

# Natural History, Outcomes and Antibiotic Treatment for Ventilator-Associated Tracheobronchitis in Critical Ill Patients

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Received 16 January 2016; accepted 26 February 2016; published 29 February 2016

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## Abstract

We assessed incidence and outcomes of patients with ventilator-associated respiratory infections (VARI) due to tracheobronchitis (VAT) and pneumonia (VAP), including length of intensive care unit (ICU) stay and ventilator days. We also examined pathogens, rate of progression from VAT to VAP, and impact of antibiotic therapy for VAT. Data analysis included 234 patients, 100 patients (43%) had at least moderate (+++) bacterial growth in their semi-quantitative endotracheal aspirate (SQ-ETA) cultures. VAT and VAP were each diagnosed in 34 (15%) patients. *Staphylococcus aureus* was the most common pathogen isolated and had the highest rate of progression from VAT to VAP. Seven (21%) of the 34 patients were diagnosed with VAT that later progressed to VAP in averaged 3 days. Patients diagnosed with VAT had significantly more ventilator days (9 vs 6,  $p < 0.001$ ), ICU days (17 vs 11,  $p < 0.001$ ) and hospital days (22 vs 17,  $p < 0.001$ ). No significant difference was observed in the clinical outcomes of the 25 VAT patients with timely, appropriate antibiotics compared to the 9 VAT patients who did not receive timely appropriate antibiotics. VAT was a risk factor for increased ventilator days, longer length of ICU and hospital stay. The time window from VAT to VAP allowed physicians to identify the pathogens and sensitivity profile needed to treat VAT with appropriate antibiotics. Data from well-designed studies were needed to assess the impact of early, appropriate antibiotic therapy for VAT, the choice of antibiotics, as well

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**How to cite this paper:** Lei, Y.X., Hudcova, J., Rashid, J., Sarwar, A., Gillespie, W., Finn, C., Goggin, M., Omran, M.B., Boroda, E. and Craven, D.E. (2016) Natural History, Outcomes and Antibiotic Treatment for Ventilator-Associated Tracheobronchitis in Critical Ill Patients. *Modern Research in Inflammation*, 5, 1-11. <http://dx.doi.org/10.4236/mri.2016.51001>

as the duration and route of administration.

## Keywords

**Ventilator-Associated Tracheobronchitis (VAT) and Pneumonia (VAP), Bacterial Pathogens, Semi-Quantitative Endotracheal Aspirate (SQ-ETA) Cultures, Antibiotic Therapy**

## 1. Introduction

Intubated, mechanically ventilated patients are at increased risk for tracheal colonization with bacterial pathogens that over time may progress to ventilator-associated tracheobronchitis (VAT) and/or ventilator-associated pneumonia (VAP) [1]-[12]. Previous studies suggest that 20% to 30% of patients with VAT may progress to VAP [6] [7] [10]. Bacterial pathogens may enter the lung at the time of intubation, later by leakage around the endotracheal tube cuff, or bacterial biofilm formation and emboli to the lung [2] [5] [6] [9]. Progression from bacterial colonization to VAT or VAP depends on the bacterial virulence, efficacy of pulmonary defenses, such as ciliated epithelium, humoral antibodies, or phagocytosis by polymorphonuclear leukocytes and/or macrophages. [5] [13]

Microbiology criteria used for diagnosing heavy colonization, VAT and VAP include a semi-quantitative tracheal aspirate (SQ-ETA) having  $\geq$  moderate (+++) growth of a pathogen which is equivalent to a quantitative tracheal aspirate (Q-ETA) having  $\geq 10^5$  colony forming units (cfu)/ml [6] [7] [10] [14]. Bronchoscopic or non-bronchoscopic protected specimen brush (PSB) or bronchoalveolar lavage (BAL) samples can also be used to differentiate VAT from VAP [1] [2] [5] [13] [15] [16].

