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Ventilator associated pneumonia: perspectives on the burden of illness

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Abstract *Objective*: The objective of this narrative review is to summarize selected current concepts and clinical evidence regarding the burden of illness of VAP, including its epidemiology, diagnosis, attributable mortality and risk factors.
Data Sources & Selection: Studies were identified through MEDLINE, EMBASE, bibliographies of primary and review articles and personal files.
Results: While cross sectional studies inform us about VAP prevalence, longitudinal studies inform us of the cumulative risk and conditional risk of developing VAP. Reported VAP rates are modulated by factors related to case mix, causative microorganisms, interventions that influence risk over time, and VAP definitions employed. Population-specific and organism-specific VAP rates are needed to avoid misleading benchmarking between different ICUs, and to minimize inappropriate between-study comparisons. Observational studies have shown that invasive sampling techniques versus non-invasive approaches to diagnose VAP facilitates more targeted antibiotic treatment; however, the influence of the diagnostic method on endpoints such as mortality is less clear. VAP is associated with approximately a 4 day increase in length of ICU stay and an attributable mortality of approximately 20–30 %. Fixed VAP risk factors include underlying cardiorespiratory disease, neurologic injury and trauma. Modifiable VAP risk factors include supine body position, witnessed aspiration, paralytic agents and antibiotic exposure. If modifiable risk factors tested in randomized trials lower VAP rates, such as semirecumbency versus supine positioning, these represent effective VAP prevention strategies.
Conclusions: Ventilator-associated pneumonia is a major morbid outcome among critically ill patients. Studies evaluating more effective prevention and treatment strategies are needed.

Key words Ventilator-associated pneumonia · Epidemiology · Diagnosis · Mortality · Length of stay · Risk factors · Prevention

Introduction

Nosocomial pneumonia represents the leading cause of death from hospital-acquired infections among patients requiring admission to the intensive care unit (ICU) [1]. Ventilator-associated pneumonia (VAP) typically refers to nosocomial pneumonia developing more than 48 hours following endotracheal intubation and mechanical ventilation. As a common and serious ICU complication, VAP has been the focus of research programs from dozens of investigative teams internationally.

The breadth, depth and quality of research on the burden of illness associated with VAP is prominent in the intensive care literature. This narrative review will discuss selected concepts and clinical evidence on this topic, including the epidemiology, diagnosis, attributable mortality, and risk factors in immunocompetent adults. Further details of the studies described herein are found in the original publications. Reports focused primarily on the microbiologic features of VAP, prevention, treatment and complications are found elsewhere.

Epidemiology of VAP

a) Prevalence, cumulative and conditional risk

The EPIC study, the largest ICU prevalence study conducted to date, revealed that VAP caused almost half of ICU infections in Europe [1]. Other studies indicate that VAP accounted for over 50% of infections in mechanically ventilated patients [2, 3].

In a multicenter study of the Canadian Critical Care Trials Group [4], we found 177/1,014 (17.5%) of patients developed VAP, 9.0 ± 5.9 days after ICU admission (median 7 days, interquartile range 5, 10 days). The risk of developing VAP increased cumulatively, with an overall rate of 14.8 cases per 1000 ventilator-days. However, the hazard rate decreased over time; VAP rates were approximately 3% per day in the first week of ventilation, 2% per day in the second week and 1% per day in the third week and thereafter. This decreasing hazard reflects the high risk of early VAP [5, 6], and suggests that long-term survivors are patients at lower intrinsic risk of developing VAP. Early-onset VAP may account for as many as 50% of cases of VAP.

b) Microbial and antimicrobial influences

The European EPIC study [1] and other rigorous surveillance initiatives in the United States such as the National Nosocomial Infection Surveillance System [7] have confirmed the high prevalence of VAP pathogens such as *Pseudomonas* species and *Methicillan-resistant Staphylococcus aureus* in Europe and North America. However, most etiologic organisms responsible for early-onset VAP represent common respiratory tract pathogens or normal oropharyngeal flora, possibly introduced at the time of intubation, or before or shortly after ICU admission. It is late-onset VAP which has a microbial etiology that includes aerobic gram negative bacilli (e.g., *Pseudomonas, Acinetobacter*) and *Staphylococcus aureus* species. Data on rates of VAP due to specific organisms help our evolving understanding of the epidemiology of VAP. One recent study reported a VAP rate of 13%; 27% of these episodes were attributable to *Pseudomonas aeruginosa* [8]; another reported a VAP rate of 21%, and 8% of these episodes were due to *Acinetobacter baumannii* [9].

