Universitat Autònoma de Barcelona

Infección Respiratoria en el Paciente Crítico: Eventos Asociados a la Ventilación Mecánica

SERGIO ANDRÉS RAMÍREZ ESTRADA

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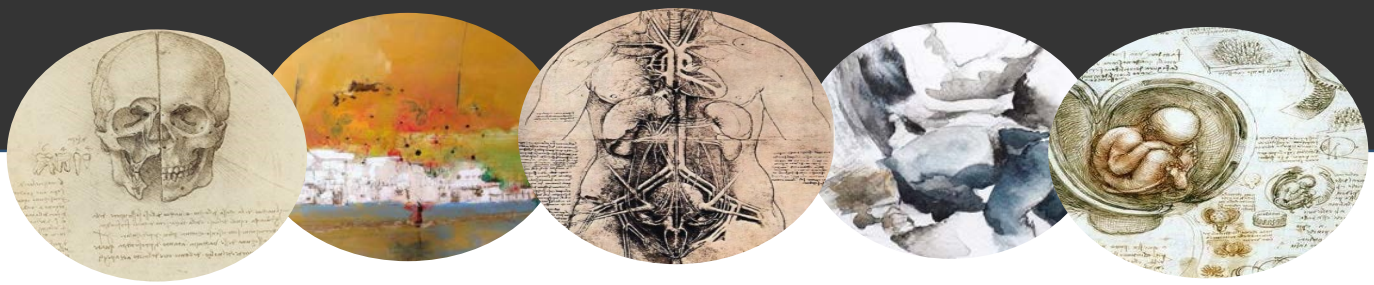

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SERGIO ANDRÉS RAMÍREZ ESTRADA
Para optar al grado de Doctor

Directores:
Profesor Jordi Rello Condomines
Profesor Benito Almirante Gragera

Tutor:
Profesor Jordi Rello Condomines

Barcelona, Mayo de 2020

Jordi Rello Condomines y Benito Almirante Gragera, Profesores Titulares de la Facultad de Medicina de la Universidad Autónoma de Barcelona.

Certifican que la tesis titulada:

Infección Respiratoria en el Paciente Crítico: Eventos Asociados a la Ventilación Mecánica

Que presenta el doctorando Sergio Andrés Ramírez Estrada se ha realizado bajo su supervisión y reúne todas las exigencias metodológicas y científicas necesarias, y autorizan su presentación para que sea defendida delante del Tribunal que corresponda

Dr. Jordi Rello Condomines
Director y tutor de la tesis doctoral

Benito Almirante Gragera
Director de la tesis doctoral

Barcelona, Mayo de 2020

ABREVIATURAS

CDC: Center for Disease Control and Prevention

FiO2: Fracción inspirada de oxígeno

IVAC: Infection-related ventilator-associated complication

IVAC-plus: Infection-related ventilator-associated complication plus

PEEP: Positive end-expiratory pressure

PVAP: Possible ventilator-associated pneumonia

SDRA: Síndrome de distrés respiratorio agudo

UCI: Unidad de cuidados intensivos

VAC: Ventilator-associated condition

VAE: Ventilator-associated event

VAP: Ventilator-associated pneumonia

VARI: Ventilator-associated respiratory infection

VAT: Ventilator-associated tracheobronchitis

Se han conservado algunas siglas en inglés con el fin de mantener la nomenclatura internacional

INDICE

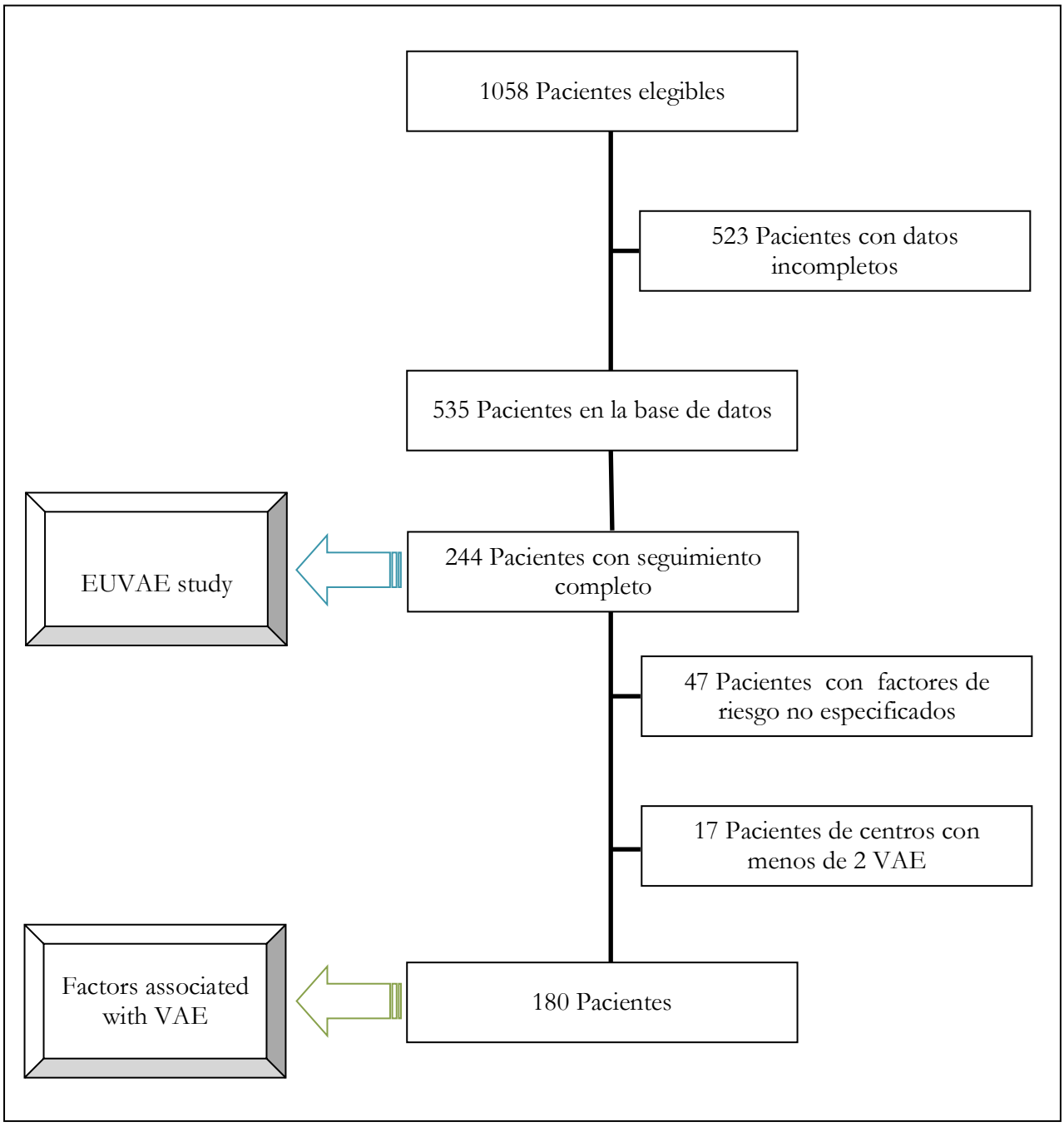
I. RESUMEN

El término VARI incluye las principales complicaciones asociadas a la ventilación mecánica: neumonía y traqueobronquitis, sin embargo esta clasificación se limita solo al espectro infeccioso excluyendo otras patologías; por otra parte la nueva clasificación de los VAE utiliza las variaciones en la FiO2 y en la PEEP como marcadores de lesión pulmonar y desplaza la radiografía de tórax como criterio diagnóstico debido a las dificultades para realizarla adecuadamente y a la alta variabilidad de su interpretación en el paciente crítico. Este nuevo enfoque tiene varias implicaciones: 1) permite diferenciar eventos infecciosos de los no infecciosos, 2) incluye patologías tanto pulmonares como sistémicas, 3) permite conocer la gravedad de la complicación independiente de su etiología, 4) el uso de variables cuantitativas permite su comparación e informatización, 5) los criterios diagnósticos familiares al personal médico, de enfermería y fisioterapia permite un abordaje precoz y multidisciplinario.

Con el fin de conocer el estado de los VAE, su aplicabilidad y correlación clínica se conformó una base de datos internacional a través de una red colaborativa en línea (http://compartint.net/euvae/), se incluyeron pacientes mayores de 18 años que recibieron ventilación mecánica durante más de 48 horas y se realizó un seguimiento diario durante 30 días o hasta finalizar la ventilación mecánica, con los datos obtenidos se llevó a cabo un estudio prospectivo observacional con 244 pacientes de 13 UCIs de 8 países valorando la presentación de VAE según la definición propuesta por el CDC y su impacto en quienes los presentaron, además se analizó su correlación con la clasificación previa (CDC 2008). Se llevó a cabo un segundo análisis retrospectivo para detectar factores asociados con VAE en el cual se incluyeron 163 pacientes con 76 episodios (34.9 VAE/1,000 días de ventilación)

La figura 1 ofrece una descripción detallada de la distribución de los pacientes incluidos en el proyecto EUVAE.

Figura 1. Distribución de los pacientes incluidos en el proyecto EUVAE



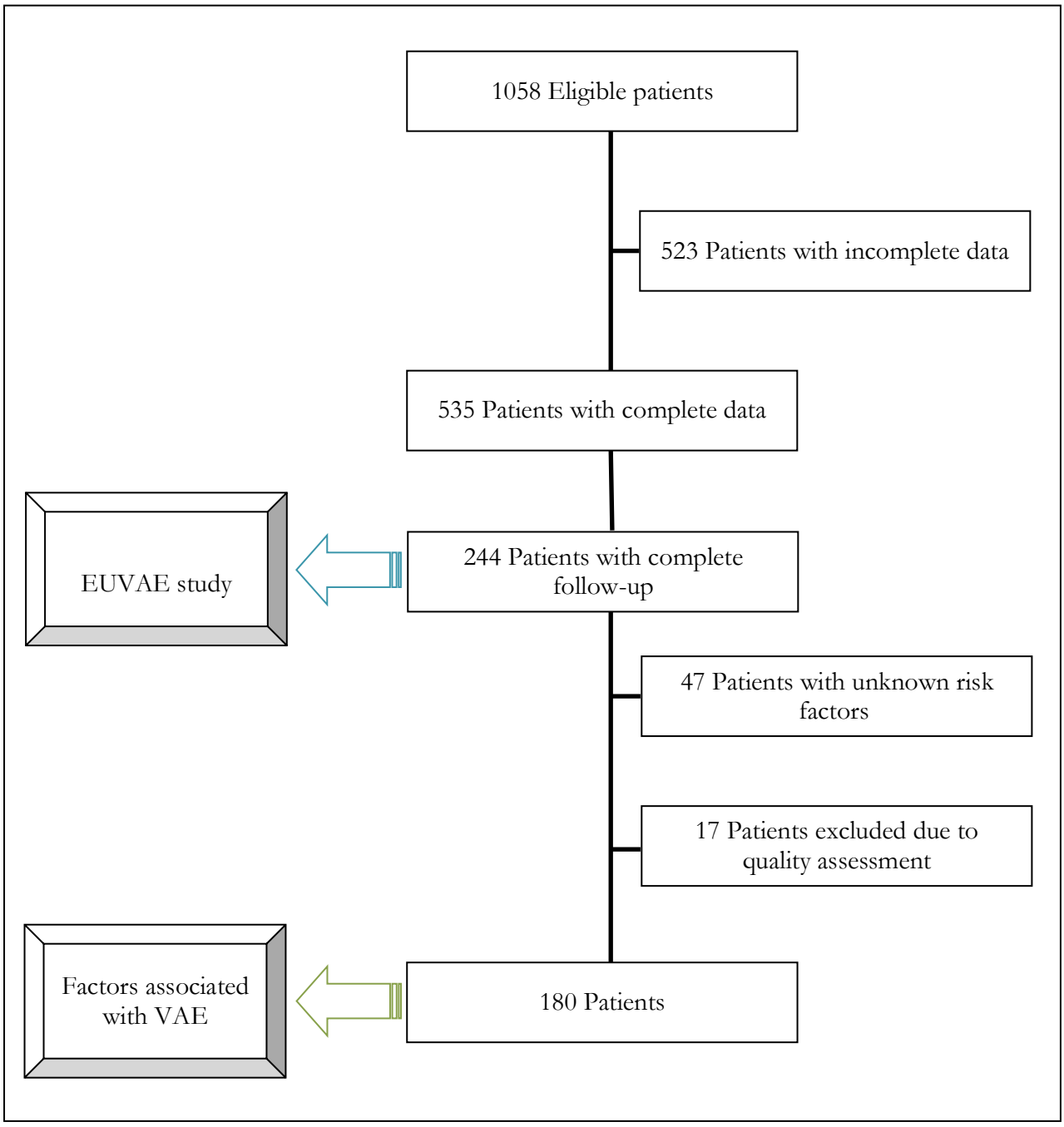
SUMMARY

A global consensus on VARI classification has been difficult to achieve, mainly due to the high variability in the interpretation of current definitions and the use of different tests for microbiological confirmation. Moreover, many complications in adult patients receiving mechanical ventilation, such as acute respiratory distress syndrome (ARDS), pulmonary edema, atelectasis, and pulmonary embolisms, may be misinterpreted as respiratory infections due to the lack of specificity of specific diagnostic criteria such as chest X-ray. In 2013 the Centers for Disease Control and Prevention (CDC) proposed a new diagnostic algorithm for ventilator-associated events (VAEs). Based on more objective criteria and easily measurable clinical features, incorporates the fraction of inspired oxygen (FiO2) and the positive end-expiratory pressure (PEEP) as surrogated measures of hypoxemia, disregarded the chest radiograph as diagnostic criteria and both included infective and noninfective complications in the surveillance. The EU-VAE project pursuit is to analyze the different definitions, incidences, risk factors, outcomes, and impact of VAEs.

A first study, conducted in 13 ICUs from eight countries, adults over 18 years of age on mechanical ventilation for more than 48 h were eligible. Initial 30 subjects from each participating center were followed up daily for 30 days and recorded the data in a collaborative web database (http://compartint.net/euvae/). Analysis of a total of 2856 ventilator days in 244 patients, identified 33 VAP and 51 VAT episodes. A secondary study identified factors associated with VAEs, 163 patients with 76 episodes of VAE were included (34.9 VAE/1,000 mechanical ventilation days

Figure 1 offers a detailed description of the patients included in the EUVAE project.

Figure 1. Flow chart of the patients included in the EUVAE project



II. INTRODUCCION

". . . when the lung long flaccid has collapsed, the beat of the heart and arteries appears wavy, creepy, twisting, but when the lung is inflated, it becomes strong again and swift and displays wondrous variations . . . and as I do this, and take care that the lung is inflated at intervals, the motion of the heart and arteries does not stop."

Andreas Vesalius (1543)

Capítulo 1. INTRODUCCIÓN GENERAL

Los primeros reportes del uso de presión positiva externa para introducir aire en los pulmones tienen su origen en los experimentos llevados a cabo por Paracelso en el siglo XVI usando un fuelle conectado a través de un tubo a la boca de un cadáver para insuflar sus pulmones, paralelamente el anatomista Andreas Vesalius publicó en su tratado *"De Humani Corporis Fabrica"* la posibilidad de mantener la actividad cardíaca de cerdos insuflando rítmicamente sus pulmones a través de un tubo conectado a su tráquea[1,2]; a pesar de la oposición de los defensores de la teoría galénica y el ambiente aún inquisitivo la inquietud de transportar el aire a través de la vía aérea se fue filtrando lentamente en la comunidad científica, así durante la edad media no era inusual el empleo de dispositivos de ventilación mecánica en el quirófano y para el tratamiento de niños con difteria y pacientes intoxicados por opio, pero fue la epidemia de poliomielitis de 1952 en la ciudad de Copenhague la que ratificó la importancia de la ventilación con presión positiva como terapia de soporte demostrando su superioridad frente a otros dispositivos como el pulmón de acero al lograr una disminución de la mortalidad cercana al 50%. Durante la segunda mitad del siglo XX la creación de Unidades de cuidados intensivos permitió extender la ventilación mecánica más allá del quirófano brindando un mayor entendimiento acerca de su influencia en el organismo y su interacción con las diferentes variables respiratorias y hemodinámicas en individuos enfermos, los conocimientos obtenidos sumados al creciente interés de la comunidad científica y de la industria permitieron la inclusión de equipos capaces de controlar el volumen, la presión y la concentración de oxígeno administradas, paralelamente la posibilidad de medir los gases en sangre permitió entender mejor los diferentes tipos de insuficiencia respiratoria y la manera de tratarla. Por otra parte, el empleo de presiones positivas para desplazar y mantener una mezcla de gases enriquecida con oxígeno a través de un sistema de baja presión altera la homeostasis de la barrera alveolo-capilar e induce daño tisular pulmonar, un mayor número de pacientes ventilados trajo consigo los primeros reportes de lesiones pulmonares inducidas por el uso de presión positiva también conocidos como "pulmón de ventilador" o síndrome de distrés respiratorio del adulto dada su similitud con el distrés respiratorio infantil[3,4]. Adicionalmente la intubación traqueal y el uso de sedantes, analgésicos y bloqueantes musculares aumenta el riesgo de infección del tracto respiratorio inferior.

Los eventos asociados a la ventilación mecánica (VAE) son interdependientes, potencialmente reversibles y están presentes en un mismo paciente en un mismo período de tiempo, de acuerdo a su naturaleza pueden dividirse en: 1) Lesiones por fuerzas mecánicas: barotrauma, volutrauma y atelectrauma; son consecuencia de la sobredistensión y ruptura de la barrera alveolocapilar producidas por el desequilibrio entre el poder mecánico del ventilador y las características elásticas del pulmón; dependen del volumen, la presión y la aceleración del gas insuflado y de la compliance y la elastancia pulmonar. 2) Lesiones por mediadores bioquímicos: biotrauma; son el resultado del estrés alveolar repetitivo y pueden originarse a nivel tanto intrapulmonar como sistémico, el daño tisular promueve la inflamación y el depósito de fibrina produciendo un aumento del shunt intrapulmonar y un mayor riesgo de barotrauma y volutrauma, además induce la respuesta inflamatoria sistémica y el fracaso multiorgánico al facilitar el paso de mediadores inflamatorios, lipopolisacáridos y otras endotoxinas al torrente sanguíneo.

A través de variables clínicas cuantitativas la nueva clasificación del CDC (Center for Disease Control and Prevention) divide las complicaciones infecciosas y no infecciosas de la ventilación mecánica en 4 grupos[5]: 1) Condiciones asociadas a la ventilación mecánica (VAC): aumento de la fracción inspiratoria de oxígeno (FiO2) superior o igual al 20% o de más de 3 cm de H_2O en la presión positiva al final de la espiración (PEEP) por más de 48 horas, 2) Condiciones asociadas a la ventilación debidas a infección-plus (IVAC-plus): VAC en las que se sospecha un proceso infeccioso y que han recibido tratamiento antibiótico por 4 días o más, 3) Posible neumonía asociada al ventilador (PVAP): IVAC-plus en las que se ha comprobado la presencia de un patógeno respiratorio y 4) Complicaciones asociadas a la infección (IVAC): IVAC-plus que no son explicadas por infección de la via aérea. Un diagrama detallado de la clasificación puede verse en la figura 1 del capítulo 3.

III. HIPÓTESIS Y OBJETIVOS

Capítulo 2. HIPÓTESIS

Los eventos asociados a la ventilación mecánica (VAE) son un síndrome complejo y dinámico que va más allá del espectro infeccioso, el empleo de variables cuantitativas de uso clínico facilita su estudio y clasificación, además permite que sean comparables y puedan incluirse en sistemas de vigilancia y programas de prevención

Capítulo 3. OBJETIVO PRINCIPAL

Realizar un análisis descriptivo de los diferentes eventos asociados a la ventilación mecánica en las unidades de cuidados intensivos, así como de su relación con resultados clínicos y factores desencadenantes.

Capítulo 4. OBJETIVOS SECUNDARIOS

1. Evaluar el estado actual de los VAE en las unidades de cuidados intensivos

2. Identificar factores de riesgo relacionados con los VAE

3. Analizar de manera independiente los eventos infecciosos y no infecciosos asociados a la ventilación mecánica

4. Determinar la incidencia de los VAE y su impacto en los pacientes que los presentan

PARTE CENTRAL. DESCRIPCIÓN DE LA INVESTIGACIÓN

"Dosis sola facit venenum"

Paracelso

IV. PROYECTO EUVAE

Capítulo 5.

ASSESSING PREDICTIVE ACCURACY FOR OUTCOMES OF VENTILATOR-ASSOCIATED EVENTS IN AN INTERNATIONAL COHORT: THE EUVAE STUDY.

Ramírez-Estrada S, Lagunes L, Peña-López Y, Vahedian-Azimi A, Nseir S, Arvaniti K, Bastug A, Totorika I, Oztoprak N, Bouadma L, Koulenti D, Rello J; the EU-VAE Study Investigators Group.

Intensive Care Med. 2018;44:1212-1220. doi: 10.1007/s00134-018-5269-7.

RESUMEN

PROPÓSITO:

Analizar el impacto de los VAE y su correlación con la neumonía asociada a la ventilación (VAP) y las traqueobronquitis (VAT).

Métodos:

Estudio prospectivo, observacional, multicéntrico e internacional realizado en 13 UCIs; por cada centro se incluyeron de manera consecutiva 30 adultos con ventilación mecánica por más de 48 horas, se les realizó un seguimiento diario que se registró en una base de datos en línea. Los VAE se evaluaron utilizando la clasificación del CDC de 2013 y su actualización de 2015.

Resultados:

Se analizaron un total de 2856 días de ventilación en 244 pacientes, identificando 33 episodios de VAP y 51 de VAT; La mortalidad en la UCI a los 30 días fue significativamente mayor (42.8 vs. 19.6%, p <0.007) en pacientes con VAP que en aquellos con VAT. De acuerdo con las definiciones del CDC de 2013, se identificaron 117 VAE: 113 (96%) se debieron a IVAC-plus, 64 (56.6%) de ellos fueron diagnosticados como posible neumonía. La presencia de VAE aumentó el número de días de ventilación y prolongó las estancias en UCI y hospitalaria (incremento en 5, 11 y 12 días, respectivamente), además se observó una tendencia al aumento de la mortalidad a los 30 días (43 vs 28%, p = 0,06). La mayoría de los episodios (26, 55%) clasificados como IVAC-plus sin criterios de PVAP fueron debidos a atelectasias. El diagnóstico de PVAP aumentó significativamente (p <0.05) los días de ventilación, así como la estancia en UCI y hospitalaria (10.5, 14 y 13 días, respectivamente). Solo 24 (72.7%) de las VAP y 15 (29.4%) de las VAT cumplieron con los criterios de IVAC-plus.

