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

Nasia Safdar, MD, MS; Cameron Dezfulian, MD; Harold R. Collard, MD; Sanjay Saint, MD, MPH

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.

All authors have disclosed that they have no financial relationships or interests in any commercial companies pertaining to this educational activity.

Wolters Kluwer Health has identified and resolved all faculty conflicts of interest regarding this educational activity.

Visit the *Critical Care Medicine* Web site (www.ccmjournal.org) for information on obtaining continuing medical education credit.

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 ≥$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

Clinical Instructor, Section of Infectious Diseases, Department of Medicine, University of Wisconsin Medical School, Madison, Wisconsin (NS); Clinical Fellow, the Critical Care Medicine Department, National Institutes of Health, Bethesda, MD, and Division of Pediatric Anesthesia and Critical Care, Johns Hopkins Hospital, Baltimore, MD (CD); Assistant Professor of Medicine, University of California, San Francisco, CA (HRC); Research Investigator, Ann Arbor VA Medical Center, Director, UM/VA Patient Safety Enhancement Program, Associate Professor of Medicine, University of Michigan Medical School, Senior Associate Division Chief, Division of General Medicine, University of Michigan, Ann Arbor, Michigan (SS).

This work was supported, in part, by a Patient Safety Fellowship award provided by C.R. Bard and the Research Foundation for the Prevention of Complications Associated with Health Care. Dr. Saint is supported by a Career Development Award from the Health Services Research & Development Program of the Department of Veterans Affairs and a Patient Safety Developmental Center Grant from the Agency for Healthcare Research and Quality (P20-HS11540).

Address requests for reprints to: Nasia Safdar, MD, MS, University of Wisconsin Madison, H4/572 Section of Infectious Diseases, 600 Highland Avenue, Madison, WI 53792. E-mail: ns2@medicine.wisc.edu.

DOI: 10.1097/01.CCM.0000181731.53912.D9

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.

[a]Clinical 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 Pa_{O_2}/F_{IO_2} 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 methods 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
Aerdts, 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					
Holzapfel, 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.

[a]Clinical 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 Pa_{O_2}/F_{IO_2} of 15 in the last 48 hrs; [b]data 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 twofold 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 studies 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 treating VAP. Using a similar technique, our study found that an episode of VAP has attributable costs of ≥$10,019 (124).

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.

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.

ACKNOWLEDGMENTS

We are indebted to Samuel R. Kaufman, MA, for independently confirming the pooled estimates of this review.