Studies conducted in the last decade have convincingly demonstrated that the microbial etiology of VAP is profoundly influenced by 2 other factors: prior antimicrobial therapy and the duration of mechanical ventilation. In a cohort of 129 consecutive episodes of VAP [10], gram positive cocci and *Haemophilus influenza* were significantly less likely among patients who had received prior antibiotics, whereas *Pseudomonas aeruginosa* was significantly more likely to be the infecting agent among patients who had received prior antibiotics. In addition to different species being involved in early versus late-onset VAP, organisms recovered from patients with late-onset VAP are more likely to be resistant to "first line" antibiotics. Trouillet and colleagues [11] analyzed independent risk factors associated with potentially drug resistant organisms (e.g., *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia, Acinetobacter baumannii* and *Staphylococcus aureus*) in 135 consecutive patients with VAP, and found 3 predictors: duration of mechanical ventilation greater than 7 days (odds ratio 6), prior antibiotic use (odds ratio 14), and prior use of broad spectrum antibiotics such as third generation cephalosporins, fluoroquinolone or imipenem (odds ratio 4). In a subsequent series of patients with and without ARDS, 90% of VAP episodes due to potentially resistant organisms occurred after 7 days of mechanical ventilation in patients with ARDS [12].

c) VAP epidemiology: a more clinical framework

In summary, although cross sectional studies inform us about the prevalence of VAP, it is only longitudinal studies that inform us about either the cumulative risk or the conditional risk (e.g., hazard) of developing VAP. Reported VAP rates vary widely, dependent upon 4 main factors related to the population (e.g., illness severity and case mix), the causative organism (e.g., oropharyngeal flora, aerobic gram negative bacilli), interventions that modulate risk over time in the ICU (e.g., antibiotic exposure and various VAP preventive strategies), and the methods used to diagnose VAP (e.g., approaches to surveillance and the definition employed).

Thus, although estimates of the overall prevalence of VAP can be informative, there are a range of population-specific VAP prevalence estimates which can be defined according to case mix, and also a range of organism-specific VAP prevalence estimates. Awareness of data describing rates of VAP framed using this kind of typology is necessary to avoid misleading inferences about benchmarking the VAP rate in one ICU with another ICU, and to avoid drawing illusionary inferences

about between-study comparisons of the burden of illness when reading the intensive care literature. Clearly, antibiotic resistance rates will vary in different settings for myriad reasons, including the rigour of microbiologic surveillance methods employed. Sophisticated typing of micro-organisms based on techniques such as chromosomal fingerprinting as reported by Rello and colleagues show great promise in taking future epidemiologic studies to a higher level of certitude than previously possible [13].

Meanwhile, at a minimum, awareness of both published and local evidence on microbiology and resistance patterns may provide a useful framework for empiric patient-specific and population-specific antibiotic treatment regimens.

Diagnosis of VAP: the challenge that won't go away

It is difficult to identify an article about VAP which does not acknowledge the challenge of diagnosis. It is well accepted that the non-specific nature of pulmonary infiltrates on chest radiograph, and other clinical and laboratory criteria (e.g., fever, leukocytosis, purulent endotracheal secretions, and isolation of a pathogen) renders VAP fraught with measurement error. Moreover, alternative diagnoses can often be found when carefully investigated [14]. To try to distinguish between organisms causing VAP and organisms that are colonizing the lower respiratory tract, improved accuracy over endotracheal aspirates and qualitative cultures has been sought using invasive techniques and/or quantitative cultures. Invasive sampling techniques include the protected (double-sheathed) specimen brush (PSB), the protected (single-sheathed) catheter, protected mini-bronchoalveolar lavage and standard bronchoalveolar lavage (BAL) (via bronchoscopy or blinded).

