Risk factors for early-onset ventilator-associated pneumonia in aneurysmal subarachnoid hemorrhage patients

J.B. Cui, Q.Q. Chen, T.T. Liu and S.J. Li
Neurosurgery Intensive Care Unit, Weifang People’s Hospital, Weifang, China

Abstract
This study aimed to investigate the risk factors related to ventilator-acquired pneumonia (VAP) in aneurysmal subarachnoid hemorrhage (SAH) patients. From January 2011 to December 2015, a single-center retrospective study including 200 SAH patients requiring mechanical ventilation (MV) ≥48 h was performed. The clinical data of these patients were collected and analyzed. The age range of the patients were 41–63 and 72 (36%) were male. The Glasgow coma scale score range was 5–15 and the Simplified Acute Physiology Score II range was 31–52. One hundred and forty-eight (74%) patients had a World Federation of Neurosurgeons (WFNS) score ≥III. Aneurysm was secured with an endovascular coiling procedure in 168 (84%) patients and 94 (47%) patients presented VAP. Male gender (OR=2.25, 95%CI=1.15–4.45), use of mannitol (OR=3.02, 95%CI=1.53–5.94) and enteral feeding above 20 kcal.kg⁻¹.day⁻¹ (OR=2.90, 95%CI=1.26–6.67) after day 7 were independent factors for VAP. Patients with early-onset VAP had a longer duration of sedation (P=0.03), MV (P=0.001) and ICU length of stay (P=0.003) and a worse Glasgow Outcome Scale score (P<0.001), but did not have a higher death rate.

Key words: Ventilator-acquired pneumonia; Aneurysmal subarachnoid hemorrhage; Risk factors; Multivariate analysis; Pathogen

Introduction
Aneurysmal subarachnoid hemorrhage (SAH) is a life-threatening condition with increasing prevalence over the years (1). In most cases, mechanical ventilation (MV) and intensive care unit (ICU) hospitalization are mandatory. SAH patients frequently present with nosocomial infections and pneumonia, which might affect recovery (2). Recently, a few studies have reported on ventilator-acquired pneumonia (VAP) in SAH patients.

Among ICU patients, VAP remains a major cause of infection (3). Several studies have reported VAP in specific populations, such as head trauma patients (4–6). In that population, a VAP prevalence of up to 40% was found, with involvement of specific pathogens (5,7). VAP can result in substantial morbidity and high health-care costs, but a rather low mortality in head trauma patients (4,7). Most episodes of VAP in trauma patients occur in the first 7 days (5,7). Previous studies have pointed out specific risk factors, including the use of barbiturates (7–9), continuous sedation (10), intracranial hypertension (5), or delayed enteral feeding (7). In the present study, we aimed to determine the risk factors and pathogens involved in the early-onset VAP in SAH patients in China.

Patients and Methods
Patients
From January 2011 to December 2015, we conducted a retrospective single-center study in the ICU of our hospital. Patients hospitalized for an aneurysmal SAH and requiring MV ≥48 h were included in the study. Exclusion criteria were: 1) patients with an intra-cerebral hemorrhage from another origin, including arterio-venous malformation, non-aneurysmal subarachnoid hemorrhage, or non-traumatic intra-cerebral hemorrhage; 2) patients who were transferred to another center after aneurysmal coiling and could not fulfill follow-up for the primary endpoint; 3) patients who died in the first 2 days of ICU hospitalization. Written informed consent was obtained from all patients and the study was performed in accordance with the Ethics Committee approval of Weifang People’s Hospital.