Currently there is no single, accepted “gold standard” for microbiologic or clinical diagnosis of VAT or VAP [1] [4] [9] [15]-[17]. VAT and VAP share similar clinical and microbiologic criteria, but VAP also requires a new and persistent infiltrate on chest X-ray or computer tomographic scan. However, chest X-rays used to diagnose VAP may lack sensitivity or specificity of lung infiltrates that can represent atelectasis, pulmonary emboli, congestive heart failure or adult respiratory distress syndrome or VAP. [18]

Limited data are available on the natural history, incidence, etiology, outcomes and antibiotics treatment of patients with ventilator-associated respiratory infections [5] [6] [14] [19] [20]. This observational study focuses on the natural history of the ventilated patients in ICUs, incidence of heavy tracheal colonization, respiratory infections, pathogens isolated, outcomes and antibiotics use in patients diagnosed with VAT.

## 2. Materials and Methods

### 2.1. Study Population and Data Collection

Details of the study population and inclusion/exclusion criteria were described in previous publication [6]. In this study, 234 ventilated patients in ICUs with SQ-ETA results were included in the data analysis. The day one of study period was defined as enrollment day after ventilation for  $\geq 48$  hours. End of study day was the day when patients were extubated, changed to tracheostomy, died or made to comfort measure only. Our research protocol was approved by the Lahey Clinic Institutional Review Board and informed consent process was waived for assessing routine ETA cultures.

### 2.2. Microbiologic Methods

Study samples from routine endotracheal suctioning were collected daily, coded and sent to the microbiology lab for Gram stain and bacterial culture for research purposes only. Gram stains were examined by microscope for the presence of moderate to many polymorphonuclear leukocytes per low power field and several bacteria per high power field using a scale from 0 to many (+++++) for both.

SQ-ETA cultures having  $\geq$  moderate (+++) growth of a pathogen was considered heavy colonization [4] [6]. Bacterial pathogens were identified by genus and species, using (Microscan®, Siemens, Sacramento, CA). Antibiotic sensitivities were performed by the Kirby-Bauer method.

### 2.3. Diagnosis of VAT and VAP

The diagnosis of VAT and VAP required heavy tracheal colonization, plus at least 2 of 3 clinical signs of infection: temperature  $\geq 38^{\circ}\text{C}$  or  $\leq 36^{\circ}\text{C}$ , leukocytosis  $\geq 12,000/\text{mm}^3$  or purulent sputum. Purulent sputum was defined as a Gram-stain with moderate (+++) or many (++++) bacteria/high power microscopic field and moderate (+++) or many (++++) polymorphonuclear leukocytes (PMNL). VAP diagnosis the above clinical and microbiology criteria plus radiologic evidence of a new infiltrate on chest X-ray. Chest X-rays read and reported by a radiologist, were evaluated independently for the presence of new or increasing infiltrate consistent with pneumonia by one of the authors (AS) and compared with the official radiology report. In case of disagreement, three investigators (AS, JH, DC) reviewed films independently and decided on the final reading.

### 2.4. Antibiotics Treatment of VAT

The antibiotics use of the study patients was ordered at the discretion of treating physicians. The reasons for antibiotic administration differed and were as follow: prophylaxis in surgical patients and treatment of various infections including respiratory infections in all patients. The pathogen identification of the daily ETA study specimens was not reported to the treating physicians. The data on antibiotic use were reviewed retrospectively. Analysis of antibiotic administration was performed with focus on the patients with diagnosis of VAT and VAP and within the study period. Antibiotic treatment was considered as appropriate if patient was treated with correct class of antibiotics based on pathogen isolated and susceptibility tests, and whether treatment was initiated within 24 hours of VAT diagnosis.

### 2.5. Statistical Analysis

All comparisons of characteristics between different patient subgroups were unpaired and all tests of significance were two-tailed. Continuous variables were compared using the Student's t-test for normally distributed variables and the Wilcoxon rank-sum test for non-normally distributed variables. The Chi-square or Fisher exact tests were used to compare categorical variables. For all analyses,  $p \leq 0.05$  (two-tailed) was considered statistically significant. The statistical analysis for this paper was generated using Statistical Analysis Software (SAS), Version 9.2 for Windows.

