Review Article

Ventilator-associated events versus ventilator-associated respiratory infections—moving into a new paradigm or merging both concepts, instead?

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Contributions: (I) Conception and design: None; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Despite ventilator-associated respiratory infections (VARI) are reported as the most common and fatal complications related to mechanical ventilation (MV), they are not the unique occurrences. The new classification of ventilator-associated events (VAE) proposed by the centers for disease control and prevention (CDC) enhance the spectra of complications due to MV including both infection-related and non-infectious events. Both VAEs and VARIs are associated with prolonged duration of MV, longer stay in hospital and in the intensive care unit (ICU) and more antibiotic consumption, nonetheless patients with VAEs have worst outcomes. The VARI and VAE algorithms are focused on different targets and the correlation between both classifications is shown to be poor. The diagnostic criteria of the traditional classification have limited accuracy and the non-infectious complications may be misinterpreted as VARI. While the VAE surveillance enhances the spectra of MV complications but excludes less severe VARIs. Noninfective events explain up to 30% of VAEs, the main causes being atelectasis, acute respiratory distress syndrome, pulmonary edema and pulmonary embolism. The bundles assessing VAE are associated with less incidence of VAP and improved outcomes but they fail to reduce the rates of VAE. Automated VAE surveillance is efficient and useful as a quality indicator in the ICU while the differences in the interpretation of VARI criteria limit its role in the design of global protocols and preventive strategies. We suggest that a more comprehensive strategy should combine both algorithms with emphasis on clinical outcomes.

Keywords: Intensive care unit (ICU); mechanical ventilation (MV); ventilator-associated events (VAE); ventilator-associated pneumonia (VAP); ventilator-associated respiratory infections (VARI)

Submitted Sep 15, 2018. Accepted for publication Oct 21, 2018.
doi: 10.21037/atm.2018.10.54
View this article at: http://dx.doi.org/10.21037/atm.2018.10.54

Introduction

Since the first report in 1967 by Ashbaugh and Cols (1), the knowledge about the complications related to mechanical ventilation (MV) is constantly evolving. Traditionally the ventilator-associated respiratory infections (VARI) have been reported as the commonest complications of MV and there is a large body of literature assessing its clinical relevance and association with worse outcomes (2-4). Despite this, the complications of MV extend beyond the ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) and the role of non-infective events in mechanically ventilated patients is less known. In 2013, and later the MV complications

were redefined by the Centres for Diseases Control and Prevention (CDC) (5,6), the fraction of inspired oxygen (FiO_2) and the positive end expiratory pressure (PEEP) were incorporated as surrogated measures of hypoxemia, the chest radiograph was disregarded as diagnostic criteria and both infective and noninfective complications were included in the surveillance. The VAE surveillance (5,6) divided MV complications into three tiers: (I) ventilator-associated condition (VAC), (III) infection-related ventilator-associated complication (IVAC), and (II) possible ventilator-associated pneumonia (PVAP). IVAC and PVAP were subsequently encompassed as IVAC-plus events in the latest update of VAE definitions (7). Detailed definitions of VARIs and VAEs are presented in the *Table 1*. The studies assessing VAE support its ability to detect noninfective complications and its good correlation with worse outcomes in both adult and paediatric patients but also highlight many undiagnosed VAPs and VATs (8,10-13). In this review we discuss the advantages and disadvantages of both classifications.

VAE, VARI and diagnostic criteria: strengths and weaknesses

Although VAE and VARI classifications are designed to detect MV complications, both have different targets and use different diagnostic criteria. While VARI algorithm uses the chest X-Ray to classify the pulmonary infections, an unreliable and non-specific tool in ventilated patients, the VAE surveillance criteria disregard this test and redirect the focus on the respiratory worsening by monitoring the changes in two ventilator parameters: FiO_2 and the PEEP. A detailed comparison between the pros and cons in both classifications is presented in *Table 2*.

Chest X-ray

While the chest X-ray is the cornerstone to diagnose VAP, its interpretation in the critically ill patient is limited (13,31,32). Many complications such as ARDS, pulmonary edema, atelectasis and pulmonary embolism may be misinterpreted as respiratory infections by chest X-ray (12,32) and lead to an unnecessary antibiotic treatment. A potentially significant variation in perceived VAP rates has been reported depending on the frequency of other non-infective conditions by using a mathematical model in which the rate of VAP in an ICU is kept constant while the rates of other non-infective conditions are varied (15). On the other hand, the likelihood of VAP lowers to 0.35 in the absence of a new infiltrate on the chest X-ray (14) and most patients with possible VAP (PVAP) do not meet the X-ray criteria for traditional VAP (22,23). The exclusion of the radiological findings as diagnostic criteria increases the objectivity and comparability of VAE surveillance but limits its capability to detect less severe conditions as respiratory events in initial stages and some VATs, which could benefit from prompt antimicrobial treatment (23,33).

