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Relationship between tracheotomy and ventilator-associated pneumonia: a case–control study

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ABSTRACT: The aim of the present study was to determine the relationship between tracheotomy and ventilator-associated pneumonia (VAP).

The study used a retrospective case–control study design based on prospective data. All nontrauma immunocompetent patients, intubated and ventilated for >7 days, were eligible for inclusion in the study. A diagnosis of VAP was based on clinical, radiographical and microbiological criteria. Four matching criteria were used, including duration of mechanical ventilation (MV). The indication and timing of tracheotomy were at the discretion of attending physicians. Univariate and multivariate analyses were performed to determine risk factors for VAP in cases (patients with tracheotomy) and controls (patients without tracheotomy).

In total, 1,402 patients were eligible for inclusion. Surgical tracheotomy was performed in 226 (16%) patients and matching was successful for 177 (78%). The rate of VAP (22 *versus* 14 VAP episodes·1,000 MV-days^{-1}) was significantly higher in controls than in cases. The rate of VAP after tracheotomy in cases, or after the corresponding day of MV in controls, was also significantly higher in control than in case patients (9.2 *versus* 4.8 VAP episodes·1,000 MV-days^{-1}). In multivariate analysis, neurological failure (odds ratio (95% confidence interval) 2.7 (1.3–5)), antibiotic treatment (2.1 (1.1–3.2)) and tracheotomy (0.18 (0.1–0.3)) were associated with VAP.

In summary, the present study demonstrates that tracheotomy is independently associated with decreased risk for ventilator-associated pneumonia.

KEYWORDS: Intensive care, nosocomial pneumonia, risk factors, tracheostomy, tracheotomy, ventilator-associated pneumonia

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STATEMENT OF INTEREST
None declared.

Ventilator-associated pneumonia (VAP) occurs in a considerable proportion of patients undergoing mechanical ventilation and is associated with substantial morbidity, two-fold mortality rate and excess cost [1]. Strategies that effectively prevent VAP are needed. Identifying modifiable risk factors for VAP could be helpful for future controlled interventional studies aiming at improving prevention of VAP [2].

Short-term tracheotomy is frequently performed in intensive care unit (ICU) patients with weaning difficulties or predicted long periods of mechanical ventilation (MV). According to the results of two recent studies performed on >40,000 patients, 7.7–10.7% of ICU patients receive invasive MV through a tracheotomy cannula during their ICU stay [3, 4].

Recent studies reported high VAP rates after surgical and percutaneous tracheotomy (25 and 18%, respectively) [5, 6]. In these studies, most VAP episodes occurred in the week following the procedure. Unfortunately, the incidence of VAP after tracheotomy was not compared with VAP incidence before tracheotomy, or with VAP incidence in patients without tracheotomy. Several recent studies identified tracheotomy as an independent risk factor for VAP [7–10]. However, only one study excluded tracheotomy from risk factor analysis when it was performed after VAP occurrence [8]. In addition, none of these studies adjusted for the duration of MV. These data suggest that tracheotomy is rather a marker of longer duration of MV than a risk factor for VAP. Moreover, based on the pathophysiology of VAP, tracheotomy could be protective against VAP. Therefore, the present

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retrospective case–control study was performed to determine the relationship between VAP and tracheotomy.

PATIENTS AND METHODS

The current retrospective observational case–control study was performed in a 30-bed ICU from January 1996–January 2001. All data were prospectively collected. As the study was observational, Institutional Review Board approval was not required in accordance with Institutional Review Board Regulation.

All patients intubated and ventilated for >7 days were eligible. Trauma patients, immunodepressed patients and patients with tracheotomy at ICU admission were not eligible for inclusion in the study.

