Intensive Care Med (2005) 31:64–70
DOI 10.1007/s00134-004-2514-z

ORIGINAL

Marc Leone
Stéphane Delliaux
Aurélie Bourgoin
Jacques Albanèse
Franck Garnier
Ioana Boyadjiev
Francois Antonini
Claude Martin

Risk factors for late-onset ventilator-associated pneumonia in trauma patients receiving selective digestive decontamination

Received: 11 June 2004
Accepted: 2 November 2004
Published online: 2 December 2004

M. Leone (✉) · S. Delliaux · A. Bourgoin · J. Albanèse · F. Garnier · I. Boyadjiev · F. Antonini · C. Martin
Département d'Anesthésie et de Réanimation,
CHU Nord,
Chemin des Bourrelys, 13915 Marseille, France
e-mail: marc.leone@ap-hm.fr
Tel.: +33-49-1968650
Fax: +33-49-1962818

Abstract *Objective:* To determine the independent risk factors for late-onset ventilator-associated pneumonia (VAP) in trauma patients receiving selective digestive decontamination (SDD). *Design:* A 4-year, prospective cohort study of trauma patients meeting the following criteria: injury severity score >15, and duration of mechanical ventilation >5 days. Predictors of late-onset VAP occurrence were assessed by logistic regression analysis. *Population:* All patients received SDD consisting of polymixin E, gentamicin, and amphotericin B applied in nostrils, mouth, and gut with a 3-day course of parenteral cefazolin. VAP was suspected on clinical and radiological signs, and confirmed by the presence of at least one microorganism at a concentration of at least 10^4 CFU/ml on the broncho-alveolar lavage. *Measurement:* Independent risk factors for late-onset VAP. *Results:* A late-onset VAP was diagnosed in 90 (56%) out of 159 patients. Predicting factors for late-onset VAP were: use of non-depolarizing muscle relaxant agents for intubation [3.4 (CI 1.08–10.73)], duration of intubation [1.06 (CI 1.01–1.17)], length of intensive care unit (ICU) stay [1.05 (CI 1.02–1.09)], and prior tracheal colonization [1.03 (CI 1.02–1.21)]. Exposure to prior antimicrobial treatment, except SDD, conferred protection [0.3 (0.12–0.74)]. *Conclusion:* This study confirms the role of duration of intubation, length of ICU stay, and prior tracheal colonization in the development of late-onset VAP. The results also highlight the importance of the initial management on the development of late-onset VAP. The type of neuromuscular blocking agents to intubate trauma patients should be evaluated in future studies.

Keywords Pneumonia · Intensive care unit · Trauma · Risk factors · Logistic regression · Decontamination

Introduction

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection among intensive care unit (ICU) patients [1]. Debate persists about the mortality attributable to VAP, but VAP causes substantial morbidity by increasing the ICU stay [2, 3, 4, 5, 6, 7]. Risk factors for VAP have been described, but few investigations have been led in specific populations [8, 9, 10, 11].

Trauma admission is a recurrent risk factor for VAP [9, 12, 13, 14, 15]. The incidence of VAP among trauma patients is high, because of pharyngeal aspiration in patients with depressed consciousness. Risk factors for nosocomial pneumonia include injury severity score (ISS) >20, head injury, emergent intubation, collapse, and blunt trauma [14, 15, 16, 17]. Moreover, trauma patients undergo transport for various procedures [18]. The supine position for prolonged periods, the manipulation of their ventilator circuits, and the aspiration of contaminated

secretions accumulated above the cuff of the tracheal tube also represent risk factors for VAP [18].

Selective digestive decontamination (SDD) has been extensively studied for preventing VAP [19, 20, 21, 22]. The SDD regimen consists of topical non-absorbed antibiotics applied orally and through a nasogastric tube, and is associated with a short course of parenteral antibiotic [19]. SDD in trauma patients leads to decreased numbers of VAP episodes [15, 21]. This research was presented during the 12th Congress of the European Society of Anaesthesiology [23].

The risk factors for late-onset VAP in severe trauma patients receiving SDD have never been investigated. In the present study, we evaluated the independent factors associated with the occurrence of late-onset VAP in severe trauma patients receiving SDD.

