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Review

Ventilator-associated events: From surveillance to optimizing management

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ABSTRACT

Mechanical ventilation (MV) is a life-support therapy that may predispose to morbid and lethal complications, with ventilator-associated pneumonia (VAP) being the most prevalent. In 2013, the Center for Disease Control (CDC) defined criteria for ventilator-associated events (VAE). Ten years later, a growing number of studies assessing or validating its clinical applicability and the potential benefits of its inclusion have been published. Surveillance with VAE criteria is retrospective and the focus is often on a subset of patients with higher than lower severity. To date, it is estimated that around 30% of ventilated patients in the intensive care unit (ICU) develop VAE. While surveillance enhances the detection of infectious and non-infectious MV-related complications that are severe enough to impact the patient's outcomes, there are still many gaps in its classification and management. In this review, we provide an update by discussing VAE etiologies, epidemiology, and classification. Preventive strategies on optimizing ventilation, sedative and neuromuscular blockade therapy, and restrictive fluid management are warranted. An ideal VAE bundle is likely to minimize the period of intubation. We believe that it is time to progress from just surveillance to clinical care. Therefore, with this review, we have aimed to provide a roadmap for future research on the subject.

Introduction

Mechanical ventilation (MV) is a life-support therapy that often required by the patients admitted to the intensive care unit (ICU). Its use is not exempt of risk and may predispose the patient to morbid and lethal complications. Over the years, different definitions of MV-related complications have been used for surveillance measures, such as the ventilator-associated pneumonia (VAP) diagnostic criteria. The ventilator-associated events (VAE) algorithm[1] was established in 2013 with the aim to detect complications that are severe enough to cause respiratory worsening in ventilated patients including but not limited to infection. Since VAE surveillance was proposed by the Center for Disease Control (CDC) in 2013, a growing number of studies assessing and validating its clinical applicability and the benefits of its inclusion in quality and surveillance programs in both pediatric ICU (PICU) and adult ICU worldwide have been published. Additionally, the accelerated knowledge obtained during the coronavirus disease 2019 (COVID-19) pandemic along with the recent research in MV, acute respiratory distress syndrome (ARDS), and infectious diseases is providing new insights on this matter.

VAE Surveillance Algorithm and Definitions

VAE are identified through a combination of objective criteria, namely respiratory deterioration after a period of stability or improvement, evidence of inflammation or infection, and laboratory evidence of respiratory infection[1] (Figure 1). This algorithm was established after consistent research highlighted the low specificity and reproducibility of diagnostic criteria used for VAP. A more reliable, objective, and reproducible set of criteria were needed to implement surveillance and ensure the efficacy of preventive measures.[2]

VAE surveillance involves the use of dynamic, objective, and comparable variables that are easy to obtain at bedside and in-

