Soluble Triggering Receptor Expressed on Myeloid Cell-1 Is Increased in Patients With Ventilator-Associated Pneumonia*

A Preliminary Report

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Rationale: **The diagnosis of ventilator-associated pneumonia (VAP) can be difficult. Soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) has been reported to be elevated in BAL fluid from patients with VAP.**

Objectives: **To evaluate the utility of sTREM-1 in the diagnosis of VAP in BAL fluid and the fluid collected in the expiratory trap from the ventilator, the exhaled ventilator condensate (EVC).**

Methods: **We prospectively collected BAL fluid and EVC from 23 patients clinically suspected of having VAP. A sensitive enzyme-linked immunosorbent assay was developed to measure sTREM-1. The results derived from this assay were confirmed using an immunoblot technique. The presence of VAP was clinically determined using a modified clinical pulmonary infection score of > 6.**

Results: **VAP was diagnosed in 14 of 23 patients. sTREM-1 was detected in the EVC from 11 of 14 subjects with VAP, but from only 1 of 9 subjects without VAP, and was significantly higher in the pneumonia patients and when expressed as picograms per milliliter or picograms per microgram protein ($p = 0.005$, both comparisons). In contrast, sTREM-1 was detected in the BAL fluid of all 14 VAP subjects but also in 8 of 9 subjects with no pneumonia, and did not differ in the VAP subjects compared to the nonpneumonia subjects when expressed as picograms per milliliter or picograms per microgram protein ($p > 0.05$ both comparisons).**

Conclusion: **sTREM-1 is detectable in EVC and may be useful in establishing or excluding the diagnosis of VAP.** ***(CHEST 2007; 132:58–63)***

Key words: BAL; exhaled breath condensate; soluble triggering receptor expressed on myeloid cells; ventilator-associated pneumonia

Abbreviations: BLOTTO = bovine lactotransfer technique optimizer; CPIS = clinical pulmonary infection score; EBC = exhaled breath condensate; ELISA = enzyme-linked immunosorbent assay; EVC = exhaled ventilator condensate; PBS = phosphate-buffered saline solution; rhTREM-1 = recombinant human triggering receptor expressed on myeloid cell-1; sTREM-1 = soluble triggering receptor expressed on myeloid cell-1; VAP = ventilator-associated pneumonia

The diagnosis of ventilator-associated pneumonia (VAP) can be a clinical challenge.[1–3] A clinical diagnosis of pneumonia can be made when a new radiographic infiltrate develops in a patient with fever, leukocytosis, purulent tracheal secretions, decreasing Pao_2, and when microorganisms are isolated from the airways. These clinical parameters

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have been used to develop the clinical pulmonary infection score (CPIS), which although imperfect is clinically useful in detecting the onset of VAP.[4] Unfortunately, many noninfectious processes may be responsible for fever and new pulmonary infiltrates, and this, combined with the imperfection of the CPIS, have led to the use of other techniques such as BAL quantitative cultures and protected brush microbial cultures to demonstrate VAP.[5–8] However, these require invasive procedure and results can be delayed and often false negative because of the empiric administration of antibiotics.

In this context, many biological markers have been studied in an effort to improve the diagnostic accuracy of VAP, most with disappointing results.[9–13] However, detection of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in BAL from patients who are receiving mechanical ventilation has been initially reported as a good clinical indicator of VAP with a sensitivity of 98% and a specificity of 90%.[14] However, a more recent report[15] suggests the utility of this marker as a single measurement in the diagnosis of VAP may be lower with a sensitivity of 75% and specificity of 84%. This is within the range reported in some series for the CPIS score.[8] These reports illustrate the need for additional, more sensitive and specific biomarkers of VAP and the need for additional studies regarding the utility of sTREM-1 measurement in diagnosing VAP.

