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Research Article

Outcomes associated with ventilator-associated events (VAE), respiratory infections (VARI), pneumonia (VAP) and tracheobronchitis (VAT) in ventilated pediatric ICU patients: A multicentre prospective cohort study

Yolanda Peña-López [a,b,i], María Slocker-Barrio [c,d], Juan-Carlos de-Carlos-Vicente [e], Marta Serrano-Megías [f], Iolanda Jordán-García [g,h,†], Jordi Rello [i,*,†], EUVAE-Kids Study Investigators Group Investigators

[a] Microbiome Research Laboratory, Immunology Department, University of Texas Southwestern Medical Center, Dallas, 75390 TX, United States
[b] Pediatric Intensive Care Department, Vall d' Hebron University Hospital, Vall d' Hebron Research Institute, Passeig de la Vall d' Hebron 119-129, 08035 Barcelona, Spain
[c] Pediatric Intensive Care Department, Gregorio Marañón University Hospital and Gregorio Marañón Biomedical Research Institute, 28009 Madrid, Spain
[d] Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin Network (RICORS), RD21/0012/0011, Instituto de Salud Carlos III, 28029 Madrid, Spain
[e] Pediatric Intensive Care Unit, Hospital Son Espases, 07120 Palma de Mallorca, Spain
[f] Greenlife Research Group, Health Science, University of San Jorge, Zaragoza, Spain
[g] Pediatric Intensive Care Unit, Hospital Sant Joan de Déu and Immunological and Respiratory Disorders in the Pediatric Critical Patient Research Group, Institut de Recerca Sant Joan de Déu, 08950 Barcelona, Spain
[h] Consortium of Biomedical Research Network for Epidemiology and Public Health (CIBERESP), 28029 Madrid, Spain
[i] Global Health eCore, Vall d' Hebron Institute of Research, Passeig de la Vall d' Hebron 129, AMI-14 08035 Barcelona, Spain

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ABSTRACT

Objectives: An objective categorization of respiratory infections based on outcomes is an unmet clinical need. Ventilator-associated pneumonia and tracheobronchitis remain used in clinical practice, whereas ventilator-associated events (VAE) are limited to surveillance purposes.
Research methodology/design: This was a secondary analysis from a multicentre observational prospective cohort study. VAE were defined as a sustained increase in minimum Oxygen inspired fraction (FiO2) and/or Positive end-expiratory pressures (PEEP) of $\geq$ 0.2/2 cm H_2O respectively, or an increase of 0.15 FiO_2 + 1 cm H20 positive end-expiratory pressures for $\geq$ 1 calendar-day.
Setting: 15 Paediatric Intensive Care Units.
Main outcome measures: Mechanical ventilation duration, intensive care and hospital length of stay; (LOS) and mortality.
Results: A cohort of 391 ventilated children with an age (median, [Interquartile Ranges]) of 1 year[0.2–5.3] and 7 days[5–10] of mechanical ventilation were included. Intensive care and hospital stays were 11 [7–19] and 21 [14–39] days, respectively. Mortality was 5.9 %. Fifty-eight ventilator-associated respiratory infections were documented among 57 patients: Seventeen (29.3 %) qualified as ventilator-associated pneumonia (VAP) and 41 (70.7 %) as ventilator-associated tracheobronchitis (VAT). Eight pneumonias and 16 tracheobronchitis (47 % vs 39 %,P = 0.571) required positive end-expiratory pressure or oxygen increases consistent with ventilator-

Abbreviations: VAT, Ventilator-Associated Tracheobronchitis; VAP, Ventilator-Associated Pneumonia; VARI, Ventilator-Associated Respiratory Infection; VAE, Ventilator-Associated Event; IVAC, Infection Related Ventilator-Associated Complication; PVAP, Possible Ventilator-Associated Pneumonia; PICU, Pediatric Intensive Care Unit; PEEP, Positive End Expiratory Pressure; MAP, Mean Airway Pressure; FiO_2, Fraction of inspired oxygen; PRISM III score, Pediatric Risk Mortality score; PELOD score, Pediatric Logistic Organ Dysfunction score; LOS, Length of stay; MV, Mechanical Ventilation; IQR, Interquartile range; US – CDC, United States Centre for Disease Control and Prevention; ARDS, Acute Respiratory Distress Syndrome.

* Corresponding author at: Vall d' Hebron University Hospital, Vall d' Hebron Research Institute, Passeig de la Vall d' Hebron 119-129, AMI-14, 08035 Barcelona, Spain

E-mail addresses: yolanda.pena-lopez@utsouthwestern.edu (Y. Peña-López), maria.slocker@salud.madrid.org (M. Slocker-Barrio), juanc.decarlos@ssib.es (J.-C. de-Carlos-Vicente), mserranom@usj.es (M. Serrano-Megías), yolanda.jordan@sjd.es (I. Jordán-García), jrello@crips.es (J. Rello).

† I. Jordán-García and J. Rello shares senior co-authorship.

