Ascension

Guideline for Evaluation and Treatment of Ventilator-Associated Tracheitis (VAT)

For use in pediatric patients with tracheostomy or ETT

Situation

Increasing survival rates in the intensive care unit (ICU) have led to a rise in utilization of invasive devices as well as incidence of nosocomial infections.[1] While it is common to have bacterial growth present when one of the most commonly used devices, the endotracheal tube (ETT), is cultured, it is often difficult to differentiate between colonization and true infection. Ventilator-associated tracheitis (VAT) is generally characterized by clinical signs and symptoms of respiratory tract infection without radiological evidence of pneumonia. Ventilator-associated tracheitis is a common occurrence among mechanically ventilated patients and it is important to diagnose and treat VAT appropriately to avoid associated morbidity. However, disadvantages of overtreating VAT should not be overlooked. These include increased rates of antimicrobial resistance, toxicities, and costs. Diagnosis and treatment of VAT often varies across Ascension Health facilities. There is an opportunity to standardize management by providing recommendations for when to obtain tracheal aspirates, antimicrobial selection, as well as duration of therapy for pediatric VAT.

Background

Ventilator-associated tracheitis (VAT) is likely in the middle of the spectrum between lower respiratory tract colonization and ventilator-associated pneumonia (VAP).[1-2] Nosocomial lower respiratory tract infections (LRTIs) are an important cause of morbidity and mortality in ICU patients. While most studies have not found that VAT is associated with an increase in mortality, increased length of ICU stay, increased duration of mechanical ventilation, and reduced progression to VAP have been observed.[3-7]

The etiology of airway colonization varies by age and involves multiple infectious agents such as viruses, bacteria, and fungi. The oropharyngeal cavity becomes colonized by both endogenous flora and exogenous bacteria acquired in the ICU environment.[3] Common bacteria associated with colonization of artificial airways include *Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Serratia marcescens, Klebsiella* species, *Acinetobacter* species, *Escherichia coli, Enterobacter* species, *Stenotrophomonas maltophilia,* and *Pseudomonas aeruginosa*.[1,8,9] Disabled airway reflexes, constant secretion accumulation, subsequent microaspiration, and potential biofilm formation within the ETT can all contribute to VAT or VAP.[3]

An infant or child with VAT often presents with symptoms including tachypnea, fever, cough, increased secretions, stridor, and/or somnolesce.[8] Findings on the physical examination that may suggest potential tracheal infection include change in the color, viscosity, and/or odor of tracheal secretions, increased work of breathing, new crackles, rhonchi, and/or wheezing, new fever or elevation fever from baseline, increased requirement for suctioning of airway, increased in baseline ventilatory support settings or oxygen supplementation.[9]

It may be difficult to differentiate the diagnosis of VAT in children with artificial airways from LRTIs. The most commonly used diagnostic criteria for VAT stem from the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) surveillance definition.[10] This definition includes "the absence of clinical or radiographic evidence of pneumonia and positive culture obtained by deep tracheal aspirate or bronchoscopy, AND ≥2 of the following signs or symptoms with no other recognized cause: fever >38°C…, cough, new or increased sputum production, rhonchi and/or wheezing, in infants ≤1 year of age: respiratory distress, apnea, and/or bradycardia". This definition was created for surveillance purposes and diagnosis of VAT remains a challenge due in part to the lack of a clear and widely accepted definition for clinical diagnosis.[3]

While chest radiographs have limitations in regard to sensitivity and specificity in ICU patients, chest imaging should be obtained to distinguish VAT from VAP.[3] Elevated white blood cell count is often used as an indicator of infection but lacks sensitivity and specificity, Inflammatory biomarkers such as C-reactive protein and procalcitonin have not been validated for utilization in the diagnosis of VAT in the pediatric population.[9]

Microbiological results (gram stain and culture of tracheal aspirates) can be helpful in the diagnosis of VAT. Gram stain should be compared with previous cultures, if available. Gram stains should be assessed for presence of microorganisms and polymorphonuclear neutrophils (PMNs). Neither one of these alone are sensitive or specific in the diagnosis of VAT. Growth of likely pathogen on tracheal aspirate culture does support the diagnosis of bacterial VAT. However, microorganisms yielded may often be indicative of colonization, rather than infection. Polymicrobial growth, low levels of growth, and growth of nonpathogenic bacteria are often more suggestive of contamination.[9]