Clinical criteria

Clinical criteria by CDC-2008 for VAP are nonspecific in ventilated patients. In fact, they have been using the same criteria for hospital-acquired pneumonia in non-ventilated patients. Some of their clinical items are focused on detecting an increase in the work of breathing: cough, dyspnea, and tachypnea which have limited relevance in mechanically ventilated and sedated patients. As for patients subjected to spontaneous modes of ventilation, these items are highly variable depending on few ventilator setting parameters (pressure support, triggering) and a good clearance of respiratory secretions; Thus, it is difficult to differentiate between patient-ventilator dys synchrony and a real respiratory worsening by itself only through the criteria set in the definitions (34,35). On the other hand, wheezing, rales and particularly bronchial sounds are frequently observed in ventilated patients due to a lack of secretion clearance. Finally, the worsening in gas exchange is not well defined.

In 2012 a simplified CDC-2008 criteria was proposed for ventilator-associated respiratory infections avoiding all the non-specific clinical criteria in ventilated patients, and including VAT and microbiological criteria (36). It is noteworthy that these simplified criteria included purulent secretions and provide objective data to define them. However, the respiratory worsening was not properly redefined and it continued to be a subjective item with different interpretations.

The VAE algorithm focuses primarily on the respiratory worsening as a key finding in the definition of VAC. Less severe episodes would be systematically excluded. On the other hand, in case of an infectious episode it shares with the old definition the more powerful clinical criteria by adding the condition of a minimum of 4 days of antimicrobial therapy thus avoiding inclusion of some non-infectious events that can mimic VARIs. This is a marked improvement compared to the previous definition but it continues to have some weaknesses in the new algorithm.

Table 1 Comparison between ventilator-associated infection definitions (5,6,8,9)

Diagnostic criteria	VARI[a] (CDC 2008)		Infective events of VAE (CDC 2013)	
	VAT	VAP	PVAP	IVAC-plus
Clinical	Suspicion of infection[g]	One of the following: worsening gas exchange[k]; tachypnea or dyspnea; change in sputum characteristics[l]; rales or bronchial breath sounds; apnea in pediatric patients	Increase in FiO_2 ≥0.20 or in PEEP ≥3 cmH_2O with a previous period of stability or improvement ≥2 days	Increase in FiO_2 ≥0.20 or in PEEP ≥3 cmH_2O with a previous period of stability or improvement ≥2 days
	In infants ≤1 year old: respiratory distress; apnea; bradycardia[h]	And at least one: suspicion of infection[g]; altered mental status in adults ≥70 years old; bradycardia[h] or tachycardia[m] in infants ≤1 year old	And suspicion of infection[g]	And suspicion of infection[g]
			And beginning of a new antibiotic	And beginning of a new antibiotic
			Pediatric patients: increase in FiO_2 ≥0.20 or in PEEP ≥1 cmH_2O or increase in FiO_2 ≥0.15 plus PEEP ≥1 cmH_2O with a previous period of stability/ improvement ≥1 day	
Chest X-ray	Absence of radiologic criteria for pneumonia	New or progressive infiltrate, consolidation or cavitation	Not included	Not included
		Pneumatocele in infants ≤1 year old		
Microbiology	Purulent sputum[i] and positive endotracheal aspirate culture[j]	Significative growth of a pathogen in respiratory samples[j]	Significative growth of a pathogen in respiratory samples[j]	Not included
		>5% Cells with intracellular bacteria in bronchoalveolar lavage	Insufficient growth of a pathogenic microorganism plus purulent sputum[i]	
		Pathogenic microorganism in pleural fluid cultures	Pathogenic microorganism in pleural fluid cultures	
		Histopathologic evidence of lung infection[n]	Histopathologic evidence of lung infection[n]	
		Positive growth in blood culture[o]	Positive test for pathogenic virus in respiratory samples	
			Positive test for Legionella species	

