Ventilator-Associated Events

Epidemiology, Risk Factors, and Prevention

Jeremy Weinberger, MD[a,b,c], Noelle Cocoros, DSc, MPH[a], Michael Klompas, MD, MPH[a,b,*]

KEYWORDS

• Ventilator-associated events • Ventilator-associated pneumonia
• Mechanical ventilation • Quality improvement • Infection control and prevention

KEY POINTS

- Ventilator-associated events definitions were designed to improve the objectivity, breadth, and seriousness of adverse event surveillance in mechanically ventilated populations
- The most common conditions that trigger ventilator-associated events are pneumonia, fluid overload, acute respiratory distress syndrome, and atelectasis
- Promising strategies to prevent ventilator-associated events include minimizing sedation, enhancing paired daily spontaneous awakening and breathing trials, promoting early mobility, setting low tidal volume ventilation, using intravenous fluids conservatively after resuscitation, and implementing restrictive transfusion thresholds.
- An increasing number of reports document that multifaceted quality improvement initiatives are associated with lower ventilator-associated event rates

INTRODUCTION

Up to 800,000 patients per year receive mechanical ventilation in the United States and the incidence is increasing over time.[1–3] This procedure can be lifesaving for patients with acute respiratory failure, but being on a ventilator also increases the risk of an array of complications that can prolong ventilator dependence and sometimes hasten death. Some of these complications are caused directly by mechanical ventilation, others only indirectly. The objective of this article is to provide an up-to-date review on the epidemiology, outcomes, risk factors, and prevention strategies for ventilator-associated

Conflicts of Interest: None.
[a] Department of Population Medicine, Harvard Medical School, Harvard Pilgrim Health Care Institute, 401 Park Street, Suite 401, Boston, MA 02215, USA; [b] Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA; [c] Division of Pulmonary, Critical Care, and Sleep Medicine, Tufts Medical Center, 200 Washington Street, Boston, MA 02111, USA
* Corresponding author. Department of Population Medicine, 401 Park Street, Suite 401, Boston, MA 02215.
E-mail address: mklompas@partners.org

Infect Dis Clin N Am 35 (2021) 871–899
https://doi.org/10.1016/j.idc.2021.07.005
id.theclinics.com

events (VAEs), including pneumonia. We focus on the adult patient population, but also briefly describe relevant work in pediatric and neonatal populations.

VENTILATOR-ASSOCIATED EVENTS VERSUS VENTILATOR-ASSOCIATED PNEUMONIA

Before January 2013, the Centers for Disease Controls and Prevention's (CDC) National Healthcare Safety Network (NHSN) only provided surveillance definitions for ventilator-associated pneumonia (VAP). The NHSN switched the focus of surveillance from VAP to VAE in early 2013, however, in response to increasing concerns about the suitability of traditional VAP definitions to support quality improvement and benchmarking initiatives.[4]

The VAE framework includes a nested set of definitions designed to detect both infectious and noninfectious complications in mechanically ventilated patients.[5] Some of these complications may be direct adverse consequences of mechanical ventilation (such as pneumonia), whereas others are indirect events that can complicate the course of mechanical ventilation (such as pulmonary edema). **Fig. 1** provides a summary of adult VAE surveillance definitions. The core definition in the VAE set is called a ventilator-associated condition (VAC). A VAC is designed to detect respiratory deterioration after a period of stability or improvement. To be eligible for a VAC, a patient must first demonstrate at least 2 days of stable or improving ventilator settings, namely, the daily minimum fraction of inspired oxygen (Fio_2) or positive end-expiratory pressure (PEEP). If a patient subsequently requires an increase in the daily minimum Fio_2 by 0.20 or more or an increase in the daily minimum PEEP by 3 or more cm H_2O, and the increase is sustained for at least 2 calendar days relative to both baseline days, then the patient meets VAC criteria and has a VAE. The increase in ventilator settings is presumed to indicate that the patient may have suffered a complication or deleterious change in their clinical status, but does not in and of itself indicate what might have gone wrong. There are consequently additional VAE criteria to identify the subset of VACs that may be attributable to infection and the subset of those that might be due to pneumonia. An infection-related ventilator-associated complication (IVAC) occurs in a patient with VAC who has concurrent inflammatory changes (abnormal white blood cell count or temperature) and in whom clinicians begin and continue a new course of antibiotics ($\geq$4 days of new antimicrobials starting within 2 days of the VAC). Both VAC and IVAC intentionally capture both pulmonary and nonpulmonary complications.[6] The last surveillance tier of the VAE definition set identifies the subset of IVACs that are possible VAPs (PVAP). This final tier is flagged by a case of IVAC with concurrent inflammatory pulmonary secretions and/or positive respiratory cultures. IVAC-plus refers to IVACs that include PVAPs (whereas IVAC-alone is IVAC excluding PVAPs).

Why the Shift to Ventilator-associated Events?

Numerous concerns catalyzed the shift from VAP to VAE. From a technical and practical perspective, the old NHSN VAP criteria were challenging.[7] The definitions included multiple pathways for different patient populations and many of the surveillance criteria were subjective, insensitive, and nonspecific (eg, "new or progressive infiltrates," "change in the character of sputum," or "worsening cough").[8] The definition correlated poorly with histologic pneumonia and the clinical information needed to apply traditional VAP definitions was hard to collect, making surveillance difficult to implement.[9,10] The subjective components of the VAP definition led to high rates of interobserver variability.[11–14] Finally, VAP criteria did not consistently identify patients at increased risk for poor outcomes, and interventions that decreased VAP rates often had no effect on more patient-centered outcomes, such as the duration of mechanical

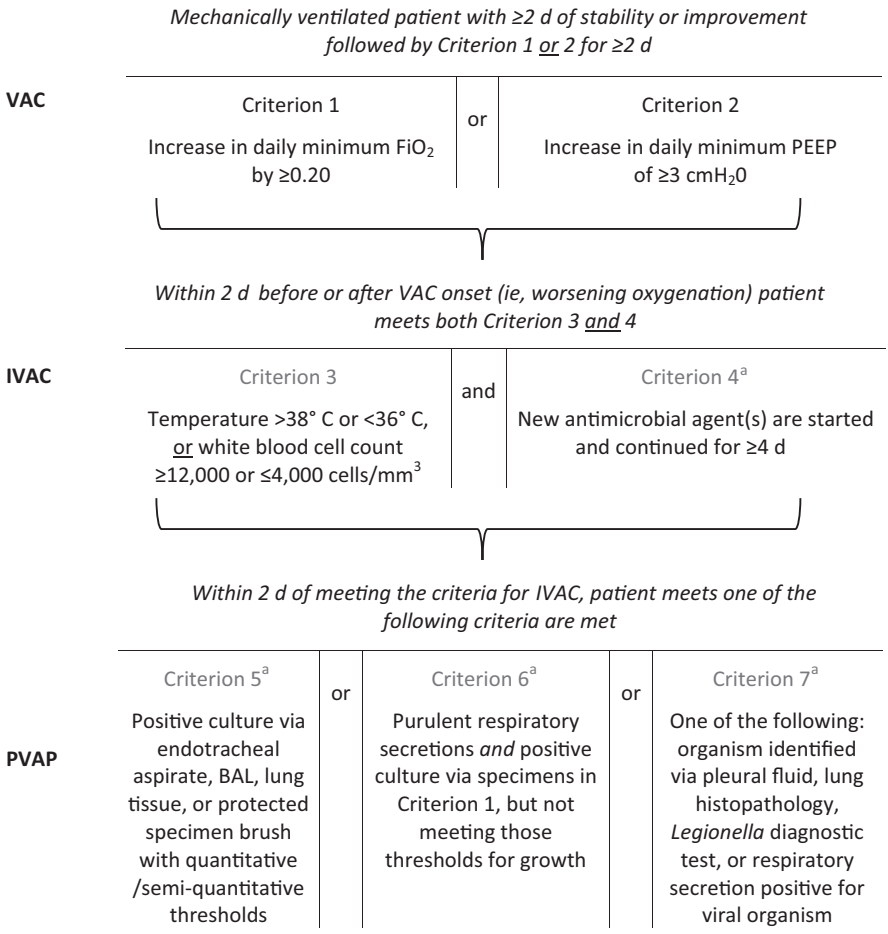

Fig. 1. National surveillance definitions for VAEs in adults. [a]See the full CDC NHSN protocol for details related to each criterion (CDC 2020). BAL, bronchoalveolar lavage. Surveillance "day 1" is the day of intubation and initiation of mechanical ventilation; the earliest day VAE criteria can be fulfilled is day 4 and the earliest event date for VAE is day 3 of mechanical ventilation.

ventilation or hospital mortality.[15–19] Indeed, recent estimates suggest that the attributable mortality of VAP is only about 10%.[20,21]

The failure of most VAP prevention strategies to yield better outcomes for ventilated populations begs the question of whether VAP is the best target to drive surveillance and prevention programs. Quality improvement initiatives should ideally focus on identifying and preventing objective, morbid complications that are unambiguously associated with poor outcomes. By broadening the scope of surveillance from VAP to VAE, CDC acknowledged that both infectious and noninfectious complications can arise in ventilated patients and all should be considered when designing prevention programs.

VAE surveillance is based on quantitative clinical criteria that can be collected, detected, and reported electronically.[22–27] Although some of the VAE criteria reflect underlying clinical judgment—such as adjusting ventilator settings, starting and continuing antimicrobial treatment, and obtaining respiratory cultures—the definition components

themselves are clear and reproducible, the key characteristics of good case definitions for public health surveillance.[28] The objective criteria associated with VAEs have comparable meanings and can be collected in comparable ways across institutions.

EPIDEMIOLOGY AND OUTCOMES

Descriptive Epidemiology of Ventilator-associated Events

The proportion of mechanically ventilated patients who develop a VAE has generally been reported as 5% to 10%, although studies that restricted eligibility to patients on mechanical ventilation for longer periods of time have reported rates of more than 20%.[15,19,25,27,29–36] Incidence rates reported to the CDC for the first full year of VAE surveillance (2014) varied from 2.59 to 11.79 per 1000 ventilator-days, with higher rates found in larger teaching hospitals.[37] VAE incidence varies by intensive care unit (ICU) type, a finding common to VAP as well. One large academic medical center, for example, observed VAE rates per 1000 ventilator days of 16.0, 15.7, 12.9, and 12.1 in the general surgery, medical, thoracic surgery, and cardiac medicine units, respectively, compared with rates of 9.8 and 5.8 in the neuroscience and cardiac surgery units, respectively.[30] The rates of probable or possible pneumonia, based on older versions of the PVAP surveillance definition, also varied by ICU type ranging from 1.7 to 4.5 events per 1000 ventilator days. Likewise, the fraction of VACs that qualify as IVACs vary by ICU type and ranges from about one-third to one-half, with higher fractions in trauma, burn, and surgical ICUs compared with medical ICUs.[29,30,37]

An increasing number of large case series are being published from around the world describing VAE epidemiology. VAE rates in recent series largely mirror earlier reports.[27,33,34,36] A study of more than 6000 ventilated patients in 5 ICUs across medical and surgical specialties at an academic medical center in China, for example, reported VAC, IVAC, and PVAP rates of 13.7, 6.3, and 2.2 per 1000 ventilator days, respectively.[36] However, lower rates were reported in a study of 7 urban hospitals in Japan (6.4 VAEs per 1000 ventilator days) and higher rates within a multinational cohort in Europe (40.8 VAEs per 1000 ventilator days).[38,39] Interestingly, the European cohort reported that 96% of VAEs qualified as IVACs or PVAPs (vs one-third to one-half in most US studies), a finding that may represent differences in patient populations and/or local practices in antimicrobial prescribing. **Table 1** summarizes these and other key findings related to the epidemiology of VAEs.