Studies have reported that appropriate antibiotic treatment of VAT is associated with reduced progression to VAP.[3,6] However, treatment decisions still remain challenging in clinical practice. Choice of empiric therapy aims at covering most likely pathogens; therefore, initial broad-spectrum antimicrobial therapy remains the hallmark of therapy.[8,9] Empiric antibiotic selection may vary depending on recent microbiological culture data, severity of illness, results of the Gram stain, allergies, drug interactions, or other factors. Due to increasing rates of resistance of both gram-negative and gram-positive microorganisms, it is important to practice

antimicrobial stewardship principles by appropriate empiric antimicrobial selection and deescalating antimicrobial therapy according to respiratory cultures as soon as possible. Overtreatment of VAT may lead to increased adverse effects and selective pressure for the development of microbiologic resistance.[3]

Empiric coverage for MRSA is warranted if patient has history of colonization or infection with methicillin-resistant S. aureus (MRSA), has a Gram stain with gram-positive cocci in clusters identified, has high severity of infection, or likelihood of MSA due to local susceptibility patterns.[9] Similarly, risk factors for extended spectrum beta-lactamase (ESBL) or carbapenemase-producing organisms such as history of confirmed infection or colonization with these organisms and extensive broad-spectrum antimicrobial use, should be evaluated. Intravenous antibiotic therapy is indicated for patients who are systemically or critically ill. There is little data surrounding the utilization of enteral antibiotics for the treatment of VAT in the pediatric population. However, it is reasonable to consider the transition from parenteral to oral antibiotics in patients who have clinically improved and have documented susceptibility to an oral option.

The use of aerosolized antibiotics remains controversial for the adjuvant treatment of VAT due to conflicting evidence. Nebulized antibiotics have been used in for the treatment of RTIs in patients with cystic fibrosis (CF) with variable clinical efficacy.[11] The safety profiles of nebulized antibiotics in the treatment of tracheitis have not been thoroughly reported.[12] Risks of the utilization of IV formulations via nebulizer include exposure to potentially irritants or toxic additives with inappropriate pH or osmolality ranges.[12] Pediatric data on this subject is even more limited. One case series describes the use of inhaled colistin in three critically ill pediatric patients without CF (one with pneumonia and two with tracheobronchitis).[13] These three cases were discharged from the ICU and no bronchoconstriction or colistin-related toxicity was observed. However, due to the extremely small sample size, the authors concluded that more studies are needed to elucidate the role of inhaled colistin in critically ill patients without CF. A recent study compared nebulized gentamicin to nebulized tobramycin for tracheitis in 19 pediatric patients.[12] While there were no differences in safety or efficacy detected between the inhaled tobramycin or gentamicin groups, a comparator group with no adjuvant inhaled antibiotics was not studied. Additionally, patients in the study resolved the CDC definition of tracheitis after approximately 3 days of nebulized therapy, despite the patients receiving treatment for an average of 10-13 days, potentially increasing risk of acquiring resistance (degree of resistance was not analyzed in this study).[12] Further, a systematic review of six randomized controlled-trials in adult patients describing the efficacy of inhaled antibiotics in the treatment of VAP and VAT concluded that the use of inhaled antibiotics are not sufficiently supported by available evidence for these disease states.[14] In agreement with this, a position paper from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

recommended against the use of nebulized antibiotic adjuvants for the treatment of VAT due to low quality of evidence.[15]

Although multiple studies and clinical guidelines address optimal duration of therapy in VAP, the optimal duration of therapy of VAT in children is still debated.[16] Because VAT is more localized of an infection as compared to VAP, it is possible that VAT can be treated with shorter courses of antibiotics.[1] To our knowledge, there is one published study addressing this question in the pediatric population that found similar clinical outcomes in short- versus prolonged- courses of antibiotic therapy for VAT, showing clinical success with an average duration of therapy of 5 days. This study defined VAT using the presence of clinical, microbiological, and radiographic criteria found in **Appendix B**.[1] Several studies from the Pediatric Acute Lung Injury and Sepsis Investigator (PALISI) Network attempt to develop a guideline for the decision to continue or stop antibiotics at 48-72 hours.[17,18] Multiple posters from academic conferences have found similar results to Tamma, et al.[19-21] Therefore durations of therapy of tracheitis of 5 days are no worse than longer durations and are preferred due to the cost, drug-related toxicities, and development of resistance associated with longer durations of antimicrobial therapy.

Assessment

Pediatric literature on the diagnosis and management of VAT is summarized in table form in **Appendix B**. Limiting broader than necessary antibiotic choice and excess durations of therapy for VAT could limit the number of multidrug resistant strains in the ICU as well as the costs and toxicities associated with antibiotic use.