REFERENCES

1. Bonten MJ, Kollef MH, Hall JB: Risk factors for ventilator-associated pneumonia: From epidemiology to patient management. *Clin Infect Dis* 2004; 38:1141–1149
2. Valles J, Mesalles E, Mariscal D, et al: A 7-year study of severe hospital-acquired pneumonia requiring ICU admission. *Intensive Care Med* 2003; 29:1981–1988
3. Diaz O, Diaz E, Rello J: Risk factors for pneumonia in the intubated patient. *Infect Dis Clin North Am* 2003; 17:697–705
4. Leu HS, Kaiser DL, Mori M, et al: Hospital-acquired pneumonia. Attributable mortality and morbidity. *Am J Epidemiol* 1989; 129: 1258–1267
5. McEachern R, Campbell GD Jr: Hospital-acquired pneumonia: Epidemiology, etiology, and treatment. *Infect Dis Clin North Am* 1998; 12:761–779
6. Richards MJ, Edwards JR, Culver DH, et al: Nosocomial infections in combined medical-surgical intensive care units in the United States. *Infect Control Hosp Epidemiol* 2000; 21:510–515
7. Warren DK, Shukla SJ, Olsen MA, et al: Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center. *Crit Care Med* 2003; 31:1312–1317
8. Heyland DK, Cook DJ, Griffith L, et al: The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. *Am J Respir Crit Care Med* 1999; 159:1249–1256
9. Bercault N, Boulain T: Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit: A prospective case-control study. *Crit Care Med* 2001; 29:2303–2309
10. Rello J, Ausina V, Ricart M, et al: Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. *Chest* 1993; 104:1230–1235
11. Fagon JY, Chastre J, Domart Y, et al: Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. *Am Rev Respir Dis* 1989; 139:877–884
12. Stevens RM, Teres D, Skillman JJ, et al: Pneumonia in an intensive care unit. A 30-month experience. *Arch Intern Med* 1974; 134:106–111
13. Celis R, Torres A, Gatell JM, et al: Nosocomial pneumonia. A multivariate analysis of risk and prognosis. *Chest* 1988; 93:318–324
14. Rello J, Torres A, Ricart M, et al: Ventilator-associated pneumonia by Staphylococcus aureus. Comparison of methicillin-resistant and methicillin-sensitive episodes. *Am J Respir Crit Care Med* 1994; 150:1545–1549
15. Kollef MH: The prevention of ventilator-associated pneumonia. *N Engl J Med* 1999; 340:627–634
16. Chastre J, Fagon JY: Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002; 165:867–903
17. Allen RM, Dunn WF, Limper AH: Diagnosing ventilator-associated pneumonia: the role of bronchoscopy. *Mayo Clin Proc* 1994; 69:962–968
18. Baselski V: Microbiologic diagnosis of ventilator-associated pneumonia. *Infect Dis Clin North Am* 1993; 7:331–357
19. Bauer TT, Ferrer R, Angrill J, et al: Ventilator-associated pneumonia: incidence, risk factors, and microbiology. *Semin Respir Infect* 2000; 15:272–279
20. Craven DE. Epidemiology of ventilator-associated pneumonia. *Chest* 2000; 117: 186S–187S
21. Baughman RP: Diagnosis of ventilator-associated pneumonia. *Curr Opin Crit Care* 2003; 9:397–402
22. Alcon A, Fabregas N, Torres A: Hospital-acquired pneumonia: Etiologic considerations. *Infect Dis Clin North Am* 2003; 17: 679–695
23. Bowton DL: Nosocomial pneumonia in the ICU—Year 2000 and beyond. *Chest* 1999; 115:28S–33S
24. Wunderink RG: Diagnosis of pneumonia. *Curr Opin Pulm Med* 1996; 2:213–217
25. Laird NM, Mosteller F: Some statistical methods for combining experimental results. *Int J Technol Assess Health Care* 1990; 6:5–30
26. Breslow NE, Day NE. International Agency for Research on Cancer. Statistical methods in cancer research. In: Analysis of Case-Control Studies. Davis W (Ed). Oxford University Press, 1980, No. 32, Vol 1
27. Saint S, Chenoweth C, Fendrick AM: The role of economic evaluation in infection control. *Am J Infect Control* 2001; 29: 338–344
28. Drummond MF, O'Brien B, Stoddart GL, et al: Methods for the Economic Evaluation of Health Care Programmes. New York, Oxford University Press, 1997
29. Moine P, Timsit JF, De Lassence A, et al: Mortality associated with late-onset pneumonia in the intensive care unit: Results of a multi-center cohort study. *Intensive Care Med* 2002; 28:154–163
30. Timsit JF, Chevret S, Valcke J, et al: Mortality of nosocomial pneumonia in ventilated patients: Influence of diagnostic tools. *Am J Respir Crit Care Med* 1996; 154: 116–123
31. Kollef MH, Silver P, Murphy DM, et al: The effect of late-onset ventilator-associated pneumonia in determining patient mortality. *Chest* 1995; 108:1655–1662
32. Bonten MJ, Bergmans DC, Ambergen AW, et al: Risk factors for pneumonia, and colonization of respiratory tract and stomach in mechanically ventilated ICU patients. *Am J Respir Crit Care Med* 1996; 154: 1339–1346
33. Rello J, Sonora R, Jubert P, et al: Pneumonia in intubated patients: role of respiratory airway care. *Am J Respir Crit Care Med* 1996; 154:111–115
34. Elatrous S, Boujdaria R, Merghli S, et al: Incidence and risk factors of ventilator-associated pneumonia: A one year prospective survey. *Clin Intensive Care* 1996; 7:276–281
35. Alvarez-Lerma F: Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit.

