

Clinical and economic consequences of ventilator-associated pneumonia: A systematic review

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Define the incidence of ventilator-associated pneumonia (VAP) in mechanically ventilated patients.
2. Explain the economic consequences of VAP.
3. Use this information in a clinical setting.

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Background: Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in critically ill patients. The clinical and economic consequences of VAP are unclear, with a broad range of values reported in the literature

Objective: To perform a systematic review to determine the incidence of VAP and its attributable mortality rate, length of stay, and costs.

Data Source: Computerized PUBMED and MEDLINE search supplemented by manual searches for relevant articles, limited to articles published after 1990.

Study Selection: English-language observational studies and randomized trials that provided data on the incidence of VAP were included. Matched cohort studies were included for calculation of attributable mortality rate and length of stay.

Data Extraction: Data were extracted on patient population, diagnostic criteria for VAP, incidence, outcome, type of intensive care unit, and study design.

Data Synthesis: The cumulative incidence of VAP was calculated by combining the results of several studies using standard formulas for combining proportions, in which the weighted average and variance are calculated. Results from studies comparing intensive care

unit and hospital mortality due to VAP, additional length of stay, and additional days of mechanical ventilation were pooled using a random effects model, with assessment of heterogeneity.

Results: Our findings indicate a) between 10% and 20% of patients receiving >48 hrs of mechanical ventilation will develop VAP; b) critically ill patients who develop VAP appear to be twice as likely to die compared with similar patients without VAP (pooled odds ratio, 2.03; 95% confidence interval, 1.16–3.56); c) patients with VAP have significantly longer intensive care unit lengths of stay (mean = 6.10 days; 95% confidence interval, 5.32–6.87 days); and d) patients who develop VAP incur \geq \$10,019 in additional hospital costs.

Conclusions: Ventilator-associated pneumonia occurs in a considerable proportion of patients undergoing mechanical ventilation and is associated with substantial morbidity, a two-fold mortality rate, and excess cost. Given these findings, strategies that effectively prevent VAP are urgently needed. (*Crit Care Med* 2005; 33:2184–2193)

KEY WORDS: ventilator-associated pneumonia; prevention; prospective cohort; nosocomial pneumonia; outcomes; mortality; cost

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Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in the intensive care unit (ICU) (1–6). Several studies report that patients with VAP have an increased length of stay and hospital costs (7, 8); some studies have even found mortality attributable to VAP (9). The literature also suggests that late-onset VAP (variably defined as VAP developing 48–96 hrs after the onset of mechanical ventilation) is usually caused by more pathogenic organisms compared with early-onset VAP and thus leads to even greater morbidity and mortality rates (10–15). Unfortunately, studies of patients with VAP have often provided contradictory results, making it challenging to provide an overall estimate of the clinical and economic consequences of VAP.

We thus undertook a quantitative systematic review to answer the following questions: What is the incidence of VAP in mechanically ventilated patients? What is the attributable mortality of VAP? What is the prolongation of ICU stay attributable to VAP? What are the attributable costs of VAP?

Although recent reviews on the epidemiology of VAP have been published, none has used a systematic approach to quantitatively combine the results of available studies to provide a summary measure of the incidence and impact of VAP (16–24). A systematic approach is essential to identify all relevant studies and appropriately synthesize the literature; the use of *a priori* explicitly stated inclusion criteria minimizes bias.

METHODS

Search Strategy. We performed a computerized search of PUBMED (including MEDLINE), Current Contents, CINAHL, and the Cochrane Network using the following keywords: *ventilator-associated pneumonia, prevention, prospective cohort, nosocomial pneumonia, outcomes, mortality, cost*, and various combinations of these search terms. The end date of the search was March 1, 2004. The search was conducted by one author (NS). Reference lists of articles were searched to identify additional articles.

As the management of mechanically ventilated patients in the ICU has changed substantially over the past two decades, we chose to include only those studies published after 1990. To be included, articles had to satisfy specific criteria depending on the outcome (e.g., VAP incidence, attributable mortality).

