Abstract

Introduction: Incubated, mechanically ventilated patients are at increased risk for tracheobronchial colonization with a wide spectrum of bacterial pathogens that may progress to Ventilator-Associated Respiratory Infections (VARI) manifest as Ventilator-Associated Trachea Bronchitis (VAT) or Ventilator-Associated Pneumonia (VAP). Previous studies report 10% to 30% of patients with VAT can progress to VAP, resulting in increased patient morbidity and mortality, as well as significant acute and chronic healthcare costs that range from $20,000 to $40,000 per patient. In “Thinking outside the box” we emphasized use of serial lung surveillance cultures to identify and pre-emptively treat specific lung pathogens with appropriate antibiotics to reduce VAT, VAP, ventilator days, and length of Intensive Care Unit (ICU) stay, healthcare costs, patient morbidity and mortality.

Methods: We previously studied significant bacterial lung colonization in 100 consecutive ICU patients ventilated >48 hours with serial Semi-Quantitative Endo Tracheal Aspirates (SQ-ETA) with a positive endo tracheal Gram-stain with bacteria, polymorphonuclear leukocytes and lung culture having >+++ (moderate) growth of a pathogen. We identified 34 patients with VAT and 34 patients with VAP. However, 7 (21%) of the 34 VAT patients later progressed to VAP. Both VAT and VAP patients had significantly increased ventilator days (p<.001) and longer ICU stays (p<.001). Of note are the recent data by Stulik et al. emphasizing the low efficacy of vancomycin and oxacillin therapy for VAT and VAP due to Staphylococcus aureus.

Conclusions: Serial surveillance cultures can help identify specific bacterial pathogens, use earlier appropriate antibiotic therapy for ventilated patients with significant lung bacterial colonization, VAT, or VAP that can improve patient outcomes and reduce healthcare costs. Both Quantitative Endo Tracheal Lung Aspirates (Q-ETA) or Semi-Quantitative (SQ-ETA) in can be cultured and treated. Aerosolized and/or intravenous antibiotic therapy can be used to treat Multi-Drug Resistant (MDR) pathogens. Data support early, appropriate antibiotic therapy to improve patient outcomes, reduce lung bacterial burden and healthcare costs.
Introduction

Recent data suggest that Ventilator-Associated Respiratory Infections (VARI) may begin with tracheal colonization that can multiply and progress to Ventilator-Associated Tracheobronchitis (VAT) or Ventilator-Associated Pneumonia (VAP), as shown in Figures 1-2 [1-12].

![Figure 1: Schematic of an incubated intensive care unit (ICU) patient with an Endo Tracheal Tube (ETT), or Oro Gastric Tube (OGT) with high concentrations of bacteria in sub glottis secretions that collect above the ETT cuff, which can leak around the cuff into the lung. Also, bacteria-encased biofilm develops in the ETT lumen over time that can be emobilised into the tracheal bronchial tree and lung parenchyma with ETT suctioning or bronchoscopy causing significant tracheal colonization, Ventilator-Associated Tracheobronchitis (VAT) and/or pneumonia (VAP). Heavy endotracheal colonization, VAT and VAP are defined by Quantitative-Endo Tracheal Aspirates (Q-ETA) >10^5 colony forming units (cfu)/ml or Semi-Quantitative ETA (SQ-ETA) aspirates having > ++/+++ growth of a pathogen on agar plates. Gram-stained ETAs are examined for polymorph nuclear leukocytes and/or presence of bacteria/high power field that is consistent with a diagnosis of bacterial colonization, VAT or VAP.](image)

![Figure 2: Schematic of the extensive the left tracheobronchial tree surrounded by thousands air-filled alveoli shown in insert (B) using electron microscopy of air filled lung tissue. In VAP insert A, allows entering right lung bacteria causing significant airway colonization, Ventilator-Associated Tracheobronchitis (VAT) or pneumonia (VAP) shown in insert (A) with bacterial pathogens that enter the lower respiratory tract from the oropharynx or by leakage of bacteria or lung secretions around the Endo Tracheal Tube (ETT) tube cuff, or biofilm-encased bacteria forming in the ETT lumen. Note numerous polymorph nuclear macrophages or polymorph nuclear leukocytes in VAP Part A. Lung bacterial burden can be reduced by early appropriate intravenous and/or aerosolized antibiotics to reduce lung colonization, VAT and/or VAP. Adapted in part from: Craven DE, et al. “Antibiotic Treatment of Ventilator-Associated Tracheobronchitis”.