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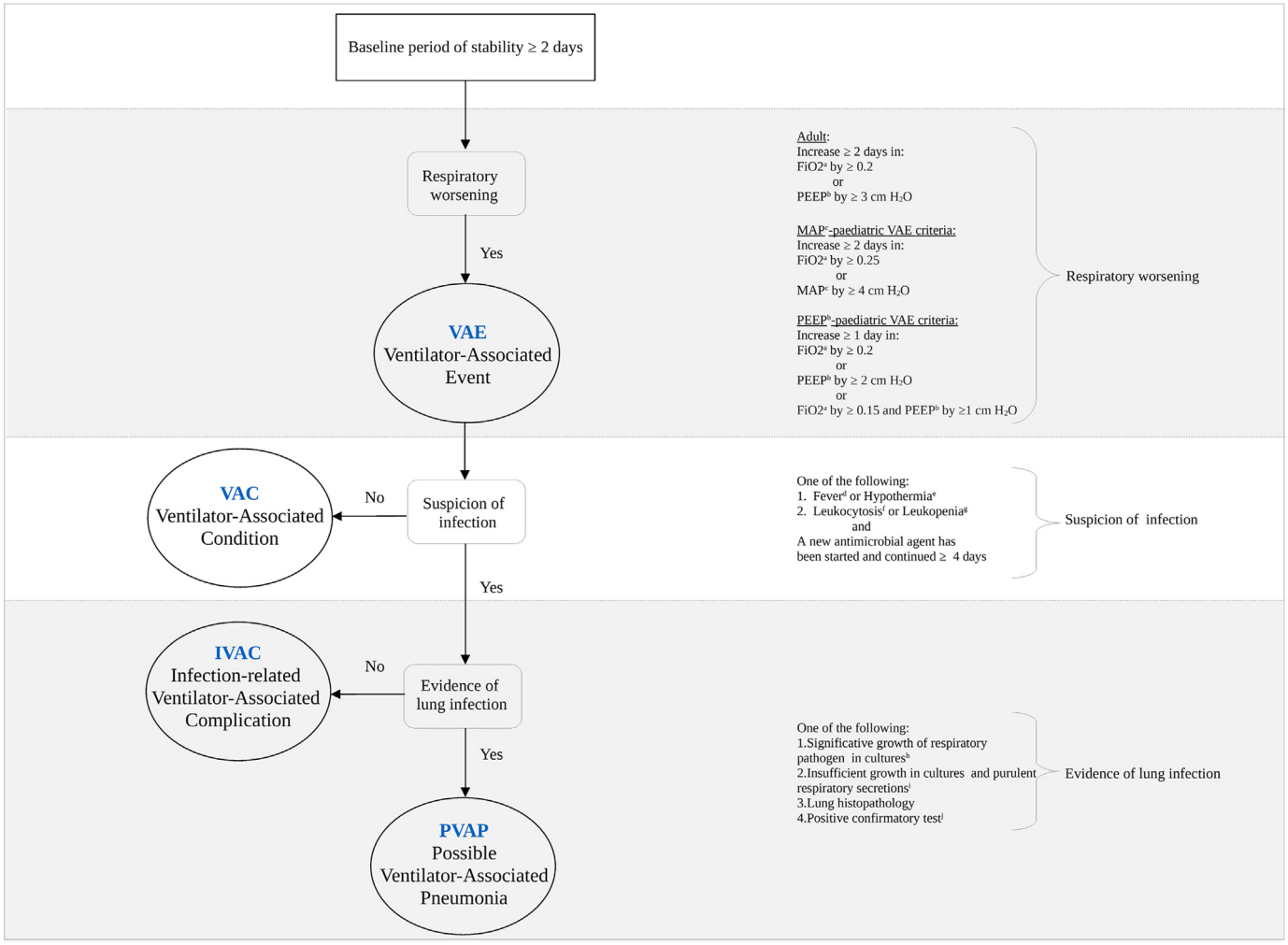

Figure 1. VAE algorithm and definitions.
*Fever: Temperature >38°C;
†Hypothermia: Temperature <36°C;
‡Leukocytosis: ≥12,000 cells/mL;
§Leukopenia: ≤4000 cells/mL;
||Significant growth in cultures: 105 CFU/mL for endotracheal aspirate, 104 CFU/mL for bronchoalveolar lavage or lung tissue, and 103 CFU/mL for protected specimen brush;
¶Purulent respiratory secretions: >25 neutrophils and ≤10 squamous epithelial cells per low power field; and
**Diagnostic test for Legionella species, influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, and coronavirus.
FiO_2: Fraction of inspired oxygen; IVAC: Infection-related ventilator-associated complication; MAP: Mean airway pressure; PEEP: Positive end expiratory pressure; PVAP: Possible VAP; VAC: Ventilator-associated condition; VAE: Ventilator-associated events; VAP: Ventilator-associated pneumonia.

tegrate in electronic health records. The most common events are due to infection, ARDS, fluid overload, or atelectasis.[3–5] Less common events include pneumonitis and pulmonary embolism, which account for <1% of VAE.[3] More importantly, VAE include only patients with conditions severe enough to cause impaired gas exchange, and therefore has a stricter association with mortality than the traditionally used VAP criteria.[2]

