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ARTICLE

# Risk factors and pathogens involved in early ventilator-acquired pneumonia in patients with severe subarachnoid hemorrhage

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**Abstract** Ventilator-acquired pneumonia (VAP) is a common burden in intensive care unit (ICU) patients, but, to date, specific data are not available in patients with severe aneurysmal subarachnoid hemorrhage (SAH). A single neuro-ICU retrospective analysis of 193 patients with SAH requiring mechanical ventilation (MV) ≥48 h admitted from January 2005 to May 2010 was undertaken. The diagnosis of early VAP was prospectively upheld during a multidisciplinary staff meeting, according to the American Thoracic Society (ATS) 2005 guidelines with a threshold of 7 days after the onset of MV. Patients had a median age of 53 (44–62) years and 70 (36 %) were male. The median Glasgow coma scale (GCS) score before MV was 9 (5–14). 142 (74 %) patients had a World Federation of Neurosurgeons (WFNS) score≥III. Aneurysm was secured with an endovascular coiling procedure in 162 (84 %) patients. 81 (48.7 %) patients declared an early VAP. On multivariate analysis, male sex (odds ratio [OR] 2.26, 95 % confidence interval [CI] [1.14–4.46]), use of mannitol before day 7 (OR 3.03, 95 % CI [1.54–5.95]), and achieving enteral nutrition ≥20 kcal $kg^{-1}$ $day^{-1}$ after day 7

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(OR 2.91, 95 % CI [1.27–6.67]) remained independent risk factors of VAP. The main pathogens involved were methicillin-susceptible *Staphylococcus aureus* (MSSA) (34.9 %), *Haemophilus influenzae* (28.1 %), *Streptococcus pneumoniae* (15.5 %), and Enterobacteriaceae (10.7 %). Early VAP was associated with a longer duration of MV and ICU stay, but not with an excess of mortality. Early VAP bears significant morbidity in patients with severe SAH. Pathogens involved in early VAP are susceptible to antibiotics. Among modifiable risk factors of VAP, early enteral nutrition could be an easy and effective target.

## Background

Aneurysmal subarachnoid hemorrhage (SAH) is a life-threatening condition and its prevalence has not decreased over the years [1]. In the most severe forms, mechanical ventilation (MV) and intensive care unit (ICU) hospitalization are mandatory. Nosocomial infections and pneumonia are common in patients with SAH and might alter the patient's recovery [2], but, to date, no study has focused on ventilator-acquired pneumonia (VAP) in patients with severe SAH.

VAP remains a major health-related infection among ICU patients [3]. Several studies have focused on specific populations, such as head-trauma patients [4–6]. Specific aspects were underlined, such as the high prevalence of VAP in this population, which reaches up to 40 %, and the specific pathogens involved [5, 7]. VAP bears substantial morbidity and high health-care costs in head-trauma patients, but a rather low mortality [4, 7]. Most episodes of VAP in severe trauma occur in the first 7 days [5, 7]. Specific risk factors of early VAP were also pointed out, such as the use of barbiturates [7–9], continuous sedation [10], intra-cranial hypertension [5], or delayed enteral feeding [7]. We sought to determine the risk factors and pathogens involved in early VAP in patients with severe SAH.

## Methods

We conducted a retrospective single-center study in a neurosurgical ICU of a University Hospital (CHU de Nantes, France) from 1st January 2005 to 1st May 2010. According to French legislation (articles L.1121-1 paragraph 1 and R1121-2, Public Health Code), no informed consent is needed in order to use data for epidemiological analysis.

### Inclusion criteria

Patients hospitalized for an aneurysmal SAH and requiring MV ≥48 h were eligible for the study.

### Exclusion criteria

Patients with an intra-cerebral hemorrhage from another origin, such as arterio-venous malformation, non-aneurysmal subarachnoid hemorrhage, or non-traumatic intra-cerebral hemorrhage, were excluded. Patients who were transferred to another center after aneurysmal coiling and who could not fulfill follow-up for the primary end-point were excluded. Patients who died in the first 2 days of ICU hospitalization were excluded.