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associated criteria. Pneumonias did not significantly impact on outcomes when compared to tracheobronchitis. In contrast, infections (pneumonia or tracheobronchitis) following VAEs criteria were associated with > 6, 8 and 15 extra-days of ventilation (16 vs 9.5, $P = 0.001$), intensive care stay (23.5 vs 15; $P = 0.004$) and hospital stay (39 vs 24; $P = 0.015$), respectively.

Conclusion: When assessing ventilated children with respiratory infections, VAE apparently is associated with higher ventilator-dependency and LOS compared with pneumonia or tracheobronchitis.

Implications for practice: Incorporating the modification of ventilatory settings for further categorization of the respiratory infections may facilitate therapeutic management among ventilated patients.

Introduction

Objective criteria for the accurate diagnosis of ventilator-associated respiratory infections (VARI) are lacking, being categorized into ventilator-associated pneumonia or ventilator-associated tracheobronchitis. Unfortunately, the lack of effect on patient's outcomes and antibiotic consumption revealed the need for other quality indicators among mechanical ventilation patients (Fabregas et al., 1999; Nseir et al., 2014; Nora and Póvoa, 2017; Blot et al., 2011; Klompas, 2012).

Ten years ago, the US Centres for Disease Control and Prevention (CDC) replaced ventilator-associated pneumonia surveillance for ventilator-associated events (VAE) (Klompas, 2013). The focus was turned from chest radiograph to respiratory worsening defined by a sustained increase of the minimum daily fraction of inspired oxygen (FiO_2) and/or the positive end expiratory (PEEP). The goal of this shift towards the VAE concept was to broaden the focus of surveillance and increase the impact of preventive policies in patients' outcomes. In clinical practice, the utility of VAE criteria remains to be determined. Whereas VAE definition has greater accuracy assessing patient's outcomes, only the most severe tracheobronchitis and pneumonia episodes require an increase of the ventilator settings (FiO_2, PEEP) that qualify as VAE (Ramirez-Estrada et al., 2018). As a consequence, the VAE concept has not been incorporated into the routine clinic dissertation. In contrast, a ventilator-associated pneumonia or ventilator-associated tracheobronchitis diagnosis, frequently triggered by positive culture results, is followed by changes in antibiotic prescription at the bedside (Prinzi et al., 2021). Additionally, the use point-of care lung ultrasound shows the same limitations as conventional chest-X ray for ventilator-associated pneumonia diagnosis in terms of specificity (Sperandeo et al., 2016; Rajagopalan, 2021). Furthermore, the discussion over the treatment of tracheobronchitis or the duration of antibiotic therapy is still running (Nseir et al., 2014; Martin-Loeches et al., 2017).

On the other hand, adult VAE criteria resulted extremely restrictive in children (Iosifidis et al., 2016; Chomton et al., 2018), highlighting the need of a paediatric adaptation (Iosifidis et al., 2018). The variation of VAE based on the mean airway pressure (MAP) adopted by the US CDC (Cocoros et al., 2016) resulted even more restrictive (Willson et al., 2018; Arthur et al., 2022; Gionfriddo et al., 2018), missing 84 out of 89 ventilator-associated infections in a multicentre study conducted at 47 paediatric ICUs (Willson et al., 2018) due to the extremely low basal VAE rates, between 0.9 and 1.9 per 1,000 ventilator-days (Arthur et al., 2022; Gionfriddo et al., 2018). In contrast, a definition of VAE based on slighter PEEP increases resulted the least restrictive and the only VAE criteria independently associated with worse outcomes among children (Peña-López et al., 2018, 2022; Papakyritsi et al., 2023). Still, it did not encompass all ventilator-associated pneumonia and tracheobronchitis (Peña-López et al., 2022). Our hypothesis was that the application of VAE respiratory settings criteria on patients diagnosed from VARIs selects those episodes with worse outcomes.

Methods

Objectives

The aim of our study was to compare the impact on outcomes (in ventilated children with respiratory infections) when using changes on respiratory settings consistent with VAE versus other standardized CDC criteria (Ventilator-associated pneumonia vs ventilator-associated tracheobronchitis).

Study design, setting and participants

This was a pre-planned secondary analysis of a multicentre, observational, prospective cohort study (Peña-López et al., 2022). It was conducted in 15 PICUs.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board on human research at the coordinating Hospital [PR(AMI)330/2018] and all the participating hospitals.

Participants

Exclusion criteria were age < 30 days, infants with a corrected gestational age of < 44 weeks, and age > 18 years, previous mechanical ventilation, extracorporeal life support, right-to-left shunt, and pulmonary hypertension. Subjects with missing data or incomplete follow-up were also excluded from the statistical analysis. Duration of mechanical ventilation was considered until extubation or ICU death. In patients with more than one episode of mechanical ventilation, only the first episode was considered.

