Published in final edited form as:
Best Pract Res Clin Anaesthesiol. 2008 September 1; 22(3): 437–449. doi:10.1016/j.bpa.2008.05.002.

Ventilator-Associated Pneumonia: Problems with Diagnosis and Therapy

Jeanine P. Wiener-Kronish, MD
Henry Isaiah Dorr Professor of Research and Teaching in Anaesthetics and Anaesthesia, Harvard Medical School, Department of Anesthesia and Critical Care, Anesthetist-in-Chief, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114, Fax: 617-724-8500, Phone: 617-726-3030, jwiener-kronish@partners.org

Abstract

The diagnosis of ventilator-associated pneumonia, VAP, is problematic because of a lack of objective tools that are utilized to make an assessment of bacterial-induced lung injury in a heterogeneous group of hosts. Clinical symptoms and signs are used to identify patients that may have a “lung infection”. However, the symptoms and signs can be produced by a myriad of other conditions. Recent clinical data also suggests bacterial-induced pathologic processes occur prior to the onset of the symptoms and signs. Utilizing bacterial culture alone, health care practitioners are forced to wait for days for results and will have to order days of empiric antibiotic therapy. Exploratory molecular studies utilizing clone libraries and molecular arrays for microbial identification document the inability of culture-based techniques to even identify all the microbes involved in VAP. These molecular studies also offer evidence that oral flora present in the lungs of patients with VAP, suggesting aspiration of oral secretions and/or biofilms on endotracheal tubes, supply the bacteria for VAP. Much more investigation is needed to determine the optimal timing of antibiotic treatment and which diagnostic molecular methods can be utilized in the ICU.

Keywords

Ventilator associated pneumonia; Quantitative Cultures; Molecular arrays; Clone libraries; Biomarkers; Chlorhexidine; Nosocomial pneumonia; PAI-1

PATHOGENESIS OF VAP

It has been recognized for more than 30 years that oropharyngeal colonization by gram-negative pathogens occurs rapidly in critically ill patients and that nosocomial pneumonia occurs more often in patients who are colonized [1]. Studies have documented that biofilms rapidly form on endotracheal tubes, [2,3] and investigators suggest that the biofilms are the reservoir for the ongoing contamination of the tracheobronchial tree. An investigation of previously healthy trauma victims documented that in 21 consecutive patients, the interior of the endotracheal tube had bacterial-laden secretions as early as 12 hours, increasing in quantity until a peak was reached at 48 hours [3]. These investigators performed sequential cultures of the oropharynges and lung secretions and found that the first site to be colonized

by pathogenic bacteria was the mouth after 36 hours, which was then followed by colonization of the endotracheal tube and lower respiratory tract [3].

Since it appears that the oral flora is leaking into the lower airways and/or that the biofilms on the endotracheal tube [formed by oral airway bacteria] provides the bacteria to the lower airways, recent investigations have considered closely examining the oral flora in intubated patients [4]. Conventional culture methodology does **not** identify all the bacteria in the oropharynx and so would also not identify all the bacteria in the airways of intubated patients [4]. To more precisely characterize the total group or community of bacteria in the oral pharynx and in the secretions from the airspaces of the lung, molecular identification of bacteria is necessary [4–5]. In a recent study where trauma patients were enrolled when they were about to undergo bronchoalveolar lavage [BAL] to diagnose VAP, oral swabs from the tongues of intubated patients were obtained to compare to the patient's BAL. Clone libraries and molecular sequencing as well as standard culture were used on each sample [4]. The investigators found that 88% of the VAP patients had the same bacteria in their oral cavities as in their lungs suggesting the mouth flora was the source of bacteria in the lungs. These investigators also found that 56% of the pathogens were not identified by the cultures done in the clinical microbiology laboratory [4]. Similarly, Flanagan et al. using similar molecular techniques as well as molecular microarrays on the endotracheal secretions from patients with *P. aeruginosa* VAP, found that many of the bacteria in the secretions were not identified by the cultures that had been done for patient care [5]. These two studies further suggest that when a patient is diagnosed as having VAP, their oral flora is the same as the bacteria in their lung secretions and BAL. It is likely that patients without VAP also have their oral bacteria in their lungs; the question is whether there is a difference between patients who meet the criteria of VAP and those who do not.

These studies also suggest that strategies that manipulate the oral flora might prevent VAP and that, if possible, strategies that prevent oral flora from entering the lung might also be advantageous. Further investigation may allow the identification of "high-risk" oral flora that will lead to lung infections and it will be possible to identify the specific beneficial effects of antiseptics on oral flora in the patients who do and do not develop VAP.