Conclusiones:

Las infecciones respiratorias (principalmente las VAT) fueron la complicación más frecuente. La nueva clasificación de los VAE solo identificó aquellos episodios con deterioro grave de la oxigenación y falló en detectar una cuarta parte de los episodios de VAP y tres cuartas partes de las VAT. La identificación de las VAT (que a menudo no cumplen criterios de IVAC-plus) es importante, ya que su pronóstico es diferente al de las VAP.

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ORIGINAL

Assessing predictive accuracy for outcomes of ventilator-associated events in an international cohort: the EUVAE study

Sergio Ramírez-Estrada[1,2], Leonel Lagunes[2,3], Yolanda Peña-López[1,2], Amir Vahedian-Azimi[5], Saad Nseir[6,7], Kostoula Arvaniti[8], Aliye Bastug[9], Izarne Totorika[10], Nefise Oztoprak[11], Lilla Bouadma[12], Despoina Koulenti[13,14], Jordi Rello[1,3,4,15*] and the EU-VAE Study Investigators Group

Abstract

Purpose: To analyze the impact on patient outcome of ventilator-associated events (VAEs) as defined by the Centers for Disease Control and Prevention (CDC) in 2008, 2013, and the correlation with ventilator-associated pneumonia (VAP) or tracheobronchitis (VAT).

Methods: This was a prospective, observational, multicenter, international study conducted at 13 intensive care units (ICUs); thirty consecutive adults mechanically ventilated for ≥ 48 h per site were eligible, with daily follow-up being recorded in a collaborative web database; VAEs were assessed using the 2013 CDC classification and its 2015 update.

Results: A total of 2856 ventilator days in 244 patients were analyzed, identifying 33 VAP and 51 VAT episodes; 30-day ICU mortality was significantly higher (42.8 vs. 19.6%, $p < 0.007$) in patients with VAP than in those with VAT. According to the 2013 CDC definitions, 117 VAEs were identified: 113 (96%) were infection-related ventilator-associated complication-plus (IVAC-plus), while possible ventilator-associated pneumonia (PVAP) was found in 64 (56.6%) of them. VAE increased the number of ventilator days and prolonged ICU and hospital LOS (by 5, 11, and 12 days, respectively), with a trend towards increased 30-day mortality (43 vs 28%, $p = 0.06$). Most episodes (26, 55%) classified as IVAC-plus without PVAP criteria were due to atelectasis. PVAP significantly increased ($p < 0.05$) ventilator days as well as ICU and hospital LOS (by 10.5, 14, and 13 days, respectively). Only 24 (72.7%) of VAP and 15 (29.4%) of VAT episodes met IVAC-plus criteria.

Conclusions: Respiratory infections (mainly VAT) were the most common complication. VAE algorithms only identified events with surrogates of severe oxygenation deterioration. As a consequence, IVAC definitions missed one fourth of the episodes of VAP and three fourths of the episodes of VAT. Identifying VAT (often missed by IVAC-plus criteria) is important, as VAP and VAT have different impacts on mortality.

Keywords: Ventilator-associated pneumonia, Ventilator-associated tracheobronchitis, Ventilator-associated events, Surveillance, Hypoxemia

Introduction

Despite progress in the treatment of infectious diseases, ventilator-associated pneumonia (VAP) remains a major infection among adult critically ill patients with overall attributable mortality of 13% [1, 2]. Infections of the lower respiratory tract are the main reason for antibiotic

*Correspondence: jrello@crips.es
[1] Vall d'Hebron Institute of Research, Pg Vall d'Hebron 119-129, AMI-14, 08035 Barcelona, Spain
Full author information is available at the end of the article

The members of the EU-VAE study Investigators Group are listed in the Acknowledgements and in the electronic supplementary material.

prescription in the intensive care unit (ICU), and they are associated with increased length of stay (LOS) and costs [1, 3, 4].

A global consensus on VAP diagnosis has been difficult to achieve, largely due to the high variability in the interpretation of current definitions and the use of different tests for microbiological confirmation. Moreover, many complications in adult patients receiving mechanical ventilation, such as acute respiratory distress syndrome (ARDS), pulmonary edema, atelectasis, and pulmonary embolisms, may be misinterpreted as respiratory infections due to the lack of specificity of certain diagnostic criteria such as chest X-ray [5]. Previous reports have highlighted the poor correlation between clinical diagnosis of VAP and the histopathology findings [6, 7]. All these limitations have implications for clinical practice, surveillance initiatives, and the design of preventive strategies [8].

In 2013 the Centers for Disease Control and Prevention (CDC) proposed a new diagnostic algorithm for ventilator-associated events (VAEs) based on more objective criteria and easily measurable clinical features. It divided the causes of respiratory worsening in critically ill patients into four tiers: ventilator associated complication (VAC), iInfection-related ventilator associated complication (IVAC), probable ventilator-associated pneumonia, and possible ventilator associated pneumonia. In the 2015 update of this algorithm, probable and possible ventilator-associated pneumonia were amalgamated as possible ventilator-associated pneumonia (PVAP) and a new category, infection-related ventilator-associated complication-plus (IVAC-plus) was created.

The EU-VAE project was developed with the aim of analyzing the different definitions, incidences, risk factors, outcomes and impact of VAEs in non-USA ICUs, according to the 2013 CDC definition and its 2015 update [3, 9]. Preliminary data were reported at ECCMID 2016 and 2017 [10, 11].

Patients and methods

A prospective, observational, international, multicenter study was conducted in 13 ICUs from eight countries (Australia, France, Greece, Iran, Italy, Slovenia, Spain, and Turkey) with the capacity for treating adults with medical or surgical conditions or trauma. Nine (69%) of these ICUs were located in university hospitals.

Persons over 18 years of age who had been on mechanical ventilation for more than 48 h were eligible; the first 30 subjects from each participating center were followed up daily for 30 days. The exclusion criteria were mechanical ventilation for less than 48 h, age below 18, and presence of respiratory viral infection. Only the first episode of VAE in each patient was included in the study. Subjects with incomplete follow-up data were eliminated. Extubation, ICU discharge, or death in the ICU were recorded as outcome end-points. The following characteristics were recorded: age, sex, weight, APACHE II score [12], immunosuppressive therapy, reason for and site of intubation, hospital and ICU LOS, implementation of preventive measures for ventilator-associated respiratory infections (VARI), clinical and laboratory parameters of inflammatory response [13], microbiological data, use of antibiotics, sedation and medical paralysis, fluid balance, and need for tracheostomy during the ICU stay. Daily follow-up data were recorded in a collaborative web database (http://compartint.net/euvae/). The current adult definitions for VAEs implemented in the CDC 2013 National Healthcare Safety Network and its 2015 update [3, 14] were assessed (Table 1). There are three definition tiers within the VAE algorithm: (1) VAE, (2) IVAC, and (3) PVAP (Fig. 1). Cases of VAP or ventilator-associated tracheobronchitis (VAT) were recorded according to the 2008 CDC criteria [15]. In brief, VAP was defined as the presence of a new or progressive and persistent pulmonary infiltrate, consolidation, or cavitation plus at least three of the following in a patient under mechanical ventilation for >48 h: (1) temperature ≥38 °C or ≤36 °C with no other recognized cause; (2) leukocyte count ≥12,000/mm^3 or <4000/mm^3; (3) new onset of purulent tracheal secretions or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements; (4) new-onset or worsening dyspnea or tachypnea; (5) wheezing, rales, or bronchial breath sounds; (6) worsening gas exchange, increased oxygen requirement, or increased ventilator demand; (7) altered mental status in a patient >70 years old. The definition of VAT [16, 17] was based on the absence of clinical and radiographic evidence of pneumonia and presence of the following criteria: positive culture obtained by deep tracheal aspirate plus at least two of these signs in a patient under mechanical ventilation for >48 h: fever >38 °C, new or increased purulent tracheal secretions, rhonchi, or wheezing (Table 1). Quantitative definitions of significant growth in cultures and purulent respiratory secretions are detailed in the electronic supplementary material (ESM) appendixes 2 and 3. Atelectasis was defined as collapse of a part of the lung due to a decrease in the amount of air in the alveoli, resulting in volume loss and increased density. Pulmonary edema was diagnosed based on air space opacification in a classic batwing distribution, possibly accompanied by air bronchograms, with peribronchial cuffing and perihilar haze, septal lines (Kerley lines), and thickening of interlobar fissures. The final diagnosis was established by the investigator based on the radiologist's interpretation. In unclear cases, lung ultrasound was performed to differentiate opacities [18].

Table 1 Comparison between ventilator-associated infection definitions [3, 9, 15, 16]

	PVAP (CDC 2013 definition)	VAP (CDC 2008 definition)	VAT
Clinical criteria	Increase in $FiO_2 \geq 0.20$ or in PEEP ≥ 3 cmH_2O with a previous period of stability/improvement ≥ 2 days And Suspicion of infection[c] And Beginning of a new antibiotic	One of the following: 1. Worsening gas Exchange[a] 2. Tachypnea or dyspnea 3. Change in sputum characteristics[b] 4. Rales or bronchial breath sounds And at least one: 1. Suspicion of infection[c] 2. Altered mental status in adults ≥ 70 years old[g]	Suspicion of infection[c]
Radiological criteria	Not included	New or progressive infiltrate, consolidation or cavitation	Absence of radiologic criteria for pneumonia
Microbiological criteria	1.Significative growth of a pathogen in respiratory samples[d] 2. Insufficient growth of a pathogenic microorganism plus purulent sputum[f] 3. Pathogenic microorganism in pleural fluid cultures 4. Histopathologic evidence of lung infection[e] 5. Positive test for pathogenic virus in respiratory samples 6. Positive test for *Legionella* species	1. Significative growth of a pathogen in respiratory samples[d] 2. > 5% Cells with intracellular bacteria in bronchoalveolar lavage 3. Pathogenic microorganism in pleural fluid cultures 4. Histopathologic evidence of lung infection[e] 5. Positive growth in blood culture[g]	Positive endotracheal aspirate culture And Purulent sputum[f]

PVAP possible ventilator associated pneumonia, *VAP* ventilator associated pneumonia, *VAT* ventilator associated tracheobronchitis

[a] Worsening gas exchange: increased oxygen requirements or in ventilator demand

[b] Change in sputum characteristics: new onset of purulent respiratory secretions or increase in its production or in suctioning requirements

[c] Suspicion of infection: leukocytosis ($\geq$ 12,000 cells/mL) or leukopenia ($\leq$ 4000 cells/mL) or fever ($\geq$ 38 °C) or hypothermia ($\leq$ 36 °C)

[d] 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

[e] 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

[f] Purulent sputum: ^{3}25 neutrophils and $\leq$ 10 squamous epithelial cells per low power field

[g] Without other recognized focus

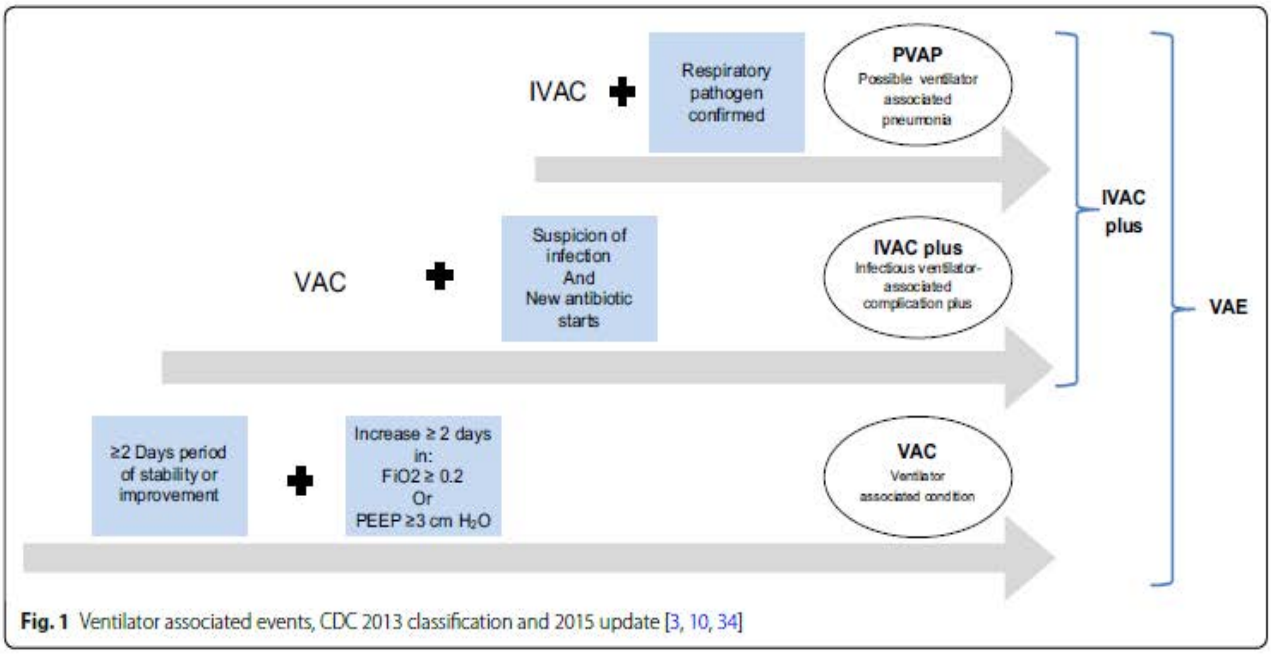

Fig. 1 Ventilator associated events, CDC 2013 classification and 2015 update [3, 10, 34]

An episode of mechanical ventilation was defined as the period between tracheal intubation (day 1) and 24 h after successful extubation (or disconnection from the ventilator in the case of tracheotomized patients).

Continuous data were reported as medians and interquartile ranges and categorical data as numbers and percentages; the T test or Mann–Whitney test was used for comparison of continuous variables, while the Chi squared test or Fisher's exact test was used to compare categorical variables. The clustered Wilcoxon rank sum test was used for clustered data following the Datta–Satten method. Relative risks and 95% confidence intervals were calculated; a p value ≤ 0.05 was considered statistically significant and a p value between 0.05 and ≤ 0.10 was considered as showing a trend toward statistical significance. All analyses were performed in R, version 3.4.1 (R Core Team 19).

The study protocol was approved by the institutional review board on human research of each participating center and at Vall d´Hebron University hospital as the coordinating center [PR(AG)28/2014]. Patients, or the relatives of unconscious patients, were asked to provide written consent prior to participating in the study.

Results

The study cohort comprised 244 adults (of a total of 1078 eligible patients) who between them had 2856 ventilator days with full follow-up. A flow-chart showing the patients enrolled and the exclusion criteria can be found in the ESM (appendix 4). The median APACHE II score at admission of the patients included was 20.6 (25–75% IQR 14–27). The ICU LOS was 14 days (25–75% IQR 8–26.2), the hospital LOS was 25 days (25–75% IQR 11.7–45), and 30-day mortality (for the entire cohort) was 21.7%. Almost all patients were intubated within 24 h of hospitalization; sites of and reasons for intubation are detailed in the ESM (appendix 5). The patients' baseline characteristics are shown in Table 2.

Eighty-four VARI were recorded (29.3 per 1000 ventilator days). Using the 2008 CDC criteria, 33 (39.3%) of these incidents were VAP (12.2 per 1000 ventilator days) and 51 (60.7%) were VAT (17.8 per 1000 ventilator days) (Fig. 2). In addition, 33 (39%) adults with VARI did not meet the criteria of VAE because they did not require sustained positive end-expiratory pressure (PEEP) or FiO_2 increase. Patients with VARI had a significantly longer ventilation period than non-VARI patients (excess: 6 days). Details of hospital LOS and mortality can be found in the ESM (appendix 6). Patients classified

Table 2 CDC 2013 classification, patients characteristics and outcomes [3, 9]

Variable	All (n 244)	2013 CDC criteria (VAE vs. No VAE)			2013 CDC criteria (PVAP vs. No PVAP)		
		VAE (n 117)	No VAE (n 127)	P	PVAP (n 64)	No PVAP (n 178)	p
Male n (%)	154 (63.1)	76 (65)	78 (61)	0.56	50 (32.5)	104 (58.4)	0.01
Age median (95% CI)	56 (49–69)	60 (50–73)	56 (45–67)	0.27	61 (44–74)	56 (49–67)	0.18
Weight kg median (95% CI)	80 (70–90)	80 (70–92)	80 (70–87)	0.94	86 (67–93.7)	75 (70–85)	0.009
APACHE II at admission median (95% CI)	20 (14–27)	19 (9–21)	22.5 (16–29)	0.06	19.5 (13–24)	21 (14–28)	0.49
Preexisting condition n (%)							
Diabetes	65 (28)	38 (33)	27 (22)	0.07	13 (20)	52 (30)	0.12
Kidney disease	33 (14)	15 (13)	18 (15)	0.64	5 (7)	28 (16)	0.08
Cancer	20 (8)	8 (7)	12 (10)	0.41	3 (5)	17 (10)	0.20
Heart disease	65 (27)	36 (31)	29 (24)	0.20	20 (31)	45 (26)	0.43
Liver disease	6 (3)	1 (1)	5 (4)	0.10	–	6 (3)	0.12
Lung disease	48 (20)	25 (21)	23 (19)	0.60	9 (14)	39 (22)	0.14
Immunosuppression	23 (10)	9 (8)	14 (12)	0.31	7 (11)	16 (10)	0.74
Type of patient n (%)				0.07			0.31
Medical	141(58)	62 (53)	79 (62)		34 (51)	107 (61)	
Surgical	61 (25)	37 (32)	24 (19)		21(32)	40 (22)	
Traumatic	42 (17)	18 (15)	24 (19)		11 (16)	31 (17)	
Tracheostomy n (%)	44 (29)	36 (47)	8 (11)	< 0.001	27 (50)	17 (17)	< 0.001
MV days median (95% CI)	9 (5–15)	12 (9–21)	7 (5–10)	< 0.001	17.5 (9–28)	7 (5–11)	< 0.001
ICU LOS median (95% CI)	14 (8–26)	23 (10–36)	12 (7–20)	0.001	25(12–38)	11 (7–21)	< 0.001
Hospital LOS median (95% CI)	25 (11–45)	31 (17–54)	19 (10–38)	0.04	32 (10–55)	19 (10–39)	0.02
Mortality n (%)	53 (22)	31 (43)	22(29)	0.06	22(40)	31(33)	0.38

ICU intensive care unit, *MV* mechanical ventilation, *LOS* length of stay, *VAE* ventilator associated event, *PVAP* possible ventilator associated pneumonia

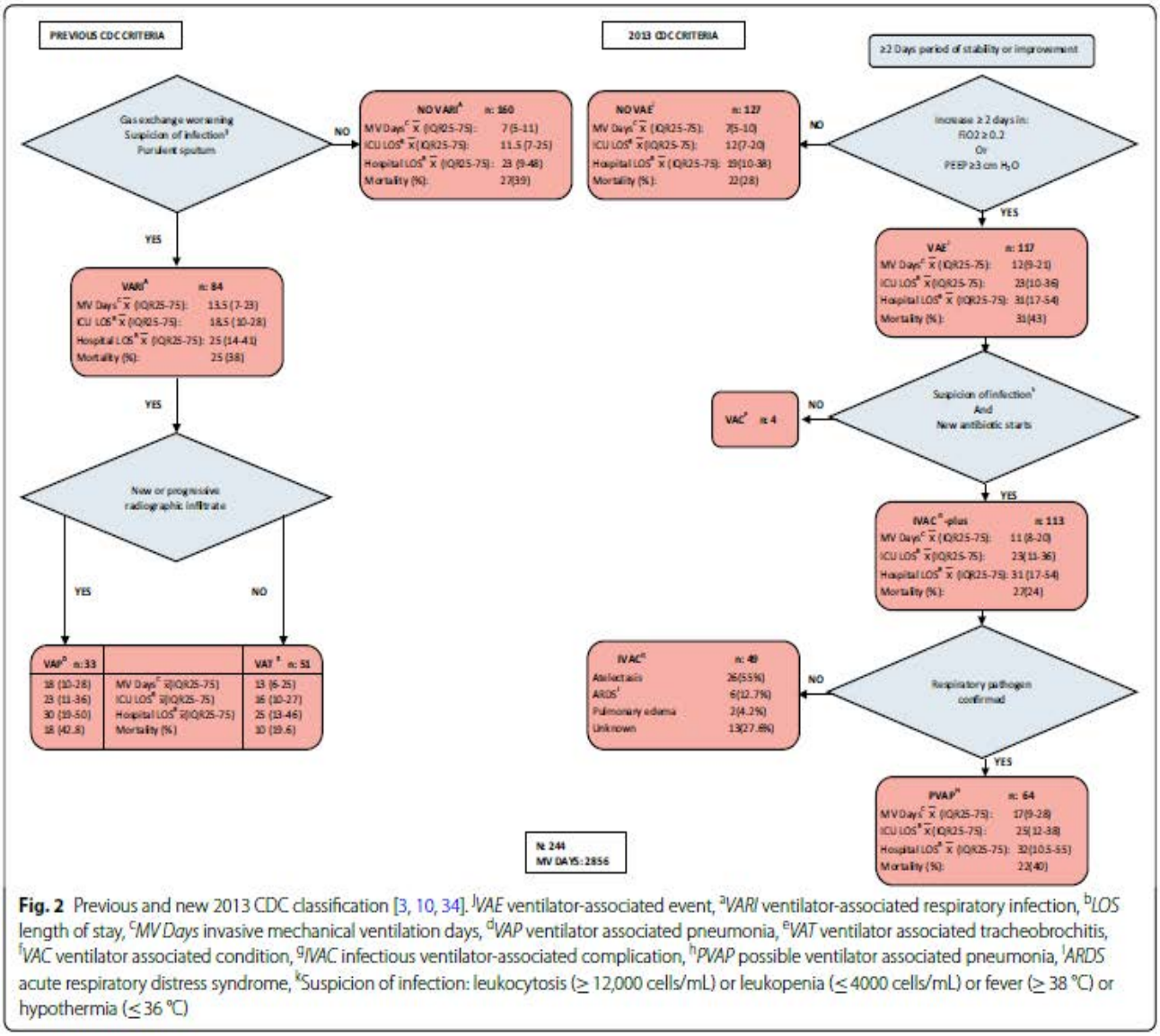

Fig. 2 Previous and new 2013 CDC classification [3, 10, 34]. [F]*VAE* ventilator-associated event, [A]*VARI* ventilator-associated respiratory infection, [B]*LOS* length of stay, [C]*MV Days* invasive mechanical ventilation days, [D]*VAP* ventilator associated pneumonia, [E]*VAT* ventilator associated tracheobrochitis, [F]*VAC* ventilator associated condition, [G]*IVAC* infectious ventilator-associated complication, [H]*PVAP* possible ventilator associated pneumonia, [I]*ARDS* acute respiratory distress syndrome, [K]Suspicion of infection: leukocytosis (≥ 12,000 cells/mL) or leukopenia (≤ 4000 cells/mL) or fever (≥ 38 °C) or hypothermia (≤ 36 °C)

as having VAP presented higher mortality than VAT patients (42.8 vs 19.6%, p = 0.007). However, no statistically significant differences were observed in number of ventilator days or in ICU or hospital LOS (ESM appendix 7).

