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Potential Strategies to Prevent Ventilator-Associated Events

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Abstract:

The Centers for Disease Control and Prevention (CDC) released ventilator-associated event (VAE) definitions in 2013. The new definitions were designed to track episodes of sustained respiratory deterioration in mechanically ventilated patients after a period of stability or improvement. Over 2000 U.S. hospitals are reporting VAE rates to CDC but there has been little guidance to date on how to prevent VAEs. Existing ventilator-associated pneumonia prevention bundles are unlikely to be optimal insofar as pneumonia only accounts for a minority of VAEs. This review will propose a framework and potential intervention set to prevent VAEs based on recent studies of VAE epidemiology, risk factors, and prevention. Work to date suggests that the majority of VAEs are caused by four conditions: pneumonia, fluid overload, atelectasis, and acute respiratory distress syndrome. Interventions that minimize ventilator exposure and target one or more of these conditions may therefore prevent VAEs. Potential strategies include avoiding intubation, minimizing sedation, paired daily spontaneous awakening and breathing trials, early exercise and mobility, low tidal volume ventilation, conservative fluid management, and conservative blood transfusion thresholds. Interventional studies have thus far affirmed that minimizing sedation, paired daily spontaneous awakening and breathing trials, and conservative fluid management can reduce VAE rates and improve patient-centered outcomes. Further studies are needed to evaluate the impact of the other proposed interventions, to identify additional modifiable risk factors for VAEs, and to measure whether combining strategies into VAE prevention bundles confers additional benefits over implementing one or more of these interventions in isolation.

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Introduction

The U.S. Centers for Disease Control and Prevention (CDC) released a new surveillance paradigm for complications of mechanical ventilation in 2013.(1) The new paradigm, called ventilator-associated events (VAE), was designed to overcome many of the limitations of ventilator-associated pneumonia (VAP) as a quality metric including its complexity, subjectivity, low frequency, and marginal attributable mortality.(2-9) VAE definitions shift the focus of surveillance away from pneumonia in particular to complications in mechanically ventilated patients in general.(10) The proposed advantages of this shift are two-fold: 1) it broadens the focus of surveillance to include additional potentially preventable morbid complications of mechanical ventilation such as acute respiratory distress syndrome (ARDS), fluid overload, and atelectasis; and 2) it allows for simple, objective, and potentially automatable surveillance definitions based upon trajectory changes in patients' ventilator settings. Whether VAE will ultimately prove to be a more robust and impactful quality metric than VAP remains to be seen.

A VAE is defined by ≥2 days of stable or decreasing ventilator settings followed by ≥2 days of increased ventilator settings. In particular, the definition requires an increase in the daily minimum positive end expiratory pressure (PEEP) of ≥3cm H_2O or an increase in the daily minimum fraction of inspired oxygen (FiO2) of ≥20 points relative to the preceding two days (Figure 1). Additional criteria allow for the subclassification of VAEs into infection-related ventilator-associated complications (IVAC) and/or possible pneumonias (PVAP).(10)

VAE definitions were designed for the purposes of population surveillance and quality improvement. They were not designed to inform the immediate clinical management of deteriorating patients (indeed, by definition, a VAE is only apparent 2 days following the onset of deterioration). Instead, VAE surveillance is intended to provide hospitals with a big-picture view of complication rates, a more objective basis for comparison with other hospitals, and an anchor around which to explore the reasons why some patients deteriorate in their institution and thereby inform possible system-level improvements in care that can be applied to future patients.

Multiple studies have characterized the incidence and attributable mortality of VAEs. Incidence rates vary by ICU type but generally range from 10-15 events per 1000 ventilator-days or 4-7 events per 100 episodes of mechanical ventilation.(11-14) Most studies report that patients with VAEs are approximately twice as likely to die as matched patients without VAEs.(11-19) VAEs are also associated with more time on mechanical ventilation, longer ICU stays, and higher rates of antimicrobial utilization.(11, 12, 17, 19)

The relative frequency of VAEs and their high attributable morbidity and mortality make them potentially useful targets for prevention and quality improvement programs. A number of papers have been published on risk factors and interventions to prevent VAEs but as yet there is no single, comprehensive guide to preventing VAEs. This paper will propose a framework and bundle of interventions to prevent VAEs based upon studies to date of clinical correlates, risk factors, and prevention strategies for VAEs.

