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Ventilator-Associated Conditions Versus Ventilator-Associated Pneumonia: Different by Design

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Abstract The Centers for Disease Control and Prevention (CDC) released a new surveillance concept called *ventilator-associated conditions* (VACs) in early 2013. VAC was created to overcome some of the limitations of traditional ventilator-associated pneumonia (VAP) definitions, including their complexity, subjectivity, and insensitivity to complications other than pneumonia. VAC is defined by sustained increases in ventilator support after ≥2 days of stable or decreasing settings. The VAC definition was designed to be objective, reproducible, and amenable to automated analysis. Moreover, VAC purposefully broadens the scope of surveillance to include physiologically significant complications of care in addition to pneumonia, most commonly pulmonary edema, atelectasis, and acute respiratory distress syndrome. VAC definitions offer an opportunity for hospital quality improvement programs to get a fuller picture of the breadth and burden of complications in their critically ill populations and to use these data to catalyze enhanced prevention and control programs to better prevent these conditions.

Keywords Ventilator-associated conditions · Ventilator-associated pneumonia · Quality improvement · Healthcare epidemiology

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Introduction

Hospital quality improvement programs have traditionally tracked ventilator-associated pneumonia (VAP) rates to measure quality of care in ventilated patients. VAP is a tenuous metric for quality improvement, however, because identifying VAP is complicated, subjective, and often inaccurate. Surveys of infection preventionists reveal marked differences in their VAP classifications [1–3, 4••, 5]. This introduces substantial variability into surveillance and precludes meaningful comparisons between surveyors, between institutions, and between time periods. In addition, increasing pressures from payors and regulators to minimize VAP rates have likely been biasing surveillance towards progressively stricter interpretations of subjective surveillance criteria, leading to spurious decreases in observed VAP rates [6–8].

Of further concern, tracking VAP alone gives an incomplete picture of quality of care. Ventilated patients are at risk for multiple complications in addition to pneumonia, including acute respiratory distress syndrome (ARDS), pulmonary edema, atelectasis, pneumothorax, pulmonary embolism, pulmonary hemorrhage, and hypersensitivity reactions. Indeed, recent attributable mortality estimates suggest that VAP accounts for only a very small fraction of ICU mortality [9]. In recognition of the many limitations of traditional VAP surveillance definitions, the Centers for Disease Control and Prevention (CDC) collaborated with stakeholder organizations to develop a new surveillance framework called *ventilator-associated events* (VAEs). The primary event in the VAE framework is called a *ventilator-associated condition* (VAC).

In this article, we will review the rationale behind the new surveillance definitions, summarize the epidemiology of VACs, survey the emerging literature on differences between VAC and traditionally defined VAP, and consider ways in which VAE/VAC surveillance can help hospitals enhance their quality improvement programs.

Rationale for VAE Definitions

VAE definitions grew out of the deliberations of a working group of stakeholder organizations [10••]. The working group first met in the fall of 2011 and included representatives from critical care, respiratory therapy, nursing, infectious disease, hospital epidemiology, and infection prevention societies as well as state and federal health authorities. The working group advised shifting the focus of surveillance from pneumonia alone to complications of mechanical ventilation in general for three reasons: (1) it is a more accurate description of what can and cannot reliably be determined using surveillance criteria alone, (2) it encourages quality improvement and safety programs to broaden their focus to include additional important complications of mechanical ventilation other than pneumonia, and (3) it allows for simple and objective surveillance definitions that are amenable to automation using electronic health data. CDC accepted the working group's recommendations and replaced their traditional VAP surveillance definitions with VAE definitions in early 2013 [10••].