DIAGNOSTIC UNCERTAINITY

Since most of patients with endotracheal tubes will have oral flora soiling their lower airways, when does a lung infection occur? Most of the diagnostic criteria for VAP demand clinical symptoms and signs of infection, including fever, leukocytosis and chest radiograph findings typical of lung infections in ambulatory settings. Clinical criteria are nonspecific; an autopsy investigation documented that only 52% of patients with pneumonia at autopsy had localized infiltrates on their chest radiographs close to their deaths [6]. Forty percent of these patients also did not have leukocytosis close to their deaths [6]. These and other findings suggest clinical signs and symptoms **do not** identify all the patients with VAP. Therefore, there have been multiple evaluations for biomarkers that more clearly identify patients with "lung infections". These biomarkers will be discussed below.

In an attempt to make clinical guidelines, the following diagnostic criteria are offered [7]:

> **Heath care associated pneumonia [HCAP]-** This category includes patients who a] receive home intravenous antibiotics, home nursing, or home wound care; b] patients who reside in nursing homes or long-term care facilities; c] patients who have been hospitalized for > 2 days in the past 90 days; d] patients who have received dialysis or IV therapy at a hospital-based clinic in the past 30 days.

1. **Hospital acquired pneumonia [HAP]-** Patients who are in the hospital when they develop pneumonia. This is now the second most common nosocomial infection after urinary tract infection but the leading cause of mortality due to hospital-acquired infections [7].
2. **Ventilator associated pneumonia [VAP]-** Patients who have been in the hospital for 48 hours or intubated for 48 hours and then develop signs of a lung infection, including new or progressive radiographic infiltrate, new onset of fever, purulent sputum, leukocytosis and decline in oxygenation. If there is no new infiltrate, then a diagnosis of nosocomial tracheobronchitis can be entertained, which has been associated with prolonged length of stays and prolonged mechanical ventilation but no increase in mortality [8].

The reason for these different definitions is to highlight that these lung infections appear to be caused by different microorganisms than cause community acquired lung infections [9]. Patients are frequently divided into whether they appeared to develop their lung infections within 5 days of being hospitalized or those who develop the infections at or after 5 days of hospitalization. It is thought that within 5 days, the patients are often infected by organisms more reflective of the community, including *Haemophilus influenzae*, *Escherichia coli* or methicillin-sensitive *Staphylococcus aureus* [8]. This is true only if patients have no underlying lung disease, no prior hospitalizations, or no prior antibiotic treatment [10].

It is possible to see highly resistant organisms, including *Pseudomonas aeruginosa*, MRSA and *Acinetobacter* in patients who have been in the hospital for less than 5 days if they have received antibiotics prior to hospitalization. Other factors that increase the chances of a patient having a highly antibiotic resistant organism include coma, head trauma, diabetes mellitus and renal failure, corticosteroid use and underlying lung disease. The choice of initial antibiotic treatment needs to be based on the antibiotic resistance data in the patient's hospital.

THE RISK OF VAP IN TRAUMA PATIENTS

Several groups of trauma patients have increased risks for the development of VAP. Twenty-two to forty-four percent of patients who have severe head and neck trauma develop VAP [11]. In a case-controlled investigation in Spain of trauma patients, the risk factors for VAP also included a history of prior therapy with bronchodilators, the use of paralytic agents and the administration of parenteral nutrition. An independent predictor of VAP was that the patient had sustained head and neck trauma [11].

A difference seen between VAP in trauma patients and in other hospitalized patients is that *H.influenzae* seems more prevalent as a microbial pathogen in these patients, and it is found both in early and in late VAP [11–12]. Patients with chronic lung disease often have colonization of the lower airways with *H. influenzae* and up to 80% of normal healthy patients have colonization of the upper airway with *H. influenzae* [13]. Future vaccination against nontypeable *H. influenzae* may provide protection against this infection.

NONSPECIFIC CRITERIA LEAD TO OVERTREATMENT

Critically ill patients have multiple medical problems that make the diagnosis of a lung infection difficult. These patients may have radiologic abnormalities from ARDS, atelectasis and other underlying lung diseases. They can also have multiple etiologies for fevers, from infections in other sites or from drugs. The criteria of fever, leukocytosis, new or persistent change in chest radiographs and the presence of bacteria in the sputum or endotracheal aspirates are sensitive, in that it is unlikely to miss a case of nosocomial pneumonia.

However, the criteria are non-specific, so that you will treat many patients with antibiotics who do not have VAP [7,14].