Around 30% of all ventilated patients in the ICU develop VAE[6–8] and up to 1.5% can experience more than one episode.[7] A recent study using electronic surveillance to assess VAE in China found a 28% incidence with 16.7 VAE per 1000 ventilator days[7]; similar results were reported in septic patients in south of Taiwan, China.[5] Up to 30% of surgical patients admitted to the ICU develop VAE, while this risk is <15% in trauma, post cardiac surgery, and neurocritical patients.[2,3] Most VAE occur within the first week of ventilation[3,6,7]; early VAE pose a 4-fold increase in risk of death.[5] The presence of VAE is associated with increased mortality, prolonged hospital stay, and longer duration of MV, independent of the cause of admission.[6,7,9] Table 1 shows a comparison of the outcomes in different types of patients with VAE.

VAE are divided in three tiers: ventilator-associated condition (VAC), infection-related ventilator-associated complication (IVAC), and possible VAP (PVAP)[1] (Figure 1). Factors associated with increased risk of VAE are positive fluid balance, selective oral decontamination with chlorhexidine, and stress ulcer prophylaxis,[5,10–13] while blood transfusion, use

Table 1
Comparison of the outcomes in different types of patients with VAE.

Study	Study design	Type of patient	Sample size	VAE (%)	Media of VAE onset* (days)	Early VAE† (%)	MV days		ICU LOS		Hospital LOS		Global mortality		ICU mortality (%)		APACHE II (mean value)
							VAE	No-VAE	VAE	No-VAE	VAE	No-VAE	VAE	No-VAE	VAE	No-VAE	
He et al.[7]	Observational	Mixed	6252	28	6	68	14	8	20	13	28	22	NA	NA	19	13	20
Rello et al.[52]	Prospective	Mixed	244	47	5	51	12	7	23	12	31	19	43	29	NA	NA	20
Fang et al.[5]	Retrospective	Septic	453	26	13	27	36	23	20	12	NA	NA	82	22	50	7	24
Zhu et al.[6]	Cohort	Mixed	6426	29	NA	NA	13	7	19	12	27	22	NA	NA	NA	NA	20
Wu et al.[59]	Cohort	Neurological	855	15	5	NA	17	8	20	12	29	26	34	31	NA	NA	NA
He et al.[60]	Retrospective	Post cardiac surgery	1709	10	NA	NA	NA	NA	13	3	29	19	9	1.5	NA	NA	NA
Weinberger [8]	Retrospective	COVID-19	628	29	6	49	19	9	NA	NA	NA	NA	NA	NA	60	41	NA

APACHE: Acute Physiology and Chronic Health Evaluation; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; LOS: Length of stay; MV: Mechanical ventilation; NA: Not available; VAE: Ventilator-associated events.

* Days since the MV was started.

† VAE in the first 7 days since the MV was started.

of immunomodulators, and central-line catheters are independently associated with higher rates of mortality in patients with VAE.[6,12] Patients with VAE have increased risk for extubation failure, tracheostomy, disability, and death (Figure 2). The other related outcomes are prolonged duration of MV, longer hospital admission, and increased hospitalization cost.[1,2,6,7,9]

Non-infectious VAE: VAC

The main causes of non-infectious VAE are ventilator-induced lung injury (VILI), atelectasis, pulmonary edema, and ARDS.[7,9]

VILI

VILI is the result of the disbalance between the energy applied during MV and the elastic properties of the lung. Under normal physiological conditions, the lungs are not prepared to deal with high pressures that might be imposed by MV. Supra-physiological tidal volumes have been used in atelectasis prevention, and although deemed effective in the perioperative context, it has been associated with other VAE such as VILI and barotrauma.[14]