Stevens and colleagues[25] found that patients with a VAE were more likely to be male and younger (unadjusted analyses) compared with mechanically ventilated patients without a VAE. Some investigators have found that patients who develop VAEs have more severe illness at baseline compared with those who do not.[19,40] Most studies, however, have not found significant demographic differences between patients with and without VAEs.[15,24,27,31,32,34–36,38,39,41]

Like VAP, most VAEs occur early in the course of mechanical ventilation. One study found a mean daily rate of 2.9 per 100 patients on day 3 and 2.0 per 100 patients on day 7, with a steady decrease to between 1.0 and 1.5 per 100 patients from day 14 onwards.[30] Another found that 68% of VAEs occurred before day 7, 86% before day 14, and that the rate decreased to less than 1 VAE per 1000 ventilator days after day 21.[27] The median time to VAE onset is typically 5 to 6 days after the initiation of mechanical ventilation.[29,30,35,37,38,42]

Adverse Outcomes Among Patients with a Ventilator-associated Event

Most studies report that patients with VAEs are approximately 1.5 to 2.0 times more likely to die in the hospital compared with similar patients without

Table 1
The epidemiology of VAE in adults

	Incidence	Hospital Mortality	Ventilation Duration	ICU and Hospital Length of Stay
Klompas et al,[15] 2011 (VAC) N = 597 patients, half ventilated 2–7 d and half ventilated >7 d	21/1000 vent days	OR 2.0 (1.3–3.2)	14.2 (12.5–16.0) vs 9.1 (8.2–10.0) days of ventilation	25.4 (224–29.0) vs 23.7 (21.6–25.9) days, hospital LOS 17.4 (15.4–19.7) vs 13.1 (11.9–14.4) days, ICU LOS
Klompas et al,[10] 2012 (VAC) N = 8735 ventilation episodes (no restrictions)	12.0/1000 vent days	OR 2.4 (1.6–3.6)	1.9 (1.7–2.1), ratio of ventilator days from VAC to extubation in cases vs controls	1.4 (1.2–1.5), ratio of hospital days from VAC to hospital discharge in cases vs controls
Muscedere et al,[31] 2013 N = 1320 patients ventilated >48 h		VAC: 49.6% vs 31.7% IVAC: 44.6% vs 33.0%	VAC: Median 15.4 vs 6.2 d of ventilation IVAC: Median 16.9 vs 6.4 d of ventilation	VAC: Median 31.7 vs 21.8 d, hospital LOS VAC: Median 18.9 vs 9.0 d, ICU LOS IVAC: Median 34.6 vs 22.5 d, hospital LOS IVAC: Median 22.0 vs 9.3 d, ICU LOS
Hayashi et al,[32] 2013 (VAC) N = 543 patients ventilated ≥48 h		HR 0.9 (0.6–1.4) for days to ICU death	HR 0.7 (0.6–0.8) for days of ventilation	HR 0.8 (0.5–1.1) for days to hospital discharge HR 0.5 (0.4–0.6) for days to ICU discharge
Klein Klouwenberg et al,[24] 2014 N = 2080 patients ventilated ≥2 d	VAC: 10/1000 vent days IVAC: 4.2/1000 vent days Possible or probable VAP: 3.2/1000 vent days	VAC: HR 3.9 (2.9–5.3) IVAC: HR 2.5 (1.5–4.1) Possible or probable VAP: 2.0 (1.1–3.6)		VAC: HR for ICU discharge 0.38 (0.3–0.6) IVAC: HR for ICU discharge 0.47 (0.3–0.7) Possible or probable VAP HR for ICU discharge: 0.6 (0.3–1.1)

(*continued on next page*)

Table 1
(*continued*)

	Incidence	Hospital Mortality	Ventilation Duration	ICU and Hospital Length of Stay
Klompas et al,[30] 2014 N = 20,356 ventilation episodes (no restrictions)	VAC: 6–16/1000 vent days, variable by ICU type IVAC: 3–7/1000 vent days, variable by ICU type PVAP: 0.8–2/1000 vent days, variable by ICU type	VAC: OR 2.4 (1.9–2.9) IVAC: OR 1.9 (1.4–2.4) PVAP: OR 2.2 (1.4–3.2)	VAC: OR for days to extubation 3.1 (2.9–3.3) IVAC: OR for days to extubation 3.5 (3.2–3.7) Possible VAC: OR for days to extubation 3.2 (2.8–3.5)	VAC: OR for days to hospital discharge 1.5 (1.4–1.6) IVAC: OR for days to hospital discharge 1.5 (1.4–1.6) Possible VAC: OR for hospital discharge 1.4 (1.2–1.6)
Stevens et al,[25] 2014 (VAE) N = 10,998 patients ventilated ≥4 d		38% vs 24% OR 1.9 (1.5–2.4)		Mean 24 vs 18 d, hospital LOS Mean 18 vs 11 d, ICU
Boyer et al,[29] 2015 N = 1209 patients ventilated ≥2 d	VAC: 7.0/1000 vent days IVAC: 3.6/1000 vent days	66% vs 14%	14.7 vs 6.3 d of ventilation	
Lilly et al,[132] 2014 N = 8408 episodes of mechanical ventilation	VAC: 13.8/1000 vent days IVAC: 8.8/1000 vent days	VAC: 42% vs 24% OR 1.84 (0.95, 3.6) IVAC: 43% vs 24% OR 1.32 (0.66, 2.6)	14.8 (VAC) and 14.5 (IVAC) vs 4.8 d of ventilation	25.3 (VAC) and 25.1 (IVAC) vs 15.1 d, hospital LOS
Fan et al,[44] 2016 N = Meta-analysis of 18 studies, 61,489 patients receiving mechanical ventilation	VAC: 13.8% (9%–18.6%) IVAC: 6.4% (4.8%–8.1%) PVAP: Possible, Probable 1.1% (0.5%–1.7%), 0.9% (0.6%–1.2%)			
Magill et al,[37] 2016 N = 1824 health care facilities representing 32,772 mo of VAE data	VAE (any): 2.59–11.79/1000 vent days, variable by ICU type IVAC plus: 0.4–5.46/1000 vent days, variable by ICU type	VAC: 33.65% I VAC plus: 27.43%		

Kobayashi et al,[34] 2017 N = 407 patients ventilated ≥4 d	VAC: 13.4% IVAC plus: 5.7%	VAC: 57.4%, HR 1.45 (0.97–2.18) IVAC plus: 65.2%, HR 2.42 (1.39–4.2) Without VAE and VAP: 34.9%	VAC: 15 d IVAC plus: 13 d Without VAE and VAP: 6 d	17 (VAC) and 15 (IVAC) days for median ICU LOS 47 (VAC) and 47 (IVAC) days for median hospital LOS
Rawat et al,[121] 2017 N = 120,519 ventilator days (no restrictions)	VAE rate from first study quarter to after 2 y of study intervention: VAE 7.34–4.58/1000 vent days IVAC: 3.15–1.56/1000 vent days PVAP: 1.41–0.31/1000 vent days			
Chao et al,[33] 2018 N = 1158 patients ventilated (no restrictions)	VAE: 7.7/1000 vent days, 7.3% VAC: 2.9/1000 vent days IVAC: 2.6/1000 vent days PVAP: 2.1/1000 vent days	Non-PVAP (VAC + IVAC): 66.1% PVAP: 60.9%	Non-PVAP 17 d (11–29.3) vs PVAP 22 d (12–38) PVAP: 22 d (12–38)	ICU LOS: Non-PVAP 18.5 d (13–26.3) vs PVAP 20 d (12–33) Hospital LOS: Non-PVAP 30 d (18.3–48) vs PVAP 41 d (26–53)
Meagher et al,[19] 2018 N = 1533 trauma patients ventilated ≥3 d	VAE: 8.1% VAP: 7.4% Both: 4.1%	VAE vs VAP: HR 2.86 (1.44–5.68) VAE vs no-VAP: HR 2.83 (1.83–4.38)	Ventilator-free days, mean (SD): VAE: 8.9 (8.8), VAP 10.9 (7.9), both 7.6 (6.9)	ICU LOS, mean (SD): VAE 19.2 (±13.3), VAP 18.8 (±11.2), both 26.3 (±16.2) Hospital LOS, mean (SD): VAE 31.9 (28.6), VAP 31.4 (22.4), both 36.7 (19.9)
Nakahashi et al,[39] 2018 N = 785 patients ventilated ≥2 d	VAE: 5.7% of patients ventilated ≥2 d 6.4/1000 vent days. VAC: 2.20/1000 vent days IVAC: 1.90/1000 vent days PVAP: 2.29/1000 vent days	ICU mortality rate: VAE: 42.9% No VAE: 15.4% Unadjusted OR: 4.13	VAE: 22.4 d No VAE: 8.7 d	ICU LOS: VAE: 25.2 d No VAE: 13.6 d

(*continued on next page*)

Table 1
(*continued*)

