Tracheobronchitis in the Intensive Care Unit 35

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35.1 Introduction

Tracheobronchitis can be broadly defined as inflammation of the airways between the larynx and the bronchioles. Clinically, this syndrome is recognized by an increase in the volume and purulence of the lower respiratory tract secretions and is frequently associated with signs of variable airflow obstruction. In the intensive care unit (ICU), tracheobronchitis is a relatively common problem with an incidence as high as 10.6 % [1]. Although tracheobronchitis is associated with a significantly longer length of ICU stay and a prolonged need for mechanical ventilation, it has not been shown to increase mortality. These outcomes can be improved through the use of antimicrobial agents [1].

Tracheobronchitis results from two dominating processes: colonization of the oropharynx and its contiguous structures (dental plaque, the sinuses, the stomach) by potentially pathogenic organisms and aspiration of contaminated secretions from these anatomic sites [2]. Mechanically ventilated patients are particularly at risk for tracheobronchitis given the presence of an endotracheal tube. These devices contribute to the pathogenesis of tracheobronchitis (and pneumonia) in a variety of manners: bypassing natural host defenses, acting as a nidus for biofilm formation, allowing pooled secretions and bacteria to leak around the cuff and into the trachea, damaging the ciliated epithelium and reducing bacterial clearance directly or via frequent suctioning to maintain airway patency [3, 4].

In contrast to nosocomial pneumonia, nosocomial tracheobronchitis does not involve pulmonary parenchyma and, thus, does not cause radiographic pulmonary infiltrates. However, high quality portable chest radiographs may be difficult to obtain in the ICU, where poor patient cooperation, inconsistent technique and other obstacles lead to suboptimal studies [5]. Furthermore, common processes such as atelectasis, pulmonary edema, or pleural effusions can cause infiltrates that mimic pneumonia making the clinical distinction between pneumonia and tracheobronchitis difficult [6].

35.2 Bacterial Tracheobronchitis

Bacterial infection is the most common cause of infectious tracheobronchitis in the ICU. Infectious tracheobronchitis is clinically diagnosed when a patient develops fever, purulent respiratory secretions, and leukocytosis but the chest radiograph shows no new infiltrate [7]. Tracheobronchitis is "microbiologically confirmed" when a patient with clinically diagnosed tracheobronchitis yields culture specimens that identify a causative pathogen at appropriately high densities. When a patient lacks fever or leukocytosis (or if culture specimens reveal few organisms) the differentiation between colonization and infection is difficult and controversial. Furthermore, the significance of tracheobronchial colonization as a risk factor for subsequent lower respiratory tract infection remains unclear.

Alterations in the oropharyngeal flora of the hospitalized host have been associated with several factors including age, severity of acute illness, comorbid chronic illnesses, and duration of hospitalization [8–10]. One study of outpatients with chronic tracheostomy concluded that although these patients were routinely colonized with massive amounts of potentially pathogenic bacteria, rates of severe respiratory tract infections were low [11]. However, hospitalized patients with a tracheostomy or a translaryngeal endotracheal tube have higher rates of tracheobronchial colonization (especially with gram-negative enteric bacteria and *Pseudomonas aeruginosa*) and nosocomial pneumonia [8, 12–15].

The upper airways and proximal tracheobronchial tree provide a mechanical barrier function and a mucociliary mechanism for removing particulate matter and microbes that have been deposited within the respiratory tract. The effectiveness of mucociliary clearance depends on the composition of airway secretions, the function of the mucociliary escalator apparatus, and the presence of an effective cough reflex [16]. Artificial airways promote both colonization and the subsequent development of tracheobronchitis or pneumonia as they provide direct access for bacteria to the lower respiratory tract, reduce the effectiveness of cough re-

flexes, and compromise the mucociliary escalator [17, 18]. Furthermore, endotracheal tube insertion and suctioning may cause tracheal epithelial cell damage allowing bacterial adherence and increased mucus secretion and stagnation [19, 20]. Respiratory therapy devices, including medication nebulizers, ventilator spirometers, and ventilatory circuits with their attendant condensate, may play roles in harboring and transmitting bacteria [21,22].

