Novel Insights from Clinical Practice

Respiration

Tracheobronchitis Caused by Methicillin-Resistant *Staphylococcus aureus* as a Cause of Chronic Wheezing in a Non-Ventilated Adult Patient with Tracheobronchomalacia

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Established Facts

- Although bacterial tracheobronchitis is a rare entity (long considered to be a pediatric disease), a different form of tracheobronchitis, called exudative tracheitis (ET), has recently been described in patients without any signs of systemic infection.
- The diagnosis of tracheomalacia in adults can masquerade as persistent asthma.

Novel Insights

- The first case of methicillin-resistant *Staphylococcus aureus* (MRSA) exudative tracheobronchitis and tracheomalacia in a non-ventilated adult.
- We also suggest, based on published scientific evidence, that colonization of sputum with MRSA and development of tracheobronchitis can potentially contribute to the development of tracheobronchomalacia and lead to multiple exacerbations of COPD, as was noticed in our patient.

Abstract

Bacterial tracheobronchitis is an extremely rare entity, which was long considered to be a pediatric disease. We report the case of a 65-year-old woman who presented with persistent wheezing, worsening productive cough and sore throat. Computed tomography of the chest revealed the presence of tracheomalacia, confirmed at bronchoscopy. The presence of purulent exudate, coating the trachea and main bronchi, was consistent with bacterial tracheobronchitis. Culture of the tracheal aspirates grew methicillin-resistant *Staphylococcus aureus* (MRSA). As the patient was afebrile

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and not systemically ill, the clinical picture was consistent with exudative tracheobronchitis. To our knowledge, this is the first case of MRSA exudative tracheobronchitis and tracheomalacia in a non-ventilated adult. Other adult cases of bacterial tracheobronchitis and MRSA tracheobronchitis in mechanically ventilated patients reported in the literature are also reviewed. Physicians should be aware of the diagnosis of tracheomalacia in adults, which can masquerade as persistent asthma and may be associated with the development of serious infections including MRSA tracheobronchitis.

Introduction

Bacterial tracheobronchitis is a clinical entity that has mainly been described in the pediatric population. It rarely occurs in adults, except in patients who are intubated and mechanically ventilated [1, 2]. A different form of tracheobronchitis called exudative tracheitis (ET) has recently been described [3] in patients without any signs of systemic infection.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major nosocomial pathogen and its incidence has been increasing during the last decades in the community, in hospitals and in long-term care facilities. MRSA tracheitis is very rare in the adult population, with only 2 cases being described in non-ventilated patients [4, 5].

Tracheobronchomalacia in adults is an underdiagnosed clinical entity characterized by excessive collapsibility of trachea or bronchi. Its acquired form is associated with many clinical conditions, including chronic obstructive pulmonary disease (COPD), chronic infection and chronic use of corticosteroids.

We describe a case of tracheomalacia in a woman who presented with chronic refractory COPD, characterized by 17 admissions for recurrent wheezing and shortness of breath during the last 2 years. Once tracheomalacia was identified on CT scan of the chest, bronchoscopy confirmed tracheomalacia and ET caused by MRSA. In this report, we summarize the available literature regarding cases of tracheobronchitis in adults caused by MRSA.

Case Report

A 65-year-old Hispanic female with a history of tobacco use (25 pack years) and a diagnosis of COPD presented with worsening productive cough and dyspnea. In the last 2 years, she had multiple admissions to the hospital for persistent wheezing and
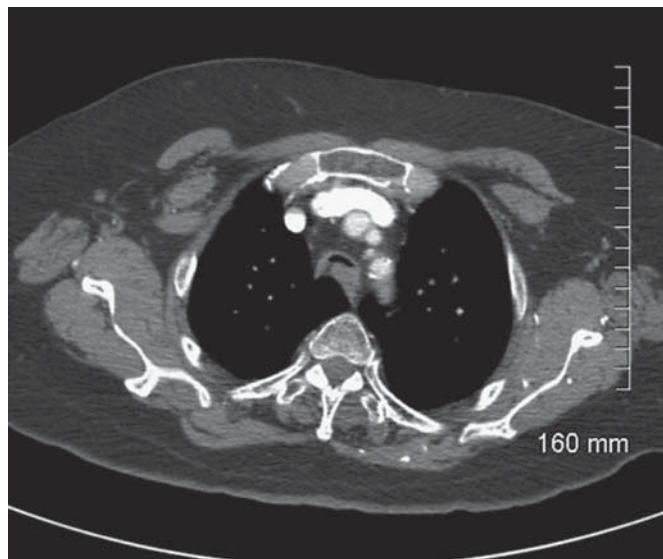

Fig. 1. Axial CT scan shows excessive reduction in tracheal lumen, consistent with tracheomalacia.

