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Biomarkers for Ventilator-Associated Pneumonia: Review of the Literature

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Introduction

Ventilator-associated pneumonia (VAP) is a healthcare-associated bacterial infection of the lung.[1,2] Patients with VAP are hospitalized longer and have higher costs associated with their stay.[1–6] A clinical diagnosis of VAP, based on pulmonary infiltrates on the chest radiograph and at least one additional criteria of leukocytosis, fever, or purulent respiratory secretions, has high sensitivity,[7] but overestimates the incidence of VAP, resulting in the use of antibiotics in patients that do not have an infectious process.[8] Diagnostic strategies to increase specificity are utilized in some settings, but their accuracy is debatable and still results in misclassification of patients.

Clinical Pulmonary Infection Scoring (CPIS) was introduced to improve the specificity of clinical diagnosis.[9] CPIS combines clinical, radiological, physiological, and microbiological (culture of tracheal aspirate) data into a single numerical value. However, recent studies suggest that CPIS has a lower specificity [1,10,11] for the diagnosis of VAP compared to quantitative culture of bronchoalveolar lavage fluid (BALF).[12–14] Consequently, patients diagnosed using the CPIS may be misclassified as having VAP.

Several invasive or semi-invasive methods can be used to diagnose VAP. Endotracheal aspirates do not sample deeply into the lung, and cultures may represent colonization of the endotracheal tube, rather than true infection.[15,16] Non-directed BAL (blind, “mini” BAL), utilized to retrieve fluid from the lung without direct visualization, may miss the area of infection, resulting in a false negative test. Quantitative culture of bronchoalveolar lavage fluid (BALF) retrieved by direct bronchoscopic methods yields the best sensitivity and specificity to diagnose VAP and can differentiate true infection from colonization or inflammation.[8,17] Diagnostic techniques based on quantitative culture of BALF reduces the amount and duration of antibiotic therapy.[8] However, bronchoscopy is an invasive procedure and requires specialized skills.

Biomarkers are proteins whose presence correlates with disease, making them a potentially useful diagnostic tool. Biomarkers can be detected in any biological sample including:

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serum, BALF, and exhaled breath condensate (EBC). A biomarker for VAP should be low or absent when infection is not present and elevated in the presence of infection.[18] Ideally, biomarker results would be available sooner than quantitative culture of BALF, which can take up to 48 hours. EBC from intubated patients collects in the expiratory ventilator tubing and drain cup of the ventilator. Analyzing EBC for biomarkers is an appealing option since it is easily accessible to bedside nurses and does not require invasive procedures.

The validity of a screening test depends on the ability of the test to correctly classify patients with and without VAP (Table 1), using a directed, quantitative culture from BALF as the standard for diagnosis. False negative results may delay the start of antibiotic therapy in patients who need it.[18] False positive results may lead to unnecessary antibiotic use and potential development of antibiotic resistance. Diagnostic methods with good sensitivity already exist for VAP, such as clinical criteria and CPIS. By increasing the specificity of a screening test, the fewer false positive results reduce the use of antibiotics and costly, invasive diagnostic strategies. A biomarker with high specificity may also guide the clinician towards alternative sources of infection.

One confounding factor in the diagnosis of VAP is prior use or recent change of antibiotics. Antibiotics suppress the bacterial load in the lower airways and decrease the amount of bacteria in the lung tissue. Prior antimicrobial therapy may result in a large percentage of false-negative test results because the diagnostic threshold used for quantitative culture is not adjusted to account for antibiotic-induced bacterial suppression. Bacterial suppression decreases circulating levels of biomarkers in biological fluids which may lead to false-negative test results and failure to treat if the appropriate threshold is not established.[19]

Objective

The purpose of this article is to analyze evidence for the usefulness of three biomarkers for predicting VAP: soluble triggering receptor expressed on myeloid cells type 1 (sTREM-1), procalcitonin (PCT), and C-reactive protein (CRP). Aims are to present a brief biology of the biomarkers, summarize the study design and methods, and discuss confounding factors that limit methods for diagnosing VAP.