Management of SAH patients
Computed tomography (CT) brain scan was used for aneurysmal SAH diagnosis. The aneurysm was confirmed
followed by a continuous infusion of 2
thiopental), with an intravenous (

vated after osmotherapy, barbiturates were injected (sodium

employed during the study period. When ICP remained ele-

kg, mannitol was applied. Hypertonic saline was not

20 kcal

cian

and nutrition procedures were left to the attending physi-

protocol was available in our ICU during the period of study

feeding tube in the stomach. Patients were fed continuously

vasospasm was given during arteriography by an experi-

21 days (1). Screening of vasospasm was performed once a

administered via enteral feeding tube (360 mg/day) during

Nimodipine (1

a chest X-ray was used to con

hypertension was de

X

tained

guidelines (11). Cerebral perfusion pressure was main-

and midazolam (0.2

sion. As soon as the enteral feeding started, nimodipine was

rm location of the tip of the

were calculated.

Data collection

Gender, age, Simplified Acute Physiology Score II (SAPS II),

medical history, GCS score on scene, World Federation of

Neurosurgeons score (WFNS), Fisher score, aneurysm

location, surgery upon admission, ventriculostomy realiza-

type of aneurysm, clip or coiling, and antibioprophyl-

axis were prospectively recorded. Stress-ulcer prophylaxis,

barbiturates, corticosteroids, insulin therapy, length of

sedation, and nutrition data were also noted during the

ICU stay. ICU length of stay (LOS), mortality rate at the

time of ICU discharge, and duration of sedation and of MV

were calculated.

Statistical analysis

All statistical analyses were performed in SPSS 18.0

(SPSS Inc., USA). Continuous data are reported as medians

and percentiles (25–75%) or means ± SD, and categorical
data as numbers and percentage. The χ² or Fisher’s exact
test was employed for qualitative variables, and Student’s
t-test or the Wilcoxon non-parametric test was used for
quantitative variables. Potential risk factors were deter-
moved by multivariate logistic regression model and back-
ward selection. The final model is presented with crude
odds ratios (OR) and 95% confidence intervals (CI). P < 0.05
was considered statistically significant.

Results

Patient demographic data

A total of 200 patients who met the criteria were included.
The age range of the patients was 41–63 and 72 (36%) were
male. The GCS score range was 5–15 and the

SAPS II range was 31–52. One hundred and forty-eight
(74%) patients had a WFNS ≥III and 146 (73%) had a
Fisher score of 4. One hundred and twenty-eight
(64%) patients were treated with ventriculostomy. Aneu-
rysm was secured with an endovascular coiling procedure
during an arteriography with an endovascular coiling in the
first 24 h. The choice of the treatment modality (coil or clip
method) was made when a consensus was reached about
the disease between the neurosurgeon and neuroradiologist. Patients with a Glasgow coma scale (GCS) score ≤8 were
sedated with a continuous intravenous infusion of fentanyl
(2–5 μg·kg⁻¹·h⁻¹) or sufentanil (0.2–0.5 μg·kg⁻¹·h⁻¹) and

midazolam (0.2–0.5 mg·kg⁻¹·h⁻¹) according to the
guidelines (11). Cerebral perfusion pressure was maint-
inated ≥60 mmHg by using norepinephrine. Intra-cranial
hypertension was defined as an intracranial pressure
(ICP) ≥25 mmHg and treated by a bolus of mannitol
(0.5 g/kg) (11). When plasmatic osmolality was ≤320 mOsm/
kg, mannitol was applied. Hypertonic saline was not
employed during the study period. When ICP remained ele-

the lack of speci-

diation or hypothermia (≤36°C), or hypothermia (≤36°C), or

leukocytosis (≥12,000/mL) or leukocytosis (≤4000/mL), and purulent pulmonary secre-

tions. Patients suspected of having pneumonia underwent

either endotracheal aspirates or fiberoptic bronchoscopy
to obtain samples by means of protected specimen brush or
bronochoalveolar lavage. The diagnosis was upheld if

more than 10³, 10⁴, or 10⁵ colony forming units (CFU)/mL

were found on protected specimen brush, bronchoalveolar
lavage, and endotracheal aspirates, respectively. Pneu-

monia was considered ventilator-associated when onset

occurred after tracheal intubation. Early-onset of VAP

(EVAP) was defined as VAP occurring in the first
7 days after orotracheal intubation (5). VAP occurring
after the 7th day was defined as late-onset VAP (5). All
episodes of suspected VAP were prospectively evaluated
during a weekly staff meeting with attending neuro-

intensivists, infectious disease specialists, microbiologists,

and hygiene specialists. Diagnosis was upheld according
to the ATS criteria (3).