	Incidence	Hospital Mortality	Ventilation Duration	ICU and Hospital Length of Stay
Ramirez-Estrada et al,[38] 2018 N = 244 patients ventilated ≥2 d	VAC: 1.2/1000 vent days IVAC plus: 39.6/1000 vent days PVAP: 22.3/1000 vent days	30-d mortality rate: VAE: 43% No VAE: 29%	VAE: 31 d (17–54) No VAE: 12 d (7–20)	ICU LOS: VAE: 23 d (10–36) No VAE: 12 d (7–20) Hospital LOS: VAE: 31 d (17–54) No VAE: 19 d (10–38)
Liu et al,[35] 2019 N = 428 patients ventilated ≥4 d	VAC: 7.53/1000 vent days IVAC: 3.52/1000 vent days PVAP: 2.26/1000 vent days	VAE: 56.7% No VAE: 11.8% Relative risk, 9.77 (4.66–21.38)	VAE: 11 d (7–15), $P < .001$ No VAE: 7 d (5–10)	ICU LOS: VAE: 13 d (8–19), $P = .01$ No VAE: 9.5 d (7–150 Hospital LOS: VAE: 20 d (11.5–33.25), $P = .77$ No VAE: 21 d (10–33)
He et al,[27] 2021 N = 6252 patients ventilated ≥4 d	VAC plus: 7.29–23.72/1000 vent days, variable by ICU type IVAC plus: 3.59–9.44/1000 vent days, variable by ICU type PVAP: 0.62–2.18/1000 vent days, variable by ICU type	Non-VAE: 13.7% VAC plus: 20.7% IVAC plus: 19.9% PVAP: 22.3%	Non-VAE: 8 d (5–13) VAC plus: 14 d (8–22) IVAC plus: 15 d (10–25) PVAP: 20 d (11–31)	ICU LOS: Non-VAE: 13 (8–21) VAC plus: 20 (12–33) IVAC plus: 21 (14–33) PVAP: 23 (15–35) Hospital LOS: Non-VAE: 22 (15–34) VAC plus: 28 (17–43) IVAC plus: 30 (19–44) PVAP: 30 (21–46)
Zhu et al,[36] 2021 N = 6426 patients ventilated ≥4 d	VAE: 22.2/1000 vent days VAC: 13.7/1000 vent days IVAC: 6.3/1000 vent days PVAP: 2.2/1000 vent days	ICU Mortality VAE: 18.8% No VAE: 12.3%	VAE: 13 (8–22) No VAE: 7 (5–13)	ICU LOS: VAE: 19 (11–30) No VAE: 12 (8–20) Hospital LOS: VAE: 27 (17–42) No VAE: 22 (15–34)

Caution should be used directly comparing rates and outcomes between the listed studies given varying inclusion criteria for ventilated patients in the VAE denominator. Note that some of the studies reported here did not apply the current specific VAE definitions (CDC 2020).

Abbreviations: HR, hazard ratio; IVAC, infection-related VAC; LOS, length of stay; OR, odds ratio; vent, ventilator.

VAEs.[10,15,19,24,25,27,30,31,36,39,43] VAEs are also associated with more time on mechanical ventilation, longer ICU stays, and longer hospital stays, as summarized in **Table 1**. These findings have been observed across a variety of ICU types with heterogeneous patient populations. Studies that have compared VAE mortality with VAP mortality generally report that patients with VAEs are about 50% more likely to die compared with patients with VAP.[44] Patients with IVAC and PVAP have longer attributable ventilator and hospital days relative to patients with VAC alone. Patients with PVAP have outcomes similar to those with IVAC alone.[27,30,33,36,38]

Higher rates of antimicrobial use have been reported for patients with VAEs compared with matched controls.[45] Some investigators have suggested that the strong association between antimicrobial consumption and VAEs allows for the possibility that VAE surveillance in general and the ratio of IVACs to VACs in particular may be useful metrics for antimicrobial stewardship programs.[8]

CLINICAL TRIGGERS AND RISK FACTORS FOR VENTILATOR-ASSOCIATED EVENTS

Clinical Triggers Identified in Case Series

Table 2 summarizes findings from studies that assessed the clinical etiologies of consecutive VAEs within defined populations. These studies used medical chart reviews to identify the clinical conditions that necessitated the acute and sustained increase in ventilator settings that triggered VAE criteria. Respiratory infections, fluid overload, acute respiratory distress syndrome (ARDS), and atelectasis were the most common conditions that triggered VAEs.[15,24,29,32,33,38,40,46] Pneumonia and respiratory infections accounted for approximately 25% to 40% of cases, pulmonary edema and/or fluid overload accounted for 20% to 40% of cases, atelectasis for 10% to 15%, and ARDS for 10% to 20%. The proportion of cases with no identified trigger ranged from 6% to 41%, depending on the series.[15,24,32,38] Prospective studies were more apt to identify causes for VAEs compared with retrospective studies. Hayashi and colleagues[32] found that although more than 30% of VAC patients did not have a particular diagnosis documented in the chart at the time of VAE, many of these were functionally treated for presumed respiratory infections and/or pulmonary edema with antibiotics and/or furosemide.

Potential Risk Factors for ventilator-associated Events

Fluid overload

Excess fluid balance has been identified across multiple studies as a risk factor for VAE. Lewis and colleagues[47] identified positive fluid balance as a risk factor (odds ratio [OR]. 1.2 per liter; 95% confidence interval [CI], 1.0–1.4) and congestive heart failure (CHF) as protective, presumably because patients with a history of CHF were given about one-third less fluid compared with patients without CHF. An analysis of VAEs among 1608 patients admitted to the medical ICU of a tertiary care center in Taiwan identified renal replacement therapy (OR, 8.9; 95% CI, 1.5–54.6), and a positive cumulative 2-day fluid balance (OR, 1.5 per liter increase; 95% CI, 1.2–2.0) as independently associated with VAEs owing to pulmonary edema.[33] A 2018 case-control study including 186 VAEs from an academic medical center in Ohio identified total parenteral nutrition as a risk factor for VAC, whereas CHF was protective.[48] A study of 2 ICUs in Eastern China including 5532 patients also found a strong association between positive fluid balance and VAEs (relative risk, 8.4; 95% CI, 3.0–23.5).[35] Blood transfusions are associated with volume overload and may increase risk for ARDS, and in multiple logistic regression analysis have been associated with the development of VAE after cardiac surgery (OR, 19.7; 95% CI, 7.3–41.4).[49]

Table 2
Clinical triggers identified among adult patients with VAE

	Klompas et al,[15] 2011	Hayashi et al,[32] 2013	Klein Klouwenberg et al,[24] 2014		Boyer et al,[29] 2015		Whiting et al,[46] 2015	Nakahashi et al,[40] 2016	Chao et al,[33] 2018	Ramirez-Estrada et al,[38] 2018
	n = 44 VAE	n = 153 VAE	n = 81 VAE	n = 31 IVAC	n = 67 VAE	n = 34 IVAC	n = 19 VAE	n = 37 VAE	n = 85 VAE	n = 49 IVAC
Pneumonia and/or aspiration	10 (23%)	66 (43%)	28 (35%)	15 (48%)	22 (33%)	21 (62%)	4 (21%)	14 (38%)	22 (26%)	-
Pulmonary edema, pleural effusion, and/or fluid overload	8 (18%)	40 (26%)	23 (28%)	12 (39%)	10 (15%)	-	5 (26%)	15 (41%)	19 (22%)	2 (4%)
ARDS	7 (16%)	10 (7%)	-	-	14 (21%)	3 (9%)	2 (11%)	5 (14%)	7 (8%)	6 (13%)
Atelectasis/mucous plugging	6 (13%)	25 (16%)	12 (15%)	5 (19%)	6 (9%)	-	4 (21%)	8 (22%)	20 (24%)	26 (55%)
Extrapulmonary infection/sepsis syndrome	1 (2%)	-	9 (11%)	5 (16%)	3 (5%)	-	-	-	12 (14%)	-
Pulmonary embolism	2% (1)	3 (2%)	0 (0%)	0 (0%)	-	-	-	-	-	-
Pneumothorax	-	-	2 (2%)	-	2 (3.0%)	-	-	-	4 (5%)	-
TRALI/TACO	-	-	-	-	2 (3.0%)	-	-	-	-	-
Abdominal compartment syndrome/distention	1 (2%)	2 (1%)	9 (11%)	4 (13%)	-	-	-	-	1 (1%)	-
Radiation pneumonitis	1 (2%)	-	-	-	-	-	-	-	-	-
Acute neurologic event	-	-	10 (12%)	3 (10%)	-	-	-	-	-	-
Other	-	-	-	-	7 (13%)	4 (12%)	4 (21%)	-	-	-
No trigger identified	41% (18)	11 (17%)	10 (12%)	2 (6%)	6 (9%)	6 (18%)	-	-	-	13 (28%)

Abbreviations: ARDS, acute respiratory distress syndrome; TRALI, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload; Totals per study do not equal 100% because multiple triggers could be identified and reported per VAC event.

Sedation

Deep sedation and paralysis are also associated with increased risk of VAE. The aforementioned study out of Eastern China found sedative administration between the first and fourth days of mechanical ventilation to be associated with VAE development (relative risk, 15.7; 95% CI, 1.6–152.1).[35] Klompas and colleagues[50] analyzed 9603 consecutive episodes of mechanical ventilation in a large academic hospital to measure associations between different kinds of sedatives and VAEs. The analysis took into account the day-to-day patterns of sedative exposures for each patient. The authors found that benzodiazepines and propofol were associated with an increased risk for VAEs, whereas dexmedetomidine was not. They also found that propofol and dexmedetomidine were associated with less time to extubation compared with benzodiazepines, and that dexmedetomidine was associated with less time to extubation compared with propofol. In a matched case-control study, Lewis and colleagues[47] identified exposures to paralytics (OR, 2.3; 95% CI, 0.79–80), sedation with benzodiazepines (OR, 5.0; 95% CI, 1.3–29), and total opioid exposure (OR, 2.3; 95% CI, 0.9–16) as risk factors for VAEs. They found liver disease to be protective against VAE, and that physicians used opioids and sedatives more sparingly among this population; patients with liver disease were given about one-quarter fewer opioids compared with patients without liver disease.[47]

Mandatory ventilation and driving pressure

Mandatory modes of mechanical ventilation as well as high tidal volumes or driving pressures have also been associated with increased risk of VAE. Mandatory modes of ventilation, defined as all mechanical ventilation modes other than pressure support, were associated with an OR of 3.4 (95% CI, 1.6–8.0) for VAEs.[47] Higher driving pressures were also risk factors for VAEs on multivariate analysis of 303 ventilated patients at an academic center in Japan (HR 1.12; 95% CI, 1.04–1.22). Ogbu and colleagues[42] found an association between tidal volumes and VAE risk. They matched 167 patients with VAEs with 668 controls. On multivariable conditional logistic regression, the odds of VAE increased by 1.21 for each milligram per kilogram of tidal volume greater than 6 mL/kg of predicted body weight ($P = .03$).

As pointed out by Lewis and associates,[47] mandatory modes of ventilation may or may not be independent predictors of VAEs. On the one hand, mandatory modes may cause more volume and pressure trauma to patients' alveoli than spontaneous modes. This could trigger or worsen ARDS and thus cause VAEs. On the other hand, the association between mandatory modes of mechanical ventilation and VAE may be confounded by severity of illness. Patients with severe, progressive pulmonary disease are more likely to require mandatory modes of mechanical ventilation and progressively higher ventilator settings that might trigger VAE criteria. Similarly, a high driving pressure is associated with poorly compliant lungs that may be at greater risk for volume and pressure trauma. There may also be an interplay between mandatory modes of mechanical ventilation and other risk factors for VAEs: patients who require mandatory modes of ventilation are also more likely to require heavy sedation and/or neuromuscular blockade, which in turn could also increase their risk for VAEs.