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Clinical Conditions Associated with VAEs

Five case series enumerate the clinical events that most commonly trigger VAEs. Four of the five case series were based on open-ended chart reviews designed to elicit any possible causes for patients' VAEs. In these series, the majority of VAEs were caused by one of four conditions: pneumonia, fluid overload, atelectasis, and ARDS (Table 1). Depending on the series, pneumonia accounted for about 25-40% of VAEs, fluid overload (including pulmonary edema) for 20-40%, atelectasis for 10-15%, and ARDS for 10-20% (12, 15, 17, 20). The fifth case series retrospectively applied a variant definition for VAE to a multicenter cohort of 13,702 patients.(19) The variant definition included higher thresholds for significant changes in PEEP and the option of using changes in PaO2:FiO2 ratios to trigger VAEs. These investigators identified 2,331 VAEs and attributed 27% to nosocomial infections (mainly pneumonia), 14% to iatrogenic complications (atelectasis, pneumothorax, thromboembolism, failed extubations, etc.), 17% to transport, and 5% to fluid resuscitation. Attributions were restricted, however, to a limited list of complications that were predefined in 1997. Across all series, investigators were unable to identify the clinical precipitants for rising ventilator settings in 10-40% of cases.(12, 15, 17, 19, 20)

Strategic Framework for Preventing VAEs

There are three major approaches to prevent VAEs: 1) avoid intubation, 2) minimize duration of mechanical ventilation, and 3) target the specific conditions that most frequently trigger VAEs. In practice, these approaches are often highly congruent. Many of the most effective strategies to avoid intubation and minimize ventilator time have also been associated with lower rates of infection, fluid overload, atelectasis, and/or ARDS.

Likewise, the most reliable strategies to prevent these complications are arguably those that have been shown to also decrease duration of mechanical ventilation, length-of-stay, and/or mortality.

Using this framework, potential strategies to prevent VAEs include avoiding intubation, minimizing sedation, improving performance of coordinated daily spontaneous awakening and breathing trials (SATs and SBTs), early mobility, low tidal volume ventilation, conservative fluid management, and conservative blood transfusion thresholds. These interventions were selected because randomized controlled trials suggest these strategies can decrease duration of mechanical ventilation, and in most cases, lower the incidence of one or more of the four conditions most frequently associated with VAEs (pneumonia, excess fluid, atelectasis, and/or ARDS). The interplay between these effects is shown in Figure 2. The rationale, general evidence, and VAE-specific evidence supporting each of these interventions are described below.

Avoiding intubation through non-invasive positive pressure ventilation or high-flow oxygen via nasal cannula is associated with better outcomes in selected populations.(21-24) These strategies can be used to avoid intubation and/or facilitate earlier extubation. Neither intervention, however, has been studied in regard to VAEs. In addition, VAE surveillance is currently limited to patients receiving invasive mechanical ventilation. CDC recommends ventilator-days or ventilator episodes as denominators when reporting VAE rates hence the metric is likely blind to systematic efforts to avoid intubations. This gap could be corrected by developing parallel VAE criteria for patients receiving non-invasive

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positive pressure ventilation and/or by reporting VAE rates relative to all ICU admissions, but the value of these approaches has not been studied. This review will therefore focus on strategies to prevent VAEs amongst patients receiving invasive mechanical ventilation.

Strategy #1: Minimize sedation

An increasing body of evidence associates choice, depth, and duration of sedation with increased risk for a range of adverse effects including delirium, immobility, infection, VAEs, prolonged mechanical ventilation, increased length-of-stay, and death.(25-31) Deep and/or sustained sedation likely increase VAE risk in two ways: 1) by prolonging duration of mechanical ventilation and hence time at risk for VAEs, and 2) by increasing risk for specific complications that may be associated with VAEs. For example, deep sedation may increase the risk for atelectasis, aspiration, and impaired clearance of respiratory secretions that in turn may increase risk for pneumonia.(32) A case-control study of risk factors for VAEs found that benzodiazepine and opioid exposures were independent risk factors for infection-related ventilator-associated complications (IVAC). (30) Another analysis found that benzodiazepines and propofol were associated with increased risk for VAEs whereas dexmedetomidine was not.(33)

Minimizing the depth and duration of sedation is associated with less time to extubation and possibly lower mortality rates.(34) Most strikingly, a randomized controlled trial comparing routine sedation with propofol and midazolam versus a strategy of no sedation reported that mechanical ventilation without sedation was associated with 4.2 more ventilator-free days compared to management with sedation.(35)

Some of the success of this investigation may have been attributable to their use of 1:1 nursing insofar as patients randomized to no sedation had significantly more episodes of agitation compared to patients on sedation. It is therefore not clear whether a strategy of no sedation is generalizable to routine practice in U.S. hospitals where 1:1 nursing is not routinely possible and where ICU culture still favors at least some degree of sedation.(36, 37) Nonetheless, this trial at the very least challenges our assumptions about the minimum amount of sedation that patients require to tolerate mechanical ventilation and critical illness.