For calculating the incidence of VAP, we included observational studies or randomized controlled trials that provided adequate data to obtain the incidence of VAP (i.e., number of patients who were mechanically ventilated and the proportion who developed VAP). For calculating the incidence of VAP from randomized controlled trials that compared an intervention with control, we used only data provided from the control arm. The incidence of VAP was calculated separately for cohort studies and the control arm of randomized trials.

For assessing mortality and length of stay related to VAP, we included studies reporting outcome data of VAP (e.g., mortality, length of ICU stay) only if they were matched cohort studies and if data were provided on the crude mortality in both the exposed and nonexposed group.

Data were extracted by one author (NS) using a standardized form for each relevant study and included the total number of mechanically ventilated patients, the proportion with VAP, the patient population evaluated, diagnostic criteria used for VAP, and, if provided, stratification of the incidence of VAP by duration of mechanical ventilation. Data on the length of stay, cost, and mortality attributable to VAP were also extracted. No formal assessment of validity of studies was performed, beyond the application of our inclusion criteria to all studies extracted. For assessment of incidence of VAP, all included studies provided the data necessary to determine incidence, using either a clinical or an invasive diagnostic criterion for VAP. For assessment of outcomes related to VAP, only matched cohort studies were included, all of which used similar methodology.

Statistical Analysis. The cumulative incidence of VAP was calculated by combining the results of several studies using standard formulas for combining proportions, in which the weighted average and variance are calculated (25). Results from studies comparing ICU and hospital mortality due to VAP, additional length of stay, and additional days of mechanical ventilation were pooled using a random effects model, with assessment of heterogeneity (26). Statistical analyses were done using SAS software (version 8.2, Cary, NC) and StatsDirect (2002, UK).

Calculation of Costs. The economic estimates were derived using microcosting techniques (27, 28), with costs from the University of Wisconsin Medical Center serving as a reference. Estimates for cost related to length of stay were based on literature review and expert opinion. Antimicrobial costs were estimated using the average wholesale price from the Pharmacy Red Book (2003). Physician and other health care personnel charges and indirect costs, such as lost days from work and disability associated with VAP, were not included in our cost calculations.

RESULTS

Incidence of VAP. Eighty-nine studies were identified that assessed the risk of VAP in patients receiving mechanical ventilation (7–9, 29–50, 51–114). These studies were of two types: prospective cohort studies or nonrandomized quasi-experimental trials and randomized controlled trials. They will be discussed separately. Importantly, most of the published studies assessing the incidence of VAP excluded patients who received mechanical ventilation for <48 hrs.

Thirty-eight prospective cohort or nonrandomized studies encompassing 48,112 patients were identified (Table 1) (7–9, 29–57, 106–111). Overall, the pooled cumulative incidence of developing VAP in patients receiving mechanical ventilation was 9.7% (95% confidence interval [CI], 7.0–12.5). The incidence of VAP in medical-surgical patients (24 studies) and medical ICUs alone (six studies) was 9.1% (95% CI, 5.9–12.3%) and 17.0% (5.9–28.0%) respectively.

Fifty-one prospective randomized trials encompassing 4,802 patients in the comparator arms were retrieved (Table 2) (58–105, 112–114). Overall, the pooled cumulative incidence of developing VAP in patients receiving mechanical ventilation was 22.8% (95% CI, 18.8–26.9%).

Mortality and Length of Stay Attributable to VAP. We identified eight matched cohort studies encompassing nine reports on the attributable mortality of VAP (8, 9, 42, 108, 115–117) (Table 3). Matching criteria varied widely among studies; most, however, matched by severity of illness using the Simplified Acute Physiology Score, Acute Physiology and Chronic Health Evaluation, or Abbreviated Injury Scale score. Seven studies were performed in patients in medical-surgical or medical ICUs. Five studies used protected specimen brush/bronchoalveolar lavage for diagnosis of VAP (8, 9, 42, 108, 116). Six studies used ICU mortality as an outcome (8, 9, 42, 108, 115–117); three measured hospital mortality as the outcome. Length of stay in the ICU was measured by five studies (8, 9, 42, 116, 117), and five also evaluated hospital length of stay. Only three studies reported data on additional length of mechanical ventilation due to VAP.