Aspiration

Aspiration has been identified as a potential trigger for VAE. Not surprisingly then, many risk factors for aspiration have also been identified as risk factors for VAEs.[13,29,32,33,40,46] These include gastric residuals or more than 200 mL (relative risk, 9.3; 95% CI, 1.9–45.5),[35] oral care with chlorhexidine where aspiration may cause

a chemical pneumonitis and ARDS (OR, 1.42; $P = .03$),[51] and tube feeds (which can inhibit upper and lower esophageal sphincter function).[48]

Risk factors for infection-related ventilator-associated complications

Risk factors for IVAC have been evaluated by fewer studies. Lewis and colleagues[47] identified benzodiazepines started between admission and intubation (OR, 5.0; 95% CI, 1.3–29), prescriptions for opioids (OR, 3.3 per 100 μg fentanyl equivalents per kg; 95% CI, 0.9–16), and the use of paralytics while intubated (OR, 2.3; 95% CI, 0.8–8.0). There were also trends toward more IVACs with higher minimum tidal volumes (OR, 1.5 per mL/kg; 95% CI, 0.91–2.9) and positive daily fluid balances (OR, 1.1 per liter positive; 95% CI, 0.90–1.5). Kubbara and colleagues[48] identified COPD, tube feeds, and total parenteral nutrition as risk factors for IVAC plus, whereas morphine and prednisone use were protective. Morphine use may have been in place of longer acting sedatives, leading to shorter and lighter sedation. The mechanisms by which prednisone may decrease the rate of IVAC plus are numerous, with blunting of the fever response as one plausible explanation.

Care-related risk factors

Bouadma and colleagues[45] noted that patient transport was associated with 17% of VAEs in their multicenter retrospective dataset of 2331 cases. Nakahashi and colleagues[40] identified 4 care-related variables (as opposed to host-related variables) associated with VAEs among 3122 patients admitted to a Japanese ICU: absence of intensivist participation in managing ventilated patients, the use of higher ventilator driving pressures, development of edema, and greater body weight increases.

PREVENTION INTERVENTIONS

Because only a small proportion of VAEs are attributable to pneumonia, standard VAP prevention bundles may only partially lower VAE rates. A logical framework for preventing VAEs is to select interventions that decrease the duration of mechanical ventilation (and hence the time at risk for VAEs) and/or prevent one or more of the major conditions associated with VAEs (pneumonia, fluid overload, atelectasis, and ARDS).[52] Using this framework, 6 interventions have been proposed to prevent VAEs: minimize sedation, speed extubation by optimizing the performance of daily paired spontaneous awakening and breathing trials, mobilize patients, use conservative fluid management, ventilate patients with low tidal volumes, and set restrictive thresholds for transfusions (**Fig. 2**).[53] There are likely additional institution-specific strategies to improve care for ventilated patients that could be identified by conducting root-cause analyses of individual VAEs.[29,45] **Table 3** provides an overview of studies to date assessing interventions to prevent VAEs.

Minimize Sedation

Deep and sustained sedation is associated with numerous adverse events, including increased mortality, prolonged mechanical ventilation, and a higher risk for VAEs.[54–57] Deep and/or sustained sedation may trigger VAEs by prolonging time on mechanical ventilation, increasing the need for mandatory modes of mechanical ventilation (which in turn may increase the risk of lung injury), decreasing clearance of respiratory secretions, and increasing the risk of atelectasis and aspiration.[58] Collectively, these effects predispose patients to pneumonia, atelectasis, and/or ARDS, 3 of the 4 clinical conditions most commonly associated with VAEs.

Because sedation is associated with ICU-acquired infection—via a number of potential mechanisms—minimizing sedatives and opioids is recommended to decrease

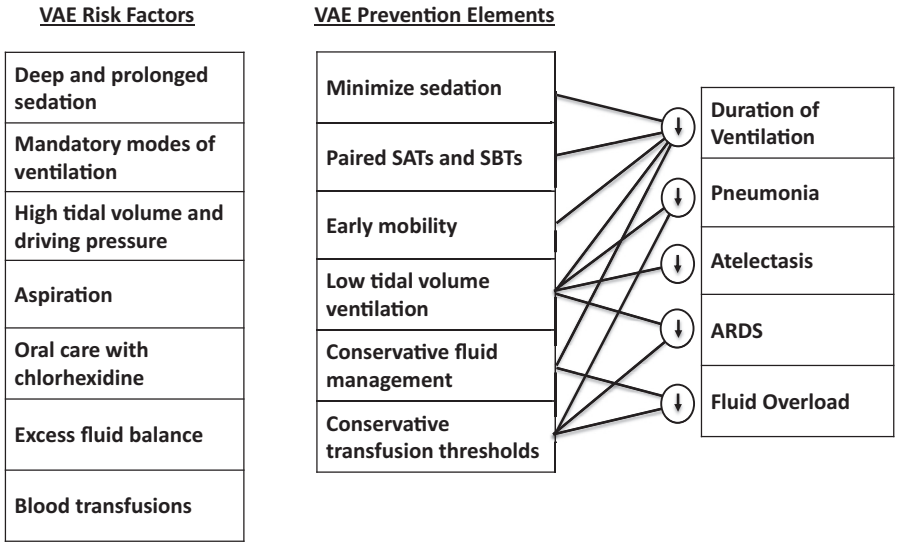

Fig. 2. Potential strategies to prevent VAEs. Interventions that decrease duration of mechanical ventilation and target 1 or more of the conditions that most commonly trigger VAEs are highlighted. SATs, spontaneous awakening trials; SBTs, spontaneous breathing trials.

time on the ventilator and time in the ICU.[59,60] The short-acting sedatives propofol and dexmedetomidine have been associated with less time to extubation compared with benzodiazepines, and dexmedetomidine has been associated with a lower risk for VAEs. Conversely benzodiazepines, opioids, and paralytics have been associated with an increased risk for IVACs.[47,50,61]

Daily Coordinated Spontaneous Awakening Trials and Spontaneous Breathing Trials

Spontaneous awakening trials and spontaneous breathing trials are 2 of the best-studied interventions to decrease VAEs. Spontaneous awakening and spontaneous breathing trials are designed to decrease sedation and the duration of mechanical ventilation by identifying the lowest level of sedation a patient needs to be comfortably ventilated and the earliest time at which they can safely be extubated. Both interventions reduce time at risk for VAEs.[56,62–64] Coordinating spontaneous awakening trials and spontaneous breathing trials to perform spontaneous breathing trials during sedative interruptions (so that patients are more awake and hence more likely to pass their spontaneous breathing trials) further decreased the time to extubation compared with spontaneous breathing trials alone.[56,65]

Multiple studies have documented inverse associations between spontaneous awakening trials and/or spontaneous breathing trials and VAEs. Muscedere and colleagues[31] found that the percentage of ventilator days with spontaneous awakening trials and spontaneous breathing trials was associated with lower VAC and IVAC rates. Other investigators reported decreased rates of VAEs and IVAC in hospitals compliant with spontaneous breathing trial guidelines.[66] A prospective quality improvement collaborative among 12 ICUs subsequently confirmed that increasing the performance rate of paired daily spontaneous awakening trials/spontaneous breathing trials can lower VAE rates.[56] Over a 19-month period, the collaborative noted 37% fewer VAEs

Table 3
Interventions to prevent VAE in adults

Study	Intervention	Impact
Muscedere et al,[31] 2013	Retrospective analysis after implementation of VAP clinical practice guidelines sequentially introduced over 24 mo	Overall VAE rate decreased by 29% over the study period. Rates of VAC decreased, although the IVAC rates remained steady. Those who developed VAC were more likely to be orally intubated and had less frequent humidifier and suction system exchanges. The percentage of ventilator days with SATs and SBTs was associated with a trend toward lower VAC and IVAC rates.
Mekontso Dessap et al,[85] 2014	Retrospective analysis of a randomized controlled trial targeting depletive fluid management using BNP in ventilated patients	In the BNP guided group, patients received more diuretics, had a more-negative daily fluid balance (mean −640 mL vs −37 mL), and shorter time to extubation (42.4 h vs 58.6 h). There was a 50% lower incidence of VAE in the fluid depletive group vs usual care (8.6% vs 17.8%)
Klompas et al,[56] 2015	Prospective study of a protocol for increasing paired daily SAT and SBT (collaborative group) over a 19-month period	Among intervention ICUs, SAT performance rate increased from 14% to 77% of days where indicated. SBT performance rates increased from 49% to 75% of days where indicated. Mean duration of mechanical ventilation decreased by 2.4 d, but there was no change in ICU mortality. The VAE rate went from 9.7 events per 100 episodes of mechanical ventilation to 5.2 events per 100 episodes of mechanical ventilation. IVAC rates went from 3.5 to 0.52 events per 100 episodes of mechanical ventilation. PVAP rates did not significantly change. There was no change in VAE rate in the surveillance group ICUs.

(*continued on next page*)

Table 3
(continued)

Study	Intervention	Impact
Rawat et al,[121] 2017	Multifaceted collaborative including unit teamwork, safety culture and adherence to 6 evidence-based interventions (head of bed elevation, subglottic suctioning, oral care, chlorhexidine mouth care, SAT, and SBT)	Over a 24-month period, there was a 37% decrease in VAE (7.34–4.58 VAE per 1000 ventilator days). IVAC (3.16–1.56) and PVAP (1.41–0.31) cases per 1000 ventilator days also decreased. Compositive compliance in the 6 interventions increased from 14% to 20% over the study. Regression analysis suggested that a 10% increase in composite compliance was associated with a 12% VAE decrease.
Anand et al,[122] 2018	Quality improvement intervention to improve VAP bundle (head of bed elevation, oral care, peptic ulcer prophylaxis, daily SAT/SBT) adherence among trauma patients	Compliance with the VAP bundle increased from 65% at baseline to more than 90% within 1 year of the quality initiatives. Mean ventilator days did not change over the course of the study, but PVAP rates fell from 12% at baseline to 3% at 1 y, 2% at 2 y, and then 0%.
Chumpia et al,[67] 2019	Multifaceted intervention including education around electronic order sets and nurse and respiratory driven protocols to improve SAT/SBT adherence	SAT and SBT order rates increased and duration of mechanical ventilation decreased (mean 7.2 d at baseline to 4.7 d after the intervention) This was associated with a drop in VAEs from 5.2 per 100 episodes at baseline to 0.7 per 100 episodes after intervention.
Seaver et al,[79] 2020	Multidisciplinary team collaboration on VAE prevention including electronic health record optimization and protocol driven ventilator liberation	The rate of VAE decreased from 12.8 VAE per 1000 ventilator days at baseline to 2.8 VAE per 1000 ventilator days after intervention. As part of the intervention, PEEP was initiated at 6 cm H_2O instead of historically used 5 cm H_2O such that VAE would not be triggered by an increase of PEEP to 8 cm H_2O.