Definitions

An episode of mechanical 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. VARI included ventilator-associated pneumonia and tracheobronchitis (Rello, LIsboa & Koulenti; 2014). Ventilator-associated pneumonia and tracheobronchitis were defined according to 2008 CDC criteria (Horan et al., 2008; Foglia et al., 2007) and VAE criteria in accordance with the most sensitive VAE definition for children, that was based on lower PEEP variations (Peña-López et al., 2018). Compared to the adult VAE definition, it contemplated an increase in the minimum daily PEEP of ≥ 2 H_2O instead of ≥ 3 cm H_2O, a change in the ventilator settings sustained for ≥ 1 day instead of ≥ 2 days, and an increase in minimum daily FiO_2 by 0.15 plus an increase in minimum daily PEEP of ≥ 1 cm H_2O sustained for ≥ 1 days (Peña-López et al., 2018). Likewise adult VAE criteria, VAE in children was defined by a 14-day period, starting on the first day of respiratory worsening, during which a VAE could not be reported.

Also similarly (Klompas, 2013), three definition tiers (Fig. S1) within the children VAE algorithm were defined: a) ventilator-associated condition (VAC), when the respiratory worsening fulfilled some criteria for detecting hypoxemia defined as a change in the ventilator settings exposed above; b) infection-related ventilator-associated complication (IVAC), if in view of the above, and the presence of general evidence of

infection/inflammation, a new antimicrobial prescription has been started and sustained for at least 4 calendar days by the attending physician; and c) possible Ventilator-Associated Pneumonia (PVAP), if in addition of the above, there is a microbiological confirmation of a lower respiratory tract infection. These three tiers are mutually exclusive, no one including another. Only IVAC-plus encompasses the last two tiers (IVAC + PVAP), frequently referred as the "infectious VAE" (Fig. 1 and Fig. S1 Definitions). VAE-VARI was defined as the ventilator-associated respiratory infection that met the respiratory settings criteria of VAE. Non-VAE-VARI was defined as the ventilator-associated respiratory infection that did not meet the respiratory settings criteria of VAE.

Data collection

Medical, trauma, and surgical patients were included. Clinical and demographic features, including the Paediatric Risk of Mortality (PRISM) III (Pollack et al., 1996) at ventilation onset and the Paediatric Logistic Organ Dysfunction score (PELOD) during the episode of mechanical ventilation were recorded. Multi organ failure was defined as PELOD > 13 (El-NAwawy et al., 2017). Duration of mechanical ventilation was defined as the number of days from the start of mechanical ventilation until successful extubation or ICU death during a given mechanical ventilation episode. The following outcomes were considered as end-points: duration of mechanical ventilation, ICU and hospital length of stay (LOS), and mortality during the episode of mechanical ventilation. ICU and hospital LOS were calculated from the start of the episode of mechanical ventilation until ICU/hospital discharge, respectively.

Data analysis

Results were reported as percentages for qualitative variables and median and interquartile range (IQR) for quantitative variables. Comparison of proportions was performed using Pearson and X^2 tests, while comparison of medians was performed using the Mann-Whitney *U* test. Clustered Wilcoxon rank sum test was used for clustered data following the Datta-Sutton method. Statistical significance was considered if the p value was < 0.05. All statistical analyses were performed with R software version 1.2.1335.

Results

The study cohort included 391 children and 3,626 ventilator-days from a total of 412 eligible patients. One patient who developed pneumonia and tracheobronchitis (meeting only one of them VAE criteria) was excluded from subgroups' analysis. Three patients who developed VAE classified as non-infectious (VAC) during the VARI episode also