QUANTITATIVE CULTURES

As the clinical criteria lack specificity, there have been numerous publications on methods to improve the distinction between the patients with lung infections in contrast to patients who are “colonized”. Quantitative cultures of sputum or endotracheal aspirates obtained by suctioning intubated patients can be done in an attempt to identify patients who have high burdens of bacteria [See below]. In an investigation that compared quantitative cultures of endotracheal aspirates to quantitative cultures of BAL, a threshold of 10^6 cfu/ml was the most accurate threshold for bacteria in endotracheal aspirates and had a sensitivity of 68% and a specificity of 84% [15].

Bronchoscopy has been utilized since the 1980s to collect lavage fluid [BAL] from lung areas that appear to be “infected”; samples are then sent to the laboratory for quantitative cultures. Chastre and his colleagues validated the accuracy of BAL. They documented the similarity between BAL quantitative cultures obtained from patients who were dying with VAP and their quantitative cultures of lung tissues obtained right after their death [16–17]. Bronchoscopy was performed within 1 hour of death while mechanical ventilation was continued and BAL and protected brush specimens were obtained. Patients included had never had prior lung infections until this final episode and had fever, white count and chest radiographs that were suspicious of infection right before they died. Immediately after bronchoscopy, a thoracotomy was done and the lung was obtained that had been sampled by bronchoscopy. All lung segments grew more than 10^4 cfu/g of tissue, suggesting infection. BALs with greater than or equal to 10^4cfu/ml had a 91% sensitivity and 78% specificity and had a 83% positive predictive value and an 89% negative predictive value in identifying the lung tissue that contained bacteria [17]. BALs have about 75% reproducibility in patients with positive cultures. All quantitative cultures can be affected by antibiotic treatments; investigations have suggested that patients need to be on no antibiotics or on the same antibiotics for 72 hours to obtain a quantitative culture that reflects lung cultures [14].

Obtaining quantitative cultures has not been shown to consistently improve patient mortality, although in one study it did improve mortality compared to patients who were treated on the basis of qualitative endotracheal aspirates [18]. What has been shown is that by obtaining quantitative cultures, antibiotic treatment can be stopped without increasing the mortality of the patients [19]. A meta-analysis of the randomized, controlled trials of invasive diagnostic strategies included 628 patients; the meta-analysis confirmed that invasive testing affected antibiotic utilization and led to treatment modification in over 50% of patients [20]. Therefore, invasive quantitative cultures allow the discontinuation of antibiotics when negative cultures are obtained and often lead to changes in antibiotic treatments when positive cultures are obtained.

QUANTITATIVE CULTURES IN TRAUMA PATIENTS

The literature on VAP in trauma patients suggests that the outcome of infections in these patients is better. This probably is true because trauma tends to occur in younger men with fewer underlying diseases. The bacterial thresholds utilized by the surgeons in trauma critical care are different than those proposed in the medical critical care units; the surgeons require greater than or equal to 10^5cfu/mL in BAL fluid quantitative cultures prior to antibiotic therapy whereas the accepted threshold for quantitative cultures in medical patients has been 10^4cfu/mL [21]. Certainly the mortality from acute lung injury/ARDS in trauma patients is much lower than medical patients and whether different microbial pathogens or different kinds of lung injury are involved is unclear. Most of the

investigations in trauma victims are at single centers and with small numbers of patients. Therefore, more research is needed to evaluate whether the infections in hospitalized trauma patients are different than those seen in hospitalized medical patients.

DIAGNOSTIC BLIND VS BRONCHOSCOPIC BAL

A recent investigation of bronchoscopic evaluation done for acute respiratory failure in immunocompromised patients documented that the results from bronchoscopy **did not** decrease mortality but increased the need for mechanical ventilation [22]. In fact, even when the results from the BAL provided a diagnosis, survival **was not** improved in this patient population [22]. These results suggest that even in patients with very low immunity due to immunosuppression, performing invasive studies may not be reasonable. However, this study did confirm that mortality was increased when the cause of acute respiratory failure was not determined and suggested the great need for new diagnostic strategies.

Patients that have endotracheal tubes can undergo procedures besides BAL; sterile catheters can be placed beyond the endotracheal tube to obtain quantitative cultures from the distal airways. Both blind protected brushes or blind minilavages [blind mini-BAL] can be done in these patients, often by trained respiratory therapists. These procedures are less expensive and more readily available, as they do not require physicians, so they can be done during evenings and weekends. The results obtained from these procedures have also been compared to postmortem lung histology and cultures from patients with VAP, and the data from blind mini-BALs has a sensitivity and specificity of 80% [23].

BIOMARKERS OF LUNG INFECTION

A recent small report noted that patients who were chronically ventilated and lived in a ventilator facility were found to have large bacterial burdens in BALs, that would have met the criteria for infections [See above under quantitative cultures] and they did not have fever, leukocytosis, chest radiograph findings that are found in outpatients who have lung infections [24].