Using the 2013 CDC definition (Table 1), 117 episodes of VAE were recorded (40.8 per 1000 ventilator days). VAE were present after a median of 4 days' ventilation (25–75% IQR 3–7); 59 VAEs (50.9%) developed within the first 4 days of mechanical ventilation (ESM appendixes 10, 11). The main cause of VAE was IVAC-plus (39.6 per 1000 ventilatory days). IVAC-plus accounted for 113 (96%) episodes, 64 (56.6%) of which met the CDC criteria for PVAP (22.3 per 1000 ventilator days). The rest of the events were classified as VAC (5.58 per 1.000 ventilator days). In patients classified as IVAC-plus without PVAP criteria, most episodes were due to atelectasis (26, 55%); a minority (six, 12.7%) were ARDS, and only two (4.2%) were pulmonary edema (Fig. 2). Both VAE and IVAC-plus definitions had a negative predictive value of 98% but predicted VAP in only one out of three adults (ESM appendix 8).

Patients in the VAE group had significant increases in ventilator days (5 days) and in ICU and hospital LOS (11 and 12 days, respectively) compared with the non-VAE group (Table 2). A trend towards an increase in 30-day mortality was observed in the VAE group (43 vs 28%, p 0.065) (Table 2).

PVAP patients had increases (p < 0.05) of 10.5 days of ventilation, 14 days of ICU stay and 13 days of hospital stay compared to patients without PVAP. Compared to VARI, the PVAP group had 4.5 day more days of ventilation (p < 0.027), 6.5 more days in the ICU and 7 days more in hospital (p < 0.05) (ESM appendix 9). Non-significant

differences were detected when non-infected patients were compared using either the 2013 or 2015 classifications (non-VARI vs. non-VAE) (appendix 6 ESM). Correlations between the 2008 and 2013 CDC classifications are shown in Fig. 3.

Discussion

To the best of our knowledge, this is the first prospective, international, multicenter study to assess the incidence and outcomes of VAEs in adult ventilated subjects in ICUs. This study identified both VAP and VAT (often missed in earlier studies). Moreover, our study systematically implemented the 2013 CDC classification of VAE and its 2015 update and demonstrated the frequent occurrence of these events in mechanically ventilated adults. Our findings suggest that respiratory infection was the main cause of VAEs, but both the 2013 and 2008 definitions missed a significant proportion of respiratory infections (three out of every four VAT episodes did not meet the criteria of IVAC).

Our findings are consistent with the results of a recent meta-analysis by Fan and colleagues [20] in demonstrating that VAE were associated with increased mortality, more days of mechanical ventilation, and greater hospital LOS than traditional VAP criteria. Worsening in FiO_2 and in PEEP are commonly used in clinical practice as surrogates of poor oxygenation [21–23], and both are employed by the VAE definition to detect deterioration in oxygenation. Several studies have reported notable reductions in the time taken to detect VAE when automatic surveillance was used [24, 25]. Not surprisingly, the association between poor oxygenation and outcomes in patients with VAP has previously been reported [21, 22]. In 2012, Klompas et al [23] evaluated the feasibility of 32 possible surveillance definitions for VAP, reporting that only those including quantitative evidence of respiratory deterioration were associated with increased morbidity and mortality. In the same way, the VAE paradigm broadens the spectrum of complications associated with mechanical ventilation, identifying conditions severe enough to cause respiratory worsening, including respiratory infection-related events such as VAP as well as tracheobronchitis and non-infective and extra-pulmonary events. PaO_2/FiO_2 ratio, the presence of infection, and the level of PEEP [23, 26–28] enhanced the power of VAE surveillance. In our cohort, PVAP was the most frequent complication but non-negligible incidences of atelectasis, ARDS, and pulmonary edema were also documented. Similar results have been reported elsewhere [20, 29, 30], and there is growing evidence that

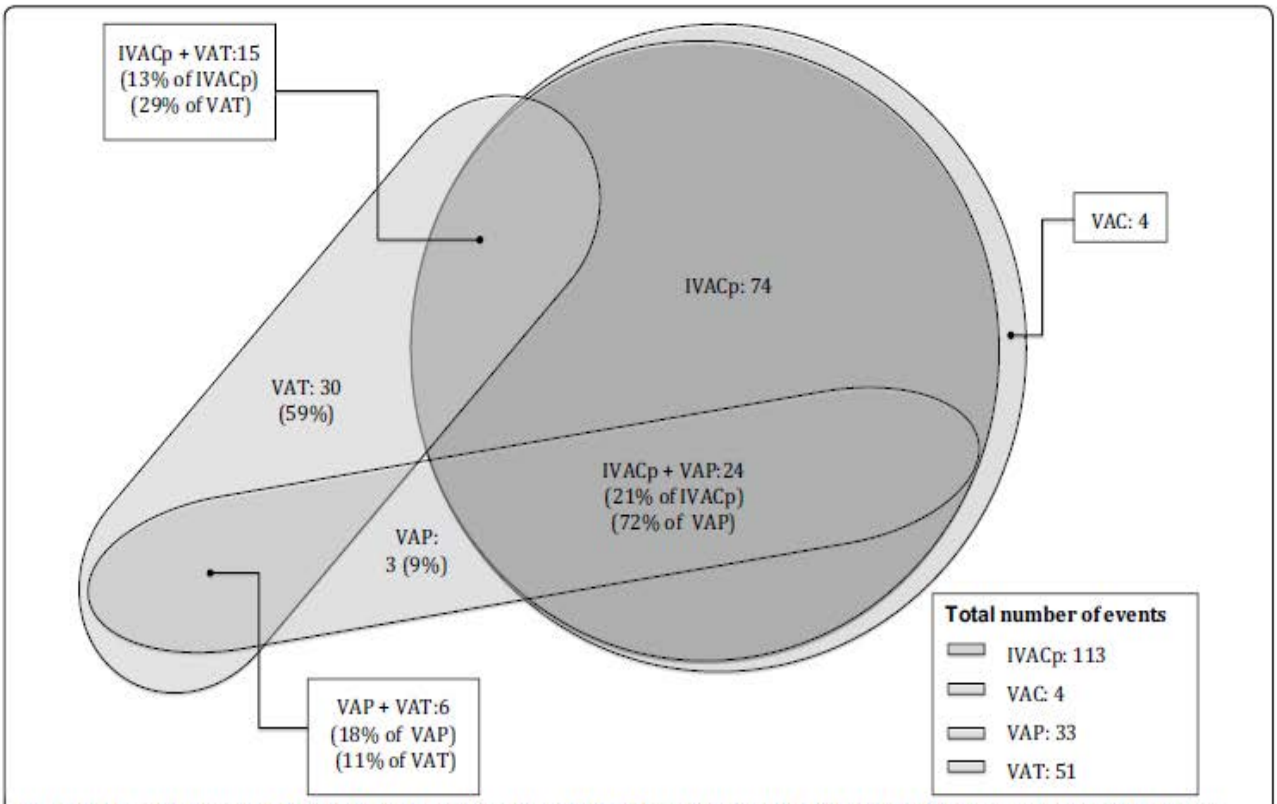

Fig. 3 Relationship between 2008 and 2013 CDC classifications [10, 15, 36]. 2013 classification is represented with circles and 2008 classification with ovals. *VAC* ventilator associated condition, *IVACp* infectious ventilator-associated complication plus, *VAP* ventilator associated pneumonia, *VAT* ventilator associated tracheobronchitis

many of these events are preventable [14, 31, 32]. In our study, only 59% of patients with suspicion of pulmonary infection had PVAP and almost 39% of cases were due to a noninfectious event (atelectasis, ARDS, pulmonary edema). In the pediatric population, the presence of VAE was also associated with worse outcomes, including mortality; however, IVAC was less prevalent than in adults. Indeed, the incidence of ARDS and pulmonary edema was lower, while atelectasis was the most frequent event [33, 34]. This confirms that the newer VAE classification moves the focus beyond respiratory infections but selects only the most severe cases.

Our study suggests that identifying VAT (often missed by IVAC-plus criteria) is important, because VAP and VAT have different impacts on mortality. Low agreement has previously been reported between the novel CDC definition and VAP in series in the USA and elsewhere [20, 35, 36]. In the present cohort, almost 30% of VAP cases were not diagnosed as IVAC-plus and only 29% of VAT episodes met the IVAC-plus criteria (Fig. 3). These findings suggest that VAE selects only the most severe cases and discards those without sufficient deterioration in oxygenation to increase the ventilation demands to a level required to reach diagnosis thresholds.

IVAC-plus was the most prevalent event in VAE surveillance and is defined by the suspicion of infection and the beginning of a new antibiotic treatment. The 2015 VAE update [3] amalgamated overall events meeting or exceeding the definition of IVAC into the category IVAC-plus, which includes patients with a confirmed respiratory infection (PVAP) and those with hypoxemia in a non-confirmed pulmonary infectious-related context (IVAC). In our cohort, 43% of IVAC-plus episodes were classified as IVAC, the main causes being atelectasis, ARDS, and pulmonary edema, while the remaining 57% were classified as PVAP and were associated with worse outcomes (Fig. 2). Our study suggests that VAT produced a sustained increase ≥ 2 days in FiO_2 ≥ 0.2 or PEEP ≥ 3 cm H_2O and fulfilled VAE criteria in around 25% of episodes.

The strengths of our study include the use of a large database with prospective data collection, the inclusion of medical, trauma, and surgical patients, its prospective, multicenter international design and its use of predefined outcomes rather than simply reported rates. This study also has some potential limitations: Its initial design limits the blinding process, which is a potential source of bias. Selection bias is a potential important concern, and due to the heterogeneity of the ICUs' case mix it might affect generalization. Owing to the high proportion of university hospitals, some of the results might not be globally representative, while the exclusion of children, chronically ill patients, and patients ventilated outside the ICU may limit the extrapolation of the results to other settings. Our cohort presented a lower VAC rate than those reported in previous studies [35, 37], possibly due to differences in institutional antibiotic policies and practices between hospitals. Klompas [38] reported high interobserver variability in diagnosis of respiratory infections, and several studies reported differences in surveillance practice across hospitals [15, 39]; however, these differences could be used to identify variables as independent factors. Finally, given the low incidence of some of the events, the power to demonstrate statistical differences is sometimes limited by small cohort size.

Our study also has important implications that drive new research questions for future developments. There is a need to investigate the effects of new management algorithms for ventilated adults using more subtle definitions of VAE, as has been done in children [33]. Further studies should identify better breakpoints for ventilatory settings and should not omit VAT.

Conclusions

Respiratory infections (mainly VAT) were the most common complications in mechanically ventilated adults. All tiers were associated with significantly worse outcomes. Our findings suggest that the VAE algorithms identified only those events with surrogates of severe oxygenation deterioration. As a consequence, IVAC definitions missed one fourth of the episodes of VAP and three fourths of the episodes of VAT. Identifying VAT (often missed by IVAC-plus criteria) is important, with VAP and VAT having different impacts on patient outcome.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5269-7) contains supplementary material, which is available to authorized users.

Abbreviations

ARDS: Acute respiratory distress syndrome; CDC: Centers for disease control and prevention; CFU: Colony-forming unit; ECCMID: European Congress of Clinical Microbiology and Infectious Diseases; ESM: Electronic supplementary material; ICU: Intensive care unit; IVAC: Infection-related ventilator-associated complication; LOS: Length of stay; PVAP: Possible ventilator-associated pneumonia; VAC: Ventilator-associated condition; VAE: Ventilator-associated event; VAP: Ventilator-associated pneumonia; VARI: Ventilator-associated respiratory infection; VAT: Ventilator-associated tracheobronchitis.

Author details

[1] Vall d'Hebron Institute of Research, Pg Vall d'Hebron 119-129, AMI-14, 08035 Barcelona, Spain. [2] Medicine Department, Universitat Autónoma de Barcelona, Barcelona, Spain. [3] Clinical Research in Pneumonia and Sepsis, Vall d´Hebron Research Institute, Barcelona, Spain. [4] European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Study Group for Infections in Critically Ill Patients (ESGCIP), Basel, Switzerland. [5] Trauma Research Center, Nursing Faculty, Baqiyatallah University of Medical Sciences, Tehran, Iran. [6] Critical Care Center, Centre Hospitalier Universitaire Lille, Lille, France. [7] Inflammation Research International Center, Université Lille, Lille, France. [8] Papageorgiou General Hospital, Thessaloníki, Greece. [9] Infectious Diseases and Clinical Microbiology Department, Ankara Numune Training and Research Hospital, Ankara,

Turkey. [10] Intensive Care Department, Donostia University Hospital, Donostia, Spain. [11] Antalya Education and Research Hospital, Antalya, Turkey. [12] Hôpital Bichat-Claude-Bernard, Diderot, Paris, France. [13] Burns, Trauma and Critical Care Research Centre-UQCCR, Faculty of Medicine, University of Queensland, Brisbane, Australia. [14] Critical Care Department, Attikon University Hospital, Athens, Greece. [15] Centro de Investigación Biomédica en Red, Enfermedades Respiratorias, CIBERES, Madrid, Spain.

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Aliye Bastug, Ankara Numune Training and Research Hospital, Turkey; Amir Vahedian-Azimi, Baqiyatallah University of Medical Sciences, Vanak Square, Tehran, Iran; Asumanlnan, Haydarpasa Numune Hospital, Istanbul, Turkey; Benito Almirante Gragera, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Despoina Koulenti, University of Queensland, Brisbane, Australia and Attikon University Hospital, Athens, Greece; Garyphallia Poulakou, Attikon University Hospital, Athens, Greece; George Dimopoulos, Attikon University Hospital, Athens, Greece; Ilkay Bozkurt, Ondokuz Mayis University, Samsun, Turkey; Igor Muzlovic, University Medical Centre, Ljubljana, Slovenia; Izarne Totorika Hospital Universitario de Donostia, Donostia, Spain; Jordi Rello, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Kostoula Arvaniti, Papageorgiou General Hospital, Thessaloniki, Greece; Leonel Lagunes, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Lilla Bouadma, Hôpital Bichat-Claude-Bernard, Paris, France; Loreto Vidaur, Hospital Universitario de Donostia, Donostia, Spain; Marina Oikonomou, Papageorgiou General Hospital, Thessaloniki, Greece; MatteoBassetti, Infectious Diseases Clinic, Santa Maria Misericordia Hospital, University of Udine, Udine, Italy; Nefise Oztoprak, Antalya Education and Research Hospital, Turkey; Saad Nseir, Hospital Universitaire Lille, Lille, France; Sergio Ramírez-Estrada, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Yolanda Peña-López, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

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Capítulo 6.

FACTORS ASSOCIATED WITH VENTILATOR-ASSOCIATED EVENTS: AN INTERNATIONAL MULTICENTER PROSPECTIVE COHORT STUDY.

Rello J, **Ramírez-Estrada S**, Romero A, Arvaniti K, Koulenti D, Nseir S, Oztoprak N, Bouadma L, Vidaur L, Lagunes L, Peña-López Y; EUVAE Study Group

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RESUMEN

Propósito:

Identificar los factores asociados con los VAE en adultos con ventilación mecánica superior a 48 horas. Los objetivos secundarios fueron identificar variables asociadas a los VAE en el subgrupo de pacientes con intubación endotraqueal y en aquellos que fueron ventilados por más de 7 días.

Métodos:

Se realizó un análisis secundario de una cohorte multicéntrica prospectiva en 6 UCIs en cuatro países europeos (Francia, Grecia, España y Turquía). Se incluyeron sujetos que habían sido sometidos a ventilación mecánica por mas de 48 horas. En pacientes con múltiples episodios de ventilación solo se seleccionó el primero. Las definiciones de VAE se tomaron de la actualización del 2015 de la clasificación del CDC. Los factores asociados a los VAE se calcularon mediante el análisis multivariado de riesgos proporcionales de Cox.

Resultados:

Entre 163 adultos (42 traqueostomías), se documentaron 76 VAE (34,9 VAE/1,000 días con ventilador): 9 de ellos fueron VAC y 67 IVAC-plus (9 IVAC y 58 PVAP). Los VAE se desarrollaron después de una mediana de 6 días (rango intercuartil: 4-9). Los VAE se asociaron de forma independiente con el uso de sedantes y analgésicos de acción prolongada (HR: 4.30), la descontaminación digestiva selectiva (HR: 0.38) y la admisión por cirugía o trauma (HR: 2.30). Entre los 116 sujetos con intubación endotraqueal, la descontaminación digestiva (HR: 0,21) y el ingreso quirúrgico o traumático (HR: 3,11) permanecieron asociados con los VAE. Entre los 102 sujetos ventilados durante más de 7 días, solo los sedantes y analgésicos de acción prolongada (HR: 8,69) permanecieron asociados de forma independiente con los VAE.

Conclusiones:

la implementación de la descontaminación digestiva y la restricción en el uso de analgésicos y sedantes de acción prolongada pueden prevenir VAE tempranos y tardíos, adicionalmente los protocolos desarrollados para prevenir los VAE deben incluir ambas intervenciones.

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ORIGINAL ARTICLE

Factors associated with ventilator-associated events: an international multicenter prospective cohort study

Jordi Rello[1,2,3] · Sergio Ramírez-Estrada[4,5] · Anabel Romero[1,2] · Kostoula Arvaniti[3,6] · Despoina Koulenti[3,7,8,9] · Saad Nseir[10] · Nefise Oztoprak[11] · Lila Bouadma[12] · Loreto Vidaur[13] · Leonel Lagunes[3,14] · Yolanda Peña-López[2,15] · for the EUVAE Study Group

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Abstract

A secondary analysis of a prospective multicenter cohort was performed in six intensive care units (ICU) in four European countries (France, Greece, Spain and Turkey). The main objective was to identify factors associated with ventilator-associated events (VAEs) in adults who underwent mechanical ventilation (MV) ≥ 48 h. Secondary objectives were to identify: variables influencing VAE in the subpopulation with endotracheal intubation and in those subjects who were ventilated > 7 days. Subjects who had undergone MV ≥ 48 h were included. In subjects with multiple episodes of MV, only the first one was eligible. The adult definitions for VAEs were adjusted to the 2015 update of the CDC's 2013 National Healthcare Safety Network Association. Factors associated with VAE were estimated through multivariate Cox proportional hazards analysis. Among 163 adults (42 tracheostomies), 76 VAEs (34.9 VAEs/1,000 ventilator-days) were documented: 9 were Ventilator-Associated Conditions (VAC) and 67 Infection-related Ventilator-Associated Complications (IVAC)-plus (9 only IVAC and 58 Possible Ventilator-Associated Pneumonia). VAEs developed after a median of 6 days (interquartile range: 4–9). VAEs were independently associated with long-acting sedative/analgesic drugs (Hazard Ratio [HR]: 4.30), selective digestive decontamination (SDD) (HR: 0.38), and surgical/trauma admission (HR: 2.30). Among 116 subjects with endotracheal tube, SDD (HR: 0.21) and surgical/trauma admission (HR: 3.11) remained associated with VAE. Among 102 subjects ventilated >7 days, only long-acting sedative/analgesic agents (HR: 8.69) remained independently associated with VAE. In summary, SDD implementation and long-acting analgesic/sedative agents restriction prescription may prevent early and late VAEs, respectively. Bundles developed to prevent VAEs should include these two interventions.

Keywords Ventilator-associated pneumonia · Selective digestive decontamination · Midazolam · Prevention bundles · Mechanical ventilation · Safety

Introduction

The implementation of ventilator bundles should be based on variables that influence the risk of ventilator-associated events (VAEs) [1]. Few studies have defined the risk factors for VAEs or how best to prevent these events. As healthcare systems differ according to geographical region, the composition of the bundles proposed is not the same in the USA, a country where private practice predominates, and in the European Union, with its national health care systems [1–3]. Certain practices such as selective digestive decontamination (SDD) [4] also present regional variations. Thus, potential new ventilator bundles should be based on evidence derived from analyses of associations between VAEs and clinical practice. The variability in clinical practice provides an opportunity to identify potential areas that might benefit from intervention.

Recently, two prospective studies with a similar design [5, 6] carried out by our group have described VAEs in adults and children undergoing mechanical ventilation (MV). Subjects recruited at six different sites from Europe were studied in

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✉ Anabel Romero
arm.anabel@gmail.com

Extended author information available on the last page of the article

order to identify variables associated with a first VAE. Our hypothesis was that many variables would be suitable for intervention. Our main objective was to identify factors associated with VAEs in patients who underwent MV ≥ 48 h. Secondary objectives were to identify variables influencing VAE in the subpopulation with endotracheal intubation, and in patients who underwent MV during more than 7 days.

Methods

Study design and inclusion criteria

The study was a secondary analysis of a prospective, international, multicenter study [6]. Thirty consecutive subjects who had undergone MV for 48 h or more were eligible. Sites reporting less than two VAE episodes or less than two controls were excluded (Figure 1 of the electronic supplementary material). Subjects with ICU-acquired respiratory viral infections were also excluded. Daily follow-up was implemented for 30 days. Duration of MV was considered until extubation or ICU death. In patients with more than one episode of MV, only the first one was considered. Data were collected through a collaborative web database (http://compartint.net/euvae/). An external quality assessment was performed for severity-of-illness score in a 5% sample of variables, which reported an agreement above 83%.

Definitions

An episode of ventilation was defined by the number of consecutive days during which the patient was ventilated. A period of at least one calendar day off the ventilator, followed by re-initiation of ventilation, defined a new episode of ventilation. The adult definitions for ventilator-associated events were adjusted to the 2015 update [7] (Fig. 1) of the CDC's 2013 National Healthcare Safety Network [8]. Delirium definition was reported elsewhere [9].

Study variables

The following patients' characteristics were considered: gender, age, presence of comorbidities, body mass index, and severity-of-illness index. High severity was defined as an APACHE II score above 20. Medical, surgical, and trauma patients were included.