We previously studied significant lung colonization in 100 out of 234 consecutive incubated patients ventilated >48 hours that had many different bacterial pathogens shown in Table 1 and Figure 3. There were 39 ventilated patient’s with heavy bacterial colonization, and 61 patient shad VARI, which included 34 patients with VAT and 34 with VAP [12]. However, 7 (21%) of the 34 patients initially diagnosed with VAT subsequently developed VAP.

<table>
<thead>
<tr>
<th>Bacterial Pathogens</th>
<th>Antibiotic Therapy</th>
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<tr>
<td><strong>Gram-Negative Bacilli</strong></td>
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<tr>
<td><em>Pseudomonas aeruginosa</em>, <em>Escherichia coli</em></td>
<td>Anti-pseudomonal cephalosporin e.g., cefepime, cefazidime OR</td>
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<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>Anti-pseudomonal carbapenem e.g. imipenem or meropenem OR</td>
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<tr>
<td><strong>Enterobacter species</strong></td>
<td>Anti-pseudomonal penicillin e.g. piperacillin–tazobactam PLUS</td>
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<tr>
<td></td>
<td>Anti-pseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR</td>
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<td></td>
<td>Aminoglycoside (amikacin, gentamicin, or tobramycin)</td>
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<tr>
<td><strong>Extended Spectrum Beta-Lactamase, ESBL+ (Klebsiella pneumoniae and Other GNRs</strong></td>
<td>Carbenapen</td>
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<tr>
<td><strong>Acinetobacter species</strong></td>
<td>Carbapenem +/- aminoglycoside IV OR</td>
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<tr>
<td><strong>Stenotrophomonas maltophilia</strong></td>
<td>Colistin IV +/- aerosolized aminoglycoside Fosfomycin*</td>
</tr>
<tr>
<td><strong>Legionella pneumophila</strong></td>
<td>Trimethoprim-sulfamethoxazole</td>
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Note: ESBL = Extended Spectrum Beta-Lactamase.
Table 1: Recommendations for initial broad-spectrum empiric therapy for patients with significant lung colonization, VAT or VAP due to different pathogens with variable virulence and antibiotic therapy profiles shown below.

Patients diagnosed with VAT and/or VAP had serial Endo Tracheal Aspirates (ETA) examined daily for bacterial colonization and Polymorphonuclear Leukocytes (PMNL), and had significantly more ventilator days ICU days (p<0.001) and ICU days and as shown in Figure 3 [1-4]. Intubation with mechanical ventilation increased the risk of VAP from 6 to 20-fold [2]. VAP patients had a crude mortality rate of 20-40% and attribute able mortality of 6-14%, which translates into acute and chronic healthcare costs ranging from $20,000 to $40,000 per patient [2,13-15]. Muscedere and coworkers also emphasized inadequate antibiotic therapy for suspected VAP leads to increased ventilator days (16 vs 7 days, p<0.001), ICU stay (14 vs 8 days, p=0.02) and hospital days (42 vs 28 days, p=0.04), as well as greater ICU mortality (35% vs 12%, p<0.001) & hospital mortality (49% vs 20%, p<0.001) [16].

Figure 3: In our study of 234 patients ventilated > 48 hours, 39 (43%) had heavy colonization and 61 patients had either VAT or VAP. Note that VAT and VAP patients had significantly more (p<.001) more ventilator days, longer ICU stay and more hospital days (all p<0.001). However, 7 patients initially diagnosed with VAT later progressed to VAP.