Study population

Patients were intubated either *via* the oral or nasal route according to the clinical status and the habits of the physician in charge. The oropharyngeal cavity was cleaned four times a day with chlorhexidine solution. Continuous subglottic suctioning was not utilised. The ventilator circuit was not changed routinely. In all patients, a heat–moisture exchanger was positioned between the Y piece and the patient, the heat–moisture exchangers were changed every 48 h or more frequently if visibly soiled. Patients were kept in a semi-recumbment position during most of their MV period. The intracuff pressure of the endotracheal tube and tracheotomy cannula was maintained at ~25 cmH_2O. In tracheotomised patients, tracheotomy cannula was changed twice a week. There was no systematic stress ulcer prophylaxis and no selective digestive decontamination. Infection control policy included isolation techniques in patients with multidrug-resistant (MDR) bacteria, written antibiotic treatment protocol and continuous surveillance of nosocomial infections. The indication and timing of tracheotomy were at the physicians' discretion. Only surgical tracheotomy was performed during the study period. In most patients, tracheotomy was performed by ICU physicians at the patient's bed. In patients with anticipated difficult tracheotomy, the procedure was performed in the operating room by a surgeon.

Definitions

All cases were tracheotomised patients and controls were patients without tracheotomy. Tracheotomy was considered as late if it was performed >7 days after the initiation of MV. VAP was defined by the presence of new or progressive radiographical infiltrate associated with two of the following criteria: temperature >38.5°C or <36.5°C; leukocyte count >10,000·μL^{-1} or <1,500·μL^{-1}; purulent tracheal aspirate; and a positive ($\geq 10^6$ colony forming units·mL^{-1}) tracheal aspirate culture. VAP episodes were identified by prospective surveillance of nosocomial infections. First episodes of VAP occurring >48 h after the initiation of MV, relapses, and superinfections were taken into account in this study. Recurrence of bacterial infection (same antibiotic susceptibility) during treatment for the first episode of VAP was considered to be a persistent VAP, however, recurrence after the end of treatment was defined as a relapse; other episodes of VAP were considered superinfections [11]. VAP episodes occurring <5 days after starting MV were considered as early-onset. Late-onset VAP was defined as VAP diagnosed ⩾5 days after the initiation of MV. Immunodepression was defined as active solid or haematological malignancy, or organ transplantation antecedent with chronic use of immunosuppressive therapy. During the study period, no HIV-infected patient was admitted to the ICU. Prior antibiotic use was defined as any antibiotic treatment during the 2 weeks preceding ICU admission. MDR bacteria were defined as: methicillin-resistant *Staphylococcus aureus* (MRSA), ceftazidime or imipenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, extending-spectrum β-lactamase-producing Gram-negative bacilli and *Stenotrophomonas maltophilia*.

Matching criteria

Each case patient was matched to one control according to all the following criteria. 1) Age ± 5 yrs; 2) Simplified Acute Physiology Score (SAPS) II on admission ±5 points; 3) category of admission (medical/surgical); 4) duration of mechanical ventilation ±3 days; and 5) date of ICU admission when more than one potential control was well matched to a case.

Statistical analysis

Cases were compared with controls using a Chi-squared test or Fisher's exact test when appropriate for qualitative variables, and Mann–Whitney U-test for quantitative variables. Results are presented as frequency (%) for qualitative variables or mean±SD for quantitative variables.

VAP rates were compared between cases and controls. Rates of VAP occurring after tracheotomy in cases, or after the corresponding day of mechanical ventilation in controls were also compared between the two groups.

Univariate and multivariate analyses were performed to determine variables associated with VAP. The following variables were included in the univariate analysis: age; sex; SAPS II at ICU admission; transfer to the ICU from a ward; diabetes mellitus; chronic obstructive pulmonary disease (COPD) [12]; prior antibiotic use; surgery; organ failure [13]; stress ulcer prophylaxis; antibiotic use during ICU stay; duration of antibiotic treatment during ICU stay; tracheotomy; and duration of MV. In patients with VAP, only exposure to potential risk factors before the last VAP episode was taken into account. Variables with a p-value <0.2 were included in the stepwise logistic regression model and any potential interactions were tested.

