Diagnosing Ventilator-Associated Pneumonia in Burn Patients:
Endotracheal Aspirates Versus Bronchoalveolar Lavage

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Abstract

Introduction: Ventilator-associated pneumonia (VAP) is associated with increased mortality, ventilator days, intensive care unit days and length of stay, especially in the thermal burn patient. In addition to poorer patient outcomes it is estimated that VAP increases the cost of care, making the prevention of VAP a high priority within healthcare. While no "gold standard" diagnosis for VAP exists, criteria typically include clinical suspicion, radiography and microbiological testing. The purpose of this study was to correlate results of endotracheal tube swabs (ETT), endotracheal aspirates (TA) and broncheoalveolar lavage (BAL) in burn patients with suspected VAP. The goal of this study is to determine if TA sampling is a viable alternative to BAL in the diagnosis of VAP in burn patients.

Methods: This was a non-interventional prospective study of 42 adult burn patients with suspected VAP. Respiratory specimens via ETT, TA, and BAL were collected and cultured. Basic demographics, clinical signs and symptoms and culture results were collected and descriptive statistics were performed.

Results: Concurrent cultures were performed on the 42 patients with suspected VAP. Correlations were done between TA, BAL and ETT. TA and BAL correlated 87% of the time while TA and ETT correlated 49% of the time. The correlation between ETT and BAL was 40%. Calculated sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) for TA and BAL were roughly equal, while the values for ETT were much lower.

Conclusions: TA is nearly as reliable as BAL in identifying the causative organisms in VAP, and should be considered as an economical and easily obtained initial diagnostic test in burn patients suspected to have VAP.

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Introduction/Significance:

Healthcare in the United States is changing. Bundled payments, value based care, and evidenced based medicine are the new buzz words in an era where healthcare spending represents 17.4% of the national GDP.[1] Just as important as the accurate diagnosis and treatment of disease, prevention of complications and hospital-acquired infections is paramount. Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in intensive care units (ICUs), and contributes greatly to the morbidity, mortality, length of hospital stay, cost of care, and antibiotic use of ICU patients.[2-9] In one retrospective cohort study the average cost of ventilator associated pneumonia was roughly $40,000.[10]

Risk factors for the development of VAP include non-modifiable variables such as male sex, age > 60, underlying lung disease, coma, and organ system failure. Modifiable risk factors include supine position, use of antacids, receipt of enteral nutrition, use of antibiotics, and intracuff pressure <20 cm H2O.[11] Patients who are admitted to the ICU because of burn injury are especially prone to acquiring VAP because they are often in a state of systemic inflammation, immunosuppression and electrolyte/hemodynamic imbalance.[12,13] Additionally, burn patients who have inhalation injury have increased incidence of mechanical ventilation and subsequently, VAP.[14]

Accurate diagnosis of VAP can be difficult, such that a high index of clinical suspicion and signs and symptoms (leukocytosis/leukopenia, fever, purulent secretions, new or progressive infiltrates on chest x-ray) generally prompt clinicians to begin empiric antibiotic therapy.[5,15] The same state of systemic inflammation, immunosuppression and electrolyte/hemodynamic balance that puts burn patients at risk for VAP, also complicates the clinical presentation of VAP and makes clinical predictors less useful.[16] Currently there is no agreed-upon “gold standard” diagnostic criterion for VAP.[3,17-19] This inadequacy can lead to the use of unnecessary antibiotic regimens, the emergence of antibiotic-resistant organisms, and a possible delay in the actual diagnosis.[3,20]

Clinically suspected VAP is often confirmed with quantitative/qualitative culture and gram stain of either upper airway (non-invasive) or lower airway (invasive) samples.[4,7,19]

Bronchoalveolar lavage (BAL) is the primary form of invasive sampling in the diagnosis of VAP, and is usually performed by a physician with the assistance of a respiratory therapist. This is widely used as the technique of choice for confirming VAP in critical care patients and has been associated with decreased mortality of VAP patients.[2,21-25] Its effectiveness, however, has not been explored in a patient sample consisting solely of burn patients.[13]