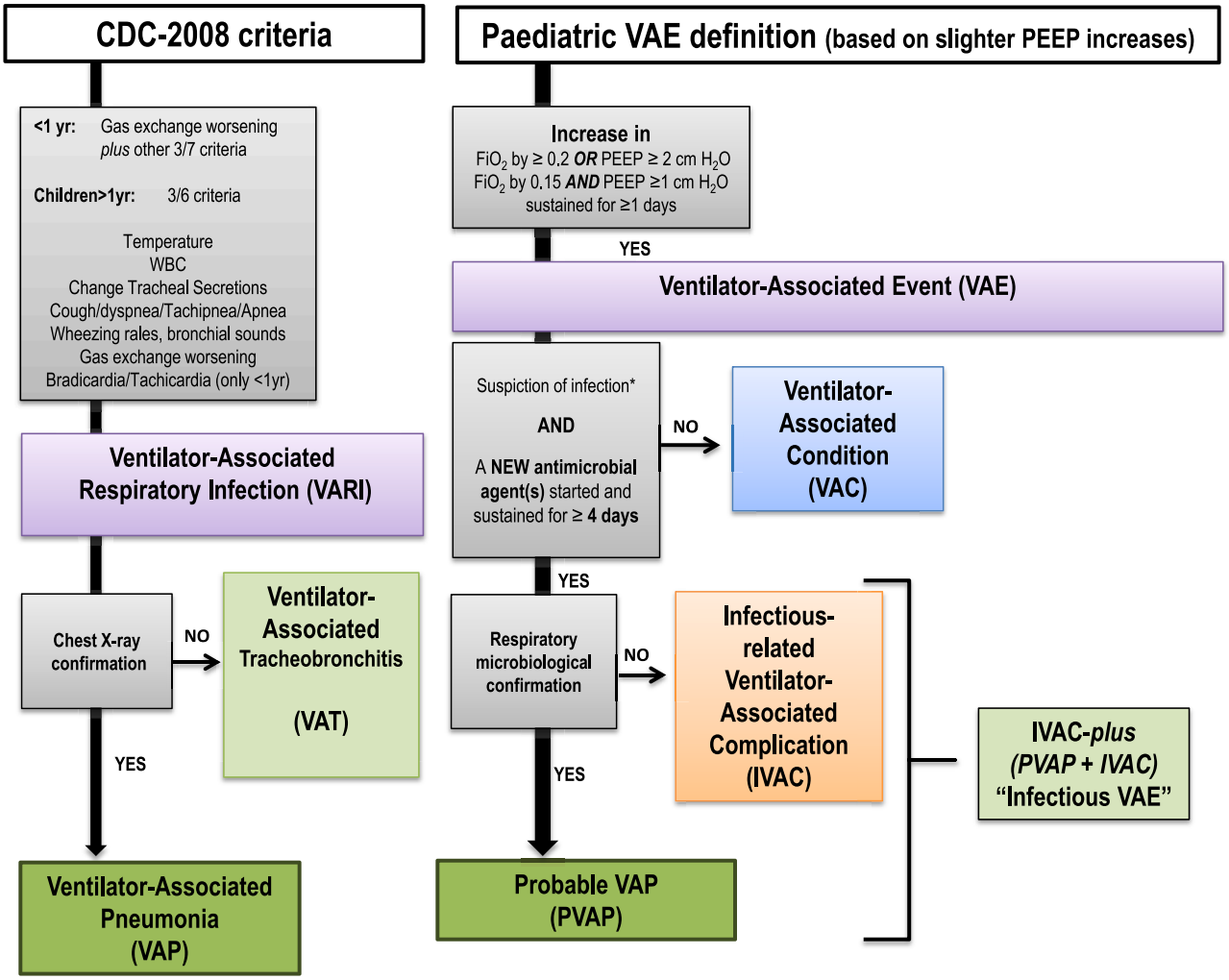

Fig. 1. Study Definitions (children).

were excluded from the subgroup's analysis. Patients' baseline characteristics of the overall population and VARI groups are summarized in Table 1. Baseline patient characteristics did not significantly differ among groups except for PRISM III score (risk of mortality) at the mechanical ventilation onset between patients developing pneumonia vs tracheobronchitis ($P = 0.019$). Main reason for mechanical ventilation was respiratory failure, and the presence of one or more comorbidities was identified in more than 60 % in the overall population and across groups.

Fifty-eight (14.8 %) VARI were identified in 57 patients. Forty-one (70.6 %) were diagnosed as tracheobronchitis, and seventeen (29.3 %) as ventilator-associated pneumonia. The median from the onset of mechanical ventilation to VAE or a respiratory infection did not differ: 5 [3–7.75] and 5 [4–7.5] days, respectively. According to VAE criteria, there were 45 (59.2 %) Ventilator-Associated Conditions (VAC), 12 (15.8 %) Infection-related Ventilator-Associated Complications (IVAC) and only 19 (25 %) qualified as possible Ventilator-associated Pneumonia (PVAP). Even when considering all the "infectious VAE" (IVAC-plus), they did not encompass all VARI (31 IVAC-plus vs 58 VARI). (Fig. 2 - Flow chart long).

When categorizing VARI using the VAE respiratory settings criteria, 24 out of 58 (41.3 %) VARI qualified as VAE: eight out of 17 as ventilator-associated pneumonia (47 %) and 16 out of 41 as tracheobronchitis (39 %) ($P = 0.571$). All but three VAE-VARI were subclassified in the VAE algorithm as "infectious VAE" (19 possible VAP + 2 Infectious-related ventilator-associated complications) (Fig. 3. VARI subclassifications). Developing ventilator-associated pneumonia did not significantly impact on outcomes when compared to tracheobronchitis. In contrast, children who developed VARI and required an increase of ventilator settings according to VAE criteria were associated with more than 6, 8 and 15 extra-days of mechanical ventilation (16 vs 9.5, $P = 0.001$), pediatric intensive care (23.5 vs 15; $P = 0.004$) and hospital stays (39 vs 24; $P = 0.015$), respectively, compared to those who did not (Table 2). Similar impact on outcomes was observed when those patients with respiratory infections and VAE classified as "non-infectious VAE" were not excluded from the analysis (Table 3).

Discussion

This is the first prospective multicentre study to assess patients with respiratory infections using ventilator settings increases consistent with VAE to compare its performance versus the standard categorization of pneumonia or tracheobronchitis. Two thirds of respiratory infections were documented as tracheobronchitis. Our data showed that the categorization of these patients according to radiological criteria (pneumonia or tracheobronchitis) did not significantly discriminated patients with worse outcomes. Interestingly, less than half required modification of ventilatory settings consistent with VAE. This subset had a substantial impact on ventilatory dependency and hospitalization periods, indeed. These findings challenge the relevance of lung images techniques in the standard clinical practice and shift the focus on the modification of the ventilatory settings as a surrogate of hypoxemia. Our findings add value to the literature, opening a door for the clinical application of VAE at the bedside. Consequently, categorizing respiratory infections based on increases of FiO2 and/or PEEP consistent with VAE may be more useful to guide the antibiotic prescription than the distinction between pneumonia and tracheobronchitis.