### Management of patients with SAH

The diagnosis of aneurysmal SAH was confirmed by a computed tomography (CT) brain scan. The aneurysm was secured during an arteriography with an endovascular coiling in the first 24 h. Ventriculostomy was performed by a neurosurgeon when hydrocephalus was visible on a CT brain scan. According to guidelines [11], 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 $kg^{-1}$ $h^{-1}$) [12]. This therapeutic sedation protocol was continued during the period of intracranial hypertension and stopped when control of the intracranial pressure (ICP) was deemed appropriate. No other sedatives agents such as propofol or dexmedetomidine were used during the study period. Cerebral perfusion pressure (CPP) was maintained≥60 mmHg with norepinephrine. Intra-cranial hypertension was defined as an ICP≥25 mmHg and treated by a bolus of mannitol (0.5 g $kg^{-1}$) [12]. Mannitol was used in the setting of plasmatic osmolality≤320 mosm $kg^{-1}$. Hypertonic saline was not used during the study period. If ICP remained elevated after osmotherapy, barbiturates were added (sodium thiopental) with an intravenous bolus of 2–3 mg $kg^{-1}$, followed by a continuous infusion of 2–3 mg $kg^{-1}$ $h^{-1}$ [13]. CPP was maintained≥60 mmHg with norepinephrine. Nimodipine was intravenously administered (1–2 mg $h^{-1}$) at admission in the ICU . As soon as enteral feeding was started, nimodipine was administered via the enteral feeding tube (360 mg $day^{-1}$) during 21 days [1]. The screening of vasospasm was performed once a day by transcranial Doppler (TCD) of the middle cerebral artery. An arteriography was performed whenever the mean artery flow velocity assessed by TCD was 50 % higher than on the first day, or above 120 cm $s^{-1}$ [14]. Arteriography was also performed when an unexplained fever or a new neurologic deficit appeared. The diagnosis of vasospasm was upheld during arteriography by a trained neuro-radiologist.

Before starting enteral nutrition, location in the stomach of the tip of the feeding tube was confirmed with a chest X-ray. Patients were fed continuously with a peristaltic feeding pump. No written enteral nutrition protocol was available in our ICU during the study period. The nutrition procedures were left to the attending physician's discretion. Achieving an

enteral nutrition threshold 20 kcal $kg^{-1}$ $day^{-1}$ was deemed appropriate for the needs of our study, since it is recommended by the last European conference consensus on enteral nutrition as an objective in the early phase of ICU stay [15].

Weaning from MV was not protocolized during the study period, owing to the lack of recommendations in this specific ICU population. Weaning started as soon as ICP control was deemed appropriate. Sedative and morphinomimetic agents were progressively stopped when ICP was controlled. Criteria for extubation were not protocoled during the study period and were left to the attending physician, because of the lack of recommendations in the most recent guidelines on the subject [16]. In spite of evidence favoring early tracheostomy [17], this procedure was performed in our ICU only in patients with a prolonged MV (≥15 days of MV [18]).

## Primary outcome

VAP was defined according to the American Thoracic Society (ATS) criteria [3] as the presence of a new or progressive pulmonary infiltrate on the chest radiography and two of the following items: hyperthermia (≥38.0 °C) or hypothermia (≤36.0 °C) leukocytosis (≥12,000/ml) or leukopenia (≤4,000/ml) purulent pulmonary secretions. Patients suspected of having pneumonia underwent either endotracheal aspirates or fiberoptic bronchoscopy to obtain samples by means of protected specimen brush or bronchoalveolar lavage. The diagnosis was upheld if more than $10^3$, $10^4$, or $10^6$ colony-forming units (CFU)/ml were found on protected specimen brush, bronchoalveolar lavage, and endotracheal aspirates, respectively. Pneumonia was considered as ventilator-associated when onset occurred after tracheal intubation. Early onset of VAP (EOVAP) was defined as VAP occurring in the first 7 days after oro-tracheal intubation [5]; VAP occurring after the seventh 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 diseases specialists, microbiologists, and hygiene specialists. Diagnosis was upheld according to the ATS criteria [3].