Many studies have examined the sensitivity, specificity and accuracy of these different techniques. Studies of diagnostic tests are most useful when the population under study is representative of those to whom we would like to apply the results, when an independent, blind comparison is made of the test results with a reference standard, and when the reference standard is performed on all patients. In this field, however, some studies compare an invasive approach to a non-invasive approach, some compare 2 non-invasive approaches with each other, some compare 2 invasive approaches with each other, and some compare one approach with histologic evidence of VAP. Thus, the reference standard shifts across different studies, and it is certainly not a "gold standard". Even diagnosis based on open lung biopsy has been called into question lately, by studies such as one showing that the diagnosis of VAP based on histology varied from 18% to 38% among 4 different pathologists [15].

Additional key criteria supporting the value of a diagnostic test include establishing that it adds useful information beyond that which exists, that the test is available for use in practice, that it has acceptable risks and costs, and that it results in administration of beneficial treatment. Although PSB and BAL may increase diagnostic accuracy and are available and safe in many centers, what is known about the influence of this diagnostic information on caregiver behaviour? Empiric antibiotic therapy in patients suspected of having VAP is often inadequate in centers in which invasive testing is routine [16]. In a country in which invasive testing is not routine, among 90 patients with suspected VAP [17], we evaluated the effect PSB or BAL results on physician perception of the probability of VAP, physician confidence in that diagnosis, and changes in antibiotic prescribing. As compared with endotracheal aspirate culture results, after obtaining bronchoscopic results, physicians considered VAP significantly less likely, their confidence in the diagnosis of VAP and their comfort with their management plan was significantly increased, fewer antibiotics were administered, and significantly more antibiotics were discontinued.

Other comparative studies [18, 19, 20], regression analysis [21] and decision analysis [22] have linked invasive testing with more appropriate antibiotic treatment relative to non-invasive testing, although the impact of diagnostic approach on mortality has been inconsistent. A randomized trial in Spain examining PBS or BAL and quantitative endotracheal aspirates (24 patients) versus quantitative endotracheal aspirates alone (27 patients) [23] found that 42% of patients in the invasive group had antibiotic modification, versus 16% in the non-invasive group ($p < 0.05$); however, the mortality rates were not significantly different (46% versus 26%, respectively). In contrast, another randomized trial in France presented in abstract form at the American Thoracic Society showed not only lower antibiotic consumption but also a survival advantage in the invasive diagnosis group [24].

Many scholarly reports and debates in public and in print have highlighted our difficulty in identifying the "best" way to diagnose VAP [25, 26]. Without a reproducible reference standard, however, establishing the most accurate method is truly an elusive goal. Although the debate about which diagnostic techniques are best suited to which settings will be better informed by randomized trials examining the effect of different approaches on clinically important outcomes, as with many other aspects of medicine, clinical policies may not change swiftly based on randomized trial results. In reality, different diagnostic approaches to VAP are often suited to different clinical environments. Moreover, physician preferences, research interests, access to and costs of these tests, and environmental exigencies also exert pervasive influences on practice patterns.

While the diagnostic challenge of VAP will continue to stimulate researchers [27], another pragmatic way to manage this diagnostic uncertainty is to try to understand the influence of different VAP diagnostic criteria on clinical decision making, and when interpreting the literature. For example, we should be aware that we are likely to administer more (and perhaps broader spectrum) antibiotics to patients with VAP suspected only on clinical grounds. While this pragmatic approach may be the only feasible option in some settings, we should be cognizant of potential disadvantages such as antibiotic administration which could be inappropriate, excessive, harmful or costly. In some situations, the VAP diagnostic method may not influence clinical decision making. For example, stress ulcer prophylaxis with ranitidine is 50 % more effective at bleeding prevention than sucralfate, but is associated with a non-significant trend toward an increased risk of VAP, across 5 different VAP diagnostic criteria [28]. Thus, in mechanically ventilated patients at highest risk of ICU-acquired bleeding [29], effective bleeding prevention is conferred by histamine-2-receptor antagonist; concern about the potential risk of VAP means that effective VAP prevention strategies are also implemented in these patients.