COPD exacerbations. Her last pulmonary function tests 2 years prior to this admission had revealed a mild-moderate obstructive pattern which was minimally reversible. Due to her persistent wheezing, the patient had also been diagnosed as asthmatic in the past. Her most recent hospitalization occurred 1 week prior to this admission and for that she was being treated with corticosteroids. She also complained of chronic hoarseness which was attributed to a previous stroke. On physical examination, she was afebrile, hemodynamically stable and her oxygen saturation was 97% on room air. She had diffuse expiratory wheezing but no stridor. Her white blood cell count at the time of admission was 8,100/ml with 79% polymorphonuclear cells. A Gram stain from the sputum and tracheal aspirate revealed Gram-positive cocci in clusters, 25 polymorphonuclear cells per low power field, and 0–5 squamous epithelial cells, whereas the culture showed moderate growth of MRSA, which was sensitive to vancomycin, trimethoprim-sulfamethoxazole, tetracycline and rifampin. A chest roentgenogram revealed cardiomegaly but no infiltrate. A computed tomography scan of the chest revealed marked narrowing of the trachea consistent with tracheomalacia and absence of lung infiltrates (fig. 1). Spirometry showed FEV_1 of 2.34 liters (86%) and FVC of 3.48 liters (107% of reference value). Although the volume-time curve did not have morphologic alterations, visual inspection of the flow-volume loop revealed reproducible flow oscillations on the expiratory curve consistent with tracheobronchomalacia. A bronchoscopy confirmed the diagnosis of tracheobronchomalacia (fig. 2) and revealed the presence of purulent thick secretions coating the trachea. The patient was treated with nebulizers (ipratropium bromide and albuterol sulfate), corticosteroids, vancomycin and levofloxacin for a total of 8 days and was referred for placement of an endotracheal stent as treatment of her tracheomalacia.

Discussion

Bacterial tracheitis has been described almost exclusively in the pediatric population, and its clinical manifestations, microbiology, radiographic findings and treatment in that population have been reviewed elsewhere [6–8]. In adults, bacterial tracheobronchitis is occasionally seen in patients who are intubated and mechanically ventilated [1, 2]. Ventilation-associated tracheobronchitis (VAT) is probably an intermediate process between lower respiratory tract colonization and ventilation-associated pneumonia [9, 10]. VAT should be suspected in intubated patients with clinical signs of lower respiratory tract infection (such as fever, leukocytosis and purulent sputum) with a Gram stain demonstrating microorganisms and polymorphonuclear leukocytes, with either semi-quantitative or quantitative cultures in the absence of new or progressive infiltrates on chest roentgenograms [10, 11]. VAT is difficult to differentiate from colonization. Quantitative criteria may help discriminate between lower airway colonization and infection [12]. Moderate-heavy growth of a pathogen(s) is usually considered significant in semi-quantitative cultures of the endotracheal aspirate. The complex interactions between the quantity and virulence of the bacterial pathogen(s) entering the lower respiratory tract and the patient's host defenses determine if colonization will progress to VAT, and in some cases to ventilation-associated pneumonia [13, 14]. Bacterial virulence is also very important and clearly varies between and within species including Gram-positive species of MRSA [15].

The crude incidence of VAT varies from 2.7 to 10% [11, 16, 17]. Common pathogens for VAT include *Pseudomonas aeruginosa*, *Acinetobacter* spp. and MRSA [11, 17]. Nosocomial tracheobronchitis is associated with an increased length of stay and duration of mechanical ventilation in both surgical and medical patients [11] and in patients without chronic respiratory failure [18].

Some physicians consider VAT to be simple colonization whereas others routinely treat patients with VAT [19, 20]. Data from two recent randomized clinical trials [9] support the latter approach with targeted antibiotic therapy resulting in shorter duration of mechanical ventilation and intensive care unit stay [21]. However, since extensive use of antimicrobial agents is associated with selection of multidrug-resistant pathogens and complications such as *Clostridium difficile* colitis [10], the risk-benefit ratio for using antibiotic therapy for VAT needs further evaluation in clinical trials.