Abbreviation: BNP, B-type natriuretic peptide.

(OR, 0.63; 95% CI, 0.42–0.97) and 65% fewer IVACs (OR, 0.35; 95% CI, 0.17–0.71) per episode of mechanical ventilation. These improvements were also associated with a 2.4-day decrease in the mean duration of mechanical ventilation, a 3.0-day decrease in ICU length of stay, and a 6.3-day decrease in hospital length of stay. A 2019 study at a Los Angeles Veterans Affairs Hospital aimed to decrease VAE rates by decreasing duration of mechanical ventilation via improved spontaneous awakening/spontaneous breathing trial protocols and adherence. Spontaneous awakening and spontaneous

breathing trial order rates increased and duration of mechanical ventilation decreased (mean of 7.2 days at baseline to 4.7 days after the intervention; $P = .049$). This strategy was associated with a decrease in VAEs from 5.2 per 100 episodes at baseline to 0.7 per 100 episodes after the intervention; $P = .06$).[67]

Importantly, spontaneous awakening trials and spontaneous breathing trials are means, not ends. The intent of these 2 interventions is to decrease the overall level of sedation and to lessen the period from readiness for extubation to actual extubation. Merely checking the box on spontaneous awakening trial or spontaneous breathing trial performance is not sufficient to decrease VAE rates if not paired with active attempts to decrease sedative use and speed extubation. A well-rounded quality improvement initiative will thus include not only mechanisms to increase spontaneous awakening trial and spontaneous breathing trial rates, but also education around best practices for sedation and protocols to move patients from successful spontaneous breathing trials to extubation. This need was evident in a clinical trial that found that adding daily sedation interruptions to a sedation protocol did not decrease the duration of mechanical ventilation or hospital stay compared with a sedation protocol alone.[68] The patients randomized to sedative interruptions in this trial paradoxically received more boluses and higher daily doses of midazolam and fentanyl compared with patients being managed by protocol alone. Presumably this outcome reflected a persistent culture of sedation, wherein patients who became agitated during sedative interruptions were reflexively managed with more sedation rather than trying to manage their agitation using nonsedating strategies.

Programs for Early Exercise and Mobility

Immobility is associated with atelectasis and pneumonia—common triggers for VAEs—as well as a longer duration of hospital stay and time on the ventilator. To date, no studies that have examined the independent impact of early mobility on VAE risk; however, multiple studies have reported better patient outcomes after the introduction of early exercise and mobility programs.[69–72] Early physical and/or occupational therapy can decrease time on the ventilator, and has been associated with lower rates of complications and VAP in some studies.[73,74] Although there are challenges with mobilizing someone on a ventilator and surveys of practice suggest that early mobility is not yet commonly used, adverse outcomes have not been observed when such programs are instituted.[75–78] A small prospective study of quality improvement programs around ventilator liberation, including daily exercise and ambulation, observed a decrease in the VAE rate after the intervention, although the data for adherence to the exercise component were not provided.[79]

Low Tidal Volume Ventilation

Low tidal volume ventilation has been associated with improved outcomes in ventilated patients with and without ARDS and it may prevent several triggers of VAEs, namely ARDS, atelectasis, and lung infections.[80–84] Neto and colleagues[82,83] performed 2 meta-analyses of the impact of low tidal volume ventilation on patients without lung injury at the start of ventilation. Lower tidal volumes were associated with a lower risk for ARDS, fewer pulmonary infections, and less atelectasis when compared with higher tidal volumes. A shorter hospital length of stay and decreased mortality were also observed. Ogbu and colleagues[42] affirmed the potential value of lower tidal volumes to prevent VAEs in a case-control study that documented an increased odds of VAE with each milligram er kilogram of tidal volume that is greater than 6 mL/kg.

Conservative Fluid Management

A positive fluid balance has consistently been associated with VAEs.[15,29,32,40,47,85] Excess fluids increase the risk of pulmonary edema, ARDS, and pneumonia, 3 of the 4 most common conditions that trigger VAEs.[86] Conversely, conservative fluid management is associated less time to extubation, shorter ICU stays, and lower hospital mortality rates, particularly among patients with ARDS.[87,88]

One randomized controlled trial thus far has affirmed that conservative fluid management can prevent VAEs. Mekonsto Dessap and colleagues[85] retrospectively applied VAE definitions to data from a randomized controlled trial of conservative fluid management versus usual practice during the weaning phase of mechanical ventilation. Conservative fluid management in this trial was driven by daily measurements of B-type natriuretic peptide (BNP). Patients randomized to daily measurement of BNP levels were administered less fluids and more diuretics, and had greater negative fluid balances compared with patients in the usual practice arm. Conservative fluid management was associated with more ventilator-free days and substantially lower VAE rates. There were 52% fewer VAEs in the intervention group compared with usual care group.

What remains to be seen is how conservative fluid management is best operationalized. Wiedemann and colleagues used a complex protocol that included invasive monitoring devices and a complicated management algorithm, whereas Mekontso Dessap and colleagues used daily BNP levels.[85,87] Neither of these approaches is optimal: invasive monitoring devices can be harmful, overly complex protocols are difficult to generalize and error prone, and daily BNP levels can be expensive and challenging to interpret in patients with renal impairment. Additional approaches are required. Possibilities include daily weight monitoring, noninvasive ultrasound measurements, or simplified protocols for interpreting common physiological data.[89] Work in this area is ongoing.

Conservative Blood Transfusion Thresholds

Restrictive red blood cell transfusion strategies have been associated with decreased risk for hospital-acquired infections, including pneumonia.[90] In addition, blood transfusions may increase the risk of ARDS and pulmonary edema.[80,86,91] Two recent studies, one among adult patients in the cardiac ICU and another in 6 pediatric hospitals, found associations between blood transfusions and VAE risk.[49,92] No studies to date, however, have directly evaluated whether restrictive transfusion thresholds can decrease VAE rates.

Ventilator-associated Pneumonia Prevention

The VAE prevention bundle proposed in this article is designed to include and supersede VAP prevention bundles. VAP accounts for about one-third of VAEs and thus VAE prevention bundles must by right include VAP prevention strategies. The proposed VAE prevention bundle includes most of the VAP prevention practices associated with shorter durations of mechanical ventilation and/or lower mortality rates as recommended in the Society for Healthcare Epidemiology of America's Compendium of Strategies to Prevent VAP.[93] Some of the additional strategies classically used to prevent VAP such as elevating the head of the bed, oral care with chlorhexidine, and subglottic secretion drainage are discussed elsewhere in this article. There are still grounds to include some of these interventions in comprehensive prevention bundles for ventilated patients, particularly head of bed elevation.

Elevating the head of the bed to prevent VAP is common practice in almost all US hospitals.[94] Although there are compelling physiologic arguments to support this practice, there are very few data describing its impact on patients' outcomes. In a Cochrane review encompassing 10 randomized controlled trials and 878 participants, the semirecumbent position ($\geq 30^{\circ}$) significantly decreased the risk of clinically suspected VAP, but had no impact on objective outcomes such as duration of ventilation, ICU length of stay, or mortality.[95] There are very few data, however, suggesting any risk of harm associated with elevating the head of the bed, the practice is free of charge, and it is possible that larger studies in the future may yet document clear benefits. As such, elevating the head of the bed still seems to be a reasonable practice to include in prevention bundles for ventilated patients.

Routine oral care with chlorhexidine, by contrast, may be a source of harm for some fraction of patients. Recent meta-analyses question the association between oral care with chlorhexidine and lower VAP rates in non–cardiac surgery patients and note that there may be a signal toward higher mortality rates in patients randomized to chlorhexidine.[96–98] The mechanism of increased mortality risk is unknown, but a possible explanation may be occasional episodes of aspiration of antiseptic precipitating ARDS.[99–102] Note that the concern with oral care with chlorhexidine is specifically with the chlorhexidine component of the regimen. Oral care alone still seems very reasonable for patient hygiene and comfort. Few studies have rigorously assessed the impact of oral care alone without an antiseptic on VAP and other outcomes, but in contrast with chlorhexidine there is no suggestion of a safety signal.[103–106]

One area of ongoing controversy is whether selective digestive decontamination with a combination of oral and parenteral antibiotics can be helpful for patients. A series of large randomized controlled trials have suggested that this strategy may not only prevent VAP but also decrease mortality rates.[107–109] The practice is controversial, however, owing to fear that prescribing antibiotics for all ICU patients or all ventilated patients may cultivate and promote multidrug-resistant organisms that might ultimately compromise the care of future ICU patients.[110] A 2018 multicenter cluster randomized controlled trial of selective digestive decontamination specifically conducted in ICUs with higher rates of antibiotic use and higher baseline prevalences of antibiotic resistant organisms, however, reported no impact on mortality rates (or the frequency of multidrug resistant infections).[106] The decontamination regimen in this study did not include a course of parenteral third-generation cephalosporin antibiotics, in contrast with prior studies of digestive decontamination that reported mortality benefits. It is unknown, whether this factor accounts for the lack of a mortality signal in this study or if other factors were at play. The literature on the long-term impact of selective digestive decontamination on ICU resistance rates and patient outcomes is still relatively sparse, but studies thus far have not clearly confirmed enhanced risk.[111–113] Indeed, some studies suggest that digestive decontamination may paradoxically lower overall antibiotic use, presumably by averting some infections. Many hospitals in Europe routinely practice selective digestive decontamination, but it is almost never practiced in North America.

An additional practice commonly adopted to prevent VAP is endotracheal tubes with subglottic secretion drainage. These devices are designed to minimize the pooling of secretions above the endotracheal tube cuff and hence to diminish the volume of microbe-laden secretions seeping around the cuff and into the lungs. Early meta-analyses of this strategy suggested that these devices can both decrease VAP rates and shorten the duration of mechanical ventilation, leading to a recommendation in favor of subglottic secretion drainage in VAP prevention guidelines.[93,114–117] These analyses were based on a possible misinterpretation of 1 key trial, however, that

was responsible for much of the signal toward shorter ventilator episodes.[118] A 2016 meta-analysis that excluded this trial failed to find any improvements in the duration of mechanical ventilation, ICU length of stay, or mortality.[119] A more recent systemic review and meta-analysis did report a mortality improvement, but double-abstracted 1 article and used per-protocol rather than intention-to-treat results for another.[120]

Ventilator Bundle Compliance and Ventilator-associated Pneumonia

An increasing number of centers and quality improvement collaboratives have published data showing that bundling together multiple measures to prevent VAEs is effective at decreasing VAE rates. A 2017 study including 56 ICUs from 2 states tested a bundle of 6 interventions traditionally used for VAP prevention: head of bed elevation, subglottic suctioning, oral care, chlorhexidine mouth care, spontaneous awakening trials, and spontaneous breathing trials.[121] The study was collaborative by nature, encouraged peer learning, and used a structured change management process. Rates of VAC, IVAC, and PVAP per 1000 ventilator days all significantly decreased over the course of the study. The incidence of VAC in particular decreased by 37.6%. Each 10% increase in composite compliance was estimated to decrease the VAE rate by 12% (incident rate ratio, 0.88; 95% CI, 0.78–0.99; $P = .032$). The authors noted that head of bed elevation and subglottic suctioning compliance did not change over the course of the study, and thus it seemed that oral care, chlorhexidine mouth rinse, and/or increased compliance with spontaneous awakening trials and spontaneous breathing trials were responsible for the decrease in VAE rates. Alternatively, given only modest increases in these measures and the potential for chlorhexidine to be associated with harm, the drop in VAE may have been due to other unmeasured factors, such as improvements in safety culture.