A total of 200 patients who met the criteria were included.
The age range of the patients was 41–63 and 72 (36%) were
male. The GCS score range was 5–15 and the

SAPS II range was 31–52. One hundred and forty-eight
(74%) patients had a WFNS ≥III and 146 (73%) had a
Fisher score of 4. One hundred and twenty-eight
(64%) patients were treated with ventriculostomy. Aneu-
rysm was secured with an endovascular coiling procedure

Primary outcome

According to the criteria of the American Thoracic Society (ATS) (3), VAP was defined as the presence of a new
or progressive pulmonary infiltrate on the chest radiogéraphy and two of the following items: hyperthermia (≥38°C)
or fever or hypothermia (≤36°C), leukocytosis (≥12,000/mL) or leukocytosis (≤4000/mL), and purulent pulmonary secre-

tions. Patients suspected of having pneumonia underwent

either endotracheal aspirates or fiberoptic bronchoscopy
to obtain samples by means of protected specimen brush or
bronochoalveolar lavage. The diagnosis was upheld if

more than 10³, 10⁴, or 10⁵ colony forming units (CFU)/mL

were found on protected specimen brush, bronchoalveolar
lavage, and endotracheal aspirates, respectively. Pneu-

monia was considered ventilator-associated when onset

occurred after tracheal intubation. Early-onset of VAP

(EVAP) was defined as VAP occurring in the first
7 days after orotracheal intubation (5). VAP occurring
after the 7th day was defined as late-onset VAP (5). All
episodes of suspected VAP were prospectively evaluated
during a weekly staff meeting with attending neuro-

intensivists, infectious disease specialists, microbiologists,

and hygiene specialists. Diagnosis was upheld according
to the ATS criteria (3).
in 168 (90%) patients. Fifty (25.0%) patients received 2 g of cefazolin during a ventriculostomy procedure (antibiotic prophylaxis), and antibiotics were systematically discontinued after surgery. One hundred and ninety (95%) patients received stress ulcer prophylaxis. Forty-eight (24%) patients received antacids and 142 (71%) patients received sucralfate. Ninety-eight (47%) patients presented a VAP, 80 (40%) of which were EOVAP. Among the 80 patients with EOVAP, 14 (17.5%) patients displayed criteria of acute lung injury or acute respiratory distress syndrome. Forty-one (20.5%) patients died in the ICU during the study period. The median duration of sedation was 11 (6–15) days, the median duration of MV was 19 (11–29) days, and the median ICU LOS was 23 (15–34) days. Twenty-eight (14.0%) patients underwent a late tracheostomy in order to wean MV, performed during a median of 28 (22–32) days.

Univariate analysis of the risk factors related to EOVAP

According to the univariate analysis, male gender, seizures before intubation, use of mannitol, and enteral feeding above 20 kcal·kg⁻¹·day⁻¹ before day 7 showed significant difference between patients with or without EOVAP (Table 1).

### Table 1. Risk factors analysis for early-onset ventilator-acquired pneumonia (EOVAP) in patients with aneurysmal subarachnoid hemorrhage (SAH).