[g], suspicion of infection: fever (≥38 ℃) or hypothermia (≤36 ℃) or leukocytosis (≥12,000 cells/mL in adults or ≥15,000 cells/mL in ≤12 years old) or leukopenia (≤4,000 cells/mL); [h], bradycardia in children ≤1 year old: <100 beats per minute; [i], purulent sputum: ≥25 neutrophils with <10 squamous epithelial cells per low power field; [j], significative growth in respiratory samples: endotracheal aspirate: $\geq 10^5$ CFU/mL, bronchoalveolar lavage: $\geq 10^4$ CFU/mL, lung tissue: $\geq 10^4$ CFU/g, protected specimen brush: $\geq 10^3$ CFU/mL; [k], worsening gas Exchange: Increased oxygen requirements or in ventilator demand (mandatory criteria for infants ≤1 year old); [l], change in sputum characteristics: New onset of purulent respiratory secretions or increase in its production or in suctioning requirements; [m], tachycardia in infants ≤1 year old: >170 beats per minute; [n], histopathologic evidence of lung infection: abscess formation or foci of consolidation with intense polymorphonuclear accumulation or positive quantitative culture of parenchyma or evidence of parenchyma invasion by fungus or virus; [o], in absence of other recognized focus. VARI, ventilator-associated respiratory infection; VAE, ventilator-associated events; VAT, ventilator-associated tracheobronchitis; VAP, ventilator-associated pneumonia; PVAP, possible-ventilator associated pneumonia; IVAC-plus, infectious-ventilator associated complication plus.

Table 2 PROS and CONS of VAE and VARI definitions

PRO/CON	VAE	VARI	References
Clinical correlation	+++	++	(14-17)
Physician-friendly concept	–	+++	(12,18,19)
Objectiveness (kappa index)	+++	+	(15,17,18,20,21)
Sensibility	–	+++	(11,12,22-24)
External comparability	+++	+	(15,25)
Diagnosis of VAT	–	+++	(8,10-12,22)
Diagnosis of VAP	–	+++	(8,10-13,17,22,23)
Non-infective events	+++	–	(8,10-13,15)
Impact on outcomes	+++	++	(2,8,12,21,24,26,27)
Surveillance	+++	++	(25,28-30)
Quality indicator	+++	+	(11,21,25,30,31)
Histological findings	NA	+	(9,14,16)

VAE, ventilator-associated event; VARI, ventilator-associated respiratory infection. +++, good; ++, fair; +, poor; –, none.

The use of early empiric antibiotics for the management of suspected sepsis and septic shock is a standard of care nowadays and is crucial for better clinical outcomes (37). Thus, it is easy to understand that, in clinical practice IVAC-plus will additionally include any respiratory worsening due to non-respiratory infections. Antimicrobial initiation might also be a response to an increase in acute phase reactants which cannot differentiate respiratory and non-respiratory focus of infection. Moreover, the rate of IVAC-plus will depend on the attending physician's decision to continue antibiotics for the next four days, strength of his clinical suspicion, the patient's clinical response, availability, speed and reliability of microbiological results (38,39) and the antibiotic de-escalation policies of each centre (20,40).

Microbiological criteria

There are few limitations in the interpretation of VARI diagnosis (41) in areas such as the role of quantitative cultures especially when not coupled with a respiratory worsening, and the nature respiratory samples are still a matter of controversy (9). Up to 44% of patients with VAP diagnosis do not have histological criteria of pneumonia (16,17). In the VAE algorithm, some PVAP microbiological criteria are similar to VAP/VARI but its specificity increases because the criteria of respiratory worsening is fulfilled in all cases. Even though, some cases of PVAP can be misinterpreted due to previous colonization in patients with chronic and persistent purulent secretions and in those with other non-respiratory infection.

Clinical correlation of VAE

The first tier of the CDC-2013 algorithm, the VAC, explain up to 30% of VAEs in adults (10,12) and about 45% in children (8), the main causes being atelectasis, ARDS, pulmonary edema, and pulmonary embolism (4,12,24). They also are named in clinical practice as the non-infective events. Children differ from the adult population in that most of these VAC are due to atelectasis whilst frequent causes of VAC in adults are ARDS and pulmonary edema that are uncommon in the pediatric population (26,42). This goes in line with the epidemiology of complications described in ventilated-children (43). On the other hand, these non-infective episodes are not considered in the VARI classification but frequently they are misdiagnosed as VAP due to the misinterpretation of chest X-ray, as it has been pointed earlier.

At this point, it should be noted that some confusion has been generated in the literature due to the inappropriate application of the terms designed by the CDC. Frequently VAE are referred as VAC while VAC include only those events with respiratory worsening. While it is true that all VAE (VAC, IVAC, and PVAP) meet criteria for VAC, the

term VAC is reserved only for those events with respiratory worsening thus excluding IVAC and PVAP events. VAE and not VAC, encompasses VAC, IVAC and PVAP. The different tiers of VAE should be cautiously interpreted while studying and interpreting the clinical correlations and outcomes.

