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Major Article

Risk factors for ventilator-associated events: A prospective cohort study

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Key Words:

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VAP
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Background: In January 2013, the Centers for Disease Control and Prevention released new surveillance definitions for ventilator-associated event (VAE) to replace ventilator-associated pneumonia (VAP) in adult patients. VAEs are associated with prolonged mechanical ventilation and hospital death, but little is known about their risk factors and how best to prevent them.

Methods: We compared VAE cases with non-VAE cases with regard to demographics, comorbidities, sedative exposures, opioids exposures, paralytic exposures, routes of nutrition, blood products, gastric retention, and fluid balance. Patients mechanically ventilated for ≥ 4 days between January 1, 2017, and December 31, 2017, in 2 adult intensive care units of a tertiary care teaching hospital in China were included.

Results: On multivariable logistic regression, significant risk factors for VAEs were positive daily fluid balances of ≥ 50 mL between day of intubation and the fourth day of mechanical ventilation (relative risk [RR], 8.39; 95% confidence interval [CI], 2.99–23.50), sedative administered between the first day and the fourth day of invasive mechanical ventilation (RR, 15.69; 95% CI, 1.62–152.06), and daily gastric retention of ≥ 200 mL between day of intubation and the fourth day of mechanical ventilation (RR, 9.27; 95% CI, 1.89–45.47).

Conclusions: Positive daily fluid balances of ≥ 50 mL, sedatives administered, and gastric retention of ≥ 200 mL are risk factors for VAEs. Intervention studies are needed to determine if targeting these risk factors can lower VAE rates.

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In January 2013, the Centers for Disease Control and Prevention (CDC) released new surveillance definitions for ventilator-associated events (VAE) to replace ventilator-associated pneumonia (VAP) in adult patients. The VAE framework purposefully expands the scope of surveillance from pneumonia alone to all complications of invasive mechanical ventilation (IMV).¹

The VAE framework includes events of 3 levels. The first level is ventilator-associated condition (VAC), which is defined as at least 2 days of increased ventilator settings after ≥ 2 days of stable or improving settings. The second level is “infection-related ventilator-associated complication” (IVAC), which is defined as the subset of VACs with concurrent inflammatory signs and at least 4 days of new antibiotics. The third level is possible VAP, which is defined as patients with IVAC and concurrent purulent sputum plus positive pulmonary cultures possibly have pneumonia.

VAEs have been strongly associated with prolonged mechanical ventilation, longer lengths of stay, and higher hospital mortality rates.^{2–5} However, there are few reports about the risk factors and preventive measures of VAEs. Therefore, it is urgent to define the risk factors of VAEs, which are required for formulating preventive strategies against VAEs. A prospective cohort study was conducted to identify potentially modifiable risk factors for VAEs.

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METHODS

Study design

We prospectively investigated patients' electronic medical records to identify demographics, medications, and laboratory values. We referred to the VAE data collection and antimicrobial worksheet recommended by the CDC. On the worksheet, we recorded the information of patients with tracheal intubation or tracheostomy who were invasively mechanically ventilated ≥ 4 days, including acute physiology and chronic health evaluation score II (APACHE II score), comorbidities, daily minimum positive end-expiratory pressure (PEEP), daily minimum FiO_2 , daily maximum and minimum body temperature, daily maximum and minimum white blood cell count, antibacterial agents use, bacteriological results (blood, sputum or other), and other data. The results were used to determine whether the patient had VAEs and their types. We collected outcomes and potential risk factors for the patients, including: Glasgow Coma Scale score, emergent intubation, episodes of IMV; sedative exposures, opioid exposures, and paralytic medications ordered between the first day and the fourth day of IMV; surgical site between day of admission and the fourth day of IMV; and fluid balance, blood products, routes of nutrition, and gastric retention between day of intubation and the fourth day of IMV. We applied the CDC's VAE criteria.¹ On the basis of reviewing relative papers, a total of 11 factors were investigated. The articles on VAE risk factors have been summarized in [Table 1](#).