Culture of endotracheal aspirates (TA) is the primary form of non-invasive sampling. Many institutions utilize TA because it is less expensive and easily obtained by ICU staff.[26] The diagnostic accuracy of this method, relative to BAL, remains controversial in the general critical care population and unexplored in the subpopulation of burn patients.[3,7,13,23-25,27-33] In addition, non-inasive culturing of the endotracheal tube (ETT) can provide additional information regarding the upper airway and VAP.[34] The latest recommendations from the American Burn Association regarding the diagnosis of VAP are consistent with this methodology and call for a microbiologic based strategy in the setting of suspected VAP.[13]

Given that burn ICU patients are at increased risk of VAP, and that lower airway culture plays a critical role in the diagnosis and treatment of VAP, it is important that an accurate, and cost effective microbiologic sampling strategy is in place. The purpose of this study is to first explore the diagnostic utility of BAL, ETT, and TA in the diagnosis of VAP in an exclusive population of adult burn patients. Second, the culture results of ETT, TA and BAL will be correlated and sensitivities, specificties and predictive values will be calculated. The goal of this study is to determine if the less expensive and less invasive TA sampling is a viable alternative to BAL in the diagnosis of VAP in burn patients.

Materials and Methods:

This study took place at the Arizona Burn Center at Maricopa Medical Center, an American Burn Association verified regional burn center. As the second largest burn center in North America it serves all of Arizona, parts of the surrounding states and Northern Mexico.

This was a prospective, non-interventional study of all intubated adult patients admitted to the burn ICU from November 2009 to July 2013 who were suspected to have VAP. Out of 51 total patients, 6 were excluded due to non-burn related injury, and 3 were excluded because they were studied the same day that ventilation was initiated.

Respiratory specimens via ETT, TA, and BAL were collected and cultured. Basic demographics, clinical signs and symptoms and culture results were collected and descriptive statistics were performed.

Bronchoscopy, performed by a physician, was done in the selected the pathologic lobe(s) or areas of purulence. The scope was wedged in the bronchus; one irrigation/suction was performed and discarded. A second Irrigation/suction was performed obtaining at least 15 mL of aspirate. Endotracheal aspirate was obtained by deep placement of the suction catheter, and subsequent Irrigation and suction into an In-line suction trap. Endotracheal tube culture was obtained at the deep tip of the endotracheal tube with a large cotton swab.

Clinically suspected diagnosis of ventilator associated pneumonia was considered confirmed if the BAL quantitative culture grew a causative organism (not including mixed or normal flora) with $> 10^4$ cfu/mL. Endotracheal aspirate and endotracheal tube cultures were qualitative. Each of the organisms identified from each method were recorded for each patient and statistical analysis was performed.

Statistical Analysis:

Demographic and clinical characteristics of VAP patients and non-VAP patients were evaluated using descriptive statistics including means and standard deviations for continuous variables, frequencies and proportions for categorical variables.
Furthermore, frequencies and proportions of patients were estimated for the category of causative organism thresholds (0, 1, 2, or $\geq$ 3) extrapolated from the TA, BAL, and ETT cultures respectively. The Wilcoxon Rank Sum was conducted to assess the difference in means between the VAP patients and non-VAP patients. The Fisher's exact test was used to compare proportions between the same groups.

To determine the association between selected patient characteristics and VAP diagnosis, adjusted odds ratios, and 95% confidence intervals were calculated using unconditional logistic regression. The final model included patients' age, white blood cell count, temperature, gender, increased sputum, new chest radiograph infiltration, and the number of days on the ventilator. The model was adjusted by all other variables in the model. Unconditional logistic regression was also implemented to calculate adjusted odds ratios, 95% confidence intervals to determine the association between TA, BAL, ETT statuses respectively and VAP diagnosis. Age, gender, and the number of days on the ventilator were added to the final model because they were labeled as confounders.