In addition, a series of studies over the past decade suggest that benzodiazepines are associated with poorer outcomes compared to non-benzodiazepines such as propofol and dexmedetomidine.(31) Minimizing sedation may increase the incidence of agitated delirium and self-extubations, which in turn may require higher staffing levels, emergent re-intubations, and more patient contact time. On balance, though, protocols to reduce sedation and avoid benzodiazepines appear to lower pneumonia risk and decrease time to extubation without long-term adverse consequences.(38-45)

Strategy #2: Perform daily coordinated spontaneous awakening trials and breathing trials

Two of the most potent strategies to diminish duration of mechanical ventilation and hence time at risk for VAEs are daily SATs and SBTs. At least 3 studies have found that SATs and/or SBTs are protective against VAEs.(18, 46, 47) There are rich randomized controlled trial data establishing that SATs and SBTs can decrease time to extubation by 1.5-2.5 days compared to usual care.(48-50) Coordinating these two interventions together appears to

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be synergistic, presumably because patients are more likely to pass SBTs if they are awake for the trial. Pairing SATs and SBTs together has been associated with 3.1 more ventilator-free days compared to daily SBTs alone.(34)

A subsequent trial reported that sedative interruptions conferred no additional benefit in patients already being managed with a sedation protocol.(51) However, patients randomized to sedative interruptions in this study received *higher* average daily doses of midazolam and fentanyl compared to patients being managed by protocol alone. This paradoxical result is an important reminder that SATs are means not ends. The intent of both SATs and sedation protocols is to facilitate minimizing sedation. Their success is contingent upon them driving less sedative use, not simply upon their institution alone.

Enhancing the frequency and reliability of paired daily SATs and SBTs can reduce VAE rates. The CDC Prevention Epicenters' Wake Up and Breathe Collaborative brought together 12 ICUs affiliated with 7 hospitals to increase the frequency of paired daily SATs and SBTs.(46) Over a 19-month period, the collaborative increased the frequency of SATs from 14% to 77% of days where indicated, SBTs from 49% to 75% of days where indicated, and the fraction of SBTs done off sedation from 6.1% to 87%. These improvements were associated with a decrease in VAEs from 9.7 to 5.2 events per 100 episodes of mechanical ventilation (adjusted odds ratio 0.63, 95% CI 0.42-0.97) and a decrease in IVACs from 3.5 to 0.52 events per 100 episodes of mechanical ventilation (adjusted odds ratio 0.35, 95% CI 0.17-71). These were further accompanied by a 2.4 day decrease in 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. There was no change in mortality rates.

Strategy #3: Implement programs for early exercise and mobility

Immobility has long been recognized as a risk factor for prolonged length-of-stay, pneumonia, atelectasis, delirium, and other complications of critical illness.(52) Mobilizing patients while still on mechanical ventilation is increasingly recognized as a potent strategy to decrease duration of mechanical ventilation, prevent delirium, and enhance patients' sense of well being. One randomized controlled trial found that early physical and occupational therapy in mechanically ventilated patients who were functionally independent at baseline was associated with 2.4 more ventilator-free days and 2.0 fewer days of delirium compared to daily interruption of sedation alone.(53) Other investigators have reported similar improvements after implementing early mobility programs.(54-59) In practice, early mobility programs can be difficult to implement given the complexity of safely mobilizing a patient while still on a ventilator. Recent surveys suggest that most ICUs are still struggling to provide this intervention to most patients.(60, 61)

There are no studies to date directly assessing the impact of early mobility on VAE risk. However, to the extent that early mobility can decrease patients' time on mechanical ventilation, it is also likely to decrease their risk for VAEs. Early mobility may also decrease the incidence of atelectasis (which accounts for about 10-15% of VAEs) and pneumonia (which accounts for 25-40% of VAEs).(54, 62, 63)

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There may be important synergies between minimizing sedation, performing daily SATs, and SBTs, and early mobility. Less sedation decreases ventilator dependence and risk of delirium. Coordinating SBTs and early mobility with sedative interruptions increases patients' chances of success. Preventing delirium and encouraging physical activity decreases the need to use sedatives to calm patients. Quality advocates suggest combining these five interventions into the so-called ABCDE package (Awakening and Breathing Coordination, Delirium monitoring and management, Early exercise and mobility). A before-after study of the ABCDE bundle in 7 different units of one hospital reported that patients in the post-implementation period had 3 more ventilator-free days and nearly half the frequency of delirium compared to patients in the pre-implementation period.(57) On the other hand, a randomized controlled trial of early tracheotomy versus prolonged intubation in cardiac surgery patients found no difference in ventilator-free days, ICU length-of-stay, or mortality rates despite significantly less sedation and higher levels of mobility amongst patients randomized to early tracheotomy.(64) Randomized controlled trials assessing the impact of ABCDE on VAE are needed.