The prediction accuracy on outcomes of VAE has been extensively confirmed in adults and children (Ramirez-Estrada et al., 2018; Iosifidis et al., 2016; Peña-López et al., 2018; Papakyritsi et al., 2023; Fan et al., 2016). Despite this, the proposed shift from ventilator-associated pneumonia to VAE is still raising concerns (Gionfriddo et al., 2018; Willson, 2019; Ziegler et al., 2019; Sick-Samuels and Priebe, 2023), stressing the importance of assessing this new quality indicator in clinical practice (Iosifidis and Coffin, 2020). VAE have many potential causes: pneumonia, fluid overload, cardiac pulmonary edema, atelectasis, and acute respiratory distress syndrome (ARDS), among others, not all of them preventable (Klompas, 2019). Possible ventilator-associated pneumonia is the most frequent event reported when the VAE algorithm is applied in adults (Klompas, 2015). In contrast, non-

Table 1
Baseline patient characteristics.

	Overall (n = 391)	**VARI** (n = 58)[a]	**VAT** (n = 41)[a]	**VAP** (n = 17)[a]	**VAE-VARI** (n = 24)[a,b]	**Non-VAE-VARI** (n = 34)[a]
Male sex, n (%)	214 (54.7)	29 (50.1)	23 (57.5)	5 (31.2)	10 (50)	19 (55.9)
Age (yr) [median, IQR]	1 [0.2—5.3]	1 [0.2–9.7]	0.9 [0.3–10]	1.3 [0.1–9.5]	3.6 [0.4–11]	0.6 [0.2–9.3]
PRISM III score [median, IQR]	7 [3—13]	6 [3–10]	6 [5–11.2]*	3 [1.5–7]*	6 [3–13.2]	6 [4.2–10]
PELOD score [median, IQR]	11 [1–17.5]	11 [2–21]	11 [7.7–21]	8 [1.7–11.2]	11 [10–20.5]	11 [2–18.7]
Comorbidities						
None	150 (38.3)	19 (33.3)	14 (35)	5 (31.2)	7 (35)	11 (32)
One	152 (38.9)	23 (40.4)	14 (35)	9 (56.3)	7 (35)	16 (47)
Two or more	89 (22.8)	15 (26.3)	12 (30)	2 (12.5)	6 (30)	7 (21)
Place of intubation, n (%)						
PICU	224 (57.3)	28 (49.1)	17 (42.5)	10 (62.5)	9 (45)	18 (53)
Operating room	96 (24.7)	15 (26.3)	13 (32.5)	2 (12.5)	6 (30)	8 (23.5)
Emergency room/Ward	27 (6.9)	3 (5.3)	1 (2.5)	2 (12.5)	1 (5)	1 (2.9)
Out-of-hospital setting	44 (11.3)	11 (19.3)	9 (22.5)	2 (12.5)	4 (20)	7 (20.6)
Type of patient						
Medical	270 (69.0)	37 (65.0)	22 (55)	14 (87.5)	11 (55)	24 (70.5)
Surgical	101 (25.8)	13 (22.8)	11 (27.5)	2 (12.5)	5 (25)	7 (20.5)
Trauma-burn	20 (5.2)	7 (12.2)	7 (17.5)	0 (0.0)	4 (20)	3 (8.8)
Reason for mechanical ventilation						
Respiratory failure	190 (48.6)	24 (42.1)	16 (40.0)	8 (50.0)	6 (30)	16 (47)
Surgery/other procedures	92 (23.5)	14 (24.5)	11 (27.5)	2 (12.5)	6 (30)	7 (20.5)
Septic shock	35 (9)	3 (5.2)	2 (5.0)	1 (6.25)	1 (5)	2 (6)
Cardiogenic shock/cardiac arrest	22 (5.6)	4 (7.0)	2 (5.0)	2 (12.5)	2 (10)	2 (6)
Altered level of consciousness	52 (13.3)	12 (21.0)	9 (22.5)	3 (18.75)	5 (25)	7 (20.5)

Data are medians [interquartile range] unless otherwise specified. VAT = Ventilator-Associated Tracheobronchitis; VAP = Ventilator-Associated Pneumonia; VARI = Ventilator-Associated Respiratory Infection; VAE = Ventilator-Associated Event; IQR = Interquartile range; PRISM III score = Pediatric Risk Mortality score; PELOD score = Pediatric Logistic Organ Dysfunction score. PICU = Pediatric Intensive Care Unit; LOS = Length of stay; MV = Mechanical Ventilation. [a]One patient who developed both ventilator-associated respiratory infections, VAT and VAP, was excluded from the analysis. [b]Three patients who developed ventilator-associated events classified as non-infectious during the VARI episode were excluded from the analysis.