## Data collection

Age, sex, Simplified Acute Physiology Score II (SAPS II), medical history, GCS score on scene, World Federation of Neurosurgeons (WNFS) score, Fisher score, aneurysm location, surgery upon admission, ventriculostomy realization, type of aneurysm, clip or coiling, and antibioprophylaxis 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

Patients who developed both early- and late-onset VAP were analyzed in the group "with EOVAP", whereas patients who developed only late-onset VAP were analyzed in the group "without EOVAP" (Fig. 1). Continuous data were expressed

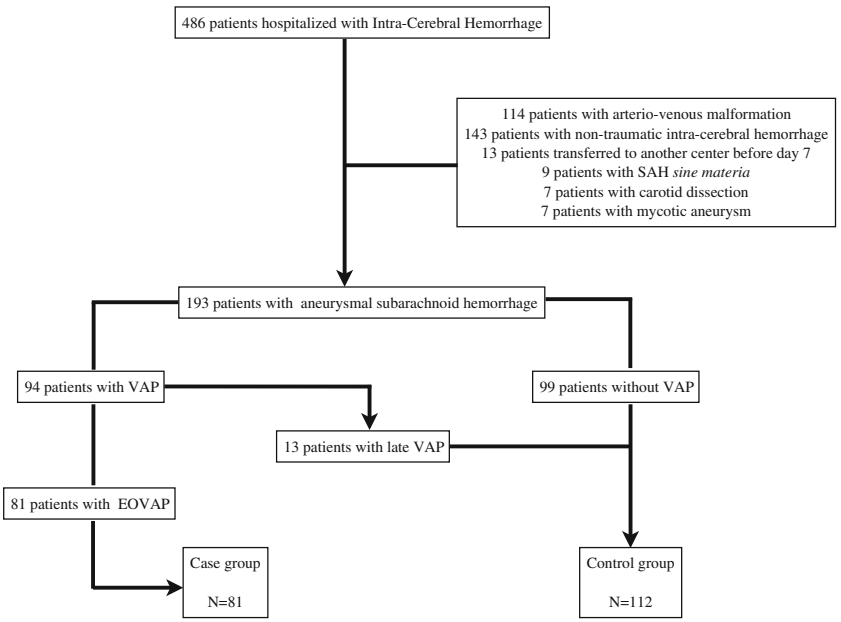


**Fig. 1** Flow chart of a 5-year retrospective cohort surveillance, 2005–2010

as medians and percentiles (25–75 %), unless otherwise stated, and categorical data as numbers and percentage. Univariate analysis was conducted to determine potential risk factors of EOVAP occurrence. The $\chi^2$ or Fisher's exact test was used for qualitative variables, and Student's *t*-test or the Wilcoxon non-parametric test was used for quantitative variables. Variables identified as potential risk factors by the univariate analysis with a cut-off at 0.20 were included in a multivariate logistic regression model and backward selection was applied. The calibration of the model was tested by a Hosmer–Lemeshow's test. The final model was presented with the crude odds ratio (OR) and 95 % confident interval (CI). The outcomes of patients in the group "with EOVAP" and those in the group "without EOVAP" were compared with the $\chi^2$ or Fisher's exact test for qualitative variables or with a stratified log-rank test for censored data to consider death. The significance level was set at a $p$-value ≤0.05. Statistical analysis was performed using SAS statistical software (SAS 9.3 Institute, Cary, NC).

## Results

During the study period, 193 patients met the inclusion criteria (flow chart, Fig. 1). Patients had a median age of 53 (44–62) years and 70 (36 %) were male. The median GCS score was 9 (5–14) and the median SAPS II was 41 (31–50). One hundred and forty-two (74 %) patients had a WFNS score≥III and 142 (73 %) had a Fisher score of 4. A ventriculostomy was performed in 124 (64.2 %) patients. Aneurysm was secured with an endovascular coiling procedure in 162 (90 %) patients. Forty-eight (24.9 %) patients received 2 g of cefazolin during a ventriculostomy procedure (antibiotic prophylaxis), and antibiotics were systematically discontinued after surgery. One hundred and eighty-three (94.8 %) patients received stress ulcer prophylaxis. Forty-six (23.8 %) patients received antacids and 137 (70.9 %) patients received sucrafate. Ninety-four (48.7 %) patients presented a VAP, 81 (42 %) of which were EOVAP (Fig. 1). Among the 81 patients with EOVAP, 14 (17.2 %) patients displayed criteria of acute lung injury or acute respiratory distress syndrome [19]. Forty patients (21 %) 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-seven (13.9 %) patients underwent a late tracheostomy in order to wean MV and was performed during a median of 28 (22–32) days.