Of the nine reports, four failed to find a statistically significant attributable mortality of VAP (8, 42, 45, 108); the remainder reported an excess mortality that varied between approximately 15%

Table 1. Incidence of ventilator-associated pneumonia (VAP) in patients requiring mechanical ventilation in prospective cohort studies and nonrandomized trials

First Author, Year	Minimum Duration of Mechanical Ventilation as Inclusion Criteria	No. of Patients Requiring Mechanical Ventilation	No. with VAP (%)	Diagnosis of VAP ^a	Patient Population
Moine, 2002 (29)	≥96 hrs	764	89 (12)	Clinical and PSB/BAL	Medical-surgical ICU
Timsit, 1996 (30)	>48 hrs	387	56 (14)	Clinical and PSB/BAL	Medical-surgical ICU
Kollef, 1997 (107)	>48 hrs	680	63 (9)	Clinical and mini-BAL	Cardiac surgery ICU
Stoller, 2003 (106)	Any	146	2 (1)	Clinical	Medical ICU, NR
Kollef, 1997 (111)	>12 hrs	521	77 (15)	Clinical	Medical-surgical ICU
Kollef, 1995 (31)	>120 hrs	314	87 (28)	Clinical	Medical-surgical, trauma, neurologic ICU
Bonten, 1996 (32)	Any	141	31 (22)	Clinical and PSB/BAL	Medical-surgical ICU
Rello, 1996 (33)	Any	83	21 (25)	BAL	Medical-surgical ICU
Elatrous, 1996 (34)	Any	73	28 (38)	Clinical and BAL	Medical ICU
Alvarez-Lerma, 1996 (35)	Any	16,872	530 (3)	Clinical and PSB/BAL	Medical-surgical ICU
Kappstein, 1992 (36)	>24 hrs	270	78 (29)	Clinical	Medical-ICU, 24 hrs
Warren, 2003 (7)	>24 hrs	819	127 (16)	Clinical	Medical-surgical ICU
Bouza, 2003 (37)	Any	356	28 (8)	Clinical	Cardiac surgery ICU
Kanafani, 2003 (38)	≥48 hrs	70	33 (47)	Clinical	Medical-surgical ICU and respiratory care unit
Eggimann, 2003 (39)	>48 hrs	452	127 (28)	Clinical and BAL	Medical ICU
Rello, 1991 (40)	>48 hrs	264	58 (22)	Clinical and bronchoscopy	Medical-surgical ICU
Cook, 1998 (41)	≥48 hrs	1,014	177 (17)	Clinical and PSB/BAL	Medical ICU
Papazian, 1996 (42)	≥48 hrs	586	97 (17)	Clinical and PSB/BAL	Medical-surgical ICU
Memish, 2000 (43)	Any	202	41 (20)	Clinical	Medical-surgical ICU
Ibrahim, 2001 (44)	Any	880	132 (15)	Clinical	Medical-surgical ICU
Rello, 2002 (45)	>24 hrs	9,080	842 (9)	ICD-codes	Medical-surgical ICU
Apostolopoulou, 2003 (46)	≥24 hrs	175	56 (32)	Clinical	Medical-surgical ICU
Soufianou, 2000 (47)	>48 hrs	198	67 (34)	Clinical	Medical-surgical ICU
Simsek, 2001 (48)	Any	1,716	36 (2)	Clinical	Cardiothoracic surgical ICU
Beck-Sague, 1996 (49)	Any	145	15 (10)	Clinical	Surgical ICU
Akca, 2000 (50)	>48 hrs	260	81 (31)	Clinical	Medical-surgical ICU
Bochicchio, 2004 (51)	Any	714	125 (18)	Clinical	Trauma ICU
Hess, 1995 (52)	>24 hrs	3,423	174 (5)	Clinical ± PSB	Medical-surgical ICU
Ibrahim, 2000 (53)	Any	1,855	397 (21)	Clinical	Medical-surgical ICU
Kollef, 1993 (54)	>24 hrs	277	43 (16)	Clinical	Medical-surgical ICU
Fagon, 1996 (55)	≥48 hrs	1,118	313 (28)	PSB/BAL	Medical-surgical ICU
Rodriguez, 1991 (56)	Any	294	130 (44)	Clinical	Trauma ICU
Fink, 1998 (57)	Any	637	52 (8)	Clinical	Respiratory and medical ICU
Heyland, 1999 (8)	>48 hrs	1,014	177 (17)	Clinical and PSB/BAL	Medical-surgical ICU
Baker, 1996 (108)	Any	514	30 (6)	Clinical and PSB/BAL	Trauma ICU
Bercault, 2001 (9)	≥48 hrs	1,144	141 (12)	Clinical and PSB	Medical-surgical ICU
Daumal, 1999 (110)	≥48 hrs	361	55 (15)	Clinical and PSB	Medical-surgical ICU
Ibrahim, 2002 (109)	≥24 hrs	150	60 (40)	Clinical ± BAL	Medical-surgical ICU