RESULTS

Study population

In total, 1,402 patients were eligible for inclusion into the current study. Surgical tracheotomy was performed in 226 (16%) patients and matching was successful for 177 (78%). The mean duration of MV before tracheotomy was 21±12 days. Tracheotomy was performed >7 days after the start of MV in 128 (72%) out of 177 patients. A total of 178 VAP episodes were diagnosed in 124 patients, including 151 (84%) with late-onset VAP. There were 69 VAP episodes that occurred after tracheotomy in case patients, or after the corresponding day of MV in control patients (fig. 1). The mean time between the start of MV and first episode of VAP was 15±10 days. The mean time between tracheotomy, or the corresponding day of MV in control patients, and subsequent VAP episode was

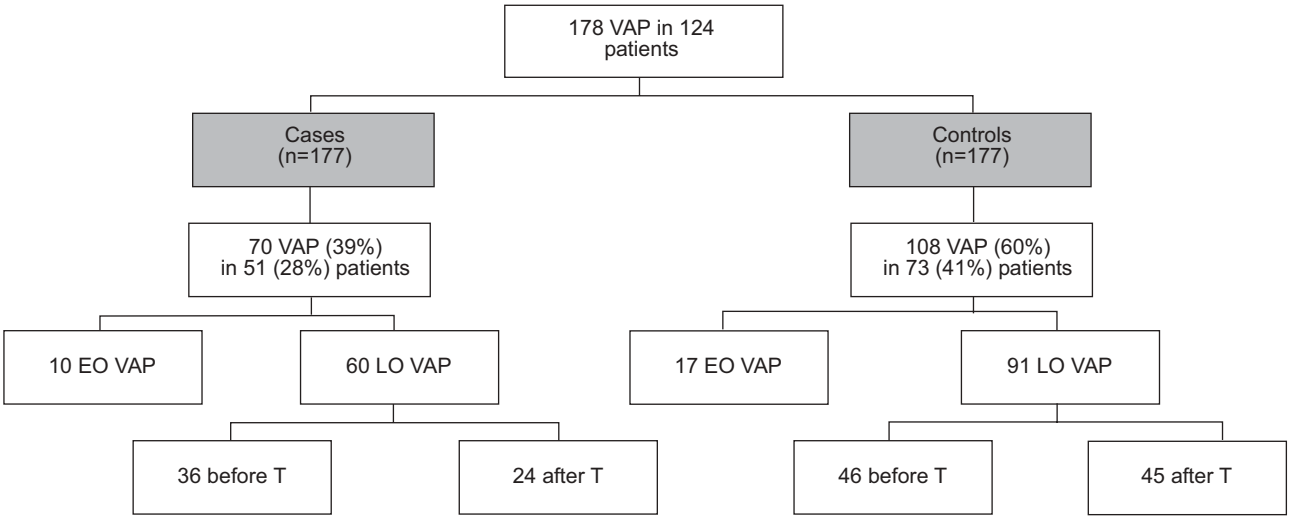

FIGURE 1. Distribution of ventilator-assisted pneumonia (VAP) episodes in case and control patients. EO: early-onset; LO: late-onset. T: the day of tracheotomy in cases or the corresponding day of mechanical ventilation in controls.

4.5±2.1 *versus*. 4.9±2.5 days (p=0.514) in case and control patients, respectively.

Although male sex and COPD rates were significantly higher in cases than in controls, transfer to the ICU from a ward was more frequent in controls than in cases. Other patient characteristics were similar in case and control patients (table 1).

Microbiological results

A total of 248 bacteria were associated with 178 VAP episodes in 124 patients. VAP was polymicrobial in 35 (19%) out of 178 episodes. MDR bacteria were associated with 61 (34%) out of 178 VAP episodes. *P. aeruginosa* (25%), *A. baumannii* (14%) and MRSA (10%) were the most frequently isolated bacteria (table 2).