ICU-Acquired Pneumonia Study Group. *Intensive Care Med* 1996; 22:387–394
36. Kappstein I, Schulgen G, Beyer U, et al: Prolongation of hospital stay and extra costs due to ventilator-associated pneumonia in an intensive care unit. *Eur J Clin Microbiol Infect Dis* 1992; 11:504–508
37. Bouza E, Perez A, Munoz P, et al: Ventilator-associated pneumonia after heart surgery: A prospective analysis and the value of surveillance. *Crit Care Med* 2003; 31: 1964–1970
38. Kanafani ZA, Kara L, Hayek S, et al: Ventilator-associated pneumonia at a tertiary-care center in a developing country: Incidence, microbiology, and susceptibility patterns of isolated microorganisms. *Infect Control Hosp Epidemiol* 2003; 24:864–869
39. Eggimann P, Hugonnet S, Sax H, et al: Ventilator-associated pneumonia: caveats for benchmarking. *Intensive Care Med* 2003; 29:2086–2089
40. Rello J, Quintana E, Ausina V, et al: Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. *Chest* 1991; 100:439–444
41. Cook DJ, Walter SD, Cook RJ, et al: Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998; 129:433–440
42. Papazian L, Bregeon F, Thirion X, et al: Effect of ventilator-associated pneumonia on mortality and morbidity. *Am J Respir Crit Care Med* 1996; 154:91–97
43. Memish ZA, Cunningham G, Oni GA, et al: The incidence and risk factors of ventilator-associated pneumonia in a Riyadh hospital. *Infect Control Hosp Epidemiol* 2000; 21: 271–273
44. Ibrahim EH, Tracy L, Hill C, et al: The occurrence of ventilator-associated pneumonia in a community hospital: Risk factors and clinical outcomes. *Chest* 2001; 120:555–561
45. Rello J, Ollendorf DA, Oster G, et al: Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest* 2002; 122:2115–2121
46. Apostolopoulou E, Bakakos P, Katostaras T, et al: Incidence and risk factors for ventilator-associated pneumonia in 4 multidisciplinary intensive care units in Athens, Greece. *Respir Care* 2003; 48:681–688
47. Sofianou DC, Constandinidis TC, Yannacou M, et al: Analysis of risk factors for ventilator-associated pneumonia in a multidisciplinary intensive care unit. *Eur J Clin Microbiol Infect Dis* 2000; 19:460–463
48. Simsek S, Yurtseven N, Gercekogalu H, et al: Ventilator-associated pneumonias in a cardiothoracic surgery centre postoperative intensive care unit. *J Hosp Infect* 2001; 47: 321–324
49. Beck-Sague CM, Sinkowitz RL, Chinn RY, et al: Risk factors for ventilator-associated pneumonia in surgical intensive-care-unit patients. *Infect Control Hosp Epidemiol* 1996; 17:374–376
50. Akca O, Koltka K, Uzel S, et al: Risk factors for early-onset, ventilator-associated pneumonia in critical care patients: Selected multiresistant versus nonresistant bacteria. *Anesthesiology* 2000; 93:638–645
51. Bochicchio GV, Joshi M, Bochicchio K, et al: A time-dependent analysis of intensive care unit pneumonia in trauma patients. *J Trauma* 2004; 56:296–301
52. Hess D, Burns E, Romagnoli D, et al: Weekly ventilator circuit changes. A strategy to reduce costs without affecting pneumonia rates. *Anesthesiology* 1995; 82: 903–911
53. Ibrahim EH, Ward S, Sherman G, et al: A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting. *Chest* 2000; 117: 1434–1442
54. Kollef MH: Ventilator-associated pneumonia. A multivariate analysis. *JAMA* 1993; 270:1965–1970
55. Fagon JY, Chastre J, Vuagnat A, et al: Nosocomial pneumonia and mortality among patients in intensive care units. *JAMA* 1996; 275:866–869
56. Rodriguez JL, Gibbons KJ, Bitzer LG, et al: Pneumonia: Incidence, risk factors, and outcome in injured patients. *J Trauma* 1991; 31:907–912