PSB, protected specimen brush; BAL, bronchoalveolar lavage; ICU, intensive care unit.

^aClinical diagnosis of VAP: new or progressive infiltrate on chest radiograph and at least two of the following: fever (>38.5°C) or hypothermia (<36°C), leukocytosis (>12), purulent tracheobronchial secretions, or a reduction of Pao₂/Fio₂ of 15 in the last 48 hrs.

and 50% in cases compared with controls (115, 116, 117, 9). The summary estimate (odds ratio) for ICU mortality in the six studies in which it was reported was 2.03 (95% CI, 1.16–3.56); however, significant statistical heterogeneity was found ($p = .05$).

Pooled results from the four studies that evaluated mortality during the entire duration of hospitalization showed an odds ratio of 1.64 (95% CI, 0.86–3.14) (42, 45, 115).

Pooled results for ICU length of stay (LOS) showed that VAP was associated with a mean ICU LOS of 6.10 additional days (95% CI, 5.32–6.87). Although no

statistically significant heterogeneity was found, only three studies provided sufficient data to calculate a pooled LOS (42, 45, 117).

Attributable VAP Costs. Our pooled estimate from the literature indicated that the increased length of ICU stay due to VAP ranges from 5 to 7 days. Using the low range of this estimate as the attributable LOS, we then added the costs of the diagnostic tests and the cost of treatment (piperacillin-tazobactam, ciprofloxacin, and vancomycin) to derive the direct cost of VAP. The additional cost of evaluating and treating a patient with VAP using noninvasive diagnostic meth-

ods and a typical antibiotic regimen for eight days of treatment at the University of Wisconsin would be \$10,019 (Table 4). If we use the upper limit of LOS (i.e., 7 days), attributable VAP cost is estimated to be \$13,647.

DISCUSSION

Our review indicates that VAP is a common hospital-associated infection, occurring in between 10% and 20% of patients receiving mechanical ventilation for >48 hrs. The difference in incidence found among cohort and randomized trials is likely due to differing criteria for

Table 2. Incidence of ventilator-associated pneumonia (VAP) in patients requiring mechanical ventilation in control groups of randomized trials