A 2018 study at a large academic medical center further investigated the association between ventilator bundle compliance and the incidence of VAE.[51] Among 273 VAEs and 984 controls, there was no association between overall bundle scores in the 3 days before VAE, and a risk of VAE trigger (OR, 1.15, $P = .34$). During this time period, the same bundle implementation was associated with decreased rates of VAP, highlighting the limited overlap between VAE and VAP. Compliance with oral chlorhexidine was associated with a higher risk of VAE (OR, 1.45; $P = .007$) as well as IVAC plus (OR, 1.73; $P = .0006$), a finding that persisted on multivariate analysis. In a retrospective single center trauma surgical ICU population, improved compliance with a VAP prevention bundle after a multifaceted educational intervention was associated with decreased PVAP rates (12% from 2009 to 2010, 0% in from 2013 to 2016) and a near 50% decrease in mortality, although ventilator days remained similar.[122]

All told, the data on ventilator bundles are promising but more work is needed to identify the ideal components to include in ventilator bundles and to better determine their impact on VAE and other outcomes.

Pediatric Ventilator-Associated Conditions

Investigators continue to explore the application of VAE surveillance to children and neonates. Cocoros and colleagues[123] examined whether adult VAC criteria should be revised for a pediatric VAC definition given the inherent differences between adults, children, and neonates. They evaluated a range of potential alternative approaches to identify pediatric VAC and ultimately recommended identifying worsening oxygenation by increases in daily minimum Fio_2 or mean airway pressure (MAP) after a period of ventilator improvement or stability. The authors opted for MAP instead of PEEP because MAP more accurately reflects lung compliance, whereas PEEP is set by

clinicians. They reported incidence rates of approximately 3 per 1000 ventilator days in the pediatric ICU (PICU), neonatal ICU, and cardiac ICU. They also reported a substantially increased risk of hospital mortality, increased hospital and ICU lengths of stay, and a longer ventilation duration among children with a VAC compared with matched patients without a VAC across all ICU types.

The need for a VAC definition tailored to children and neonates led to CDC developing a Pediatric VAE (PedVAE) definition (**Fig. 3**). PedVAEs, like adult VAEs, are identified by a deterioration in respiratory status after a period of stability or improvement on the ventilator.[124] There are important differences, however, including the use of MAP in lieu of PEEP and the exclusion of nested VAE subtypes, namely, IVAC and

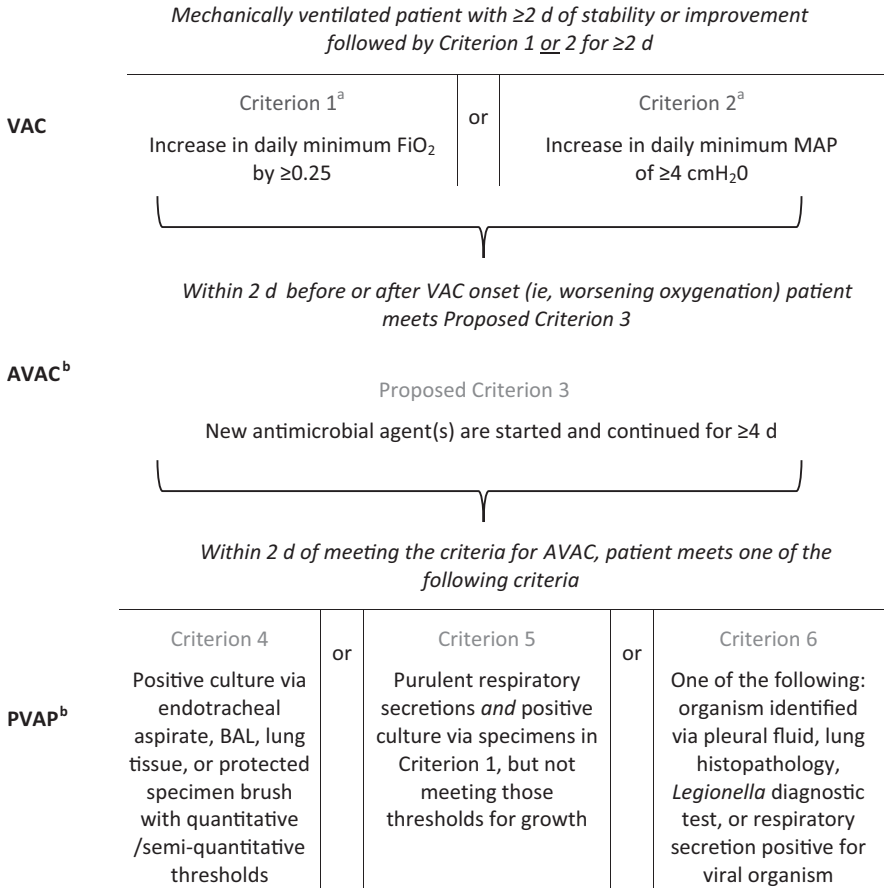

Fig. 3. National surveillance and proposed definitions for PedVAEs. Surveillance "day 1" is the day of intubation and initiation of mechanical ventilation; the earliest day PedVAE criteria can be fulfilled is day 4 and the earliest event date for PedVAE is day 3 of mechanical ventilation. [a]See the full CDC NHSN protocol for details related to each criterion (CDC 2021). For patients <30 days old, daily minimum MAP values of 0 to 8 cm H_2O are considered equal to 8 cm H_2O for the purposes of surveillance and for patients ≥30 days old, 0 to 10 cm H_2O are considered equal to 10 cm H_2O for the purposes of surveillance. [b]AVAC and Pediatric PVAP are proposed definitions and not currently included in CDC guidelines. AVAC, pediatric VAC with antimicrobial use; MAP, mean airway pressure; PVAP, pediatric possible VAP.

PVAP. However, a simplified algorithm encompassing pediatric VAC with antimicrobial use has been proposed as an alternative to IVAC.[125] This pediatric VAC with antimicrobial use definition differs from IVAC insofar as the only additional criterion beyond VAC is the initiation of new antimicrobials within 2 days of the PedVAE; abnormal temperature and white blood cell counts are not required, a reflection of the fact that most ventilated patients have abnormal white blood cell counts and/or temperatures, and these criteria have minimal impact on case counts and add little specificity.

Several studies have now applied adult and PedVAE definitions to real-world pediatric populations. Phongjitsiri and colleagues[126] applied the adult VAE definitions to patients in a PICU and found that approximately 15% of patients met the adult VAC definition (21/1000 ventilator days) and about half had an IVAC (13/1000 ventilator days). Those with a VAC had increased hospital mortality and longer ventilator, hospital, and ICU stays compared with those without. These findings of worse outcomes among those with VAC were affirmed in a 2018 study from a tertiary care PICU.[127] Beardsley and colleagues[128] assessed 300 episodes of mechanical ventilation in the PICU and identified 30 episodes of IVAC (2.16 events per 1000 ventilator days). There was little overlap in the diagnosis of IVAC, traditional VAP, and tracheobronchitis with only 9 episodes meeting more than 1 definition.

A 2018 study compared clinical outcomes between patients who met criteria for VAP, traditional VAE, and a modified PedVAE algorithm based on a more liberal definition for PEEP or Fio_2 increases.[129,130] Among 656 children, there were 7 VAEs (2.74 per 1000 ventilator days), 29 PedVAEs (11.34 per 1000 ventilator days), and 11 VAPs or VATs (4.3 per 1000 ventilator days). VAEs were associated with significant increases in ventilator duration and mortality, PedVAE was only associated with increased duration of ventilation, and VAP was not associated with worse outcomes. The authors expressed concern that the adult VAE definition is too restrictive in identifying only the most severely ill patients. They noted that VAE rates in children tend to be lower than adults, and associated mortality higher, and that the less restrictive PedVAE definition may, therefore, be more suitable for pediatric populations. This concern was shared by Cirulis and colleagues,[129] who noted in a single-center study that 80% of VAP cases did not meet VAC criteria, but were associated with similarly poor outcomes.

Risk factors for VAEs in pediatric and adult populations may differ, requiring new analyses and perhaps different approaches for prevention in neonates and children. Recent studies, however, have identified overlap of VAE risk factors between adult and pediatric patients. A case-control study of 192 pediatric VAC cases and controls across 6 hospitals in the United Stated identified neuromuscular blockade (OR, 2.3; 95% CI, 1.1–4.9), positive fluid balance (OR, 7.8; 95% CI, 2.1–28.6), and blood product use (OR, 1.52; 95% CI, 0.7–3.3) as potential risk factors for VAC.[92] These risk factors were shared between PICU, cardiac ICU, and neonatal ICU patients, and a recent surgical procedure was also associated with increased risk in neonatal ICU patients. Weaning from sedation or sedation interruption was protective against VAC across ICU types. A 2018 case control study of 70 VAE and 140 controls using adult VAE definitions identified a higher mean peak inspiratory pressure (OR, 1.1; 95% CI, 1.0–1.2) and acute kidney injury (OR, 2.9; 95% CI, 1.4–5.7) as risk factors for VAC.[127] These risk factors were also observed in a case-control study conducted in a tertiary care PICU, which identified a composite score for fluid overload and kidney injury (FOKIS score) to be associated with VAC.[131] The degree of fluid overload, kidney injury severity, and high peak inspiratory pressure were independently associated risk factors for both VAC and IVAC.

SUMMARY

The introduction of VAE definitions transformed national surveillance for complications in adults receiving mechanical ventilation. VAE definitions expanded the purview of surveillance to include both infectious and noninfectious conditions and transitioned hospitals toward using objective data to measure events. VAEs are associated with higher mortality rates, prolonged mechanical ventilation, and longer lengths of stay. Excess fluid balance, blood transfusions, deeper levels of sedation, prolonged sedation, high tidal volumes, high inspiratory driving pressures, oral care with chlorhexidine, and stress ulcer prophylaxis are risk factors for VAEs. The most common and consistent complications that trigger VAE criteria are pneumonia, pulmonary edema, ARDS, and atelectasis. Conservative fluid management, enhancing the performance of spontaneous awakening trials and spontaneous breathing trials, and minimizing sedation can prevent VAEs and combining these measures into VAE prevention bundles in multidiscipline collaboratives can facilitate implementation and maximize their impact.