Available evidence supports maintaining a oxygen saturation (SpO_2) range between 92% and 96% in critically ill adult patients and between 88% and 92% for those with chronic hypoxemia.[15,16] Both hypoxemia and hyperoxia are associated with worst outcomes in ventilated patients: hypoxemia causes irreversible tissue damage, while hyperoxia is associated with absorption atelectasis, tissue oxidative stress, and cell death.[17,18] Studies assessing conventional *vs.* conservative oxygen strategies did not find extra benefit in those patients with partial pressure of oxygen (PaO_2) >150 mmHg.[16–18]. In patients admitted to the ICU with severe hypoxemia, a goal of PaO_2 >90 mmHg does not appear to improve survival or health-related quality of life 1 year after admission compared with a restrictive O_2 strategy (PaO_2: 60 mmHg).[19] Protective ventilation must avoid overdistention and overpressure, limiting opening and closing movements of the alveoli while maintaining an adequate diaphragm function. However, in critical patients, the lungs do not have uniformely distributed aerated areas. Rather, there are collapsed and inflamed areas, resulting in non-uniform volume being administered during MV. Additionally, compensatory mechanisms for increase in transpulmonary pressure are impaired in sedated patients. A lung protective sedation strategy has been advocated to prevent VILI.

Atelectasis

Pulmonary atelectasis is a common complication of MV, particularly in perioperative patients. Obesity, extremes of age, and previous pulmonary conditions (such as pulmonary edema and chronic obstructive pulmonary disease) increase the risk of atelectasis in perioperative patients.[20] Over the years, some strategies have been developed to reduce MV-related atelectasis. Evidence suggests that slight increase in positive end expiratory pressure (PEEP) may decrease VAE in trauma patients.[21] While an open lung strategy in patients aiming to increase lung recruitability reduces the risk of atelectasis,[22] elevated levels of PEEP are associated with lung overdistention and diaphragmatic atrophy.[23]

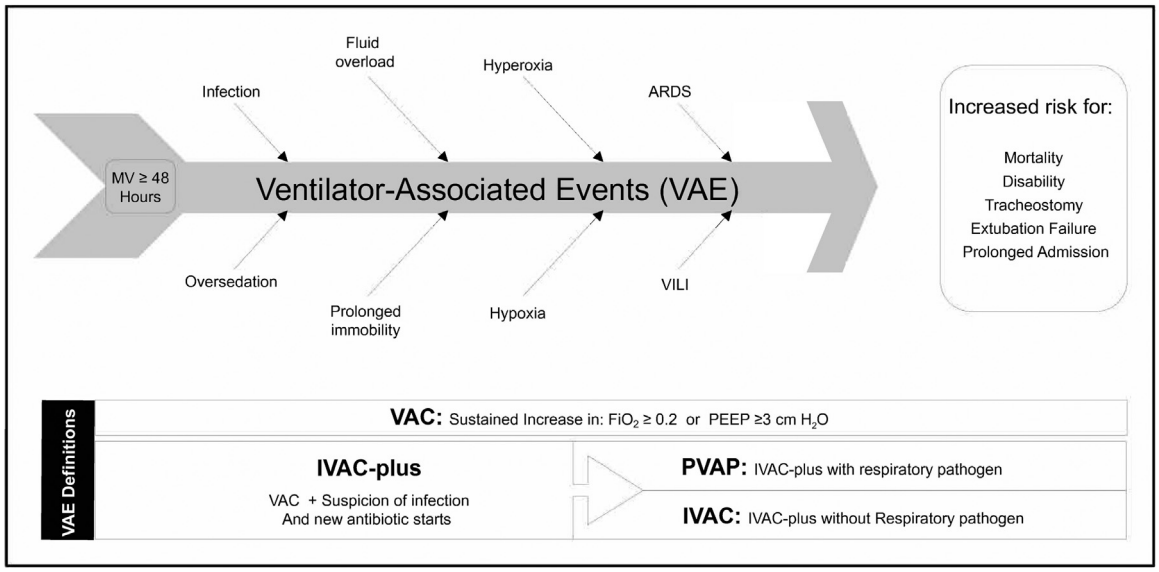

Figure 2. VAE's causes, and outcomes.
ARDS: Acute respiratory distress syndrome; FiO_2: Fraction of inspired oxygen; IVAC: Infection-related ventilator-associated complication; MV: Mechanical ventilation; PEEP: Positive end expiratory pressure; PVAP: Possible VAP; VAC: Ventilator-associated condition; VAE: Ventilator-associated events; VAP: Ventilator-associated pneumonia; VILI: Ventilator-induced lung injury.