TABLE 1 Characteristics of study patients

	Case patients	Control patients	p-value	OR (95% CI)
Subjects	177	177		
At ICU admission				
Age yrs	59±16	60±15	0.891	
Male	141 (79)	122 (68)	0.021	1.7 (1–2.7)
SAPS II	41±12	42±12	0.872	
Transfer to ICU from ward	137 (77)	158 (89)	0.002	1.6 (1.1–2.4)
Diabetes mellitus	25 (14)	24 (13)	0.550	
COPD	106 (59)	84 (47)	0.013	1.2 (1–1.5)
Prior antibiotic treatment	102 (57)	111 (62)	0.193	
Surgery	39 (22)	39 (22)	0.551	
Failed organs	1.4±0.6	1.6±0.8	0.575	
Type of organ failure				
Cardiac	27 (15)	40 (22)	0.052	
Respiratory	146 (82)	153 (86)	0.189	
Renal	24 (13)	30 (16)	0.230	
Neurological	29 (16)	21 (11)	0.143	
Digestive	7 (3)	7 (3)	0.607	
During ICU stay				
Stress ulcer prophylaxis	91 (51)	95 (53)	0.375	
Antibiotic treatment	106 (59)	104 (58)	0.457	
Duration of antibiotic treatment days	12±12	15±15	0.060	

Data are presented as n, mean±SD or n (%), unless otherwise stated. OR: odds ratio; CI: confidence interval; ICU: intensive care unit; SAPS: simplified acute physiology score; COPD: chronic obstructive pulmonary disease.

TABLE 2 Bacteria isolated in 124 patients with 178 ventilator-associated pneumonia (VAP) episodes

Microorganisms	VAP			p-value#
	All episodes	Cases	Controls	
Subjects	178	70	108	
All bacteria	248	96	152	
Gram-negative	194 (78)	71 (73)	123 (80)	0.128
Pseudomonas aeruginosa	62 (25)	22 (22)	40 (26)	0.328
Acinetobacter baumannii	35 (14)	11 (11)	24 (15)	0.223
Escherichia coli	21 (8)	9 (9)	12 (7)	0.426
Enterobacter species	21 (8)	7 (7)	14 (9)	0.390
Serratia species	19 (7)	8 (8)	11 (7)	0.465
Stenotrophomonas maltophilia	16 (6)	5 (5)	11 (7)	0.363
Klebsiella species	13 (5)	5 (5)	8 (5)	0.614
Proteus species	7 (2)	4 (4)	3 (1)	0.263
Gram-positive	54 (21)	25 (26)	29 (19)	0.128
Methicillin-resistant *S. aureus*	25 (10)	9 (9)	16 (10)	0.475
Methicillin-sensitive *S. aureus*	23 (9)	13 (13)	10 (6)	0.055
Streptococcus pneumoniae	6 (2)	3 (3)	3 (1)	0.429
Polymicrobial VAP	35 (19)	13 (18)	22 (20)	0.463
VAP related to MDR bacteria	61 (34)	19 (27)	42 (38)	0.073

Data are presented as n or n (%). *S. aureus*: *Staphylococcus aureus*; MDR: multi-drug resistant. #: VAP in cases *versus* controls.

Outcome of study patients

The outcomes of study patients are presented in table 3 and the outcomes of case patients with early or late tracheotomy are presented in table 4. The duration of MV (31±14 *versus* 24±14 days, p<0.001), ICU stay (33±14 *versus* 27±17 days, p=0.002) and ICU mortality (72 (58%) out of 124 *versus* 96 (41%) out of 230 patients, p=0.001; odds ratio (95% confidence interval) 2 (1.2–3.1)) were significantly higher in patients with VAP than in patients without VAP.