Ventilated ICU patients are at high risk for colonization with different bacteria due to the primarily one-way lung entry shown in Figures 1&2, the endo tracheal tube and bacterial biofilm formation due to the wide spectrum of bacteria shown in Table 1, and risk of distal emboli with tracheal suctioning that can increase the risk of VARI [5-7,10,17]. Bacterial pathogens have easy, one-way entry into lung parenchyma coupled with limited cough and exit routes as shown in Figures 1&2.

VAT can be a precursor to VAP with similar clinical and microbiologic data and no lung infiltrates compared to VAP that requires evidence of lung consolidation. Both VAT and VAP may be caused by Gram-negative and/or Gram-positive bacterial pathogens listed in Table 1. Significant risk factors and bacterial virulence factors leading to airway colonization, VAT and VAP are summarized in Table 2. Assessing initial antibiotic therapy and efficacy based on serial ETA help assess lung bacterial burden, response to antibiotics, lung damage and cost of effective antimicrobial therapy, as well as effective choices for antibiotic therapy and impact of increased risk summarized in Table 2. Special attention should be aimed at the low efficacy of some current antibiotic therapy for Staphylococcus aureus [18-22].
### Patient Risk Factors and Pre-emptive Antibiotic Therapy for Lung Colonization VAT, VAP, Can Improve Patient Outcomes

We studied lung significant colonization in that developed in 100 of 234 incubated ICU patients ventilated >48 hours, using serial Endo Tracheal Aspirate (ETA) surveillance cultures and Gram stains for species of bacteria and neutrophils indicating inflammation/infection in patients ventilated >48 hours (Figure 2&3) [12]. There were 34 patients diagnosed with VAT and 34 had VAT of which 7VAT patients later progressed to VAP. Cultures were examined by an ETA Gram-stained smear for polymorphonuclear leukocytes and presence of bacteria/high power field, as well as use of serial Semi-Quantitative ETAs (SQ-ETA) or Quantitative ETAs (Q-ETA). Finally, VAT and VAP patients had significantly more ventilator days (p<.001), longer ICU stays (p<.001), as well as an increased risk for complications such as delirium or post-traumatic stress disorder and enormous healthcare costs [12-16].

Patient’s diagnosed with VAT and/or VAP have an increased risk of morbidity, mortality, debility and significant healthcare risk factors. Also, recent data from Stulik et al. focused attention on the low efficacy of current antibiotic therapy for treating *Staphylococcus aureus* lung colonization, VAT or VAP. Vancomycin also failed to reduce Methicillin-Resistant *S. aureus* (MRSA) lung colonization or Methicillin-Sensitive *S. aureus* (MSSA) lung burden. Also, antibiotic therapy with intravenous oxacillin was ineffective for treating MSSA colonization in 30% of patients discussed in Table 2 [2-4,15,2-19].

In “Thinking outside the box” recommends serial surveillance cultures and pre-emptive, appropriate antibiotic therapy aimed at specific lung pathogens seen on ETA smear due to trachea bronchial colonization, VAT or VAP, all of which can lead to poor patient outcomes, such as lung abscess, empyema, increased ventilator days, length of ICU stay, debility or Post-Traumatic Stress Disorder (PTSD), all of which translate into enormous acute and chronic healthcare costs [2,5,15,23,24]. However, recently Stulik et al. and an excellent commentary by Burnham &Kollef emphasized the low efficacy of antibiotic treatment for lung colonization, VAT, VAP due to *Staphylococcus aureus* [18,20,25].

Ventilated, ICU patients are often critically ill and at high risk for developing VARI due to impaired mechanical clearance of lung pathogens and primarily have one-way entry through or around the endo tracheal tube lumen with biofilm encased bacterial emboli aimed at distal parts of the lung making it more difficult to treat with antibiotics. Numerous patient risk factors for VAP...
and VAT contribute to poor outcomes in ventilated ICU patients discussed in Tables 1&2 [1,2,4-9,11,13-15,26]. Also, VAT and VAP patients are often elderly with acute and chronic medical and surgical diseases, or complications that increase lung colonization with a wide spectrum of bacterial pathogens, known as the “the infectious vortex”.