Fluid overload

Fluid overload, which includes pulmonary edema, accounts for up to 48% of VAE.[24] Fluid imbalance is associated with prolonged time of MV in adults[25,26] and children,[27,28] and it has been established as a risk factor for VAE.[2] The inclusion of clinically relevant pulmonary edema in the VAE algorithm is one of the greatest differences between the VAP and VAE algorithms, which is relevant considering the latter highlights strategies aimed at improving fluid balance, such as parsimonious fluid resuscitation and initiation of diuretics when indicated.[29] Preventing fluid overload is particularly challenging in patients with heart and/or kidney failure and in sepsis, considering that fluid resuscitation is part of the initial management.

ARDS

ARDS accounts for 5–20% of VAE[2] and has varied etiologies such as viral pneumonia (such as influenza and SARS-CoV-2), bacterial pneumonia, massive transfusion, fluid overload, and MV.[30] Some strategies have been developed to prevent ARDS, particularly regarding protective ventilation; many others have been shown to be ineffective, such as inhaled N-acetyl-cysteine and surfactants. Yadav et al.[31] classified ARDS prevention in the context of primary, secondary, and tertiary prevention. Primary ARDS prevention includes administering influenza and pneumococcal vaccination, preventing aspiration pneumonitis, and using rapid sequence intubation; secondary prevention involves protective ventilation and preventing fluid overload; tertiary prevention includes reducing the impact of post-intensive care syndrome.

Miscellaneous

Other non-infectious VAE include pulmonary thromboembolism, mucous plugging, pneumothorax, and abdominal distension/compartment syndrome. Taken together, these conditions account for at least 5% of VAE.[24]

Infectious VAE: IVAC-plus

The concept of IVAC-plus was created in the 2015 VAE update to include all respiratory worsening following VAE criteria due to infection, regardless of its origin.[32] Moreover, within IVAC-plus, PVAP and IVAC were supposed to refer to a pulmonary or extra-pulmonary origin, respectively.

However, the absence of microbiological confirmation does not always entirely exclude a pulmonary infection (as it can result from previous antibiotic use), and other systemic or local inflammatory responses such as autoimmune diseases or lung transplant rejection which can mimic sepsis or pneumonia. In both cases, the severity of the illness and/or the lack of rapid laboratory results frequently lead to prolonged antibiotic therapy for >4 days. This dependence on clinical criteria has been noted as a limitation[33] considering that it could lead to a misclassification of VAC as IVAC-plus. Nonetheless, despite referring to IVAC-plus as infectious VAE is not completely accurate, it helps to achieve an overall understanding of the tiers.

On the other hand, PVAP has not been adopted as the new VAP surveillance because of its most restrictive criteria, corresponding to IVAC-plus with a microbiologically confirmed pulmonary infection. Moreover, when assessing patients with a traditional ventilator-respiratory infection based on VAE criteria, IVAC-plus misses 25% of all VAP and 75% of ventilator-associated tracheobronchitis (VAT).[3] Despite this, or, from a different point of view, IVAC-plus only includes VAP and VAT that have a real impact on patient outcomes.

Interestingly, patients with infectious VAE have more MV days and prolonged ICU and hospital stays than patients with other causes of VAE.[3] In adults, almost half of VAE are associated with respiratory infections. In a multicentric analysis of VAE in European ICUs, our group found that 54% of VAE were

related to VAP or VAT[3]; a recent study assessing VAE in China found that 40% of events were due to infection.[7]

Finally, although a large proportion of VAE are not infection-related, some events that can cause VAC (non-infectious VAE), such as ARDS, are a risk factor for pulmonary infection and vice versa.[13] In a secondary analysis of a multicenter randomized, placebo-controlled, double-blind trial of cisatracurium in severe ARDS patients, microbiologically confirmed VAP was diagnosed in 29% of patients and was an independent risk factor for ICU mortality despite using strictly standardized lung-protective strategies.[34]

