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VAT vs VAP

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to the ICU?[1] These patients need to be further characterized. The lessons learned from the full characterization of interstitial lung disease (ILD)[6] should spur us to fully characterize the population described by Quartin et al.[1] Once ILD was characterized, it was realized that ILD consisted of different diseases that present clinically and on CXRs in a similar way.[6] It was found that patients with each of the diseases in the ILD spectrum respond differently to different drugs, and some do not respond at all.[6] This makes it easier and more efficient to manage ILD. This group of ALI/ARDS patients described by Quartin et al[1] should be worked up fully, including an echocardiogram to exclude heart disease.

In summary, we believe the following: first, the consensus conference definition of ALI/ARDS is now inadequate and needs revision; second, not all ALI/ARDS patients should be treated in the ICU; third, basic clinical acumen is still an important tool in medicine; and fourth, this group of ALI/ARDS patients described by Quartin et al[1] should be further characterized, as discussed above.

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VAT vs VAP

Are We Heading Toward Clarity or Confusion?

The Centers for Medicare and Medicaid Services have recently stopped reimbursing hospitals for several preventable complications including nosocomial infections such as vascular catheter-related bloodstream infections and catheter-associated urinary tract infections. The proposal that reimbursement for ventilator-associated pneumonia (VAP) would be one of the next "preventable complications" added to the list for nonreimbursement was met with disapproval by many intensivists and hospital administrators as there is often some degree of uncertainty in making the diagnosis and because VAP is likely not entirely preventable. However, this disagreement has refocused interest in strategies for preventing VAP and decreasing associated morbidity, mortality, and health-care costs.

Two recent randomized, placebo-controlled trials[1,2] have been published suggesting that early antimicrobial treatment of the condition known as *ventilator-associated tracheobronchitis* (VAT) can decrease the number of subsequent diagnoses of VAP, improve the duration of mechanical ventilation, and even reduce mortality. In this issue of *CHEST* (see page 521), Dr. Craven and colleagues[3] review the limited data currently available pertaining to VAT and advocate initiating targeted antibiotic therapy based on serial surveillance cultures of endotracheal tube aspirates when quantitative culture results reveal concentrations of a pathogenic organism $\geq 10^5$ to 10^6 cfu/mL. This management paradigm is based on the hypothesis that VAT represents a distinct entity on a continuum between lower respiratory tract colonization with potentially pathogenic microorganisms and VAP. It is theorized that antibiotic treatment of VAT could halt the transformation of VAT into VAP. The benefits of this strategy might include not only a lower incidence of VAP but also reduced overall antibiotic usage as VAT might be successfully treated with short courses of antibiotics or simply with aerosolized antibiotics.

Several epidemiologic studies[4–7] have confirmed that VAT as defined by Craven et al[3] is relatively common in ICU patients receiving mechanical ventilation, with an incidence likely ranging between approximately 3% and 10%. Adverse outcomes such as increased length of ICU stay and increased duration of mechanical ventilation in patients meeting the criteria for the diagnosis of VAT have also been repeatedly demonstrated.[4,5,7] However, the majority of these data have been obtained in a single center,

and their confirmation in larger, multicenter data sets is needed. The impact of meeting the criteria for the diagnosis of VAT on mortality has not been conclusively established, but most studies[4,5,7] have not demonstrated increased mortality. Thus far, only one study[6] has demonstrated increased mortality in patients in whom VAT has been diagnosed. However, this finding may be invalid as only a small number of patients with VAT were analyzed in the study,[6] and patients in whom VAP subsequently developed were not excluded from the VAT group.