Strategy #4: Low tidal volume ventilation

High quality randomized controlled trials suggest that low tidal volumes are associated with lower mortality rates in patients with ARDS and a growing number of studies suggest that low tidal volume ventilation may help prevent ARDS, atelectasis, and lung infections in patients without ARDS.(65-69) Given that these three conditions collectively account for the majority of VAEs, there is a reasonable likelihood that low tidal volume ventilation will also prevent VAEs. A recent case-control study affirmed that high tidal volumes are

independently associated with higher risk for VAEs: each ml increase above 6ml/kg predicted body weight increased the odds of VAE by 21%.(70)

The most robust evidence to date that low tidal volume ventilation is helpful in patients without ARDS comes from a meta-analysis of 20 studies.(68) Low tidal volume ventilation was associated with significantly lower rates of lung injury, pulmonary infection, and atelectasis, as well as shorter hospital length-of-stay and lower mortality rates. The majority of studies included in the meta-analysis, however, were short-term evaluations of surgical patients (median time of per-protocol protective ventilation 6.9 hours, median duration of follow-up 21 hours) hence the applicability of these studies to longer periods of mechanical ventilation in critically ill patients is unclear. Nonetheless, at least one randomized controlled trial suggests that low tidal volume ventilation may also be beneficial in critically ill patients. Determann and colleagues randomized 150 patients expected to require >72 hours of mechanical ventilation to tidal volumes of 6ml/kg versus 10ml/kg predicted body weight.(66) Patients randomized to low tidal volumes had significantly lower rates of acute lung injury (2.6% vs 13.5%, P=0.01). There were no differences between groups in ventilator-free days or mortality but the trial was not powered to assess these outcomes and the study predated the development of VAE definitions. A patient-level analysis of data from this trial combined with mainly observational data from other trials affirmed lower rates of ARDS but only trends towards less pneumonia and lower mortality rates.(69) Further data are therefore required to confirm whether low tidal ventilation can shorten time to extubation, prevent VAEs, and lower mortality in critically ill patients without ARDS.

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Strategy #5: Conservative fluid management

Qualitative analyses suggest that 20-40% of VAEs are attributable to fluid overload including congestive heart failure, pulmonary edema, and new pleural effusions (12, 15, 17, 20). A case-control study found positive fluid balance to be an independent risk factor for VAEs (30) and a randomized controlled trial has demonstrated that conservative fluid management can significantly decrease the incidence of VAEs.(71) These observations mirror the increasing recognition in the critical care community that excess fluids may increase morbidity and mortality, particularly in the post-resuscitation phase of severe sepsis and/or during ventilator weaning.(72-76) Positive fluid balance is also a risk factor for ARDS and may potentiate risk for pneumonia.(71, 77, 78)

The Fluid and Catheter Treatment Trial (FACTT) showed that conservative fluid management is associated with more ventilator-free days in patients with ARDS.(79) Emerging studies suggest that conservative fluid management during ventilator weaning can also increase ventilator-free days in patients without ARDS.(80) Mekontso Dessap and colleagues, for example, randomized patients to daily B-type natriuretic peptide (BNP) level measurements versus usual care to guide fluid management during weaning from mechanical ventilation.(80) Patients randomized to daily BNP levels were given more diuretics and achieved greater median negative fluid balances (-2,320ml vs -180mls). This was associated with less time to extubation and more ventilator-free days. The investigators subsequently applied VAE criteria to their dataset and found that the incidence of VAEs was 50% lower amongst patients randomized to daily BNP levels.(71)

It is not clear how best to operationalize conservative fluid management into routine care. The FACTT trial utilized a complicated protocol that specified different management strategies for 20 different permutations of central venous pressure, pulmonary-artery occlusion pressure, mean arterial pressure, urinary output, and cardiac index or clinical examination findings.(79) The complexity of this protocol limits its generalizability to routine practice for all patients. Daily BNP levels are attractively simple by comparison, however BNP levels can be difficult to interpret in patients with renal impairment, a common condition in critically ill patients. The FACTT investigators recently published a simplified protocol that may prove easier to implement (Table 2).(81) While the simplified protocol appears promising, it has not yet been tested in patients without ARDS and its impact on VAEs is unknown. In addition, the original FACTT protocol was associated with higher rates of long-term cognitive impairment amongst survivors of ARDS.(82) It will be important to assess whether this risk extends to patients without ARDS as well.

