Ventilator-associated pneumonia: risk factors and patient mortality

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Among critically ill and mechanically ventilated patients, ventilator-associated pneumonia (VAP) is the most common nosocomial infection. Although VAP has a high mortality rate, it is unknown whether patients die from VAP or underlying illness. This article reviews the association between VAP and mortality, and discusses whether prevention of VAP will improve the outcome of mechanically ventilated patients.

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection among critically ill patients receiving mechanical ventilation. It is defined as inflammation of the lungs diagnosed after a period of artificial ventilation of at least 48 hours. The infection is usually caused by enteric Gram-negative bacteria, *Pseudomonas aeruginosa* or *Staphylococcus aureus*. These bacteria are frequently entitled potentially pathogenic microorganisms (PPMO). VAP has been associated with prolonged hospital stay, increased health-care costs and higher mortality rates. Therefore, prevention of this infection, with decreased morbidity and mortality as ultimate goals, remains important in intensive care medicine. In this article we review the current evidence about the association between the development of VAP and patient mortality, and speculate to what extent infection prevention may decrease intensive care unit (ICU) mortality.

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INCIDENCE OF VAP

Reported incidences of VAP vary widely because of the different diagnostic methods that have been used and the differences in patient populations that were studied. In a large surveillance study performed on a single day in 1992 in 1417 European ICUs, the point-prevalence of pneumonia was 46.9%, representing 39% of all ICU-acquired infections (Vincent et al, 1995). Others reported incidence rates of VAP have ranged from 7.8% to 85%.

DIAGNOSIS OF VAP

Conventionally, VAP is diagnosed using parameters such as fever, leucocytosis, purulent tracheal secretions, number of leucocytes and bacteria in Gram stain and a new or progressive infiltrate on chest X-ray. However, precise diagnosis of VAP is difficult in critically ill patients, who suffer from serious underlying disease and are frequently colonized with PPMO in the respiratory tract.

Reasons for elevated body temperature and leucocytosis or leucopenia are numerous and changes on chest X-ray may be the result of pulmonary oedema, pulmonary infarction or atelectasis. Kirtland and coworkers (1997) compared five clinical criteria (temperature, leucocytosis, sputum culture, chest X-ray and gas exchange) with absence or presence of histological pneumonia at autopsy. None of the five clinical criteria tested showed agreement with histological pneumonia. Torres and coworkers (1994) found that a combination of clinical parameters (leucocytosis, new and persistent pulmonary infiltrate and purulent secretions) had a specificity and sensitivity of 45% and 70% respectively, when compared to findings at autopsy.

Since the upper respiratory tract of ventilated patients is frequently colonized with PPMO, cultures of tracheal secretions may not distinguish between colonization or infection. As a result, many patients who do not have bacterial pneumonia will be treated unnecessarily with antibiotics, which may result in induction and selection of antibiotic-resistant microorganisms. In addition, for the individual patient, antibiotics will facilitate colonization with resistant microorganisms (such as *Ps. aeruginosa*, *Acinetobacter* species, *Stenothrophomonas malthophilia*, methicillin-resistant *Staph. aureus* and yeasts), thereby increasing the risk of serious superinfections. Furthermore, valuable time may be lost for elucidating the right cause of inflammation.

TABLE 1.
Diagnostic criteria of ventilator-associated pneumonia

			Memphis‡	
Criteria	Modified CDC*	CPIS†	Probable pneumonia	Definite pneumonia
New, progressive or persistent radiographical infiltrate	I	+	+	+
Temperature	II	+		
Leucocytosis or leucopenia	II	+		
Purulent sputum	II		+	+
Isolation of pathogenic bacteria from endotracheal aspirate	II	+		
Number of tracheal secretions		+		
Oxygenation (PaO_2/FiO_2)		+		
Radiographical pulmonary abscess and positive needle aspirate culture			+	
Open-lung biopsy or postmortem histological examination of lung tissue			+	+
Negative quantitative culture of lung parenchyma (>10^4)			+	
Positive quantitative culture of lung parenchyma (>10^4)				+
Positive quantitative culture of bronchoalveolar lavage or protected specimen brush			+	
Presence of positive blood culture			+	