The difficulty of correctly diagnosing VAP has been well documented. Not only are many different sets of diagnostic criteria available for use, but many of the clinical signs of VAP are not specific to the diagnosis.[8] How to correctly define VAT is an even murkier issue. A "gold standard" for diagnosing VAT does not exist, and there is no evidence-based definition. The most common diagnostic criteria noted in the literature are the presence of fever without another recognizable cause, new or increased endotracheal tube secretions, a positive culture of the tracheal tube aspirate, and lack of a new or progressive infiltrate seen on a chest radiograph.[2,4–6] However, one of the recent studies[2] that supports antibiotic therapy for VAT defined the condition simply as the production of ≥ 2 mL of sputum with positive Gram stain results in the absence of VAP. It is not known whether quantitative culture adds to the specificity of diagnosing VAT and what threshold of bacterial growth should be used. Portable chest radiographs have been shown to be insensitive in identifying pneumonia in mechanically ventilated patients.[9] It is possible that a significant number of VAT cases actually represent VAP with the "new or progressive infiltrate" not visible on poor-quality portable chest radiographs. Studies evaluating VAT cases with more sensitive imaging modalities such as chest CT scans have not been performed. The quantification of new or increased tracheal secretions is primarily a subjective matter. Nursing reports[10] of endotracheal tube secretions and actual measurements of secretion volume are known to correlate poorly. Patients with a tracheostomy undergoing prolonged mechanical ventilation have increased sputum volume, increased concentrations of markers of inflammation present in tracheal secretions, and high levels of bacteria both in the upper and lower respiratory tract, even in the absence of identifiable infection.[10,11] The applicability of VAT to this patient population is unknown. Several biomarkers such as procalcitonin, C-reactive protein, and soluble triggering receptor expressed on myeloid cells (sTREM) have shown promise for diagnosing VAP, but their role in the diagnosis of VAT is not known.[12]

There are very few new antibiotic drugs under development for the treatment of the multi-drug-resistant, Gram-negative organisms that often colonize endotracheal tubes and cause VAP.[13] Accepting VAT as a true clinical entity requiring treatment will likely increase antibiotic utilization in the ICU. An increase in antibiotic utilization might lead to worsening problems with antibiotic resistance as well as other complications such as *Clostridium difficile* infection. For example, several studies[14,15] have shown increased rates of drug resistance when the strategy of selective digestive decontamination to prevent VAP has been used. Dennesen et al[16] have shown that the treatment of VAP with appropriate antibiotics (based on *in vitro* susceptibility testing) fails to clear endotracheal colonization with organisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and Enterobacteriaceae. Additionally, treatment of VAP beyond 7 days was associated with endotracheal colonization with antibiotic-resistant organisms.[16] What then should the end point of VAT treatment be? Are multiple rounds of therapy to be used if endotracheal secretions persist and flora change?

In addition to questions relating to the criteria used to diagnose VAT and concerns about the effect of treating VAT on antibiotic usage, the presumed pathogenetic link between VAT and VAP is unproven. Craven et al[3] contend that VAT is a precursor for VAP much like cystitis may be a precursor for pyelonephritis, and propose that surveillance cultures of endotracheal aspirates should be monitored periodically and therapy initiated when quantitative culture results reach a certain level of positivity in the setting of signs of systemic infection.[1] However, this practice may be questioned as the causative organism for VAP is often different from the organisms previously cultured from endotracheal tube aspirates.[6,17]

Both VAP and pyelonephritis share pathophysiologic mechanisms. Both often involve the introduction of foreign bodies (*eg*, Foley catheter and endotracheal tubes) that can become colonized with pathogenic organisms. Additionally, biofilms appear to play an important role in the development of both infections.[18,19] However, both pyelonephritis and VAP commonly occur without preceding cystitis or VAT being clinically recognized. This suggests that cystitis and VAT are clinically silent in many patients or that VAP and pyelonephritis can occur without these antecedent events. For VAP, there is some evidence to support the direct development of pneumonia without preceding VAT. Certain pathogens such as viruses, Legionella species, and mycobacteria can cause pneumonia by direct inoculation of contaminated aerosols or water droplets. Aerosols are known to form in ventilator circuits and represent a

direct method for lung inoculation with pathogenic bacteria.[20,21] Additionally, contaminated secretions or liquids (*eg*, ventilator circuit condensate, subglottic secretions above endotracheal tube cuffs, upper airway secretions, and gastric contents) can be directly aspirated into the lung, resulting in pneumonia. Similarly, biofilm from devices like endotracheal tubes can be directly delivered into the lung with mechanical breaths resulting in infection.