This report highlights two problems with previous studies of patients that had been performed in patients intubated for shorter durations. Control groups, or intubated patients who do not have fever, leukocytosis, or chest radiograph findings, have never been evaluated systematically to determine the quantity of bacteria in their airways. Furthermore, the presence of bacteria may be necessary for the diagnosis of lung infection, but is it sufficient? Particularly in patients who have tracheostomies or have endotracheal tubes for long durations, does the presence of bacteria, even in large quantities signify that the lung is being injured, or that there is a lung infection?

Several groups have tried to find biomarkers that might reflect lung injury or lung infection. The importance of the biomarkers is that they could be measured within hours compared to the two to three days required to obtain culture results and they may verify that the bacteria that are present are injuring the lung. It is possible that antibiotic treatment could be administered based on the presence of a biomarker and not on the presence of a bacterial culture, as the biomarker might identify bacteria that were causing lung injury in contrast to bacteria that were just colonizing the airspaces. To date, no such ideal biomarker has yet to be found for patients with any of the three categories of nosocomial pneumonias discussed.

1. sTREM

Soluble triggering receptor is expressed on myeloid cells [s-TREM] and was measured in the BAL obtained by a blind mini-lavage catheter. The s-TREM was shown to be 98%

sensitive and 90% specific when compared to quantitative cultures in patients with presumed VAP and with community acquired pneumonia [25]. The problem with this study was it was done using a dot blot, which is not as accurate as an ELISA. Furthermore, sTREM appears to be very sensitive to antibiotics [personal communication, M. Schultz, M.D.].

A second investigation was done in 28 patients. Nine of the 28 patients developed VAP and 19 did not; plasma concentrations of sTREM were no different between the patients with and without VAP. Patients with VAP had increased values of sTREM of 200pg/ml [measured by ELISA] in blind mini-lavages whereas lower values were detected in the control groups. A level of 200pg/ml had a diagnostic sensitivity of 75% and a specificity of 84%[26].

2. Fibrin Deposition in Infected Lungs/ PAI-1

Other potentially useful biomarkers include some of the biomarkers of coagulation, including plasminogen activator inhibitor-1, or PAI-1. PAI-1 inhibits fibrinolysis and so allows fibrin to persist. PAI-1 has been shown to be elevated in patients with VAP and not elevated in patients who do not meet the criteria of VAP [27]. These data came from an investigation of 10 healthy volunteers, 10 patients who were mechanically ventilated without signs of VAP and 5 patients who had VAP that was unilateral. Bronchoscopic lavage was done on both the infected and non-infected lungs. Activation of coagulation was found only in the BAL fluid obtained from the infected lung, and not from the uninfected lungs. High concentrations of thrombin-antithrombin complexes, soluble tissue factor and factor VIIa were found in the lavage fluid from the infected lungs as well as high concentrations of plasminogen activator inhibitor-type I [27].

Markers of coagulation appear to be of increasing importance in both lung injury due to bacteria and in ARDS from a variety of causes [28]. A high concentration of PAI-1 in the plasma of patients with ARDS has been found to be associated with significant increases in mortality [29]. It is of interest that PAI-1 is confined to the lungs in patients with VAP but once severe lung injury is present, PAI-1 is present in the systemic circulation. It may be that the presence of PAI-1 in the systemic circulation signifies a significant breakdown of the alveolar epithelium. Notably, the concentrations of PAI-1 in ARDS do not correlate with the clinical lung injury score or measurements of oxygenation.

3.C-reactive protein and bacterial load

A prospective observational study analyzed 68 patients with suspected VAP. The diagnosis of VAP required a new and persistent pulmonary infiltrate in conjunction with purulent respiratory secretions and a fever, or the presence of leukocytosis [30]. Quantitative cultures were done of endotracheal aspirates on the day of entry and 96 hours later. C-reactive protein, CRP, was measured in serum using an automated nephelometric technique [30]. Interestingly, there was **no** correlation between the quantitative culture values and white blood cell counts, organ failure assessment nor the P02/FI02 values. When appropriate empiric antibiotics were administered, serum CRP fell as did the quantity of bacteria cultured [30]. As discussed below, performing a second culture and obtaining a biomarker, such as CRP, may be useful in assessing the success of treatment, particularly in patients with MRSA and gram negative bacteria, which have been shown to cause recurrences [See below]. The value of CRP is that it can be done rapidly [30], results obtained the same day, whereas culture results take days to obtain.