Soluble Triggering Expressed on Myeloid Cells Type 1

Triggering receptor expressed on myeloid cells-1 (TREM-1) is a glycoprotein member of the immunoglobulin (IgG) superfamily whose expression on phagocytes is up-regulated by exposure to bacteria and fungi.[20] TREM-1 triggers the secretion of pro-inflammatory mediators through a signaling pathway (DAP12) and functions as an amplifier of the inflammatory response.[21] In response to infection, soluble TREM-1 (sTREM-1) is either secreted or shed and can be measured in body fluids.[21–23] sTREM-1 is almost undetectable in patients with non-microbial inflammation.[20]

The positive association between sTREM-1 and infection prompted investigators to determine whether sTREM-1 in BAL could be utilized to distinguish infection from inflammation. In an early study, Gibot and Cravoisy,[24] demonstrated high specificity and sensitivity, suggesting sTREM-1 was useful in predicting VAP. However, subsequent studies have shown much lower sensitivity and specificity for sTREM-1, despite standardized methods to detect sTREM-1 (Table 2). One possible contributing factor to lower sensitivity and specificity in subsequent studies was the prior use of antibiotics. For example, in the study by Anand and Zuick,[25] more than half of the enrolled patients (53%) received antibiotics prior to and during BAL retrieval. Oudhuis and Beuving,[26] did not report previous or concurrent antibiotic use in their study. Previous antibiotic use may have decreased the bacterial burden below the established culture threshold, resulting in a false

negative VAP diagnosis. In addition, the performance characteristics of tests for VAP diagnosis depend on how one defines VAP. The two latest studies, Anand and Zuick,[25] and Oudhuis and Beuving,[26] which showed the lowest sensitivity and specificity also used the most stringent method to diagnose VAP, directed bronchoscopy.

EBC collection is a non-invasive method to sample the lung. Horenenko et al.,[27] is the only published study to date demonstrating detectable sTREM-1 in EBC. Further research is needed to determine whether EBC is a valid representation of the lung space and whether it is a useful sample to use for biomarker measurement for VAP.

To summarize, sTREM-1 is detectable in BALF and EBC. EBC sTREM-1 levels are detectable in lower concentrations than in BALF.[27] BALF and EBC sTREM-1 concentrations are higher in VAP positive patients than in VAP negative patients. The usefulness of sTREM-1as a biomarker for VAP has not been conclusively demonstrated. Inconsistent findings may be due to the methods used for BAL sample collection, diagnostic criteria defining VAP, as well as use of antibiotics during the sample collection period. In addition, more recent studies suggest sTREM-1 may be elevated in non-infectious causes of inflammation suggesting sTREM-1 may not be as specific for infection as initially thought.[28,29] Further studies are needed that enroll large populations of ICU patients using similar study designs and standardized methods for sample collection and analysis.

Procalcitonin

Procalcitonin (PCT) is a prohormone secreted into serum most likely from neuroendocrine cells in the lungs or intestine as part of the systemic inflammatory response.[30,31] Circulating levels of plasma PCT are almost non-existent in healthy individuals, but detectable in patients with systemic bacterial induced inflammation.[31] Its physiological role remains unknown. The rapid release and long half-life of procalcitonin makes it potentially useful as a diagnostic indicator of VAP.

Five studies report the use of serum PCT as a marker for VAP [3,32–35] (Table 3). Sensitivities ranged between 41% and 100% with lower sensitivities indicating the potential to miss many positive VAP patients. Specificity was higher in two of five studies[32,34] with a range of 97–100%. Variable cutoff values and dissimilar study designs across the studies contribute to the difficulty in interpreting the results. The different patient populations across studies may have contributed to elevated PCT levels that were unrelated to VAP. In addition, the methods to diagnose VAP and quantify bacterial infection of the lung differed across studies. Previous antibiotic use may have contributed to misclassification of patients as VAP negative, affecting the mean serum PCT level and sensitivity and specificity. Taken in summary, these studies suggest that serum PCT is not a good biomarker for VAP.