Patients and methods

This prospective study was conducted from January 1998 to 2002 in a 700-bed teaching hospital. The protocol was in accordance with the ethical standards of our hospital's Committee for the Protection of Human Subjects. Informed consent was not obtained because this study did not modify existing diagnosis or therapeutic strategies. The ICU has 16 beds admitting medical, surgical, and trauma patients. To be eligible for evaluation patients had to have an ISS >15, and duration of mechanical ventilation >5 days. A team consisting of a senior physician with a nurse managed patients on the field. Criteria for intubation were Glasgow Coma Scale score (GCS) <9, acute respiratory distress, or agitation. The use of neuromuscular blockers for intubation, as well as the choice of agents, was dependent on the decision of this team.

All ventilated patients were monitored daily for the development of VAP. Age, sex, simplified acute physiology score (SAPS) II, ISS, GCS after resuscitation, and sepsis-related organ failure assessment (SOFA) scale were recorded on admission. The following dates were recorded: admission and discharge from the ICU and the hospital, onset of pneumonia. ICU and hospital lengths of stay, mortality rate at the time of discharge from ICU and hospital, and duration of mechanical ventilation were calculated. All events and interventions occurring until the ICU discharge were collected.

All patients received SDD as described elsewhere [22]. SDD agents consisted on polymixin E, gentamicin, and amphotericin B. A 2% mixture of these drugs in Orabase was applied four times daily on the oral mucosa and in the digestive tract until extubation. For the first 3 days, systemic cefazolin (1 g × 3 daily) was given to SDD patients.

Stress-ulcer prophylaxis was used in patients with a history of ulcer. Sucralfate was recommended in our protocol, but histamine-2 receptor antagonist was kept on in patients already treated with this drug (two patients). Patients received early enteral nutrition except those with a bowel perforation. They were in semi-recumbent position, and underwent mechanical ventilation with the ventilator set in volume-controlled mode. Heat and moisture exchanger bacterial filters (Gibeck, Stockholm, Sweden) were inserted between the endotracheal tube and the ventilator circuit except for patients with acute respiratory distress syndrome (ARDS). Boluses of cistracurium were administered to assist in the treatment of patients with increased intracranial pressure (ICP), to facilitate mechanical ventilation, and to decrease oxygen demand in patients with ARDS [24].

Tracheal colonization was defined by the presence of potentially pathogenic microorganisms, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. in the tracheal aspirate obtained upon admission in the ICU and then twice weekly [13].

The diagnosis of VAP was established when the following criteria were fulfilled: 1) bronchial purulent sputum; 2) body temperature >38 °C or <36 °C; 3) worsening of arterial oxygenation; 4) white blood cells >12,000/mm^3 or <4,000/mm^3; 5) chest radiograph showing new or progressive infiltrates; and 6) presence of at least one microorganism at a concentration of at least 10^4 colony-forming units/ml on the broncho-alveolar lavage [25].

The antimicrobial therapy was administered according to our local guidelines. Empirical treatment was administered after the collection of microbiological samples. For early-onset nosocomial infections, ceftriaxone was selected. Piperacillin-tazobactam was used for patients with peritonitis. For late-onset nosocomial infections, cefepime or imipenem was selected. An aminoglycoside or a quinolone was added according to the clinical impression of the patient's treating senior physician. Vancomycin was prescribed when methicillin-resistant staphylococci were suspected. De-escalation of antibiotic therapy consisted of either deleting one of the antibiotics of the prescribed combination or, whenever possible, to use a beta-lactam with a narrower spectrum.

Prior antimicrobial treatment was defined as the treatment of a documented or suspected infection before the occurrence of the late-onset VAP. Antibiotics administered for SDD, including cefazolin, and those for surgical prophylaxis, were excluded from this definition.