TREATMENT OF VAP

Chastre and colleagues [31] performed a randomized trial in 51 ICUs in France and randomized over 400 patients with VAP, established by bronchoscopic quantitative cultures, to either 8 or 15 days of antibiotic therapy. Notably the patients who received antibiotics for 8 days had no excess mortality, had more antibiotic free days and were less likely to have multiresistant pathogenic bacteria if infections recurred. The patients who had *Pseudomonas aeruginosa* did have a higher recurrence rate when only treated for 8 days. The suggestion is that patients with *Pseudomonas aeruginosa* in their BAL should be treated with 15 days of therapy, but that other VAP infections require 8 days of antibiotic treatment only [31].

Most recently a meta-analysis of 41 different trials that included 7000 patients was done to evaluate different treatment strategies for VAP [32]. No mortality benefit was shown for any antibiotic regimen. Furthermore, no evidence was found that combination antibiotic therapy was superior to monotherapy; all regimens had about a 37% rate of failure. The authors suggested that the clinical trials were too small to detect any significant difference between treatments [32]. Another possibility is that there was lack of consistent clinical decisions made utilizing culture data. This was suggested by the only trial where empiric ciprofloxacin was consistently stopped when culture data was negative and there was a reduction in rates of superinfection and improved clinical outcomes [33]. The authors of the meta-analysis offered a final explanation that antibiotic therapy may not improve outcomes in this patient group and suggested that large controlled trials are needed to address this issue [32].

RESOLUTION OF VAP

A recent investigation of 401 patients with VAP documented that within 28 days of the onset of VAP, there was about a 14% recurrence rate and 19% of the patients become superinfected [34]. Patients who developed recurrences were sicker and more frequently had MRSA or gram negative bacteria in their first episodes of VAP. The mortality of patients who had recurrences was 34% compared to a mortality of 24% in patients who did not have recurrences. Patients who died were older, sicker, more frequently had gram-negative bacteria in their first VAP episode, and had more severe lung injury noted on their initial day in the ICU [34].

EVIDENCE-BASED PRACTICE STRATEGIES TO REDUCE NOSOCMIAL LUNG INFECTIONS

1. It is clear that **removal of the endotracheal tube decreases the incidence of VAP**. All strategies that speed up extubation will decrease VAP. This has been documented in several investigations. Limiting sedation and using propofol instead of lorazepam leads to faster extubations and fewer ICU days [35]. Performing daily tests to assess readiness for extubation and the use of non-invasive ventilation in patients who can tolerate it will also decrease the incidence of VAP [36].
2. **Careful handwashing with alcohol-based soap** will decrease the incidence of nosocomial infections [37].
3. **Control of antibiotic use** has been associated with decreased incidence of antibiotic resistance. Different paradigms of antibiotic use have been advocated with various outcomes, but stopping antibiotics when quantitative cultures are negative is the best practice to insure optimal patient care and decreased antibiotic resistance [19].

Other interventions that may help- need more evidence

4. **Surveillance cultures**, taken at entry into the ICU and then on a regular basis, may be helpful in determining which antibiotics to give when an infection seems likely. A recent single hospital retrospective analysis over 10 years evaluated endotracheal aspirate cultures obtained for surveillance within 48–96 hours prior to finding positive bacterial cultures of blood. Surveillance was done three times a week; infection control personnel obtained oral swabs, urine cultures and endotracheal aspirates. Anal swabs were obtained once a week and wound cultures were also once a week [38].

   Evaluation of 112 episodes of bacteremia was found to be associated with pneumonia where all data was available. Ninety-six percent of the patients were mechanically ventilated and 107/112 episodes had simultaneous endotracheal aspirates. In 86 episodes, the blood and endotracheal aspirate had the same organism. Forty-one percent of these episodes were caused by multidrug resistant organisms [MDR], which were predicted 85% of the time by prior cultures of endotracheal aspirates. In only 15% of the prior endotracheal cultures were the organisms different than those found in the bacteremia cultures [38].

   Others have also found value in surveillance cultures. Delclaux et al [39] found that ARDS was preceded 66% of the time by colonization of the lower airways, assessed by blind protected catheter aspiration and quantitative culturing every 48–72 hours. However, more recently a prospective study documented that surveillance cultures of 125 consecutive VAP episodes were predictive in only 31% of the episodes [40]. Similarly in a prospective investigation of 356 heart surgery patients where 28 developed VAP, only one episode was caused by a pathogen isolated from a surveillance culture. However, surveillance cultures were only done once a week [41]. More recently Bouza et al. did find that surveillance cultures of catheter insertion sites found 77% of the cultures of the insertions sites did predict the bacteria found in bacteremia [42]. Therefore, it is not clear whether surveillance cultures are only beneficial when they are done frequently and therefore may be less cost-effective.