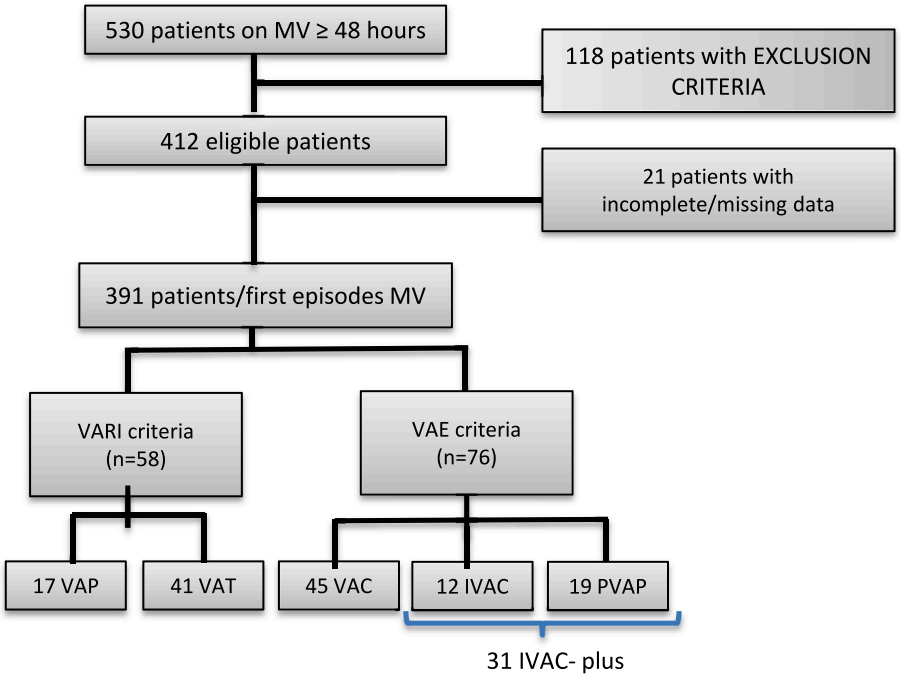

Fig. 2. Flow chart long.

infectious complications are the most frequent cause of pediatric VAE, atelectasis and fluid overload being more frequently reported in children than ARDS (Peña-López et al., 2018, 2022; Vaewpanich et al., 2019; Karandikar et al., 2019). Notably, the subclassification of VAE as an infectious-related event relies on the start of antibiotic therapy and its continuation during almost 4 days. This is highly variable, clearly depending on physician criteria, and, subsequently, on the classical concepts (Prinzi et al., 2021; Karandikar et al., 2019; Beardsley et al., 2016).

Our findings confirm tracheobronchitis as the most frequent lung infection in children (Beardsley et al., 2015) and support grouping tracheobronchitis and ventilator-associated pneumonia together as VARI (Beardsley et al., 2016). Regarding the correlation between VARI and VAE, a *meta*-analysis conducted by Fan et al. showed that the VAE algorithm frequently missed many pneumonia (Fan et al., 2016). In Europe, a prospective multicenter study in adults assessing VAEs and both VARI found that infections were the main cause of VAE despite that they missed almost 30 % of ventilator-associated pneumonia and up to 71 % of tracheobronchitis (Ramirez-Estrada et al., 2018). Pediatric studies have also confirmed the poor agreement between VAE and pneumonia/tracheobronchitis criteria in children (Iosifidis et al., 2016; Willson et al., 2018; Gionfriddo et al., 2018; Peña-López et al., 2018; Ziegler et al., 2019;Mohd Ali et al., 2019). In our study, above than 50 % of ventilator-associated pneumonia and 60 % of tracheobronchitis were missed by the VAE algorithm, despite using the least restrictive definition.

Since there is not good clinical correlation between VAE and clinical respiratory infection, it seems reasonable not to abandon the concept of VARI (Ramirez-Estrada et al., 2018). Nevertheless, our findings support that VAE criteria may be used to categorize respiratory infections in children due to their significant impact on outcomes. Thus, VAE would be not only worthy of appropriate efforts for prevention purposes (ie. fluid overload) (Wu et al., 2023), but also it may be taken into consideration for antibiotic management (Coffin et al., 2021). In agreement, other authors (Iosifidis et al., 2016) found that children diagnosed with ventilator-associated pneumonia following adult VAE criteria had higher mortality than all those diagnosed with pneumonia. Other authors suggested the pediatric VAE based on mean airways pressure with antimicrobial use for $\geq$ 4 days to improve antimicrobial use (Karandikar et al., 2019). In our study, applying the least restrictive VAE definition (based on PEEP) to VARI showed better discrimination of poorer outcomes than the distinction between tracheobronchitis and pneumonia. Since hypoxemia has been suggested as the main variable for assessing pneumonia resolution (Vidaur et al., 2005a), changes in ventilator settings as surrogate markers for oxygenation would be the cornerstone for antimicrobial therapy management, going one step beyond chest X-ray opacities and inflammatory parameters (Vidaur et al., 2005b). Accordingly, short courses of antibiotics have been suggested in suspected or confirmed infectious episodes non fulfilling VAE criteria (Klompas et al., 2017). Our results support that it may be more appropriate to decide the duration of antimicrobial therapy by using the VAE criteria than the distinction between pneumonia and tracheobronchitis. A further assessment of ventilator-associated pneumonia based on VAE criteria may also identify which patients could benefit from shorter antibiotic courses.