Although PCT is not a promising predictor for VAP, a recent meta-analysis determined that a PCT guided strategy in septic patients reduced the duration of antibiotic therapy without harmful effects when compared to standard therapy.[36] The ProHOSP study, a large, multi-center, randomized controlled trial,[37] and a smaller trial,[38] both used PCT to determine the duration of antibiotic therapy in patients with lower respiratory tract infections. Antibiotic use was significantly decreased in the PCT algorithm group versus control group in both studies with no difference in adverse events. Patients also had a shorter stay in the ICU. However, hospital stay and mortality were unchanged between groups. A recent multicenter trial (PRORATA) demonstrated safe discontinuation of antibiotics in patients with low serum PCT levels.[19] Limiting exposure to antibiotics decreases costs and decreases the risk of the emergence of resistant bacteria. Thus, following serial PCT levels in patients with known VAP may allow earlier cessation of antibiotic therapy.

C–Reactive Protein

C-reactive protein (CRP) is a non-specific biological marker of inflammation synthesized in the liver.[39] The synthesis of CRP occurs rapidly in response to infection and falls quickly once the stimulus is removed.[40] In healthy individuals, serum CRP levels are low (typically around 1mg/L), but can raise sharply in the presence of bacterial infection, trauma, burns, surgery, and cancer.[39] Serum CRP is a quick and non-invasive way to determine if inflammation is present. A limited number of small studies have examined serum CRP as a marker for VAP.

A limited number of studies have examined serum and BALF CRP as a marker for VAP. The small sample size of the three studies [30,35,41] may have limited the likelihood of finding differences in sensitivity and specificity that exist in the population. Protocols for sampling the lung space were not described in the Ramerez et al. study.[30] Therefore, it remains unclear whether BALF CRP levels are elevated in locally infected regions of the lung which may yield better diagnostic indicators of VAP. Sensitivity was low in one of the studies [30] resulting in many false negative results and specificity was high in another study [42] resulting in very few false positive results. The same assay was used to measure CRP in both the Ramerez et al.,[30] and Povoa et al.,[41] studies; yet, the cutoff values differed between them, thus, limiting the generalizability of their results. Oppert et al.,[35] reported that CRP was not useful for VAP diagnosis, but they did not report sensitivity or specificity.

Conclusions

The utility of CRP, PCT, and sTREM-1 as predictors of VAP has not been demonstrated. There is increased recognition that all 3 biomarkers may be elevate in both non-infectious and infectious causes of inflammation. Studies of all 3 biomarkers are marred by inconsistent methods to diagnose VAP, prior antibiotic use, and variable sensitivities and specificities. None of the studies of sTREM-1 have reported analysis of trauma patients as a subgroup, despite the high risk for VAP. Monitoring biomarkers as a method for guiding antibiotic therapy is intriguing, yet has only been investigated with PCT. Although, Gibot et al.,[24] and Detterman et al.,[34] reported declines in sTREM-1 levels upon initiation of antibiotic therapy, it was not an investigational endpoint, so, uncertainty exists as to the utility of the results. To clarify the role of biomarkers in predicting VAP, the following study methods are recommended: Use direct BAL to obtain BALF; exclude patients who have received antibiotic or corticosteroid therapy prior to obtaining BALF, report sensitivity and specificity using cutoff values cited in similar literature for the biomarker; and include a homogeneous patient population.

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Table 1

Sensitivity and Specificity: a/(a+c) = sensitivity; d(b+d) = specificity

	VAP Positive	VAP Negative
Biomarker Positive	a (true positive)	b (false positive)
Biomarker Negative	c (false negative)	d (true negative)

Table 2

Characteristics of five clinical studies of sTREM-1 levels.