Special conditions

COVID-19

During the COVID-19 pandemic, the sudden increase in patients requiring prolonged ventilation and receiving immunomodulatory therapies resulted in a vertiginous increase in MV-related complications worldwide. Additionally, health care personnel burnout may have affected the adherence of prevention protocols for hospital-acquired infections. In 2020, the US National Healthcare Safety Network reported a 45% increment in VAE and significant increases in infections related to central lines and urinary tract catheters.[35] A recent study assessing VAE in the pandemic *vs.* pre-pandemic period found a 50% increase in the first group, although the rates of VAE per 1000 ventilation days were similar in both cohorts.[8] A recent study by Weinberger et al.[36] that assessed VAE in COVID-19 patients reported a VAE incidence of 29%, similar to other patients (Table 1). COVID-19 patients with VAE had higher mortality during the second wave of the pandemic than during the first wave (60% *vs.* 30%), and VAE rates per episode of MV decreased. However, the VAE rates per ventilatory days remained stable. In the initial stages of the pandemic, most patients with severe COVID-19 were promptly intubated and ventilated, while overtime MV was progressively reserved for the most severe cases owing to the increasing evidence supporting the benefits and safety of other less invasive devices. Another reason was the unavailability of MV devices for all COVID-19 patients with ARDS during the most severe outbreaks and under conditions where health systems collapsed.

Critical patients with COVID-19 have higher IVAC-plus risk than non-COVID patients, including those with other viral infections such as influenza.[15] SARS-CoV-2-induced endothelial dysfunction and micro-thrombosis may promote lung infection and bacterial translocation. VAE increases the MV time and risk of developing another VAE episode in 20% patients with COVID-19.[36]

Pediatric VAE (PedVAE)

The VAE surveillance definition algorithm was initially available only for adult patients.[37] Shortly thereafter, retrospective pediatric studies were conducted to evaluate the application of VAE; it was noticed that the use of these new criteria in children would require an adaptation of the VAE definition in accordance with the peculiarities of the pediatric population.[38–41]

All first modified PedVAE proposals, apart from CDC, focused on changing the thresholds to meet the first tier of VAE (VAC) and retain the parameters for IVAC and PVAP used in adult definitions.[4,41] The reasons argued by the authors for this less restrictive algorithm for PedVAE definitions are that most children present good pulmonary baseline conditions and can withstand mechanical complications better than children suffering from chronic conditions or adults, and that children needed a shorter recovery time than adults. Indeed, when the VAE adult criteria were applied by Peña-López et al.[4] to children in PICU, the incidence of VAE was fewer than in adults and their repercussion on mortality was higher. By contrast, they obtained a 4-fold increase in VAE and a 2-fold increase of PVAP when using their less restrictive criteria for a respiratory worsening in their PedVAE proposal based on PEEP (PEEP-PedVAE), and keeping the repercussion on outcomes. As in the adult population, the agreement between the new 2013-VAE and old 2008-CDC PNU/VAP definitions in children is poor[42] and is the same for the newly proposed pediatric definitions tested.[4]

The 2017 US-CDC definition of PedVAE emerged from a consensus of experts based on a retrospective study and a matched cohort analysis.[43] As the main items of the definition, they advocated for the use of mean airway pressure (MAP) instead of PEEP setting (MAP-PedVAE) and a higher increase in the fraction of inspired oxygen (0.25 instead of 0.20). They also simplified the tier IVAC for AVAC, defined as pediatric VAC with antimicrobial use, thereby eliminating the need of tracking white blood cell counts and temperatures. Pediatric AVAC with a positive respiratory diagnostic test was considered a pediatric PVAP.

