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Ventilator-associated Events in Children Controversies and Research Needs

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Healthcare-associated infections (HAIs) constitute a common but highly preventable event during hospitalization. Healthcare-associated pneumonia, including ventilator-associated pneumonia (VAP), together with healthcare-associated primary bloodstream infection, represents the largest proportion of HAIs.¹ The estimated median disability-adjusted life years associated with healthcare-associated pneumonia was estimated to be 170 per 100,000 population by the European Center for Disease Control. VAP constitutes one of the most common HAI experienced by critically ill children and has been related to increased morbidity, length of stay, broad-spectrum antibiotic usage and cost.^{2,3}

Despite the high burden and complications of VAP, currently, a major impediment in VAP prevention is the lack of a precise, reproducible and clinically meaningful definition. This has a significant impact on VAP surveillance, clinical management and prevention.

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To improve the quality of surveillance data, essential to drive local improvement and to a benchmark of quality of care, there has been an effort to improve the definition of VAP. An imaging-based VAP definition was used by US Centers for Disease Control and Prevention (CDC) for many years and widely adopted by most HAI surveillance networks, including the International Nosocomial Infection Control Consortium, as well as national databases supported by other developed and developing countries.³ More recently, however, this imaging-based definition has been abandoned by many HAI surveillance programs due to the subjective nature of key criteria, such as radiologic findings. Radiologic criteria for the original VAP definition included new or worsening infiltrates on a chest radiograph, a nonspecific finding that occurs in other disease processes such as atelectasis, acute respiratory disease syndrome and alveolar hemorrhage. Similarly, clinical signs and symptoms of the original VAP definition, such as fever, purulent bronchial secretions and leukocytosis, are common in critically ill patients who have noninfectious disease processes.³ Although other definitions have been used for VAP surveillance, such as the Clinical Pulmonary Infection Score, these definitions are also flawed because of the inclusion of criteria related to radiographic abnormalities.^{2,3}

Because of shortcomings in the original VAP and other existing definitions, CDC introduced a broader and potentially more objective definition for ventilator-associated events (VAE) in adults.² This algorithm is based on objective criteria, including the

fraction of inspired oxygen (FiO₂), positive end-expiratory pressure (PEEP); no radiographic criteria are included. The VAE algorithm consists of 3 tiers: ventilator-associated complications (VACs), infection-related ventilator-associated complications (IVAC) and possible/probable VAP (Table 1). These categories have been used for surveillance in adult critically ill patients by CDC since 2013.⁴

Simultaneous use of VAE and VAP algorithms in critically ill adult patients has confirmed that there is poor agreement between these definitions.^{2,5} Both the original VAP as well as the ventilator-associated tracheitis have been misdiagnosed by VAE definition and vice versa. However, patients identified with VAE have been demonstrated to have worse outcomes than those who do not develop VAE, suggesting a degree of clinical validity.^{2,5} Currently, the impact of this new

TABLE 1. Adult CDC VAE Algorithm

<p>Tier 1: "Oxygen deterioration" based on changes in FiO₂ and PEEP</p> <ul style="list-style-type: none"> • No → no VAE • Yes → tier 2 <p>Tier 2: Temperature/white blood cells AND initiation of a new antimicrobial agent (within a time window of 5 d)</p> <ul style="list-style-type: none"> • No → VAC • Yes → tier 3 <p>Tier 3: Respiratory microbiologic confirmation</p> <ul style="list-style-type: none"> • No → IVAC • Yes → Possible ventilator-associated pneumonia
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VAE algorithm in critically ill neonates and children is not yet known.

CONTROVERSIAL ISSUES OF VAP AND VAE IN NEONATES AND CHILDREN

Surveillance

Similar to adults, HAI surveillance in children needs to be based on objective measures and prior surveillance definitions for VAP suffered from the inclusion of subjective criteria. The most commonly used definition for surveillance in children is the original VAP definition followed by other imaging-based definitions such as CPIS score. The incidence of VAP using imaging-based definitions ranged between 1 and 63 per 1000 ventilator days in studies conducted in neonatal and pediatric intensive care units globally.²

The new CDC VAE definition developed for adults may provide a useful framework for surveillance for lower respiratory tract infection among ventilated pediatric patients. Several studies have been conducted in neonatal and pediatric critically ill children using the new CDC VAE definition, although initially without appropriate adaptation. Most of these studies confirmed the poor agreement between the original VAP definition used for surveillance in children as compared with this new VAE algorithm with adult criteria.² The majority of these studies were single-center, retrospective and conducted in the United States and Europe. Applying this VAE algorithm with adult criteria to pediatric patients, the estimated incidence of VAC ranged between 4 and 21/1000 ventilator days.⁴

Intrinsic differences in the respiratory physiology and current ventilator management strategies between adults and children raise concerns about simply applying the adult VAE algorithm to children. Current evidence supports that different cut-off values of FiO_2 and PEEP in children result in major differences in the detection of VAE in the pediatric population. For this reason, alternate criteria have been proposed to define the term “pediatric worsening oxygenation” based on modifications of the threshold for PEEP, minimum duration for worsening oxygenation and/or use of mean airway pressure instead of PEEP (Table 2). The rationale for this final criterion is that mean airway pressure may better represent changes in lung compliance in children and neonates.⁶