Exhaled breath condensate (EBC), the condensate obtained from exhaled breath vapor, has been proposed as a noninvasive method of sampling the lower respiratory tract.[16] Most lipids and proteins that can be detected in BAL can also be detected in EBC, albeit in lower concentrations. In intubated subjects, exhaled breath is collected in the collection trap in the expiratory ventilator line.[17] We termed this collection *exhaled ventilator condensate* (EVC) and hypothesized that sTREM-1 is detectable in EVC collected from subjects with VAP and may provide for a useful clinical diagnostic for characterizing individuals with pneumonia. We collected BAL and EVC from subjects suspected of having VAP, and we successfully detected sTREM-1 in most of the EVC samples collected from these subjects but not in subjects who did not have pneumonia with a single exaction. These results suggest the potential utility to EVC sTREM-1 measurement in detecting VAP.

Materials and Methods

Patients

Patients ≥ 18 years old who were hospitalized in our medical ICU were prospectively enrolled in the study if they required mechanical ventilation and there was a clinical suspicion of infectious pneumonia in whom bronchoscopy was planned. Our Institutional Review Board approved the study but waived informed consent.

Sample Collection

BAL was performed through an endotracheal tube using five 20-mL aliquots. An additional aliquot was performed and sent to the clinical laboratory for quantitative culture. The remaining BAL fluid was centrifuged to remove cellular debris (10,000 revolutions per minute; 30 min; 4°C [Eppendorf 5415C; Eppendorf; Hamburg, Germany]),[14] and the supernatant fluid and EVC were frozen until studied. One patient was studied twice. EVC was collected from the expiratory line at the time of the BAL. The EVC was removed from the expiratory line trap at the time of the completion of BAL. No effort was made to collect fluid for a standardized time, but the expiratory trap is emptied every 2 h, and therefore the sample was collected over < 2 h.

Five normal, nonintubated subjects were also studied. Their EBC was collected by cold condensation of their exhaled breath for 15 min as previously described.[16]

We used the CPIS to classify the patients as having VAP for the purposes of this study.[18] The CPIS was calculated as previously described using a 0–2 scoring system using fever, leukocytosis, tracheal aspirates, oxygenation, radiographic infiltrates, and semiquantitative cultures of tracheal aspirates with Gram stain. We used a colony count of 10^3 organisms per milliliter as significant because of the technique of the BAL.[19] A score > 6 was considered indicative of VAP. The duration of mechanical ventilation and the length and the outcome (death or discharge) of stay in the ICU were also recorded.

Two intensivists (G.H. and R.A.R.) reviewed all medical records pertaining to the patient, and independently classified the diagnosis as VAP or no pneumonia based on the CPIS. A consensus concerning the diagnosis was achieved in all cases. The one patient studied twice was classified as VAP once and no pneumonia once.

Antibodies

Mouse anti-human TREM-1 (cat no. 841555), biotinylated goat anti-human TREM-1 (part 841556), and conjugated streptavidin horseradish-peroxidase (part 890803) were obtained from R&D Systems Inc. (Minneapolis, MN).

Chemicals

Bovine serum albumin (cat. no. A7030–10G) was purchased from Sigma-Aldrich (St. Louis, MO). Concentrated buffered surfactant (cat. no. WA126), substrate solutions consisting of hydrogen peroxide and chromogen (color reagents A & B; cat no. DY999), and stop solution consisting of 2N sulfuric acid (cat. no. DY994) were obtained from R&D Systems Inc.

Antigen Standard

Calibration curves were prepared using recombinant human TREM-1 (rhTREM-1) [cat. no. 841557; R&D Systems Inc.] ranging from 0 to 2,000 pg/mL by serially diluting rhTREM-1 in a solution consisting of phosphate buffered saline solution (PBS) [pH 7.3] supplemented with 1% bovine serum antigen (Sigma-Aldrich).

Human sTREM Assay Procedure

Flat-bottom 96-well immunomicrotiter plates (cat no. 468667; Nalge Nunc International; Rochester, NY) were coated with 100

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