The following criteria were assessed as potential risk factors: 1) qualitative criteria related to past medical history: age, gender, diabetes, smoking, chronic alcoholic intoxication, immunodepression, pre-existing organ dysfunction; 2) qualitative criteria available on admission: intubation on the scene or in ICU, oral or nasal intubation, surgery on admission, vasopressors, type of trauma, head trauma, type of head trauma, chest trauma, type of chest injury, abdominal trauma, association of chest and abdominal trauma, tracheal colonization, neuromuscular blockers for intubation, mean arterial pressure <70 mmHg for longer than 5 min; 3) quantitative criteria on admission: SAPS II, ISS, SOFA, number of vasopressors, number of rib fractures, alcohol blood concentration; 4) qualitative criteria available during the ICU stay: ICP monitoring, mydriasis, ICP >25 mmHg, osmotherapy, cerebrospinal fluid derivation, use of propofol, hyperventilation, craniectomy, positive end-expiratory pressure (>5 cmH_2O), tracheostomy, vasopressor, transfusion (>4 red blood cell packs), nasogastric tube, sedation (midazolam, ketamine, propofol, pentobarbital, sufentanil), neuromuscular blockers, steroids, stress-ulcer prophylaxis, chest tube, organ dysfunction, prior use of antimicrobial treatment except SDD, ARDS; and 5) quantitative criteria during the ICU stay: number of intubations, number of catecholamines, duration of sedation, duration of chest tube, number of organ dysfunction, duration of intubation, mechanical ventilation, ICU stay, central venous line placement, arterial catheter placement, antimicrobial treatment except SDD.

Statistical analysis was performed using the Statistical Analysis software package (version 5, SAS Institute, Cary, N.C., USA). Univariate analysis was conducted to determine potential risk factor of VAP occurrence. The χ^2 or Fisher's exact test was used for qualitative variables, and Student *t*-test was used for quantitative variables. The required significance level was set at a P-value less than 0.05. Multivariate analysis quantified the respective effect of each variable on the occurrence of late-onset VAP. Stepwise logistic regression was performed (forward method, likelihood ratio). Explanatory variables in the logistic regression were: a) variables identified as potential risk factor by the univariate analysis with a cut off at 0.2; and b) variables known as risk factors by the scientific community. The condensed model was presented with crude odds ratio and 95% confident interval.

Table 1 Characteristics of patients on admission with *P*-value comparing patients with and without late-onset ventilator associated pneumonia. (*SAPS* Simplified Acute Severity Score, *ISS* Injury Severity Score, *GCS* Glasgow Coma Scale, *SOFA* Sepsis-related Organ Failure Assessment scale).

Characteristics on admission	Overall	Patients without VAP	Patients with VAP	*P*
	(*n*=159)	(*n*=69)	(*n*=90)	
Age (years, mean±SD)	35±15	36±15	34±15	0.72
Male/female	132/27	55/14	77/13	0.33
SAPS II (mean±SD)	44±11	45±10	44±11	0.43
ISS (mean±SD)	36±8	37±7	35±9	0.26
GCS (median [minimum-maximum])	6 [3–13]	5 [3–12]	6 [3–13]	0.15
SOFA (mean±SD)	6.3±5.5	6.4±5.2	6.1±5.8	0.68
Isolated head trauma (%)	47 (29)	19 (27)	28 (31)	0.24
Chest trauma (%)	85 (53)	38 (55)	47 (52)	0.72
Abdomen trauma (%)	28 (18)	14 (20)	14 (15)	0.8
Extremities (%)	59 (37)	34 (49)	25 (28)	0.5
Surgery at admission (%)	43 (27)	22 (31)	21 (23)	0.22
(including neurosurgery (%))	[19 (12)]	[11 (16)]	[8 (8.8)]	0.17
Intubation				
Oral/nasal (%)	148/11 (93/7)	65/4 (95/5)	83/7 (91/9)	0.42
Scene/ICU (%)	133/26 (84/16)	60/9 (87/13)	73/17 (81/19)	0.68
Vasopressor on scene (%)	28 (17)	12 (17)	16 (18)	0.94

Table 2 Univariate analysis: significant qualitative criteria associated with the occurrence of late-onset ventilator-associated pneumonia.