While colonization with gram-positive organisms occurs, gram-negative bacilli are much more common colonizers in ICU patients with many studies showing *Pseudomonas* species as the most prevalent organism [1, 23 – 26]. While there are no useful parameters to reliably predict which colonized patients will develop infectious tracheobronchitis, it is clear that tracheobronchitis often develops in patients with tracheobronchial colonization. In one study, 7 of 15 patients with a chronic tracheostomy were colonized with various *Pseudomonas* species: all seven of them subsequently developed an episode of purulent tracheobronchitis [27]. George et al. found that tracheal colonization was a significant independent risk factor for VAP and could be documented in 93.5 % of VAP cases [28]. The relationship between infectious tracheobronchitis and nosocomial pneumonia is not well defined. One relatively small study found that tracheobronchitis was not a risk factor for subsequent pneumonia [1].

Although aerobic enteric gram-negative bacilli as a group account for the majority of respiratory infections in ventilated patients, *Staphylococcus aureus* is one of the most common individual pathogens and accounts for ~20 % of nosocomial respiratory infections. *S. aureus* is found in the nasopharynx in 20 – 40 % of healthy adults and the carrier rate can be as high as 70 % in hospitalized patients. Patients with structural lung diseases, such as cystic fibrosis or chronic obstructive pulmonary disease, frequently have tracheobronchial colonization with *S. aureus*. The emergence of nosocomial methicillin-resistant strains of *Staphylococcus aureus* (MRSA) and community-acquired MRSA poses a unique therapeutic problem. Infection with this pathogen is not limited to nosocomial pneumonia but also has been reported to cause fulminant tracheobronchitis [29]. MRSA tracheobronchitis may present as pseudomembranous lesions, clinically mimicking the presentation of fungal tracheobronchitis (see below) [30].

Another important nosocomial pathogen that opportunistically infects ICU patients with impaired host defenses is *Acinetobacter baumannii*. In addition to causing tracheobronchitis and pneumonia, other infectious syndromes attributable to *A. baumannii* include endocarditis, peritonitis, skin and soft tissue infection, urinary tract infection, and bloodstream infection. *A. baumannii* infections have been linked to contaminated respiratory therapy equipment, intravascular access

devices, and transmission via hands of hospital personnel [31]. Seifert and coworkers observed that tracheobronchitis was the presumed portal of entry for nosocomial *A. baumannii* bacteremia in 19 of 87 (22 %) episodes. This study also confirmed the results of other studies suggesting that the major determinants for developing *A. baumannii* bacteremia included treatment in an intensive care unit, major surgery, mechanical ventilation, total parenteral nutrition, broad-spectrum antimicrobial therapy, and the presence of intravascular catheters [32]. This organism's routine association with multi-drug resistance results in mortality rates as high as 46 % [33, 34].

While *Mycoplasma pneumoniae* infection is best known for producing atypical pneumonia in young adults, it may result in bronchitis ~30 times more often than it causes pneumonia [35]. *M. pneumoniae* outbreaks occur sporadically but have a predilection for the late fall and early winter [36]. *M. pneumoniae* is associated with acute bronchiolitis, bronchiolitis obliterans, and bronchiolitis obliterans with organizing pneumonia (BOOP) in infants, children and adults. In children, *M. pneumoniae* is a relatively infrequent cause of bronchiolitis, accounting for 11 % of cases of bronchiolitis caused by an identified agent [37]. Although acute infectious bronchiolitis requiring hospitalization is unusual in adults, *M. pneumoniae* should be considered as a cause for acute bronchitis or bronchiolitis in hospitalized patients.

Mycoplasma pneumoniae infections typically begin insidiously with fever, nonproductive cough, headache, malaise and occasional chills. Upper respiratory symptoms of rhinitis and sore throat are present in 50 % of cases. Myalgias, arthralgias, skin rash or gastrointestinal symptoms are rare; bullous myringitis and ARDS occasionally develop [38]. Rare cases of profound hypoxemia with airflow obstruction and hypercapnia have been reported, presumably as a result of widespread bronchiolitis [39].