Risk factors for VAP

Prior antibiotic treatment, neurological failure, antibiotic treatment during ICU stay, duration of antibiotic treatment during ICU stay and tracheotomy were significantly associated with VAP in univariate analysis (table 5). Neurological failure and antibiotic treatment during ICU stay were independently associated with increased risk for VAP. Tracheotomy was independently associated with decreased risk for VAP (table 6).

DISCUSSION

The present study demonstrates that tracheotomy is independently associated with lower rates of VAP. Neurological failure and antibiotic treatment are independent risk factors for VAP. In addition, early tracheotomy is associated with lower rates of VAP and ICU mortality, and shorter duration of MV and ICU stay as compared with late tracheotomy.

Previous studies identified tracheotomy as an independent risk factor for VAP [7–10]; however, no adjustment was performed for the duration of MV, which is probably the most important risk factor for VAP [14]. To the present authors' knowledge, the current study is the first to evaluate the relationship between tracheotomy and VAP using matching for several important confounding factors, including duration of MV. The high rate of VAP found by this study could be explained by the fact that only patients requiring mechanical ventilation for >7 days were included.

Based on the pathophysiology of VAP in intubated patients, it can be argued that tracheotomised patients are at decreased risk for VAP than patients with translaryngeal intubation. Several factors support this hypothesis. In intubated patients, the endotracheal tube allows aspiration of contaminated oropharyngeal secretions into the lung, which contributes to tracheal colonisation and subsequent VAP development [15]. Liberation of the vocal cords in tracheotomised patients results in normal closure and reduces the risk of aspiration of secretions from the oropharyngeal cavity. In addition, the endotracheal tube provides a surface for the formation of a bacterial biofilm [16], which plays an important role as a reservoir for infecting microorganisms. Fragments of biofilm may be dislodged and carried further into the lung by ventilator gas flow, and bacteria encased in this biofilm are

TABLE 3 Outcomes of study patients

	Case patients	Control patients	p-value	OR (95% CI)
Subjects	177	177		
Patients with VAP	51 (28)	73 (41)	0.010	1.7 (1.1–2.6)
VAP episodes·1000 MV-days^{-1}	14	22	0.009	
Patients with VAP after T	24 (13)	43 (24)	0.003	2.1 (1.2–3.7)
VAP episodes after T·1000 MV-days^{-1}	4.8	9.2	0.005	
Duration of MV days	28±14	27±14	0.765	
Length of ICU stay days	31±17	30±14	0.120	
ICU mortality	73 (41)	95 (53)	0.010	1.6 (1.1–2.5)

Data are presented as n, n (%) or mean±SD, unless otherwise stated. OR: odds ratio; CI: confidence interval; VAP: ventilator-associated pneumonia; MV: mechanical ventilation; T: tracheotomy day in cases, or the corresponding day of mechanical ventilation in controls; ICU: intensive care unit.

TABLE 4 Outcomes of patients with early and late tracheotomy

	Early tracheotomy	Late tracheotomy	p-value	OR (95% CI)
Subjects	49	128		
Patients with VAP	9 (18)	42 (32)	0.041	1.7 (1–3.3)
VAP episodes·1000 MV-days^{-1}	13	18	0.047	
Duration of MV days	12±4	34±15	<0.001	
Length of ICU stay days	20±15	37±18	<0.001	
ICU mortality	7 (14)	66 (51)	0.001	3.6 (1.7–7.3)

Data are presented as n, n (%) or mean±SD, unless otherwise stated. OR: odds ratio; CI: confidence interval; VAP: ventilator-associated pneumonia; MV: mechanical ventilation; ICU: intensive care unit.

relatively resistant to the action of antimicrobials and host defences [17, 18]. Changing the tracheotomy cannula once or twice a week could be associated with reduced bacterial biofilm formation along the inside of the tracheotomy cannula. Furthermore, tracheotomy facilitates weaning from MV, resulting in a shorter duration of MV and probably a reduced risk for VAP [19, 20]. However, because of matching according to duration of MV, this factor could not be assessed in the present study.