5. **Enteral Feeding**- A recent investigation to determine the incidence of aspiration in mechanically ventilated patients found that 89% of patients had pepsin-positive tracheal aspirates, suggesting they aspirated at least once. There was a strong correlation between aspiration frequency and the development of pneumonia [43]. The percentage of pepsin-positive tracheal secretions was twice as high for patients with pneumonia as those without. Patients who developed pneumonia had significantly increased length of stays and required longer ventilator support. The higher the patient was sitting, the less they aspirated but patients were most often only elevated 30 degrees. Patients who had GCS scores less than 9 were at high risk for repeated aspirations and patients who were paralyzed had a higher risk of aspiration. Finally, a postpyloric feeding site did seem to be associated with fewer aspiration events [43]. However, a recent meta-analysis did not find that gastric feeding was associated with an increased incidence of aspiration or pneumonia [44]. Metheny's study confirmed that the rate of aspiration was the same in patients with feeding tubes placed in their nares as the rate in patients who had gastrostomy tubes.

6. **Subglottic secretion drainage**- There are 5 studies with a limited number of patients that suggest a special endotracheal tube with subglottic suctioning decreases pneumonia. Experts in the field suggest that the tracheal damage associated with the continuous suctioning may lead to other problems [personal communication, J. Chastre]. A new endotracheal tube with a different cuff and

suctioning system is now being investigated and may be more helpful in decreasing aspiration [45].

7. **Oral hygiene-** The use of antiseptic mouthwashes and weekly plaque removal has been associated with reduced rates of aspiration pneumonia [46]. Furthermore, the application of chlorhexidine in a gel or as a mouthwash has been shown to decrease VAP significantly in ICU and in perioperative patients [47–50]. A recent meta-analysis also suggests chlorhexidine is successful in preventing VAP [51]. These studies have not shown which bacterial organisms are being killed or decreased by the antiseptic or whether it is the quantity of oral flora is being decreased by the treatment [49–50]. To establish the changes in oral flora would require molecular tools for proper assessment.

SUMMARY

The endotracheal tube is a conduit from the mouth to the airways of the lungs for oral secretions and for the bacteria in these secretions. These bacteria include oral flora, gastrointestinal flora that have been aspirated into the mouth and fungi This community of microbes may injure the lungs of intubated patients depending on the immunity of the patient, the integrity of the lungs, the quantity and members of the microbial community and the ability of the host defense mechanisms to prevent proliferation and dissemination of the bacteria. The community of microbes changes when antibiotics are given to these patients; selection of highly resistant bacteria can occur in these bacterial communities, which then leads to lung injury and death.

Prevention of bacterial-induced lung injury, or VAP, is achieved by removing the endotracheal tube, by decreasing the quantity of pathogens in the oral secretions with antiseptics [ie:chlorhexidine] and perhaps by early recognition of increasing bacterial quantities[surveillance cultures] and/or by following biomarkers that reflect the state of host defense [ie:CRP and/or PAI-1]. Ultimately, molecular identification of bacteria may allow rapid diagnosis of lung infections in these patients, and the distinction of pathogenic and more benign communities of microbes in the oropharynx and in the lungs of intubated patients.

PRACTICE POINTS

- Removing endotracheal tubes as quickly as possible is essential for improving patient outcomes
- Using strict sedation protocols and combining them with spontaneous breathing trials improves the rate of extubation
- Oral hygiene with chlorhexidine appears to be a successful and a low cost technique for preventing VAP
- Stopping antibiotics when culture data is negative is as important as initiating proper antibiotics when infection is a concern

FUTURE RESEARCH AGENDA

- Evaluate the changes in oral and lung microbial communities using molecular tools in patients with and without VAP
- Evaluate multiple biomarkers in patients with and without VAP—using biomarkers to initiate and terminate antibiotic treatment

- Compare new diagnostic guidelines utilizing molecular tools and biomarkers compared to clinical symptoms and signs in terms of patient outcomes
- Compare single and combined prevention strategies, including subglottic suction, and chlorhexidine, in terms of improvement in decreasing the incidence of VAP