Study population

We developed a cohort of consecutive patients ≥ 18 years old who were ventilated for ≥ 4 days in 2 intensive care units (ICUs) of The Affiliated Hospital of Xuzhou Medical University, which is an academic, urban tertiary care center located in Xuzhou, Jiangsu province, China between January 1, 2017, and December 31, 2017. Patients on high-frequency ventilation or extracorporeal life support were excluded from VAE surveillance. We chose patients whose invasive mechanical ventilation days were ≥ 4 days because VAC events require at least 2 calendar days of stable or improving ventilator settings and at least 2 calendar days of worsening settings. There are more than 6,000 beds in our hospital. The department of nosocomial infection management in our hospital monitored VAEs, bloodstream infection events (central line-associated bloodstream infection and non-central line-associated bloodstream infection), and urinary tract infection events (catheter-associated urinary tract infection and non-catheter-associated urinary tract infection). Our hospital is enhancing the performance of paired daily spontaneous awakening trials and spontaneous breathing trials to prevent VAEs on the basis of existing ventilator bundles (ie, sedative interruption, spontaneous breathing trial, head-of-bed elevation, stress ulcer prophylaxis, deep venous thrombosis prophylaxis, and oral care with chlorhexidine). The study was approved by the Institutional Review Board of The Affiliated Hospital of Xuzhou Medical University. The need for patient consent was waived by the Institutional Review Board.

Data collection

Before starting the new study, all members of our research group received training in the nosocomial infection management department of our hospital. The training content included study design, data collection methods, diagnostic criteria, data entry and verification, and quality monitoring. Infection control practitioners gathered ventilator-related data, including invasive mechanical ventilation days, daily minimum fraction of inspiration oxygen (FiO_2), and daily minimum PEEP through reviewing patient records. Six collectors were divided

into 3 groups to ensure that data could be collected in the ICUs every day. We retrieved data on demographics, body temperature, laboratory values, medication orders, endotracheal aspirate Gram stains, and culture results from the hospital's electronic medical record system. We merged these data using medical record identification and dates of mechanical ventilation. Two researchers entered the data using Epi-Data Entry (version 3.1; EpiData Entry Software, Odense, Denmark) twice after review.

We would terminate the monitoring or follow-up when the patient was diagnosed as VAC, removed from the artificial airway, stopped mechanical ventilation for 48 h, or died. We assessed the patients' comorbidities using the International Classification of Disease, 10th Revision.⁶ The worst values of routine blood tests and blood gas analysis in all eligible patients at the first 24 hours were collected as the values of the score, and the scores were graded according to the APACHE II score.⁷ The Glasgow Coma Scale score below 8 points was considered a coma. Emergency tracheal intubation referred to the tracheal intubation of patients with the following indications: the sudden stop or weakening of the spontaneous breathing, the inability to remove the upper respiratory secretions, mistaken aspirates, acute respiratory failure (non-pulmonary), and the presence of upper respiratory tract injuries or strictures affecting normal ventilation. The difference between emergency and selective intubation is whether patients can maintain spontaneous breathing without any auxiliary ventilator or maintain normal ventilation and oxygenation with the assistance of an oxygen mask. If the mechanical ventilation time interval was < 1 calendar day, it was still considered continuous and takes the cumulative time, but if the discontinuous time was > 1 calendar day, the longest consecutive number of days was counted. Average daily fluid balance = (daily intake – daily output)/monitoring days. The nurses had added the patient's inconspicuous evaporative fluid volume (approximately 500 mL per day) to the daily fluid output. Because of the error in measurement and computation, we defined the average daily fluid balance as the difference value was 50 mL rather than 0 mL. For patients who were on continuous venovenous hemofiltration, we recorded their total net volume change calculated by data marked on their continuous venovenous hemofiltration flow sheets. We only studied whether sedatives, opioids, muscle relaxants, and blood products were used during the observation period (ie, they were studied only as yes/no binary variables). The ways of tube feeding for patients receiving enteral nutrition included oropharyngeal, nasopharyngeal, gastric, or jejunal tubes. At 6:00 am to 7:00 am every morning between day of intubation and the fourth day of IMV, the syringe was used to pump gastric contents through the enteral nutrition pipeline, and daily gastric contents ≥ 200 mL were regarded as gastric retention. Topical antibiotic use was not included in antibiotic therapy.