## 3. Results

### 3.1. Incidence and Outcomes of VAT and VAP

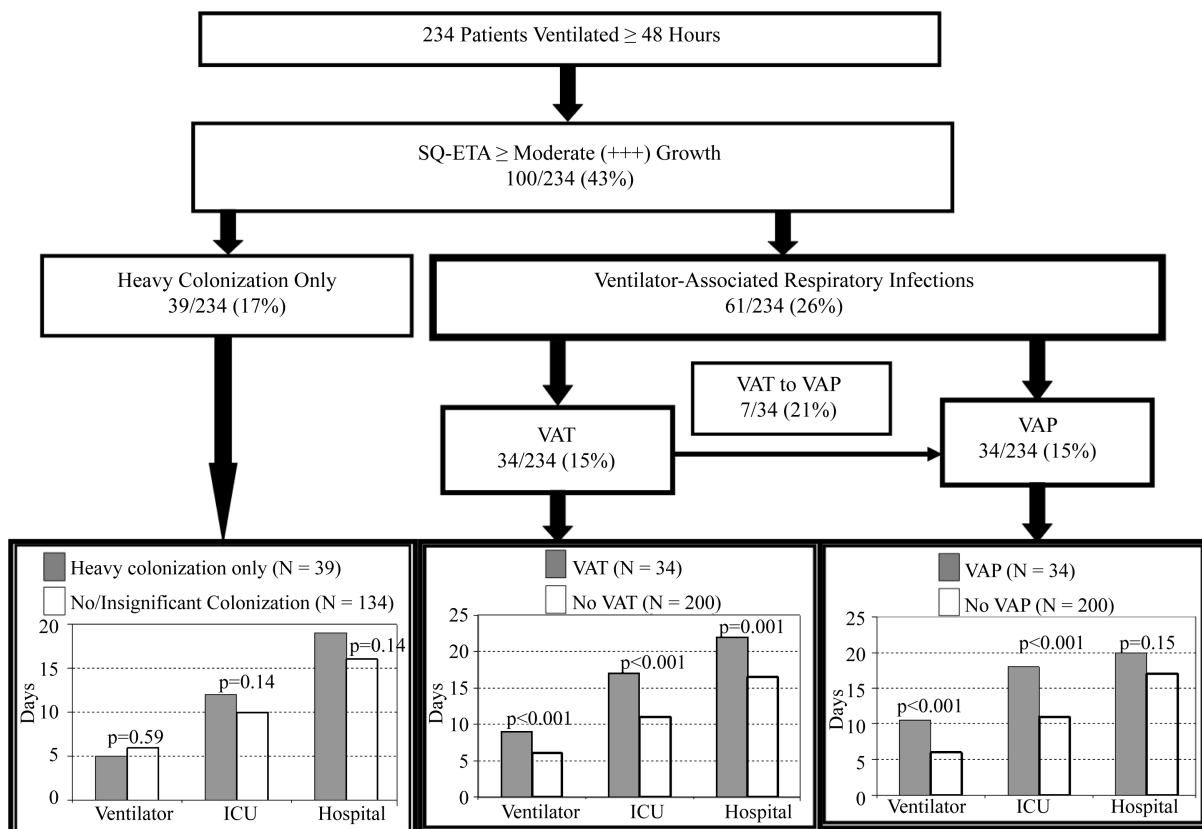
We studied 234 consecutive medical and surgical patients ventilated  $\geq 48$  hours (**Figure 1**), of which 100 patients (43%) had a SQ-ETA with  $\geq$  moderate (+++) growth of a pathogen on bacterial culture. There were 39 patients (17%) who only had heavy tracheal colonization, 34 patients (15%) developed VAT and 34 patients (15%) developed VAP. Seven of the 34 VAT patients later progressed to VAP in 1 to 7 days or averaged 3 days. **Figure 2** demonstrates cumulative incidence rates for patients developing heavy colonization only, VAT and VAP by study day. The rates of heavy colonization, VAT and VAP increased rapidly from study day 1 to study day 10, and then leveled off.

Baseline variables for the 34 patients diagnosed with VAT, when compared to the 200 patients without VAT (**Table 1**), demonstrated significant higher CPIS scores ( $p < 0.0001$ ) at study entry and average CPIS scores and fewer patients treated with antibiotics at study entry ( $p < 0.01$ ).