Finally, we assessed the diagnostic characteristics of TA, BAL and ETT by calculating the specificity, sensitivity, positive predictive value and negative predictive values which were derived from the receiver-operating characteristic curve. The Spearman's correlation coefficient was estimated between TA and BAL, TA and ETT, and BAL and ETT respectively.

Results:

Concurrent cultures were performed on 42 adult patients with suspected VAP. Means were calculated for age (43.9 years, ± 16.1), days on ventilator at time of suspected infection (19.1 ± 17.6) temperature (38.28 °C ± 0.94), total body surface area burn (39%, ± 22%) and white blood cell count (14.6 ± 7.1 x 10^9/L). Of the 42 patients, 73.9% were male and 26.1% female. Clinical parameters included increased sputum (76.2%) and the presence of new infiltrates on chest radiograph (64.3%) (Table 1).

The frequencies and percentages of the number of causative organisms for each test, stratified by the presence of ventilator-associated pneumonia were calculated. The results for both TA and BAL were statistically significant, while those for ETT were not (Table 2). Pseudomonas aeruginosa, MRSA, Staphylococcus areus, Acinetobacter baumannie, and Haemophilus influenzae were the most common organisms identified.

Adjusted odds ratios were calculated for select variables and the presence of ventilator associated pneumonia. The only statistically significant variable was white blood cell count. For every 1 increase in this value, the risk of VAP increased by 1.2 fold (Table 3). Adjusted odds ratios were also calculated for each test and the risk of having VAP. This was adjusted for age, gender, and number of days on ventilator. If an organism was identified on TA there was a 5.3 fold increase in the risk of having VAP compared to having a culture with no organisms identified. If an organism was identified on BAL, there was a 9.6 fold increased risk. The value for ETT was not statistically significant (Table 4).

Correlations were done between TA, BAL and ETT. TA and BAL correlated 87% of the time while TA and ETT correlated 49% of the time. The correlation between ETT and BAL was 40%. These results were statistically significant (Table 5).

Table 1. Demographic and Clinical Characteristics of Patients stratified by Ventilator-Associated Pneumonia Status

Variables	Total Population N=42	No VAP N=15	VAP N=27	P-Value[1]
Mean (SD)				
Age (years)	43.9 (16.1)	46.1 (12.1)	42.8 (18.1)	0.45
WBC count (x 10^9/L)	14.6 (7.1)	12.3 (4.8)	15.8 (7.9)	0.21
TBSA Burn	0.39 (0.22)	0.37 (0.2)	0.42 (0.2)	0.74
Temperature (^{o}C)	38.3 (0.94)	38.3 (0.89)	38.3 (0.99)	0.85
Number of Days on Vent	19.1 (17.6)	18.3 (16.2)	19.5 (18.6)	0.96
Sex (male, %)	31 (73.9)	10 (66.7)	21 (77.8)	0.48
Increased Sputum (yes, %)	32 (76.2)	10 (66.7)	22 (81.5)	0.45
New CXR Infiltration (yes, %)	27 (64.3)	9 (60.0)	18 (66.7)	0.66

[1]P-Values calculated using Wilcoxon Rank-Sum for Continuous Variables and Fischer's Exact for Categorical Variables.
VAP- Ventilator Associated Pneumonia, WBC- White Blood Cell, Vent- Ventilator, CXR- Chest X-Ray

Table 2. Frequencies and Percentages of Causative Organisms Extrapolated from TA, BAL, and ETT stratified by Ventilator-Associated Pneumonia.

# of Organisms	No VAP	VAP	P-Value[1]
Type of Tests	N(%)	N(%)	
TA			0.003
0	8 (53.3)	2 (7.4)	
1	5 (33.3)	10 (37.0)	
2	2 (13.3)	14 (51.9)	
≥3	0 (0.0)	1 (3.7)	
BAL			<0.001
0	8 (53.3)	0 (0)	
1	5 (33.3)	13 (48.2)	
2	2 (13.3)	13 (48.2)	
≥3	0 (0.0)	1 (3.7)	
ETT			0.59
0	7 (46.7)	8 (29.4)	
1	7 (46.7)	13 (48.2)	
2	1 (6.7)	5 (18.5)	
≥3	0 (0)	1 (3.7)	

[1]P-Values calculated using Fischer's Exact Test.
VAP- Ventilator Associated Pneumonia, TA- Endotracheal Aspirate, BAL- Bronchoalveolar Lavage, ETT- Endotracheal Tube

Table 3. Adjusted Odds Ratios (95% Confidence Intervals) Assessing the Association between Selective Covariates and Ventilator-Associated Pneumonia.