Statistical analysis

Normally distributed continuous variables, reported as mean (SD), were compared using the unpaired Student t test. Nonnormally distributed variables were expressed as median with interquartile ranges and analyzed by Mann-Whitney U test. The χ^2 test or Fisher exact test was used for independent observations to determine differences between groups of categorical variables. We performed univariate logistic regression analyses examining the associations between each covariate and VAE. Multivariate logistic regression analysis was used to look for independent risk factors of VAEs among study variables. We incorporate coma, thoracic operation, positive daily fluid balances ≥ 50 mL, the use of sedatives, opioids administered, paralytics administered, blood products, tube feeding ≥ 7 days, and gastric retention ≥ 200 mL into the model. We initially included all variables with P values ≤ 0.1 as well as variables of particular clinical interest and then sequentially removed the least significant variables and

Table 1
Summary of researches on the risk factors of VAEs

Author	Region	Design	Setting	Population	Baseline period	VAE cases / controls	Univariate analysis of risk factors for VAEs	Multivariable analysis of risk factors for VAEs
Lewis et al ¹⁵	San Francisco, California, USA	Retrospective case-control study	Medical, surgical, cardiac, and neuroscience units of a tertiary care teaching hospital	VAC patients	2011.01–2011.12	110/110	Risk factors for VACs were net positive fluid balance and mandatory ventilator modes at the time of maximum daily tidal volume; risk factors for IVACs were total opioids and less fluid output and higher average minimum daily tidal volumes	Risk factors for VACs were mandatory modes of ventilation and positive fluid balances; risk factors for IVACs were starting benzodiazepines prior to intubation, total opioid exposures, and paralytic medications.
Dessap et al ²⁴	France	Randomized controlled trial	9 ICUs across Europe and America	Inclusion criteria were those allowing early initiation of ventilator weaning	2007.05–2009.07	152/152*	NA	A depletive fluid management strategy when initiating the weaning process has the potential for lowering VAC risk in mechanically ventilated patients. [†]
Sim et al ²⁵	Seoul, Republic of Korea	Retrospective observational study	ICU of Korea University Guro Hospital, Seoul, Korea	Patients treated with mechanical ventilation for ≥ 2 calendar days	2013.01–2014.06	92/939	Respiratory disorder, trauma, and pulmonary edema	Trauma and pulmonary Edema
Harris et al ²⁶	Tennessee, USA	Nested case-control study	6 adult ICUs at an academic tertiary care center in Tennessee	All adult ICU patients who were mechanically ventilated	2013.01–2014.12	273/984	Higher compliance with chlorhexidine oral care	Higher compliance with chlorhexidine oral care
Guess et al ²⁷	Houston, Texas, USA	Matched case control study	Children's hospital at a tertiary care academic medical center	All patients admitted to PICU who received invasive mechanical ventilation for more than 48 hours	2012.10–2013.09	70/140	Risk factors for VACs were the development of AKI, increases in percentage peak cumulative FO, mean PIP and mean Paw, use of an neuromuscular blockade infusion, and steroid exposure; risk factors for IVACs were the diagnosis of AKI and neuromuscular blockade infusion	Risk factors for VACs were mean peak inspiratory pressure and acute kidney injury; Risk factors for IVACs were acute kidney injury and neuromuscular blockade

AKI, acute kidney injury; FO, fluid overload; ICU, intensive care unit; IVAC, infection-related ventilator-associated complication; NA, not available; Paw, mean airway pressure; PIP, peak inspiratory pressure; USA, United States of America; VAC, ventilator-associated condition; VAE, ventilator-associated event.

*Interventional group/usual care group.

[†]A competing risk model (cumulative incidence function of the Gray model) was used.

clinically overlapping variables until the models converged. If removing a variable led to a substantial change in the estimated effect size for any of the remaining variables, we returned the variable to the model. All analyses were performed using the SPSS program (version 16.0; SPSS, Chicago, IL). All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

During the study period, a total of 5,532 patients were enrolled. A total of 428 patients met the inclusion criteria. The number of mechanical ventilation episodes was 523 times, the total number of hospitalization days was 11,079, and the total number of IMV days was 3,982. There were 30 VACs, 14 IVACs, and 9 possible VAPs (7.53, 3.52, and 2.26 events per 1,000 ventilator days, respectively). **Figure 1** shows the median time to VAC was 6 days (interquartile range, 4.25–9.00 days).