Overview of VAE Definitions

The VAE framework includes a hierarchy of four related events. The foundational event is called a ventilator-associated condition. VAC is conceptually intended to identify patients with deteriorating respiratory status after a period of stability or improvement. Changes in respiratory status are identified by tracking ventilator settings. Two ventilator settings in particular are considered: the positive end-expiratory pressure (PEEP) and the fraction of inspired oxygen (FiO_2). Specifically, VAC requires an increase in the daily minimum PEEP of ≥3 cm H_2O and/or the daily minimum FiO_2 of ≥20 points sustained for ≥2 days after ≥2 days of stable or decreasing daily minimum PEEPs and/or FiO_2s, respectively (Fig. 1).

The VAC definition is purposefully nonspecific. It makes no attempt to identify the cause of pulmonary deterioration but simply notes pulmonary deterioration alone. The definition follows from the recognition that mechanical ventilation, while lifesaving, is uncomfortable and potentially dangerous for patients. Intubation and mechanical ventilation typically require sedation, limit mobility, facilitate the passage of pathogens from the mouth to the lungs, and subject the lungs to atypical and potentially damaging forces. In addition, sustained high levels of PEEP and FiO_2 can be detrimental in and of themselves [11–16]. Normative practice is therefore to maintain patients on the lowest possible settings that provide adequate oxygenation and to try to wean patients from mechanical ventilation as quickly as possible. As such, a trajectory change from stable or decreasing ventilator settings to sustained increases often signals some sort of a complication.

Following detection of a VAC, the VAE framework includes daughter definitions to try to identify the subset of VACs that might be infection related and the subset of infection-related complications that might be pneumonias [10••]. An *infection-related ventilator-associated*

Date	Daily Minimum PEEP (cm H_2O)	FiO2
July 1	10	100
July 2	5	60
July 3	5	50
July 4	5	40
July 5	5	40
July 6	10	55
July 7	10	50
July 8	8	45
July 9	5	40
July 10	5	40

Daily minimum PEEP has risen from a stable baseline of 5cm H_2O (July 4-5) to 10cm H2O (July 6-7). The increase is ≥3cm H_2O and is sustained for ≥2 calendar days. This therefore qualifies as a ventilator-associated condition (VAC).

Fig. 1 Example of a ventilator-associated condition. *PEEP* positive end-expiratory pressure, *FiO_2* fraction of inspired oxygen

complication (IVAC) requires an abnormal temperature or white blood cell count within 2 days of VAC onset and evidence of clinical concern for infection as marked by the initiation of new antibiotics for 4 days or more. Possible pneumonia is defined as a patient with IVAC and concurrent purulent pulmonary secretions or a positive pulmonary culture for a potentially pathogenic organism. Probable pneumonia is defined as a patient with IVAC and concurrent purulent pulmonary secretions and a positive quantitative or semiquantitative culture for a potentially pathogenic organism. Purulence is defined as ≥25 neutrophils and ≤10 epithelial cells per low-power field on Gram stain of an endotracheal aspirate or bronchoalveolar lavage specimen. Patients can also qualify for probable pneumonia on the basis of histological changes or positive laboratory tests for *Legionella* sp. and selected respiratory viruses.

In addition to broadening the focus of surveillance, VAE definitions were designed to be objective, reproducible, and amenable to automation. A number of centers have now reported their experiences applying VAE definitions electronically [17•, 18•, 19••, 20•]. Likewise, the CDC publishes an online *VAE calculator* that allows infection preventionists to enter key parameters for a single patient (daily minimum PEEPs and FiO_2s, daily minimum and maximum temperatures and white blood cell counts, and daily antibiotic exposures) and to receive back a determination on whether or not the patient meets criteria for VAC or IVAC [21]. The fact that it is feasible to program a computer to apply VAE criteria is a proof that VAE surveillance can be objective and reproducible. By contrast, multiple studies have documented substantial differences between different surveyors applying traditional VAP definitions [2, 3, 4••, 5]. Some variability in VAE rates between centers is likely still possible due to differences in the ways clinicians manage patients, differences in laboratory protocols for working up respiratory specimens, and/or differences in how ventilator settings are recorded and collated [19••]. VAE definitions minimize variability, however, due to differences in surveyor judgments.