Special attention is recommended for use of serial ETA surveillance cultures examined by Gram stain to assess neutrophils & bacterial morphology, and bacterial culture to specifically identify more virulent pathogens, such as *S. aureus* or *P. aeruginosa*, which have toxins, may be encapsulated, and have virulence factors that can circumvent host defenses and increase tissue damage [18-22,27-31]. ETA samples can be routinely checked daily for purulence and bacterial burden on a Gram stained smear and confirmed by a SQ-ETA or Q-ETA cultures ranging to ≥10,000 to 100,000 bacteria/ml, with either routine microbiology or use of more rapid diagnostics, such as “Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) mass spectrometry [27].

Serial lung bacterial surveillance data helps support preemptive, appropriate intravenous or aerosolized antibiotic therapy for patients having SQ-ETA cultures +++/++++ growth, Q-ETA with ≥1,000 to 100,000 bacteria/ml of a pathogen, or mixed pathogens with the aim of reducing VARI, ventilator days, ICU stay, patient morbidity and mortality that translate into enormous healthcare costs. In randomized trials 7% to 30% of patients developing VAT will progress to VAP with an incidence ranging from 2.7% to 11.5% [8-30]. Due to the wide spectrum of Gram-negative bacterial pathogens shown in Table 2, are responsible for >75% of VAT episodes, but virulence and antibiotic sensitivity profiles may vary. For example, *P. aeruginosa* isolates have toxins that cause tissue damage, and other Gram-negative bacilli may be Multi-Drug Resistant (MDR) [31]. There are also increased concerns regarding use of intravenous antibiotic therapy for *Staphylococcus aureus* isolates discussed below [18-22,28,29].

**Pathogenesis & Treatment of Lung Colonization, VAT and VAP**

Placement of an Endo Tracheal Tube (ETT) increases the risk of VAP 6 to 20-fold, by allowing bacteria colonizing the oropharynx access to the lung parenchyma by leakage around the ETT cuff or direct entry into the left or right tracheobronchial tree and surrounding alveoli, as shown in Figures 1-3 [19,20]. Bacteria entry into the lungs is primarily one way, which can multiply rapidly increasing host colonization, lung damage or progression to VARI. Also of note are biofilm-encased bacteria which can form on the endo tracheal tube lumen, and over time increase the risk of distal lung emboli to all parts of the tracheobronchial tree and lung alveolar spaces. In addition, bacteria encased in biofilm have increased resistance to host cellular and humeral host defenses and may limit the efficacy of systemic or aerosolized antibiotic therapy. Mortality rates for VAP range from 20% to 40% with healthcare costs estimated at $15,000 to $40,000 per episode. These data underscore the importance and need for pre-emptive, appropriate antibiotic therapy to reduce ICU stay, ventilator days and associated healthcare costs [1,2]. “Thinking outside the box” we focused on the rationale and benefits of treating ETA surveillance cultures using serial Gram stained smears and microbiologic cultures obtained from ICU patients ventilated >48 hours, in order to identify and treat the wide spectrum of different Gram-negative and Gram-positive pathogens based on antibiotic sensitivity data needed for early, appropriate antibiotic therapy, as shown in Table 1&2.

**Low Efficacy of Antibiotic Therapy for *S. aureus* Airway Colonization, VAT & VAP**

Stulik and coworkers recently reported low efficacy of antibiotics against *S. aureus* airway colonization in ventilated patients that progressed to VAT or VAP, and included methicillin susceptible *S. aureus* (MSSA) isolates with alpha-hemolysis is activity, as well as methicillin-resistant *S. aureus* (MRSA) isolates having toxins that increase lung tissue damage and are also difficult to treat [6,18,19]. The low efficacy of antibiotic treatment for *S. aureus* airway colonization was noted in 48 mechanically ventilated patients using serial Semi-Quantitative Endo Tracheal Aspirate (SQ-ETA) cultures which were treated with vancomycin or oxacillin for at least two consecutive days. Vancomycin failed to reduce MRSA or MSSA airway burden and oxacillin was also ineffective for treating MSSA colonization in 15 of 39 of patients (30%) and responders that were co-administered additional antibiotics. No change in antibiotic susceptibility of *S. aureus* isolates was noted during antibiotic treatment that was ineffective in reducing *S. aureus* colonization, VAT or VAP. These data underscore the need for alternative strategies to improve patient therapy for *S. aureus* and patient outcomes [18-20,27].