Several studies have attempted to standardize diagnosis and management of VAT with the creation of treatment guidelines. A chest X-ray should be obtained to assist in distinguishing VAT from VAP. In addition to the the absence of clinical or radiographic evidence of pneumonia, criteria for the diagnosis of VAT is met if the patient must have an increase in quantity of secretions AND any ONE of the following:

- Increased vent settings (PIP or PEEP >2, FiO2>20% for ≥4 hours)
- New onset of fever (>38 °C) or hypothermia (<36 °C)
- Leukocytosis (>12K) or leukopenia

Tracheal aspirates should be collected appropriately (see collection procedure in **Appendix A**) and sent for Gram stain and culture. Without the presence of microbiological results (at least moderate amounts of PMNs and bacteria present on Gram stain and/or growth of potential pathogen on culture), the treatment of tracheitis is not recommended and the patient should be evaluated for an alternate source of infection. Tracheal aspirate cultures should not be repeated any sooner than 72 hours.

Recent tracheal culture and susceptibility results should be reviewed and targeted with the choice of an empiric antibiotic for VAT, if possible. If there is no history of recent positive respiratory cultures, then cefepime 50 mg/kg intravenous every 8 hours (renally adjusted if appropriate) is a reasonable empiric antimicrobial choice to cover common endogenous and exogenous bacteria that colonize artificial airways. The addition of vancomycin should be guided by local susceptibility rates and patterns. Due to increasing rates of resistance of both gram-negative and gram-positive microorganisms, it is important to optimize antimicrobial therapy according to respiratory cultures as soon as possible. If started empirically, vancomycin should be discontinued in the absence of resistant gram-positive organisms growth on culture.

There is insufficient evidence to recommend the use of aerosolized antibiotics for the adjuvant treatment of VAT due to conflicting evidence regarding clinical outcomes. There is little data surrounding the utilization of enteral antibiotics for the treatment of VAT.

A duration of therapy of 5 days is recommended based on studies demonstrating both short and longer courses of therapy are similar in efficacy. The shortest effective duration of therapy should be selected to minimize exposure of both pathogens and normal flora to antibiotics limiting the selection of antibiotic resistance. Transition from intravenous to oral antibiotic therapy can be considered for those showing clinical improvement and if microorganism is susceptible to oral antibiotic option.

Recommendations

Adopt the recommended evaluation and treatment for pediatric patients with VAT as detailed in **Appendix A** across Ascension. Adoption can be achieved via:

- Educating providers who order tracheal aspirates and prescribe antibiotics for VAT
- Monitoring of quantity and appropriateness of tracheal aspirates obtained
- Adoption of cefepime as first line antimicrobial agent for the management of pediatric VAT, unless empiric selection driven by previous culture results
- Monitoring for appropriate total antibiotic duration

Metric of Success

Adherence to these recommendations will be measured by daily defined doses (DDD) or days of therapy (DOT) of broad spectrum beta-lactams and vancomycin in pediatric patients as available.