Criteria		Patients without VAP	Patients with VAP	*P*
		(*n*=69) (%)	(*n*=90) (%)	
Tracheal colonization	No	24 (35)	19 (21)	
	Yes	45 (65)	71 (79)	0.03
Neuromuscular blockers for intubation	No	45 (66)	47 (52)	
	Depolarizing	18 (26)	15 (17)	
	Non-depolarizing	6 (8)	28 (31)	0.01
Mean arterial pressure	>70 mmHg	58 (84)	61 (68)	
	<70 mmHg	11 (16)	29 (32)	0.02
Prior antimicrobial treatment[a]	No	37 (54)	64 (72)	
	Yes	32 (46)	26 (28)	0.02
ARDS[b]	No	62 (90)	67 (75)	
	Yes	7 (10)	23 (25)	0.01

[a] Except selective digestive decontamination and intravenous cefazolin on admission
[b] Acute respiratory distress syndrome

Results

Of the 159 severe trauma patients requiring at least 5 days of mechanical ventilation, 90 (56%) exhibited 116 late-onset VAP episodes on day 10.7±6.1 days after admission [range, 5–40 days] (Table 1). The main pathogens involved in late-onset VAP were *H. influenzae* (32%), *S. aureus* (31%), and *S. pneumonia* (13%), *Escherichia coli* (12%), and *A. baumanii* (7%). Among Gram-positive bacteria, 6% of *S. aureus* were methicillin-resistant, whereas 7% of Gram-negative bacteria were multi-resistant to antibiotics. *P. aeruginosa* was isolated in two patients. Prior antimicrobial treatment was administered in 58 patients with early-onset ventilator-associated pneumonia (20), intra-abdominal sepsis (18), catheter-associated urinary tract infection (6), and miscellaneous infections (14). Prior tracheal colonization was observed in 119 (75%) patients, and 77 (65%) among them developed a late-onset VAP. The same bacteria were found in colonization and infection in 53 patients.

The significant results of univariate analysis related to the qualitative events are reported in Table 2. Age, sex, significant past medical history of chronic alcohol abuse or smoking, immunosuppression, the place where intubation has been performed, the route of intubation, the need for surgery at admission, the type of injury, the severity of illness according to SAPS II, ISS, SOFA scores, the need for vasopressors, and alcohol intoxication were not found to be associated with an increased risk for late-onset VAP (Table 3). The criteria related to the ICU stay are collected in Fig. 1. The univariate analysis showed that the duration of intubation, mechanical ventilation, ICU stay, need for central line and arterial catheter, and prior antimicrobial treatment (excluding SDD) were significantly increased in patients with late-onset VAP compared with those without late-onset VAP. On the contrary, neurological events (ICP monitoring, osmotherapy, hyperventilation) were not observed more often in these patients. The following events were not related with a significant increase in late-onset VAP:

Table 3 Univariate analysis. Factors not related to the development of late-onset ventilator-associated pneumonia. (*SAPS* Simplified Acute Severity Score, *ISS* Injury Severity Score, *GCS* Glasgow Coma Scale, *SOFA* Sepsis-related Organ Failure Assessment scale).

Criteria on admission	*P*	Criteria in hospital	*P*	Score on admission	*P*
Age	0.72	Intracranial pressure monitoring	0.14	SAPS II	0.43
Sex	0.33	Mydriasis	0.1	ISS	0.26
Chronic alcohol abuse	0.19	Increased intracanial pressure	0.54	SOFA	0.43
Smoking	0.11	Osmotherapy	0.65		
Immunosuppression	0.16	Hyperventilation	0.16		
Pre-existing organ dysfunction	0.69	Use of propofol/pentobarbital	0.67/0.27		
Intubation on the field or hospital	0.68	Positive expiratory pressure (>5 cmH_2O)	0.3		
Oral or nasal intubation	0.42	Tracheostomy	0.16		
Surgery on admission	0.22	Catecholamines	0.68		
Vasopressors	0.94	Transfusion (>4 red blood cell packs)	0.36		
Isolated versus multiple trauma	0.24	Sedation/duration	0.09/0.07		
Head trauma (GCS <9)	0.07	Neuromuscular blockers	0.9		
Brain contusion	0.43	Steroids	0.6		
Subdural hematoma	0.75	Stress-ulcer prohylaxis	0.84		
Brain edema	0.38	Chest tube/duration	0.41/0.65		
Chest trauma	0.5	Organ dysfunction	0.47		
Rib fractures	0.19	Reintubations	0.18		
Pulmonary contusion	0.96				
Abdominal trauma	0.8				
Abdominal and chest trauma	0.48				
Alcohol blood level positive	0.17				