VAC Versus VAP

There is a growing body of literature from around the world comparing surveillance using VAE definitions versus traditional VAP definitions [19••, 20•, 22–24, 25••]. The majority of published studies focus on VAC; hence, this paper will focus on VAC as well. The recurring message from these investigations is that VAC is different from VAP. The two surveillance targets differ in incidence rates, attributable morbidity and mortality, and populations identified. We will review these differences.

VAC affects about 5–10 % of mechanically ventilated patients (Table 1) [17•, 18•, 19••, 20•, 24]. VAP has been variously reported to affect between 0 and 20 % of patients [7•, 26, 27]. Knowing the true rate of VAP is challenging, given the substantial differences in surveillance definitions and differences in surveyor judgments. Five studies have compared VAC versus traditional VAP surveillance in common populations [19••, 20•, 22, 24, 25••]. Total VAC rates tend to be quite similar across all studies but higher than VAP rates in US studies and similar to VAP rates in non-US studies. This discrepancy likely says more about differences in VAP surveillance in the USA versus abroad than about relative VAC versus VAP rates. VAP rates in the USA tend to be lower than VAP rates in similar centers outside the USA, presumably because US payment and reporting pressures favor interpreting subjective surveillance criteria as strictly as possible [6•, 7•, 8]. However, even in centers that found that VAC rates were similar to VAP rates, there was very little overlap between the specific patients flagged by either definition [19••, 25••].

As with VAP, the incidence of VAC varies substantially by unit type. In one large tertiary care center, for example, VAC rates ranged from 8.8 and 10.2 events per 100 episodes of mechanical ventilation in surgical intensive care and medical intensive care units, respectively, to 1.4 and 4.9 events per 100 episodes of mechanical ventilation in cardiac surgery and neuroscience units, respectively [18•].

VACs appear to be highly morbid. VAC is associated with a two- to threefold increase in the risk of death as well as more time on mechanical ventilation, longer intensive care stays, and longer hospital lengths of stay compared to patients without VAC [17•, 19••, 22, 25••, 28••]. Four studies have simultaneously estimated the VAC- and VAP-attributable mortality within the same population (Table 2). All four studies found that patients with VAC were more likely to die than patients without VAC. Three studies found that VAC-attributable mortality was higher than VAP-attributable mortality, and one study found the reverse. Some of the variability

Table 1 Incidence of ventilator-associated condition (VAC) versus ventilator-associated pneumonia (VAP) amongst studies of unselected populations (i.e., studies that included all patients on mechanical ventilation during a defined time period)

Study	Year	VAC per 100 episodes	VAC per 1,000 ventilator days	VAP per 100 episodes	VAP per 1,000 ventilator days
Klein Klouwenberg et al. [19]	2014	6.9	10.0	5.5	8.0
Lilly et al. [24]	2014	4.6	13.8	1.0	3.0
Stevens et al. [4, 20]	2014	6.1	14.4	0.3	0.6

Table 2 Attributable mortality of ventilator-associated conditions (VAC) versus ventilator-associated pneumonia (VAP)

Study	Year	Measure of effect	VAC	VAP
Klompas et al. [22]	2011	Odds ratio (95 % CI)	2.0 (1.3–3.2)	1.1 (0.5–2.4)
Klompas et al. [5, 17]	2012	Odds ratio (95 % CI)	1.9 (1.5–2.3)	–
Hayashi et al. [28]	2013	Hazard ratio (95 % CI)	0.9 (0.6–1.4)	–
Muscedere et al. [25]	2013	Hazard ratio (95 % CI)	2.1 (1.6–2.8)	1.5 (1.1–2.1)
Klein Klouwenberg et al. [19]	2014	Subdistribution hazard ratio (95 % CI)	3.9 (2.9–5.3)	7.2 (5.1–10.3)
Klompas et al. [18]	2014	Odds ratio (95 % CI)	2.0 (1.6–2.4)	–
Lilly et al. [24]	2014	Odds ratio (95 % CI)	1.8 (1.0–3.6)	1.0 (0.6–1.7)
Stevens et al. [4, 20]	2014	Odds ratio (95 % CI)	1.9 (1.5–2.4)	–

between comparative estimates of the VAP-attributable mortality may be due to differences in case identification across studies.