First Author, Year	Duration of Mechanical Ventilation as Inclusion Criteria	No. of Patients Requiring Mechanical Ventilation	No. With VAP (%)	Diagnosis of VAP ^a	Patient Population
Preventive strategy: selective digestive decontamination					
Wiener, 1995 (58)	≥48 hrs	31	8 (26)	Clinical	Medical-surgical ICU
Winter, 1992 (59)	≥48 hrs	92	18 (20)	Clinical and BAL	Medical-surgical ICU
Ferrer, 1994 (60)	>72 hrs	41	10 (24)	Clinical and PSB/BAL	Respiratory ICU
Pugin, 1991 (61)	>48 hrs	27	21 (78)	Clinical	Surgical ICU
Gastinne, 1992 (62)	≥24 hrs	225	33 (15)	Clinical	Medical-surgical ICU
Cockerill, 1992 (63)	>72 hrs	75	14 (19)	Clinical	Medical-surgical trauma ICU
Sanchez Garcia, 1998 (64)	>48 hrs	140	98 (70)	Clinical	Medical-surgical, trauma ICU
Bergmans, 2001 (65)	>48 hrs	139	38 (27)	Clinical and BAL or PSB	Medical-surgical, trauma, neurologic ICU
Verwaest, 1997 (66)	≥48 hrs	185	40 (22)	Clinical and bronchoscopy	Medical-surgical ICU
Lingnau, 1997 (67)	≥48 hrs	148	61 (41)	NR	Trauma ICU
Rocha, 1992 (68)	>72 hrs	54	25 (46)	Clinical	Medical-surgical ICU
Korinek, 1993 (69)	>120 hrs	60	25 (42)	Clinical and BAL/PSB	Neurosurgical ICU
Quinio, 1996 (70)	Any	72	37 (51)	Clinical	Trauma ICU
Aerdt, 1991 (71)	≥5 days	39	10 (26)	Clinical	Medical-surgical ICU
Abele-Horn, 1997 (72)	>96 hrs	30	23 (77)	Clinical	Medical-surgical ICU
Continuous subglottic suction					
Smulders, 2002 (73)	Any	75	12 (16)	Clinical	General ICU
Valles, 1995 (75)	Any	95	25 (26)	Clinical and PSB/BAL	Medical-surgical ICU
Mahul, 1992 (74)	>72 hrs	75	21 (28)	Clinical and BAL	Medical-surgical ICU
Kollef, 1999 (76)	Any	183	16 (9)	Clinical	Cardiac surgery
Treatment of sinusitis					
Holzappel, 1999 (77)	>7 days	200	51 (26)	PSB	Medical-surgical ICU
Ventilator circuit changes					
Kollef, 1995 (78)	>120 hrs	153	44 (29)	Clinical	Medical-surgical ICU
Long, 1996 (79)	Any	234	26 (11)	Clinical	Medical and neurosurgical ICU
Dreyfuss, 1991 (80)	>48 hrs	38	8 (21)	Clinical and PSB/BAL	Medical-surgical ICU
Semirecumbent position					
Drakulovic, 1999 (81)	Any	47	16 (34)	Clinical and PSB/BAL	Medical ICU
Heat moisture exchanger vs. heated humidification					
Dreyfuss, 1995 (82)	>48 hrs	70	8 (11)	Clinical and PSB/BAL	Medical-surgical ICU
Kirton, 1997 (83)	Any	140	46 (33)	Clinical	Trauma ICU
Hurni, 1997 (84) ^b	≥48 hrs	56	7 (13)	Clinical	Medical ICU
Roustan, 1992 (85)	Any	61	9 (15)	Clinical	Medical-surgical ICU
Boots, 1997 (112)	≥48 hrs	41	7 (17)	Clinical	Medical-surgical ICU
Kollef, 1998 (86)	Any	147	15 (10)	Clinical	Medical-surgical ICU
Memish, 2001 (105)	≥48 hrs	120	19 (16)	Clinical	Medical-surgical ICU
Stress ulcer prophylaxis					
Apte, 1992 (87)	Any	18	9 (50)	Clinical	Medical ICU
Metz, 1993 (88)	Any	79	15 (19)	Clinical	Trauma ICU
Hanisch, 1998 (113)	≥48 hrs	57	12 (21)	Clinical	Surgical ICU
Ben-Menachem, 1994 (89)	≥24 hrs	100	6 (6)	Clinical	Medical ICU
Eddleston, 1994 (90)	≥4 days	12	0 (0)	Clinical	Medical-surgical ICU
Pickworth, 1993 (91)	Any	39	6 (15)	Clinical	Trauma ICU
Eddleston, 1991 (92)	Any	30	3 (10)	Clinical	Medical-surgical ICU
Thomason, 1996 (93)	≥24 hrs	82	30 (37)	Clinical	Medical-surgical/trauma ICU
Prod'hom, 1994 (94)	≥24 hrs	81	18 (22)	Clinical	Medical-surgical ICU
O'Keefe, 1998 (95)	Any	47	10 (21)	Clinical	Trauma ICU
Cook, 1998 (96)	≥48 hrs	604	98 (16)	Clinical and PSB/BAL	Medical-surgical ICU
Mustafa, 1995 (97)	Any	15	3 (20)	None	Medical-surgical ICU
Bonten, 1995 (98)	Any	74	16 (22)	Clinical and PSB/BAL	Medical-surgical ICU
Daily changes in suction catheters					
Kollef, 1997 (114)	>12 hrs	263	39 (15)	Clinical	Medical-surgical ICU
Darvas, 2003 (99)	>48 hrs	53	10 (19)	Clinical	Medical-surgical ICU
Closed vs. open suction					
Zeitoun, 2003 (100)	>48 hrs	23	7 (30)	Clinical	Medical-surgical ICU
Johnson, 1994 (101)	Any	16	8 (50)	Clinical	Trauma, general surgery ICU
Enteral feeding					
Bonten, 1996 (102)	Any	30	5 (17)	PSB/BAL	Medical-surgical ICU
Kearns, 2000 (103)	>24 hrs	23	3 (13)	Clinical	Medical ICU
Prophylactic antibiotics					
Sirvent, 1997 (104)	Any	50	25 (50)	PSB/BAL	Head trauma, coma