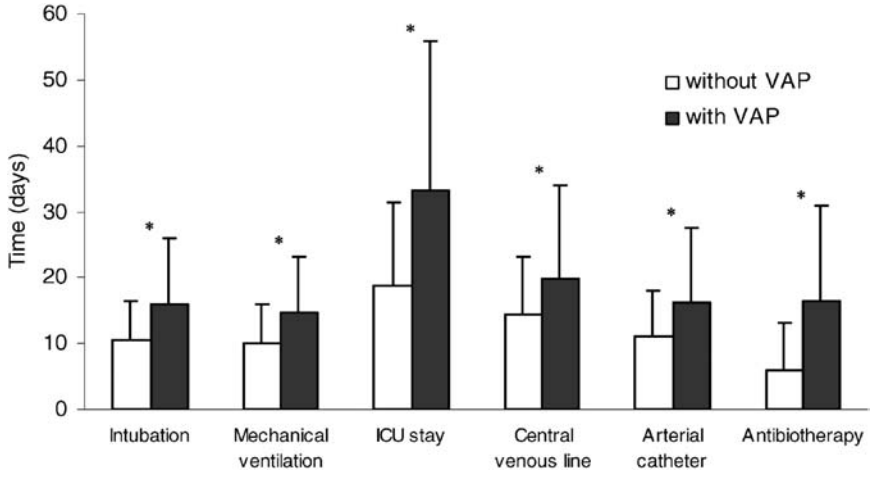

Fig. 1 Duration of intubation, mechanical ventilation, ICU stay, central line catheterization, arterial catheterization, and antibiotherapy treatment in patients with and without late-onset ventilator-associated pneumonia. *P<0.05

Table 4 Multivariate analysis: criteria associated with the occurrence of late-onset ventilator-associated pneumonia.

Criteria		Odd ratio	CI 95%	*P*
Prior antimicrobial therapy	No	1		
	Yes	0.31	0.12–0.74	0.009
Neuromuscular blockers for intubation	No	1		
	Depolarizing	0.54	0.19–1.54	0.25
	Non-depolarizing	3.41	1.08–10.73	0.03
Prior bronchial colonization	No	1		
	Yes	1.03	1.02–1.21	0.02
Duration of intubation		1.06	1.01–1.17	0.05
Length of ICU stay		1.05	1.02–1.09	0.002

catecholamine, transfusion of red blood cells, tracheotomy (n=5), positive expiratory pressure >5 cmH_2O (n=41), chest tube (n=42). Interventions like sedation (n=134) including neuromuscular blockers (n=48), steroids (n=14), stress ulcer prophylaxis (n=38), re-intubation (n=62) were not associated with an increased risk for late-onset VAP.

The condensed model is presented in Table 4. The multivariate analysis identified the following factors: prior tracheal colonization, duration of intubation, length of ICU stay, and the use of non-depolarizing neuromuscular blockers for intubation. Exposure to prior antimicrobial treatment [odds ratio, 0.31 (CI, 0.12–0.74)] conferred a protection.

The ICU mortality was of 30%. There is no significant difference between patients with late-onset VAP (26%) and those without late-onset VAP (37%).

Discussion

We examined the risk factors for late-onset ventilator-associated pneumonia, occurring in 56% of a cohort of 159 severe trauma patients receiving SDD. It is essential to emphasize that 88% of our patients presented a GCS score below 9 and 53% a chest trauma; both are two well-described risk factors for early-onset VAP [12, 13, 14, 17]. Patients with head trauma have compromised local airway immune defense mechanisms [12]. Traumatic injuries create a state of relative immunosuppression [26]. Moreover, the chest X-ray interpretation is complex in this context, which could have increased the number of positive diagnosis. Thus, the high incidence can be explained by the selection of patients with head and chest injuries requiring prolonged mechanical ventilation [17]. However, one hypothesis may be that the SDD delayed the outbreak of VAP, resulting in an increase number of late-onset VAP.

The use of neuromuscular blocking agents is not associated with an increased risk for late-onset VAP in our study. Nevertheless, non-depolarizing agents are linked with a 3.4-fold increase in late-onset VAP occurrence. Depolarizing agents tend to be associated with a protective effect. There is no strong recommendation concerning the use of neuromuscular blockers for the endotracheal intubation of trauma patients [27]. One hypothesis is that short-acting agents provide good conditions for intubation, which results in a decrease of the amount of aspiration [28]. However, suxamethonium induces a transient rise of the ICP [29]. Regarding neuromuscular blockers for intubation, our results suggest the need for future investigations.