Baseline characteristics

Baseline characteristics and outcomes of cases for patients with VAEs and controls without VAEs, who have also been mechanically ventilated ≥ 4 days, were presented in **Table 2**. There were no notable differences in age, sex, APACHE II score, and comorbidity distribution between patients with and without VAEs. The VAE cases were ventilated for significantly more days than non-VAE cases. VAE cases also had higher hospital mortality rates (56.7% vs 11.8%; relative risk [RR], 9.77; 95% confidence interval [CI], 4.46–21.38). The hospitalization time in ICU of VAE cases was more likely to have longer days than

Table 2

Characteristics and outcomes of patients with and without VAEs

Characteristic	VAE (N = 30)	Non-VAE (N = 398)	P value
Sex (%), male	23 (76.7)	271 (68.1)	.33
Age (y), median (IQR)	60.00 (49.00–72.25)	64.00 (50.00–74.25)	.40
APACHE II score, median (IQR)	24.50 (15.50–27.25)	19.00 (15.00–25.00)	.05
Comorbidities (%)	25 (83.3)	252 (63.3)	.03
Outcomes			
Ventilator-days, median (IQR)	11.00 (7.00–15.00)	7.00 (5.00–10.00)	<.001
Hospital-days, median (IQR)	20.00 (11.50–33.25)	21.00 (10.00–33.00)	.77
ICU-days, median (IQR)	13.00 (8.00–19.00)	9.50 (7.00–15.00)	.01
Hospital death (%)	17 (56.7)	47 (11.8)	<.01

NOTE. Statistical analysis by Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables. Bold values highlights comparisons where the P value for the difference between VAE and Non-VAE group is $\leq .05$.

APACHE II score, acute physiology and chronic health evaluation score II; ICU, intensive care unit; IQR, interquartile range (25th to 75th percentiles); VAE, ventilator-associated event.

non-VAE cases (13 days vs 9.5 days, $P = .01$). There were no differences in mean duration of hospitalization for VAE cases compared with non-VAE cases.

Univariate logistic regression analysis of the risk factors for VAE

On univariate analysis, patients with VAEs were more likely to be comatose (86.7% vs 27.1%, $P < .001$), more likely to have daily fluid balance which was ≥ 50 mL (76.7% vs 15.6%, $P < .001$), more likely to be on sedatives (96.7% vs 49.2%, $P < .001$), opioids (70% vs 43.7%, $P < .01$), paralytics (53.3% vs 20.4%, $P < 0.001$), and blood products (43.3% vs 18.6%, $P = .002$). VAE patients were also significantly more likely to be on gastric retention (93.3% vs 24.6%, $P < .001$), more likely to be fed through tubes for more than 1 week (90% vs 71.9%, $P = .04$), more likely to have thoracic operation (13.3% vs 4.0%, $P = .03$). There were no significant differences between cases with and without VAEs in episode of mechanical ventilation and emergency tracheal intubation.

Multivariate logistic regression analysis of the risk factors for VAE

In the multivariable model for VAE (**Table 3**), significant predictors of VAEs were positive daily fluid balances ≥ 50 mL between day of intubation and the fourth day of IMV (RR, 8.39; 95% CI, 2.99–23.50), sedative administered between the first day and the fourth day of IMV (RR, 15.69; 95% CI, 1.62–152.06), and daily gastric retention ≥ 200 mL between day of intubation and the fourth day of IMV (RR, 9.27; 95% CI, 1.89–45.47).

DISCUSSION

CDC’s new VAE definitions allow objective and reproducible surveillance for complications of mechanical ventilation. The goal of this study was to identify risk factors for VAEs that might inform prevention strategies in the east of China through prospective research methods. We identified 3 significant risk factors for VAEs. Sedatives ordered between the first day and the fourth day of IMV, average gastric retention ≥ 200 mL, and greater net fluid balance between day of intubation and the fourth day of IMV increased the likelihood of VAEs. To our knowledge, this is the first study conducted in China to find risk factors of VAEs.

A total of 1,824 health care facilities reported 32,772 location months of VAE surveillance data to the National Healthcare Safety Network in 2014, and ICU-pooled mean ventilator-associated event