Fig. 2. Bronchoscopy revealed bowing of the posterior wall and excessive reduction in the tracheal lumen during expiration consistent with tracheomalacia.

Risk factors that are associated with the development of tracheobronchitis include virus-induced impairment in mucocilliary clearance of organisms [6, 22], immune deficiency [23] and mechanical ventilation [24]. In one study of patients >60 years, COPD and antimicrobial therapy during the 2 weeks preceding intensive care unit admission was significantly associated with nosocomial tracheobronchitis [11]. COPD is associated with impaired mucosal clearance which predisposes to colonization by bacteria [25, 26] and can cause further bacterial adherence, growth and dysfunction of host defenses [27]. Presence of preexisting anatomic pathology in the airways such as repaired tracheoesophageal fistula [28] or following tracheal mucosal injury [29] may facilitate the development of bacterial tracheitis in children. In only 1 case in the literature has tracheobronchomalacia been described as a probable risk factor for the development of bacterial tracheitis in a 3-year-old male [30]. However, to our knowledge, tracheobronchitis in adults has not been associated with tracheomalacia previously, and this clinical entity in non-ventilated adults has not been reviewed in the literature to date.

According to the Centers for Disease Control (CDC) criteria [31], tracheobronchial infections were defined as follows: fever (>38°C) with no other recognizable cause, new or increased sputum production and a positive tracheal aspirate culture without radiographic evidence of pneumonia. We completed our PubMed search (from 1980 to November 2008) of the English literature applying the term 'tracheobronchitis, tracheitis.' Using the CDC definition, and to avoid potential ambiguity of the clinical diagnosis of bacterial tracheitis, only patients with endoscopic confirmation were included. The references cited in these articles were examined to identify

additional reports. We found 35 cases of tracheobronchitis in non-ventilated adults [4, 5, 32–45]. We excluded 19 of them since the diagnosis was not based on endoscopic findings [34, 35, 43–45]. Five cases were not from the English literature and were also excluded [5, 39]. Thus 11 cases were included in our analysis (table 1) [4, 32, 33, 36–38, 40–42]. Females seem to have a higher incidence of tracheobronchitis than males (8/11, 72.7%). Some authors postulate that the smaller size of the trachea in females renders them more susceptible to tracheitis [42]. All 3 males were immunocompromised either from HIV infection [37], from chronic steroid use [38] or from recent systemic viral illness [4]. On the other hand, only 25% (2/8) of female patients were immunocompromised (underlying malignancy) [36, 42]. However, the rarity of the condition prohibits definite characterization of its epidemiology. Bronchoscopy was used for diagnosis of tracheobronchitis in 5/10 (50%) cases [4, 36–38, 42], laryngoscopy in 6/10 (60%) cases [33, 37, 40–42] and both methods were used in 1 case [37]. The diagnosis was based on autopsy in 1 case [32]. *S. aureus* was isolated in 7/9 (77.8%) cases, and only in 1 case was the agent identified as MRSA [4]. No cultures were sent in 2 cases [33, 42]. Mortality was noticed to be 18.2% in the cases reviewed (2/11).

Exudative Tracheitis

Salamone et al. [3] have suggested that the term ET is a more accurate descriptive term than bacterial tracheitis for the patients who did not have the classic description of the toxic, febrile patient with stridor [3]. This implies that bacterial tracheitis may be more of a local process caused by bacteria or virus which leads to the formation of tracheobronchial exudates [3]. The results of another study also suggest that bacterial tracheitis may be a less morbid condition [46]. ET may represent a point on a continuum of disease from mild upper-respiratory infection to severe bacterial tracheitis. Although less severe than classic bacterial tracheitis, patients with ET require aggressive local and systemic management as obstruction and respiratory collapse can occur. Treatment includes bronchoscopy with removal of the characteristic thick tracheal membranes associated with intravenous antibiotics. Patients with ET recover rapidly with appropriate management. Intubation is not always necessary, and multiple debridement procedures are typically not needed.