Most cases of VAC appear to be triggered by one of four conditions: pneumonia, pulmonary edema, atelectasis, and/or ARDS [19••, 22, 28••, 29••]. Depending on the series, pneumonia accounts for 25–40 % of VACs, pulmonary edema for 15–30 %, atelectasis for 10–15 %, and ARDS for 10–20 % [19••, 22, 28••, 29••]. The fact that the majority of patients with VAC have conditions other than pneumonia reflects the original intent of CDC and the VAE working group to expand the scope of surveillance beyond pneumonia to include additional, morbid complications of critical care.

Conversely, a number of studies have documented that VAC surveillance misses a substantial number of pneumonias. Only about 25–35 % of patients that meet various traditional surveillance definitions for VAP meet VAC criteria [19••, 20•, 23, 25••, 29••]. At the first blush, the poor sensitivity of VAC surveillance for traditionally defined pneumonia is a concern. The pneumonias missed by VAC surveillance, however, merit contemplation. By definition, these events did not require sustained increases in ventilator support at or above the VAC PEEP and/or FiO_2 thresholds. While it is certainly conceivable that some patients might develop mild pneumonias that impose little extra physiological burden, one wonders about the clinical significance of these events.

Moreover, clinical and surveillance diagnoses of VAP using traditional criteria are notoriously inaccurate [30]. Autopsy series suggest that one third to one half of patients clinically diagnosed with VAP do not have pneumonia [30, 31]. Similarly, quality improvement programs that adjudicate clinical VAP diagnoses overrule the majority of VAPs diagnosed by frontline clinicians. At Johns Hopkins University, for example, a panel of expert physicians rejected 68 % of VAPs diagnosed by frontline clinicians [32•]. It is therefore highly likely that many of these physiologically benign *pneumonias* that did not require increased ventilator support were not pneumonias at all, but rather instances of bacterial colonization of the endotracheal tube and/or oropharynx.

The VAC definition by contrast sets a severity threshold. Only events that lead to significant deterioration in respiratory status are identified. This may decrease sensitivity but presumably also increases the clinical significance of cases. This is reflected by the consistently high attributable mortality rate associated with VAC. Focusing on the most morbid VAPs may help quality improvement programs to concentrate their analyses on the highest yield patients. This issue requires further research.

VAC's relative insensitivity for clinically diagnosed VAP might appear to limit VAC's utility for pneumonia prevention and monitoring efforts. However, this is not necessarily the case. First, as noted above, the clinical significance of the VAPs missed by VAC surveillance is unclear. Second, a quality improvement program informed by VAC surveillance will necessarily include pneumonia prevention interventions since VAC prevention must target all of the major causes of VAC (pneumonia, pulmonary edema, atelectasis, and ARDS). Third, all of the limitations of traditional VAP definitions that propelled the development of VAC still stand. Utilizing traditional VAP definitions in order to enhance the sensitivity of surveillance for clinically defined pneumonia will simply reintroduce all the old concerns about VAP definitions, including their complexity, subjectivity, susceptibility to bias, and questionable accuracy.

Interestingly, a recurring critique of traditional VAP surveillance definitions prior to the introduction of VAE definitions was their diminishing sensitivity to clinically diagnosed pneumonias [33–35]. During 2012, for example, the median VAP rate in US medical intensive care units using CDC's old surveillance definitions reached 0 despite clinicians' attestations that they were still diagnosing and treating many pneumonias [27]. The mismatch between surveillance VAP rates and clinical VAP rates was attributed to pressures from government, quality agencies, payors, and hospital leaders to minimize VAP rates [6•, 7•, 8]. It is ironic that now that CDC has replaced their traditional VAP definitions with VAE definitions that VAP surveillance using traditional definitions is again finding large numbers of cases.