When retrospectively applied, the MAP-based pediatric variation of VAE adopted by the US CDC (MAP-PedVAE)[1] missed 84 out of 89 ventilator-associated infections in a multicenter study conducted across 47 PICUs in the United States, Canada, and Australia.[33] Moreover, Arthur et al.[44] recently reported a rate as low as 0.9 per 1000 ventilator-days in newborns. Conversely, in a multicenter prospective study conducted by 15 Spanish PICUs, the pediatric definition of VAE based on slighter PEEP increases (PEEP-PedVAE) was the least restrictive, and it was the only VAE definition that was independently associated with increased MV and length of ICU stay in children.[45] In another study, all VAE algorithms (PEEP-PedVAE, MAP-PedVAE, and adult VAE) were associated with adverse outcomes, including higher mortality rates when retrospectively applied in a pediatric population.[46] Thus, a unified PedVAE definition is needed. Prospective validation of these proposed PedVAE variations along with the identification of risk factors associated with PedVAE are needed to improve the definition of VAE in children and tailor it to critically ill patients in the cardiac ICU, neonatal ICU, and PICU.

Prevention and Research

A prospective study in a tertiary hospital to assess the effectiveness of a multidisciplinary strategy to prevent VAE, including physicians, nurses, and physiotherapists, used protocolized weaning, protective ventilation, and early daily mobilization and found a significant reduction in VAE rates (77%) after 5 years. However, the external validity of the results needs to be corroborated.[47]

Table 2
Main opportunities for future research.

Items	Details
VAE definitions	VAE patterns are different in specific populations of critical patients such as cardiac, trauma, and neurocritical patients. These might have different VAE etiologies, and preventive strategies may differ according to the type of criticality. More research will be needed in the next years to assess the effect of less restrictive VAE criteria in previously healthy adults. Early VAE are strongly associated with mortality risk, and detecting VAE at an earlier stage, when the progression to a major event might be prevented, impacts prognosis. Therefore, more research on the differences between early and late VAE and in the detection of early changes in clinical and non-clinical variables is needed.
Preventive strategies	Most care bundles focus on VAP prevention. Although infections are the most frequent cause of VAE, two-thirds of VAE and 90% of PedVAE have other etiologies. New bundles, directed to reduce infectious but also non-infectious events, need to be designed and validated.
VAE management	The role of bedside ultrasound, a tool that has been proven to be crucial in different diagnosis inside the ICU, is not clear with regard to VAE. Studies evaluating the role of bedside ultrasound in VAE diagnosis and management are warranted. Traditionally, events are analyzed independently; however, in clinical practice, patients can have more than one cause of VAE at the same time. Future studies analyzing these interactions and its impact in outcomes need to be designed.

ICU: Intensive care unit; PedVAE: Pediatric VAE; VAE: Ventilator-associated events; VAP: Ventilator-associated pneumonia.

Using quantitative variables in the VAE algorithm reduces interobserver variability and facilitates its incorporation in electronic medical records.[8] Computerized VAE surveillance reduces time and effort and limits the risk of operator bias.[45,48] Shenoy et al.[49] compared automated *vs.* manual surveillance and found an increase in sensitivity and positive predictive value (40% *vs.* 71% and 70% *vs.* 87%) using completely automated models. Frequent errors in the manual surveillance cohort were missed detections, false detections, and misclassification. VAE electronic surveillance is a useful metric tool to monitor the quality of patient care. Studies combining electronic surveillance with the analysis of improvement efforts through a Plan-Do-Study-Act cycle are proven to decrease VAE.[47]

Artificial intelligence helps to detect patients at risk for major complications and facilitates clinical decision; however, the results may be limited because of differences in concepts. A recent meta-analysis comparing different diagnostic and prognostic prediction models (electronic nose, natural language processing, and gas chromatography-mass spectrometry) in patients at risk of VAP found a high variability in sensitivity, specificity, accuracy, and positive and negative predictive values; unfortunately, the definition of VAP was not uniform between the studies.[50]

VAE are directly related with the type and duration of MV; VAE risk is increased with mandatory modes.[19] Most events occur between days 5 and 6 (Table 1), thus early extubation must be considered whenever possible. Daily awakening tests, sedation vacation, spontaneous breathing trials, and use of light sedatives accelerate weaning and reduce MV duration.[2,10] In patients with severe-to-moderate ARDS, short courses of neuromuscular blocking agents do not seem to exert a significant effect on the development of VAE, while long-acting sedation increases the risk of developing VAE by 4-fold.[51,52] Partial neuromuscular blockade appears helpful in achieving protective ventilation goals without affecting diaphragm activity in patients with excessive respiratory efforts.[53]