Stulik and coworkers [8,19] emphasized the low efficacy of antibiotics against for *S. aureus* airway colonization in reducing MRSA and MSSA colonization or preventing VAT or VAP, all of which suggest certain antibiotics can up regulate cytotoxin production in *S. aureus* which has been noted in vitro and in vivo studies [22,28,29]. The low efficacy of antibiotics also may be due to poor lung penetration, host inflammation or difficulty in achieving adequate epithelial lining levels, especially for MRSA isolates treated with a vancomycin MIC >1 mg/L [20,27].

The recent commentary by Burnham and Kollef entitled “Prevention of VAP Due to *S. aureus*: Conventional Antibiotics Won’t Cut It” raises several important points for clinicians regarding use of parenteral anti-staphylococcal antibiotics such as vancomycin, linezolid and trimethoprim-sulfamethoxazole, nebulized antibiotics directly into the lung or use monoclonal antibody therapy [20].

Stulik et al. studied 48 mechanically ventilated patients colonized with *S. aureus* who were treated with “Appropriate” anti-staphylococcal antibiotics for ≥2 days with isolates that were sensitive, but were not reduced, and progressed to VAT and VAP [21,22]. The poor outcomes for *S. aureus* were in sharp contrast to the treatment of ventilated patients with VAT or VAP due to Gram-negative bacteria. Non-response to antibiotics may be also related to lung endo tracheal biofilm formation, or presence of “bacteria that...
Persist” or have small colony variants which are inert to multiple antibiotics, and associated with worse patient outcomes [20,27]. Despite antibiotic exposure, 15 of 39 patients (38%) colonized only by \textit{S. aureus} and treated with appropriate antibiotics for at least 2 days still progressed to VAP without any change in the antibiotic susceptibility of the \textit{S. aureus} isolates. Also, Paling et al reported that despite low levels of \textit{S. aureus} colonization, there was a 15-fold increase risk of \textit{S. aureus} pneumonia with vancomycin therapy for MRSA and also reported that line zolid therapy was associated worse patient outcomes [21]. In a retrospective study trimethoprim-sulfamethoxazole was superior to vancomycin and oxacillin therapy was ineffective for treating MSSA colonization, which emphasizes the need for alternative strategies to improve patient outcomes. These data underscore the growing interest in better treatments for \textit{S. aureus} colonization and infection, such as anti-infective, monoclonal antibody therapy as a promising strategy for use in ICU patients, that can bind or neutralize virulence factors that have been identified in animal studies [18,20]. Stulik et al are currently conducting a phase 2 Arsaina is multi-center trial (ASN100), using a combination of two human monoclonal antibodies that can neutralize six important \textit{S. aureus} cytotoxins associated with VAP pathogenesis [18].

**Ventilated Patients Have a Wide Spectrum of Risk Factors**

The wide spectrum of risk factors in incubated, ventilated ICU patients at risk for VARI is delineated in Table 2, which includes the presence of bacterial biofilm encased bacteria in the endotracheal tube lumen that can multiply rapidly or may include more that one pathogen, especially in patients with advanced age or acute or chronic underlying that limit later host responses in ventilated ICU patients. Appropriate, pre-emptive antibiotic therapy is aimed at reducing the “Infection vortex” leading to bacterial lung colonization, VAT and/or VAP, and to improve patient outcomes by reducing ventilator days, ICU stay, healthcare costs, and un appreciated complications, such as lung abscesses, empyema, delirium or Post-Traumatic Stress Disorder (PTSD) [13]. Models are needed to monitor lung colonization leading to VAT and/or VAP as shown in Figures 1-3. Unfortunately, tracheal colonization is not routinely used to monitor and identify different virulent pathogens, and antibiotic sensitivity data needed to initiate appropriate, pre-emptive antibiotic therapy to reduce VARI and improve outcomes [5]. Use of serial ETA surveillance samples allows early diagnosis and use of appropriate, pre-emptive antibiotic treatment to reduce significant tracheal colonization and risk of progression to VARI, delirium or Post-Traumatic Stress Disorder (PTSD) that translate into increased ventilator days, longer ICU stays and increase health care costs [6,9,32-34].