REFERENCES

1. Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. Chest 2000;118(4):1100–5.
2. Wunsch H, Linde-Zwirble WT, Angus DC, et al. The epidemiology of mechanical ventilation use in the United States. Crit Care Med 2010;38(10):1947–53.
3. Mehta AB, Syeda SN, Wiener RS, et al. Epidemiological trends in invasive mechanical ventilation in the United States: a population-based study. J Crit Care 2015;30(6):1217–21.
4. Magill SS, Fridkin SK. Improving surveillance definitions for ventilator-associated pneumonia in an era of public reporting and performance measurement. Clin Infect Dis 2012;54(3):378–80.
5. Centers for Disease Control and Prevention. Ventilator-associated event protocol. 2021. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/10-vae_final.pdf. Accessed February 27, 2021.
6. Magill SS, Klompas M, Balk R, et al. Developing a new, national approach to surveillance for ventilator-associated events. Crit Care Med 2013;41(11):2467–75.
7. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36(5):309–32.
8. Klompas M. Complications of mechanical ventilation–the CDC's new surveillance paradigm. N Engl J Med 2013;368(16):1472–5.
9. Klompas M, Kleinman K, Khan Y, et al. Rapid and reproducible surveillance for ventilator-associated pneumonia. Clin Infect Dis 2012;54:370–7.
10. Klompas M, Magill S, Robicsek A, et al. Objective surveillance definitions for ventilator-associated pneumonia. Crit Care Med 2012;40(12):3154–61.
11. Klompas M. Interobserver variability in ventilator-associated pneumonia surveillance. Am J Infect Control 2010;38(3):237–9.
12. Stevens JP, Kachniarz B, Wright SB, et al. When policy gets it right: variability in U.S. hospitals' diagnosis of ventilator-associated pneumonia. Crit Care Med 2014;42(3):497–503.
13. Klein Klouwenberg PM, Ong DS, Bos LD, et al. Interobserver agreement of centers for disease control and prevention criteria for classifying infections in critically Ill patients. Crit Care Med 2013;41(10):2373–8.

14. Kerlin M, Trick W, Anderson D, et al. Interrater reliability of surveillance for ventilator-associated events and pneumonia. Infect Control Hosp Epidemiol 2016;38:1–7.
15. Klompas M, Khan Y, Kleinman K, et al. Multicenter evaluation of a novel surveillance paradigm for complications of mechanical ventilation. PLoS One 2011; 6(3):e18062.
16. Klompas M. The paradox of ventilator-associated pneumonia prevention measures. Crit Care 2009;13(5):315.
17. Bonten MJ. Healthcare epidemiology: ventilator-associated pneumonia: preventing the inevitable. Clin Infect Dis 2011;52(1):115–21.
18. Khan R, Al-Dorzi HM, Al-Attas K, et al. The impact of implementing multifaceted interventions on the prevention of ventilator-associated pneumonia. Am J Infect Control 2016;44(3):320–6.
19. Meagher AD, Lind M, Senekjian L, et al. Ventilator-associated events, not ventilator-associated pneumonia, is associated with higher mortality in trauma patients. J Trauma Acute Care Surg 2019;87(2):307–14.
20. Nguile-Makao M, Zahar JR, Francais A, et al. Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. Intensive Care Med 2010;36(5):781–9.
21. Melsen WG, Rovers MM, Groenwold RH, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis 2013;13(8):665–71.
22. Nuckchady D, Heckman MG, Diehl NN, et al. Assessment of an automated surveillance system for detection of initial ventilator-associated events. Am J Infect Control 2015;43(10):1119–21.
23. Mann T, Ellsworth J, Huda N, et al. Building and validating a computerized algorithm for surveillance of ventilator-associated events. Infect Control Hosp Epidemiol 2015;36(9):999–1003.
24. Klein Klouwenberg PM, van Mourik MS, Ong DS, et al. Electronic implementation of a novel surveillance paradigm for ventilator-associated events: feasibility and validation. Am J Respir Crit Care Med 2014;189(8):947–55.
25. Stevens JP, Silva G, Gillis J, et al. Automated surveillance for ventilator-associated events. Chest 2014;146(6):1612–8.
26. Resetar E, McMullen KM, Russo AJ, et al. Development, implementation and use of electronic surveillance for ventilator-associated events (VAE) in adults. AMIA Annu Symp Proc 2014;2014:1010–7.
27. He Q, Wang W, Zhu S, et al. The epidemiology and clinical outcomes of ventilator-associated events among 20,769 mechanically ventilated patients at intensive care units: an observational study. Crit Care 2021;25(1):44.
28. Smith PF, Hadler JL, Stanbury M, et al. "Blueprint version 2.0": updating public health surveillance for the 21st century. J Public Health Manag Pract 2013;19(3): 231–9.
29. Boyer AF, Schoenberg N, Babcock H, et al. A prospective evaluation of ventilator-associated conditions and infection-related ventilator-associated conditions. Chest 2015;147:68–81.
30. Klompas M, Kleinman K, Murphy MV. Descriptive epidemiology and attributable morbidity of ventilator-associated events. Infect Control Hosp Epidemiol 2014; 35(5):502–10.

31. Muscedere J, Sinuff T, Heyland D, et al. The clinical impact and preventability of ventilator-associated conditions in critically ill mechanically ventilated patients. Chest 2013;144(5):1453–60.
32. Hayashi Y, Morisawa K, Klompas M, et al. Toward improved surveillance: the impact of ventilator-associated complications on length of stay and antibiotic use in patients in intensive care units. Clin Infect Dis 2013;56(4):471–7.
33. Chao WC, Chang WL, Wu CL, et al. Using objective fluid balance data to identify pulmonary edema in subjects with ventilator-associated events. Respir Care 2018;63(11):1413–20.
34. Kobayashi H, Uchino S, Takinami M, et al. The impact of ventilator-associated events in critically Ill subjects with prolonged mechanical ventilation. Respir Care 2017;62(11):1379–86.
35. Liu J, Zhang S, Chen J, et al. Risk factors for ventilator-associated events: a prospective cohort study. Am J Infect Control 2019;47(7):744–9.
36. Zhu S, Wang W, Kang Y, et al. Clinical outcomes and risk factors for mortality from ventilator-associated events: a registry-based cohort study among 30,830 intensive care unit patients. Infect Control Hosp Epidemiol 2021;1–8.
37. Magill SS, Li Q, Gross C, et al. Incidence and characteristics of ventilator-associated events reported to the National Healthcare Safety Network in 2014. Crit Care Med 2016;44(12):2154–62.
38. Ramírez-Estrada S, Lagunes L, Peña-López Y, et al. Assessing predictive accuracy for outcomes of ventilator-associated events in an international cohort: the EUVAE study. Intensive Care Med 2018;44(8):1212–20.
39. Nakahashi S, Imai H, Imanaka H, et al. Ventilator-associated events: prevalence and mortality in Japan. J Thorac Dis 2018;10(12):6942–9.
40. Nakahashi S, Yamada T, Ogura T, et al. Association of patient care with ventilator-associated conditions in critically Ill patients: risk factor analysis. PLoS One 2016;11(4):e0153060.
41. Rello J, Ramírez-Estrada S, Romero A, et al. Factors associated with ventilator-associated events: an international multicenter prospective cohort study. Eur J Clin Microbiol Infect Dis 2019;38(9):1693–9.
42. Ogbu OC, Martin GS, Sevransky JE, et al. High tidal volumes are independently associated with development of a ventilator-associated condition in the ICU. Am J Respir Crit Care Med 2015;191:A3117.
43. Khan RM, Al-Juaid M, Al-Mutairi H, et al. Implementing the comprehensive unit-based safety program model to improve the management of mechanically ventilated patients in Saudi Arabia. Am J Infect Control 2019;47(1):51–8.
44. Fan Y, Gao F, Wu Y, et al. Does ventilator-associated event surveillance detect ventilator-associated pneumonia in intensive care units? A systematic review and meta-analysis. Crit Care 2016;20(1):338.
45. Bouadma L, Sonneville R, Garrouste-Orgeas M, et al. Ventilator-associated events: prevalence, outcome, and relationship with ventilator-associated pneumonia. Crit Care Med 2015;43(9):1798–806.
46. Whiting J, Edriss H, Nugent K. Frequency and etiology of ventilator-associated events in the medical intensive care unit. Am J Med Sci 2015;350(6):453–7.
47. Lewis SC, Li L, Murphy MV, et al. Risk factors for ventilator-associated events: a case-control multivariable analysis. Crit Care Med 2014;42(8):1839–48.
48. Kubbara A, Barnett WR, Safi F, et al. Case-control study investigating parameters affecting ventilator-associated events in mechanically ventilated patients. Am J Infect Control 2019;47(4):462–4.

49. He S, Wu F, Wu X, et al. Ventilator-associated events after cardiac surgery: evidence from 1,709 patients. J Thorac Dis 2018;10(2):776–83.
50. Klompas M, Li L, Szumita P, et al. Associations between different sedatives and ventilator-associated events, length-of-stay, and mortality in mechanically ventilated patients. Chest 2016;149:1373–9.
51. Harris BD, Thomas GA, Greene MH, et al. Ventilator bundle compliance and risk of ventilator-associated events. Infect Control Hosp Epidemiol 2018;39(6):637–43.
52. Klompas M. Ventilator-associated events surveillance: a patient safety opportunity. Curr Opin Crit Care 2013;19(5):424–31.
53. Klompas M. Potential strategies to prevent ventilator-associated events. Am J Respir Crit Care Med 2015;192(12):1420–30.
54. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med 2012;186(8):724–31.
55. Shehabi Y, Chan L, Kadiman S, et al. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med 2013;39(5):910–8.
56. Klompas M, Anderson D, Trick W, et al. The preventability of ventilator-associated events. The CDC prevention epicenters wake up and breathe collaborative. Am J Respir Crit Care Med 2015;191(3):292–301.
57. Aragón RE, Proaño A, Mongilardi N, et al. Sedation practices and clinical outcomes in mechanically ventilated patients in a prospective multicenter cohort. Crit Care 2019;23(1):130.
58. Metheny NA, Clouse RE, Chang YH, et al. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors. Crit Care Med 2006;34(4):1007–15.
59. Nseir S, Makris D, Mathieu D, et al. Intensive care unit-acquired infection as a side effect of sedation. Crit Care 2010;14(2):R30.
60. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263–306.
61. Zhang Z, Chen K, Ni H, et al. Sedation of mechanically ventilated adults in intensive care unit: a network meta-analysis. Sci Rep 2017;7(1):44979.
62. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 1995;332(6):345–50.
63. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996;335(25):1864–9.
64. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342(20):1471–7.
65. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008;371(9607):126–34.
66. Posa P, Barnes D, Bogan B, et al. Compliance with spontaneous breathing trial protocol associated with lower VAE rates. Crit Care Med 2014;42(Suppl 1):A1547.