REFERENCES

*** Most important**

1. Johanson WG, Pierce AK, Sanford JP, et al. Nosocomial respiratory infections with Gram-negative bacilli: the significance of colonization of the respiratory tract. Ann Intern Med. 1972; 77:701–706. [PubMed: 5081492]
2. Sottile FD, Marrie TJ, Prough DS, et al. Nosomical pulmonary infection: possible aetiologic significance of bacterial adhesion to the endotracheal tube. Crit Care Med. 1986; 14:265–270. [PubMed: 3956213]
3. Feldman C, Kassel M, Cantrell J, et al. The presence and sequence of endotracheal tube colonization in patients undergoing mechanical ventilation. Eur Respir J. 1999; 13:546–551. [PubMed: 10232424]
4. Bahrani-Mougeot FK, Paster BJ, Coleman S, et al. Molecular analysis of oral and respiratory bacterial species associated with ventilator-associated pneumonia. Journal of Clinical Microbiology. 2007; 45:1588–1593. [PubMed: 17301280]
5. Flanagan J, Li W, Lynch SV, et al. Changes in bacterial diversity in intubated patients colonized with *P. aeruginosa*. Journal of Clinical Microbiology. 2007; 45:1954–1962. [PubMed: 17409203]
6. Fabregas N, Ewig S, Torres A, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. Thorax. 1999; 54:867–873. [PubMed: 10491448]
7. Flanders SA, et al. Nosocomial pneumonia: State of the Science. Am J Infect Control. 2006; 34:84–93. [PubMed: 16490612]
8. Guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005; 171:388–416. [PubMed: 15699079]
9. Jackson WL, et al. Update in ventilator-associated pneumonia. Curr Opin Anaesthesiol. 2006; 19:117–121. [PubMed: 16552216]
10. Ibrahim EH, et al. A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting. Chest. 2000; 117:1434–1442. [PubMed: 10807834]
11. Cavalcanti M, et al. Risk and prognostic factors of ventilator-associated pneumonia in trauma patients. Crit Care Med. 2006; 34:1067. [PubMed: 16484918]
12. Stephan F, et al. Ventilator-associated pneumonia leading to acute lung injury after trauma: importance of *Haemophilus influenzae*. Anesthesiology. 2006; 104:235–241. [PubMed: 16436840]
13. Jacobs R, et al. Endotracheal tubes; the conduit for oral and nasal microbial communities to the lungs. Anesthesiology. 2006; 104:224–225. [PubMed: 16436838]
14. Mayhall CG. Ventilator-associated pneumonia or not? Contemporary Diagnosis. Emerging Infectious Diseases. 2001; 7:200–204. [PubMed: 11294706]
15. Jourdain B, et al. Role of quantitative cultures of endotracheal aspirates in the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med. 1995; 152:241–246. [PubMed: 7599831]
16. Chastre J, et al. Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. Am Rev Respir Dis. 1984; 130:924–929. [PubMed: 6497170]
17. Chastre J, et al. Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med. 1995; 152:231–240. [PubMed: 7599829]
18. Fagon JY, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia: a randomized trial. Ann Intern Med. 2000; 132:621–630. [PubMed: 10766680]

19. Kollef MH, et al. Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated pneumonia and negative quantitative BAL culture results. Chest. 2005; 128:2706–2713. [PubMed: 16236946]
20. Shorr AF, et al. Invasive approaches to the diagnosis of ventilator-associated pneumonia; a meta analysis. Crit Care Med. 2005; 33:46–53. [PubMed: 15644647]
21. Croce MA, et al. The futility of the clinical pulmonary infection score in trauma patients. J Trauma. 2006; 60:523–528. [PubMed: 16531849]
22. Azoulay E, Mokart D, Rabbat A, et al. Diagnostic bronchoscopy in hematology and oncology patients with acute respiratory failure: prospective multicenter data. Crit Care Med. 2008; 36:100–107. [PubMed: 18090351]
23. Bregeon F, et al. Diagnostic accuracy of protected catheter sampling in ventilator-associated bacterial pneumonia. Eur Respir J. 2000; 16:969–975. [PubMed: 11153601]
24. Baram D. Stable patients receiving prolonged mechanical ventilation have a high alveolar burden of bacteria. Chest. 2005; 127:1353–1357. [PubMed: 15821215]
25. Gibot S, et al. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Eng J Med. 2004; 350:451–458.
26. Determann RM, et al. Serial changes in soluble triggering receptor expressed on myeloid cells in the lung during development of ventilator-associated pneumonia. Intensive Care Med. 2005; 31:1495–1500. [PubMed: 16195904]
27. Choi G, et al. Disturbed alveolar fibrin turnover during pneumonia is restricted to the site of infection. Eur Respir J. 2004; 24:786–789. [PubMed: 15516673]
28. Schultz MJ, et al. Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia-a review. Crit Care Med. 2006; 34:871–877. [PubMed: 16521285]
29. Prabhakaran P, et al. Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid are associated with mortality in acute lung injury. Am J Physiol Lung Cell Mol Physiol. 2003; 285:L20–L28. [PubMed: 12730079]
30. Lisboa T, Seligman R, Diaz E, et al. C-reactive protein correlates with bacterial load and appropriate antibiotic therapy in suspected ventilator-associated pneumonia. Crit Care Med. 2008; 36:166–171. [PubMed: 18007271]
31. Chastre J, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA. 2003; 290:2588–2598. [PubMed: 14625336]
32. Aarts M-AW, Hancock JN, Heyland D, et al. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. Crit Care Med. 2008; 36:108–117. [PubMed: 18007262]
33. Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med. 2000; 162:505–511. [PubMed: 10934078]
34. Combes A, Luyt C-E, Fagon J-Y, et al. Early predictors for infection recurrence and death in patients with ventilator-associated pneumonia. Crit Care Med. 2007; 35:146–154. [PubMed: 17080004]
35. Carson SS, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med. 2006; 34 EPUB ahead of Print].
36. Girou E, et al. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA. 2000; 284:2361–2367. [PubMed: 11066187]
37. Doebbeling BN, et al. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. N Engl J Med. 1992; 327:88–93. [PubMed: 1285746]
38. Depuydt PO, et al. Antimicrobial resistance in nosocomial bloodstream infection associated with pneumonia and the value of systematic surveillance cultures in an adult intensive care unit. Crit Care Med. 2006; 34:653–659. [PubMed: 16505649]
39. Delclaux C, et al. Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 1997; 156:1092–1098. [PubMed: 9351607]