The present study highlights the protective effect of prior antimicrobial treatments on the occurrence of late-onset VAP, as previously described by Cook et al. [9]. Actually, antibiotic administration was related to both an increased and a decreased risk for VAP [30]. The bacteria causing the late-onset VAP are typical of early-onset pathogens in 74% of our patients, with a low rate of multiresistant bacteria. This confirms the moderate effect of SDD on microbial ecology [22], and could be related to our protocols recommending short duration of treatment for ventilator-associated pneumonia. This statement should be confirmed by a rigorous study. However, as highlighted by others, the use of prophylactic antibiotic for selective digestive decontamination purpose is not associated with an increase of bacterial resistance [31, 32].

The relationship between the tracheal colonization and VAP has been demonstrated [12]. Both the upper airways and stomach represent independent reservoirs for tracheal colonization with ICU-acquired pathogens and VAP. Tracheal colonization within 24 h of intubation is an independent risk factor for VAP in patients with head injury [13]. The selective decontamination of the subglottic area in mechanically ventilated trauma patients significantly reduced tracheal colonization [33]. However, the use of SDD is never followed by a complete eradication of tracheal colonization. Colonization is significantly reduced, but still persistent, although at much lower levels. In the study of Bergmans et al., the use of SDD decreased colonization by 50% (52% in the control group versus 22% in the treated group) [34]. Bonten et al. observed a persistent or acquired colonization in 28–50% of patients receiving SDD. The persistence of tracheal colonization could be of concern, since it may lead to the subsequent development of nosocomial VAP [35]. However, in the present study, early tracheal colonization increased the risk for late-onset VAP by only 0.03. The hypothesis could be a persistent colonization with a low inoculum of bacteria which interferes itself with the emergence of late-onset pathogens. The SDD could induce a delay in the development of VAP with these persistent bacteria, explaining the number of early-onset pathogens causing late-onset VAP.

In agreement with other studies, ICU length of stay and duration of intubation are independent risk factors for VAP [5, 9]. Long-term intubation is related to prolonged mechanical ventilation due to head trauma. Regression analysis identified the length of intubation as an independent risk factor instead of head trauma or prolonged mechanical ventilation. We did not collect data on body position, but a causal relationship between supine position and VAP have been documented in many studies [30, 36, 37, 38]. For instance, transport in the supine position to the site of the radiological procedure could be linked to an increased risk for VAP, but this issue was not examined [39].

Some known risk factors were not found in our patients receiving SDD. The need for re-intubation has been associated with VAP [8]. In the present study, a sample-size effect may limit the effect of this risk factor. Chest trauma has been related to a 3.1 increase of the risk for early-onset VAP [16]. A combined abdominal and thoracic trauma represents the strongest risk factor for early-onset pneumonia [17]. This is not confirmed in our study since neither chest nor abdominal trauma are associated with late-onset VAP. Similarly, factors reflecting the severity of trauma, i.e. hypotension, ARDS, and GCS

score are not found as independent risk factors. Moreover, SAPS II, ISS, and SOFA are not reliable to predict late-onset pneumonia. Probably, the most severely ill patients develop an early-onset VAP, with a protective effect of antibiotics on the occurrence of late-onset VAP. However, in a study focusing on early-onset pneumonia, the APACHE II score was not significantly different between patients with and without VAP [17]. The occurrence of a late-onset VAP is not associated with an increase of mortality, which confirms the results of previous studies [2, 40]. A significant reduction of mortality has been demonstrated in mixed medical and surgical patients receiving SDD [31].

In conclusion, this study investigates the risk factors for late-onset VAP in trauma patients receiving SDD. As we previously demonstrated, the occurrence of a VAP induces an increase in the duration of mechanical ventilation and ICU stay. In trauma patients receiving SDD, several independent risk factors for the development of late-onset VAP are similar to those found in other patients: duration of intubation, length of ICU stay, and prior tracheal colonization. Some other independent risk factors were not found: re-intubation, chest trauma, abdominal trauma, hypotension, ARDS, and low GCS. The use of neuromuscular blocking agents is not associated with the risk for late-onset VAP and the type of neuromuscular blocking agents should be evaluated in future studies by a rigorous protocol.