Limitations

This study has the following strengths: First, it was prospectively designed and carried out. Second, to assess the performance of each definition on patient outcomes, length of stay was considering the period only from intubation onset until ICU or hospital discharge. Besides, some confounding factors are referred to the mechanical ventilated episode and not to the whole ICU admission period (ie. the mortality risk and multiorgan failure scores). Third, local investigators were blinded to the least restrictive VAE criteria, avoiding any bias on the ventilator management strategies. Further VAE criteria assessment was carried out independently by the same researcher who was also initially blinded to VARI results. Finally, the multicenter character of our study makes the findings more generalizable than studies from single centers.

Our study has also several limitations. First, the pediatric VAE criteria used in this paper does not align with that used by the U.S. Centers for Disease Control and Prevention in the United States. Second, this study was conducted in referral centers in Spain and findings may not be generalizable to other countries with different case-mix, severity-

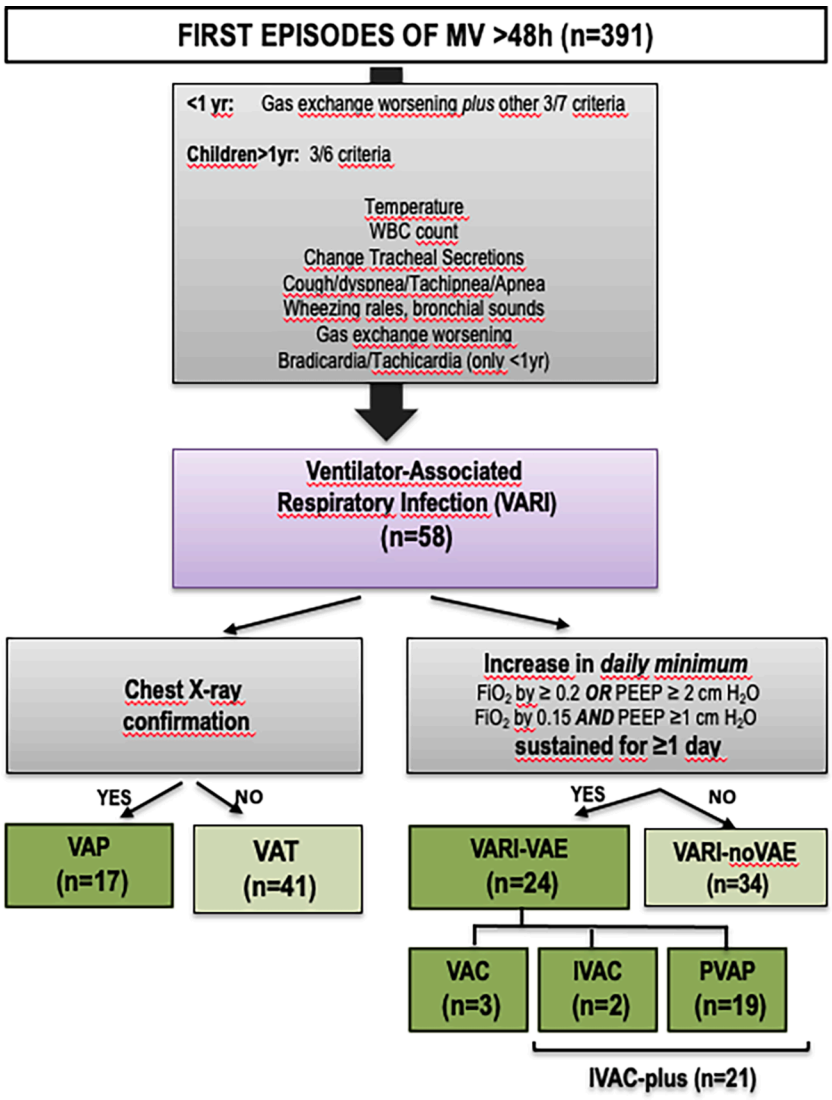

Fig. 3. Ventilator-associated respiratory infections subclassifications.

Table 2
Outcomes of patents developing Ventilator-Associated Respiratory Infections classified according to CDC-2008 (VAP vs VAT) and Ventilator-Associated Event criteria (VARI vs non-VARI).