On univariate analysis, factors associated with EOVAP were: male sex, active smoking, history of seizures after hemorrhage, ventriculostomy, administration of mannitol, and enteral feeding above 20 kcal $kg^{-1}$ $day^{-1}$ after day 7 (Table 1). On multivariate analysis, male sex (OR 2.26, 95 % CI 1.14–4.46), use of mannitol before day 7 (OR 3.03, 95 % CI 1.54–5.95), and achieving enteral nutrition ≥20 kcal $kg^{-1}$ $day^{-1}$ after day 7 (OR 2.91, 95 % CI 1.27–6.67) remained independent risk factors for EOVAP (Table 2).

Microorganisms culture retrieved a single bacteria in 74 EOVAP and multiple microorganisms in seven. The main pathogen involved was methicillin-susceptible *Staphylococcus aureus* (MSSA) (34.9 %) (Table 2). Other pathogens were *Haemophilus influenzae* (28.1 %), *Streptococcus pneumoniae* (15.5 %), and Enterobacteriaceae (10.7 %). MSSA (53.8 %)

**Table 1** Univariate analysis of risk factors associated with early-onset ventilator-acquired pneumonia (EOVAP) in patients with severe subarachnoid hemorrhage

| Characteristics | Patients without EOVAP $N=112$ | Patients with EOVAP $N=81$ | $p$-Value* |
|---|---|---|---|
| SAPS II | 40±14 | 43±13 | 0.08 |
| Age | 54±13 | 52±13 | 0.29 |
| Male sex | 34 (30.3) | 36 (44.4) | 0.04 |
| GCS score | 9±4 | 9±5 | 0.93 |
| Active smoking | 16 (14.3) | 20 (24.7) | 0.07 |
| Seizures before intubation | 27 (24.1) | 30 (37) | 0.05 |
| Aneurysmal coiling | 97 (91.5) | 65 (86.7) | 0.45** |
| Ventriculostomy | 72 (64.3) | 44 (54.3) | 0.16 |
| Antibioprophylaxis | 25 (22.3) | 23 (28.4) | 0.33 |
| Angiographic vasospasm before day 7 | 10 (9.4) | 11 (14.9) | 0.26 |
| Enteral nimodipine | 38 (34) | 29 (35.8) | 0.79 |
| Insulin therapy | 86 (76.8) | 63 (77.8) | 0.87 |
| Stress ulcer prophylaxis | 106 (94.6) | 77 (95.1) | 0.90** |
| Use of mannitol | 30 (26.8) | 42 (51.9) | 0.0004 |
| Barbiturates use (days) | 3±2 | 4±3 | 0.58** |
| Achievement of enteral feeding ≥20 kcal $kg^{-1}$ $day^{-1}$ before day 7 | 66 (58.9) | 65 (80.2) | 0.008 |

Continuous data are expressed as mean ± standard derivation

Categorical data are expressed as *n* (%)

*SAPS* Simplified Acute Physiology Score II, *GCS* Glasgow coma scale

*$\chi^2$ test or Student's test

**Fisher's exact test or Wilcoxon test

**Table 2** Multivariate analysis of risk factors associated with EOVAP in patients with severe subarachnoid hemorrhage (SAH) (multivariate logistic regression)

| Variables | OR | 95 % CI | $p$-Value |
|---|---|---|---|
| Male sex | 2.26 | [1.14; 4.46] | 0.01 |
| Use of mannitol | 3.03 | [1.54; 5.95] | 0.001 |
| Achievement of enteral feeding ≥20 kcal $kg^{-1}$ $day^{-1}$ before day 7 | 2.91 | [1.27; 6.67] | 0.01 |