PSB, protected specimen brush; BAL, bronchoalveolar lavage; ICU, intensive care unit.

^aClinical diagnosis of VAP: new or progressive infiltrate on chest radiograph and at least two of the following: fever (>38.5°C) or hypothermia (<36°C), leukocytosis (>2), purulent tracheobronchial secretions, or a reduction of PaO₂/FIO₂ of 15 in the last 48 hrs; ^bdata obtained from Ref. 124.

Table 3. Attributable mortality and length of stay for ventilator-associated pneumonia (VAP) found in matched studies

First Author, Year	Diagnostic Criteria	Patient Population	Patient Population for Mortality, n		Patient Population for LOS, n		Included in Meta-analysis of Mortality, ICU LOS or Both
			VAP	no VAP	VAP	no VAP	
Papazian, 1996 (42)	Clinical and PSB/BAL	Medical-surgical ICU	85	85	85	85	Both
Heyland, 1999 (8)	Clinical and PSB/BAL	Medical-surgical ICU	173	173	164	164	Mortality
Kappstein, 1992 (36)	Clinical	Medical and trauma	78	192	34	69	Neither
Bercault, 2001 (9)	Clinical and PSB	Medical-surgical ICU	135	135	135	135	Both
Rello, 2002 (45)	ICD code	Medical-surgical ICU	816	2243	816	2243	ICU LOS
Baker, 1996 (108)	Clinical and PSB/BAL	Trauma ICU	29	58	29	58	Mortality
Cunnion, 1996 (115)	Clinical	Surgical ICU	20	40	20	40	Neither
Cunnion, 1996 (115)	Clinical	Medical ICU	20	40	20	40	Neither
Fagon, 1993 (116)	PSB/BAL	Medical ICU	48	48	48	48	Mortality
Craig, 1984 (117)	Clinical	Medical ICU ^b	54	54	43	51	Both

LOS, length of stay; ICU, intensive care unit; PSB, protected specimen brush; BAL, bronchoalveolar lavage; MV, mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; GCS, Glasgow Coma Scale; ICD, International Classification of Diseases; AIS, Abbreviated Injury Score.

^a $p < .05$; ^b p value not provided.

inclusion in these two types of studies. Most cohort studies we reviewed included consecutive ICU admissions (some of whom were probably at low risk for VAP), whereas the randomized trials included primarily those at higher risk of developing VAP.

Our results also suggest a likely two-fold increase in ICU mortality attributable to VAP; however, this result should be viewed cautiously as significant statistical heterogeneity was found.