The second tier of the CDC-2013 algorithm, the infection-related ventilator-associated complications (IVAC) was designed to detect those respiratory worsening due to an infectious agent but not microbiologically confirmed as respiratory origin. Thus, it refered to those respiratory conditions possibly leading to sepsis excluding probable ventilator-associated pneumonia. Once again, there has been some confusion in the use of the term IVAC in the scientific literature. Most studies referred to it as the sum of IVAC and probable VAP (PVAP). The last update of the new algorithm solved this problem adding a new concept in the algorithm: the IVAC-plus events.

Finally, the third tier of the new algorithm, the probable ventilator-associated pneumonia (PVAP) seemed to resolve confusions about VAP. It has a good negative predictive value but its sensitivity is low thus excluding most VAP. On the other hand, in case of electronic surveillance, it is possible to misclassify any respiratory worsening as PVAP in patients with previous airway colonization when the antibiotic policy of the hospital is weak.

Clinical correlation of VARI

The VARI classification is widely recognized by the health care professionals and its association with worse clinical outcomes is well known (2,4,27). It has long been considered the standard of diagnosis of the respiratory infections related to MV (2,4,18). Sometimes the clinical and radiologic criteria for VARI can be explained by more than one cause including non-infective conditions (10,12), the prevalence of VAP can increase up to 5-fold depending on the frequency of noninfective complications as ARDS, atelectasis or pulmonary edema due to a misinterpretation of the X-chest ray (15). Due to subjectivity in the interpretation of the chest X-ray and in the clinical manifestations, the inter-observer variability when the VARI diagnostic algorithm is used is high (Kappa 0.4) (14,17). As a result, the real incidence of VARIs is not clear (18). Even the anatomopathological studies taking the autopsy and the lung biopsy findings as gold standard, up to 44% of patients with VAP diagnosis did not have histological criteria of pneumonia (14,16).

Ventilator-associated tracheobronchitis (VAT)

In the recent years there is accumulating evidence supporting VAT as a clinically important nosocomial infection by its own right in children and adults with different impact on outcomes compared to VAP (9,44-47). Although VAT and VAP may overlap, these are two newly recognised different conditions. On one hand, the adequate antimicrobial treatment of VAT has demonstrated to protect against the development of subsequent VAP and decreased MV days and ICU stay (44,45,47,48). On the other hand, in clinical practice not all VAP are preceded by VAT and not all VAT progress to VAP (45,47,48). Additionally, few translational researchers have reported different patterns of microbiome and adaptive responses when comparing VAT and VAP (49,50). Thus, a new entity is ensuing in the coming years and the need for antibiotic prescription is a hot topic in those patients.

Clinical correlation between VARI and VAE

A poor correlation between VAP and VAE is supported by several studies. This seems logical as both VAP and VAE have different targets, as discussed above. Maybe the designation of VAE as the "new CDC definition of VAP" has arisen confusion about the new concept and strong rejection by some authors. While it's obvious that VAP is not the same as VAE, there is an increased interest in VAE due to its inclusion of diverse complications related to mechanical ventilation. Studies comparing both VARI versus VAE report an increase in the rate of complications when the new criteria are assessed (10,12,24), which was expected; however, in a meta-analysis (24) including more than 6,000 patients, VAE failed to detect VAP in almost 50% of cases. Despite excluding non-infectious complications among VAE, the rates of PVAP and even IVAC-plus rates were lower than traditional VARI (12,24). Two retrospective analysis assessing complications of mechanical ventilation in both European (10) and North American (11) ICUs reported that those patients who had IVAC-plus were more likely to be diagnosed with VAP but a significant number of VAP were not diagnosed as IVAC-plus.

Moreover, diagnosis of VAT has been omitted in the VAE algorithm, although it could be included in the PVAP tier. In the European VAE surveillance multicentric study 1/3rd of adult mechanically ventilated patients developed VARIs, 60% of them were due to VAT (29.3 per 1,000 ventilatory

days) but only 25% of those VAT achieved VAE criteria (12). A significant percentage of cases of VAP without the time frame required by the VAE classification have been reported in medical (71%) and traumatic (82%) patients (22,51), interestingly these rate decreases to 39% in surgical ICUs. Additionally, some series report a negative predictive value for VAE and PVAP nearly to 100% (12,22,24).