| Characteristics                                      | Patients without EOVAP (n=120) | Patients with EOVAP (n=80) | P value |
|------------------------------------------------------|-------------------------------|-----------------------------|---------|
| SAPS II                                              | 41 ± 14                       | 42 ± 13                     | 0.82    |
| Age                                                  | 53 ± 13                       | 54 ± 13                     | 0.76    |
| Gender (male)                                        | 36 (30)                       | 36 (45)                     | 0.04    |
| GCS score                                            | 9 ± 4                         | 9 ± 5                       | 0.66    |
| WFNS ≥ III                                          | 88 (59.4)                     | 60 (75)                     | 0.79    |
| Active smoking                                       | 17 (14.2)                     | 20 (25)                     | 0.08    |
| Seizures before intubation                           | 29 (24.2)                     | 30 (37.5)                   | 0.04    |
| Aneurysmal coiling                                   | 104 (86.6)                    | 64 (80)                     | 0.29    |
| Ventriculostomy                                      | 77 (64.2)                     | 44 (55)                     | 0.19    |
| Antibiotic prophylaxis                               | 27 (22.5)                     | 23 (28.8)                   | 0.32    |
| Angiographic vasospasm before day 7                  | 11 (9.2)                      | 12 (15)                     | 0.21    |
| Enteral nimodipine                                   | 40 (33.3)                     | 29 (36.3)                   | 0.78    |
| Insulin therapy                                      | 92 (76.7)                     | 62 (77.5)                   | 0.89    |
| Stress ulcer prophylaxis                             | 114 (95)                      | 76 (95.0)                   | 0.74    |
| Use of mannitol                                      | 32 (26.7)                     | 42 (52.5)                   | 0.0003  |
| Corticosteroids                                      | 6 (5)                         | 4 (5)                       | 0.74    |
| Barbiturates use (days)                              | 3 ± 2                         | 4 ± 3                       | 0.47    |
| Achievement of enteral feeding ≥ 20 kcal·kg⁻¹·day⁻¹  | 71 (59.2)                     | 64 (80)                     | 0.003   |

Data are reported as means ± SD or number and percentage. SAPS: Simplified Acute Physiology Score; GCS: Glasgow coma scale; WFNS: World Federation of Neurosurgeons score. The χ² or Fisher’s exact test was employed for qualitative variables, and Student’s t-test or the Wilcoxon non-parametric test was used for quantitative variables.
lower GOS score (P < 0.001). Death rate was 23.8% in patients with EOVAP and 18.3% in patients without EOVAP (Table 4).

**Discussion**

In the present study, 94 (47%) patients presented with VAP, which was comparable to a previous study (17). The results from multivariate analysis showed that male gender, use of mannitol, and delayed enteral nutrition were confirmed as the independent risk factors for EOVAP, while MSSA was found as the main pathogen of EOVAP.

According to previous reports, the incidence of VAP in the ICU was about 40% (5,7) when the patient presented with traumatic brain injury (18). The incidence of VAP in SAH patients was rather high in the current study, which was comparable to that in head-trauma patients, indicating a higher susceptibility to nosocomial pneumonia in brain-injury patients. Previous studies have shown that brain injuries could induce a state of nosocomial infections-associated immune paralysis (19). Recently, Frontera et al. (2) found a lower incidence of nosocomial pneumonia (20%). MV was considered highly associated with nosocomial pneumonia, suggesting that it is of critical importance in patients with SAH requiring MV. In head trauma patients (4,5,7), EOVAP was associated with increasing length of MV and ICU LOS, but the mortality rate was not high in SAH patients.

Moreover, we found that enteral nutrition was independently associated with EOVAP. In a previous study, enteral nutrition was reported to play an important role in nosocomial infections, especially VAP in head trauma patients (20% mortality). In the current study, the incidence of EOVAP in patients with enteral nutrition was significantly higher than in those without enteral nutrition. This finding supports the importance of early enteral nutrition in preventing EOVAP.

---

**Table 2. Multivariate analysis of the risk factors for early-onset of ventilator-acquired pneumonia.**

| Variables                                    | OR    | 95% CI       | P value |
|----------------------------------------------|-------|--------------|---------|
| Gender (male)                                | 2.25  | 1.15–4.45    | 0.01    |
| Use of mannitol                              | 3.02  | 1.53–5.94    | 0.001   |
| Achievement of enteral feeding ≥ 20 kcal kg⁻¹ day⁻¹ before day 7 | 2.90  | 1.26–6.67    | 0.01    |

OR: odds ratio; CI: confidence interval.