ETA surveillance cultures allow earlier diagnosis and pre-emptive treatment for “Significant colonization” defined as a SQ-ETA ≥ ++/+++ bacteria/ml which is equivalent to a Q-ETA ≥ 10^3 cfu/ml that we used for our first 100 (43%) study patients at risk for VARI [3,4,35-37]. A wide spectrum of Gram-negative / Gram-positive pathogens isolated need early, appropriate antibiotic therapy for VARI summarized in Table 1, to reduce VARI and improve patient outcomes [5]. A lower threshold to define “Significant” tracheal colonization” and most effective therapy should be considered for patients infected with more virulent pathogens [9,32,33]. For example, heavy lung colonization due to \textit{S. aureus} and \textit{P. aeruginosa}, is more virulent and often equipped with toxins that increase lung damage and result in poor patient outcomes [19,38]. Multi-Drug Resistant (MDR) pathogens can also alter outcomes and increase the risk of VARI and poor outcomes as shown in (Tables1&2). Infections and underlying diseases due to VARI are also higher in elderly, post-surgery patients with serious underlying chronic diseases, debility, immuno suppression, organ failure or prior antibiotic therapy which can alter patient outcomes [2,4,17,39].

Assessing daily clinical signs and serial surveillance culture data can help clinicians assess the impact of specific antibiotics and pre-emptive therapy, aimed at reducing lung colonization and VARI (Tables1&2). ETA samples should be routinely checked daily for purulence and bacterial burden on a Gram stained smear and confirmed by a SQ-ETA or Q-ETA culture shaving ≥ 10,000 bacteria/ml, with either routine microbiology or use of more rapid diagnostics, such as “Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) mass spectrometry [27]. Finally, a lower bacterial threshold has been suggested for initiating, early, appropriate antibiotic therapy for more virulent bacterial pathogen(s) such as \textit{S. aureus} (MSSA or MRSA), \textit{P. aeruginosa}, Multi-Drug Resistant (MDR) Gram-negative bacilli. Response to pre-emptive intravenous and/or aerosolized antibiotic therapy should also be carefully monitored over time in high risk intubated, ventilated patients in order to reduce VARI and improve patient outcomes for difficult pathogens such as \textit{P. aeruginosa} or any other Multi-Drug Resistant (MDR) isolates and MRSA (Table1) [19].

Michael and coworkers obtained Q-ETA twice weekly in an incubated cohort compared to a culture from Broncho Alveolar Lavage (BAL) performed at the time of VAP, in which a causative organism was identified in 83% of study patients [32]. Deputdt et al used weekly Q-ETA to detect VAP due to MDR pathogens and found that MDR pathogens were present in 69% of the episodes and that ETA surveillance cultures led to improved appropriate antibiotic therapy for 96% of the patients [9]. A similar study of BAL-confirmed VAP by Haydon and coworkers reported that Q-ETA surveillance cultures identified at least one of the pathogens isolated by BAL and had a high predictive value for cultures obtained within 72 hours of the VAP diagnosis [40,41]. It is important to emphasize the wide spectrum of host risk factors that contribute to lung bacterial burden, virulence factors and antibiotic susceptibility data which can alter outcomes and are difficult to measure. Muscedere et al confirmed that inadequate antibiotic therapy in patients with clinically suspected VAP increases ICU mortality (33% vs 12%, p<.001), hospital mortality (49% vs 20%, p<.0001), ventilator days (16 vs 7 days, p<.0005), ICU days (14 vs 8, p=.02), and hospital days (42 vs 28, p=.04). Thus, appropriate pre-emptive intravenous and/or aerosolized antibiotic therapy can reduce tracheal colonization and the risk of progression to VAT and/or VAP.
A ‘Court et al studied tracheal colonization in 150 mechanically ventilated patients, using serial quantitative, non-bronchoscopic, bronchial lavage samples, and reported that lower respiratory tract colonization increased over time and appeared to peak about two days prior to the onset of clinical signs of VAP (Table 2) [35]. In addition, a prospective, observational cohort of medical and surgical patients by Nseir et al. development of VAT was associated with increased length of ICU stay, more mechanical ventilator days and a higher mortality rate in medical but not surgical ICU patients [3].