67. Chumpia MM, Ganz DA, Chang ET, et al. Reducing the rare event: lessons from the implementation of a ventilator bundle. BMJ Open Qual 2019;8(2):e000426.
68. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308(19):1985–92.
69. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. Arch Phys Med Rehabil 2010;91(4):536–42.
70. Engel HJ, Tatebe S, Alonzo PB, et al. Physical therapist-established intensive care unit early mobilization program: quality improvement project for critical care at the University of California San Francisco Medical Center. Phys Ther 2013;93(7):975–85.
71. Fraser D, Spiva L, Forman W, et al. Original research: implementation of an early mobility program in an ICU. Am J Nurs 2015;115(12):49–58.
72. Klein K, Mulkey M, Bena JF, et al. Clinical and psychological effects of early mobilization in patients treated in a neurologic ICU: a comparative study. Crit Care Med 2015;43(4):865–73.
73. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373(9678):1874–82.
74. Titsworth WL, Hester J, Correia T, et al. The effect of increased mobility on morbidity in the neurointensive care unit. J Neurosurg 2012;116(6):1379–88.
75. Nydahl P, Ruhl AP, Bartoszek G, et al. Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany*. Crit Care Med 2014;42(5):1178–86.
76. The Team Study Investigators. Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. Crit Care 2015;19:81.
77. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med 2008;36(8):2238–43.
78. Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. Crit Care Med 2007;35(1):139–45.
79. Seaver J, Grant K, Lunn J, et al. A multidisciplinary approach to reducing ventilator-associated events in a busy urban hospital. Am J Infect Control 2020;48(7):828–30.
80. Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care 2010;14(1):R1.
81. Li G, Malinchoc M, Cartin-Ceba R, et al. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. Am J Respir Crit Care Med 2011;183(1):59–66.
82. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA 2012;308(16):1651–9.
83. Serpa Neto A, Simonis FD, Barbas CS, et al. Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome: a systematic review and individual patient data analysis. Crit Care Med 2015;43:2155–63.

84. Gajic O, Frutos-Vivar F, Esteban A, et al. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med 2005;31(7):922–6.
85. Mekontso Dessap A, Katsahian S, Roche-Campo F, et al. Ventilator-associated pneumonia during weaning from mechanical ventilation: role of fluid management. Chest 2014;146:58–65.
86. Jia X, Malhotra A, Saeed M, et al. Risk factors for ARDS in patients receiving mechanical ventilation for > 48 h. Chest 2008;133(4):853–61.
87. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354(24):2564–75.
88. Rosenberg AL, Dechert RE, Park PK, et al. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. J Intensive Care Med 2009;24(1):35–46.
89. Grissom CK, Hirshberg EL, Dickerson JB, et al. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome. Crit Care Med 2015;43(2):288–95.
90. Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. JAMA 2014;311(13):1317–26.
91. Mitchell KH, Carlbom D, Caldwell E, et al. Volume overload: prevalence, risk factors, and functional outcome in survivors of septic shock. Ann Am Thorac Soc 2015;12(12):1837–44.
92. Cocoros N, Priebe G, Gray J, et al. Factors associated with pediatric ventilator-associated conditions in six U.S. hospitals: a nested case-control study. Pediatr Crit Care Med 2017;18:1.
93. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35(8):915–36.
94. Krein SL, Fowler KE, Ratz D, et al. Preventing device-associated infections in US hospitals: national surveys from 2005 to 2013. BMJ Qual Saf 2015;24:385–92.
95. Wang L, Li X, Yang Z, et al. Semi-recumbent position versus supine position for the prevention of ventilator-associated pneumonia in adults requiring mechanical ventilation. Cochrane Database Syst Rev 2016;2016(1):CD009946.
96. Klompas M, Speck K, Howell MD, et al. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. JAMA Intern Med 2014;174(5):751–61.
97. Price R, MacLennan G, Glen J. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. BMJ 2014;348:g2197.
98. Deschepper M, Waegeman W, Eeckloo K, et al. Effects of chlorhexidine gluconate oral care on hospital mortality: a hospital-wide, observational cohort study. Intensive Care Med 2018;44(7):1017–26.
99. Hirata K, Kurokawa A. Chlorhexidine gluconate ingestion resulting in fatal respiratory distress syndrome. Vet Hum Toxicol 2002;44(2):89–91.
100. Orito K, Hashida M, Hirata K, et al. Effects of single intratracheal exposure to chlorhexidine gluconate on the rat lung. Drug Chem Toxicol 2006;29(1):1–9.

101. Xue Y, Zhang S, Yang Y, et al. Acute pulmonary toxic effects of chlorhexidine (CHX) following an intratracheal instillation in rats. Hum Exp Toxicol 2011; 30(11):1795–803.
102. Seguin P, Laviolle B, Dahyot-Fizelier C, et al. Effect of oropharyngeal povidone-iodine preventive oral care on ventilator-associated pneumonia in severely brain-injured or cerebral hemorrhage patients: a multicenter, randomized controlled trial. Crit Care Med 2014;42:1–8.
103. Panchabhai TS, Dangayach NS, Krishnan A, et al. Oropharyngeal cleansing with 0.2% chlorhexidine for prevention of nosocomial pneumonia in critically ill patients: an open-label randomized trial with 0.01% potassium permanganate as control. Chest 2009;135(5):1150–6.
104. Mori H, Hirasawa H, Oda S, et al. Oral care reduces incidence of ventilator-associated pneumonia in ICU populations. Intensive Care Med 2006;32(2):230–6.
105. Alhazzani W, Smith O, Muscedere J, et al. Toothbrushing for critically ill mechanically ventilated patients: a systematic review and meta-analysis of randomized trials evaluating ventilator-associated pneumonia. Crit Care Med 2013;41(2):646–55.
106. Wittekamp BH, Plantinga NL, Cooper BS, et al. Decontamination strategies and bloodstream infections with antibiotic-resistant microorganisms in ventilated patients: a randomized clinical trial. JAMA 2018;320(20):2087–98.
107. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 2009;360(1):20–31.
108. de Smet AM, Kluytmans JA, Blok HE, et al. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. Lancet Infect Dis 2011;11:372–80.
109. Silvestri L, van Saene HK, Milanese M, et al. Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients. Systematic review of randomized, controlled trials. J Hosp Infect 2007;65(3):187–203.
110. Buelow E, Gonzalez TB, Versluis D, et al. Effects of selective digestive decontamination (SDD) on the gut resistome. J Antimicrob Chemother 2014;69(8): 2215–23.
111. Daneman N, Sarwar S, Fowler RA, et al. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. Lancet Infect Dis 2013;13(4):328–41.
112. Noteboom Y, Ong DS, Oostdijk EA, et al. Antibiotic-induced within-host resistance development of gram-negative bacteria in patients receiving selective decontamination or standard care. Crit Care Med 2015;43(12):2582–8.
113. Houben AJ, Oostdijk EA, van der Voort PH, et al. Selective decontamination of the oropharynx and the digestive tract, and antimicrobial resistance: a 4 year ecological study in 38 intensive care units in the Netherlands. J Antimicrob Chemother 2014;69(3):797–804.
114. Muscedere J, Rewa O, McKechnie K, et al. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. Crit Care Med 2011;39(8):1985–91.
115. Dezfulian C, Shojania K, Collard HR, et al. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. Am J Med 2005; 118(1):11–8.
116. Wang F, Bo L, Tang L, et al. Subglottic secretion drainage for preventing ventilator-associated pneumonia: an updated meta-analysis of randomized controlled trials. J Trauma Acute Care Surg 2012;72(5):1276–85.

117. Frost SA, Azeem A, Alexandrou E, et al. Subglottic secretion drainage for preventing ventilator associated pneumonia: a meta-analysis. Aust Crit Care 2013;26:180–8.
118. Valles J, Artigas A, Rello J, et al. Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. Ann Intern Med 1995;122(3):179–86.
119. Caroff DA, Li L, Muscedere J, et al. Subglottic secretion drainage and objective outcomes: a systematic review and meta-analysis. Crit Care Med 2016;44(4):830–40.
120. Pozuelo-Carrascosa DP, Herráiz-Adillo Á, Alvarez-Bueno C, et al. Subglottic secretion drainage for preventing ventilator-associated pneumonia: an overview of systematic reviews and an updated meta-analysis. Eur Respir Rev 2020;29(155):190107.
121. Rawat N, Yang T, Ali KJ, et al. Two-state collaborative study of a multifaceted intervention to decrease ventilator-associated events. Crit Care Med 2017;45(7):1208–15.
122. Anand T, Ponce S, Pakula A, et al. Results from a quality improvement project to decrease infection-related ventilator events in trauma patients at a community teaching hospital. Am Surg 2018;84(10):1701–4.
123. Cocoros NM, Kleinman K, Priebe GP, et al. Ventilator-associated events in neonates and children-a new paradigm. Crit Care Med 2016;44(1):14–22.
124. Centers for Disease Control and Prevention. Pediatric Ventilator-Associated Event (PedVAE) protocol. 2021. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/pedvae-current-508.pdf. Accessed February 27, 2021.
125. Cocoros NM, Priebe GP, Logan LK, et al. A pediatric approach to ventilator-associated events surveillance. Infect Control Hosp Epidemiol 2017;38(3):327–33.
126. Phongjitsiri S, Coss-Bu J, Kennedy C, et al. The centers for disease control and prevention's new definitions for complications of mechanical ventilation shift the focus of quality surveillance and predict clinical outcomes in a PICU. Crit Care Med 2015;43(11):2446–51.
127. Guess R, Vaewpanich J, Coss-Bu JA, et al. Risk factors for ventilator-associated events in a PICU. Pediatr Crit Care Med 2018;19(1):e7–13.
128. Beardsley AL, Nitu ME, Cox EG, et al. An evaluation of various ventilator-associated infection criteria in a PICU. Pediatr Crit Care 2016;17:73–80.
129. Cirulis MM, Hamele MT, Stockmann CR, et al. Comparison of the new adult ventilator-associated event criteria to the centers for disease control and prevention pediatric ventilator-associated pneumonia definition (PNU2) in a population of pediatric traumatic brain injury patients. Pediatr Crit Care Med 2016;17(2):157–64.
130. Peña-López Y, Pujol M, Campins M, et al. Assessing prediction accuracy for outcomes of ventilator-associated events and infections in critically ill children: a prospective cohort study. Clin Microbiol Infect 2018;24(7):732–7.
131. Vaewpanich J, Akcan-Arikan A, Coss-Bu JA, et al. Fluid overload and kidney injury score as a predictor for ventilator-associated events. Front Pediatr 2019;7:204.
132. Lilly CM, Landry KE, Sood RN, et al. Prevalence and test characteristics of national health safety network ventilator-associated events. Crit Care Med 2014;42:2019–28.