Variables	Adjusted OR[1]	(95% CI)	P-Value[2]
Age	0.98	(0.94, 1.03)	0.51
WBC count (x 10^9/L)	1.2	(1.03, 1.4)	0.02
TSBA Burn	14.2	(0.2, 134.9)	0.22
Temperature	1.2	(0.5, 3.2)	0.70
Sex	0.3	(0.04, 1.9)	0.18
Increased Sputum	11.7	(0.87, 156.7)	0.06
New CXR Infiltration	0.8	(0.13, 4.8)	0.82
Numb of Days on Vent	0.97	(0.92, 1.03)	0.44

[1] Odds Ratios adjusted for all other covariates within the model.
[2] P-values calculated using Logistic Regression.
WBC- White Blood Cell, TBSA- Total Body Surface Area, CXR- Chest X-Ray, Vent- Ventilator

Table 4. Adjusted Odds Ratios (95% Confidence Intervals) Assessing the Association between TA, BAL, ETT and Ventilator-Associated Pneumonia Respectively.

Type of Tests	OR (95%CI)	P-Value[1]
TA	5.3 (1.8, 15.8)	0.003
BAL	9.6 (2.3, 41.1)	0.002
ETT	2.1 (0.8, 5.4)	0.13

[1] Logistic Regression Models adjusted for Age, Gender and Number of Days on Vent.
TA- Endotracheal Aspirate, BAL- Bronchoalveolar Lavage, ETT- Endotracheal Tube

Table 5. Correlations between the TA, BAL, ETT cultures.

Types of Cultures	Rho	P-Value[1]
TA vs Bal	0.871	<0.001
TA vs ETT	0.491	0.001
BAL vs ETT	0.395	0.009

[1] P-Values calculated using the Spearman's Correlation Test

TA- Endotracheal Aspirate, BAL- Bronchoalveolar Lavage, ETT- Endotracheal Tube

Sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) were also calculated for each of the three methods. If there was one causative organism, TA had a sensitivity of 92.6%, whereas BAL, since it was this study's gold standard, had a sensitivity of 100%. ETT had a sensitivity of 70.4%. For all three tests the sensitivities sharply decreased as the number of causative organisms needed to diagnose increased. A positive BAL had a PPV of 100% while a positive TA had a PPV of 96.3% (Table 6).

Table 6. Specificity, Sensitivity, Positive Predictive Value, Negative Predictive Value of VAP Diagnosis stratified by TA, BAL and ETT.

Type of Tests	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
TA			96.3	53.3
≥0	0.0	100.0		
≥1	53.3	92.6		
≥2	86.7	55.6		
≥3	100.0	3.7		
>3	100.0	0.0		
BAL			100.0	53.3
≥0	0.0	100.0		
≥1	53.3	100.0		
≥2	86.7	51.8		
≥3	100.0	3.7		
>3	100.0	0.0		
ETT			70.4	46.7
≥0	0.0	100.0		
≥1	46.7	70.4		
≥2	93.3	22.2		
≥3	100.0	3.7		
>3	100.0	0.0		

Derived from the Receiving Operating Characteristic Curve
VAP- Ventilator Associated Pneumonia, TA- Endotracheal Aspirate, BAL- Bronchoalveolar Lavage, ETT- Endotracheal Tube

Discussion:

Ventilator-associated pneumonia (VAP) is associated with increased mortality, ventilator days, intensive care unit days and length of stay, especially in the thermal burn patient. In addition to causing poorer patient outcomes, VAP increases the cost of care, making the prevention of VAP a high priority within healthcare. This study was undertaken in order to determine if the cultures of endotracheal aspirates or endotracheal tubes are as reliable as lower airway sampling with bronchoalveoloar lavage in ventilated burn patients.