Although crude ICU mortality rates of 16–76% have been reported for VAP in a number of studies (7, 11, 41, 54, 108, 118), the extent of mortality attributable to VAP (and, therefore, modifiable by the prevention of VAP) is unclear. Some studies have reported risk ratios for mortality in patients with VAP compared with those without VAP of 2.2–4.4 (9, 115, 116), but others have failed to find a statistically significant increased risk (8, 45, 108). This discrepancy may be partially explained by the inclusion of different patient populations across studies with varying baseline risks for death (119). Second, methodological differences among the individual stud-

ies also likely contribute to this discordance. Specifically, the choice of matching variables in the case of matched studies (Table 3) and the use of covariates for adjustment in the case of unmatched cohort studies could lead to differing results. Third, variation in the diagnostic criteria for VAP used in individual studies may result in varying attributable mortality rates. Finally, variations in institutional microbiology (particularly the presence of pathogens resistant to multiple antimicrobials) (31) and relative prolongation of the duration of mechanical ventilation may account for increased attributable mortality (29).

The results of unmatched cohort studies using multivariable analyses conducted to evaluate the independent role played by VAP in causing death have been conflicting. In a study by Craven et al. (120), the investigators compared medical and surgical ICU patients with regard to mortality from nosocomial pneumonia; most patients in both groups were receiving mechanical ventilation. Overall, patients in the medical ICU had a higher fatality rate than patients in the surgical ICU (18% vs. 10%, $p < .0001$); however,

the mortality rate from nosocomial infection was not significantly different (8.0% vs. 6.0%). In contrast, stepwise logistic regression analysis in another study demonstrated that ICU-acquired pneumonia significantly increased the risk of death (odds ratio, 1.91; 95% CI, 1.6–2.3); however, not all patients in this study were receiving mechanical ventilation (121). In a study of 1,118 patients receiving mechanical ventilation, Fagon et al. (122) found that VAP was associated with a one and half-fold increased risk of death (odds ratio, 1.51; 95% CI, 1.11–2.03), after adjusting for severity of illness, presence of organ dysfunction, and underlying disease. However, the microbial etiology and the treatment of VAP were not reported.

Data on the financial impact of VAP are limited. Comparison of costs across studies is difficult for several reasons. First, the methodology for calculating costs varies. Many studies have relied on hospital charges rather than true costs (45, 108), thereby overestimating the actual cost of VAP. In a retrospective case-control study of trauma patients, Baker et al. (108) found that hospital charges in-

Table 3.—Continued

Outcomes Evaluated	Length of ICU Stay, Days		ICU LOS Attributable to VAP, Days	ICU Mortality, %		ICU Mortality Attributable to VAP, %	Matching Criteria for Mortality
	VAP	no VAP		VAP	no VAP		
ICU mortality, ICU LOS	32.9	24.5	8.4 ^a	40.0	38.8	1.2	Underlying disease, diagnosis, reason for MV, age, gender, duration of MV prior to VAP, year of admission, APACHE II at admission
ICU mortality, ICU LOS	NR	NR	4.3 ^a	23.7	17.9	5.8	Medical/surgical status, time in ICU prior to VAP, duration of MV prior to VAP, day 1 APACHE II score, MOD score of day prior to VAP
ICU LOS and ICU costs	NR	NR	10.1 ^b	No matched analysis for mortality	NR		Underlying disease, age, duration of MV, duration of ICU stay prior to VAP
ICU mortality, ICU LOS	31.0	26.0	5.0 ^a	41.5	14.1	27.4 ^a	Admission diagnosis, reason for MV, immune status, cardiac status. SAPS II, GCS score, age
Hospital mortality, hospital LOS, ICU LOS, hospital costs	11.7	5.6	6.1 ^a	30.5	30.4	0.1	Duration of MV, severity of illness, type of admission, age
ICU LOS, ICU mortality, hospital costs	20.5	15.0	5.5 ^a	24.1	24.1	0.0	Age, AIS score, gender, no. of discharge diagnoses
Hospital LOS, hospital mortality	30.0	22.3	7.7 ^b	55.0	5.0	50.0 ^a	ICU LOS >48 hrs
Hospital LOS, hospital mortality	40.9	23.1	17.8 ^b	55.0	7.5	47.5 ^a	ICU LOS >48 hrs
ICU mortality, ICU LOS	34.0	21.0	13.0 ^a	54.2	27.1	27.1 ^a	Age, SAPS, indication for MV, date of admission and duration of MV
ICU mortality ICU LOS	12.0	4.3	7.7 ^a	20.4	5.6	14.8 ^a	Age, gender, admission diagnosis, surgical procedure, "host factors"