TABLE 5 Risk factors for ventilator-associated pneumonia (VAP) in univariate analysis

	VAP patients	No VAP patients	p-value	OR (95% CI)
Subjects	124	230		
At ICU admission				
Age yrs	59±14	60±16	0.476	
Male	96 (77)	167 (72)	0.233	
SAPS II	43±13	41±11	0.591	
Transfer to ICU from ward	106 (85)	189 (82)	0.261	
Diabetes mellitus	19 (15)	30 (13)	0.330	
COPD	64 (51)	126 (54)	0.323	
Prior antibiotic treatment	83 (66)	130 (56)	0.036	1.5 (1–2.4)
Surgery	23 (18)	55 (23)	0.152	
Failed organs	1.6±0.7	1.5±0.7	0.220	
Type of organ failure				
Cardiac	23 (18)	44 (19)	0.507	
Respiratory	109 (87)	190 (82)	0.123	
Renal	18 (14)	36 (15)	0.453	
Neurological	25 (20)	25 (10)	0.014	2 (1.1–3.7)
Digestive	7 (5)	7 (3)	0.180	
During ICU stay				
Stress ulcer prophylaxis	72 (58)	114 (49)	0.078	
Antibiotic treatment	84 (67)	126 (54)	0.012	1.7 (1–2.7)
Duration of antibiotic treatment days	12±15	9±10	0.012	
Tracheotomy	24 (19)	126 (54)	<0.001	0.19 (0.11–0.33)
Duration of MV days	22±13	24±14	0.213	

Data are presented as n, n (%) or mean±SD, unless otherwise stated. In VAP patients, only exposure to potential risk factors before last VAP episode was taken into account. OR: odds ratio; CI: confidence interval; ICU: intensive care unit; SAPS: simplified acute physiology score; COPD: chronic obstructive pulmonary disease. MV: mechanical ventilation.

Early tracheotomy was associated with lower rates of VAP and mortality as compared with late tracheotomy. In addition, the duration of MV ventilation and ICU stay were significantly shorter in patients with early tracheotomy than in patients with late tracheotomy. Several previous studies have compared outcomes of patients with early and late tracheotomy [21–29]. In a recent retrospective study, MOLLER *et al.* [21] found significantly lower rates of VAP in patients with early tracheotomy as compared with patients with late tracheotomy. Two other retrospective studies found similar results [22, 23]. However, many prospective randomised trials [24–26, 28, 29] failed to demonstrate any significant association between VAP and early tracheotomy. In contrast, a recent prospective randomised study found early tracheotomy to be associated with shorter duration of MV and ICU stay, and lower rates of VAP and mortality [27]. However, early tracheotomy was defined as tracheotomy performed within 48 h of ICU admission. In addition, only patients with an Acute Physiology and Chronic Health Evaluation II score >25 were included in that study.

A systematic review and meta-analysis of studies on the timing of tracheotomy in adult patients undergoing MV was recently published [30] in which five randomised and quasi-randomised studies on 406 patients were analysed. Although early tracheotomy significantly reduced the duration of MV and ICU stay, no significant association was found between early

TABLE 6 Risk factors for ventilator-associated pneumonia in multivariate analysis

	p-value	OR (95% CI)
Neurological failure	0.004	2.7 (1.3–5)
Antibiotic treatment#	0.008	2.1 (1.1–3.2)
Tracheotomy	<0.001	0.18 (0.10–.31)

OR: odds ratio; CI: confidence interval. #: during intensive care unit stay.

tracheotomy and pneumonia. However, as outlined by GRIFFITHS *et al*. [30], the limited number of patients included in that study, and the heterogeneity of studied population and definitions of VAP and early tracheotomy, leave some doubt as to the accuracy of the results. Further well-conducted multicentre randomised studies are needed to determine the relationship between the timing of tracheotomy and VAP.