	VAP (n = 17)[a]	VAT (n = 41)[a]	*p value*	VAE-VARI (n = 24)[a,b]	Non-VAE-VARI (n = 34)[a]	*p value*
Duration of mechanical ventilation (days)	12 [8.7–15]	13 [7–19.5]	0.21	16 [14–26]	9.5 [8–14]	**<0.01**
PICU LOS since onset of MV (days)	18 [13.7–24.5]	20 [13.7–29.2]	0.36	23.5 [18–34.5]	15 [11–21]	**<0.01**
Hospitalization LOS (days)	25.5 [20.7–46.2]	30 [21–52.2]	0.48	39 [26.5–60.2]	24 [18–44.5]	**0.01**
Mortality during episode MV, n (%)	0 (0.0)	2 (4.7)	0.58	2 (10)	0 (0)	**Not Applicable**
PICU mortality, n(%)	0 (0.0)	3 (7.1)	0.54	2 (10)	1 (2.9)	**Not Applicable**

Data are medians [interquartile range] unless otherwise specified. CDC = Center for Disease Control and Prevention; VARI = Ventilator-Associated Respiratory Infection; VAE = Ventilator-Associated Event; PRISM III = Pediatric Risk Mortality Score; PELOD = Pediatric Logistic Organ Dysfunction; PICU = Pediatric Intensive Care Unit; LOS = length of stay; [a]One patient who developed both ventilator-associated respiratory infections, VAT and VAP (meeting one of them VAE criteria) was excluded from all groups' analysis; [b] Three patients who developed VAE classified as non-infectious during the VARI episode were excluded from the VARI-VAE subgroup's analysis.

of-illness, preventive measures, therapeutic approaches or ventilation duration. The mortality rate was relatively low, the ventilatory strategy was not standardized and the number of patients enrolled in each site is small, representing a potential selection bias. Therefore, a multinational study should be recommended to validate our findings. Third, exclusion of previous ventilated patients limits generalization to tracheotomized patients or those who are re-intubated; the same applies for children on right-to-left shunt or pulmonary hypertension, also excluded from the study. Future studies assessing VAE on these specific populations are needed. Fourth, the current definitions of pneumonia and tracheobronchitis are subject to a lack of gold standard. Five, the low incidences of pneumonia and tracheobronchitis limited the cohort size and its subgroups. The absence of statistically significant differences between pneumonia and tracheobronchitis patient's outcomes may be due to a

Table 3
Outcomes of patients developing Ventilator-Associated Respiratory Infections and Ventilator Associated Events vs only Ventilator-Associated Respiratory Infections.

	VAE-VARI (n = 24)*	Non-VAE-VARI (n = 34)*	*p value*
PRISM III	6 [2.5–10.5]	6 [4.2–10]	0.647
PELOD	11 [10–20.5]	11 [2–18.75]	0.233
Duration of mechanical ventilation (days)	16 [14–26.5]	9.5 [8–14]	**<0.001**
PICU LOS from onset of MV (days)	24 [19–33]	15 [11–21]	**0.002**
Hospitalization LOS (days)	35 [28–58.5]	24 [18–44.5]	**0.011**
Mortality during episode MV, n (%)	2 (8.6)	0	0.148
PICU mortality, n(%)	2 (8.6)	1 (2.9)	0.543

Data are medians [interquartile range] unless otherwise specified. CDC = Center for Disease Control and Prevention; VARI = Ventilator-Associated Respiratory Infection; PRISM III = Pediatric Risk Mortality Score; PELOD = Pediatric Logistic Organ Dysfunction; PICU = Pediatric Intensive Care Unit; LOS = length of stay; *One patient who developed both ventilator-associated respiratory infections, VAT and VAP, was excluded from the analysis.

beta statistical error. Nevertheless, the impact on duration of mechanical ventilation and ICU stay between patients developing pneumonia and tracheobronchitis might be less compared to the impact between patients with VAE versus those who do not develop VAE (6.5 and 9 days, respectively). External validation with larger sample sizes is needed.

Our study has several implications for clinical surveillance, clinical practice, and research. First, the least restrictive pediatric VAE definition succeeds in predicting outcomes on respiratory infections, in contrast to the distinction between pneumonia and tracheobronchitis. Second, these VAE criteria also fulfill the requirements to become a new reference standard for a ventilator bundle in children, along with respiratory infections. Third, incorporating the modification of ventilatory settings for further categorization of the respiratory infections in medical practice may facilitate antibiotic management in ventilated patients based on outcomes. The better prognostic prediction, the shorter antimicrobial therapy. Future studies should stratify respiratory infections by different severities (following VAE criteria) and elucidate the effect of an inadequate increase of PEEP on extending the duration of mechanical ventilation. Lastly, further clinical trials on antibiotic therapy might benefit of incorporating modification of ventilatory criteria in the inclusion criteria and should not enroll or exclude patients based on image criteria.

Conclusion

When assessing ventilated children with respiratory infections, VAE apparently is associated with higher ventilator-dependency and lengths of stays compared with pneumonia or tracheobronchitis.

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Notation of prior abstract presentation

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Conflicts of interest statement

JR has served on the speakers' bureau and as a consultant for ROCHE, Pfizer, and MSD. The remaining authors have disclosed no other conflicts of interest.

CRediT authorship contribution statement

Yolanda Peña-López: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **María Slocker-Barrio:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Juan-Carlos de-Carlos-Vicente:** Writing – review & editing, Investigation, Data curation. **Marta Serrano-Megías:** Writing – review & editing, Validation, Software, Methodology, Formal analysis, Data curation. **Iolanda Jordán-García:** Writing – review & editing, Validation, Investigation, Data curation. **Jordi Rello:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Fig. S1. CDC Definitions.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.iccn.2024.103664.

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