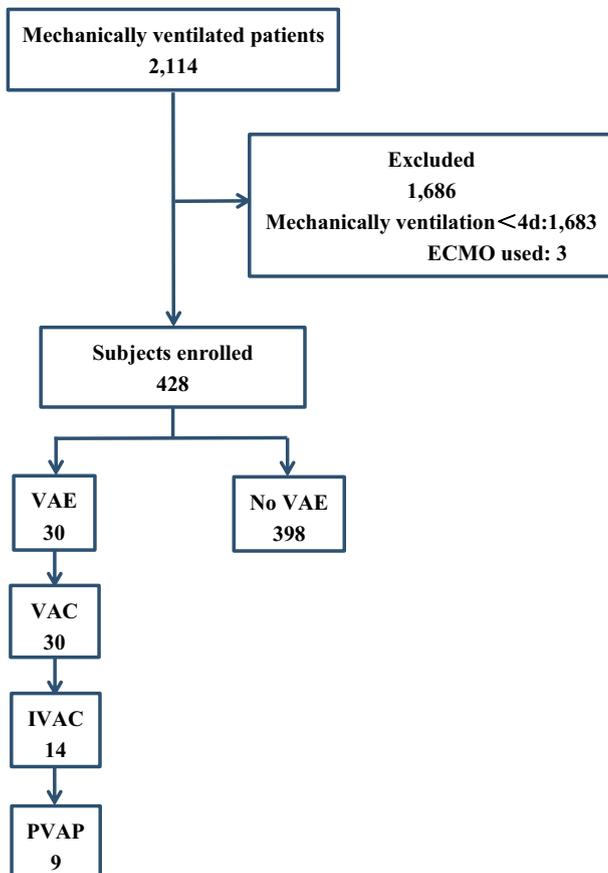


Fig 1. Flowchart. ECMO, extracorporeal membrane oxygenation; VAE, ventilator-associated event; VAC, ventilator-associated condition; IVAC, infection-related ventilator-associated complication; PVAP, possible ventilator-associated pneumonia.

Table 3
Multivariable analysis of risk factors for VAEs

Variable	RR	95% CI	P value
Coma	2.52	0.70–9.14	.16
Thoracic operation between day of admission and the fourth day of IMV	2.52	0.36–17.57	.35
Daily net fluid balance ≥ 50 mL between days of intubation and the fourth day of IMV	8.39	2.99–23.50	<.001
Sedative administered between the first day and the fourth day of IMV	15.69	1.62–152.06	.02
Opioid administered between the first day and the fourth day of IMV	0.32	0.08–1.22	.10
Muscle relaxant administered between the first day and the fourth day of IMV	3.06	0.92–10.15	.07
Blood product between day of intubation and the fourth day of IMV	1.04	0.38–2.88	.94
Tube feeding ≥ 7 days between day of intubation and the fourth day of IMV	2.68	0.64–11.14	.18
Daily gastric retention ≥ 200 mL between day of intubation and the fourth day of IMV	9.27	1.89–45.47	<.01

NOTE. Bold values are statistically significant ($P < .05$). CI, confidence interval; IMV, invasive mechanical ventilation; RR, relative risk; VAEs, ventilator-associated events.

incidence rates ranged from 2.00 to 11.79 per 1,000 ventilator days.⁸ Klompas et al⁹ studied all critically ill patients in an academic tertiary care center between January 1, 2006, and December 31, 2011, and among 20,356 episodes of mechanical ventilation, there were 1,141 (5.6%) VAC events and 431 (2.1%) IVACs. Zhu et al¹⁰ conducted a study, which to our knowledge is the first VAE surveillance study in a developing country of 15 adult ICUs, of 15 hospitals in West China, and a total of 94 VAE cases (4.0% of all patients on invasive mechanical ventilation and 14.8% of those on invasive mechanical ventilation for >2 days) were identified. The current incidence of VAEs in different countries and regions is different. The results of this study are 7.01% (7.53 per 1,000 ventilator days) VAEs, which is lower than the domestic research in China and similar to those in developed countries such as the United States. This may be caused by the different kinds of diseases of the patients and the different ways in which doctors perceive of invasive mechanical ventilation. The 2 ICUs in our hospital receive more patients who have acute respiratory distress syndrome and other respiratory diseases. Our ICU doctors use the new definition of Berlin to treat ARDS patients. They chose a high-level and equal level PEEP treatment plan, which results in a failure to conform to the definition of VAE. Additionally, in China, sputum or extract aspirate samples are often not collected within the VAE window period or not being processed for culture due to the shortage of personnel or lack of the concept of infection prevention and control. Therefore, the incidence of possible pneumonia might have been underestimated in this study.