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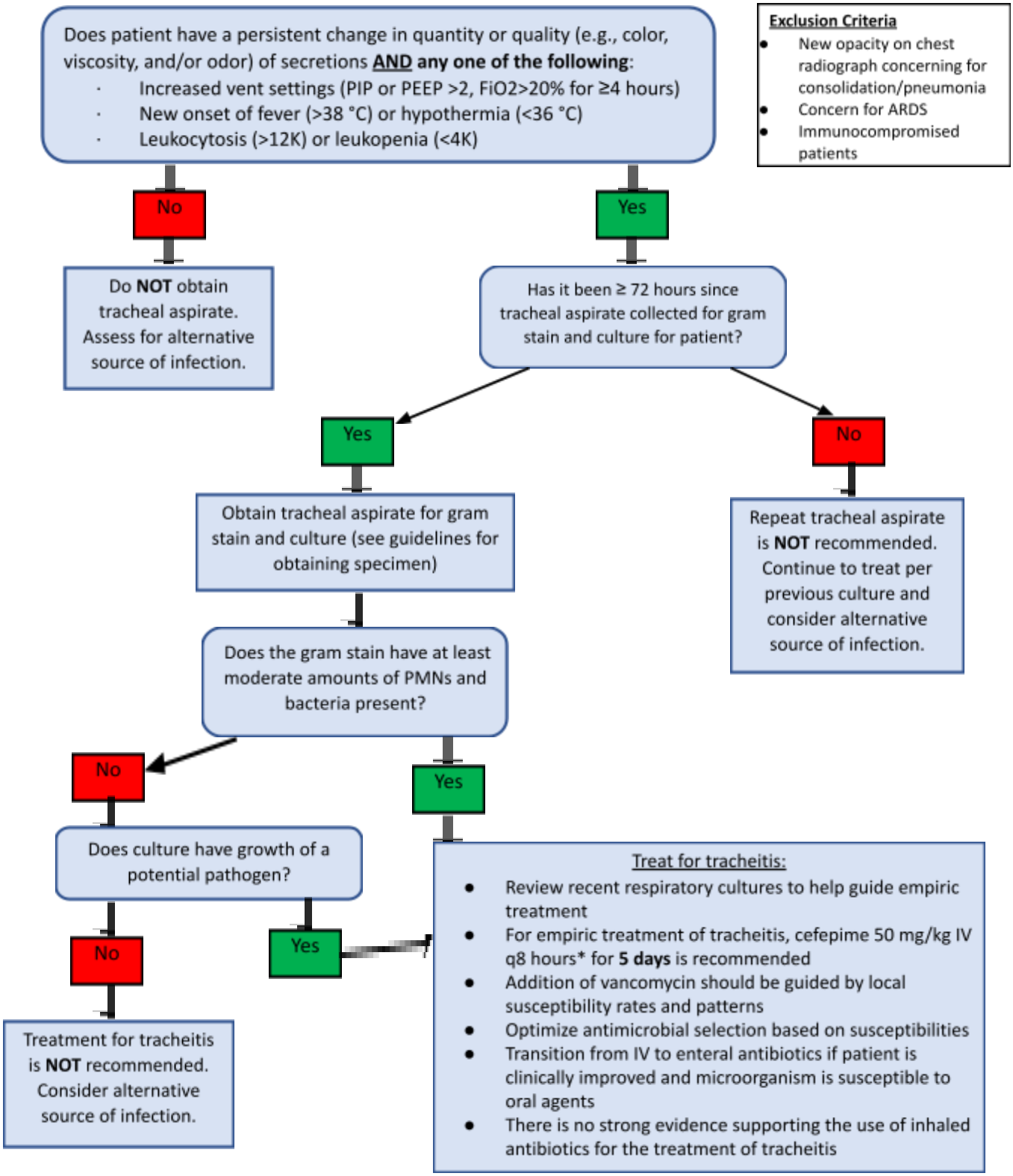
Appendix A: Algorithm for the Evaluation and Treatment of Ventilator-Associated Tracheitis (VAT) in Pediatrics

For use in pediatric patients with tracheostomy or ETT



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For use in pediatric patients with tracheostomy or ETT

Table 1. Tracheal Aspirate Collection Guidelines

1.	Utilize new, sterile suction catheter (open or closed system)
2.	It is strongly recommended that specimen be obtained on first pass of catheter (if unable to obtain an adequate specimen on first pass, consider collection with next suction)
3.	Suction catheter should pass the end of the artificial airway (NO more than 1 cm beyond)
4.	Recommended minimum volume for specimen is 1 mL
5.	Minimize use of sterile normal saline (goal maximum of ≤0.5 mL) to clear specimen from catheter into collection container
6.	Instillation of normal saline into artificial airway is not recommended during specimen collection as this will dilute the sample
7.	Specimen type on label should say tracheal aspirate or ETT aspirate, not sputum

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Appendix B: Summary of Pediatric Literature Surrounding Diagnosis and Management of Tracheitis

Study & Design, n	Population	Diagnostic Requirements	Results	Conclusions/ Limitations
Tamma CID 2011; Retrospective cohort review at 175 bed tertiary care pediatric hospital with 26 bed PICU and 45 bed NICU, 118 patients	Children ≤18 years, hospitalized in ICU and intubated for ≥48 h from 01/2007 – 12/2009 & received antibiotic for VAT	· Presence of clinical criteria (Fever (temperature >38 C) or hypothermia (temperature <36C), leukocytosis >12,000 leukocytes/mm3 or leukopenia <4000 leukocytes/mm3, plus new onset of purulent endotracheal secretions), · Microbiological criteria (Gram stain with moderate-heavy PMNs with moderate-heavy bacterial growth) · No radiographic evidence of a new lung infiltrate	· Prolonged courses of abx (≥7d) not protective against development of HAP or VAP (23% vs 20% in prolonged- and short-course groups, respectively). · MDRO colonization or infection associated with prolonged course, combination abx, and days of hospital exposure prior to completing abx · The median time to develop VAP from discontinuation of antibiotics for VAT was 4.5 days	Short-course= prolonged course efficacy for protection against VAT->VAP Excluded children with tracheostomies, almost no immunocompromised patients included.