Study	(Gibot & Cravoisy, 2004)	(Determann et al., 2005)	(Horonenko et al., 2007)	(Anand, Zuick, Klesney- Tait, & Kollef, 2009)	(Oudhuis et al., 2009)
Number of Patients	148	28	23	105	240*
Setting	MICU	Mixed ICU	MICU	MICU	Mixed ICU
Assay	Immunoblot	ELISA	ELISA	ELISA	ELISA
Type of BAL	Non- directed	Non- directed	NS	Directed	Directed
Confirmation of VAP	$>10^3$cfu/ml	$\geq 10^4$cfu/ml	CPIS > 6	$>10^4$cfu/ml	$\geq 10^4$cfu/ml
Previous and/or concurrent antibiotic use (%)	47%	NR	100% PNA (−)71% PNA (+)	53%	NR
VAP Positive Patients	46	9	14	19	90
Mean BALF sTREM-1 in VAP + Group (pg/ml)	34	894	403	172	227
BALF sTREM-1 Cutoff (pg/ml)	5	200	≤7pg/ml	200	NR
EBC sTREM- 1 Cutoff (pg/ml)	NR	NR	≤7pg/ml	NR	NR
Sensitivity	100%	75%	100% BALF 71% EBC	42%	65
Specificity	91%	84%	10% BALF 89% EBC	76%	48

VAP, Ventilator-associated pneumonia; BAL, bronchoalveolar lavage; cfu, colony forming units; sTREM-1, soluble triggering receptor expressed on myeloid type-1 cells; ICU, intensive care unit; PNA, pneumonia; NR, not reported; NS, not specified

*This is the number of samples collected from 207 patients. An additional BAL sample from the same patient was included in the study if ≥2 weeks passed between bronchoscopy.

Table 3

Characteristics of four clinical studies of PCT.

Study	(Duflo et al., 2002)	(Gibot & Cravoisy, 2004)	(Determan, et al, (2005)	(Luyt et al., 2008)	Oppert et al., 2002)
Number of Patients	96	148	20	73	28
Setting	Mixed ICU	Medical ICU	Medical ICU	Mixed ICU	Post CPR
Type of BAL	Non- directed	Non- directed	Directed	Directed	NR
Confirmation of VAP	$\geq 10^3$ cfu/ml	10^3 cfu/ml	$\geq 10^4$ cfu/ml	$\geq 10^4$ cfu/ml	NR
Previous and/or concurrent antibiotic use (%)	None	47% VAP (−) patients	NR	84% VAP group 95% non-VAP group	NR
VAP Positive Patients	44	46	9	32	12
Mean Serum PCT in VAP + Group ng/ml	11.5	2.6	3.89	1.07	6.0
Mean BALF PCT in BAP + Group ng/ml	NR	NR	0.07	NR	NR
Serum PCT Cutoff (ng/ml)	≥3.9	NR	≥2.99	≥0.5	1.0
Sensitivity	41%	NR	78%	72%	100%
Specificity	100%	NR	97%	24%	75%

VAP, Ventilator-associated pneumonia; BAL, bronchoalveolar lavage; cfu, colony forming units; PCT, procalcitonin; ICU, intensive care unit; NR, not reported

Table 4

Characteristics of two studies of CRP levels.

Study	**(Póvoa et al., 2005)**	**(Ramirez et al., 2008)**	**(Oppert, et al, 2002)**
Number of Patients	84	20	28
Setting	Mixed ICU	Medical ICU	ICU – post resuscitation patients
Type of BAL	NR	NR	NR
Confirmation of VAP	$\geq 10^4$ cfu/ml	NR	Sputum cultures and radiograph and/ or positive blood culture
Previous and/or concurrent antibiotic use (%)	None	None	NR
VAP Positive Patients	48	9	12
Mean Serum CRP Value in VAP + Group (mg/ dl)	19.6 (range 6.3– 32.9)	19.69 (range 11– 20.4)	NR
Serum CRP Cutoff Value (mg/dl)	9.6	19.69	NR
Sensitivity	88%	56%	NR
Specificity	86%	91%	NR

VAP, Ventilator-associated pneumonia; BAL, bronchoalveolar lavage; cfu, colony forming units; CRP, C-reactive protein; ICU, intensive care unit; NR, not reported