57. Fink JB, Krause SA, Barrett L, et al: Extending ventilator circuit change interval beyond 2 days reduces the likelihood of ventilator-associated pneumonia. *Chest* 1998; 113:405–411
58. Wiener J, Itokazu G, Nathan C, et al: A randomized, double-blind, placebo-controlled trial of selective digestive decontamination in a medical-surgical intensive care unit. *Clin Infect Dis* 1995; 20:861–867
59. Winter R, Humphreys H, Pick A, et al: A controlled trial of selective decontamination of the digestive tract in intensive care and its effect on nosocomial infection. *J Antimicrob Chemother* 1992; 30:73–87
60. Ferrer M, Torres A, Gonzalez J, et al: Utility of selective digestive decontamination in mechanically ventilated patients. *Ann Intern Med* 1994; 120:389–395
61. Pugin J, Auckenthaler R, Lew DP, et al: Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia. A randomized, placebo-controlled, double-blind clinical trial. *JAMA* 1991; 265: 2704–2710
62. Gastinne H, Wolff M, Delatour F, et al: A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. The French Study Group on Selective Decontamination of the Digestive Tract. *N Engl J Med* 1992; 326:594–599
63. Cockerill FR III, Muller SR, Anhalt JP, et al: Prevention of infection in critically ill patients by selective decontamination of the digestive tract. *Ann Intern Med* 1992; 117: 545–553
64. Sanchez Garcia M, Cambronero Galache JA, Lopez Diaz J, et al: Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients. A randomized, double-blind, placebo-controlled, multicenter trial. *Am J Respir Crit Care Med* 1998; 158:908–916
65. Bergmans DC, Bonten MJ, Gaillard CA, et al: Prevention of ventilator-associated pneumonia by oral decontamination: A prospective, randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med* 2001; 164:382–388
66. Verwaest C, Verhaegen J, Ferdinande P, et al: Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients in a multidisciplinary intensive care unit. *Crit Care Med* 1997; 25:63–71
67. Lingnau W, Berger J, Javorsky F, et al: Selective intestinal decontamination in multiple trauma patients: Prospective, controlled trial. *J Trauma* 1997; 42:687–694
68. Rocha LA, Martin MJ, Pita S, et al: Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract. A randomized, double blind, placebo-controlled study. *Intensive Care Med* 1992; 18:398–404
69. Korinek AM, Laisne MJ, Nicolas MH, et al: Selective decontamination of the digestive tract in neurosurgical intensive care unit patients: A double-blind, randomized, placebo-controlled study. *Crit Care Med* 1993; 21:1466–1473
70. Quinio B, Albanese J, Bues-Charbit M, et al: Selective decontamination of the digestive tract in multiple trauma patients. A prospective double-blind, randomized, placebo-controlled study. *Chest* 1996; 109:765–772
71. Aerdts SJ, van Dalen R, Clasener HA, et al: Antibiotic prophylaxis of respiratory tract infection in mechanically ventilated patients. A prospective, blinded, randomized trial of the effect of a novel regimen. *Chest* 1991; 100:783–791
72. Abele-Horn M, Dauber A, Bauernfeind A, et al: Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal decontamination (SOD). *Intensive Care Med* 1997; 23:187–195
73. Smulders K, van der Hoeven H, Weers-Pothoff I, et al: A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. *Chest* 2002; 121:858–862
74. Mahul P, Auboyer C, Jospe R, et al: Prevention of nosocomial pneumonia in intubated patients: Respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. *Intensive Care Med* 1992; 18: 20–25
75. Valles J, Artigas A, Rello J, et al: Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. *Ann Intern Med* 1995; 122:179–186
76. Kollef MH, Skubas NJ, Sundt TM: A randomized clinical trial of continuous aspira-