*Modified CDC = Modified criteria of the Centers for Disease Control and Prevention (Centers for Disease Control, 1989; Cook et al, 1998a). Ventilator-associated pneumonia must meet criterium I and two or more of criteria II. † CPIS = Clinical Pulmonary Infection Score (Pugin et al, 1991). Score ranging from 0–12, obtained by awarding clinical criteria with 0–2 points depending on presence. Pneumonia is defined as a score > 7 points. ‡ Memphis criteria = Criteria of Memphis Consensus Conference (Pingleton et al, 1992).

In order to improve the specificity for diagnosing VAP, flexible fibreoptic brochoscopy has been used to obtain material from the lower respiratory tract, thereby avoiding contamination from the colonized upper respiratory tract. In this regard, protected specimen brush (PSB) and bronchoalveolar lavage (BAL) have been studied most extensively. In reports using histological and quantitative cultures of lung tissue as a 'gold standard', specificities of 45% to 100% and 42% to 95% have been reported for BAL and PSB respectively. Sensitivities ranged from 50% to 91% and 36% to 82% for BAL and PSB respectively (Rouby et al, 1992; Torres et al, 1994; Chastre et al, 1995; Marquette et al, 1995; Papazian et al, 1995). These differences could be due to the threshold used for PSB and BAL, prior antibiotic use, and patient selection.

Several combinations of diagnostic criteria have been formulated both for clinical practices and for research (*Table 1*). The criteria from the Centers for Disease Control (CDC) include clinical, microbiological and radiographical criteria (Centers for Disease Control, 1989). Pugin and coworkers introduced the Clinical Pulmonary Infection Score (CPIS), which also consists of the above mentioned criteria (Pugin et al, 1991). The Memphis criteria were formulated during a consensus conference in 1992, and include the results from BAL and PSB, added to the CDC criteria (Pingleton et al, 1992).

In a large study, all three sets of diagnostic criteria were used and the incidence of VAP decreased as its definition became more strict: being 22% with the CDC criteria, 20% with CPIS, and 9% with the criteria for probable pneumonia from the Memphis criteria (Cook et al, 1998a). Therefore, incidence rates of VAP must be interpreted carefully and attention must be paid to whether investigators just used clinical, microbiological and radiographical criteria or also included bronchoscopic techniques.

RISK FACTORS FOR DEVELOPING VAP

Risk factors associated with developing VAP have been determined in different settings and using different criteria for diagnosis (*Table 2*). The results of these studies may help to elucidate the pathogenesis of the infection and may direct preventive strategies. The risk factors that have been identified can be subdivided into two categories: those present on admission and which cannot be influenced, and those occurring during ICU stay and which may be prevented or modulated. Among the latter group, some risk factors have been identified repeatedly, whereas others have been identified only once.

Patients with chronic lung disease have an increased risk of developing VAP (Craven et al, 1986; Torres et al, 1990), with a relative risk (RR) as high as 18 in one study (Rello et al, 1994). This may be related to an increased risk of airway colonization by Gram negative microorganisms in these patients. Recently, Cook et al (1998b) reported additional underlying illnesses to be independently associated with the develop-

ment of VAP:cardiovascular disease (RR 2.7), thoracic or abdominal surgery (RR 2.7), gastrointestinal disease (RR 1.8), central nervous system disease (RR 3.4), trauma (RR 5) and burns (RR 5.1). The fact that the primary admitting diagnosis seems to influence the risk of developing VAP may be a reason for the large differences in incidences of VAP and mortality observed in studies with different patient populations.