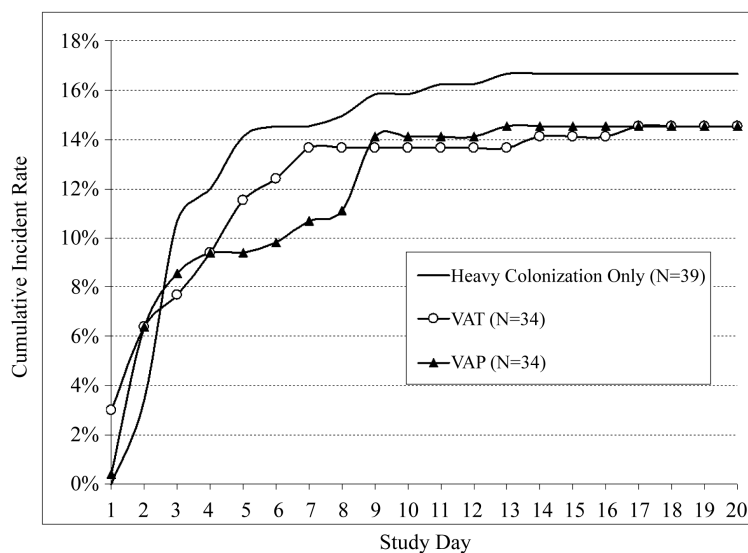
As shown in **Figure 1**, the outcomes for the 39 patients who had heavy colonization only were not significantly different from the 134 patients with insignificant endotracheal colonization. By comparison, outcomes of the 34 patients diagnosed with VAT when compared to the 200 patient with no VAT demonstrated significantly increased ventilator days (9 vs 6,  $p < 0.001$ ), ICU days (17 vs 11,  $p < 0.001$ ) and hospital days (22 vs 17,  $p < 0.001$ ) (**Figure 1**). Patients diagnosed with VAP versus no VAP also had significantly more ventilator days (10.5 vs 6,  $p < 0.001$ ) and ICU days (18 vs 11,  $p < 0.001$ ). No significant difference was noted in mortality rates for patients diagnosed with VAT versus no VAT (18% vs 29%,  $p = 0.24$ ) or for patients with VAP versus no VAP (27% vs 28%,  $p = 0.90$ ).

### 3.2. Bacterial Pathogens Identified

The spectrum of bacterial pathogens isolated from the 34 patients with VAT, which included 27 patients that did



**Figure 1.** Of the 234 study patients ventilated > 48 hours, 39 (43%) had heavy colonization only, 34 patients (15%) developed ventilator-associated tracheobronchitis (VAT) and 34 (15%) were diagnosed with ventilator-associated pneumonia (VAP). Note that 7 patients diagnosed with VAT later progressed to VAP. Patients diagnosed with VAT or VAP experienced significantly more ventilator days ( $p < 0.001$ ) and longer length of stay in the intensive care unit (ICU) ( $p < 0.001$ ), when compared to patients without VAT or VAP.



**Figure 2.** Cumulative incident rates of patients developing heavy colonization, ventilator-associated tracheobronchitis (VAT) and pneumonia (VAP) over time using Kaplan-Meier curves. Note that incident rates increased rapidly during the first ten study days and then leveled off.

**Table 1.** Comparison of baseline variables for patients developing ventilator-associated tracheobronchitis (VAT) versus no VAT.

Baseline Variables	VAT N = 34	No VAT N = 200	p value
Age (years)	62.1 ± 13.6	65.7 ± 13.6	0.16
Male	73.5%	60.5%	0.15
Body Mass Index	33.0 ± 13.0	29.9 ± 9.4	0.12
Charlson Comorbidity	1.7 ± 1.9	2.3 ± 2.1	0.10
APACHE II <sup>a</sup>	18.1 ± 6.9	17.6 ± 5.7	0.74
CPIS <sup>b</sup> at Study Entry	5 (2 - 8)	4 (1 - 8)	0.0001
Average CPIS <sup>c</sup>	5 (4 - 8)	4 (1 - 8)	<0.0001
CPIS <sup>d</sup> at Diagnosis Day	6 (4 - 10)	-	-
Antibiotics at Study Entry	73.5%	89.5%	0.01
MICU <sup>e</sup> (N = 153)	13.1% (20)	86.9% (133)	0.38
SICU <sup>f</sup> (N = 81)	17.3% (14)	82.7% (67)	