**Table 3. Pathogens analysis of the early- and late-onset ventilator-acquired pneumonia (VAP) in aneurysmal subarachnoid hemorrhage patients.**

| Pathogens involved in VAP                     | Early-onset (n=80) | Late-onset (n=14) |
|-----------------------------------------------|-------------------|-------------------|
| Total                                         | 100 (100)         | 14 (100)          |
| Methicillin-susceptible *Staphylococcus aureus* (MSSA) | 35 (35)          | 8 (57.1)          |
| *Haemophilus influenzae*                      | 28 (28)          | –                 |
| *Streptococcus pneumoniae*                   | 15 (15)          | –                 |
| *Enterobacteriaceae*                         | 11 (11)          | 6 (42.9)          |
| Other pathogens                              | 11 (11)          | –                 |

Data are reported as number and percentage.
patients (7,20). However, enteral feeding was limited due to the risk of micro-inhalation. Poulard et al. (21) reported that early initiation (<48 h) associated with a rapid increase in the enteral nutrition intake was not correlated with VAP in a general ICU population. Furthermore, Reignier et al. (22) recently showed that residual gastric monitoring was not mandatory to prevent VAP but led to less enteral intake in patients. These results suggested that early nutrition, without residual gastric monitoring, could be safely performed in brain-injured patients. In accordance with previous consensus on enteral nutrition in the ICU, we upheld the threshold of 20 kcal·kg⁻¹·day⁻¹ within the period <7 days (14). Our results suggested an association but not a causation between low enteral nutrition intake and early-onset VAP. In brain-injured patients, an evidence-based extubation readiness bundle including early enteral nutrition was safe and decreased the length of MV (23).

We also found that use of mannitol was independently associated with VAP. Several studies have found that barbiturate was considered a risk factor for immunosuppression and VAP in brain-injured patients (5,7,9). To date, no authors have reported mannitol as a risk factor for VAP, but some immunomodulatory effects of osmotherapy have been described with hypertonic saline solution in the setting of experimental hemorrhagic shock. Some authors found a decrease of TNF production and polymorphonuclear neutrophils activation with mannitol (24). On the other hand, other investigators have found a decrease of pro-inflammatory cytokines and T lymphocytes proliferation in the setting of hemorrhagic shock (24). Intra-cranial hypertension exhibited some immunosuppressive functions that might increase the susceptibility to pneumonia in the setting of brain-injured immune dysfunction (19,25). In all studies focusing on brain-injured patients, barbiturates and mannitol were used to reduce intra-cranial hypertension (12). Barbiturate coma and mannitol were administered to most patients who displayed an immune impairment in the presence of VAP (18). It must be kept in mind that mannitol is probably a confounding factor and it is hard to delineate the exact role of mannitol versus elevated ICP on the genesis of VAP.

In addition, we found that male gender was associated with an increased risk of VAP. Few experimental data have pointed out some protective effects of estrogen after hemorrhage and, notably, phagocytosis capacity on Kupffer cells (26). To date, no hormonal therapy is available in the ICU to avoid nosocomial infections, but this could be considered as a potential target in the future.

Pathogens involved in EOVAP were MSSA, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. MSSA is also the main pathogen in head-trauma patients with VAP (5,7). This pathogen remains highly specific for VAP in brain-injured patients and is not found with such a high prevalence in medical patients (17,27,28). *Haemophilus influenzae* and *Streptococcus pneumoniae* are also frequently retrieved among head trauma patients (5,7). Based on the risks of multidrug-resistant bacteria, the cut-off of early- and late-onset VAP has been set at day 5 after the initiation of MV by the last conference consensus (3). However, in head-trauma patients, Bronchard et al. (5) found that pathogens remained susceptible to most of the antibiotics recommended by the ATS guidelines in the first 7 days after the initiation of MV. Therefore, we chose this cut-off, as we hypothesized that pathogens involved in VAP in patients with SAH would be similar to those in head-trauma patients. In the setting of late-onset VAP, MSSA was still retrieved along with *Enterobacteriaceae*. These results suggested that early-onset VAP flora in patients with SAH was similar to that in patients with head trauma and the 7-days cut-off determining the emergence of antibiotic-resistant pathogens may be used in patients with SAH. However, this question was not completely answered by our study. Further studies are needed to confirm these results.