Strategy #6: Conservative blood transfusion thresholds

Blood transfusions are associated with increased risks for both pulmonary edema and ARDS (66, 77, 83-85), two of the four conditions responsible for most VAEs. Blood transfusions can also lower immunity and increase risk for serious infections, including pneumonia, a third condition responsible for many VAEs.(86) First principals therefore suggest that conservative transfusion strategies may lower VAE rates. There have not been any interventional trials thus far specifically evaluating the association between blood transfusions and VAE risk, however, there are ample trial data suggesting that conservative

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transfusion thresholds are safe (85-91) and potentially beneficial for many patients with the possible exception of those convalescing after cardiac surgery.(92) Studies specifically evaluating the impact of conservative transfusion thresholds on VAEs are needed.

Common VAP prevention strategies unlikely to prevent VAEs

Two interventions frequently included in ventilator bundles are unlikely to prevent VAEs: oral care with chlorhexidine and subglottic secretion drainage. Both of these strategies have been associated with lower VAP rates but the balance of evidence suggests that these interventions primarily lower the frequency of false positive VAP diagnoses attributable to oropharyngeal colonization and/or high volumes of secretions. A meta-analysis of oral care with chlorhexidine reported lower VAP rates in open-label studies but not in double-blind studies.(93) Furthermore, oral care with chlorhexidine did not decrease ventilator days, ICU length-of-stay, or mortality. Indeed, oral care with chlorhexidine has been associated with possible *increases* in mortality.(93, 94) Likewise, two recent meta-analyses of subglottic secretion drainage failed to demonstrate any decreases in ventilator days, ICU days, or mortality.(95, 96) One randomized controlled trial of subglottic secretion drainage included both VAP and VAE as outcomes: there was a significant decrease in VAPs but no change in VAEs, ventilator days, or ICU days suggesting that the drop in VAPs may have been cosmetic.(97)

Elevating the head of the bed

Elevating the head of bed of critically ill patients is now ubiquitous in U.S. practice. Almost 99% of hospitals report routinely using semi-recumbent positioning to prevent VAP.(98)

Notwithstanding the very high adoption rate for this intervention, the evidence base supporting head-of-bed elevation is sparse. Observational studies suggest that the supine position may be a risk factor for VAP.(99) Randomized controlled trial data are more limited; only 3 trials with a collective enrollment of 337 patients have been published.(100-102) One of the 3 trials reported a significant decrease in VAP rates, the other two did not. Multiple studies attest to the practical challenge of continually maintaining patients in a semi-recumbent position.(102-105) Some investigators hypothesize that the lateral recumbent position may be a more effective strategy to prevent VAP.(106, 107) To the extent that head-of-bed elevation may protect against VAP it may also protect against VAEs. Indeed, investigators from Japan found an association between head-of-bed elevation and fewer VAEs (OR 0.26, 95% CI 0.07-0.91) after adjusting for age, sex, chronic disease, sedative interruptions, and duration of intubation (personal communication: Kimitaka Tajimi, Akita University Hospital, Japan). There is little basis from currently available data to prioritize elevating the head of the bed to prevent VAP or VAE but neither is there any urgency to disrupt current practice given possible benefit, no cost, and minimal evidence of harm. Further study is warranted.

Choosing the right denominator for VAE surveillance

Hospital safety monitoring programs have traditionally reported VAPs per 1000 ventilator-days. Ventilator-days may not be the best denominator to track VAE rates, however, because the most effective strategies to prevent VAEs likely also decrease mean duration of mechanical ventilation. If VAE rates are tracked using ventilator-days as the denominator, these interventions are liable to shrink the denominator and precipitate a paradoxical

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increase in observed VAE rates. Tracking VAEs using episodes rather than ventilator-days as the denominator can help avert this problem. The CDC Prevention Epicenters' Wake Up and Breathe Collaborative highlighted this issue insofar as they observed no change in the risk of VAEs per ventilator-day but a significant decrease in VAEs per episode of mechanical ventilation.(46) CDC recently modified their VAE reporting rules to allow hospitals to use episodes in addition to ventilator-days as denominators.

VAE prevention and best practices in critical care

All of the VAE prevention strategies proposed in this review are congruent with widely-accepted best practice initiatives including the ABCDE bundle, the Choosing Wisely Campaign, the Society of Critical Care Medicine's Pain-Agitation-Delirium Guidelines, the Surviving Sepsis Campaign, and the Society for Healthcare Epidemiology of America's Strategies to Prevent Ventilator-Associated Pneumonia (Table 3).(108-112) The congruence between practices likely to prevent VAEs and the practices recommended by these initiatives suggests that VAE surveillance may be able to serve as an objective metric to monitor the progress and impact of quality improvement efforts inspired by these campaigns.