References

1. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M (1995) 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 274:639–644
2. Leone M, Bourgoin A, Giuly E, Antonini F, Dubuc M, Viviand X, Albanese J, Martin C (2002) Influence on outcome of ventilator-associated pneumonia in multiple trauma patients with head trauma treated with selected digestive decontamination. Crit Care Med 30:1741–1746
3. Kollef MH, Silver P, Murphy DM, Trovillion E (1995) The effect of late-onset ventilator-associated pneumonia in determining patient mortality. Chest 108:1655–1662
4. Papazian L, Bregeon F, Thirion X, Gregoire R, Saux P, Denis JP, Perrin G, Charrel J, Dumon JF, Auffray JP, Gouin F (1996) Effect of ventilator-associated pneumonia on mortality and morbidity. Am J Respir Crit Care Med 154:91–97
5. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, Kollef MH; VAP Outcomes Scientific Advisory Group (2002) Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 122:2115–2121
6. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C (1993) Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 94:281–288
7. Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun-Buisson C (1999) 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 159:1249–1256
8. Ibrahim EH, Tracy L, Hill C, Fraser VJ, Kollef MH (2001) The occurrence of ventilator-associated pneumonia in a community hospital: risk factors and clinical outcomes. Chest 120:555–561
9. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, Jaeschke RZ, Brun-Buisson C (1998) Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 129:433–440
10. Bonten MJ, Bergmans DC, Ambergen AW, de Leeuw PW, van der Geest S, Stobberingh EE, Gaillard CA (1996) Risk factors for pneumonia, and colonization of respiratory tract and stomach in mechanically ventilated ICU patients. Am J Respir Crit Care Med 154:1339–1346
11. Beck-Sague CM, Sinkowitz RL, Chinn RY, Vargo J, Kaler W, Jarvis WR (1996) Risk factors for ventilator-associated pneumonia in surgical intensive-care-unit patients. Infect Control Hosp Epidemiol 17:374–376
12. Ewig S, Torres A, El-Ebiary M, Fabregas N, Hernandez C, Gonzalez J, Nicolas JM, Soto L (1999) Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. Am J Respir Crit Care Med 159:188–198
13. Sirvent JM, Torres A, Vidaur L, Armengol J, de Batlle J, Bonet A (2000) Tracheal colonisation within 24 h of intubation in patients with head trauma: risk factor for developing early-onset ventilator-associated pneumonia. Intensive Care Med 26:1369–1372
14. Rello J, Ausina V, Castella J, Nets A, Prats G (1992) Nosocomial respiratory tract infections in multiple trauma patients: influence of level of consciousness with implications for therapy. Chest 102:525–529
15. Rodriguez JL, Gibbons KJ, Bitzer LG, Dechert RE, Steinberg SM, Flint LM (1991) Pneumonia: Incidence, risks factors, and outcome in injured patients. J Trauma 31:907–914
16. Akça O, Koltka K, Uzel S, Cakar N, Pembeci K, Sayan MA, Tutuncu AS, Karakas SE, Calangu S, Ozkan T, Esen F, Telci L, Sessler DI, Akpir K (2000) Risk factors for early-onset, ventilator-associated pneumonia in critical care patients: Selected multiresistant versus non resistant bacteria. Anesthesiology 93:638–645
17. Antonelli M, Moro ML, Capelli O, De Blasi RA, D'Errico RR, Conti G, Bufi M, Gasparetto A (1994) Risk factor for early onset pneumonia in trauma patients. Chest 105:224–228
18. Albanèse J, Leone M, Martin C (2001) Severe head injury in patients with multiple trauma. In: Vincent JL (ed), Yearbook of intensive care and emergency medicine. Springer, Berlin Heidelberg New York, p 353–376
19. Stoutenbeek CP, van Saene HK, Miranda DR, Miranda DR, Zandstra DF (1984) The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med 185–192