There are several limitations in this study. First, a single center retrospective study may result in bias in the multivariate analysis results. Second, incomplete information could fail to determine the effect of VAP on the neurological outcome or mortality of the patients. Third, a short-term infusion of antibiotics could reduce the rate of VAP. Finally, the Clinical Pulmonary Infection Score was not determined, which could result in controversies on VAP diagnosis.

VAP is frequently present in SAH patients requiring MV. We found that male gender, use of mannitol, and delayed enteral nutrition were confirmed as independent risk factors for EOVAP, while MSSA was found as the main pathogen for EOVAP. According to previous studies (7), enteral nutrition strategy is recommended for SAH patients in general surgical ICU patients (20) and for brain-injured patients (23).

**Acknowledgments**

This work was financially supported by the Weifang Science and Technology Bureau (No. 2016RKX031).

**References**

1. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke* 2012; 43: 1711–1737, doi: 10.1161/STR.0b013e3182587839.
2. Frontera JA, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, et al. Impact of nosocomial infectious complications after subarachnoid hemorrhage.
Pneumonia and aneurysmal subarachnoid hemorrhage

Neurosurgery 2008; 62: 80–87; discussion 87, doi: 10.1227/01.0000000000000000.

3. 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, doi: 10.1164/rcrm.200405-6445.

4. Cook A, Norwood S, Berme J. Ventilator-associated pneumonia is more common and of less consequence in trauma patients compared with other critically ill patients. J Trauma 2010; 69: 1083–1091, doi: 10.1097/TA.0b013e3181f9b51.

5. Bronchard R, Albala-dejo P, Brezacz G, Geoffroy A, Seinre PF, Morris W, et al. Early onset pneumonia: risk factors and consequences in head trauma patients. Anesthesiology 2004; 100: 234–239, doi: 10.1097/00000542-200402000-00009.

6. Antonelli M, Moro ML, Capelli O, De Blasi RA, D’Erminco RR, Conti G, et al. Risk factors for early onset pneumonia in trauma patients. Chest 1994; 105: 224–228, doi: 10.1378/chest.105.1.224.

7. Lepelletier D, Roquilly A, Demeure dit latte D, Mahe PJ, Nadal P, Nicolas JM, Font C, Villela A, Nogue S. Pneumonia in ventilated head trauma patients: the role of thiopeptaly. Eur J Emerg Med 1995; 2: 14–16, doi: 10.1097/00003310-199503000-00004.

8. Stover JF, Stocker R. Barbiturate coma may promote reversible bone marrow suppression in patients with severe isolated traumatic brain injury. Eur J Clin Pharmacol 1998; 54: 529–534, doi: 10.1007/s002280050508.

9. Nadal P, Nicolas JM, Font C, Villela A, Nogue S. Pneumonia in ventilated head trauma patients: the role of thiopeptaly. Eur J Emerg Med 1995; 2: 14–16, doi: 10.1097/00003310-199503000-00004.

10. Hydelemmark P, Brattstom O, Larsson E, Martin-CRG, Petersson J, Oldner A. High incidence of post-injury pneumonia in intensive care-treated trauma patients. Acta Anaesthesiol Scand 2013; 57: 848–854, doi: 10.1111/aas.12111.