MRSA Tracheitis

MRSA is now endemic in hospitals and long-term care facilities [47]. In adults, MRSA is frequently seen in the elderly, and most of the patients have a history of hospitalization. MRSA tracheitis is almost exclusively diagnosed in ventilated patients diagnosed with VAT. Underlying risk factors for MRSA respiratory infection include underlying COPD, prior use of antibiotics and multiple hospitalizations [20]. In table 2, we summarize all the studies that have described MRSA isolates from VAT patients [9–11, 18, 21]. However, tracheitis that develops in a previously healthy patient is a distinctly different process from tracheitis that occurs in a patient with an artificial airway. Only 2 cases of MRSA tracheitis have been described in non-ventilated patients [4, 5]. The incidence of MRSA as cause of VAT ranged between 11 and 15.9% [9–11, 18, 21]. In the largest of these studies, in 201 cases of nosocomial tracheobronchitis in mechanically ventilated patients, 31 cases (15.4%) were secondary to MRSA and 6 cases (3%) were secondary to methicillin-sensitive *S. aureus* (MSSA) [11]. Antimicrobial agents that have been reported as efficacious in the treatment of MRSA-related infections include vancomycin, linezolid, clindamycin, trimethoprim-sulfamethoxazole and rifampin (table 2). One study suggests that oral linezolid offers an effective alternative to intravenous vancomycin for the treatment of MRSA tracheitis [48]. Two cases of MRSA tracheitis were treated for 2 and 3 days with intravenous vancomycin, and therapy was changed to enteral linezolid (10 mg/kg every 12 h) to finish a 10-day course [48]. Both patients completed the therapy without the need for rehospitalization. Saralaya et al. [49] demonstrated the efficacy of a dosing regimen of linezolid of 600 mg by mouth every 12 h in adults with cystic fibrosis. However, there is no experience regarding the use of other agents such as trimethoprim-sulfamethoxazole, clindamycin or rifampin in the treatment of tracheitis caused by MRSA.

Tracheobronchomalacia

Tracheobronchomalacia, characterized by excessive collapsibility of trachea or bronchi, is an important cause of nonspecific pulmonary symptoms [50] that is frequently underrecognized. Previous studies reported an incidence of tracheobronchomalacia of 1–23%, depending on the populations studied [51, 52]. It is rare in individuals without some evidence of obstructive lung disease [50]. Tracheobronchomalacia may be congenital or acquired [50]. Acquired tracheomalacia is caused by the degeneration of normal cartilaginous support from a variety of causes and may result from endotracheal tubes and tracheostomy, COPD, external trauma and lung surgery, chronic compression of the trachea, radiation therapy, relapsing polychondritis, and chronic or recurrent

Table 1. Cases of bacterial tracheobronchitis in non-ventilated adults diagnosed endoscopically

First author	Year	Country	Age years	Sex	Pathogen	Patient characteristics	Symptoms
Tsokos [32]	2005	Germany	49	F	patient had influenza infection and co-infection with *S. aureus*	healthy	dry cough, dyspnea, malaise for 4 days, collapse
Stuchell [33]	2003	USA	19	F	no cultures were taken	healthy	cough, upper respiratory infection, sore throat, fever
Yamazaki [4]	2002	Japan	67	M	MRSA	ex-smoker (47 pack years), partial gastrectomy for a duodenal ulcer, influenza infection	fever, hoarseness, productive cough and worsening inspiratory dyspnea
Luna [36]	1993	Argentina	36	F	*S. aureus*	1 week after radical thyroidectomy medullary carcinoma, postoperative mediastinitis, mechanical ventilation	fever, dyspnea
Valor [37]	1992	USA	31	M	*S. aureus* *P. aeruginosa*	AIDS, opportunistic infections	fever, productive cough, sore throat
Craig [38]	1991	USA	63	M	*Corynebacterium pseudodiphtheriticum*	COPD on steroids	dyspnea, productive cough
Ruddy [40]	1988	England	16	F	*S. aureus* resistant to ampicillin but sensitive to flucloxacillin	healthy	dyspnea, hoarseness, fever
Campbell [41]	1988	USA	22	F	*S. aureus* and α-hemolytic streptococci	healthy	upper respiratory infection and sudden stridorous respirations
Johnson [42]	1987	USA	18	F	no cultures were sent	healthy	sore throat, dysphasia, dyspnea, low-grade fever
Johnson [42]	1987	USA	25	F	throat culture grew *Streptococcus viridans*	healthy	sore throat, dyspnea, low-grade fever
Johnson [42]	1987	USA	41	F	tracheal aspirate cultures revealed *S. aureus*	subglottic adenocarcinoma, radiation therapy, tracheotomy	stridor, dyspnea

The use of high-dose steroids may also predispose patients to developing progressive tracheobronchomalacia [50]. The diagnosis of tracheobronchomalacia has historically been made with fluoroscopy or bronchoscopy [53], but recent advances in CT technology have made it possible to diagnose this process using this technique [53, 54].