40. Hayon J, et al. Role of serial routine microbiologic culture results in the initial management of ventilator-associated pneumonia. Am J Respir Crit Care Med. 2002; 165:41–46. [PubMed: 11779728]
41. Bouza E, et al. Ventilator-associated pneumonia after heart surgery: a prospective analysis and the value of surveillance. Crit Care Med. 2003; 31:1964–1970. [PubMed: 12847390]
42. Bouza E, et al. The challenge of anticipating catheter tip colonization in major heart surgery patients in the intensive care unit: Are surface cultures useful. Crit Care Med. 2005; 33:1953–1960. [PubMed: 16148465]
43. Metheny NA, et al. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes and risk factors. Crit Care Med. 2006; 34:1007–1015. [PubMed: 16484901]
44. Marik PE, et al. Gastric versus post-pyloric feeding: a systematic review. Crit Care [London]. 2003; 7:R46–R51.
45. Young PJ, et al. A low-volume, low pressure tracheal tube cuff reduces pulmonary aspiration. Crit Care Med. 2006; 34:632–639. [PubMed: 16505646]
46. Terpenning M. Geriatric oral health and pneumonia risk. Clin Infect Dis. 2005; 40:1807–1810. [PubMed: 15909270]
47. Sequin P, et al. Effect of oropharyngeal decontamination by povidone-iodine on ventilator-associated pneumonia in patients with head trauma. Crit Care Med. 2006:34. Epub ahead of print.
48. Mori H, et al. Oral care reduces incidence of ventilator-associated pneumonia in ICU populations. Intensive Care Med. 2006; 32:230–236. [PubMed: 16435104]
49. Koeman M, van der Ven AJAM, Hak E, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med. 2006; 173:1348–1355. [PubMed: 16603609]
50. Segers P, Speekenbrink RGH, Ubbink DT, et al. Prevention of Nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate-a randomized controlled trial. JAMA. 2006; 296:2460–2246. [PubMed: 17119142]
51. Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-associated pneujmonia: a meta-analysis. Crit Care Med. 2007; 35:595–602. [PubMed: 17205028]

Other References of Interest

1. Klompas M. Does this patient have ventilator-associated pneumonia. JAMA. 2007; 297:1583–1593. 23. [PubMed: 17426278]
2. Brun-Buisson C. Prevention ventilator associated pneumonia; oral antiseptic agents should be part of a multifaceted preventive care package. BMJ. 2007; 334:861–862. [PubMed: 17463422]
3. Chan EY, Ruest A, Meade MO, Cook DJ. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. BMJ. 2007; 334:889–884. [PubMed: 17387118]
4. Minei JP, Nathens AB, West M, Harbrecht BG, Moore EE, Shapiro MB, Bankey PE, Johnson JL, Freeman B, McKinley BA, Moore FA, Maier RV. Guidelines for Prevention, Diagnosis and Treatment of Ventilator-associated pneumonia[VAP] in the trauma patient. J Trauma. 2006; 60:1106–1113. [PubMed: 16688078]
5. Canadian Critical Care Trials Group: A randomized trial of diagnostic techniques for ventilaot-associated pneumonia. N Engl J Med. 2006; 355:2619–2630. [PubMed: 17182987]
6. Fagon J-Y, Chastre J, Rouby J-J. Is bronchoalveolar lavage with quantitative cultures a useful tool for diagnosing ventilator-associated pneumonia? Critical Care. 2007; 11:123. [PubMed: 17442098]

Acknowledgments

I wish to acknowledge the funding from the NIH from grants: HL74005; HL6909, UO1 AI1075410