curred by patients with nosocomial pneumonia were 1.5 times (\$113,683 vs. \$73,739) those of controls. Using a large U.S. administrative database, Rello and colleagues (45) estimated that mean billed hospital charges were significantly greater for patients with VAP (\$104,983 vs. \$63,689) than for patients without VAP ($p < .001$).

Additionally, studies vary in their inclusion criteria for costs relevant to VAP. Papazian et al. (42) reported a \$7,752 additional cost of VAP in 1996; however, only ICU stay was included in calculation of costs. In a recent prospective cohort study of 819 mechanically ventilated patients, 127 of whom developed VAP, Warren et al. (7) found that VAP was associated with attributable costs of \$11,897 (95% CI, \$5,265–\$26,214) in 2003 in a large suburban nonteaching hospital.

Microcosting is a method used to capture costs associated with patterns of resource use. Shorr and O'Malley (123) estimated the costs associated with VAP in 2001 to be \$5,365, using microcosting that included the cost of excess ICU length of stay, diagnostic tests, and therapeutic antibiotics directed toward treat-

Table 4. Costs associated with ventilator-associated pneumonia

Variable	Cost Estimate in 2003 U.S. Dollars	Source
Chest radiograph	45.06	University of Wisconsin Hospital
Arterial blood gas	7.21	University of Wisconsin Hospital
Gram stain and culture of tracheal aspirate	23.74	University of Wisconsin Hospital
Bronchoalveolar lavage	394.15	University of Wisconsin Hospital
Blood culture	16.63	University of Wisconsin Hospital
Day in intensive care unit on mechanical ventilation	1,814.16	University of Wisconsin Hospital
Day of antibiotic therapy		
Ciprofloxacin	9.65	AWP, Red Book 2003
Piperacillin/tazobactam	64.8	AWP, Red Book 2003
Vancomycin	32.16	AWP, Red Book 2003
Cefepime	73.18	AWP, Red Book 2003
Ceftazidime	29.17	AWP, Red Book 2003
Linezolid	123.68	AWP, Red Book 2003
Tobramycin	65.25	AWP, Red Book 2003
Standard endotracheal tube	1.45	University of Wisconsin Hospital

AWP, average wholesale price.

ing VAP. Using a similar technique, our study found that an episode of VAP has attributable costs of \geq \$10,019 (124).

Our review has several limitations. We restricted our search to studies published since 1990. This was done because the management and epidemiology of VAP

have changed considerably over time. Although we believe that the inclusion of earlier studies would have limited the applicability of our results to today's VAP population, it is possible that the exclusion of earlier studies affected the accuracy of our results. We also only included

Ventilator-associated pneumonia occurs in a considerable proportion of patients undergoing mechanical ventilation and is associated with substantial morbidity, a two-fold mortality rate, and excess cost.

English language studies in our analysis. However, because of the large number of studies identified, we believe that our point estimates and confidence intervals accurately reflect the incidence and impact of VAP. Finally, since physician charges were not included in calculation of costs, our estimate of the financial impact of VAP is conservative.

CONCLUSIONS

We found that VAP is a common hospital-associated infection with a clear impact on length of stay and hospital costs and a potentially substantial attributable mortality rate. The results of our analysis can be used by clinicians, policymakers, patient safety officers, and infection control personnel to better allocate resources for prevention of nosocomial infection. We also hope our results will be of use to investigators planning to evaluate the cost-effectiveness of various strategies for preventing VAP.

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