tion of subglottic secretions in cardiac surgery patients. *Chest* 1999; 116:1339–1346
77. Holzapfel L, Chastang C, Demingeon G, et al: A randomized study assessing the systematic search for maxillary sinusitis in nasotracheally mechanically ventilated patients. Influence of nosocomial maxillary sinusitis on the occurrence of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1999; 159:695–701
78. Kollef MH, Shapiro SD, Fraser VJ, et al: Mechanical ventilation with or without 7-day circuit changes. A randomized controlled trial. *Ann Intern Med* 1995; 123: 168–174
79. Long MN, Wickstrom G, Grimes A, et al: Prospective, randomized study of ventilator-associated pneumonia in patients with one versus three ventilator circuit changes per week. *Infect Control Hosp Epidemiol* 1996; 17:14–19
80. Dreyfuss D, Djedaini K, Weber P, et al: Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 hours versus no change. *Am Rev Respir Dis* 1991; 143:738–743
81. Drakulovic MB, Torres A, Bauer TT, et al: Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. *Lancet* 1999; 354:1851–1858
82. Dreyfuss D, Djedaini K, Gros I, et al: Mechanical ventilation with heated humidifiers or heat and moisture exchangers: Effects on patient colonization and incidence of nosocomial pneumonia. *Am J Respir Crit Care Med* 1995; 151:986–992
83. Kirton OC, DeHaven B, Morgan J, et al: A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: Rates of ventilator-associated early-onset (community-acquired) or late-onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. *Chest* 1997; 112:1055–1059
84. Hurni JM, Feihl F, Lazor R, et al: Safety of combined heat and moisture exchanger filters in long-term mechanical ventilation. *Chest* 1997; 111:686–691
85. Roustan JP, Kienlen J, Aubas P, et al: Comparison of hydrophobic heat and moisture exchangers with heated humidifier during prolonged mechanical ventilation. *Intensive Care Med* 1992; 18:97–100
86. Kollef MH, Shapiro SD, Boyd V, et al D: A randomized clinical trial comparing an extended-use hygroscopic condenser humidifier with heated-water humidification in mechanically ventilated patients. *Chest* 1998; 113:759–767
87. Apte NM, Karnad DR, Medhekar TP, et al: Gastric colonization and pneumonia in intubated critically ill patients receiving stress ulcer prophylaxis: A randomized, controlled trial. *Crit Care Med* 1992; 20: 590–593
88. Metz CA, Livingston DH, Smith JS, et al: Impact of multiple risk factors and ranitidine prophylaxis on the development of stress-related upper gastrointestinal bleeding: A prospective, multicenter, double-blind, randomized trial. The Ranitidine Head Injury Study Group. *Crit Care Med* 1993; 21:1844–1849
89. Ben-Menachem T, Fogel R, Patel RV, et al: Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit. A randomized, controlled, single-blind study. *Ann Intern Med* 1994; 121:568–575
90. Eddleston JM, Pearson RC, Holland J, et al: Prospective endoscopic study of stress erosions and ulcers in critically ill adult patients treated with either sucralfate or placebo. *Crit Care Med* 1994; 22:1949–1954
91. Pickworth KK, Falcone RE, Hoogeboom JE, et al: Occurrence of nosocomial pneumonia in mechanically ventilated trauma patients: A comparison of sucralfate and ranitidine. *Crit Care Med* 1993; 21:1856–1862
92. Eddleston JM, Vohra A, Scott P, et al: A comparison of the frequency of stress ulceration and secondary pneumonia in sucralfate- or ranitidine-treated intensive care unit patients. *Crit Care Med* 1991; 19: 1491–1496
93. Thomason MH, Payseur ES, Hakenewerth AM, et al: Nosocomial pneumonia in ventilated trauma patients during stress ulcer prophylaxis with sucralfate, antacid, and ranitidine. *J Trauma* 1996; 41:503–508
94. Prod'hom G, Leuenberger P, Koerfer J, et al: Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer. A randomized controlled trial. *Ann Intern Med* 1994; 120:653–662
95. O'Keefe GE, Gentilello LM, Maier RV: Incidence of infectious complications associated with the use of histamine2-receptor antagonists in critically ill trauma patients. *Ann Surg* 1998; 227:120–125
96. Cook D, Guyatt G, Marshall J, et al: A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med* 1998; 338:791–797
97. Mustafa NA, Akturk G, Ozen I, et al: Acute stress bleeding prophylaxis with sucralfate versus ranitidine and incidence of secondary pneumonia in intensive care unit patients. *Intensive Care Med* 1995; 21:287
98. Bonten MJ, Gaillard CA, van der Geest S, et al: The role of intragastric acidity and stress ulcus prophylaxis on colonization and infection in mechanically ventilated ICU patients. A stratified, randomized, double-blind study of sucralfate versus antacids. *Am J Respir Crit Care Med* 1995; 152: 1825–1834
99. Darvas JA, Hawkins LG: The closed tracheal suction catheter: 24 hour or 48 hour change? *Aust Crit Care* 2003; 16:86–92
100. Zeitoun SS, de Barros AL, Diccini S: A prospective, randomized study of ventilator-associated pneumonia in patients using a closed vs. open suction system. *J Clin Nurs* 2003; 12:484–489
101. Johnson KL, Kearney PA, Johnson SB, et al: Closed versus open endotracheal suctioning: Costs and physiologic consequences. *Crit Care Med* 1994; 22:658–666
102. Bonten MJ, Gaillard CA, van der Hulst R, et al: Intermittent enteral feeding: the influence on respiratory and digestive tract colonization in mechanically ventilated intensive-care-unit patients. *Am J Respir Crit Care Med* 1996; 154:394–399
103. Kearns PJ, Chin D, Mueller L, et al: The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: A randomized clinical trial. *Crit Care Med* 2000; 28:1742–1746
104. Sirvent JM, Torres A, El-Ebiary M, et al: Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. *Am J Respir Crit Care Med* 1997; 155: 1729–1734
105. Memish ZA, Oni GA, Djazmati W, et al: A randomized clinical trial to compare the effects of a heat and moisture exchanger with a heated humidifying system on the occurrence rate of ventilator-associated pneumonia. *Am J Infect Control* 2001; 29: 301–305
106. Stoller JK, Orens DK, Fatica C, et al: Weekly versus daily changes of in-line suction catheters: Impact on rates of ventilator-associated pneumonia and associated costs. *Respir Care* 2003; 48:494–499
107. Kollef MH, Vlasnik J, Sharpless L, et al: Scheduled change of antibiotic classes: A strategy to decrease the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1997; 156:1040–1048
108. Baker AM, Meredith JW, Haponik EF: Pneumonia in intubated trauma patients. Microbiology and outcomes. *Am J Respir Crit Care Med* 1996; 153:343–349
109. Ibrahim EH, Mehringer L, Prentice D, et al: Early versus late enteral feeding of mechanically ventilated patients: Results of a clinical trial. *JPEN J Parenter Enteral Nutr* 2002; 26:174–181
110. Daumal F, Colpart E, Manoury B, et al: Changing heat and moisture exchangers every 48 hours does not increase the incidence of nosocomial pneumonia. *Infect Control Hosp Epidemiol* 1999; 20: 347–349
111. Kollef MH, Von Harz B, Prentice D, et al: Patient transport from intensive care increases the risk of developing ventilator-associated pneumonia. *Chest* 1997; 112: 765–773
112. Boots RJ, Howe S, George N, et al: Clinical utility of hygroscopic heat and moisture exchangers in intensive care patients. *Crit Care Med* 1997; 25:1707–1712
113. Hanisch EW, Encke A, Naujoks F, et al: A