The lack of available studies limits our ability to make robust recommendations regarding the management of VAT. Additional investigations are required to address several important issues. First, the definition of VAT, as well as the validation of VAT as a distinct entity from VAP, require careful examination in multiple centers. This is required to avoid further antimicrobial empiricism given the widespread emergence of multi-drug-resistant bacteria. Second, careful analyses need to be performed to determine whether VAT is a precursor of VAP. The implications of this are straightforward. If VAT is a necessary precursor for VAP, then early intervention could reduce the occurrence of this important nosocomial infection. Finally, if VAT is an important clinical entity, what is the best therapeutic intervention? Broader use of antibiotics runs the risk of increasing bacterial resistance in critically ill patients. Alternative approaches should be considered. One approach that may be practical is the use of a newly developed endotracheal tube with a silver coating.[22,23] This device has been shown to prevent biofilm formation and to reduce airway colonization in the tracheobronchial tree.[24–26] The time-limited application of aerosolized antibiotics may represent another alternative.[2]

Educational interventions that encourage compliance with bundled initiatives based on evidence-based practices (*eg*, routine hand hygiene, continuous aspiration of subglottic secretions, and semirecumbent positioning of patients) can significantly reduce the rate of VAP and currently represent the best strategy for reducing the morbidity, mortality, and significant health-care costs associated with this nosocomial infection.[27] To date, only one study[1] evaluating a small number of patients (n = 22 in the treatment arm) has been published to support the concept of treating VAT with systemic antibiotics. More data must be collected before the practice of routine treatment of VAT with antibiotics can be recommended.

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Adipokines and Asthma

Obesity is a risk factor for the development of asthma. The United States and much of the world are experiencing an unprecedented epidemic of obesity, and so it is estimated that obesity may be responsible for 250,000 new cases of asthma per year in the United States.[1] Not only is obesity a risk factor for asthma, but asthma in the obese has distinct features compared to disease in the nonobese. Obese asthmatics tend to have more severe disease,[2,3] respond less well to standard controller therapy,[4] and have evidence of cellular glucocorticoid resistance,[5] this despite the fact they do not appear to have worsened airway inflammation as measured by either sputum eosinophils or neutrophils.[6] Asthma in the obese represents a growing epidemic of pulmonary disease, and these patients are distinct from nonobese asthmatics. Accordingly, studies on the pathogenesis of asthma in the obese are critical to guide our understanding of this disease process; such studies will ultimately guide the development of new therapies to treat the obese asthmatic population.

Mechanical factors are certainly involved in the pathogenesis of this disease. The obese breathe at low lung volumes, and breathing at low lung volumes increases bronchial hyperreactivity.[7] Salome et al[8] have also shown that the obese have increased dyspnea from bronchoconstriction related to increased elastic load, which could contribute to symptoms in the obese. Mechanical factors are likely to be very important in the pathogenesis and clinical presentation of asthma in the obese. However, asthma in the obese is not simply a mechanical phenomenon. Shore[9] showed that obese mice have increased airway hyperreactivity (independent of lung volume), and also increased airway hyperreactivity and inflammation in response to ozone. Obese people have similar enhanced responses to ozone.[10] There appear to be nonmechanical factors that contribute to asthma in the obese; these other factors include mediators produced by adipose tissue.

Adipose tissue is not simply a passive storage organ but is a complex metabolically active tissue, with important endocrine and immune functions.[11] Adipose tissue produces a number of mediators, termed *adipokines*, which have significant metabolic effects. One of these adipokines, adiponectin, is actually decreased in the obese. Adiponectin has antiinflammatory properties: low adiponectin levels have been associated with accelerated atherosclerosis and increased metabolic stress.[12] Low adiponectin levels have also been associated with asthma in population studies.[13,14] The relevance of adiponectin to asthma may not be immediately obvious, but Shore et al[15] have shown that adiponectin infusion can decrease airway hyperreactivity in a mouse model of allergic asthma. Not only that, but allergen challenge decreases adiponectin levels in adipose tissue and serum[15]; therefore, in mice, low adiponectin may both contribute to and be a result of allergic asthma. This has not previously been studied in humans but is an important issue. If low adiponectin levels are the result of allergic asthma, this represents an interesting link between the lung and adipose tissue; but if low adiponectin levels could be involved in the pathogenesis of asthma, this suggests potential opportunity for intervention in obese asthmatics.

Sood et al[16] performed a meticulous translational study, reported in this issue of *CHEST* (see page 287), in which the investigators performed a specific antigen challenge in a group of allergic asthmatics; serum adiponectin was measured in the 24 h following this challenge. They were unable to find any decrease in serum adiponectin over this 24-h period, although, overall, asthmatics did have lower adiponectin levels than nonasthmatics. This suggests that lower adiponectin levels in asthmatics are likely not the result of asthma, at least acutely, but leave