Do major morbid outcomes matter? The case for VAP

While caring for patients in a multidisciplinary and culturally sensitive manner, ICU practitioners also seek to delay mortality, restore health, and optimize our patients' quality of life. Another of our many goals is the prevention of ICU-acquired complications. On what basis should we bother preventing major morbid outcomes such as VAP? Some might hold the view that VAP preventive efforts are not worthwhile if we have no proof that VAP increases mortality. Such a position ignores the direct and indirect costs of VAP treatment, including the growing literature on the adverse effects of antibiotic utilization worldwide. A broader view of burden of illness appreciates that the consequences of VAP are substantial, clinically and economically.

First, developing VAP increases the risk of mortality. Data supporting this statement derive from several types of studies, and understanding limitations of the inferences we can draw from these is useful. One line of evidence comes from large cohort studies that use multiple regression analysis in which the dependent variable is death or survival, and the independent variables are demographic (e. g., age, admission diagnosis), post-admission conditions (e. g., VAP, bacteremia) that might modify risk of death. Using the regression approach in almost 2,000 patients, Fagon and colleagues identified VAP as an independent risk factor for mortality [30]. This finding has been confirmed and extended by other investigators showing that late-onset VAP independently increases mortality risk [31], and that the risk of mortality associated with VAP is increased regardless of whether VAP is confirmed microbiologically by PSB or another sampling method [32]. The regression approach has the potential to mislead us since the power of the analysis is limited by the selection and exclusion of potential risk factors; in other words, if strong predictors of mortality such as ICU-acquired renal failure are not included in the model, others that are included may assume disproportionate predictive power.

A second way to evaluate the influence of VAP on mortality risk is to compare the risk of death among patients with and without VAP. This has been done in one study which suggested a significant increase in mortality among patients with VAP compared to those without [33]. This simple comparative method has very high potential to mislead us by inflating the risk of mortality in VAP patients, because other unmeasured prognostic factors are very likely to be unequally distributed across the 2 groups.

A third approach involves matching patients with and without VAP with respect to important prognostic factors, then determining the incremental mortality. While 2 studies have not shown even a trend toward an increased risk of mortality [34, 35], 3 studies have shown either a significant increase in mortality [36, 37] or a strong trend [38]. In the most recent study [38], we evaluated the attributable morbidity and mortality of VAP by matching 177 patients with VAP to patients who did not develop a clinical suspicion of VAP. We also performed sensitivity analyses to examine the effect of different populations, onset of pneumonia, diagnostic criteria, causative organisms, and adequacy of empiric treatment. Compared to matched patients who did not develop VAP, there was a significant increase in ICU length of stay of 4 days. There was also a trend towards an increase in risk of death (absolute risk increase, 5.8 %, 95 % CI –2.4 % to 14.0 %; relative risk increase of 32.3 %, 95 % CI –20.6 % to 85.1 %). Although the matched pair method may generate a more accurate estimate of the influence of VAP on risk of death than the unmatched method, the matching can inflate or attenuate the risk of death if patients are poorly matched or overmatched.

A fourth way to evaluate whether VAP confers an increased risk of mortality is through a randomized trial of prevention in which a strategy is tested for its ability to prevent VAP, controlling for other prognostic factors. To the extent that both VAP rates and mortality rates decrease with this preventive strategy, this greatly strengthens the inference that VAP has an attributable mortality. Challenges to using this approach to determine the attributable mortality of VAP include the need for large randomized trials and an extremely effective preventive strategy which successfully converge to generate sufficient power to detect differences in both

Table 1 Risk factors for ventilator associated pneumonia determined by multiple logistic regression

Factors Related To:	
Population	increased age
	cardiorespiratory disease
	chronic obstructive pulmonary disease
	adult respiratory distress syndrome
	coma
	neurosurgery
	head trauma, polytrauma
	burns
	organ system failure
Ventilator & Airway Management	mechanical ventilation
	intracuff pressure < 20 cm H_2O
	reintubation
	24 hour circuit changes
	tracheostomy
	failed subglottic aspiration
General ICU Management	enteral nutrition
	supine positioning
	aspiration
	histamine-2-receptor antagonists
	paralytic agents
	antibiotics
	transport out of the ICU