VAE surveillance may also help hospitals identify further opportunities to improve practice beyond the strategies included in current best practice guidelines. VAE surveillance identifies a specific event that providers can analyze to identify additional institution-specific risk factors for deterioration that are not included in current bundles. For example, root cause analyses of VAEs may identify intra-hospital transportation, use of

portable ventilators, inadequate PEEP for obese patients, poor endotracheal tube cuff pressure monitoring, failure to stop tube feeds during bed position changes, poor intraoperative ventilator management, low hand hygiene rates, and/or failure to create and adhere to institutional guidelines to manage ventilators as underappreciated areas for additional improvement. Some VAEs may paradoxically be caused by mid-course improvements in care (for example, a new provider on service may elect to increase PEEP in order to decrease FiO2) but in that case it may allow for review of institutional practices and protocols governing ventilator management. Not every VAE will yield lessons to be learned – indeed it is likely that some VAEs are unavoidable manifestations of respiratory deterioration and not preventable – but on the aggregate they appear to offer a focus and a pathway to identify possible opportunities to improve care.

Criticisms of VAE

Concerns have been raised about the potential utility of VAE definitions for hospital quality and safety programs.(113-116) These fall into four categories: 1) most VAEs are not pneumonias, 2) VAE surveillance misses many pneumonias, 3) VAE surveillance is susceptible to gaming and variable case finding, and 4) there is scant evidence that VAEs are preventable.

The observation that most VAEs are not pneumonias is consistent with CDC's intent to expand the focus of surveillance to include additional potentially preventable complications in mechanically ventilated patients. Whether this broader focus will lead to broader prevention efforts and hence better outcomes for ventilated populations remains

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to be determined. Nonetheless, work to date on VAE risk factors and prevention has affirmed ARDS and fluid overload as important causes of morbidity that are not well addressed by most current ventilator bundles and therefore suggest the wisdom of expanding ventilator bundles to include low tidal volume ventilation, early mobility, conservative fluid management, and conservative transfusion thresholds.

The concern that VAE surveillance misses many pneumonias highlights the tension between surveillance versus clinical diagnosis. The emphasis in clinical care is on sensitivity. Clinicians cannot afford to miss serious diagnoses, even if this comes at the cost of initially over-diagnosing and over-treating some patients.(117) Surveillance metrics, by contrast, are designed to give population level insights into major sources of morbidity that can then be used to inform population level interventions to be applied to all patients. The emphasis in surveillance is on objectivity, reproducibility, efficiency, and morbidity. VAE surveillance follows this paradigm insofar as the requirement for sustained increases in ventilator settings simultaneously facilitates the possibility of objective surveillance and sets a threshold effect for severity of illness. Only the most severe pneumonias that lead to sustained increases in ventilator settings qualify as VAEs. Nonetheless, pneumonias consistently constitute 25-40% of VAEs and hence quality improvement initiatives designed to prevent VAEs must necessarily include strategies to prevent pneumonias. These strategies will be applied to all patients and hence they are as likely to protect patients against mild pneumonias that might never have triggered VAE criteria as they are to protect against more severe pneumonias that could trigger VAEs.

Other observers have noted that VAE surveillance is susceptible to variability and gaming. Klein Klouwenberg and colleagues demonstrated that VAE case finding varies depending on whether one defines daily minimum PEEPs and FiO2s using minute-to-minute ventilator settings, hourly values abstracted from patients' flowsheets, or 10th percentile values.(12) CDC subsequently clarified, however, that if one uses minute-to-minute ventilator settings for VAE surveillance that the daily minimum PEEP and FiO2 are defined as the lowest values the patient was able to sustain for at least an hour. Mann and colleagues compared manual versus computer-based VAE surveillance in 4 hospitals. The three manual surveyors in the study missed between 18 and 54% of VAEs relative to the automated surveillance system.(118) Lilly and colleagues suggested that one can game away the majority of VAEs by alternately raising and lowering patients' PEEP by 1cm H2O each day.(13) This will preclude a stable baseline and thereby eliminate the possibility of VAEs using PEEP criteria. There is no clinical rationale, however, for alternately raising and lowering PEEP by 1cm H2O each day hence it is clear that anyone applying this strategy is only interested in avoiding VAE detection. Setting aside the lost opportunity to analyze individual VAEs to discover possible opportunities to improve care, if VAE ever becomes a formal quality metric then manipulation of this sort could risk audit and sanction.

Finally, some authors have wondered what fraction of VAEs is preventable. Boyer and colleagues, for example, audited all VAEs in their facility for a year and estimated that only 37% were potentially preventable.(20) Retrospectively estimating preventability, however, is difficult. A better guide to preventability is prospective interventional studies. More data on this question are needed but the few intervention studies to date are encouraging.