<sup>a</sup>Acute Physiology and Chronic Health Evaluation II; <sup>b</sup>Clinical Pulmonary Infection Score at study entry day 1; <sup>c</sup>Clinical Pulmonary Infection Score averaged during whole study days; <sup>d</sup>Clinical Pulmonary Infection Score at VAT diagnosis day; <sup>e</sup>MICU—Medical intensive care unit; <sup>f</sup>SICU—Surgical intensive care unit.

not progress to VAP and the 7 VAT patients that progressed to VAP are shown in **Table 2**. *Staphylococcus aureus* was isolated in 19/34 patients (56%) of the patients diagnosed with VAT, of which 13/19 (67%) were methicillin-resistant *S. aureus* (MRSA) and 6/19 (33%) were methicillin-sensitive *S. aureus* (MSSA) that likely reflects increased virulence of *S. aureus* isolates compared to the other pathogens isolated [21] [22]. Five of the 7 (71%) patients that progressed from VAT to VAP were infected with *S. aureus* (4 MSSA and 1 MRSA). *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were most common Gram-negative pathogens isolated. Seventy-nine percent of VAT patients had one pathogen infection, 12% had two pathogens and 9% had three pathogens.

As shown in **Figure 3**, the patient was diagnosed with ventilator associated tracheobronchitis (VAT) on day 2, caused by many (++++) growth of *Serratia marcescens* (solid circles). Timely and appropriate cefepime was started for VAT caused by *Serratia marcescens* on days 1 to 8. On day 4, however, there was moderate (+++) growth of *Stenotrophomonas maltophilia* (open squares). No antibiotics were received for *S. maltophilia* until day 6, when appropriate trimethoprim/sulfamethoxazole (TMP-SMX) was prescribed up to day 12. On day 8, there was few (+++) growth of *Pseudomonas aeruginosa* (open triangles). Inappropriate therapy with cefepime resistance based on susceptibility testing) was given for *P. aeruginosa* until day 11. At the end of study period on day 12, appropriate therapy with amikacin was received for *P. aeruginosa*. The patient developed ventilator-associated pneumonia (VAP) on day 9 with moderate (+++) growth of *S. maltophilia* and *P. aeruginosa*.

Of the 34 VAT patients studied, 25 who received appropriate intravenous antibiotics within 24 hours were compared to 9 patients who did not receive timely appropriate antibiotics (**Table 3**). The two groups had similar characteristics such as age, sex, body mass index, co-morbidity, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Clinical Pulmonary Infection Score (CPIS) at VAT diagnosis. As shown in **Table 4**, no significant differences were observed in VAP rate (20% vs 22%,  $p = 1.0$ ), ventilator days (11 vs 10 days,  $p = 0.9$ ), ICU days (20 vs 15,  $p = 0.1$ ), hospital days (25 vs 19,  $p = 0.3$ ), or hospital mortality (24% vs 22%,  $p = 1$ ).

#### 4. Discussion

The incident rate of VAT was 15%, of which 21% later progressed to VAP. Patients developing VAT had significantly increased ventilator, ICU and hospital days which have been observed by others [23]. Seventy-four percent of VAT patients received timely and appropriate antibiotic treatment for VAT. Antibiotic treatment can

**Table 2.** Pathogens isolated from the 34 patients with ventilator-associated tracheobronchitis (VAT). The VAT patients were grouped into 27 patients that did not progress to VAP versus the 7 patients that progressed to VAP.