Reasons for intubation included the following: respiratory failure, surgery, cardiogenic shock, altered level of consciousness, and sepsis/septic shock. Intubation could be performed in the ICU or elsewhere (operation room, pre-hospital, emergency department or hospital ward). Other variables recorded were implementation of SDD, chlorhexidine rinse (0.12%, 0.2% or 2% concentrations) for oral care, spontaneous breath trials, pharmacological paralysis, early mobility, tracheostomy, vasopressors, red blood cell units transfused, delirium, type of sedation (continuous or intermittent), drugs for sedation (midazolam, propofol), as well as drugs for analgesia (fentanyl, morphine, remifentanyl). Analgesic and sedative drugs were classified as follows: long-acting drugs (midazolam, fentanyl, morphine) and short-acting drugs (propofol, remifentanyl).

The following patients' outcomes were considered: length of stay (ICU and hospital) and ICU mortality.

Statistical analysis

A descriptive analysis was performed for patient characteristics, reporting percentages and medians, with its interquartile ranges (IQR) for quantitative variables. Two measures of VAE incidence were computed: (1) number of VAEs divided by the total number of ventilator-days and (2) number of VAEs divided by the total number of episodes of MV. To compare proportions, we used the Pearson's X^2 test, whereas to compare medians of quantitative variables (length of stay, ICU and hospital) we used the Mann-Whitney U test.

Association between factors and VAEs was estimated using Cox proportional hazards regression models. Hazard ratios (HR) and 95% confidence intervals (CI) were computed. Three multivariate models were constructed, according to the characteristics of patients included: (1) overall population, (2) patients with endotracheal tube, and (3) patients who underwent MV during more than 7 days. A fourth multivariate model was constructed to assess the association between factors and IVAC-plus. Patients were censored on extubation or death. We considered time-dependent variables for daily sedative and analgesic drugs, spontaneous breath trials and pharmacological paralysis. All multivariate analyses were adjusted by center. Variables were considered for the multivariate model if they reached a p value of 0.10 in the univariate Cox proportional hazards regression models. Statistical significance was considered if the p value was < 0.05. All statistical analyses were performed using the SPSS Statistics version 25.0 (IBM).

Results

The study population included 163 patients undergoing MV (2,178 ventilator-days) for at least 48 h at 6 intensive care units (ICU) in 4 European countries (France, Greece, Spain and Turkey). Forty-two (25.8%) underwent a tracheostomy. Males ($n = 103$, 63.2%) were predominant. Median age was 60 years (IQR: 48–72) and median APACHE II Score was 21 (IQR: 14–26). Patients' characteristics are summarized in Table 1. Acute respiratory failure was the cause of intubation in 79 (49.1%) patients. The presence of two or more

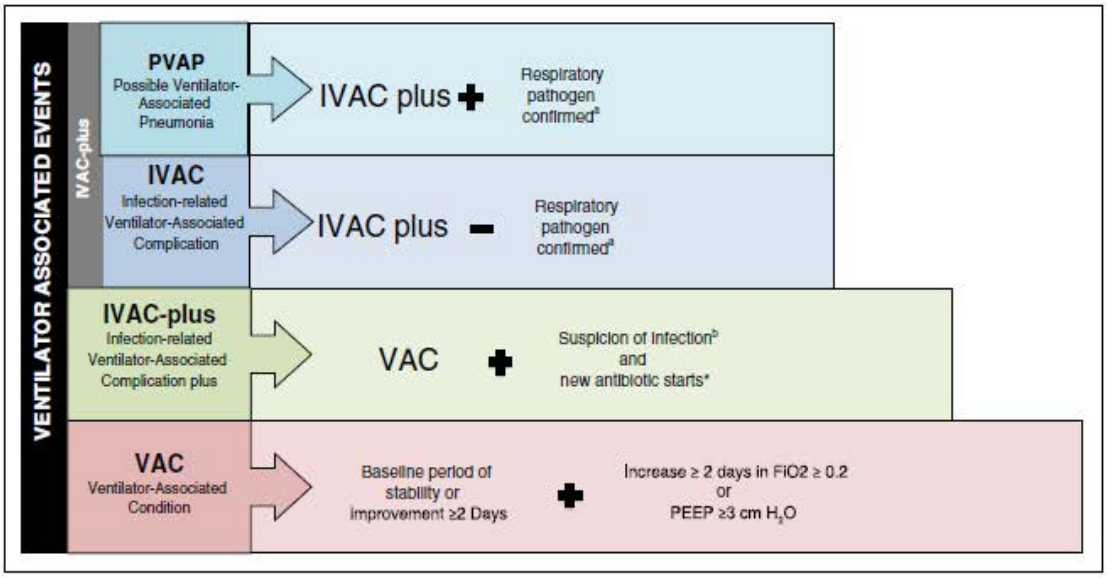

Fig. 1 Ventilator-associated events definitions. *The new antimicrobial agent must be started and sustained for at least 4 calendar days. [a]Respiratory pathogen confirmation: one of the following: (1) positive culture of respiratory samples meeting quantitative or semi-quantitative thresholds or (2) insufficient growth of a pathogenic microorganism in respiratory samples plus purulent sputum (> 25 neutrophils and ≤ 10 squamous epithelial cells per low power field) or (3) organisms identified from pleural fluid specimen, positive tests for *Legionellas* species, or positive lung histopathology. [b]Suspicion of infection: fever (≥ 38 °C) or hypothermia (≤ 36 °C) or leukocytosis (≥ 12,000 cells/mL) or leukopenia (≤ 4,000 cells/mL)

comorbidities was identified in 51 patients (32.7%). Of 76 VAEs (34.9 per 1,000 ventilator-days, 46.6 per 100 episodes), 9 were Ventilator-Associated Conditions (VAC) and 67 Infection-related Ventilator-Associated Complications (IVAC)-plus (9 only IVAC and 58 Possible Ventilator-Associated Pneumonia). Median day of VAE onset was day 6 (IQR: 4–9), with 51 (67.1%) presenting within the first 7 days of MV. IVAC-plus (the sum of IVAC and PVAP) represented 44 out of 52 VAEs (84.6%) within the first 7 days of ventilation compared with 23 out of 24 VAEs (95.8%) 7 days or more after MV ($p = 0.258$). Fifty of 163 patients (30.7%) died. VAEs were significantly more common among patients who died (58.0% vs 41.6%, $p = 0.05$). Most ICU deaths occurred early during hospitalization (median 6 days, IQR: 5–9), 36 (72.0%) of them during the first 15 days. In survivors, median length of stay was significantly higher, both for ICU (29 vs 13 $p < 0.05$) and for hospital (48 vs 23 $p < 0.05$) in patients developing VAEs.

Factors associated with VAE, adjusted by center, are reported in Table 2. In the overall population, a VAE was more likely to occur in trauma or surgical patients (HR: 2.30) than in medical patients. Long-acting drugs prescription (HR: 4.30) was identified as a risk factor for VAE, whereas the use of SDD was identified as a protective factor for VAE (HR: 0.38) ($p < 0.05$). In subjects with endotracheal tube, surgical or trauma admission was also identified as a risk factor for developing a VAE (HR: 3.11); again, SDD was identified as a protective factor (HR: 0.21) ($p < 0.05$). In patients under MV during more than 7 days, the prescription of long-acting drugs was identified as a risk factor for developing a VAE (HR: 8.69) ($p < 0.05$). Factors associated with IVAC-plus are reported in Table 3 of the electronic supplementary material section. SDD was identified as a protective factor for developing an IVAC-plus (HR: 0.31) and long-acting drugs prescription was identified as a risk factor for IVAC-plus (HR: 3.83) ($p < 0.05$). Distribution of VAE incidences, time to VAE, duration of MV, SDD use, type of patient, and the use of long-acting drugs, according to each participant ICU, is detailed in Table 4 of the electronic supplementary material.

Discussion

This study of a multicenter cohort of mechanically ventilated subjects is the first to assess variables potentially associated with VAEs. VAEs were common, being PVAP six times more frequent than IVAC alone, which emphasizes the relevance of efforts to prevent respiratory infections. Interestingly, both SDD implementation and long-acting sedative/analgesic agents use, variables that are amenable to intervention, significantly influenced VAEs, and their influence remained significant when subjects with tracheostomy were excluded. Lastly, our study confirms the association of VAEs with worse outcomes.

Our findings indicate that compliance with SDD can influence the risk of developing VAEs. The high proportion of IVAC-plus in our cohort may explain why SDD implementation independently reduced VAE rates in subjects submitted to

Table 1 Patients' characteristics

Characteristic	Total *N* (%) 163 (100.0)	VAE *N* (%) 76 (46.6)	No VAE *N* (%) 87 (53.4)
Sex *N* = 163			
Female	60 (36.8)	23 (38.3)	37 (61.7)
Male	103 (63.2)	53 (51.5)	50 (48.5)
Age* *N* = 163	60 (48–72)	62 (49–73)	59 (46–68)
≤ 40	32 (19.6)	12 (37.5)	20 (62.5)
41–60	50 (30.7)	23 (46.0)	27 (54)
>60	81 (49.7)	41 (50.6)	40 (49.4)
APACHE score* *N* = 160	21 (14–26)	20 (12–24)	23 (15–29)
High severity (>20)	83 (51.9)	34 (41)	49 (59)
Low severity (≤20)	77 (48.1)	40 (51.9)	37 (48.1)
Comorbidities *N* = 156			
≤ 1	105 (67.3)	54 (51.4)	51 (48.6)
≥ 2	51 (32.7)	22 (43.1)	29 (56.9)
Reason of intubation *N* = 161			
Respiratory failure	79 (49.1)	35 (44.3)	44 (55.7)
Other	82 (50.9)	39 (47.6)	43 (52.4)
Surgery	25 (15.5)	15 (60.0)	10 (40)
Cardiogenic shock	2 (1.2)	1 (50.0)	1 (50)
Altered level of consciousness	41 (25.5)	20 (48.8)	21 (51.2)
Sepsis. Septic shock	14 (8.7)	3 (21.4)	11 (78.6)
Place of intubation *N* = 163			
Intensive care unit	76 (46.6)	35 (46.1)	41 (53.9)
Other	87 (53.4)	41 (47.1)	46 (52.9)
Anesthesia/operating room	30 (18.4)	19 (63.3)	11 (36.7)
Pre-hospital	22 (13.5)	5 (22.7)	17 (77.3)
Emergency department	17 (10.4)	11 (64.7)	6 (35.3)
Hospital ward	18 (11.0)	6 (33.3)	12 (66.7)
Type of patient *N* = 163			
Medical	101 (62.0)	37 (36.6)	64 (63.4)
Other	62 (38.0)	39 (62.9)	23 (37.1)
Surgical	47 (28.8)	28 (59.6)	19 (40.4)
Trauma	15 (9.2)	11 (73.3)	4 (26.7)

VAE ventilator-associated event, *APACHE* acute physiology and chronic health disease classification system *median and interquartile range

Table 2 Factors associated with VAE: multivariate cox proportional hazards models

Factor	HR (95%CI)		
	Overall (*N* = 163)	Endotracheal tube (*N* = 116)	MV > 7 days (*N* = 102)
Type of patient, surgical, or trauma	**2.30 (1.04–5.1)**	**3.11 (1.04–9.32)**	1.68 (0.69–4.1)
SDD	**0.38 (0.15–0.92)**	**0.21 (0.06–0.72)**	0.43 (0.14–1.26)
Tracheostomy	0.88 (0.39–2.01)	–	0.75 (0.3–1.89)
Long-acting drugs*	**4.30 (1.62–11.42)**	2.56 (0.77–8.54)	**8.69 (2.53–29.86)**

VAE ventilator-associated event, *CI* confidence interval, *HR* hazard ratio, *MV* mechanical ventilation, *SDD* selective digestive decontamination

* Long-acting drugs: midazolam, fentanyl, and morphine. Results in bold are statistically * significant, p<0.05

long periods of MV. Another explanation for the effect of SDD on VAE is that much of VAE consists of tracheal colonization combined with a non-infectious pulmonary pathology such as pleural effusion, atelectasis, or pulmonary edema. Preventing tracheal colonization is the mechanism by which many VAP-prevention strategies such as subglottic suction, silver impregnated tubes, and oral decontamination work.

Moreover, our results also identify long-acting sedatives/analgesic agents as an independent risk factor for VAEs, rather than delirium, suggesting that intervention in sedative/analgesic prescription might be a possible strategy of prevention. This may be related with a higher probability of impregnation when prescribing drugs prone to being accumulated, and also with an underestimation of delirium if a systematic delirium-screening instrument is not used for its diagnosis in the ICU. If only clinical criteria are applied, it is the hyperactive subtype that will usually be detected [10]. However, recent data show that most delirious ICU patients have hypoactive delirium, which is more frequent in patients with more severe illness and undergoing MV [11]. Thus, the spontaneous breathing trial was not found to protect against VAE in our cohort. These findings are in line with the association between benzodiazepines and increased MV duration and ICU stay compared with other sedatives, as described in two recent meta-analyses [12, 13] and a cohort study [14]. Although midazolam may be considered as a short-acting benzodiazepine, its pharmacokinetic profile, with phase 1 and phase 2 metabolism and an end-active metabolite with renal excretion, frequently results in accumulation, over-sedation, and delayed wakening in the ICU, particularly in older and sicker patients, as it has been pointed out by Wyncoll et al. [15]. When analyzed midazolam in conjunction with morphine and fentanyl, those continuous around-the-clock drugs resulted the most important factor for developing VAE.

In the coming years, it would be interesting to analyze the role of alpha-2 agonists, which were hardly used in Europe during our study recruitment period [16], and the impact of new non-benzodiazepine sedation approach and ICU delirium guidelines on VAE [17–19]. In recent years, there has been an increasing concern with delirium in the ICU and its impact on patient safety and outcomes, and indeed delirium has been included in some evidence-based interventions designed to reduce adverse events in hospitals [20]. On the other hand, the difficulty of ventilator-associated pneumonia (VAP) diagnosis and the discrepancies in antibiotic consumption despite reporting/achieving low VAP rates [21] have shifted the focus of quality-improvement on patient outcomes beyond the mere recording of VAP rates in ventilated patients, and the concept of VAE has emerged.

Conservative rather than liberal fluid resuscitation will increase the number of ventilator-free days and several studies [14, 22] have reported a relation between VAEs and excess fluids. However, our data did not find this association, perhaps due to differences in case mix, comorbidities (cardiomyopathy), VAC rates or measurement of fluid overload, or because the other studies limited their assessment to the first 4 days of ICU stay [14]. Other studies of potentially modifiable VAE risk factors [14, 22–26] have identified blood transfusions and mandatory modes of MV with high inspiratory pressure.

This study has several limitations. First, in spite of the multicenter design, the fact that only a few events per site were analyzed limits its power to identify potential risk factors. Second, dexmedetomidine was not properly evaluated due to its low use in the ICUs during the period of study, and further studies are needed to identify its potential effect. Third, this study was conducted in Europe and the interpretations may not be applicable to other settings, due to the large variation in therapeutic strategies, and duration of MV. Fourth, some potentially relevant variables such as average gastric retention were not evaluated. Five, the number of trauma patients is small and variables can be different in other case-mixes. Lastly, we considered the entire period of MV: other variables may be relevant if the time span is limited, for instance to the first 4 days of ventilation.

Conclusions

Future bundles should include SDD implementation and long-acting analgesic/sedative agent restriction as potential strategies to prevent VAEs.

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Compliance with ethical standards

Conflict of interest Dr. Rello has served on the speakers' bureau and as a consultant for Cubist, Bayer, ROCHE, Medimmune, Pfizer, Anchoagen, and Aridis. The other authors report no conflicts of interest relevant to this article.

Ethical approval/informed consent The study protocol was approved by the institutional review board on human research at each participating center and at Vall d'Hebron Barcelona Hospital Campus, the coordinating center [PR(AG)25/2014]. Patients (or the relatives of unconscious patients) were asked to provide written consent prior to participation in the study.

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V. RESUMEN GLOBAL DE LOS RESULTADOS

El nuevo algoritmo reportó 117 episodios, 64 (57%) de ellos secundarios a infección, el 44% restante fue debido a atelectasias, SDRA y edema agudo de pulmón. La clasificación previa identificó 84 VARI, de ellos 60% correspondían a traqueobronquitis y 40% a neumonía. Los pacientes que presentaron VAEs tardaron más en ser extubados y presentaron una mayor estancia hospitalaria y en UCI (5, 12 y 11 días respectivamente), adicionalmente la presencia de infección pulmonar se asoció a un incremento en la mortalidad independientemente de la clasificación usada. Un 54% de las VARI fueron reclasificados como no infecciosos por el nuevo algoritmo, por otra parte, este último falló en determinar la proporción de neumonía y traqueobronquitis debido a la ausencia del criterio radiológico. 67% de los VAE se presentaron durante la primera semana siendo más frecuentes en los pacientes expuestos a sedantes de vida media larga (HR: 4.3) y en aquellos cuyo ingreso se debió a cirugía o traumatismo (HR 2.3) mientras que la descontaminación digestiva demostró ser un factor protector (HR 0.38); en los VAE tardíos (> 7 días) el uso de sedantes de larga acción continuó siendo una variable independiente (HR:8.7) pero el motivo de ingreso y la descontaminación digestiva perdieron su efecto.

Una descripción detallada de la correlación entre ambas clasificaciones puede verse en la figura 3 del capítulo 4.

VI. RESUMEN GLOBAL DE LA DISCUSIÓN DE LOS RESULTADOS

La discusión de los resultados se presenta en un tercer artículo (capítulo 8) en el cual se realizó un análisis comparativo de ambas clasificaciones concluyendo que son herramientas complementarias cuya aplicación e interpretación debe basarse en el juicio clínico y en las características del paciente; la nueva clasificación (VAE) presenta una mayor sensibilidad para detectar eventos no infecciosos además facilita su informatización e incorporación en sistemas de vigilancia pero su capacidad para diferenciar traqueobronquitis y neumonía es limitada, además solo selecciona los casos más severos, aspectos que constituyen la fortaleza de la clasificación previa (VARI).

Usando los conocimientos obtenidos tras la interpretación de los resultados se desarrollaron un artículo (capítulo 9) y un editorial (capítulo 10) resaltando la importancia de implementar protocolos dirigidos a disminuir la duración de la ventilación mecánica basados en el uso de sedación ligera, pruebas de respiración espontánea, movilización precoz y la descontaminación digestiva y señalando futuros campos de investigación como la inclusión del ultrasonido, nuevos biomarcadores y otras técnicas de medicina molecular en el abordaje de los VAE. El capítulo 11 ofrece una explicación detallada del algoritmo VAE y brinda pautas para su implementación en la práctica clínica y su incorporación en modelos de vigilancia, señalando los problemas que pueden presentarse durante el proceso.

VII. CONCLUSIONES Y LINEAS DE FUTURO

Capítulo 7. Conclusiones

1. Los VAE son una entidad frecuente y su presencia se asocia a un aumento en la tasa de mortalidad, prolongación de la estancia hospitalaria y retrasos en la extubación, siendo las infecciones de la vía aérea inferior, las atelectasias, el SDRA y el edema agudo de pulmón los eventos mas frecuentes.

2. La descontaminación digestiva selectiva y el uso de sedantes de vida media corta son factores protectores frente a los VAE y deben incluirse en los protocolos de manejo del paciente ventilado.

3. El uso de la FiO2 y la PEEP como variables subrogadas de la hipoxemia constituye una estrategia segura y sensible en la detección temprana de los VAE, además permite crear y modificar planes de tratamiento en tiempo real ajustados a las características de cada paciente.

4. La detección de los eventos no infecciosos permite su tratamiento precoz y evita el uso innecesario de antibióticos.

Capítulo 8. Líneas de futuro

Todo lo que un hombre pueda imaginar otros podrán hacerlo realidad

Julio Verne

1. Es necesario el diseño de estudios que analicen la inclusión de los VAE en protocolos diagnósticos y programas de vigilancia epidemiológica debido a su capacidad para detectar y discriminar eventos infecciosos y no infecciosos además de su asociación pronóstica.

2. Se requiere valorar en profundidad el papel de la hipoxemia y sus variables subrogadas como herramienta diagnóstica y pronóstica en el paciente en ventilación mecánica y establecer puntos de corte en los parámetros ventilatorios que permitan crear alertas de detección temprana.

3. Nuevas líneas de investigación deben ser diseñadas con el fin de conocer el papel de las nuevas tecnologías como los biomarcadores y la ecografía torácica en el abordaje diagnóstico y evolutivo de los pacientes con VAE.

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Las referencias de los capítulos 4,5 y del 8 al 11 se presentan en su respectivo artículo.

PARTE ADICIONAL. CONTINUACIÓN DE LA INVESTIGACIÓN

"The good physician treats the disease; the great physician treats the patient who has the disease."

Sir William Osler

IX. DISCUSIÓN DE LOS RESULTADOS

Capítulo 9.

VENTILATOR-ASSOCIATED EVENTS VERSUS VENTILATOR-ASSOCIATED RESPIRATORY INFECTIONS-MOVING INTO A NEW PARADIGM OR MERGING BOTH CONCEPTS, INSTEAD?

Ramirez-Estrada S, Peña-Lopez Y, Kalwaje Eshwara V, Rello J.

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RESUMEN

A pesar de que las VARI son la complicación más frecuentemente asociada a la ventilación mecánica no son las únicas. La nueva clasificación de los VAE propuesta por el CDC aumentó el espectro diagnóstico al incluir eventos tanto infecciosos como no infecciosos. Tanto las VAE como las VARI se asocian con una mayor duración de la ventilación, estancias más prolongadas en el hospital y en la UCI y a un mayor consumo de antibióticos; sin embargo, los pacientes con VAE tienen peores resultados. Los algoritmos VARI y VAE se centran en diferentes objetivos y la correlación entre ambas clasificaciones es baja. Los criterios diagnósticos de la clasificación tradicional tienen baja especificidad y las complicaciones no infecciosas pueden ser malinterpretadas como VARI, mientras que la nueva clasificación (VAE) amplía la capacidad para detectar eventos no infecciosos, pero excluye las VARI menos graves. Las patologías no infecciosas explican hasta el 30% de los VAE, siendo las causas principales la atelectasia, el SDRA, el edema pulmonar y la embolia pulmonar. La incorporación de los VAE en programas informáticos de vigilancia es eficiente y útil como indicador de calidad en la UCI, mientras que las diferencias en la interpretación de los criterios VARI limitan su papel en el diseño de protocolos y sistemas de prevención. En resumen, un abordaje integral de las complicaciones asociadas a la ventilación mecánica debe combinar ambos algoritmos y soportarse en la experiencia clínica.