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The Canadian Critical Care Trials Group reported an 29% decrease in VAEs by increasing concordance with ventilator guidelines, the CDC Prevention Epicenters' Wake Up and Breathe Collaborative reported a 37% decrease in VAEs through enhanced adoption and performance of SATs and SBTs, Drees and colleagues reported a 42% decrease in VAEs through optimization of PEEP, and Mekontso Dessap and colleagues found that depletive fluid management during ventilator weaning was associated with a 50% decrease in VAEs.(18, 46, 71, 119)

The role of VAE surveillance in quality improvement programs

There are too few data at present to be confident that VAE surveillance will be a net benefit to hospitals and to patients. Unless and until we have such evidence it will be premature to designate VAE as a formal quality metric in pay for performance programs. Nonetheless, the data thus far are promising. VAE surveillance brings to light a broad set of patients suffering morbid events while on mechanical ventilation including many complications aside from pneumonia. VAE surveillance therefore invites hospitals to expand their prevention programs to address the broader array of complications identified through VAE surveillance. Potential strategies to prevent VAEs include avoiding intubation, minimizing sedation, coordinated daily SATs and SBTs, early mobility, low tidal volume ventilation, conservative fluid management, and conservative transfusion thresholds. Root-cause analyses may suggest additional approaches to improve care for specific hospitals or populations. Ultimately, the success or failure of VAE definitions hinges upon the extent to which they are able to catalyze better care and outcomes. There is consequently a pressing need for further interventional studies to better define how best to prevent VAEs and the

extent to which VAE surveillance and prevention programs can improve patient-centered outcomes.

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Table 1. Clinical events associated with ventilator-associated events (VAEs)

	Klompas et al. 2011* (N=44)	Hayashi et al. 2013 (N=153)	Klein Klouwenberg et al. 2014* (N=81)	Kollef et al. 2014 (N=67)	All Studies Combined* (N=345)
Pneumonia and/or aspiration	10 (23%)	66 (43%)	28 (35%)	21 (31%)	125 (36%)
Pulmonary edema, pleural effusion, and/or heart failure	8 (18%)	40 (26%)	39 (48%)	10 (15%)	97 (28%)
Atelectasis	5 (11%)	25 (16%)	12 (15%)	6 (9.0%)	48 (14%)
Acute respiratory distress syndrome	7 (16%)	10 (6.5%)	-	14 (21%)	31 (9.0%)
Mucous plugging	1 (2%)	-	-	-	1 (0.3%)
Abdominal distension / compartment syndrome	1 (2%)	2 (1.3%)	9 (11%)	-	12 (3.5%)
Pulmonary embolus	1 (2%)	3 (2.0%)	-	-	4 (1.2%)
Pneumothorax	-	-	2 (2.5%)	2 (3.0%)	4 (1.2%)
Radiation pneumonitis	1 (2%)	-	-	-	1 (0.3%)
Sepsis syndrome / extra-pulmonary infection	1 (2%)	-	9 (11%)	3 (4.5%)	13 (3.8%)
Poor pulmonary toilet	1 (2%)	-	-		1 (0.3%)
Acute neurological event	-	-	10 (12%)		10 (2.9%)
Transfusion-associated lung injury	-	-	-	2 (3.0%)	2 (0.6%)
Other	-	-	-	9 (13%)	9 (2.6%)
No apparent pulmonary complication	18 (41%)	17 (11%)	10 (12%)	-	45 (13%)

* Some VAEs were attributed to multiple etiologies, hence the percentages exceed 100%.

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Table 2. The simplified conservative fluid management protocol from the Fluid and Catheter Treatment Trial Lite (FACTT-Lite)(81)

Central Venous Pressure	Urine Output <0.5 mL/kg/hr	Urine Output ≥0.5 mL/kg/hr
>8	Furosemide, reassess in 1 hour	Furosemide, reassess in 4 hours
4-8	Give fluid bolus, reassess in 1 hour	Furosemide, reassess in 4 hours
<4	Give fluid bolus, reassess in 1 hour	No intervention, reassess in 4 hours

Adapted from Grissom et al. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome. *Crit Care Med* 2015;43:288-295.

Table 3. Overlap between proposed strategies to prevent VAEs and established best practice initiatives for critically ill patients.