Pathogens	All VAT patients (N = 34)	VAT did not progressed to VAP (N = 27)	VAT progressed to VAP (N = 7)
<b>Gram-Positive Cocci</b>			
Methicillin-resistant <i>Staphylococcus aureus</i>	13 (38%)	12 (44%)	1 (14%)
Methicillin-sensitive <i>Staphylococcus aureus</i>	6 (18%)	2 (7%)	4 (57%)
<i>Enterococcus species</i>	2 (6%)	2 (7%)	0
<b>Gram-Negative Pathogens</b>			
<i>Pseudomonas aeruginosa</i>	3 (9%)	2 (7%)	1 (14%)
<i>Escherichia coli</i>	2 (6%)	1 (4%)	1 (14%)
<i>Klebsiella pneumoniae</i>	5 (15%)	4 (15%)	1 (14%)
<i>Klebsiella oxytoca</i>	1 (3%)	0	1 (14%)
<i>Enterobacter species</i>	1 (3%)	1 (4%)	0
<i>Serratia marcescens</i>	2 (6%)	2 (7%)	0
<i>Proteus mirabilis</i>	1 (3%)	1 (4%)	0
<i>Stenotrophomonas maltophilia</i>	2 (6%)	1 (4%)	1 (14%)
<i>Acinetobacter baumannii</i>	1 (3%)	1 (4%)	0
<i>Chryseobacterium species</i>	1 (3%)	1 (4%)	0
<i>Haemophilus influenza</i>	2 (6%)	1 (4%)	1 (14%)
<b>One Pathogen</b>	27 (79%)	23 (86%)	4 (57%)
<b>Two Pathogens</b>	4 (12%)	2 (7%)	2 (29%)
<b>Three Pathogens</b>	3 (9%)	2 (7%)	1 (14%)

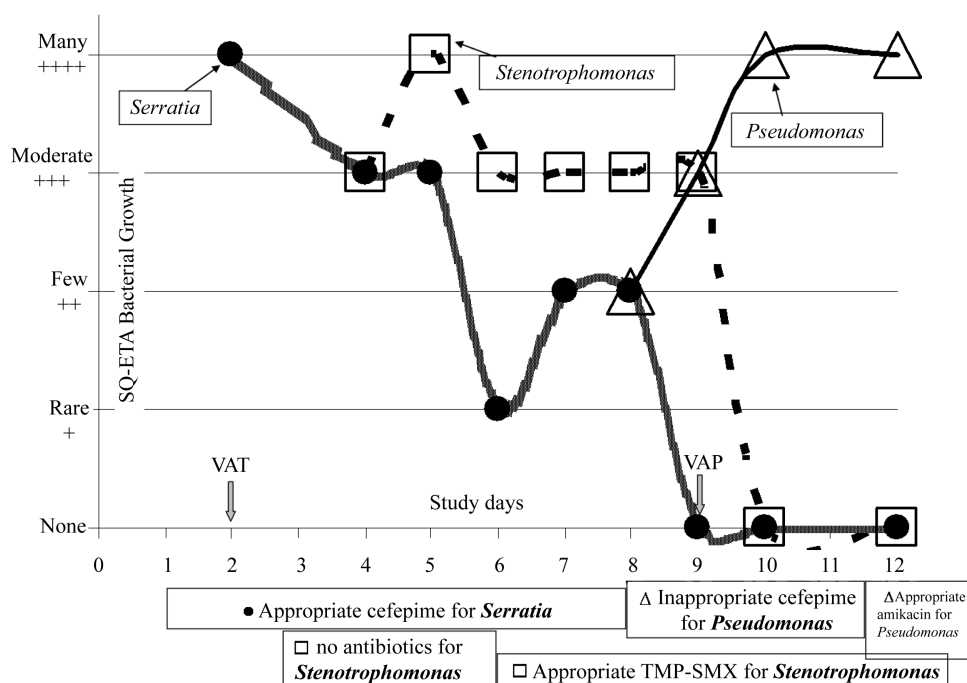
**Table 3.** Baseline variables for the 34 patients with ventilator-associated tracheobronchitis (VAT). Comparison was made between the patients who received appropriate antibiotics within 24 hours of diagnosis and the patients who did not receive appropriate antibiotics.

Baseline Variables	Appropriate antibiotics (N = 25)	Not appropriate antibiotics (N = 9)	P
Age (years)	61.7 ± 12.0	65.3 ± 17.9	0.50
Male, n (%)	18 (72.0%)	7 (77.8%)	0.74
Body Mass Index	34.5 ± 14.1	28.6 ± 7.6	0.31
Charlson Comorbidity	1.8 ± 2.1	1.6 ± 1.1	0.78
APACHE II <sup>a</sup>	18.4 ± 7.2	17.3 ± 6.4	0.70
CPIS <sup>b</sup> at VAT Diagnosis	6 (4 - 10)	5 (4 - 8)	0.20
MICU <sup>c</sup> (n = 12)	9/12 (75.0%)	3/12 (25.0%)	0.89
SICU <sup>d</sup> (n = 22)	16/22 (72.7%)	6/22 (27.3%)	