Review Article

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

Sergio Ramirez-Estrada[1,2], Yolanda Peña-Lopez[3], Vandana Kalwaje Eshwara[4], Jordi Rello[3,5]

[1]Critical Care Department, Clínica Corachan, Barcelona, Spain; [2]Medicine Department, Universitat Autónoma de Barcelona, (UAB), Barcelona, Spain; [3]Vall d'Hebron Institut of Research, Barcelona, Spain; [4]Department of Microbiology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India; [5]Centro de Investigación Biomédica en Red (CIBERES), Instituto Salud Carlos III, Madrid, Spain

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Correspondence to: Sergio Ramírez Estrada, MD. Clínica Corachan, Carrer de Buïgas, 19, 08017 Barcelona, Spain. Email: sergioramirezestrada@hotmail.com.

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)

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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 °C) or hypothermia (≤36 °C) 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.

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Footnote

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Capítulo 10.

LIMITING VENTILATOR-ASSOCIATED COMPLICATIONS IN ICU INTUBATED SUBJECTS: STRATEGIES TO PREVENT VENTILATOR-ASSOCIATED EVENTS AND IMPROVE OUTCOMES.

Peña-López Y, **Ramirez-Estrada S**, Eshwara VK, Rello J.

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RESUMEN

Propósito:
Revisión de las complicaciones infecciosas (VAP y VAT), y no infecciosas (edema pulmonar, SDRA y atelectasias) asociadas a la ventilación mecánica y de las estrategias actuales para limitar su aparición.

Métodos:
Análisis de las nuevas definiciones del CDC de los VAE incluyendo VAC, IVAC-plus, IVAC y PVAP

Resultados:
Se recomienda reemplazar las definiciones tradicionales de VAP y VAT por la nueva clasificación de VAE propuesta por el CDC

Conclusiones:
El diseño e implementación de protocolos destinados a evitar los factores desencadenantes de los VAE y la promoción de medidas que reduzcan la exposición y la duración de la ventilación mecánica deben ser una prioridad en el manejo del paciente crítico

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REVIEW

Limiting ventilator-associated complications in ICU intubated subjects: strategies to prevent ventilator-associated events and improve outcomes

Yolanda Peña-López[a], Sergio Ramirez-Estrada[b], Vandana Kalwaje Eshwara[c] and Jordi Rello[d]

[a]Pediatric Critical Care Department, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [b]Critical Care Department, Clinica Corachan, Barcelona, Spain; [c]Department of Microbiology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal University, Manipal, India; [d]Clinical Research/epidemiology In Pneumonia & Sepsis, Vall d'Hebron Institut of Research & Centro de Investigacion Biomedica en Red (CIBERES), Barcelona, Spain

ABSTRACT

Introduction: Intubation is required to maintain the airways in comatose patients and enhance oxygenation in hypoxemic or ventilation in hypercapnic subjects. Recently, the Centers of Disease Control (CDC) created new surveillance definitions designed to identify complications associated with poor outcomes.

Areas covered: The new framework proposed by CDC, Ventilator-Associated Events (VAE), has a range of definitions encompassing Ventilator-Associated Conditions (VAC), Infection-related Ventilator-Associated Complications (IVAC), or Possible Ventilator-Associated Pneumonia – suggesting replacing the traditional definitions of Ventilator-Associated Tracheobronchitis (VAT) and Ventilator-Associated Pneumonia (VAP). They focused more on oxygenation variations than on Chest-X rays or inflammatory biomarkers. This article will review the spectrum of infectious (VAP & VAT) complications, as well as the main non-infectious complications, namely pulmonary edema, acute respiratory distress syndrome (ARDS) and atelectasis. Strategies to limit these complications and improve outcomes will be presented.

Expert commentary: Improving outcomes should be the objective of implementing bundles of prevention, based on risk factors amenable of intervention. Promotion of measures that reduce the exposition or duration of intubation should be a priority.

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Complications; mechanical ventilation; surveillance; ventilator-associated event; ventilator-associated pneumonia; ventilator-associated tracheobronchitis

1. Introduction

Intubation and mechanical ventilation (MV) can be harmful as well as lifesaving. Despite implementation of less invasive strategies of oxygenation, invasive mechanical ventilation still remains a common modality of management in intensive care units (ICUs) for patients of all age groups to maintain the airways in comatose patients and enhance oxygenation in hypoxemic or ventilation in hypercapnic subjects [1–4]. But the process of invasive mechanical ventilation is not without complications encompassing those related to positive pressure ventilation and ventilator-associated respiratory infections (VARIs) [3,4]. Cox CE et al., in a review, illustrated that 1-year mortality among patients requiring MV >10 days is 50–60% and the costs incurred are nearly 10 times greater than the average for severe sepsis [5].

In this review, we discuss the complications of mechanical ventilation and the potential for their prevention under the United States Centers for Disease Control and Prevention (CDC) framework of ventilator-associated events (VAEs). Complications associated with intubation procedure per se (hypoxemia, cardiac arrest) and local complications produced by the endotracheal tube (trauma to the vocal cords, larynx, development of subglottic stenosis) are beyond the scope of this review and hence not been discussed. The plan of the review is detailed in Table 1.

2. Body

2.1. Mechanical ventilation: current scenario and types of complications

The pooled mean ventilator utilization ratio reported in critical care units by the National Health Safety Network (NHSN) of United States was between 0.24 and 0.47, highest being shown from trauma units [6]. In pediatric critical care units, the pooled mean ventilator utilization ratio reported was 0.37–0.39 [7]. In other large databases, between 39.5% and 48.8% patients in ICU were mechanically ventilated and surgical patients relatively had a higher risk of being on MV, although admission to ICUs were predominated by medical patients. ICUs in academic hospitals had the highest percentage (50.8%) of mechanically ventilated patients at any given hour [1,8]. However, practically, MV patients may far exceed this number due to shortage of beds. In a prospective multicenter study in pediatric ICUs during the season for acute lower respiratory infection, Farias et al. reported 55% of patients receiving MV [9]. Main indications

CONTACT Jordi Rello jrello@crips.es Vall d'Hebron Institut of Research & Centro de Investigacion Biomedica en Red (CIBERES), Ps. Vall d'Hebron 129, AMI-14, 08035, Barcelona, Spain

Table 1. Outline of the review.

1	Current scenario of mechanical ventilation
2	Types of complications reported in the literature and outcomes
3	Infectious complications: ventilator-associated pneumonia and ventilator-associated tracheobronchitis
4	Correlation between 2008 CDC (VAP & VAT) versus 2013 (IVAC-plus events) definitions
5	Non-infective complications and ventilator-associated conditions (VAC)
6	Limiting complications: the ventilator care bundle approach
7	Weaning practices
8	Compliance to protective ventilation and weaning practices
9	Integrated approach for successful implementation: a safety ventilator bundle of care and VAE
10	Monitoring complications and quality indicators
11	Monitoring non-infectious complications
12	Unplanned extubation rates
13	VAE rates: new quality indicators for ventilation episodes
14	Education and bundles of care

of MV were acute respiratory failure (78%), altered mental status (15%), and acute on chronic pulmonary disease in 6%.

Subjects requiring prolonged MV >21 days varied significantly between regions of differing health-care facilities. In China, where no facility for long-term care centers exists, the rate of prolonged MV was 36%, while a U.K. database showed only 6.3% [10,11]. In children, prolonged mechanically ventilated patients correspond to 2.5–3% of the population admitted to pediatric ICUs and they generally have a tracheostomy in place [12].

In 2013, the Centers for Disease Control and Prevention opened their focus and broadened the surveillance objective from VAP to any complication of mechanical ventilation with the new Ventilator-Associated Event algorithm [13]. There are three definition tiers within the VAE algorithm: (1) ventilator-associated condition (VAC), (2) infection-related ventilator-associated complication (IVAC), and (3) possible or probable pneumonia (PsVAP/PrVAP) as shown in Figure 1. In the 2015 update [14], probable and possible pneumonia were classified together as possible ventilator associated pneumonia (PVAP), and a new category (IVAC-plus) was created, comprising overall events meeting at least IVAC definition: the sum of IVAC + PVAP events.

The VAE incidence in U.S. health-care facilities is between 2 and 11.79/1000 ventilator days, trauma ICUs reporting the highest. Almost half of the adult ventilated patients develop any type of VAE during the first 30 days [15]. Patients with VAEs show high mortality, 31% dying during hospitalization [6]. Several other studies have reported worse outcomes in both adult and pediatric patients [6,16–18]. Consequently, although these definitions were created only for surveillance, there is a great interest in their clinical correlation. Thus, infectious ventilator-associated complications and non-infectious associated complications could be correlated with IVAC-plus and VAC events, respectively. Mechanical complications, such as pneumothorax, diaphragm dysfunction, or ventilator-induced lung injury (VILI) are other complications amenable to prevention (Table 2).

Traditionally, the infective complication of mechanical ventilation has been focused only on VAP. In 2009, Craven

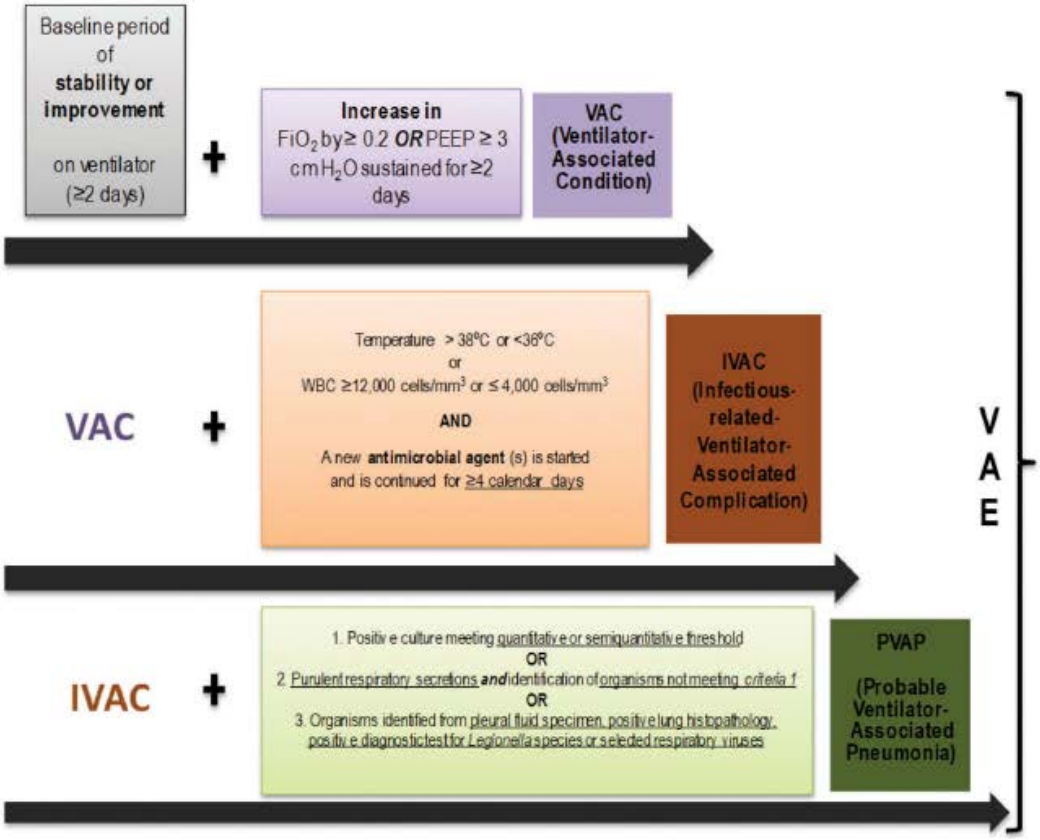

Figure 1. Three tiers of ventilator associated events (VAE) algorithm.

Table 2. Complications of mechanical ventilation.

a	Complications of intubation
b	Impaired Host Defense
c	Effects of endotracheal tube
d	Decreased cough efficacy
e	Impaired mucocilliary clearance
f	Sedation and paralysis: ventilator-induced diaphragmatic dysfunction
g	Oxygen toxicity
h	Hemodynamic compromise: auto-PEEP
i	Ventilator-induced lung injury (VILI)

introduced the role of ventilator-associated tracheobronchitis (VAT), defining VAT as a different process from tracheal colonization, only differentiated from VAP by the absence of new infiltrates on chest radiograph [19,20]. Nevertheless, in clinical practice, not all VAPs are preceded by VAT and not all VATs progress to VAP without antibiotic treatment. Few authors argued that some VATs are in fact VAPs, which have not been detected by chest X-ray yet [21]. In the last years, there is accumulating evidence for VAT as an important nosocomial infection, being associated with an increase in ventilation duration, ICU length of stay, and antibiotic consumption [20,22–25]. This evidence has reopened the debate on the need of treating VAT [26]. It has been reported that antimicrobial treatment improves weaning outcomes with a definitive tendency toward more ventilation-free days and shorter ICU days [24]. Interestingly, translational research has shown VAT and VAP as two different entities related with a different adaptive response of the host to the bacterial colonization of the lower respiratory tract [27,28]. Thus, it seems more reasonable referring to VARIs as infective complications of mechanical ventilation.

VARIs including both ventilator-associated pneumonia (VAP) and VAT occur in approximately 10–30% of all MV patients with an incidence of 1–30/1000 ventilator days in western countries [29–33]. In the pediatric population, VAT episodes are more frequent than VAP (3.13–8.30 per 1000 ventilator-days) [18,34]. Furthermore, VAT has been related to tracheostomy [35,36]. On the other hand, the impact on ICU mortality of VAP and VAT is not the same, as reported in the TAVeM study (crude mortality 40% vs 29%) [37]. Studies have shown the attributable mortality of VAP is around 4–9% varying with definitions, case-mix, bacterial types, and treatment adequacy [38,39]. Conversely, two studies excluding patients with VAT who eventually developed VAP did not found association with VAT and higher attributable mortality (OR. 1.02) [40,41].

Low agreement has been reported between the novel CDC definitions and VAP [16,42,43], whereas subjects with VAEs present higher mortality, longer mechanical ventilation, ICU days, and increased antimicrobial use [42,44–47]. These findings are consistent with a recent meta-analysis, demonstrating that VAE tiers rather than standard VAP criteria were associated with worse outcomes including mortality [16]. Additionally, subjects classified as the third tier (PVAP) by the CDC-2013 VAE algorithm had worse outcomes compared with CDC-2008 (VARI) events [17,18].

IVAC-plus is defined by VAC associated with an abnormal temperature or white blood cell count and the start of a new antimicrobial treatment which is sustained for at least 4 days, being the most prevalent event in a recent multicenter study [15]. However, these definitions remain controversial, because: (1) clinical practice guidelines advocate early initiation of antibiotic treatment when a severe respiratory infection is detected even without confirmation of the pathogen [48], (2) there are many non-respiratory conditions which mimics a respiratory infection. In these cases, the accomplishment or not of ≥4-day-therapy requirement with the new antimicrobial agent to meet IVAC-plus criteria may vary depending on the availability of molecular diagnostics, newer biomarkers for monitoring [49–52], and individual hospitals' antimicrobial stewardship program implementation [53–57], and (3) the cause of antibiotic initiation and continuation may be an extra-pulmonary infection. As a result, IVAC-plus includes many non-infective complications (and non-respiratory causes) of hypoxemia [58]. Rello et al. estimated that IVAC definitions missed ¼ episodes of VAP and ¾ VAT [15] due to lack of impact on ventilator settings. These limitations can be explained because current tiers do not support key decisions such as timing of culture, antibiotic exposure, or reassessment for infection-related parameters [59].

Interestingly, recent reports [17,18] shift the interest from labeling episodes as VAP or VAT to identify the degree of hypoxemia, which can be used to target the duration of antimicrobials. Indeed, Klompas et al. already reported that very short antibiotic courses (1–3 days) were associated with outcomes similar to courses >3 days in patients with suspected VAP but minimal and stable ventilator settings [60].

Well-known non-infective complications, such as fluid overload/hypervolemia, atelectasis, ARDS, or air leak syndromes represent a small percentage of VAC when the VAE framework is applied [6,61]. Additionally, the clinical importance of VILI is widely recognized supporting its association with ARDS and mortality [61,62]. Pneumothorax was associated with a >2-fold increase in the risk of death [63] in MV subjects. A recent multinational report on postoperative patients pointed out that the magnitude of non-infectious pulmonary complications was independently associated with peak pressure [64]. Incorporation of bedside lung ultrasounds have demonstrated higher sensitivity, specificity, and diagnostic accuracy than chest X-rays for atelectasis, consolidation, pulmonary edema, and pneumothorax in critically ill patients [65].

Subsequently to the introduction of VAE surveillance in 2013, the importance of monitoring non-infective mechanical complications has been highlighted. Patients with only VAC are more likely to die during their hospitalizations than patients with IVAC-plus [6]. Several reports identify ARDS, pulmonary edema, and atelectasis as common causes of VAC (with incidences around 16%, 15%, and 10%, respectively) [66,67]. When applying the VAE framework in adults, main causes were atelectasis (55%), ARDS (13%), and pulmonary edema (4%) [15]. In pediatric ICUs, atelectasis is more common than pulmonary edema [18], whereas the incidence of ARDS is lower in adults [36,68]. These differences in the etiology of VAC may be related to different case-mix, different diagnostic tools, and anatomical–physiological differences between adult and pediatric populations, with children having different

response to injury in mechanical ventilation and increased risk for atelectasis [69,70]. On the other hand, Millington et al. recently reported a low rate (51–57%) in expert agreement in the interpretation of lung ultrasound studies performed on mechanically ventilated patients [71]. Therefore, it seems to be beneficial to encompass both infective and non-infective complications of MV in one definition, as proposed by the 2013 CDC algorithm.

There are two diverse but mutually re-enforcing tracks to reduce the complications of MV. First, the bundle care approach to prevent VAP and secondly the improvements in pulmonary and critical care practices leading to clinical protocols endorsed by professional societies in the practice of management of MV, for example, protocols for ventilation liberation, lung protective strategies for acute lung injuries, and sedation management [72–74]. Similarly, the interest of using transesophageal pressure has been emphasized recently and it could help titrate protective ventilation. Diaphragmatic dysfunction, very often after cardiac surgery or in lung transplant recipients, will be also best prevented using diaphragmatic stimulation and early mobilization [75,76].

2.2. The ventilator care bundle approach

The interest in nosocomial infection control in critical care has increased in recent years since Pronovost et al. demonstrated the effectiveness of the bundle approach for catheter-related bloodstream infections [77]. The same approach has been adapted to VAP. At present, this issue remains controversial because of the lack of a gold standard definition for VAP and the emergence of VAT as an independent cause of morbidity. Management and prevention perspectives of VAT has been a focus in pediatric units where VAT has also been independently associated with adverse outcomes and it is an important reason for antibiotic consumption, being even more prevalent than VAP [36,78].

Certain practices have been particularly able to reduce the incidence of VAP. Several such independent evidence-based interventions when bundled together and encouraged for high compliance improve patient care processes significantly. In a large multicenter study, compliance with the care bundle was associated with a lower incidence of VAP, with units achieving >95% bundle compliance experiencing a 59% reduction in VAP rate [79]. Several smaller studies, using the similar care bundle, have reported reductions in the days on mechanical ventilation and the length of ICU stay [80]. European care bundle was a user-modified approach aimed for better acceptability and implementation [81]. This was further validated in five Spanish adult ICUs with reduction in VAP rates from 15.5% to 11.7% in spite of overall compliance being <30%. The full compliance led to 40% reduction in median length of ICU stay and 50% reduction in MV days suggesting the need for long-term follow-up [82].

The individual measures attempt to reduce the microbial load in airway and delay the entry of microbes in sufficient quantities to cause infection into the lungs. Together, the preventive measures have been particularly relevant as they are aimed to confront the two patho-physiological processes of VAP development. First, to prevent micro-aspiration of bacteria that accumulate in the upper airway (oral care, semi-recumbent position, right cuff pressure and suctioning), secondly, to prevent introduction of bacteria from environment (hand hygiene, bacterial filters, and minimal manipulation of the tubing) [28]. Oral care with antiseptics, such as chlorhexidine (CHX), is a measure implemented to decrease the bacterial load in the upper airways, and hence reducing VAP risk. Higher incidence of oral mucosa lesions has been reported in the 2% CHX group [83,84]. We recommend limiting its use to 0.12% concentration [85], which has been demonstrated to be effective in reducing VAP episodes. Moreover, a Cochrane review of the benefits in oral care of MV subjects, demonstrated reduction in VAP incidence [86], particularly in the subset of cardiac surgery. However, recent reports raised concerns on the efficacy of chlorhexidine and its safety [87]. Klompas et al. reported that higher compliance rates of CHX use did not lower VAE rates and might have increased mortality rates [88]. In contrast, sedation breaks and spontaneous breathing trials were protective. Additional concern on safety has been reported more recently [89], particularly associated with 2% CHX use in studies conducted in low- and middle-income countries [90]. Thus, the controversies should be explored with a randomized clinical trial.

Several other VAP prevention measures like semi-recumbent position and subglottic secretion drainage have revealed conflicting results by several studies leading to moderate quality of evidence in recommendations [91–95]. Additionally, hand contamination of health-care providers is a modifiable risk factor for reducing VAPs. Improving hand hygiene is a general measure to reduce health-care-associated infections. Although generally met with lower compliance, hand hygiene is shown to have a strong impact on reducing risk of VAP [82]. Electronic methods of monitoring compliance may contribute to improve implementation and reduce health-care infections.

Finally, there have been measures developed targeting microorganisms directly, like the use of silver-coated tubes and administration of probiotics in ventilated patients to decrease the risk of VAP. However, the quality of evidence is low and its routine use is therefore not recommended [96,97]. On the other hand, in a recent review it was highlighted that the evidence for the administration of antibiotics into the digestive tract to modulate gastric colonization and prevent respiratory infections associated to mechanical ventilation in ICU where MDR-GNB are endemic is limited to observational data and one small randomized controlled trial, all on selective digestive decontamination, yielding contradicting results. Moreover, in ICUs with high levels of antibiotic resistance there is still high concern about the subsequent increase in resistance development [98].

Preventive strategies have been also introduced to reduce pediatric VAP and, more recently, for VAT [36,78]. However, pediatric ventilator care bundles have not been validated. Different tailored ventilator bundles have been used in PICUs [36,78,102–101]. Size-related factors must be considered as a difficulty to introduce some of the measures [102], subglottic secretion drainage in infants and children needing endotracheal tube <5 or 5.5 mm or cuffed tubes in low-height infants, are technically not feasible. And although semi-recumbent position in children is frequently adopted, maintaining 30–45º head-of-bed elevation is challenging for infants and newborns.