11. Rondeau N, Cinotti R, Rozec B, Roquilly A, Flch O, Groeau N, et al. Dobutamine-induced high cardiac index did not prevent vasosparasim in subarachnoid hemorrhage patients: a randomized controlled pilot study. Nutric Care 2012; 17: 183–190, doi: 10.1177/1521743012457642.

12. Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. Cochrane Database Syst Rev 2012; 12: CD000033.

13. Pederson JB, Connolly ES, Jr, Balter HH, Dacey RG, Dion JE, Diringer MN, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 2009; 40: 994–1025, doi: 10.1161/STROKEAHA.108.191395.

14. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jollip J, Kazandziej G, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr 2006; 25: 210–223, doi: 10.1016/j.clnut.2006.01.021.

15. Boles JM, Bion J, Connors A, Harridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. Eur Respir J 2007; 29: 1033–1056, doi: 10.1183/09031936.00010206.

16. Rumbak MJ, Newton M, Truncale T, Schwartz SW, Adams JW, Hazard PA. 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, doi: 10.1097/01.CCM.0000143835.05161.B6.

17. Gruson D, Hilbert G, Vargas F, Valentino R, Bebear C, Allery A, et al. Rotation and restricted use of antibiotics in a medical intensive care unit. Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. Am J Respir Crit Care Med 2000; 162: 837–843, doi: 10.1164/ajrccm.162.3.9905050.

18. Depeekuyt F, Roquilly A, Cinotti R, Altar F, Asehnoune K. An in vitro model of mycobacterial granuloma to investigate the immune response in brain-injured patients. Crit Care Med 2013; 41: 245–254, doi: 10.1097/CCM.0b013e3182670582.

19. Meisel C, Schwab JM, Prass K, Meisel A, Dirmagl U. Central nervous system injury-induced immune deficiency syndrome. Nat Rev Neurosci 2005; 6: 775–786, doi: 10.1038/nrn1765.

20. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med 2001; 29: 2264–2270, doi: 10.1097/00003246-200112000-00005.

21. Lalouf M, Kettermann AK, Meisel C, Schwab JM, Meisel A, Dirmagl U. Central nervous system injury-induced immune deficiency syndrome. J Parenter Enter Nutr 2013; 37: 125–130, doi: 10.1177/0148607109344745.

22. Reigner J, Mercier E, Le Gouge A, Boulain T, Desachy A, Bellec F, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA 2013; 309: 249–256, doi: 10.1001/jama.2012.196377.

23. Roquilly A, Cinotti R, Jaber S, Vourc’h M, Pengam F, Mahe PJ, et al. Implementation of an evidence-based extubation readiness bundle in 499 brain-injured patients: a before-after evaluation of a quality improvement project. J Am Med Assoc 2013; 188: 958–966, doi: 10.1164/rcrm.201301-0116OC.

24. Mocsai A, Jakus Z, Vantus T, Berton G, Lowell CA, Ligeti E. Kinase pathways in chemotactant-induced degradation of neutrophils: the role of p38 mitogen-activated protein kinase activated by Src family kinases. J Immunol 2000; 164: 4321–4331, doi: 10.4049/jimmunol.164.8.4321.

25. Asehnoune K, Roquilly A, Abraham E. Innate immune dysfunction in trauma patients: from pathophysiology to treatment. Anesthesiology 2012; 117: 411–416, doi: 10.1097/ALN.0b013e31825f018d.

26. Yu HP, Chaudry IH. The role of estrogen and receptor agonists in maintaining organ function after trauma-hemorrhage. Shock 2009; 31: 227–237, doi: 10.1097/SHK.0b013e3181347e7.

27. Agbaht K, Lisboa T, Pobo A, Rodriguez A, Sandiumenge A, Diaz E, et al. Management of ventilator-associated pneumonia in a multidisciplinary intensive care unit: does trauma make a difference? Intensive Care Med 2007; 33: 1387–1395, doi: 10.1007/s00134-007-0729-5.

28. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003; 290: 2588–2598, doi: 10.1001/jama.290.19.2588.