<sup>a</sup>Acute Physiology and Chronic Health Evaluation II; <sup>b</sup>Clinical Pulmonary Infection Score; <sup>c</sup>MICU—Medical intensive care unit; <sup>d</sup>SICU—Surgical intensive care unit.

be complicated in patients with multiple, new or MDR pathogens, as shown in **Figure 3**. The predominant pathogens isolated in our study were *S. aureus*, *P. aeruginosa* and *K. pneumoniae*, all of which have increased virulence for lung tissue and higher mortality [21] [24]-[28].

Our analysis of 34 VAT patients with or without timely appropriate antibiotics treatment did not show statis-



**Figure 3.** The patient was diagnosed with ventilator associated tracheobronchitis (VAT) on day 2, caused by many (++++) growth of *Serratia marcescens* (solid circles). Timely and appropriate cefepime was received for *Serratia* on day 1 to 8. On day 4, there was moderate (+++) growth of *Stenotrophomonas maltophilia* (open squares). No antibiotics were received for *Stenotrophomonas* until day 6, when appropriate Trimethoprim/sulfamethoxazole (TMP-SMX) was used till day 12. On day 8, there was few (++) growth of *Pseudomonas aeruginosa* (open triangles). Inappropriate cefepime was received for until day 11. At the end of study period on day 12, appropriate amikacin was received for *Pseudomonas*. The patient developed ventilator-associated pneumonia (VAP) on day 9 with moderate (+++) growth of *Stenotrophomonas* and *Pseudomonas*.

**Table 4.** Outcomes of the patients treated with appropriate antibiotics within 24 hours of ventilator-associated thacheobronchitis. VAT diagnosis versus the patients who did not received timely appropriate antibiotics.

Outcomes	Appropriate antibiotics N = 25	Not appropriate antibiotics N = 9	p Value
VAP <sup>a</sup> Rate	5/25 (20.0%)	2/9 (22.2%)	1.00
Ventilator Days (min-max)	11 (4 - 22)	10 (6 - 18)	0.91
ICU <sup>b</sup> Days (min-max)	20 (6 - 56)	15 (10 - 31)	0.14
Hospital Days (min-max)	25 (7 - 107)	19 (11 - 51)	0.30
Mortality	6/25 (24.0%)	2/9 (22.2%)	1.00

<sup>a</sup>Ventilator-associated pneumonia; <sup>b</sup>Intensive care unit.

tically significant differences in VAP rate, ventilator days, ICU days and hospital stay (Table 4). Of note is that our study was a natural history study used daily assessment of tracheobronchial colonization, which was not reported back to treating physicians. Thus, the use of antibiotics was at the discretion of treating physicians. As shown in Figure 3, it might have been helpful to order timely and appropriate use of antibiotics, if the daily SQ-ETA results were available for treating physicians.

The finding that appropriate antibiotics treatment for VAT did not improve outcomes was disappointing. It is important to emphasize that this was a natural history study and clinicians treated patients at their discretion based on microbiological data they ordered, as they were blinded to surveillance cultures. Antibiotic administra-

tion that included prophylaxis as well as therapeutic coverage for other infections occurred throughout the course of the ICU stay. Many patients were treated with numerous antibiotics for other reasons from one day to 2 weeks. Although we evaluated appropriateness and timing of antibiotics referenced to the diagnosis of VAT, it was often impossible to map antibiotic treatment throughout the ICU stay, due to erratic patterns.