Compliance with ventilator care bundle is an important factor and when practiced, it is important to audit compliance rates and accordingly implement processes that help ensure sustained outcomes. Although causal relation between ventilator care bundles and reduction in VARI cannot be stated due to several study limitations, evidence till date strongly point toward a positive association [82,103,104]. Incidence of VAP was reduced by 59% when >95% compliance was achieved [79]. In another study, minimal compliance of 85% and 75% for oral care and hand hygiene were required to significantly reduce VAP rates [105]. European care bundle implementation study indicated hand hygiene (OR 0.35; 95% CI 0.11–0.68), oral care (OR 0.23; 95%CI 0.17–0.75), and intra-cuff pressure control (OR 0.21; 95%CI 0.25–0.92) had significant impact on reducing the risk of VAP, but hand hygiene had the lowest compliance rate (19%) [82]. Other issues of its implementational ability is of concern for processes such as head of bed elevation and daily sedation vacation where greater health-care workers support is essential. Despite good level of evidence, many processes complementing to reduce VAP occurrence are not being put to practice and the disparity is huge between different ICUs. VAP prevention guidelines were used in 64% of French ICUs, while it was only 30% in Canadian ICUs [106]. Variability of adherence to evidence-based guidelines is also reported by other authors where only 37% of intensive care physicians adhered to the guidelines [107]. Although each measure in the care bundle may not apply to all patients at all times, its daily reappraisal at patients' bedside must be reinforced. The fact that the degree of evidence does not particularly influence adherence to guidelines among key staff suggest the need for a more rational approach toward improving VAP guideline adherence. It would be prudent to understand that the bundle effect is based on synergy of several individual measures more than just the sum, since the effectiveness of each of them can vary in different case-mix populations. Most importantly, it seems that both pediatric and adult bundles have been focusing more on pathophysiological measures rather than decreasing ventilator-days, whereas sedation control is the cornerstone of any ventilator bundle. A recent meta-analysis has assessed the impact of VAP bundles on mortality [108].

Two ventilation strategies are proven to be effective in minimizing VILI and decrease mortality: low tidal volume and high level of positive end-expiratory pressure (PEEP), limiting over-distension but also warranting the recruitment of collapsed alveolar-capillary units and minimizing ventilation heterogeneity [61,109]. Its benefits in ARDS and in decreasing VILI are proven in adult population; however, there is no consensus about the ideal level of PEEP [110]. Although pediatric clinical studies do not confirm an association between large tidal volume and adverse outcomes due to a lack of randomized, controlled clinical trials assessing low versus high tidal volume in children with ARDS, these lung-protective ventilator strategies have also been advised to be adopted in the pediatric critical care units [106]. Adjunctive strategies as use of plateau pressure under 30 cm of water in healthy individuals and limit asynchrony during mechanical ventilation are advised too. Moreover, lung ultrasound managing ARDS (PINK protocol) and limiting fluid overload can avoid non-infective mechanical complications (besides other benefits as decreasing irradiation), reducing intubation period and costs in adult and pediatric ICUs [111–113].

2.3. Weaning practices and protective ventilation strategies

Because the duration of mechanical ventilation is one of the main determinants of both infectious and non-infectious complications, early extubation must be considered once the patient achieves respiratory stability. A recent study reported that stopping early sedation in postoperative patients was associated with a better prognosis [114]. Traditionally, respiratory weaning was left to the judgment of attending physicians, but it has been reported with a moderate level of evidence, reduction on duration of mechanical ventilation, weaning and ICU length of stay when a protocol was implemented [115]. Changes in strategies of weaning have been made it the last years, being recommended nowadays such as (1) inspiratory pressure augmentation (5–8 cm H_2O) during an initial spontaneous breathing test rather than without (T-piece or CPAP), (2) use of protocols attempting to minimize sedation and (3) Noninvasive ventilation immediately after extubation for patients at high risk for extubation failure (i.e. COPD and congestive heart failure) [116]. Additionally, in a recent randomized multicentric trial, Fernandez et al. reported that the reconnection to mechanical ventilation for 1 h after a successful spontaneous breathing trial reduced the rates of re-intubation within 48 h after extubation in critically ill adults [117]. Protocol-driven ventilator weaning also reduced the use of MV, rate of reintubation, and VAP [118–120].

Despite the reported superiority in adults of early (percutaneous) tracheostomy to decrease complications associated with prolonged intubation (as laryngeal injury and tracheal stenosis), three recent meta-analyses have not confirmed that tracheostomy was associated with decreased ventilation duration [121,122]. Tracheostomy in children is infrequent, being related to previous home mechanical ventilation or often performed late (and usually surgical) after PICU admission [123].

Regarding compliance with these recommended practices for mechanically ventilated patients, few reports highlight the discrepancies among clinicians to deliver optimum MV strategies for different patient conditions. A seminal study [4] demonstrated that the selection of modes of mechanical ventilation and methods of weaning varied considerably from country to country, although the primary indications for mechanical ventilation and the ventilator settings were remarkably similar across countries. Moreover, low tidal volume ventilation was used in only 2.3% of entire study cohort and in only 7.8% of those with ARDS. The variation in the adoption of protocols for ventilation and weaning still existed after several years as reported by later studies [124]. A study among anesthesiology professionals highlighted that only 6.3% of the professionals set the perioperative ventilation parameters optimally associating low TV, systematic PEEP, FiO_2 <50%, systematic I/E ratio adjustments, and recruitment maneuvers [125] .

There is growing evidence that many of VAEs are preventable and, although being a valuable preventive tool, current VAP bundles have not shown consistent utility in preventing VAC and IVACs with urgent need for additional improvements based on new evidences [44,87,126]. In a study by O'Horo JC et al. [127], only oral care with chlorhexidine was associated with decreasing risk of VAE, while stress ulcer prophylaxis slightly increased the VAE risk whereas deep venous thrombophlebitis (DVT) prophylaxis did not influence the outcome. Sedation breaks had a trend toward improvement. Contrasting findings were observed in a recent

Table 3. **The ABCDEF bundle** [modified from references 119,120].

A: Assess, prevent, and manage pain
Numerical rating score to assess pain
- Patient awake and collaborative: Behavioral Pain Scale
- Unconscious/Uncooperative: Critical-Care Pain Observation Tool
Routine administration of non-opioids
Consider regional anesthesia
Parenteral opioids as the first line to relief pain
Parenteral opioids prior to performing invasive procedures
B: Both spontaneous awakening trials (SAT) and spontaneous breathing trials
Daily once the patients is stable
C: Choice of sedative or analgesic exposure
Avoid unnecessary sedation
Goal-directed delivery of psychoactive medications
Routine level of sedation assessment
- Richmond Agitation-Sedation Scale (RASS)
- Riker Sedation-Agitation Scale (SAS)
Limit benzodiazepines
D: Delirium monitoring and management
Routine delirium assessment
- Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)
- Intensive Care Delirium Screening Checklist (ICDSC)
Avoid benzodiazepines to control agitation
Limit sleep disruption
E: Early mobility
F: Family engagement

study [87] that reported none of the bundle components aimed at preventing VAP (such as head of bed elevation, oral care with chlorhexidine, subglottic suction, and spontaneous breathing trial) had any association with VAEs prevention. Furthermore, compliance with oral care increased the risk of VAE, IVAC, and PVAP. While several bundle components were evaluated for prevention of VAP, given the fact that there is only little agreement with VAP and VAE, very little information is available on measures to reduce risk of VAEs. It seems prudent to relook at measures to prevent VAE and set new targets for evaluation.

In recent years, on the basis of successfully implemented multidisciplinary approach to nosocomial infections, the ABCDEF bundle (Table 3) was created [128,129]. Its implementation has been associated with a decrease in MV days, delirium, and ICU acquired weakness [130,131]. Fast-track surgery protocols are also in line with this concept [132].

As mentioned above, the risk to develop overall VAEs (infectious or not) is directly related to the length of mechanical ventilation and its early interruption is the main goal to prevent complications. The employment of short-term sedatives, the use of minimum possible level of sedation, and the daily spontaneous breathing trial have shown to be effective in reducing the duration of MV and hence, reduction of VAEs [74,133]. Klompas et al., in a 'Wake Up and Breathe' Collaborative initiative, further explored a coordinated nurse and respiratory therapist-driven spontaneous awakening and breathing trials (SAT, SBT) for reduction of VAEs [88]. Reinforcement and shifting the responsibility from physicians to nurses and respiratory therapists led to a marked increase in implementation of SAT and SBT along with significant reduction in risk of VAC (OR 0.63;95%CI 0.42–0.97) and IVACs (OR 0.35; 95%CI 0.17–0.71) per MV episodes but nonsignificant in risk for pneumonia (OR 0.51; 95% CI 0.19–1.3). Overall, VAE was reduced by 35%. Despite an increase in self-extubation rates, interestingly, no reintubations were documented immediately or up to 7 days [126]. In addition, a depletive fluid-management strategy when initiating the weaning process also have been reported as significantly reducing both VAC and VAP occurrence (OR 0.44 and 0.50, respectively) [134].

2.4. Monitoring complications through quality indicators

Quality indicators are standardized instruments to monitor health-care quality. They describe the performance that should occur for a particular type of patient/situation or the related health outcomes. Quality indicators can be rate- or mean-based, providing a quantitative basis for quality improvement (i.e. unplanned extubation rate) or generic measures that are relevant for most patients or disease-specific (i.e. availability of a written protocol or routine for a lung-protective ventilatory strategy) [135]. According to the classification of quality dimensions by Donabedian, they can assess aspects of structure, process (i.e. providing multi-professional staff reports on results of ventilator-associated infection surveillance and the sensitivity profile of microorganisms), or outcomes (i.e. failed extubation rate) of health care and they describe the performance that should occur for a particular type of patient [136]. They should be based and evaluated on the best available scientific evidence and, before implemented, they should be tested for reliability and validity [135].

Unplanned extubation and reintubation within 72 h (or 7 days) after planned extubation (failed extubation rates) along with other quality indicators have been considered potentially preventable in optimal intensive care practice, being a point of interest for assessing quality of care and patient safety and implementing quality-improvement programs [137].

Unplanned extubation can be life-threatening and its outcomes depend on the need of re-intubation [138–140]. Thus, continuous monitoring of intubated subjects to identify oxygen desaturation without delay is mandatory to prevent secondary cardiac and brain injuries. Unplanned extubation has been related with increased VAP risk and a significantly longer duration of mechanical ventilation, longer stay in the ICU, and longer hospital stays [141–143]. There are two types of endotracheal tube removal included in the concept of unplanned extubation: deliberate self-extubation and accidental extubation, being the highest need of reintubation in the second group [144].

The reported incidence of unplanned extubation in ICUs usually ranges from 0.3 to 4.2 per 100 ventilator-days [145,146]. Self-extubation has been reported responsible for 68–95.1% of unplanned extubations, with overall reintubation rates ranging between 28.5% and 74.7% [147]. Agitation is the most important patient-related factor associated with significantly higher risk for unplanned extubation, in adults and children, especially for self-extubation [148]. The mean contemporaneous incidence of unplanned extubation rate reported in children during the last years has been 1.19/100 intubation days. In the pediatric population, younger patients (especially <1 year) present higher rates of unplanned extubations [149]. Shorter airway length, lack of cognitive and emotional maturity to tolerate artificial airways, as well as copious secretions, uncuffed endotracheal tube use, and inadequate tube fixation (particularly when wet) may help to understand this relationship with younger ages and somehow justify higher concerns in limiting sedation in infants [150]. On the

other hand, the implementation of ABCDE bundle (which subsequently have become the ABCDEF bundle) have raised concerns about its effect on rates of unplanned extubation rates, but there is some evidence of that this practice do not involve additional risk either in adults or children [151–154].

Da Silva et al. reported the impact of a quality improvement program in a pediatric ICU with a decrease in the overall incidence of unplanned extubation from 2.9 per 100 to 0.6/100 intubation days, and he suggested a benchmark in the pediatric ICU of 1 unplanned extubation/100 intubation days [143].

Extubation failure is also associated with increased length of stay, ventilator days, and it is also a risk factor for the development of VAP. In a recent meta-analysis, Gao et al. summarized the risks that reintubation impose on VAP (OR 7.57) and mortality (OR 3.33). The risk of mortality after reintubation regarding to unplanned extubation also significantly increased [142].

The rate of extubation failure reported is between 5 and 20% in general ICU population, being similar in pediatric patients [155–157]. Kapnadak et al. evaluated the relationship between different ranges of failed planned extubation rates and clinical outcomes. They found that an intermediate range of failed planned extubation (7–15%) was associated with better outcomes than a high (>15%) and low rate (<7%) of failed extubation rate [157]. They proposed this intermediate range of failed planned extubation rates as the rate where ventilator outcomes are optimized, suggesting that 'zero tolerance' for extubation failure may prolong mechanical ventilation resulting from too conservative extubation practices.

Safety advocate Peter Pronovost's to improve ICU safety should be adapted for a new ventilator safety bundle as detailed in Figure 2. A three-fold approach should focus on: (1) to expose mistakes monitoring ventilator complications through quality indicators; (2) to develop strategies to reduce them – educate, engage, and ongoing research; (3) to evaluate progress. Identifying physician, nurse, and respiratory therapist champions is vital for implementation. Current VAE surveillance approach should target development of preventive bundles encompassing both infective and non-infective complications of MV. In addition to the currently used infection-based surveillance metrics, tracking of ventilator utilization ratios, unplanned extubation, extubation failure, and antibiotic use rates would provide insight into the risk of device-related harm (including non-infectious harms).

Since the publication of the Institute of Medicine's report 'To err is Human: Building a safer Health System' in 2000, patient safety in health-care institutions has been the focus of attention [158]. Learning effectively from preventable adverse events and implementing preventive measures to reduce related harm to patient have created a safety culture. In this context, nosocomial infections were perceived as adverse events, and they were renamed as health-care-associated infections. Building on the success of an interventional program on catheter-related bloodstream infections in the ICU reported by Pronovost et al. in 2006, the interventions expanded worldwide and to other health-care-associated infections, including VAP [77]. Zero-VAP rate was proposed as a quality indicator, with some concerns because of the lack of a gold standard definition and its feasibility in clinical practice by some authors [159,160]. In the last 10 years, sustained lower VAP rates have been reported worldwide (even the zero VAP rates by the NHSN in U.S.A.) without a parallel decrease in the use of antibiotics as it has been recently noticed [161]. This fact, along with the absence of impact on patient outcomes has dismissed VAP rates as a quality-indicator.

2.5. Vaes: from new quality indicators to an improved bedside strategy of management

The low impact of preventable measures on patient outcomes based on traditional surveillance systems focused only on VAP shifted the CDC focus to 'other complications' related with mechanical ventilation [162,163]. The newer 2013 CDC definitions were designed for surveillance and aimed to be a useful

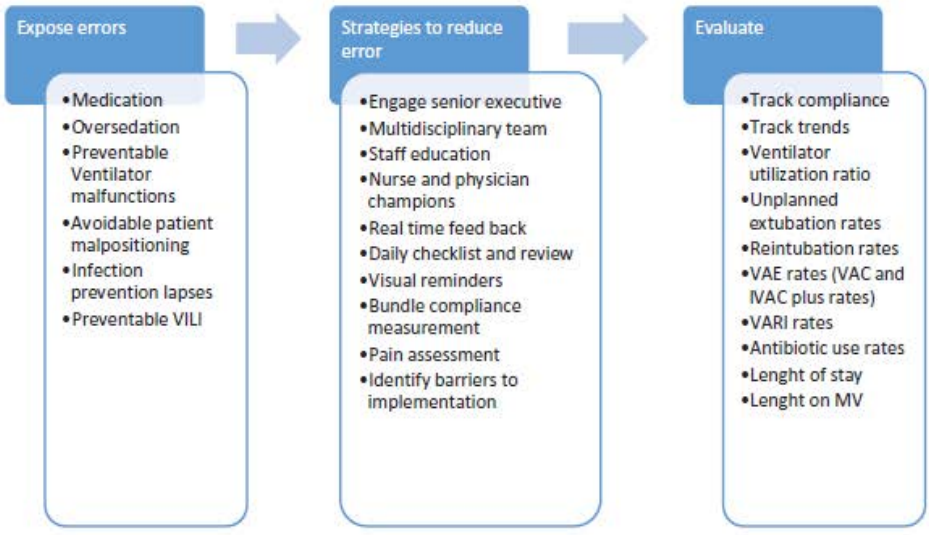

Figure 2. A 3-fold approach to improve ventilator safety.

VILI: Ventilator-induced lung injury; VAE: Ventilator-associated events; VAC: Ventilator-associated condition; IVAC: Infectious-related ventilator associated condition; VARI: Ventilator-associated respiratory infections; MV: Mechanical ventilation.

tool for defining, developing, and evaluating intervention programs for improving health-care quality with impact on patient outcomes [13]. These new definitions avoid subjective items and focus on respiratory worsening. This new effort has been controversial due to poor correlation between VAE and VAP [164–166] in clinical practice. Certainly, it has been demonstrated that newer VAEs definitions miss some VAP, but most standardized monitoring systems also ignore VAT, which is the most frequent VARI in adults and children [15,18,167].

Moreover, the relevance of hypoxemia as a prognostic factor in VARIs has been emphasized and Peña-Lopez et al. have suggested to use a less restrictive definition of VAE (compared with the CDC definition) in children [18,168]. Changes on oxygenation seem to be the earliest warning sign of complications associated with intubation, whereas degree of hypoxemia is related with worse outcomes. Thus, VAE seems to be an ideal quality indicator of mechanical ventilation complications. Indeed, two tiers of the new updated definitions of VAE, VAC, and IVAC-plus rates may be considered the indicator of non-infectious and infectious mechanical ventilation complications, respectively. The ratio between them can vary significantly according to the reported institutional variability in antibiotic use in ICU patients [169,170], but this can be tracked by the concomitant use of another important quality indicator, such as days of antibiotic therapy per 1000 patient-days.

The easy and quick detection of VAE when using automatic surveillance has documented strong association with outcomes, with growing evidence that many of these events are preventable. It makes VAE a good candidate to be a new good quality-indicator in ICUs [44,46,126,171]. The VAE algorithm is easy to encode and apply to the design of software-based alerts for the early detection of critical events in ventilated patients. This is supported by several studies reporting notable reductions in the time taken to detect VAE when automatic surveillance is implemented [172,173].

In order to increase compliance with preventive strategies and to provide a focus to design improvement strategies in the ICU, education and feedback of the staff has shown success [82,174–176]. The role of continual education programs tailored to the local needs to reduce the preventable risk factors for complications is undisputed. Further, training needs of different professionals in individual settings should be taken into account before implementing new comprehensive educational programs.

Although strictly designed for epidemiological surveillance purposes, the subtle identification of VAEs and incorporation to decision-making on individual patients, either on antimicrobial prescriptions or other management decisions, cannot be overlooked. Moreover, for successful implementation of preventive strategies, involvement of intensivists, nurses and respiratory therapists are crucial. While the limitations of accurate microbiological or radiological tools for VAP diagnosis remain unresolved, new interest should focus more on secondary hypoxemia identification, with implications in management.

Practices to prevent VARI and implement appropriate ventilator modes tailored to patients' needs are key to improve care of MV subjects, resulting in better patient outcomes with decrease in health-care resources use. Thus, a dynamic and collaborative decision-making is vital to minimize complications of MV in a complex ICU setting where the decisional responsibility lies with different professional groups, however, are influenced by individual institutional practices. Collectively, measures aimed to reduce complications of MV should cover priority areas such as reducing time on MV, thereby reducing time at risk.

3. Conclusions

VAEs are generally caused by infections, fluid overload, ARDS, and atelectasis (predominantly in children). A protective ventilatory strategy, avoiding over sedation, and limiting fluids are the basis of management of intubated subjects. Moreover, promoting measures that safely reduce the exposure or duration of intubation should be a priority objective. Multidisciplinary comprehensive education based on care bundles is the basis of improving outcomes.

4. Expert commentary

New surveillance strategies based on newer CDC recommendations in ventilated patients have introduced the paradigm of VAE, defined as FiO_2 ≥0.2 increase and/or PEEP increase of ≥3 cm H20 sustained for ≥2 days, once a period of stability has been achieved. Indeed, priorities shifted from rates to outcomes.

IVAC-plus represented the most common cause of VAE, but recent data suggest that around 75% of VATs will be missed. A new paradigm advocates to eliminate chest X-Rays from daily practice and focus on ventilatory settings to identify oxygenation variations. As a consequence, most episodes of VAT are missed, which is a shortcoming because they are more common than pneumonia and they are associated with prolonged mechanical ventilation and length of stay, needing antimicrobial therapy.

With modern electronic monitoring, these ventilatory complications can be registered without manual intervention, facilitating surveillance. Recent studies suggest that oxygenation deterioration plays a main role in pneumonia diagnosis, being quickly restored when pneumonia improves. However, oxygenation variations are often subtle and the suggested variation in oxygenation parameters suggested by the CDC missed a large percentage of respiratory infections; by contrast, antimicrobial therapy seems to be safe to stop when these oxygenation changes reverse, suggesting a quick way for antimicrobial stewardship.

Early tracheostomy has been suggested (high quality of evidence) as a measure to prevent complications associated with prolonged intubation (laryngeal injury and tracheal stenosis). However, two recent meta-analyses have not confirmed early tracheostomy was associated with decreased ventilation duration, probably because it increases VAT episodes.

Atelectasis, pulmonary edema, and acute lung injury (or ARDS) are the three most prevalent non-infectious events in ventilated subjects. Due to the differences associated with age, atelectasis predominates in children under 8 years and pulmonary edema in adults. Better understanding of the factors associated with VAE is needed, and it would be helpful to develop bundles based on better quality of evidence.

Patients could take benefit in their outcomes of limiting these complications. As a consequence, multiple care bundles have been adopted in hospitals to limit these complications. These bundle strategies prompt a practical change in patient care, which may lead to an improvement in VAP reduction in intubated subjects.

Limiting intubation (or shorten its duration) is, by far, the most effective way of prevention. Improvement in devices systems (and heated humidification) has replaced non-invasive ventilation (currently focusing on hypercapnic episodes) by high flow oxygen therapy. Unfortunately, patients who need protection of the airways (e.g. head trauma) or when hypoxemia persists over 6 h still require intubation. In this subset, sedation restriction and early ventilator weaning must be implemented (high quality of evidence). Regarding sedation, the use of alpha-2 adrenergic receptor agonists, instead of benzodiazepines, should be preferred in terms of readiness for extubation, reducing ICU length of stay and episodes of delirium.