VAE and VAP have many differences, which suggest the need for a distinctive preventive strategy. Most bundles for VAP do not improve VAE rates, and this has many possible explanations. First, VAP criteria have low specificity-as colonization or pulmonary infiltrate with different etiologies might often be misdiagnosed as VAP-,—and low reproducibility. As highlighted by Klompas[2] in 2019, the use of non-objective criteria might be misleading when evaluating the effectiveness of a preventive bundle, considering that professionals involved in preventive programs aim to report success. Additionally, the efficacy of care bundles for VAP prevention has been questioned over the past years. Metersky et al.[54] found stable VAP rates between 2005 and 2013 in the United States, despite significant declines in VAP rates reported by the CDC. Therefore, the efficacy of preventive VAP bundles was probably biased by a difference in reporting rates. Second, bundles are designed specifically for VAP, while the VAE algorithm also detects non-infectious events. Finally, another possible explanation for a disparity in preventing VAP and VAE is the poor agreement of VAE and VAP criteria. A recent study found that most cases of VAP were not detected using VAE criteria.[55] Approximately two-thirds of VAE are not associated with infections and up to 30% VAP cases and at least 60% VAT cases are not detected by VAE surveillance.[2,3] This is to be expected, considering that only a fraction of more severe VAP cases, such as those with impaired gas exchange, will fulfill the VAE criteria.

Although a large proportion of VAE are not infection-related, some events such as ARDS are the risk factors for pulmonary infection.[13] Others events such as pulmonary edema account for a large proportion of non-infectious VAE. In this sense, there is a need for objective measurements of fluid balance; the use of point-of-care ultrasound (POCUS) is becoming increasingly important to assess fluid overload, evaluate heart function, and exclude other less frequent causes of respiratory deterioration such as pulmonary embolism, pleural effusion, or pneumothorax. POCUS is particularly helpful in preventing, diagnosing, and managing non-infectious VAE.[56–58]

Preventing VAP is important to improve oxygenation and facilitate MV weaning. Considering that the traditional VAP bundles have been challenged, it is necessary to evaluate newer care bundles by using more objective diagnostic criteria for VAP. We advocate that these bundles focus on MV weaning; preventing non-infectious VAE could reduce VAP rates. Reducing the MV time through awakening tests, early mobilization, and using short-term sedatives whenever possible is required to prevent infectious and non-infectious VAE. Moreover, a multidisciplinary approach for VAE prevention, focusing on reducing exposure to MV is warranted.

Conclusions

MV-related complications increase the time of MV, in-hospital mortality rates, and hospitalization costs, thereby posing a challenge to both adult and pediatric patients in intensive

care. The VAE algorithm facilitates surveillance and detection of MV-related complications that are severe enough to impact the patient's outcomes. However, there are still many gaps in VAE classification and management, such as VAE assessment and prevention in different populations. The use of quantitative variables allows for consistency and incorporation in surveillance and quality programs.

Although VAE criteria are more specific and reproducible than the traditional VAP criteria, we believe that more objective measurements are possible. One possibility would be using PEEP variations with more adjusted breakpoints as a foundation for VAE diagnosis. Additionally, it is likely that many cases of colonization are misdiagnosed as VAP. We believe that using the stricter VAE criteria, for which impaired oxygenation is required, focusing on the VAP cases that actually benefit from antibiotic treatment and may solve pneumonia *vs.* tracheobronchitis issue. Whether the duration of antibiotic treatment can be guided by ventilatory changes remains unknown.

The efficacy of bundles traditionally used for VAP prevention has been questioned in the past years. Preventive bundles that are aimed at reducing the MV time, therefore decreasing infectious and non-infectious VAE rates, are warranted. These bundles could include using short duration and light sedatives, performing awakening tests and spontaneous breathing trials whenever possible, and ensuring conservative fluid management. Early mobility and early weaning are useful for reducing time of MV and require a multidisciplinary approach. A roadmap for future research on the subject is provided in Table 2.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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