Our Case

The purulent nature of the secretions localized in the trachea and main bronchi, and the isolation and moderate growth of a single predominant bacterial pathogen in semi-quantitative respiratory cultures in a patient without toxic symptoms and without pulmonary infiltrates on CT scan is consistent with tracheitis. The patient had chronic symptoms of hoarseness, throat pain and productive cough and wheezing for the last 2 years prior to this admission. She also had multiple admissions to the hospital for COPD exacerbation. Interestingly, MRSA had been isolated from her sputum on 6 different admissions but the patient had not undergone diagnostic CT imaging or bronchoscopy. In our opinion, chronic wheezing was secondary to tracheomalacia and the constant productive cough to ET secondary to MRSA which did not respond to multiple courses of quinolones. The use of multiple antibiotics and repeated hospitalizations most likely predisposed this patient to colonization of sputum with MRSA, whereas the anatomy of this patient's airway with narrowing and collapse of the lumen of the trachea secondary to tracheomalacia may have predisposed this

Kelesidis/Osman/Trayner/Worthington/Celli

Diagnosis	Treatment	Outcome
at autopsy, a hemorrhagic tracheobronchitis was present with trachea and main bronchi partly covered by purulent membranes	sudden death	sudden death
fiberoptic laryngoscopy showed subglottic edema, tracheal granulation	steroids, nebulizers, cefuroxime, ciprofloxacin	recovered after 3 days
bronchoscopy showed erosion of both vocal cords and the supra-glottic area, and diffuse tracheobronchitis with multiple well-defined purulent exudates and necrotic areas throughout the tracheal mucosa	10 days of imipenem and 16 days of vancomycin, tracheostomy, mechanical ventilation	septic shock, acute respiratory distress syndrome, disseminated intravascular coagulation/recovered
bronchofiberscopy revealed a friable trachea with widespread erythema and purulent secretions	mechanical ventilation, vancomycin	patient developed tracheal dilatation and rupture and died
necrotic material revealed in indirect laryngoscopy and bronchoscopy	ticarcillin, clavulanate, tobramycin	recovered
purulent secretions identified in bronchoscopy	vancomycin, ampicillin, gentamicin then clindamycin	recovered
direct laryngoscopy revealed crusting and yellow secretions in the trachea which grew S. aureus	humidification intravenous flucloxacillin, chloramphenicol and hydrocortisone	patient was discharged after 11 days
fiber-optic nasolaryngoscopy revealed a normal supraglottic and purulent intratracheal secretions	intravenous cefazolin	recovered
indirect laryngoscopy revealed that the subglottic trachea was edematous with a thick exudative material coating the tracheal walls	humidified air, epinephrine, no antibiotics	recovered
flexible fiber-optic laryngoscopy revealed mucoid secretions arising from the subglottic region	humidified air, epinephrine, cefotaxime	recovered
bronchoscopy revealed subglottic edema and thick yellow purulent material	cephalothin, cephalexin	recovered but had recurrence after 4 months

adult to tracheitis. Our case resembles that of an adult with congenital long-segment tracheal stenosis presenting as a difficult-to-treat asthmatic [55]. The authors concluded that her episodes of asthma were in fact dynamic airway narrowing when her tracheobronchial tree was compromised further from infection and inflammation [55]. Risk factors for the development of tracheomalacia in our patient include chronic use of corticosteroids and chronic infection [50]. There is also a possible association between chronic colonization with MRSA and the development of tracheomalacia. Colonization and recurrent infections of the airways with S. aureus occur in many patients with cystic fibrosis and lead to increased morbidity and mortality [56]. However, there is limited experience from cases of S. aureus tracheitis in non-ventilated adult patients without cystic fibrosis. Multiple episodes of exudative tracheobronchitis might increase the tracheal and bronchial wall compliance and may have predisposed to the development of tracheobronchomalacia [57]. In a recent study, it was shown that S. aureus α-toxin significantly increases airway epithelial P and produces epithelial sloughing, which may imply that other S. aureus-soluble proteins with potent immunomodulatory effects may thereby enter the subepithelial tissue space and play a role in the pathogenesis of S. aureus respiratory infections [58]. In only 1 case in the literature, infectious staphylococcal tracheitis was considered a possible cause of tracheal dilatation and rupture in the presence of normal intracuff pressure [36].