5. Five years' view

This new approach still does not fill important knowledge gaps, which require further research. In our views, there is a need to investigate the effects of new management algorithms for ventilated patients, based on subtle VAE definitions. Second, further studies should determine appropriate breakpoints in the ventilator parameters monitored to define VAE and activate alerts. Finally, randomized clinical trials should assess the effectiveness and safety of personalized (short) courses of therapy based on oxygenation variations and speed of improvement. Lung ultrasounds, which require a standardized training, should be delivered routinely to the bedside and might replace traditional chest X-rays. Easy identification of pneumothorax and differences between pulmonary edema from atelectasis would contribute to improve the management of intubated patients. A lot of advances are expected in limiting VILI as driving pressure monitoring, calculation of transpulmonary pressures, particularly in obese subjects [177]. Diaphragmatic dysfunction, very often after cardiac surgery or in lung transplant recipients, will also be best prevented using diaphragmatic stimulation and early mobilization. Extracorporeal CO2 replacement (ECCO2R) is being assessed to further reduce complications associated with mechanical ventilation. Similarly, extracorporeal membrane oxygenation (ECMO) has experienced an increased use after the 2009 influenza pandemics. It is important to emphasize the indication of a prone position trial before ECMO [178]. The recent EOLIA trial has been halted due to futility [179]. Thus, research efforts should focus on the selection of appropriate candidates for this salvage rescue technique.

Key issues

- VAP is not always preventable and it unlikely to reach zero rate.
- VAT is the most common respiratory infection, particularly frequent in tracheostomized subjects, prolonging the ventilatory period and length of stay.
- The most frequent non-infectious VAE are atelectasis.
- A protective ventilatory strategy is required to limit the risk of acute lung injury.
- Multiple studies have reported a decrease in the incidence of VAP when a bundle is implemented. Protocols aimed at sedation restriction and early ventilator weaning must be implemented, sedation control being the most effective way to reduce complications.
- Protective mechanical ventilation is a very important part of prevention of complications associated with intubation and mechanical ventilation.
- Diaphragmatic dysfunction will be best prevented using diaphragmatic stimulation and early mobilization.
- Agitation is the most important patient-related factor associated with significantly higher risk for unplanned extubation, especially for self-extubation.
- Benzodiacepine use should be limited, ensuring good analgesia with short acting agents, reducing the risk of delirium. Adjusting doses to scores is a useful monitoring strategy, preventing self-extubations and further complications.
- The major restrains to bundles implementation is adherence; multidisciplinary education and continued feedback are essential.

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Capítulo 11.

THE EFFECTS OF SEDATIVES, NEUROMUSCULAR BLOCKING AGENTS AND OPIOIDS ON VENTILATOR- ASSOCIATED EVENTS. AN EDITORIAL COMMENT FOR EUROPEAN JOURNAL OF ANAESTHESIOLOGY

Ramirez-Estrada S, Peña-López Y, Rello J.

Eur J Anaesthesiol 2019; 36:1–4. doi:10.1097/EJA0000000000001132

RESUMEN

Análisis comparativo de los estudios ROSE y ACURASYS soportando la asociación entre el uso de sedación ligera y una menor incidencia de VAE en pacientes con SDRA. A pesar de las diferencias metodológicas y temporales entre ambos estudios la mortalidad de los pacientes que no recibieron cisatracurio se mantuvo, mientras que la proporción de VAEs fue significativamente menor en aquellos pacientes que recibieron esquemas de sedación superficial

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EDITORIAL

The effects of sedatives, neuromuscular blocking agents and opioids on ventilator-associated events

An editorial comment for the European Journal of Anaesthesiology

Sergio Ramirez-Estrada, Yolanda Peña-López and Jordi Rello

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In recent years, the application of specific care bundles in the ICU has been proposed as a pragmatic management strategy, and their use is now expanding into areas such as haemodynamic management, delirium control and infection prevention. While sedation strategy should be a core element of ventilatory care bundles, which strategy remains to be determined. The difficulty of classifying ventilator-associated respiratory infections such as ventilator-associated tracheobronchitis and ventilator-associated pneumonia[1] and their impact on outcomes has led the Centers for Disease Control and Prevention to change the definition of ventilator-associated pneumonia to 'preventable conditions related to mechanical ventilation', or ventilator-associated events (VAE). The VAE classification focuses on hypoxaemia and it improves outcome prediction, detecting either respiratory infections or non-infective complications such as acute respiratory distress syndrome (ARDS).[2] Thus, standardising a ventilatory bundle with interventions focusing on VAE would improve patients' outcomes.

Recently, the ROSE trial[3] reported that, in ARDS, cisatracurium infusion and deep sedation achieved outcomes similar to no continuous infusion of muscle relaxant agents and light sedation, thus challenging the policy that deep sedation and muscle relaxant agents was the preferred type of management as proposed by the ACURASYS trial.[4] The two studies[3,4] seemed to have a similar design: patients with moderate-to-severe ARDS were assigned randomly to receive or not receive a 48-h continuous infusion of cisatracurium (initial bolus of 15 mg followed by an infusion of 37.5 mg h^{-1}), while using a lung protective ventilation strategy. However, while there appeared to be no significant differences between the two studies in the patients' baseline characteristics, the ROSE trial reported higher levels of positive end-expiratory pressure (PEEP) and less use of prone positioning (due to updated guidelines on ventilatory management), suggesting that the patient population in the two trials were not comparable. Curiously, despite the use of the very different sedation strategies (light vs. deep sedation), the control group mortality was similar in both the ROSE and ACURASYS trials (42.8 vs. 40.7%). In the ACURASYS study, the intervention group presented a 10% decrease in 28-day mortality (cisatracurium vs. placebo: 23.7 vs. 33.3%, $P=0.05$) and lower rates of barotrauma (5.1 vs. 11.7%, $P=0.03$) and pneumothorax (4.7 vs. 11.7%, $P=0.01$), but in the ROSE trial no statistical differences were reported for these same events. Once again it seems that the patient populations in the two trials had different degrees of severity: compared with the ROSE study, patients in the ACURASYS study had higher driving pressure levels and fewer were excluded due to neuromuscular blockade use at enrolment (1.3 vs. 13.4%). Taking these differences into consideration, and after excluding very ill-patients with refractory hypoxaemia, the findings of the ROSE study agree with a recent article[5] reporting that long-acting sedation (midazolam, fentanyl or morphine) was the most important variable independently associated with development of VAE (Fig. 1), with a hazard ratio of 8.69 in adults ventilated longer than 7 days. Significantly, neuromuscular blocking agents did not exert a significant effect on the development of VAE (hazard ratio 0.81, $P=0.83$).

From the Critical Care Department, Clinica Corachan (SR-E), Department of Medicine, Universidad Autónoma de Barcelona (SR-E), Vall d'Hebron Research Institute (YP-L, JR) and Centro de Investigación Biomédica en Red, Instituto de Salud Carlos III, Barcelona, Spain (JR)

Correspondence to Sergio Ramirez-Estrada, Intensive Care Department, Clinica Corachan, Carrer Buigas 19, Barcelona, Spain
Tel: +00 34 93254 58 00; fax: +00 34 93254 58 00; e-mail: sergioramirezestrada@hotmail.com

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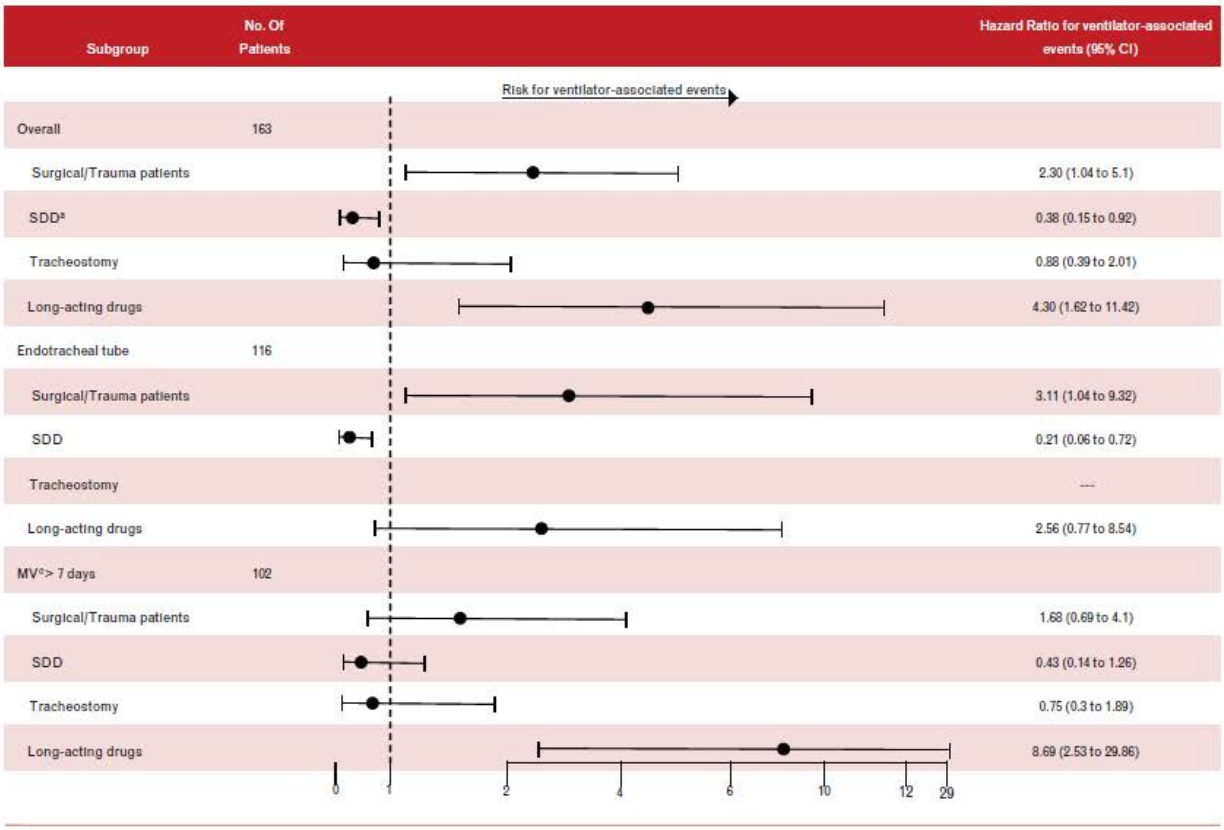
Fig. 1



Factors associated with ventilator-associated events in a multivariate Cox proportional hazard model.[5] Long-acting drugs were midazolam, fentanyl or morphine. MV, mechanical ventilation; SDD, selective digestive decontamination.

Fewer days on ventilation are associated with lower rates of infection, fluid overload, atelectasis and ARDS.[6] A large meta-analysis found that targeting light sedation levels is safe and improves outcomes for ventilated patients in the ICU.[7] Compared with benzodiazepines, short-acting sedatives like propofol were associated with shorter times to extubation,[7] and multiple studies have reported a decrease in the incidence of ventilator-associated respiratory infections when protocols designed to restrict sedation and achieve early ventilator weaning and early mobility are implemented.[8] In addition, keeping patients in a co-operative state favours early initiation of rehabilitation therapy and a trial of spontaneous breathing.[9] Spontaneous breathing modes have been shown to reduce ventilation days and ICU stay and may also decrease muscle atrophy, and the use of sedatives in patients with ARDS.[10]

The effects of the use of sedatives and opioids on the patient/ventilator interaction remain unclear. The rate of asynchronies is not affected by light sedation with propofol, but deep sedation with propofol increases the rate.[11] Asynchronies such as reverse triggering occur in deeply sedated patients without neuromuscular block.[12] Indeed, deep sedation with benzodiazepines was found to increase mortality, whereas dexmedetomidine had fewer asynchronies compared with propofol.[13] Finally, a recent study[14] reported that the overall rate of asynchronies was not different between sedatives-and-opioids, sedatives only or opioids alone, but patients receiving sedatives had a lower level of consciousness compared with those who received opioids alone. The sedatives-and-opioids protocol reduced the level of consciousness but did not decrease asynchronies, whereas the sedative dose was directly associated with a lower level of consciousness and the asynchrony rate.

In summary, the use of short-acting sedatives or minimising the use of sedation seems to reduce the duration of mechanical ventilation and lowers pneumonia and mortality rates in ventilated patients in the ICU. In ARDS, neuromuscular blocking drugs can sometimes be used when physiologically and clinically indicated.[15] Adequate opioid prescription with minimal doses of sedatives might improve patient/ventilator interaction and allow more spontaneous breathing. Optimal titration

of opioids may avoid the deleterious effects of sedatives. Further studies using artificial intelligence should determine the benefits of interventions such as recruitment manoeuvers, PEEP titration, mechanical ventilation modalities and neuromuscular blocking agents among different ARDS phenotypes. The findings should then be validated in randomised clinical trials.

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XII. ANEXO I

Capítulo 12.

VENTILATOR-ASSOCIATED EVENTS: DEFINITIONS AND USES

Peña-López Y, **Ramirez-Estrada S**, Rello J.

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RESUMEN

Capítulo perteneciente a "Encyclopedia of Respiratory Medicine", se describen de manera detallada y práctica los eventos asociados a la ventilación mecánica, señalando su importancia clínica y la necesidad de desarrollar estrategias dirigidas a disminuir su prevalencia dada su asociación pronóstica en el enfermo crítico, además se analizan las ventajas de incluirlos en programas de vigilancia epidemiológica y su valor como indicadores de calidad.

Ventilator-Associated Events: Definitions and uses

Yolanda Peña-López [1,2]
Sergio Ramírez-Estrada[3,4]
Jordi Rello[5]

[1]Pediatric Critical Care Department, Vall d'Hebron Hospital Campus, Barcelona, Spain
[2]Vall d'Hebron Institut of Research, Barcelona, Spain
[3]Critical Care Department, Clínica Corachan, Barcelona, Spain
[4]Medicine Department, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain
[5]Centro de Investigación Biomédica en Red (CIBERES), Instituto Salud Carlos III, Madrid, Spain

ABSTRACT

The use of specific care bundles to control infection has been demonstrated to be effective, including ventilator-associated pneumonia (VAP). However, the proposal of VAP rates as a quality indicator has generated debate due a lack of a gold standard definition. In 2013, the Centers for Disease Control and Prevention (CDC) replaced surveillance definitions from VAP to other preventable conditions related to mechanical ventilation (ventilator-associated events: VAE), which may predict outcomes. This represents a new opportunity to overcome many of the weaknesses of traditional VAP surveillance and broadens the focus of surveillance encompassing other preventable conditions related to mechanical ventilation.

KEYWORDS

Ventilator-associated event (VAE); Ventilator-associated pneumonia (VAP); Ventilator-associated tracheobronchitis (VAT); Ventilator-associated condition (VAC); Infection-related ventilator-associated complication (IVAC); Possible ventilator-associated pneumonia (PVAP); Pediatric ventilator-associated event (PedVAE); respiratory infection; quality improvement; chidren;

Introduction

In recent years, the use of specific care bundles to control infection in the intensive care unit has been demonstrated to be effective, including ventilator-associated pneumonia (VAP) (Heck, 2012)(López-Pueyo et al., 2013). Thus, zero VAP rates have been proposed as an indicator of quality in the Intensive Care Unit (ICU). This has generated debate regarding a lack of a gold standard definition and the recognition of ventilator-associated tracheobronchitis (VAT) not only as an intermediate status preceding VAP, but as an independent source of morbidity by itself worthy of antibiotic treatment (Craven et al., 2016)(Nseir et al., 2014)(Klompas, 2012). The difficulties with the interpretation of chest X-ray opacities in any critical patient, the sole determinant between the two of them, makes a challenge to differentiate consistently between VAT and VAP. Moreover, this difficulty on the classification of ventilator-associated infections may explain the poor correlation between the sustained decrease of VAP rates, antimicrobial use, and clinical outcomes reported in the last years (Graat et al., 2006)(Nora and Póvoa, 2017).

In view of these circumstances, in 2013, the Centres for Disease Control and Prevention (CDC) replaced surveillance definitions from VAP to other preventable conditions related to mechanical ventilation (ventilator-associated events: VAE), which may predict outcomes, focusing on respiratory worsening and removing the need for the Chest X-ray interpretation (Klompas, 2013). In these new definitions, the respiratory worsening becomes the key new point, advocating for identifying and monitoring all those processes that can cause respiratory deterioration (infectious or not) in the ventilated patient. This respiratory worsening is specified as the presence of hypoxemia and easily objectified by the changes recorded in two ventilator settings: fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure (PEEP).

2013-Ventilator-Associated Events (VAE) Definition

There are three definition tiers within the 2013-VAE algorithm (Figure 1a):

1) Ventilator-Associated Condition (VAC), when the respiratory worsening fulfills some criteria for detecting hypoxemia defined as an increase in daily minimum PEEP ≥3 cm H_2O or FiO2 ≥ 0.20 sustained for at least 2 calendar days following a baseline period (2 calendar days) of stability or improvement.

2) Infection-related Ventilator-Associated Complication (IVAC), if in view of the above, and the presence of general evidence of infection/inflammation, defined as altered leukocyte count (≥12,000 cells/mm^3 or ≤4,000 cells/mm^3) and/or temperature (>38° C or <36°C), a new antimicrobial prescription has been started and sustained for at least 4 calendar days by the attending physician, and

3) Possible or Probable pneumonia (PsVAP/PrVAP), if in addition to the above, there is a microbiological confirmation of a lower respiratory tract infection, defined as: purulent respiratory secretions or positive culture (qualitative, semi-quantitative or quantitative) in case of possible VAP or more strict microbiological criteria in case of probable VAP, where purulent secretions plus quantitative criteria are mandatory except for positive lung histopathology, positive pleural fluid culture and other tests as *Legionella* spp.

This algorithm is not a clinical definition and it was not designed for use in the management of patients, but for hospital surveillance. The aim was to establish a new surveillance system to improve reliability on detecting quickly and easily VAP and other mechanical ventilation complications related to an increased intensive care unit length of stay and mortality. The final propose use was to be implemented for public reporting, inter-facility comparisons, and pay-for-performance programs in the United States. However, its clinical correlation is currently being reviewed and actively studied area.

Tiers 1 and 2 (VAC and IVAC) were definitions suitable for potential use in public reporting and comparing among facilities. Tier 3 (Ps/PrVAP), incorporating laboratory evidence, depends on microbiological techniques, some of them unavailable in certain institutions, so it was thought for internal use definitions and internal quality improvement. These three subtiers are mutually exclusive and VAE is referred as the sum of them.

VAE surveillance updates and clinical correlation

Several modifications to the VAE definitions have been made since January 2013 in the light of the issues raised by the CDC's National Healthcare Safety Network (NHSN) users (Magill et al., 2014):

- PEEP values between 0 and 5 cm H2O were considered equivalents for the purposes of VAE surveillance. Thus, an increase in the daily minimum PEEP to at least 8 cm H2O sustained for at least 2 calendar days is mandatory to meet the VAC definition.

- Daily minimum PEEP and FiO_2 were defined as those maintained for at least 1 hour.
- Purulent respiratory secretions definition was adapted and a list of antimicrobial agents eligible for IVAC was refined by removing selected antimicrobial agents that would not be used, or would be unlikely to be used, in treating a lower respiratory infection in critically ill patient (Table 1).

In the 2015 update, probable and possible pneumonia were classified together as possible ventilator associated pneumonia (PVAP), and a new category (IVAC-plus) was created, comprising overall events meeting at least IVAC definition: the sum of IVAC + PVAP events (Fig 1b). Moreover, episodes of mechanical ventilation were advised to be monitored and used as a new denominator for surveillance.

As for ventilator monitoring settings, if no value is maintained for at least 1 hour, the lowest value is considered the daily minimum value. Upgrades regarding microbiological issues include community associated fungal pathogens exclusion, addition of six new antimicrobial agents and the use of non-culture based diagnostic test methods (e.g., PCR: polymerase chain reaction), being the current criteria to meet the PVAP definition resumed in Table 2.

Some changes are aimed to avoid misinterpretations of infection occurring during mechanical ventilation not attributable to a ventilation complication *per se.* For instance, the removal of antimicrobial agents that would be unlikely indicated in treating lower respiratory infection in a critically ill patient (e.g. oral

chloramphenicol, nitrofurantoin, enteral vancomycin, daptomycin). However, meeting Infection-related Ventilator-Associated Complication (IVAC) definition does not mean that the "infection related" event is necessarily respiratory in origin. IVAC refers to any infectious event associated with a deterioration in respiratory function. In the context of the critical patient, the new empiric antimicrobial agent may have dual purposes and not aimed, at least exclusively, to a respiratory infection. What is more, central line associated blood stream infections (CLABSI) or secondary blood stream infections can trigger an IVAC (e.g. by inducing acute respiratory distress syndrome, hydric overload). Otherwise, it could be IVAC due to a ventilator-associated respiratory infection that not meet PVAP criteria and even though VAP or VAT episodes that not meet any VAE criteria as it has been reported (Fan et al., 2016)(Ramírez-Estrada et al., 2018)(Peña-López et al., 2017)(Sim et al., 2016). Thus, infectious ventilator-associated complications and non-infectious associated complications could be correlated with IVAC-plus and VAC events, respectively, IVAC-plus encompassing IVAC and PVAP with the purpose of avoiding missing some ventilator-associated infections but not referring exclusively to them. Nevertheless, some VAP and VAT still are being omitted, as it has been pointed out above.

Considerations when reviewing VAE research in the literature

There has been a lack of understanding of the VAE algorithm that have generated confusion in the literature due to an inappropriate application of the terms designed by the CDC.

First, VAE has not to be simplified as the new ventilator-associated pneumonia/ventilator-associated respiratory infections surveillance, since it broadens the spectrum of surveillance to other mechanical ventilation complications. Thus, it seems logical that multiple studies confirm a poor correlation between VAE and VAP or VARI. What it do not make sense that this fact impels some authors against the use of the VAE algorithm by arguing that they are not the same (Pugh et al., 2016)(Nair and Niederman, 2017). Actually, the aim of the VAE algorithm is to be a good tool for surveillance and preventability purposes with impact on outcomes (Klompas and Berra, 2016)(Klompas et al., 2015). Since there is not a good clinical correlation between them, and above all, VAE not including some VARI, they has to be interpreted as those events occurring during mechanical ventilation, which are worthy of appropriate efforts to preventability purposes because of their clear impact on outcomes. Among them but not limited, the infectious ones, which represents only those ventilator-associated respiratory infections with a great impact on patient outcomes.