The demographic and clinical characteristics data illustrates that this is a homogenous population with no significant differences that could be used as useful predictors for the development of VAP (Table 1). This strengthens the rationale for the study and the need for definitive and objective microbiological findings. Additionally, the presence of leukocytosis is the only significant variable, with a slightly increased adjusted odds ratio of 1.2 (Table 3). This lack of significant clinical predictors is consistent with prior studies and supports the claim that a diagnosis of VAP can be difficult to make especially in the burned patient.[13,35]

The validity of the collection methods is supported by the frequencies and percentages of causative organisms extrapolated from TA, BAL, and ETT (Table 2). While TA and BAL are both valid collection methods to aid in the diagnosis of VAP, culturing of the endotracheal tube is not. Similarly, the adjusted odds ratio assessing the association between a positive TA, BAL, or ETT and the diagnosis of VAP shows that a positive TA or BAL culture is associated with a much greater likelihood that the patient has VAP whereas the value for ETT is not significant (Table 4). Therefore, ETT culture results were still used for the purposes of correlation between the three tests, but are not likely a reliable method for the diagnosis of ventilator-associated pneumonia in the setting of thermal injury.

The primary question, which this study seeks to answer, is to what degree do TA and ETT cultures correlate with BAL specimens in the setting of suspected VAP in burn ICU patients? In other words, if a BAL culture is positive for X number of causative organisms what percentage of the time will the TA and ETT cultures be positive for the exact same X number of organisms? As shown in Table 5, the TA and BAL cultures correlated over 87% of the time.

Moreover, the sensitivity and specificity of both tests are very similar. The literature regarding the diagnostic effectiveness of using qualitative TA versus quantitative BAL cultures in traditional ICU patients remains controversial.[4,36] This study, however shows that they are at least equivocal in this population.

Conclusion and Future Directions

What does this mean for burn patients with suspected VAP? It means that while a quantitative culture is the current recommendation, a qualitative culture of the endotracheal aspirate may suffice. This could be performed more promptly, frequently, easily, and cost effectively and therefore should not be discounted as a reliable method of sampling. It must be stated, however, that BAL has at least one advantage over TA in that while obtaining the cultures, therapeutic washings may also be performed.[37]

The question remains however, how does microbiologic data ultimately affect the diagnosis and patient outcomes? For instance, three patients in this study had no microbiologic evidence for VAP on BAL yet they were still treated with empiric antibiotics because of very high clinical suspicion.

A new surveillance definition from the CDC may help to standardize the prevention, diagnosis and treatment of VAP. Now called ventilator-associated events (VAE), a VAE is classified as hypoxemia shown by greater than 20% increase in the daily minimal fraction of inspired oxygen or an increase of at least 3 cm H_2O in the daily minimal positive end-expiratory pressure (PEEP) to maintain oxygenation.[38] VAEs are further classified into ventilator associated condition (VAC), infection-related ventilator-associated condition (IVAC), possible or probable VAP. It is unclear how this change will affect the prevalence of VAP. At least one early study shows that this surveillance definition may not correlate with actual ventilator associated infections. [39]

The diagnosis of VAP in this study was reserved for patients with a BAL > 10^4 cfu/mL. This criterion is not perfect and may have lead to an abnormally high sensitivity and specificity of the tests, but this would not affect the value of the calculated correlations. Further analysis or studies could explore stratifying the relative results of each of the culture methods by organism. This could help elucidate if the correlation is dependent upon the organism in question, and allow the clinician to understand the utility of each test given the local flora. Before any definitive clinical recommendation can be made, multicenter prospective trials examining the relative accuracy and clinical impact of each of the tests should be performed.

One future study method could include the use of screening endotracheal aspirate cultures on all ventilated burn patients and subsequent performance of BAL on those with clinical symptoms or positive cultures.[40,41]

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