20. Sun X, Wagner DP, Knaus WA (1996) Does selective decontamination of the digestive tract reduce mortality for severely ill patients? Crit Care Med 24:753–755
21. Bonten MJ, Brun-Buisson C, Weinstein RA (2003) Selective decontamination of the digestive tract: to stimulate or stifle? Intensive Care Med 29:672–676
22. Leone M, Albanèse J, Antonini F, Nguyen-Michel A, Martin C (2003) Long-term (6-year) effect of selective digestive decontamination on antimicrobial resistance in intensive care, multiple-trauma patients. Crit Care Med 31:2090–2095
23. Albanèse J, Leone M, Bourgoin A, Garnier F, Rousseau S, Boyadjev I, Martin C (2004) Risk factors of ventilator-associated pneumonia in trauma patients treated with selective digestive decontamination. Eur J Anaesth 160:A651
24. Shapiro BA, Warren J, Egol AB, Greenbaum DM, Jacobi J, Nasraway SA, Schein RM, Spevetz A, Stone JR (1995) Practice parameters for sustained neuromuscular blockade in the adult critically ill patient: an executive summary. Society of Critical Care Medicine. Crit Care Med 23:1601–1605
25. Cook DJ, Brun-Buisson C, Guyatt GH, Sibbald WJ (1994) Evaluation of new diagnostic technologies: bronchoalveolar lavage and the diagnosis of ventilator-associated pneumonia. Crit Care Med 22:1314–1322
26. Schmand JF, Ayala A, Chaudry IH (1994) Effects of trauma, duration of hypotension, and resuscitation regimen on cellular immunity after hemorrhagic shock. Crit Care Med 22:1076–1083
27. Tentillier E, Ammirati C (2000) Prehospital management of patients with severe head injuries. Ann Fr Anesth Reanim 19:275–281
28. Davis DP, Ochs M, Hoyt DB, Bailey D, Marshall LK, Rosen P (2003) Paramedic-administered neuromuscular blockade improves prehospital intubation success in severely head-injured patients. J Trauma 55:713–719
29. Ducey JP, Deppe SA, Foley KT (1989) A comparison of the effects of suxamethonium, atracurium and vecuronium on intracranial haemodynamics in swine. Anaesth Intensive Care 17:448–455
30. Cook DJ, Kollek MH (1998) Risk factors for ICU-acquired pneumonia. JAMA 279:1605–1606
31. de Jonge E, Schultz MJ, Spanjaard L, Bossuyt PMM, Vroom MB, Dankert J, Kesecioglu J (2003) Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet 362:1011–1016
32. Krueger WA, Lenhart FP, Neeser G, Ruckdeschel G, Schreckhase H, Eissner HJ, Forst H, Eckart J, Peter K, Unertl KE (2002) Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: a prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. Am J Respir Crit Care Med 166:1029–1037
33. Pneumatikos I, Koulouras V, Nathanail C, Goe D, Nakos G (2002) Selective decontamination of subglottic area in mechanically ventilated patients with multiple trauma. Intensive Care Med 28:432–437
34. Bergmans DC, Bonten MJ, Gaillard CA, Paling JC, van der Geest S, van Tiel FH, Beysens AJ, de Leeuw PW, Stobberingh EE (2001) Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med 164:382–388
35. Bonten MJ, Gaillard CA, Johanson WG Jr, van Tiel FH, Smeets HG, van der Geest S, Stobberingh EE (1994) Colonization in patients receiving and not receiving topical antimicrobial prophylaxis. Am J Respir Crit Care Med 150:1332–1340
36. Atherton ST, White DJ (1978) Stomach as source of bacteria colonizing respiratory tract during artificial respiration. Lancet 2:968–969
37. Ibanez J, Penafiel A, Raurich JM, Marse P, Jorda R, Mata F (1992) Gastroesophageal reflux in intubated patients receiving enteral nutrition: effect of supine and semirecumbent positions. JPEN J Parenter Enteral Nutr 16:419–422
38. Orozco-Levi M, Torres A, Ferrer M, Piera C, el-Ebiary M, de la Bellacasa JP, Rodriguez-Roisin R (1996) Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. Am J Respir Crit Care Med 152:1387–1390
39. Kollef MH, Von Harz B, Prentice D, Shapiro SD, Silver P, St John R, Trovillion E (1997) Patient transport from intensive care increases the risk of developing ventilator-associated pneumonia. Chest 112:765–773
40. Baker AM, Meredith JW, Haponik EF (1996) Pneumonia in intubated trauma patients: microbiology and outcomes. Am J Respir Crit Care Med 153:343–349