A study of ventilated patients with Chronic Obstructive Pulmonary Disease (COPD) by Nseir et al. noted that patients treated for VAT, when compared to “Matched” controls, had significantly fewer median days of mechanical ventilation and ICU stay, but did not appear to protect against VAP [40]. However, in a later prospective, observational case-control study of VAT, patients treated with early antibiotics had significantly fewer ventilator days and shorter ICU stays, but no difference in mortality [36]. Nseir et al. also conducted an important controlled, unblended trial of 58 patients with a clinical diagnosis of VAT, defined by a Q-ETA >10^4cfu/ml with no infiltrate on chest x-ray, who were randomized to receive targeted intravenous antibiotics versus either no or delayed therapy [23]. The antibiotic-treated group had significantly better outcomes that included more “mechanical ventilation-free days” (median 12 vs 2 days, p<0.001), lower ICU mortality (18% vs 47%, p<0.05), and a significant decrease in progression to VAP (47% vs 14%, p<0.02). The same bacterial pathogens were identified in each group, supporting the concept that VAT progresses to VAP in selected patients, and that earlier antibiotic therapy improves patient outcomes and reduces VAP. Notable limitations of this study included low numbers of patients, and an imbalance in the numbers of patients randomized to each group, lack of an independent, blinded evaluation of endpoints, such as interpretation of chest x-rays to exclude early VAP.

Aerosolized appropriate antibiotic therapy for VAT was successfully implemented by Palmer et al. in two randomized studies [41,42]. The first was a double-blind, randomized, placebo-controlled study of medical ICU and surgical ICU patients comparing aerosolized antibiotic treatment (gentamicin every 8 hours) if Gram-negative bacilli were present and vancomycin every 8 hours if Gram-positive bacteria were detected or both for patients with mixed infections for 14 days or until extubation (n=19) versus a saline placebo (n=24) [42]. VAT was defined as the production of ≥ 2 ml of purulent ETA over a 4-hour period with a Gram stain demonstrating bacteria. Systemic antibiotics were given at the discretion of treating physician and frequently prescribed in both groups. Compared to the placebo group, the antibiotic treated group had significantly better outcomes manifest as lower rates of clinical signs and symptoms of VAP, faster weaning, reduced numbers of multi-drug resistant organisms and lower use of systemic antibiotics with all endpoints (p<0.05).

**VAT and VAP vs Healthcare Costs and Outcomes in ICU Patients**

Ventilated ICU patients have enormous acute and chronic healthcare costs and unfavorable long-term outcomes. In a study of 123 ventilated ICU patients in five ICUs at Duke University, 99 patients survived and were followed for one-year after hospital discharge that included multiple transitions for health care, hospital readmissions and enormous resource utilization [15]. At one-year post discharge, only 9% of the study patients were living independently. Also, there were multiple hospital readmissions and numerous transitions of care that involved acute, long-term care and rehabilitation facilities with healthcare costs estimated at $3,5 million per survivor. Poor outcomes and high healthcare costs underscore the importance and use of early, effective, appropriate antibiotic treatment to improve patient outcomes and reduce healthcare costs.

Sir William Osler, MD, a Professor of Medicine at McGill University in Montreal and later at Johns Hopkins in Baltimore, said in 1895 regarding pneumonia: “Remember how much you don’t know”, which still exists for managing complicated, ventilated ICU patients today. As shown in Figures 1&2, incubated patients may develop endo tracheal tube biofilm-encased bacteria that increase over time, due to essentially “One-way entry” for bacteria into the huge lung left and right trachea bronchial tree surrounded by two enormous air-filled lungs with thousands of alveolar spaces, resulting in increased lung bacterial burden that can overwhelm host cellular and humeral defenses, leading to poor patient outcomes and enormous acute and chronic healthcare costs.