The present study identified neurological failure and antibiotic treatment as independent risk factors for VAP. Previous studies [10, 31] have found a significant association between coma and VAP. This association may be related to the frequent aspiration in patients with neurological impairment. One potential explanation for the association between VAP and antibiotic treatment is the fact that a first episode of VAP could be a risk factor for subsequent episodes of VAP. Antibiotic treatment is a well-known risk factor for VAP [32, 33]. In contrast, several recent observational studies found antibiotic treatment to be protective against early-onset VAP [31, 34, 35]. These conflicting results could be explained by the high rate of late-onset VAP in the current study. Two randomised open studies [36, 37] compared a short course of antibiotics to standard treatment in comatose mechanically ventilated patients. Although no difference was found in mortality rates, a significant reduction in early-onset VAP incidence was found in patients who received intravenous antibiotics as compared with those who received standard treatment.

The current study has several limitations. First, it was conducted in a single ICU; therefore, the results may not be applicable to other ICU patients. Secondly, it was a retrospective study; however, all data were prospectively collected. Thirdly, some well-known risk factors for VAP, such as reintubation, nasal intubation, enteral nutrition, transport outside the ICU and red blood cell transfusion were not investigated. Finally, 22% of tracheotomised patients could not be matched.

In summary, the present study demonstrates that tracheotomy is associated with decreased risk for ventilator-associated pneumonia. Early tracheotomy is associated with shorter duration of mechanical ventilation and stay in an intensive care unit, and lower rates of ventilator-associated pneumonia and mortality as compared with late tracheotomy. Further randomised interventional studies are needed to confirm the present results.

REFERENCES

1 Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med* 2005; 33: 2184–2193.
2 Kollef MH. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. *Crit Care Med* 2004; 32: 1396–1405.
3 Blot F, Melot C. Indications, timing, and techniques of tracheostomy in 152 French ICUs. *Chest* 2005; 127: 1347–1352.
4 Frutos-Vivar F, Esteban A, Apezteguia C, *et al*. Outcome of mechanically ventilated patients who require a tracheostomy. *Crit Care Med* 2005; 33: 290–298.
5 Georges H, Leroy O, Guery B, Alfandari S, Beaucaire G. Predisposing factors for nosocomial pneumonia in patients receiving mechanical ventilation and requiring tracheotomy. *Chest* 2000; 118: 767–774.
6 Rello J, Lorente C, Diaz E, *et al*. Incidence, etiology, and outcome of nosocomial pneumonia in ICU patients requiring percutaneous tracheotomy for mechanical ventilation. *Chest* 2003; 124: 2239–2243.
7 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.
8 Ibrahim EH, Tracy L, Hill C, Fraser VJ, Kollef MH. The occurrence of ventilator-associated pneumonia in a community hospital: risk factors and clinical outcomes. *Chest* 2001; 120: 555–561.
9 Apostolopoulou E, Bakakos P, Katostaras T, Gregorakos L. Incidence and risk factors for ventilator-associated pneumonia in 4 multidisciplinary intensive care units in Athens, Greece. *Respir Care* 2003; 48: 681–688.
10 Alp E, Guven M, Yildiz O, Aygen B, Voss A, Doganay M. Incidence, risk factors and mortality of nosocomial pneumonia in intensive care units: a prospective study. *Ann Clin Microbiol Antimicrob* 2004; 3: 1–7.
11 Combes A, Figliolini C, Trouillet JL, *et al*. Factors predicting ventilator-associated pneumonia recurrence. *Crit Care Med* 2003; 31: 1102–1107.
12 Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: S77–S121.
13 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. *Ann Surg* 1985; 202: 685–693.
14 Niederman M, Craven DE. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416.
15 Cavalcanti M, Valencia M, Torres A. Respiratory nosocomial infections in the medical intensive care unit. *Microbes Infect* 2005; 7: 292–301.
16 Feldman C, Kassel M, Cantrell J, *et al*. The presence and sequence of endotracheal tube colonization in patients undergoing mechanical ventilation. *Eur Respir J* 1999; 13: 546–551.
17 Adair CG, Gorman SP, Feron BM, *et al*. Implications of endotracheal tube biofilm for ventilator-associated pneumonia. *Intensive Care Med* 1999; 25: 1072–1076.
18 Shah C, Kollef MH. Endotracheal tube intraluminal volume loss among mechanically ventilated patients. *Crit Care Med* 2004; 32: 120–125.
19 Freeman BD, Borecki IB, Coopersmith CM, Buchman TG. Relationship between tracheostomy timing and duration of mechanical ventilation in critically ill patients. *Crit Care Med* 2005; 33: 2513–2520.
20 Hsu CL, Chen KY, Chang CH, Jerng JS, Yu CJ, Yang PC. Timing of tracheostomy as a determinant of weaning success in critically ill patients: a retrospective study. *Crit Care* 2005; 9: R46–R52.
21 Moller MG, Slaikeu JD, Bonelli P, Davis AT, Hoogeboom JE, Bonnell BW. Early tracheostomy *versus* late tracheostomy in the surgical intensive care unit. *Am J Surg* 2005; 189: 293–296.