randomized, double-blind trial for stress ulcer prophylaxis shows no evidence of increased pneumonia. *Am J Surg* 1998; 176: 453–457
114. Kollef MH, Prentice D, Shapiro SD, et al: Mechanical ventilation with or without daily changes of in-line suction catheters. *Am J Respir Crit Care Med* 1997; 156: 466–472
115. Cunnion KM, Weber DJ, Broadhead WE, et al: Risk factors for nosocomial pneumonia: comparing adult critical-care populations. *Am J Respir Crit Care Med* 1996; 153: 158–162
116. Fagon JY, Chastre J, Hance AJ, et al: Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993; 94:281–288
117. Craig CP, Connelly S: Effect of intensive care unit nosocomial pneumonia on duration of stay and mortality. *Am J Infect Control* 1984; 12:233–238
118. Torres A, Aznar R, Gatell JM, et al: Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis* 1990; 142: 523–528
119. Rello J, Rue M, Jubert P, et al: Survival in patients with nosocomial pneumonia: impact of the severity of illness and the etiologic agent. *Crit Care Med* 1997; 25: 1862–1867
120. Craven DE, Kunches LM, Kilinsky V, et al: Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. *Am Rev Respir Dis* 1986; 133: 792–796
121. Vincent JL, Bihari DJ, Suter PM, et al: The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA* 1995; 274: 639–644
122. Fagon JY, Chastre J, Domart Y, et al: Mortality due to ventilator-associated pneumonia or colonization with *Pseudomonas* or *Acinetobacter* species: Assessment by quantitative culture of samples obtained by a protected specimen brush. *Clin Infect Dis* 1996; 23:538–542
123. Shorr AF, O'Malley PG: Continuous subglottic suctioning for the prevention of ventilator-associated pneumonia: Potential economic implications. *Chest* 2001; 119: 228–235
124. Cook D, De Jonghe B, Brochard L, et al: Influence of airway management on ventilator-associated pneumonia: Evidence from randomized trials. *JAMA* 1998; 279: 781–787