Second, VAE frequently are referred as VAC in the literature (Boyer et al., 2015)(Damas et al., 2015)(Stoeppel et al., 2014)(Bouadma et al., 2015) when VAC only includes those events with respiratory worsening exclusively, excluding those events that also fulfil IVAC or PVAP criteria. Thus, all VAC are VAE but not *vice versa*. Some studies about incidence and prevalence referring to VAC as VAE may be misleading and they have to be interpreted adequately to avoid errors when comparing taxes.

On another hand, the three tiers of VAE (VAC, IVAC, and PVAP) are excluding among them and not one including another, as it can be misinterpreted by some

figures using Venn diagrams (Spalding et al., 2017). In these diagrams, the groups are depicted in a series of different size circles, frequently VAC covering IVAC and PVAP. While it is true that the three of them share the first requirement to be defined as VAE, the respiratory worsening, and IVAC shares with PVAP the changes in temperature/white cell count and the antimicrobial prescription, all three tiers only are encompassed by the term VAE. The last update of the new algorithm solved this problem adding a new concept in the algorithm: the IVAC-plus events, that encompasses the other two tiers of the algorithm, IVAC + PVAP. Lately, some authors emphasize the first two tiers as "VAC only/alone" or "IVAC only/alone" when talking about VAEs subtypes to avoid misinterpretations (Klompas et al., 2014)(Nakahashi et al., 2018) but other authors can still lead to misunderstanding using the term "IVAC only" meaning IVAC but again using the term IVAC meaning IVAC-plus (Chao et al., 2018).

In this scenario can be cautious when reading about incidence, clinical correlation and outcomes of both VAE and the three different tiers of VAE (VAC, IVAC, PVAP) apart from the updates of each definition e.g. studies corresponding to years previous to the 2015 update refer to possible pneumonia as a different concept as subsequent studies following the new update. Automated surveillance for ventilator-associated events through an updated electronic algorithm can help to solve some of these misunderstanding problems in addition to save hours of staff time spent in chart review (Hebert et al., 2018)(Shenoy et al., 2018) but again, the terms could not to be properly used (Mann et al., 2015).

Pediatric VAE definitions and VAE surveillance in children

The VAE surveillance definition algorithm implemented by the NHSN in January 2013 was initially available for use in adult locations only. Later, a Pediatric VAE definition using changes in mean airway pressure (MAP) instead of PEEP setting, in addition of changes in the fraction of inspired oxygen was proposed (Cocoros et al., 2017) (Fig. 2a) and the CDC decided move forward with Pediatric VAE (PedVAE) development and implementation in NHSN. From 2019, inpatient location eligible to participate in pediatric VAE surveillance are those neonatal and pediatric locations in acute care hospitals, long term acute care hospitals, and inpatient facilities in the United States. As adults, chronic care units in acute care facilities are not eligible to participate in paediatric VAE surveillance.

Paediatric VAE CDC definition differs from adult VAE apart from the use of MAP instead of PEEP (a sustained increase of the daily minimum MAP ≥4 cm H_2O *versus* PEEP increase ≥3 cm H_2O) also in the in changes in the fraction of inspired oxygen (increase in daily minimum FiO_2 of ≥0.25 instead of 0.20). In both cases, the respiratory worsening has to be sustained for at least 2 calendar days for meeting VAE criteria.

Likewise PEEP values considered equivalents for the purposes of surveillance in adult VAE definitions, for in patients < 30 days-old, MAP values of 0-8 cm H2O are considered equivalent and the same for MAP values 0-10 cmH2O when referring to patients ≥ 30 days-old; Therefore, an increase in the daily minimum MAP to at least 12 cm H2O and 14 cm H2O respectively, sustained for 2 calendar days, would be needed to meet the paediatric VAE definition.

Patients on high-frequency oscillatory ventilation are included in paediatric VAE surveillance and also patients who are receiving a conventional mode of mechanical ventilation or high-frequency ventilation in treatment with surfactant, corticosteroids, nitric oxide therapy, heliox or epoprotenol therapy. As in adults, paediatric VAE are defined by a 14-day period, starting on the day of onset of

worsening oxygenation (the event day) within a new paediatric VAE cannot be identified or reported until this 14-day period has elapsed.

The pediatric VAE definition adopted by the CDC is based on a multicentre retrospective cohort study involving 8862 patients in which several daily minimum MAP and FiO_2 values were tested (4, 5, 6, 7, and 0.20, 0.25,0.30, respectively). The final decision of the new definition threshold to identify VAC in pediatric patients (FiO2. 0.25 and MAP of 4 cm H_2O) was reached searching for a "reasonable" event rate associated with higher morbidity and mortality. Although officially recommended for use in USA pediatric facilities from 2019, it has not been clinically correlated or compared with the 2008-CDC definitions to date. From then on, other pediatric definitions have been proposed. The first VAE variation (Beardsley, 2016) applied a daily minimum PEEP value of at least 2 cm H_2O instead of 3 cm H_2O used in the adult VAE surveillance definition and they found that this pediatric VAE variation was consistent with PNU1/VAP surveillance definition in terms of incidence. However, only one mechanical ventilation episode met both surveillance definitions. In the same year, there was used another modification of VAC/VAE criteria (VAC/VAE_{MP}) (Cirulis et al., 2016) for also a minimum daily PEEP value greater or equal to 2 cm H_2O instead of 3 cm H_2O but sustained for at least one day instead the two calendar days considered in other pediatric and adult VAE definitions (Fig. 2b). This study, conducted in pediatric traumatic brain injury patients also showed low sensitivity to identify all PNU1/VAP using the new proposal. Another VAE variation (Peña-López et al., 2017) supported the use of an even more less restrictive new pediatric VAE definition (Ped-VAE) by expanding on Cirulis et al. proposal with an additional modification: increase in FiO_2 of 0.15 *plus* an increase in PEEP of ≥ 1 cm H2O sustained for ≥ 1 day, apart from the increase of the daily minimum PEEP value of at least 2 cm H_2O or 0.20 FiO_2 sustained for ≥1 day (Fig. 2c). This is the only pediatric VAE definition prospectively validated in a cohort of children, which was resulted to have greater prediction accuracy for outcomes than 2008-CDC definitions and the adult VAE algorithm without effect on mortality.

All modified pediatric VAE proposals apart from CDC focus on changing the thresholds to meet the first tier of VAE (VAC) and retain the parameters for IVAC and PVAP used in adult definitions. The reasons argued by the authors for this less restrictive algorithm for pediatric VAE definitions were that most children present good pulmonary baseline conditions and can withstand mechanical complications better than children suffering from chronic conditions or adults, and that childhood is needed a shorter recovery time than in adulthood. Indeed, when the VAE adult criteria were applied by Peña-López et al. to children from a Pediatric Intensive Care Unit, incidence of VAE was fewer than in adults and their repercussion on mortality higher (Peña-López et al., 2017). By contrast, they obtained a fourfold increase in VAEs and the double of PVAP when using their less restrictive criteria for a respiratory worsening in their Ped-VAE proposal, and keeping the repercussion on outcomes. As in the adult population, the agreement between the new 2013-VAE and old 2008-CDC PNU/VAP definitions in children is poor (Mohd Ali et al., 2019) and the same for the new proposed pediatric definitions tested (Peña-López et al., 2017). Once again, a misinterpretation of these definitions may lead to reject their use but, on the contrary, an in-depth review can generate great interest not only for surveillance but also for their clinical use. Until now, the importance of monitoring ventilator settings as a surrogate for oxygenation had not been previously recognized even though hypoxemia had been suggested to be a main variable in assessing pneumonia resolution. Short courses of antibiotics have been suggested in suspected or confirmed infectious episodes non fulfilling VAE criteria (Klompas et al., 2017). Oxygenation variations have been proposed as the cornerstone in the assessment of the ventilated patient when suspecting and treating a ventilator-associated infection, going one step beyond Chest X-ray opacities and inflammatory parameters (Rello et al., 2018). More research is needed to confirm this new approach.

Conclusions

In summary, the ventilator-associated event definition implemented by the CDC and proposed as the new National Healthcare Safety Network surveillance definition in the United States to replace their former definition of VAP represents a new

opportunity to overcome many of the weaknesses of traditional VAP surveillance and broadens the focus of surveillance encompassing other preventable conditions related to mechanical ventilation. The use of these new criteria in children requires an adaptation of the VAE definition in accordance with the peculiarities of the pediatric population. On another hand, neither VAE definition nor VAE tiers are neither sensitive nor specific for VAP or VAT, making difficult to create a clinical correlation; moreover, some VAE subtype terms (VAC and IVAC) are frequently misused in the literature leading to confusion. More research will be needed in the next years to establish the usefulness of the VAE algorithm and its applicability as a quality indicator.

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LIST OF RELEVANT WEB PAGES

1. CDC Device-associated Module. Ventilator-Associated Event (VAE), January 2019. https://www.cdc.gov/nhsn/PDFs/pscManual/10-VAE_FINAL.pdf
2. CDC VAE training. https://www.cdc.gov/nhsn/pdfs/training/2018/vae-508.pdf

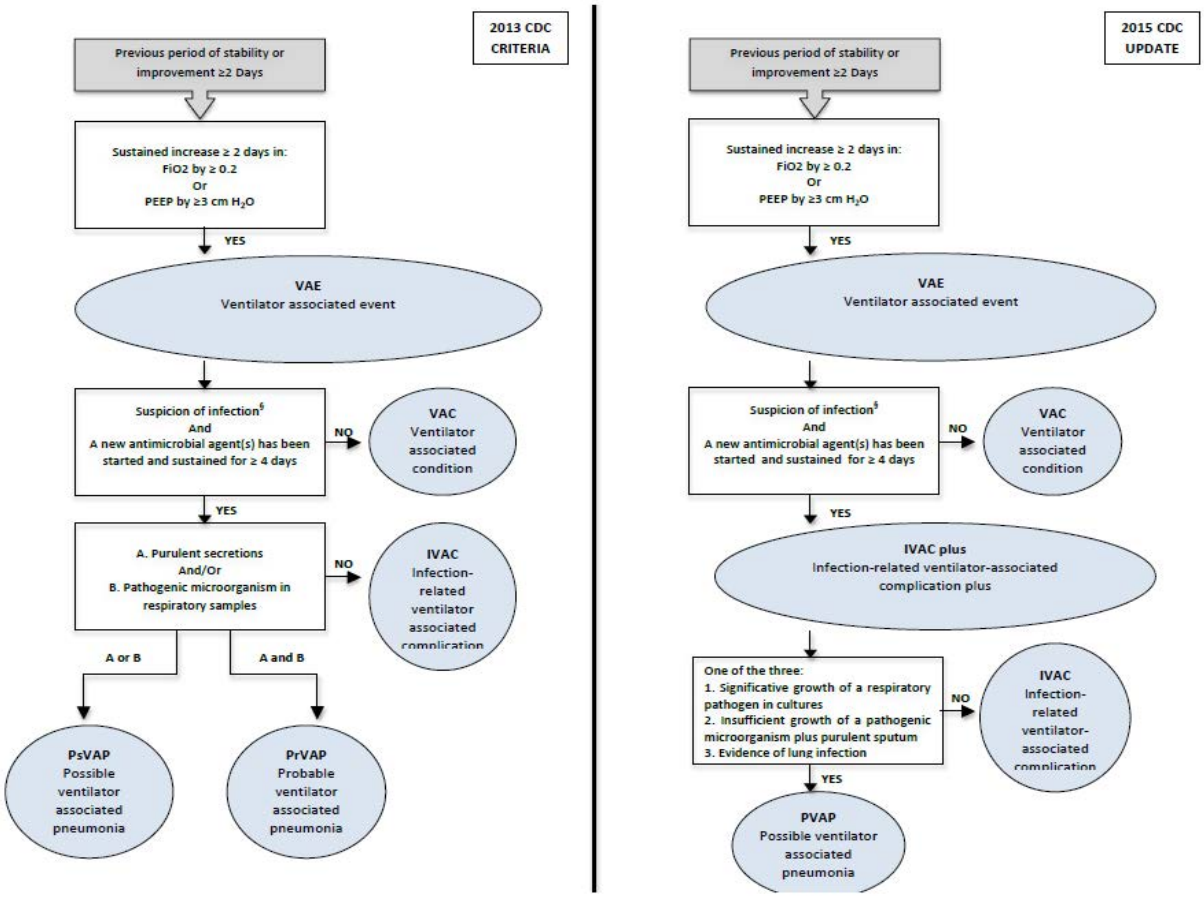

Figure 1. 2013 CDC classification and 2015 update

§Suspicion of infection: leucocytosis (≥12,000 cells/mL)/leucopenia (≤ 4000 cells/mL) or fever (≥ 38°C)/hypothermia (≤ 36°C)

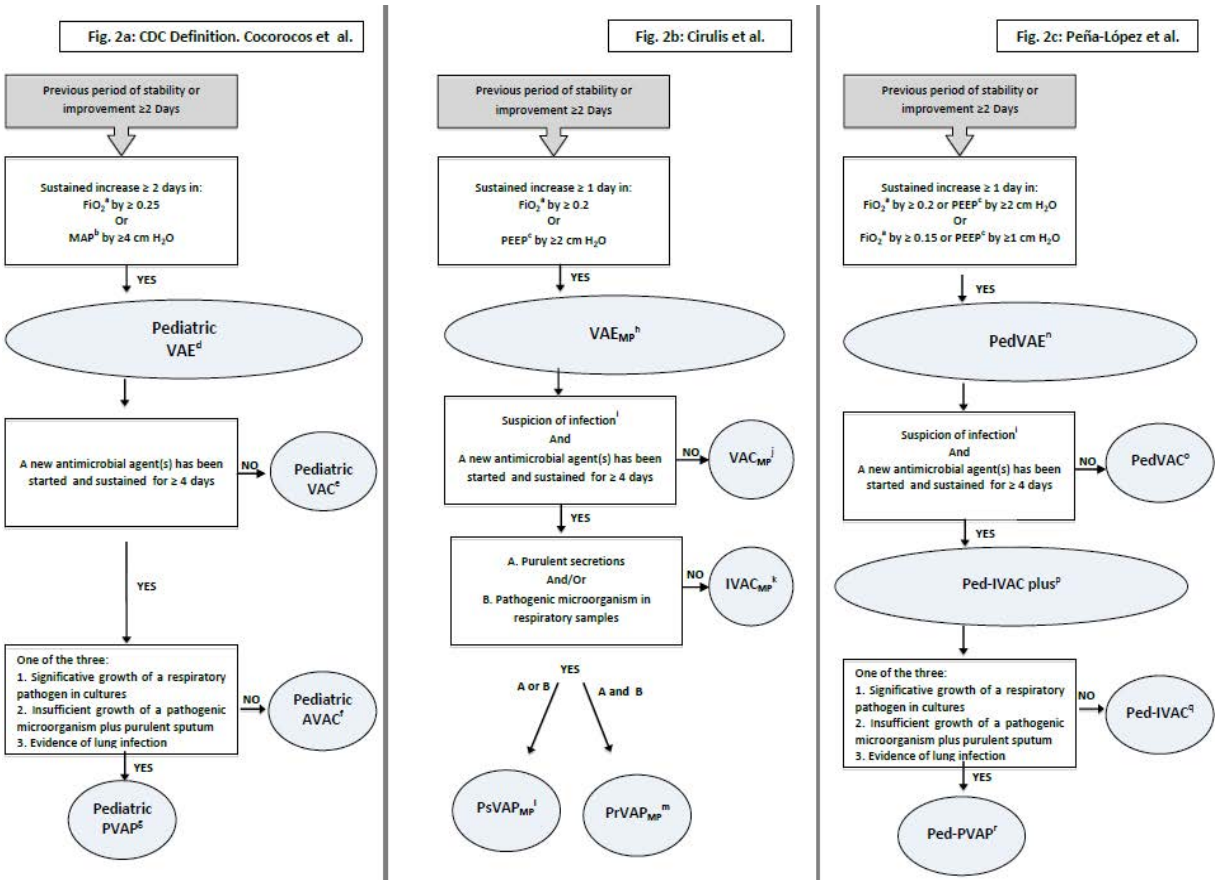

Figure 2. Pediatric VAE CDC definition and other pediatric modified proposals

[a]Fraction of inspired oxygen; [b]Mean airway pressure; [c]Positive End Expiratory Pressure; [d]Pediatric VAE (PedVAE): Pediatric Ventilator-Associated Event; [e]Pediatric VAC (PedVAC): Pediatric Ventilator-Associated Condition; [f]Pediatric AVAC: Pediatric VAC with antimicrobial use; [g]Pediatric PVAP: Pediatric Possible Ventilator-Associated Pneumonia; [i]Suspicion of infection: fever (≥38 ºC)/hypothermia (≤36 ºC) or leukocytosis (≥12,000 cells/mL)/leukopenia (≤4,000 cells/mL); [j]VAC MP**:** Ventilator associated condition modified pediatric criteria; [k]IVACMP: Infection-related Ventilator-Associated complication modified pediatric criteria; [l]PsVAPMP: Possible Ventilator-Associated Pneumonia modified pediatric criteria; [m]PrVAPMP: Probable Ventilator-Associated Pneumonia modified pediatric criteria; [n]PedVAE: Pediatric Ventilator-Associated Event; [o]PedVAC: Pediatric Ventilator-Associated VAC; [p]PedIVAC-plus: Pediatric Infection-related Ventilator-Associated complication-plus; [q]Ped-IVAC: Pediatric Infection-related Ventilator-Associated complication; [r]PedPVAP: Pediatric Possible ventilator-associated pneumonia

Table 1. Antimicrobial agents eligible for the diagnosis of IVAC[a].

Antibiotics		
Amikacin	Clindamycin	Penicillin G
Ampicillin	Colistimethate	Piperacillin
Ampicillin/Sulbactam	Dalbavancin	Piperacillin/Tazobactam
Azithromycin	Doripenem	Polymyxin B
Aztreonam	Doxycycline	Quinupristin/Dalfopristin
Cefazolin	Ertapenem	Rifampin
Cefepime	Fosfomycin	Sulfamethoxazole/Trimetho
Cefotaxime	Gemifloxacin	prim
Cefotetan	Gentamicin	Sulfisoxazole
Cefoxitin	Imipenem/Cilastatin	Tedizolid
Ceftaroline	Levofloxacin	Telavancin
Ceftazidime	Linezolid	Telithromycin
Ceftazidime/Avibactam	Meropenem	Tetracycline
Ceftizoxime	Metronidazole	Ticarcillin/Clavulanate
Ceftolozane/Tazobactam	Minocycline	Tigecycline
Ceftriaxone	Moxifloxacin	Tobramycin
Cefuroxime	Nafcillin	Vancomyin
Ciprofloxacin	Oritavancin	
Clarithromycin	Oxacillin	
Antifungals		
Amphotericin B	Fluconazole	Posaconazole
Amphotericin B Liposomal	Isavuconazonium	Voriconazole
Anidulafungin	Itraconazole	
Caspofungin	Micafungin	
Antivirals		
Oseltamivir	Zanamivir	Peramivir

Table 2. Criteria that can be used to meet the PVAP[a] definition	
1.Significative growth of a respiratory pathogen in cultures	a. Endotracheal aspirate: 10^5 CFU/mL b. Bronchoalveolar lavage: 10^4 CFU/mL c. Protected specimen brush: 10^3 CFU/mL d. Lung tissue: 10^4 CFU/g
2. Insufficient growth of a pathogenic microorganism plus purulent sputum	Purulent respiratory secretions: $\geq$ 25 neutrophils and $\leq$ 10 squamous epithelial cells per low power field
3. Evidence of lung infection	a. Pathogenic microorganism in pleural fluid cultures b. Positive lung histopathology: Abscess formation Foci of consolidation with intense polymorphonuclear accumulation Evidence of parenchyma invasion by fungus or virus c. Positive test for *Legionella* species d. Positive test for selected virus in respiratory samples[b]

[a]PVAP: Possible ventilator-associated pneumonia. [b]Pathogenic virus in respiratory samples: *Influenza, respiratory syncytial, adenovirus, parainfluenza, rhinovirus, human metapneumovirus, coronavirus.*

XIII. ANEXO II

Capítulo 13. Otras actividades derivadas de la investigación

Comparison of factors associated with adult and pediatric ventilator-associated events
Y. Peña-López, **S. Ramírez-Estrada**, Anabel Romero, L. Lagunes, D. Koulenti, J. Rello and the EUVAE Study Group
32nd European Congress of Intensive Care Medicine. Berlin, Alemania; Septiembre 28 al 2 de Octubre de 2019

Factors associated with ventilator-associated events in an international prospective cohort of adult and children.
Yolanda Peña, **Sergio Ramírez**, Anabel Romero, Leonel Lagunes, Kostoula Arvaniti, Despoina Koulenti, Saad Nseir, Nefise Oztoprak, Lilla Bouadma, Jordi Rello and the EUVAE Study group.
28th European Congress of Clinical Microbiology and Infectious Diseases. Amsterdam, Holanda; Abril 16 al 19 de 2019

Looking inside the ventilator-associated events in European Intensive Care Units. The EU-VAE Project
Ramírez-Estrada S, Lagunes L, Peña-López Y, Vahedian A, Nseir S, Arvaniti K, Bastug A, Vldaur L, Oztoprak N, Bouadma L, Koulenti D, Rello J, EU-VAE study investigators group.
27th European Congress of Clinical Microbiology and Infectious Diseases.Vienna, Austria; Abril 22 al 25 de 2017

Ventilator-Associated Events in European Intensive Care Units. The EU-VAE project.
S. Ramírez-Estrada, L. Lagunes, K. Arvaniti, A. Bastug N. Oztoprak, A. Radjou, A. Inan, I. Bozkurt, G. Poulakou, J. Rello, EU-VAE study investigators group.
26th European Congress of Clinical Microbiology and Infectious Diseases. Amsterdam, Holanda; Abril 9 al 12 de 2016

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"La tierra es de quien la trabaja"
Emiliano Zapata
(Escuchada a Jordi Rello)

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…A todos aquellos compañeros de viaje a quienes la emoción del momento me impida registrar en estas páginas les aseguro que están impresos en mi corazón.

Gracias totales!

"Tantos platos rompió, inclusive sin tocarlos, que Fernanda optó por comprarle un servicio de peltre antes de que liquidara las últimas piezas de su costosa vajilla, y aún los restantes platos metálicos estaban al poco tiempo desconchados y torcidos. Pero a cambio de aquel poder irremediable, exasperante inclusive para el mismo, tenía una cordialidad que suscitaba la confianza inmediata, y una estupenda capacidad de trabajo.

Gabriel García Márquez
100 años de Soledad