	ABCDE (108)	Choosing Wisely Campaign (109)	Pain, Agitation, Delirium Guidelines (110)	Surviving Sepsis Campaign (111)	Strategies to Prevent Ventilator-Associated Pneumonia (112)
Minimize sedation	✓	✓	✓	✓	✓
Paired daily SATs and SBTs	✓	✓	✓	✓[a]	✓
Early exercise and mobility	✓		✓	✓[b]	✓
Low tidal volume ventilation				✓[c]	
Conservative fluid management				✓[c]	
Conservative transfusion thresholds		✓		✓	

[a] daily sedative interruptions are cited as one potential strategy to minimize sedation, regular spontaneous breathing trials are recommended to "to evaluate the ability to discontinue mechanical ventilation"
[b] the guidelines stipulate that "early physical rehabilitation should be a goal"
[c] in patients with ARDS

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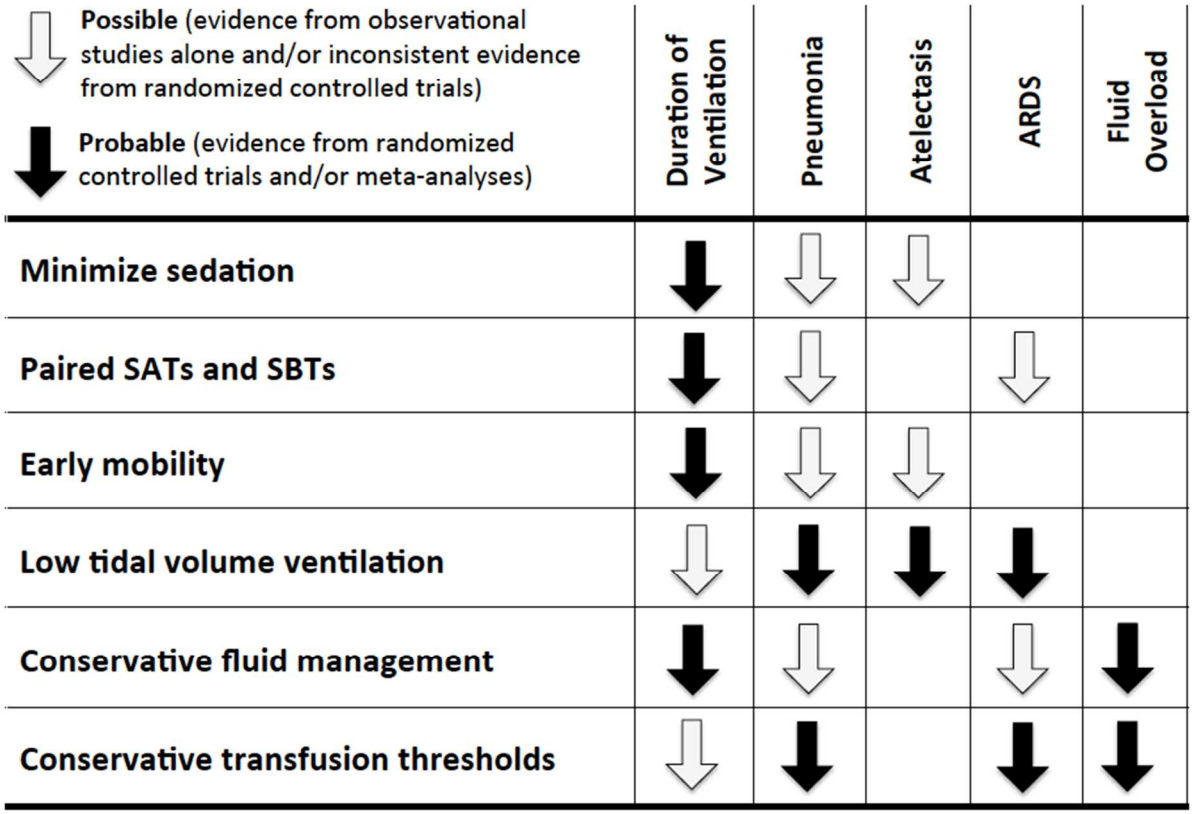
Figure 1. Ventilator-associated events (VAEs). VAEs are defined by trajectory changes in patients' ventilator settings using either positive end expiratory pressure (PEEP) or fraction of inspired oxygen (FiO2) criteria:

1. ≥2 days of stable or decreasing daily minimum PEEP followed by an increase of ≥3cm sustained for at least 2 days *or*
2. ≥2 days of stable or decreasing daily minimum FiO2 followed by an increase of ≥20 points sustained for at least 2 days

Date	PEEP (min)	FiO2 (min)
Jan 1	10	100
Jan 2	5	50
Jan 3	5	40
Jan 4	5	40
Jan 5	8	60
Jan 6	8	50
Jan 7	8	40
Jan 8	5	40
Jan 9	5	40

VAE

Figure 2. Potential strategies to prevent ventilator-associated events (VAEs). The framework to prevent VAEs reported in this paper favors interventions that a) shorten the average duration of mechanical ventilation, and b) target one or more of the four conditions that most frequently trigger VAEs. This figure demonstrates the interplay between these two objectives.



Abbreviations: ARDS – acute respiratory distress syndrome; SAT – spontaneous awakening trials; SBT – spontaneous breathing trials