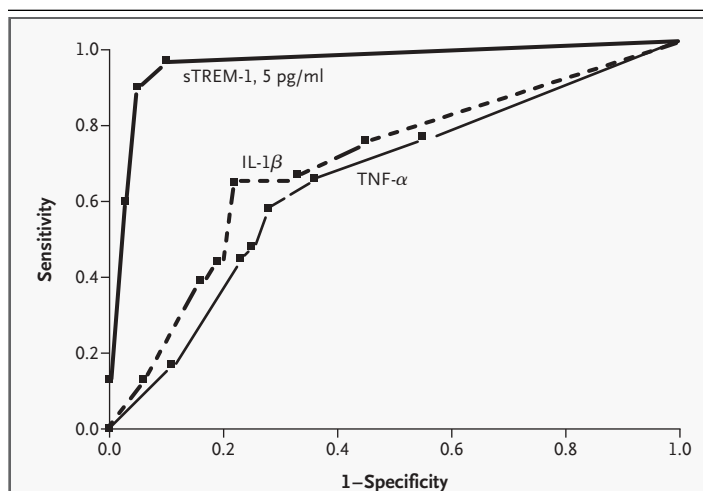


Figure 2. Receiver-Operating-Characteristic Curves for Various Cutoff Levels of Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM-1), Tumor Necrosis Factor α (TNF- α), and Interleukin-1 β (IL-1 β) in Bronchoalveolar-Lavage Fluid in Differentiating between the Presence and the Absence of Pneumonia.

Areas under the receiver-operating-characteristic curves were 0.93 (95 percent confidence interval, 0.92 to 0.95) for a cutoff value of 5 pg of sTREM-1 per milliliter, 0.64 (95 percent confidence interval, 0.62 to 0.69) for tumor necrosis factor α , and 0.69 (95 percent confidence interval, 0.67 to 0.72) for interleukin-1 β .

Table 3. Multiple Logistic-Regression Analysis of Factors Used to Differentiate between Patients with and Those without Pneumonia.*

| Predictor | P Value | Odds Ratio (95% Confidence Interval) |
|--|---------|--------------------------------------|
| Clinical pulmonary infection score >6 | 0.002 | 3.0 (1.5–5.9) |
| Tumor necrosis factor α >150 pg/ml of BAL fluid | 0.004 | 2.4 (1.8–5.8) |
| Interleukin-1 β >75 pg/ml of BAL fluid | 0.003 | 2.7 (2.0–13.2) |
| sTREM-1 >5 pg/ml of BAL fluid | <0.001 | 41.5 (20.9–77.6) |

* BAL denotes bronchoalveolar lavage, and sTREM-1 soluble triggering receptor expressed on myeloid cells.

out pneumonia. This ability should be especially useful in patients in whom the diagnosis is not clinically straightforward. The immunoblot technique is rapid, accurate, and inexpensive and can be used for small batches of specimens or even individual samples. The use of this test to detect the presence of sTREM-1 in bronchoalveolar-lavage fluid may lead to more accurate diagnoses of pneumonia in patients who are receiving mechanical ventilation.

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REFERENCES

1. Wunderink RG. Mortality and the diagnosis of ventilator-associated pneumonia: a new direction. *Am J Respir Crit Care Med* 1998;157:349-50.
2. Baker AM, Meredith JW, Haponik EF. Pneumonia in intubated trauma patients: microbiology and outcomes. *Am J Respir Crit Care Med* 1996;153:343-9.
3. Fagon JY, Chastre J, Hance AJ, Domart Y, Trouillet JL, Gibert C. Evaluation of clinical judgment in the identification and treatment of nosocomial pneumonia in ventilated patients. *Chest* 1993;103:547-53.
4. Helling TS, Van Way C III, Krantz S, Bertram K, Stewart A. The value of clinical judgment in the diagnosis of nosocomial pneumonia. *Am J Surg* 1996;171:570-5.
5. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002;165:867-903.
6. Meduri GU, Wunderink RG, Leeper KV, Beals DH. Management of bacterial pneumonia in ventilated patients: protected bronchoalveolar lavage as a diagnostic tool. *Chest* 1992;101:500-8.
7. Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia: a randomized trial. *Ann Intern Med* 2000;132:621-30.
8. Papazian L, Thomas P, Garbe L, et al. Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1995;152:1982-91.
9. Campbell GD Jr. Blinded invasive diagnostic procedures in ventilator-associated pneumonia. *Chest* 2000;117:Suppl 2:207S-211S.
10. Duflo F, Debon R, Monneret G, Bienvenu J, Chassard D, Allaouchiche B. Alveolar and serum procalcitonin: diagnostic and prognostic value in ventilator-associated pneumonia. *Anesthesiology* 2002;96:74-9.
11. Brunkhorst FM, Al-Nawas B, Krummenauer F, Forycki ZF, Shah PM. Procalcitonin, C-reactive protein and APACHE II score for risk evaluation in patients with severe pneumonia. *Clin Microbiol Infect* 2002;8:93-100.
12. Fukushima R, Alexander JW, Gianotti L, Ogle CK. Isolated pulmonary infection acts as a source of systemic tumor necrosis factor. *Crit Care Med* 1994;22:114-20.
13. Meduri GU, Kohler G, Headley S, Tolley E, Stentz F, Postlethwaite A. Inflammatory cytokines in the BAL of patients with ARDS: persistent elevation over time predicts poor outcome. *Chest* 1995;108:1303-14.
14. Monton C, Torres A, El-Ebiary, Filella X, Xaubet A, de la Bellacasa JP. Cytokine expression in severe pneumonia: a bronchoalveolar lavage study. *Crit Care Med* 1999;27:1745-53.
15. Wu CL, Lee LY, Chang KM, et al. Bronchoalveolar interleukin-1 β : a marker of bacterial burden in mechanically ventilated patients with community-acquired pneumonia. *Crit Care Med* 2003;31:812-7.
16. Bonten MJ, Froon AH, Gaillard CA, et al. The systemic inflammatory response in the development of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1997;156:1105-13.
17. Bouchon A, Dietrich J, Colonna M. Inflammatory responses can be triggered by TREM-1, a novel receptor expressed on neutrophils and monocytes. *J Immunol* 2000;164:4991-5.
18. Bouchon A, Facchetti F, Weigand MA, Colonna M. TREM-1 amplifies inflammation and is a crucial mediator of septic shock. *Nature* 2001;410:1103-7.
19. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991;143:1121-9.
20. McCabe WR, Jackson GG. Gram-negative bacteremia. *Arch Intern Med* 1982;110:847-64.
21. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270:2957-63. [Erratum, *JAMA* 1994;271:1321.]
22. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996;22:707-10.
23. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644-55.
24. Amyes SG. Strategies and options for minimizing resistance emergence in pulmonary infections. *Chest* 1998;113:Suppl:228S-232S.
25. Birmingham MC, Hassett JM, Schentag JJ, Paladino JA. Assessing antibacterial pharmacoeconomics in the intensive care unit. *Pharmacoeconomics* 1997;12:637-47.
26. Nathan C, Ding A. TREM-1: a new regulator of innate immunity in sepsis syndrome. *Nat Med* 2001;7:530-2.
27. Cohen J. TREM-1 in sepsis. *Lancet* 2001;358:776-8.

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