Legend For Table 1
These are the strongest independent risk factors for VAP determined in 9 cohort studies using logistic regression analysis (details in references 4, 7, 8 and 43–48)

VAP and mortality rates, if they truly exist. Obviously, there are many ICU-acquired events that modify the risk of death, so if an intervention causes both a lower VAP rate and a lower mortality rate in large randomized trials (particularly in blinded trials with similar cointerventions in both arms that might influence mortality), this provides quite compelling evidence that VAP is associated with an increased risk of mortality. We have evidence of such a circumstance illustrated by the meta-analysis by the SDD Trialists Collaborative Group [39] in which the risk of VAP was reduced (odds ratio 0.35, 95 % CI 0.29–0.41) and so was the risk of mortality (odds ratio 0.80, 95 % CO 0.69–0.93). More recently, Nathans and Marshall have documented this phenomenon by pooling studies primarily conducted in critically ill surgical rather than medical patients [40].

Thus, considering multiple different kinds of evidence [41], and acknowledging that it has not been universally documented, VAP likely prolongs the length of ICU stay by about 4 days, and is associated with a 20–30 % increased risk of death in critically ill patients.

Predictors of VAP: searching for modifiable risk factors

Risk factors for VAP offer prognostic information about the probability of developing VAP in individual patients and populations, help us to understand some of the mechanisms that may predispose to VAP, may lead to development of effective prophylaxis, and may allow risk stratification to target high risk patients for prevention strategies [42]. Many single center cohort studies have used univariate analyses to determine VAP risk factors. Several have used multivariable analysis to determine independent VAP predictors [43, 44, 45, 47, 47, 48]. The risk of VAP is higher among patients with neurologic conditions such as head injury or neurosurgery, chronic lung disease, ARDS, and as the duration of ventilation increases. Manipulation of the airway and/or ventilator circuit may also predispose to aspiration, as suggested by the following risk factors: reintubation, tracheostomy, frequent ventilator circuit changes, low intra-cuff pressure, and patient transport out of the ICU. Other risk factors relate to the gastrointestinal tract such as enteral nutrition, supine positioning, witnessed aspiration, and stress ulcer prophylaxis with gastric pH-altering agents (Table 1).

In the largest and most recent VAP risk factor study [4], independent predictors of VAP were an admitting diagnosis of cardiac disease, respiratory disease, central nervous system disease, burns, or trauma, in addition to mechanical ventilation, witnessed aspiration, and paralytic drugs; antibiotics conferred protection. Using a time-dependent analysis to accurately examine the temporal influence of antibiotics, we found that antibiotics were associated with lower VAP rates, consistent with randomized trials of selective digestive decontamination [39], but that the apparent protective effect of antibiotics attenuates after 2–3 weeks. Nevertheless, concern about latent emergence of antibiotic resistant organisms fuels the fear of prolonged antibiotic administration, both in the short term (for individual patients), and considering longer time horizons (for future ICU populations).

Some VAP risk factors may be amenable to simple modifications (e. g., supine positioning). Three randomized trials have shown that semirecumbancy, as compared with the supine position, is associated with lower rates of scintigraphically proven aspiration, which might be viewed as a surrogate VAP outcome [49, 50, 51]. One recent trial evaluated the influence semirecumbancy versus supine positioning on VAP and found lower rates of clinically suspected and microbiologically confirmed VAP in patients nursed in the semirecumbent position [52], suggesting that this is an easily implementable VAP prevention strategy. Several other modifiable VAP risk factors have been evaluated as possible prophylactic strategies in randomized trials summarized in

systematic reviews of ventilator circuit and secretion management [53] and nutritional approaches [54].

Summary

Ventilator associated pneumonia is among the most common of nosocomial infections. There are few ICU-acquired events with such a diverse and rich set of studies that inform us about the burden of this serious illness. Optimal VAP prevention and treatment regimens are important to consider in practice and to target for future investigations.

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