*OR* odds ratio; *95 % CI* 95 % confidence interval

**Table 3** Pathogens involved in early (≤day 7) and late ventilator-acquired pneumonia (VAP) (>day 7) in patients with severe SAH

| | Pathogens involved in VAP | |
|---|---|---|
| | Early onset, 81 patients | Late onset, 13 patients |
| Total | 103 (100) | 13 (100) |
| Methicillin-susceptible *Staphylococcus aureus* | 36 (34.9) | 7 (53.8) |
| *Haemophilus influenzae* | 29 (28.1) | – |
| *Streptococcus pneumoniae* | 16 (15.5) | – |
| Enterobacteriaceae | 11 (10.7) | 6 (46.2) |
| Other pathogens | 11 (10.8) | – |

Categorical data are expressed as *n* (%)

and Enterobacteriaceae (46.2 %) were the main pathogens in 13 late-onset VAP (Table 3).

Patients with EOVAP had a longer duration of sedation ($p=0.03$), MV ($p=0.001$), and ICU LOS ($p=0.002$) (Table 4). The death rate was 24 % in patients with EOVAP and 18 % in patients without EOVAP (Table 4).

## Discussion

In a population of patients with severe SAH, we observed a high incidence of VAP (48.7 %) compared to other populations [20]. Male sex, delayed enteral nutrition, and use of mannitol were independent risk factors of EOVAP. MSSA was the main pathogen of EOVAP.

The incidence of VAP is variable in the ICU, and in the setting of traumatic brain injury, it ranges around 40 % [5, 7]. The incidence can be even higher when focusing on the most severe brain-injured patients [21]. The incidence of VAP in patients with SAH in the current study is rather high, but is comparable to the incidence of VAP in head-trauma patients, suggesting that brain-injured patients have a high susceptibility to nosocomial pneumonia. Indeed, brain injuries were shown to induce a state of immune paralysis that has been associated with nosocomial infections [22]. In a recent study, Frontera et al. [2] found a lower incidence of nosocomial pneumonia (20 %), but the authors did not focus on mechanically ventilated SAH patients. MV was, nonetheless, highly associated with nosocomial pneumonia, suggesting that nosocomial pneumonia is of critical importance in patients with severe SAH requiring MV. As in head-trauma patients [4, 5, 7], EOVAP is responsible for increasing the length of MV and ICU LOS, but does not increase mortality in patients with severe SAH (Table 4).

In our study, delayed enteral nutrition was independently associated with EOVAP. The importance of enteral nutrition has already been underlined by several authors in the setting of surgical ICU patients [23], as early enteral nutrition may reduce the rate of nosocomial infections, especially VAP in head-trauma patients [7]. However, the risk of micro-inhalation due to massive enteral intake is often advocated. The initiation of enteral feeding is, therefore, delayed and enteral intake increase is often cautious. In a randomized study [24], early initiation (<48 h) associated with a rapid increase in the enteral nutrition intake was not associated with VAP in a general ICU population. Recently, Reignier et al. [25] showed that residual gastric monitoring was not mandatory to prevent VAP but lead to less enteral intake in patients. These results suggest that early nutrition, without residual gastric monitoring, could be safely performed in severe brain-injured patients. In accordance with the last European conference consensus on enteral nutrition in the ICU, we upheld the threshold of 20 kcal $kg^{-1}$ $day^{-1}$ within the time frame <7 days [15]. Our results suggest an association and not a causation between low enteral nutrition intake and early VAP. In the setting of severe brain-injured patients, an evidence-based extubation readiness bundle including early enteral nutrition was safe and decreased the length of MV [26].

Mannitol was independently associated with VAP. Numerous studies have identified barbiturate as a risk factor of

**Table 4** Events in the intensive care unit (ICU) and crude outcomes in study patients

| Characteristics in ICU | Patients with early onset of VAP, 81 (42) | Patients without early onset of VAP, 112 (58) | *p*-Value* |
|---|---|---|---|
| Median sedation duration (days) | 14 (8–16) | 9 (5–15) | 0.03 |
| Median duration of mechanical ventilation (days) | 22 (16–34) | 17 (10–23) | 0.001 |
| Median ICU LOS (days) | 27 (17–38) | 21 (13–31) | 0.003 |
| Death | 21 (24) | 19 (18) | 0.3** |

Continuous data are expressed as medians and percentiles (25–75 %)