Ultimately, VAC is a surveillance concept, not a clinical diagnosis. Surveillance is intended to give an estimate of the relative burden of complications in a population compared to

one's peers and one's self over time. Surveillance need not be perfectly sensitive to meet this objective. It is more important for surveillance to be efficient, objective, reproducible, and capable of detecting events strongly associated with adverse outcomes rather than perfect at identifying all possible events flagged by clinicians.

Implications for Quality Improvement Programs

VAE surveillance and VAC surveillance are promising tools to catalyze better care and hence better outcomes for mechanically ventilated patients [36•, 37•]. VAC surveillance brings to light a fuller picture of the population of patients suffering morbid complications of critical care compared to traditional VAP surveillance. VAC surveillance is therefore an opportunity to reconfigure ventilator bundles to better prevent the fuller spectrum of morbid complications that affect ventilated populations. VAC surveillance also has the potential to be more efficient than VAP surveillance (especially if implemented electronically), and VAC's objectivity minimizes the risk of spurious decreases in event rates seen with traditional VAP definitions that were due to stricter surveyor judgments rather than true improvements in care.

VAC prevention strategies can be divided into two groups: interventions designed to shorten the duration of mechanical ventilation (and hence time at risk for VAC) and interventions designed to prevent the specific complications most commonly associated with VAC (namely pneumonia, pulmonary edema, atelectasis, and ARDS). Examples of the former include minimizing sedation, implementing paired daily spontaneous awakening trials and spontaneous breathing trials, and encouraging early mobility [38–43]. Examples of the latter include elevating the head of the bed, utilizing endotracheal tubes with subglottic secretion drainage, conservative fluid management during weaning, setting conservative blood transfusion thresholds, and ventilating patients with low tidal volumes [44, 45, 46••, 47–49]. Notably, these interventions are all highly congruent with emerging best practices in critical care [50].

Two studies thus far have confirmed that improvements in care are associated with lower VAC rates. The Canadian Critical Care Trials Group retrospectively assessed the impact of a 2-year effort to increase adoption of best practices for ventilated patients in 11 ICUs [25••]. They found a small but significant decrease in VAC rates despite only modest improvements in best practice rates. The second study assessed the impact of depletive fluid management on VAC rates during weaning from mechanical ventilation [46••]. Patients were randomized to daily B-type natriuretic peptide (BNP) levels versus usual care. Patients randomized to daily BNP levels received less fluid and more diuretics compared to control patients. Depletive fluid management reduced the incidence of VAC by approximately 50 % compared to usual care. This study affirmed that reducing VAC rates likely requires more than simply targeting pneumonia alone.

Conclusions

VAC surveillance has rich potential to enhance care and outcomes for ventilated patients. VAC definitions are efficient and objective, they bring to light a more complete picture of the population of patients suffering complications of mechanical ventilation, and they provide a rigorous yardstick to measure progress at reducing complications without fear that rates are being artificially diminished by surveillance biases rather than by improvements in care. Early reports affirm that better care can lower VAC rates. Maximally reducing VAC rates, however, will likely require developing a new ventilator bundle optimized to target the fuller array of conditions flagged by VAC surveillance. Doing so has a potential to improve outcomes beyond what could be possible by focusing on pneumonia alone.

Compliance with Ethics Guidelines

Conflict of Interest Michael Klompas received grant funding from CDC. Klompas received honoraria from the Infectious Disease Society of America, Society for Healthcare Epidemiology of America, American College of Chest Physicians, American Society for Microbiology, Infectious Disease Association of California, and Texas Hospital Association.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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