Despite these persistent controversies about the performance of the pediatric VAE definition, the CDC adopted the above criteria proposed by Cocoros et al⁶ for use in neonatal and pediatric intensive care units in 2019.⁶ Preliminary data demonstrate that the

TABLE 2. Proposed Criteria for Tier 1 “Oxygen Deterioration” for Pediatric Patients

Changes in FiO_2 and PEEP (7) (2)
• Increase in daily minimum FiO_2 of ≥ 0.2 sustained for ≥ 1 calendar day, or
• Increase in daily minimum PEEP ≥ 2 cm H_2O , sustained for ≥ 1 calendar day
Changes in FiO_2 and PEEP (7)
• Increase in daily minimum $\text{FiO}_2 \geq 0.2$ sustained for ≥ 1 calendar day, or
• Increase in daily minimum PEEP by ≥ 2 cm H_2O , sustained for ≥ 1 calendar day, or
• Increase in daily minimum $\text{FiO}_2 \geq 0.15$ and PEEP by ≥ 2 cm H_2O , sustained for ≥ 1 calendar day
Changes in FiO_2 and MAP (6)
• Increase in daily minimum FiO_2 of ≥ 0.25 , sustained for > 2 calendar days, or
• Increase in daily minimum MAP values of ≥ 4 cm H_2O , sustained for > 2 calendar days

MAP indicates mean airway pressure.

incidence rate of this newly adopted pediatric VAE ranged between 1 and 4/1000 ventilator days in the United States. It is unclear whether European and other surveillance networks will convert to this surveillance definition.

Clinical Diagnosis and Clinical Correlation

In daily practice, suspicion of VAP is based on clinical criteria such as progressive hypoxemia, in addition to signs and symptoms indicative of lung and systemic inflammation (ie, appearance and volume of respiratory secretions, fever, leukocytosis). Imaging and microbiologic criteria are often used to support a clinical diagnosis of VAP. The surveillance definitions for “IVAC” and “possible VAP” have failed to address clinicians’ need for a bedside, real-time diagnostic tool to trigger initiation of antimicrobial treatment for either adults or children. The modified VAE definitions have low sensitivity for detection of pediatric patients with clinically defined “ventilator-associated respiratory infections,” which also includes the term of ventilator-associated tracheobronchitis.⁵

Using different thresholds for and duration of changes of FiO_2 and PEEP, such as those included in the modified criteria proposed by Peña-López et al,⁷ there is an increased sensitivity and better correlation of VAE definition with clinical outcomes in ventilated critically ill children.⁷

Attempts to use these different pediatric definitions to guide appropriate initiation of antimicrobial therapy have yielded inconsistent results. Future studies are needed to assess whether this revised pediatric VAE

definition may be useful in determining which patients require antimicrobial therapy.⁸

Preventive Strategies

To date, most of the evidence supporting strategies to prevent ventilator-associated infections in children has been based on the original CDC VAP definitions. These ventilator bundles have included practices such as hand hygiene, oral care, position of the head of bed, and have been associated with reduced rates of VAP rates in critically ill children,² although mortality rates have not changed.

The impact of currently used ventilator bundles in the prevention of VAC and IVAC has not been studied in children. Adult studies of the impact of ventilator bundles on VAE rates have yielded surprising findings. While some studies have demonstrated that ventilator prevention bundles had no effect on VAE, others have shown that the use of chlorhexidine for the oral care was associated with an increased risk of VAE.⁹ Reduction in the length of mechanical ventilation using protocols such as early weaning practices may have an effect on VAE incidence.⁹

Despite the absence of studies exploring the effect of ventilator bundles on rates of pediatric VAE, preliminary results from case-control studies assessing possible risk factors for VAE in children may provide useful guidance about prevention practices for pediatric VAE. Several risk factors for VAE have been identified in single-centered studies in pediatric patients: acute kidney injury (risk factor for VAE and IVAC), mean peak inspiratory pressure (for VAE), exposure to neuromuscular blockade infusion (for IVAC)¹⁰ and immunosuppression, tracheostomy dependence and chronic respiratory (for VAE).¹¹ However, all these studies have used the initial VAE algorithm proposed for adults and without adaptation to pediatric patients.

Applying the new pediatric VAE algorithm proposed by Cocoros et al⁶ in a multicenter US study, risk factors for VAC were related to management of sedation (weaning from sedation or interruption of sedation was correlated with prevention, whereas exposure to neuromuscular blockade infusion was a risk factor), transfusion thresholds (blood product use was a risk factor) and fluid management (positive fluid balance was a risk factor).⁶ Similar modifiable risk factors for VAC development have been reported in a pediatric intensive care unit including acute kidney injury and fluid overload.¹¹

RESEARCH NEEDED

For surveillance research, a definition is needed that has objective measures not

sensitive to changes in ventilator management that are not triggered by clinical deterioration. A uniform pediatric definition of ventilator-associated infections and/or events which is globally accepted is needed and could be used to drive quality improvement efforts.

There is a need for a definition that aligns with patient's morbidity and mortality. A better approach could be to merge currently available concepts for VAP and VAE and research should focus on best available indicators for ventilator-associated infections targeting quality improvement.⁵

Research is needed to identify optimal strategies to prevent VAEs and/or infections. Intensivists should improve the management of sedation, fluid and transfusion and when a VAC is found, prevention should be focused on appropriate antimicrobial use discussed with infectious disease specialists.

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