Categorical data are expressed as *n* (%)

*LOS* length of stay

*Log-rank test

**$\chi^2$ test

immunosuppression and VAP in brain-injured patients [5, 7, 9]. To date, no authors have reported mannitol as a risk factor of 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 polynuclear neutrophils activation with mannitol [27]. On the other hand, other investigators have found a decrease of pro-inflammatory cytokines and T lymphocytes proliferation in the setting of hemorrhagic shock [28]. Intra-cranial hypertension exhibits some immunosuppressive functions that may increase the susceptibility to pneumonia in the setting of brain-injured immune dysfunction [22, 29]. In all studies focusing on brain-injured patients, barbiturates and mannitol are used to reduce intra-cranial hypertension [13]. Barbiturate coma and mannitol are, thus, administered to the most severe patients who display a severe immune impairment in the presence of VAP [21]. 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.

Male sex 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 [30]. 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 of VAP in brain-injured patients and is not found with such a high prevalence in medical patients [20, 31, 32]. *Haemophilus influenzae* and *Streptococcus pneumoniae* are also frequently retrieved among head-trauma patients [5, 7]. Based on the risk of multidrug-resistant bacteria, the cut-off of early and late 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 VAP, MSSA was still retrieved along with Enterobacteriaceae. These results suggest that: (i) early VAP flora in patients with SAH or head trauma are similar and (ii) the 7 days cut-off determining the emergence of antibiotic-resistant pathogens may be used in patients with SAH. However, our study was neither designed nor powered to answer this question. Other studies on VAP in patients with severe SAH should be performed to confirm these results.

Several limits must be underlined. First, this is a single-center, retrospective study, and our results suggest only association and not causation between VAP and early enteral feeding or mannitol or male sex. Second, the present study could neither explore the potential consequences of VAP on patients' neurological outcome nor mortality, because our study was underpowered to study these outcomes. Third, a short course of antibiotics in comatose patients reduces the rate of VAP [33, 34]. Few patients received antibiotics to point out a possible efficacy on early VAP in the present study. Finally, the diagnosis of VAP is challenging and we did not calculate the Clinical Pulmonary Infection Score (CPIS). Two methodological aspects might have minimized this diagnosis issue. First, the diagnosis of VAP was prospectively recorded during a staff meeting performed each week. During this multidisciplinary staff meeting, chest X-ray and history of patients were reviewed, and this might have limited false diagnoses. Second, we found a higher duration of MV and ICU LOS in patients with early VAP compared to patients without, suggesting that our definition of VAP was accurate.

## Conclusion

Ventilator-acquired pneumonia (VAP) was common in patients with severe subarachnoid hemorrhage (SAH) requiring mechanical ventilation (MV). The main pathogens involved in our series were methicillin-susceptible *Staphylococcus aureus* (MSSA) and *Haemophilus influenzae*. Delayed enteral nutrition was independently associated with early onset of VAP (EOVAP). Considering other studies in head-trauma patients [7], in the general surgical intensive care unit (ICU) patients [23] and the specific setting of severe brain-injured patients [26], we recommend early enteral nutrition strategy in SAH patients.

## Key messages

- Ventilator-acquired pneumonia (VAP) is common in patients with severe subarachnoid hemorrhage and bears substantial morbidity
- Pathogens involved in VAP of patients with subarachnoid hemorrhage are mainly methicillin-susceptible *Staphylococcus aureus* and *Haemophilus influenzae*
- Delayed enteral nutrition is associated with an increased risk of VAP

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**Author contributions** Raphaël Cinotti designed the study, analyzed the data, and wrote the paper. Audrey Dordonnat-Moynard retrieved and analyzed the data, and edited the manuscript. Fanny Feuillet performed the statistical analysis. Antoine Roquilly designed the study and edited the manuscript. Nelly Rondeau edited the manuscript. Nathalie Asseray, Jocelyne Caillon, and Didier Lepelletier collected the data and edited the manuscript. Yvonnick Blanloeil and Bertrand Rozec edited the manuscript. Karim Asehnoune analyzed the data and wrote the paper.

**Conflict of interest** The authors declare that they have no conflict of interest.

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