Daily risks for VAP have been estimated to be 1% for each day of ventilation (Fagon et al, 1989), or even to increase daily by 3.3% for the first 5 days of ventilation, decreasing thereafter until 1.3% at day 15 (Cook et al, 1998b). This is in line with the general observation that patients are most likely to develop VAP within the first 10 days of artificial ventilation. Aspiration of oropharyngeal secretions contaminated with PPMO has been assumed to be important in the pathogenesis of VAP. Witnessed aspiration of large volumes of gastric contents has also been found to be an independent risk factor by several investigators (Torres et al, 1990; Baraibar et al, 1997; Cook et al, 1998b).

The use of muscle relaxants, which may facilitate aspiration by decreasing the cough reflex, has been identified as a risk factor for developing VAP in univariate and multivariate analyses (Cook et al, 1998b; Kollef, 1993). Aspiration may be diminished by a simple adaptation of the endotracheal tube. Oropharyngeal secretions can accumulate under the vocal cords and above the inflated cuff and may leak continuously into the lungs. Valles and coworkers demonstrated that continuous subglottic aspiration of this fluid level decreased the incidence of VAP and failure to establish adequate cuff pressure was a risk factor for VAP (Valles et al, 1995). Re-intubation has also been identified as a risk factor (Torres et al, 1990; Kollef, 1993), and routine endotracheal tube changings have therefore been advised against (Torres et al, 1990).

Enteral nutrition, the use of antacids and histamine-2 (H_2)-antagonists for stress ulcer prophylaxis, and gastric colonization were all identified as independent risk factors for VAP (Craven et al, 1986; Cook et al, 1998b), supporting an important role of the gastropulmonary route in its pathogenesis. Under physiological conditions, gastric acidity forms an effective barrier against bacterial growth, but alkalization of gastric fluid may facilitate bacterial colonization.

TABLE 2.
Risk factors for developing ventilator-associated pneumonia (VAP)

Risk factors concerning baseline characteristics of patients developing VAP	Duration of intubation	
	Severity of illness	
	History of chronic obstructive pulmonary disease	
	Primary diagnosis	Central nervous system disease
		Acute respiratory distress syndrome
		Trauma
		Burns
		Cardiovascular and respiratory disease
		Thoracic or abdominal surgery
		Age
Risk factors concerning possible prevention in developing VAP	Witnessed aspiration	
	Administration of a paralyzing agent	
	Re-intubation	
	Enteral nutrition	
	Antacids or H_2-antagonists	
	Previous antibiotic use	
Risk factors incidentally identified or needing further investigations	Transport out of intensive care unit	
	Presence of tracheostoma	
	Inadequate intracuff pressure	
	Administrations of aerosols	
	Male gender	
	Change in multiple organ dysfunction (MOD) score	

For years, stress ulcer prophylaxis has been used routinely in critically ill patients. Antacids and H_2-antagonists are assumed to reduce intragastric acidity, thereby decreasing the incidence of stress ulcers but facilitating gastric colonization. Sucralfate has been claimed to protect against stress ulcers without influencing intragastric acidity, and may even have bactericidal and bacteriostatic properties. As a result, sucralfate should, when compared to antacids and H_2-antagonists, prevent gastric colonization and reduce the incidence of VAP. However, the only two prospective randomized, double-blind studies (one including 1200 ventilated patients) failed to demonstrate significant differences in incidences of VAP when comparing sucralfate to ranitidine or antacids (Bonten et al, 1995; Cook et al, 1998a).

Interestingly, enteral nutrition has been associated with an increased risk for developing VAP (Kollef, 1993). Similar to stress ulcer prophylaxis, enteral nutrition may facilitate gastric colonization because of dilutional alkalization of gastric contents. However, so far, modulation of modes of enteral feeding (for example intermittent or acidified feeding) have not been demonstrated to decrease the incidence of VAP.

Antibiotic use has been associated with both an increased risk (Kollef, 1993; Rello et al, 1994; Kollef et al, 1997), as well as a protective effect for developing VAP (Rello et al, 1996b; Cook et al, 1998b; George et al, 1998).