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Wilson et al Prospective, observational cohort study, 229 patients	Pediatric patients ventilated for more than 48 hours undergoing respiratory secretion cultures in 47 PICUs	All patients with resp secretion cultures included in study; Modified clinical pulmonary infection score (CPIS) using fever, WBC, secretions, oxygenations, microbiology;	· Those with positive cultures are more likely to have chronic lung disease, tracheostomy, and shorter PICU stay, but no differences in ventilator days or mortality. Data demonstrate that the decision to continue antibiotics > 48–72 hours is often made based on a positive respiratory secretion culture. · The CPIS correlated with abx continuation but not with outcomes	Positive respiratory cultures were the primary determinant of continued antibiotic treatment in children with suspected VAT. Positive cultures were not associated with worse outcomes irrespective of antibiotic treatment although the lower mortality in treated subjects with endotracheal tubes is notable.
Shein et al Prospective, multicenter observational data collection and subsequent development of antibiotic guide *	Mechanically ventilated children less than 3 years old on abx for VAT in 22 PICUs	Internal scoring system using clinical findings (clinical signs, temperature, secretions), respiratory secretion analysis, chest x-ray results (infiltrates), laboratory findings (WBC, CRP, Procalcitonin, % Bands), and Ventilator changes (OSI, FiO2, Paw, Ventilator)	Phase 1 had 281 patients with suspected VAT. Higher scores correlated with duration of abx and PELOD function score but not mortality, PICU free days, or ventilator free days. Aiming for 25% reduction in antibiotic use, panel recommended stopping antibiotics at 48-72 hours for guideline scores less than or equal to 2 and continuing abx for scores≥6. Perceived sensitivity/specificity for VA-infection highest for new purulent or changed secretions, temp high/low, positive ETT, many WBC on ETT, >10^3 bacteria on BAL cx	Scoring system and recommendation to guide the decision to stop or continue antibiotics at 48–72 hours in children with VAT developed. (Will be tested in planned phase 3 of study)

Goldman JL et al (Poster) Retrospective cohort study, 220 VAT cases	All children who were hospitalized from 1/1/2009-2/28/2017 and reviewed by ASP for receiving a monitored drug with an indication for VAT	No diagnosis info	Overall mean duration of treatment was 5.47 days. Duration of treatment was shorter for VAT patients who agreed to stop (AMS recommendation) than VAT with no recommendations (4.60 vs 5.76 days, p=0.007)	ASP recommendations for the treatment of pediatric VAT were not associated with an increased likelihood of treatment failure. Further work is needed to standardize the diagnosis and treatment of VAT to avoid unnecessary antibiotic use in these children
Grabic M et al (Poster) Retrospective cohort study; 105 patients	PICU patients with VAT from 10/2016-6/2018; patients identified via ASP chart review	No diagnosis info	Mean antibiotic duration was 13day; however, 52% received >5 days and 44% received 5 days. Only 6% of patients who received 5 days of antibiotics required retreatment within 10 days versus 19% of those who received >5 days (p=0.09). Adherence to guidelines was approximately 50%; Development of C diff was low in both groups	Short-course antibiotic therapy for VAT was not associated with retreatment for VAT or subsequent diagnosis of VAP.

Iacono D et al (Poster) Retrospective review from 1/2017-12/2018;	PICU patients with VAT diagnosed by respiratory fluid with gram stain positive for ≥ +3 WBC AND ≥ +3 bacteria	· To obtain a RFCx: abnormal WBC (< 5 K/uL or > 14.5 K/uL) AND purulent or increased amount of ET secretions PLUS either (Temp < 36° C or ≥ 38.3° C) or change in baseline respiratory support · A diagnosis of VAT if RFCx shows Gram stain with ≥ +3 WBC AND ≥ +3 bacteria	Multidisciplinary team developed guidelines for VAT. Guideline limited duration of antibiotic use to 5 days. After guideline implemented, downward trend of respiratory fluid cultures (19%) and antibiotic use (24%) was observed in the PICU.	Efforts to standardize diagnosis and treatment of VAT in patients with endotracheal intubation or tracheostomy resulted in a decreased number of respiratory fluid cultures and reduced overall antibiotic use without increasing the risk of VAE.

VAT: ventilator-associated tracheitis; VAP: ventilator-associated pneumonia; HAP: hospital acquired pneumonia; abx: antibiotics; ICU: intensive care unit; ASP: antimicrobial stewardship program; VAE: ventilator- associated events; PICU: pediatric intensive care unit