Table 2. Studies describing MRSA isolates from patients with VAT (diagnosis based on CDC criteria)

First author	Year	Country	Age, years	Sex	Pathogen	Patient characteristics	Outcome
Palmer [10]	2008	USA	62 ± 20	28 M, 15 F	in a study of 43 patients with VAT 6 (14%) had MRSA and 8 (18.6%) bacterial isolates were MSSA [10]	all 43 patients had mechanical ventilation 3 had COPD	8 (18.6%) patients died
Nseir [18]	2005	USA	59.9 ± 18.2	31 M (56%) 24 F	55 cases of VAT; the more frequently isolated bacteria were *P. aeruginosa* (34%), *Acinetobacter baumannii* (18%) and MRSA 10/86 (11.6%) isolates (11%), 30 (54%) VAT episodes were polymicrobial, and 31 (56%) were related to multidrug-resistant bacteria	12 (21%) had diabetes mellitus 14 (25%) had renal failure 12 (21%) had tracheostomy	16 (29%) patients died
Nseir [21]	2004	USA	68.8 ± 7	57 M (70.3%)	19/120 (15.8%) bacterial isolates from 81 patients with nosocomial tracheobronchitis were MRSA and 6/120 (0.5%) were MSSA	all 81 patients were ventilated, 11 (13.5%) patients had diabetes, 52 (64.1%) had COPD	33 (40.7%) patients died
Nseir [11]	2002	USA	21/36 (58.3%) >60 years	26 M (72.2%) surgical patients	7/44 (15.9%) bacterial isolates from 36 surgical patients with nosocomial tracheobronchitis were MRSA and 2/44 (4.5%) were MSSA	all patients were ventilated	19 (52.7%) surgical patients died
			131/165 (79.4%) >60 years	112 M (67.8%) medical patients	31/207 (14.9%) bacterial isolates from 165 medical patients with nosocomial tracheobronchitis were MRSA and 6/207 (2.8%) were MSSA	13 (36.1%) surgical patients had COPD and 6 (16.6%) had diabetes 118 (71.5%) medical patients had COPD and 27 (16.4%) had diabetes	69 (41.8%) medical patients died

MRSA was isolated from the sputum of our patient over the last 3 years, but it is unclear whether this contributed to her multiple hospitalizations for COPD exacerbation. Several studies showed that the isolation rate of potential bacterial pathogens from sputum samples during stable disease was identical to the rate during acute exacerbations [59, 60]. This finding led to the conclusion that bacterial pathogens do not cause acute exacerbations and their presence in sputum is due to chronic colonization. However, it has recently been demonstrated that lower airway bacterial colonization in the stable state modulates the character and frequency of COPD exacerbations [27]. In a prospective study using molecular typing of sputum isolates, it was found that the acquisition of a new strain of a bacterial pathogen was significantly associated with acute exacerbations of COPD, leading to the conclusion that this finding supports the causative role of bacteria in COPD exacerbation [61]. A recent prospective study demonstrated that rising airway bacterial load and species changes were associated with greater airway inflammation and accelerated decline in FEV_1, suggesting that bacterial airway colonization in COPD patients is an important factor in disease progression [62]. Several studies have found an association between airway bacterial load and markers of inflammation in COPD patients [63–65]. Whether this reflects a direct cause-effect relationship remains to be proven.

Conclusion

To our knowledge, this is the first case report on ET secondary to MRSA in an adult without signs of systemic infection. It is also the 3rd reported case of MRSA-related tracheitis in a non-ventilated adult and the 1st case of MRSA exudative tracheobronchitis associated with tracheobronchomalacia. Clinicians should be aware of the fact that tracheobronchomalacia can masquerade as asthma in adults and can predispose to the development of serious infections, including MRSA tracheobronchitis in non-ventilated adults.

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