Thus, the VAE classification only detects those complications severe enough to produce a sustained respiratory worsening and almost 25% of VARI can be missed (10,12,22,24), most of them by not fulfilling the time frame required by the VAE classification (22,51). Because of it, the power of the VAE algorithm to detect VAT is limited too. Interestingly, a recent study in children found a fourfold increase in VAEs and the double of PVAP when less restrictive criteria for respiratory worsening were employed, and keeping the repercussion on outcomes of this less restrictive VAE definition when compared with traditional VARI criteria (8).

VAE, VARI and surveillance

The reports about VARI incidence are highly variable with rates between 2 and 18 episodes per 1,000 ventilator days (9,19,52-54) and surprisingly, in some series the prevalence of VAP is zero (24,55). In contrast, the VAE algorithm was designed to define more objective and comparable criteria and to enhance the spectra of complications related to MV. The lack of consensus limits the role of VARI in the design of global protocols and preventive strategies. While the VARI criteria are difficult to quantify and compare, the VAE paradigm is measurable, reproducible and its implementation in automated surveillance programs reduce the time spent by more than 90% with higher sensitivity and specificity (28,29) along with being a good quality indicator for benchmarking in the ICUs (25,30,31).

VARI and VAE risk factors and prevention

Despite a growing body of knowledge, the role of risk factor and its prevention in the development of VAE is not completely understood particularly in adults where the evidence is weak or controversial (31,56,57). The length of MV is a limiting factor for the development of both VARIs and VAEs therefore early weaning practices including spontaneous breathing, daily awakening trials and an adequate control of pain are highly advised (31,58). Deep and prolonged sedation is correlated with more MV days and worst outcomes (31,59). The use of long-term sedatives, opioids, paralytic medications and mandatory modes of ventilation were reported as possible risk factors for IVAC-plus (60); in a recent study (61) assessing sedative exposure in patients under MV, the use of benzodiazepines was associated with less MV-free days and increased risk to develop VAE than dexmedetomidine or propofol, additionally dexmedetomidine was also associated with less time to extubation when compared with propofol. The role of spontaneous breathing trial and spontaneous awakening trial in the prevention of VAE is controversial (57,60,62,63). A positive fluid balance (64-66) is independently associated with worse outcomes in the ventilated patients especially in those with or at risk for ARDS and its association with VAP is widely reported in the literature (31,67-69); each litre of fluid accumulated increases up to 1.2 the risk of developing any kind of VAE (60). There is a reasonable evidence that protective ventilation help to prevent VAE due its association with lower rates of ARDS, VARI and atelectasis (70-72); observational data suggest that patients with VAEs are more likely to be ventilated with a non-protective strategy (56,60), the use of mandatory modes of ventilation can increase the rate of VAC by increasing patient-ventilator dys-synchrony and ventilator induced lung injury (VILI) (60), however prospective studies in the field are needed (56,73). The use of bundles of care including semi recumbent positioning, venous thromboembolism prophylaxis and stress ulcer prophylaxis were proven to reduce the incidence of VAP in the past (10,74-77), but they are not able to decrease the incidence of VAEs (31,62,78). Furthermore, in a recent study the oral care with chlorhexidine was associated with a greater risk for VAE development. Finally, in pediatric patients risk factors for developing VAEs include immunocompromised status, tracheostomy dependence, and chronic respiratory disease (21), while the presence of acute kidney injury, prolonged ventilatory support, and neuromuscular blockade were associated with an increased risk for IVAC (79).

Conclusions

The VARI and VAE classifications help to assess the ventilator-associated complications however remain to be fully elucidated. Both classifications focus on different targets, the VARI algorithm detect respiratory infection and differentiates between VAP and VAT but many non-infective-related complications also can achieve VARI criteria. The VAE surveillance enhances the spectra of MV

complications including non-infective events and select only the most severe cases whereas many VAP and VAT are dismissed. We suggest a better strategy that should combine both algorithms with the incorporation of clinical outcomes. Further studies should assess the applicability of biomarkers of pulmonary infection and molecular diagnostic techniques in the MV complications and the design of protocols incorporating the bedside thoracic ultrasound.

Acknowledgements

This article was carried out as part of a PhD program in Health Science, in the Department of Medicine, at the Universitat Autónoma de Barcelona. Supported in part by a grant (PCI Pneumonia) from CIBERES, Instituto Salud Carlos III, Madrid, Spain.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Ramirez-Estrada S, Peña-Lopez Y, Kalwaje Eshwara V, Rello J. Ventilator-associated events versus ventilator-associated respiratory infections—moving into a new paradigm or merging both concepts, instead? Ann Transl Med 2018;6(21):425. doi: 10.21037/atm.2018.10.54