We reconfirmed that VAEs are associated with adverse outcomes, including prolonged mechanical ventilation, longer intensive care, and higher mortality rates. Effective ways to minimize the occurrence of VAEs are to strictly grasp the indications of invasive mechanical ventilation and to shorten the length of ventilator-days. This trend could be explained by the evidence that prolonged ventilation increases the risk of infection due to exposure to humidifiers and ventilator circuits, which are important sources of pathogens.¹¹ In addition, because of the establishment of an artificial airway, the respiratory tract defense mechanism is impaired. Patients with long time–positive pressure mechanical ventilation can reduce ciliary movement and weaken airway defenses. These will also increase the chance of mechanical ventilation-related complications. In light of these findings, strategies to shorten the duration of IMV may represent another key to controlling VAP, including the daily interruption for sedative-drug infusions¹² and the application of weaning protocols.¹³ When the patient's condition is stable and meets the requirements of extubation, mechanical ventilation should be terminated as early as possible, so as to reduce the chance of infection.

Excess fluids between day of intubation and the fourth day of IMV were a significant predictor for VAE in our study. The relationship between VAEs and excess fluids is consistent with randomized controlled trials. Conservative fluid resuscitation will increase the number of ventilator-free days compared with liberal resuscitation strategies.¹⁴ The association between VAEs and excess fluids is also consistent with

the analysis of Hayashi et al,³ who found that VAC patients received more furosemide than non-VAC patients, and with the analysis of Lewis et al,¹⁵ who found that positive fluid balance was a risk factor for VACs through a retrospective case-control study. Klompas et al⁵ also found that nearly a quarter of VACs were attributable to pulmonary edema. These results perhaps could explain why a history of congestive heart failure was protective against VAEs (RR = 0.66). It is because clinicians may administer fluids more restrainedly in patients with a history of heart failure. A comprehensive view of the existing research results is that improving fluids management may prevent VAEs and improve patients' poor prognosis.

Another independent risk factor for VAEs was sedation administered between the first day and the fourth day of IMV. On multivariable analysis, ordering sedatives prior to intubation was significantly correlated with VAEs. Greater doses of sedatives prolong duration of mechanical ventilation and therefore time at risk for VACs. Higher levels of sedation may also increase the need to use mandatory modes of ventilation, which Lewis et al¹⁵ found to be an independent risk factor for VAC. Nseir et al¹⁶ put forward several mechanisms by which sedatives may increase the risk of infection in ICUs. These mechanisms include prolonged exposure to risk factors for infection, such as central venous catheters and urinary catheters, intestinal dysmotility, microaspiration of gastric contents, and related microbiological imbalance and microcirculatory changes that might contribute to multisystem organ failure. There is substantial evidence that daily sedative interruptions decrease duration of IMV, length of hospitalization, and mortality.^{17–19} Minimizing sedatives is a possible strategy for the prevention of VAEs.

Our findings also indicated that average gastric retention ≥ 200 mL between day of intubation and the fourth day of IMV was an independent risk factor for VAEs. Microaspiration of gastric and oropharyngeal-contaminated secretions is the major mechanism of IMV-related complications pathogenesis in critically ill patients.^{20–22} When local and general defense mechanisms are insufficient and/or when quantity and/or virulence of aspirated microorganisms are high, lower respiratory tract infections occur.²⁰ Many risk factors for microaspiration have been identified, which could be classified into the tracheal tube, IMV, enteral nutrition, and patients. Enteral feeding and nasogastric tubes are important risk factors for microaspiration because they are related to gastric distension, loss of the anatomic integrity of the lower esophageal sphincter, and gastroesophageal reflux. Technological advances brought new ways to decrease microaspiration of contaminated secretions in intubated patients.²⁰ However, a prospective cluster group–randomized controlled crossover, open-label trial, which was conducted in 10 French ICUs, showed that no significant impact of tapered-cuff tracheal tubes on abundant microaspiration of gastric contents, and no significant difference was found for VAEs and VAP between the 2 groups.²³

We are aware of several limitations of this study. First, we gathered data from a single center and analyzed relatively few events, therefore, limiting the power to identify potential risk factors. Second,

this study was conducted in China and the interpretation of this study might not be applicable to other settings due to the large variation of patient populations and the huge difference in the treatment. In addition, due to limited conditions, the end point of the study was defined as hospital mortality. We did not track 30 or 60 days mortality.

CONCLUSIONS

This study identifies potentially modifiable patterns of care associated with VAEs. Sedatives administered between the first day and the fourth day of IMV, gastric retention, and positive fluid balance between day of intubation and the fourth day of IMV are significant risk factors for VAEs. These risk factors are potentially targets for intervention. Prospective studies are now warranted to test whether strategies targeting these risk factors can reduce VAE rates and improve the outcome of patients.

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