Several studies have supported treatment of VAT to prevent VAP and improve patient outcomes, but this is not a current “standard of care” [3] [5] [10] [13] [14] [29] [30]. A controlled and unblinded, multicenter clinical trial assessed the impact of antibiotic therapy for VAT for 22 study patients randomized to “early” antibiotic therapy versus 36 patients given “delayed” therapy” [20]. Early antibiotic therapy for VAT significantly decreased progression to VAP (13% vs 47%,  $p < 0.05$ ), increased “ventilator free” days (22 vs 36,  $p < 0.001$ ) and decreased patient mortality (18% vs 47%,  $p < 0.05$ ). [20] A more recent prospective observational study by Nseir et al demonstrated that appropriate antibiotic treatment was independently associated with reduced risk of transition from VAT to VAP [31]. There were 17 of 122 VAT patients (14%) that progressed to VAP, of which 58 (48%) received appropriate antibiotic treatment, which was the only factor independently associated with reduced transition from VAT to VAP ( $p = 0.009$ ). Our data showed that 21% of the VAT patients later developed VAP, which was higher than the 14% reported by Nseir and coworkers [31]. There is increasing interest in using intravenous +/- aerosolized antibiotics delivered by improved nebulizers, placed in the ventilators circuit, to treat more virulent or drug-resistant pathogen(s), such as *S. aureus*, *P. aeruginosa*, *K. pneumoniae* or *A. baumannii*. [21] [24] [26]-[28] [32]. Aerosolized antibiotic therapy can deliver higher doses of antibiotic(s) to lung parenchyma that is not absorbed systemically, and therefore reduces the risk of *Clostridium difficile* infection.

Our data noted time of progression from VAT to VAP was 1 to 7 days or an average of 3 days. This window allows treating physicians the opportunity to prescribe earlier targeted antibiotics to treat VAT, based on the microbiology results of surveillance cultures (e.g. SQ-ETA) and to follow the host response to treatment. Over the past two years, there has been increased interest in rapid diagnostic methods to identify bacterial pathogens and antibiotic sensitivities in sputum and blood samples, using various techniques, such as MALDI-TOF [33] [34]. These new rapid diagnostic methods may change the current management landscape and facilitate the earlier, appropriate antibiotic treatment for VAT and VAP. We currently have a universal model for treating upper and lower urinary tract infections in patients with pyuria and bacterial culture with  $\geq 10^5$  cfu/ml, which bacteria can be easily drained by urinating or bladder catheter [5] [13]. This treatment model could be extrapolated to the optimal management of VAT.

Our natural history study had several limitations. Small sample size was included in the analysis of antibiotics treatment for VAT. High proportion of patients was on antibiotics at study entry and received inconsistent treatment with antibiotics throughout the ICU stay. Controlled trials with pre-determined antibiotic coverage, strict duration of treatment, testing shorter vs. longer courses of therapy, and comparing standard intravenous +/- aerosolized therapy are needed. We recommend that future studies should focus on earlier diagnosis of VAT, use of randomized, double blind treatment models with assessment of the risks and benefits of intravenous versus aerosolized antibiotics delivered by improved delivery systems [32].

## 5. Conclusion

In our intensive care units, 15% of ventilated patients developed VAT. About one fifth of the VAT cases progressed to VAP. VAT was a risk factor for increased ventilator days, longer length of ICU and hospital stay. *Staphylococcus aureus* was the most common pathogen isolated and had the highest rate of progression from VAT to VAP. Our study showed that about three quarters of patients received timely appropriate antibiotics treatment for VAT. The data collected from the natural course of the antibiotics treatment did not show significant better clinical outcomes for patients who received appropriate antibiotics for VAT. The effectiveness of antibiotics treatment for VAT needed to be carefully assessed with well-designed, larger randomized clinical studies. The time window from VAT to VAP was an average of 3 days, which allowed physicians an opportunity to identify the pathogens, and to treat VAT with targeted appropriate antibiotics in order to prevent VAP, improve patient outcomes and reduce healthcare costs.

## Acknowledgements

The authors thank Joyce Pelletier, CRT, CRA, Sarah Zimmerman, MT and special thanks to the respiratory care team, microbiology team, the medical and surgical ICU nurses for their support and assistance with the study.



Abstracts of these data were presented at the 49<sup>th</sup> Infectious Disease Society of America (IDSA), Annual Meeting, Boston, October MA 2011; the American Society of Chest Physicians, Honolulu, Hawaii, October 2011; the Infectious Diseases of America (IDSA) Week, San Francisco, CA, October 5-8, 2013, and IDSA Week Philadelphia, PA in 2014.

## Financial Support

This work was supported by grants from the Wise Foundation, Lahey Clinic (LCID2010-004) and Pfizer Pharmaceuticals (WS480336) to D.E.C.

## Conflict of Interests

No conflict.

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