22 Lesnik I, Rappaport W, Fulginiti J, Witze D. The role of early tracheostomy in blunt, multiple organ trauma. *Am Surg* 1992; 58: 346–349.

23 Kluger Y, Paul DB, Lucke J, *et al.* Early tracheostomy in trauma patients. *Eur J Emerg Med* 1996; 3: 95–101.

24 Sugerman HJ, Wolfe L, Pasquale MD, *et al.* Multicenter, randomized, prospective trial of early tracheostomy. *J Trauma* 1997; 43: 741–747.

25 Rodriguez JL, Steinberg SM, Luchetti FA, Gibbons KJ, Taheri PA, Flint LM. Early tracheostomy for primary airway management in the surgical critical care setting. *Surgery* 1990; 108: 655–659.

26 Dunham CM, LaMonica C. Prolonged tracheal intubation in the trauma patient. *J Trauma* 1984; 24: 120–124.

27 Rumbak MJ, Newton M, Truncale T, Schwartz SW, Adams TW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Crit Care Med* 2004; 32: 1689–1694.

28 Bouderka MA, Fakhir B, Bouaggad A, Hmamouchi B, Hamoudi D, Harti A. Early tracheostomy *versus* prolonged endotracheal intubation in severe head injury. *J Trauma* 2004; 57: 251–254.

29 Saffle JR, Morris SE, Edelman L. Early tracheostomy does not improve outcome in burn patients. *J Burn Care Rehabil* 2002; 23: 431–438.

30 Griffiths J, Barber VS, Morgan L, Young JD. Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. *BMJ* 2005; 330: 1243.

31 Bornstain C, Azoulay E, De Lassence A, *et al.* Sedation, sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia. *Clin Infect Dis* 2004; 38: 1401–1408.

32 Kollef MH. Ventilator-associated pneumonia. A multivariate analysis. *JAMA* 1993; 270: 1965–1970.

33 Crouch BS, Wunderink RG, Jones CB, Leeper KV Jr. Ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. *Chest* 1996; 109: 1019–1029.

34 Rello J, Diaz E, Roque M, Valles J. Risk factors for developing pneumonia within 48 hours of intubation. *Am J Respir Crit Care Med* 1999; 159: 1742–1746.

35 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.

36 Acquarolo A, Urli T, Perone G, Giannotti C, Candiani A, Latronic N. Antibiotic prophylaxis of early onset pneumonia in critically ill comatose patients. A randomized study. *Intensive Care Med* 2005; 31: 510–516.

37 Sirvent JM, Torres A, El-Ebiary M, Castro P, de Batlle J, Bonet A. Protective effect of intravenously administrated cefuroxime against nosocomial pneumonia in patients with structural coma. *Am J Respir Crit Care Med* 1997; 155: 1729–1734.