THE INFLAMMATORY RESPONSE IN VAP

Correlations between elevated systemic cytokine and endotoxin levels and increased mortality have been reported for a wide variety of infections. If VAP increases mortality, one would expect a firm activation of local and systemic inflammatory responses. Recently, our group performed a case-control study, in which circulating levels of inflammatory mediators (interleukin-6 and interleukin-8) were determined in patients developing and not developing VAP (Bonten et al, 1997).

Only patients developing VAP which was accompanied by severe sepsis or septic shock had elevated circulating levels of inflammatory mediators. This was observed in approximately 25% of all patients developing VAP. In the remaining patients, VAP occurred without detectable systemic inflammatory reactions. Mortality related to the development of VAP was only increased in those patients in whom the clinical presentation of VAP was characterized by severe sepsis syndrome or septic shock.

These findings are more or less similar to those observed in experimental studies on Gram-negative pneumonia in rabbits (Fox-Dewhurst et al, 1997). In this study, a dose relationship between the number of bacteria inoculated into the trachea and intrapulmonary and systemic reactions was observed. Low numbers of bacteria did not result in severe sepsis or septic shock and were cleared from the lungs, whereas high inocula resulted in severe systemic inflammatory responses and death. Kollef and coworkers described a correlation between the number of Gram-negative bacteria and endotoxin concentrations in BAL fluid (Kollef et al, 1996). These findings suggest that VAP may be a compartmentalized infection in many patients, as has been demonstrated for pneumococcal community-acquired pneumonia.

MORTALITY CAUSED BY VAP

Patients who develop VAP do have high mortality rates. However, whether patients die because of VAP or just because of the severity of their underlying illnesses is a matter of controversy. In the latter scenario, the development of VAP would merely be a marker of a grim prognosis, and prevention of this infection would hardly influence mortality rates. When analyzing death rates, mortality can be subdivided into crude mortality and attributable mortality. Crude mortality is defined as the total proportion of deaths. Attributable mortality is mortality in excess of the mortality related to the underlying illness. Attributable mortality can be measured after strict matching of cases and controls to ensure that differences in survival are a result of the development of VAP (Wenzel, 1998).

Reported crude mortality rates associated with the development of VAP ranged from 33% to 55% (*Table 3*). A significant difference in crude mortality between patients developing and not-developing VAP was found in one study (Torres et al, 1990), and VAP was not significantly associated with death after stepwise logistic regression in a second study (Craven et al, 1986). Attributable mortality of VAP has been determined in four studies, all using bronchoscopic techniques for diagnosing VAP. Again, the results of these studies are contrasting. Fagon and coworkers determined an attributable mortality as a result of VAP of 27%, and even 43% when the infection was caused by *Ps. aeruginosa* or *Acinetobacter* species (Fagon et al, 1993).

Rello and coworkers found an attributable mortality of 13.5% for VAP caused by *Ps. aeruginosa* (Rello et al, 1996a). The presence of antibiotic-resistant pathogens and the risk of inappropriate empiric therapy in such settings may be an important variable in these analyses.

In our ICU, empiric antimicrobial therapy is almost always appropriate because of regular surveillance of colonization, feedback of antibiotic susceptibilities of hospital pathogens to clinicians, and the total absence of multiple resistant bacteria. In this setting, we did not find VAP to have attributable mortality (Bonten et al, 1997).

EFFECT OF PREVENTION OF VAP ON MORTALITY

Prevention of VAP and decreasing mortality are major goals in intensive care medicine. Interestingly, significant reductions in the incidence of VAP were not associated with increased patient survival. Regimens which modulate colonization of the respiratory tract with or without decontamination of the digestive tract resulted in decreased incidences of VAP by 60%, but failed to demonstrate an apparent effect on mortality (Selective Decontamination of the Digestive Tract Trialists Collaborative Group, 1993; Kollef, 1994; Heyland et al, 1994; D'Amico et al, 1998; Bergmans, 1999). These findings suggest that mortality is primarily a result of underlying illness.