Incubated patients having a Q-ETA of ≥ 10^4CFU/ml or a SQ-ETA with moderate to heavy (+++/++++) bacterial growth, are at greater risk for development of VAT or VAP, resulting in poor outcomes [5,43]. Controlled studies of patients with VAT have demonstrated that appropriate antibiotic treatment was associated with lower rates of VAP and improved patient outcomes [23,44]. Also, serial surveillance cultures to identify pathogens causing significant colonization and increased total lung burden can be reduced by early, appropriate antibiotic therapy to prevent VARI, improve patient outcomes with close monitoring of clinical and microbiologic changes to improve outcomes. Based on data presented in Tables 1&2 and our current understanding that VAT and VAP pathogenesis, use of serial ETA surveillance cultures is a valuable clinical tool to identify and monitor therapy to pre-emptively treat significant colonization and VARI aimed at specific pathogen(s), as well as use of appropriate intravenous and/or aerosolized antibiotic therapy needed to improve patient outcomes [1,42,45].

Clinical outcomes from antibiotic therapy also may vary by type of hospital, patient age, disease severity and medical vs surgical patients. Our plea is to reduce lung colonization, prevent VAT and
VAP as well as duration of ICU stay. Patient outcomes to monitor include reduction in lung bacterial burden on therapy, antibiotic sensitivity data, duration of therapy, removal of the ETT as soon as possible, and having a “walk to wean” program to improve patient outcomes, reduce ventilator days, ICU stay, readmissions, morbidity and mortality [3,4,37,42,45,46]. Critically ill, ventilated patients developing VARI are at high risk for a myriad of complications, called the “Infection vortex” which includes acute and chronic lung damage and acquired complications, such as delirium or Post-Traumatic Stress Disorder (PTSD), as well as acute and chronic disease, and others had long term depression, job loss and increased family burdens [13,14,48]. Management issues for treating and preventing VARI include assessment of host risk factors, bacterial virulence, use of pre-emptive antibiotic therapy with monitoring of host response, as summarized in (Tables 1 & 2).

Ventilated patient’s are complicated, critically ill, and at high risk for poor outcomes that include increased ventilator days, length of Intensive Care Unit (ICU) stay, and risk of developing VAT and/or VAP [5,17]. Randomized trials and a meta-analysis have demonstrated that pre-emptive, appropriate antibiotic therapy for VAT improves patient outcomes and reduces progression to VAP [23,30]. We also support use of serial surveillance cultures to assess pre-emptive, appropriate therapy aimed at tracheal colonization, VAT and VAP.

Because VAT and VAP may be difficult to distinguish clinically, “Our thinking outside the box “ includes serial bacterial surveillance cultures, as markers for initiating pre-emptive, appropriate antibiotic therapy for VARI to reduce lung colonization, VAT and/or VAP and decreased ventilator and ICU days [23,49]. Ventilated patients having lung colonization and a SQ-ETA culture with +++++/++++ growth of more virulent pathogens that include S. aureus, P. aeruginosa, or MDR Gram-negative bacilli [19].

In summary, we support use of serial ETA surveillance cultures help clinicians identify and appropriately treat patients with significant tracheal bronchial colonization, or VARI due to specific pathogens. Pre-emptive, appropriate antibiotic therapy can reduce VARI, ventilator and ICU days, and risk for delirium and Post-Traumatic Stress Disorder (PTSD), as well as the enormous associated healthcare costs.

ICU patients ventilated > 48 hours are often elderly, with underlying diseases or debility and are often sedated, which can increase bacterial lung burden, complications as well as acute and chronic lung damage due to limited exit routes for more virulent or Multi-Drug Resistant (MDR) strains [19]. Special attention is recommended to assess and monitor ventilator bundle components, such as head of the bed elevation, sedative infusion interruptions, spontaneous breathing trials, thrombo embolism prophylaxis, and effective “Walk to wean” programs to improve patient outcomes recommended by Klompas et al. [50-51].

References