A simple calculation based on the observations in the ICU of the University Hospital Maastricht reveals the following: out of 100 patients who need mechanical ventilation for at least 2 days, 70 will be colonized with PPMO in the upper respiratory tract (Bonten et al, 1995). In all, 30 patients will develop VAP (Bonten et al, 1995; Bergmans, 1999). Of these 30 patients, 25% (n=8) will develop severe sepsis or septic shock (Bonten et al, 1997). The expected mortality of patients without VAP and without VAP accompanied by sepsis syndrome or septic shock will be 25%.

The expected mortality among the 8 patients who develop VAP and severe sepsis or septic shock will be 60%. So in this group, 5 instead of 2 patients will die. The extra mortality because of VAP among 100 patients, therefore, is 3 patients, raising the mortality rate from 25% to 28%. It should be noted that these data were derived in an ICU without any problem with antibiotic resistance, with hardly any inappropriate empirical antibiotic treatment, and with VAP diagnosed with bronchoscopic techniques. In this setting, complete prevention of VAP could only result in a 10% reduction in mortality (from 28% to 25%). To prove a significant benefit of such an intervention in a prospective randomized study would need 3400 patients to be included in each study arm.

CONCLUSIONS

VAP remains a major cause of infection in ICUs, probably increasing morbidity, antibiotic use and health-care costs. Several risk factors have been identified, of which some may be useful for prevention of this infection. However, whether prevention of VAP will increase patient survival remains highly uncertain. Some careful case-control studies failed to show attributable mortality because of VAP. The development of VAP seems not to be associated with a significant systemic inflammatory response in most patients developing this infection. And finally, effective prevention of VAP, resulting in risk reductions up to 60%, hardly influenced patient survival.

It should be realized that in most of these studies VAP was diagnosed with bronchoscopic techniques, the most specific diagnostic modality available for clinical practice. This means that the association between mortality and VAP will be even lower in settings where VAP is diagnosed upon less specific criteria, as will be the case in most ICUs. All these findings suggest that a certain amount of patients will be treated with antibiotics unnecessarily, and that restriction of antibiotic use in ICU may be achieved safely. On the other hand, each intensivist knows about patients dying in septic shock as a result of

TABLE 3.
Mortality and attributed mortality of patients developing ventilator-associated pneumonia (VAP)

Reference		Number of patients	Incidence VAP (%)	Mortality with VAP (%)	Mortality without VAP (%)	Attributable mortality
Observational studies	Craven et al (1986)	233	21	55	Not measured	–
	Rello et al (1991)	264	25.7	42	37	–
	Torres et al (1990)	322	24	33	19	–
Case-control studies	Fagon et al (1993)	96	–	5427†	27	
	Rello et al (1996a)	78*	–	42	29‡	13
	Papazian et al (1996)	170	–	40	39§	1
	Bonten et al (1997)	84	–	33	31§	2

*inclusion of 26 cases and 52 controls; †relative risk of 2.0; ‡ relative risk 1.45; § $P > 0.05$

VAP. It will be a goal for future research to determine risk factors and diagnostic tests to identify these patients as soon as possible, to improve patient outcome. HM

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KEY POINTS

- Ventilator-associated pneumonia (VAP) is the most frequent occurring infection among critically ill patients in intensive care units.
- The incidence of VAP depends on the criteria used for diagnosis. As compared to the generally used criteria, addition of quantitative cultures of material obtained by bronchoscopic techniques will reduce the incidence by approximately 50%.
- Three recent findings question the assumed relationship between the development of VAP and an increase in patient mortality.
- VAP did not have attributable mortality in two case-control studies.
- The development of VAP was not associated with an increase in the systemic inflammatory response in the majority of patients developing VAP.
- Even 60% reductions in the incidence of VAP did not influence patient survival.