35.3
Fungal Tracheobronchitis

Fungal infections limited to the tracheobronchial tree are increasingly recognized in critically ill patients, particularly in the immunocompromised host [40 – 42]. Clark et al. reported that of a total of 207 patients, 15 (7 %) had infection solely or predominantly within the airways [43 – 47]. The incidence of *Candida* infection localized to the tracheobronchial tree must be much lower as the reported cases are very rare. Furthermore, some cases are poorly documented pathologically and the diagnosis of bronchial candidiasis was made solely on the basis of repeatedly positive sputum cultures and clinical improvement after treatment with

antifungal agents [48, 49]. *Candida* colonization of the respiratory tract was reported to occur in 27 % of patients intubated for more than 2 days and was associated with an increased risk of *Pseudomonas* pneumonia and longer ICU and hospital stays [50]. *Aspergillus* is the predominant pathogen occurring alone or in combination with other pathogens.

Pseudomembranous and obstructive *Aspergillus* tracheobronchitis represent two different, but sometimes overlapping, clinical presentations. The first consists of intraluminal growth involving more or less the entire circumference of the airway wall with only superficial mucosal invasion. Pathologically, such infection can appear as a pseudomembrane in which a fibrinous exudate related to airway ulceration is prominent, or as tenacious mucus/fungus plugs more or less completely occluding the tracheobronchial tree. This is perhaps the most likely form of serious fungal infection to be missed clinically. Patients may complain of cough, chest pain, increasing dyspnea, fever, hemoptysis, and, possibly, signs of upper airway obstruction. Because the parenchyma is unaffected, the chest roentgenograms may be normal. Early bronchoscopy with histological examination and cultures of the bronchial casts and airway debris confirms the diagnosis [40, 43, 51].

Obstructive tracheobronchial aspergillosis may present with radiographic findings of atelectasis due to extensive obstruction of both main and subsegmental bronchi [41]. The obstruction may be severe causing acute respiratory failure [42].

Another morphological form consists of one or several discrete plaques localized to a relatively small portion of the tracheobronchial tree. Although in the early stages of infection, invasion is limited to the airway mucosa, with progression of disease fungi penetrate beyond the bronchial wall into the adjacent lung parenchyma where they may result in focal pneumonia or abscess formation. Vascular invasion is not uncommon and may lead to parenchymal or pleural hemorrhage [43].

The explanation for why fungi colonize and invade the tracheobronchial tree in certain patients is unclear. However given the underlying disorders that patients with fungal tracheobronchitis commonly have, it is clear that a deficiency in the host immune system is a common denominator among these patients. Fungal tracheobronchitis has been seen in patients with lung and bone marrow transplantation, AIDS, and hematological malignancies [52]. Prolonged neutropenia occurring either secondary to the malignancy or chemotherapy has been shown to be a risk factor for developing invasive pulmonary aspergillosis [53]. Even in the absence of neutropenia, impaired leukocyte mobilization and function may contribute to the predisposition to fungal infection in cancer patients [54]. Pseudomembranous tracheobronchitis has also been reported

in patients with diabetes [40]. Corticosteroids predispose to the development of fungal invasion by inhibiting macrophage killing of spores, inhibiting phagocyte migration to the site of infection, and by suppressing antibody production, delayed hypersensitivity reaction, and wound healing [43, 55]. Broad-spectrum antibiotics change the normal flora and predispose to the development of fungal colonization. Cellular and humoral immune deficiency are additional risk factors [56].

Once the diagnosis of *Aspergillus* tracheobronchitis is established by bronchoscopy, histology, or culture, appropriate antifungal therapy should be started. In addition, multiple therapeutic bronchoscopies may be needed to debulk the intrabronchial debris.

35.4
Viral Tracheobronchitis

Many respiratory infections caused by viruses begin in the upper respiratory tract usually without producing lower respiratory symptoms. A variety of clinical syndromes including rhinitis, pharyngitis, laryngotracheitis (croup), bronchitis or tracheobronchitis, bronchiolitis and pneumonia can occur depending on the specific virus involved, the viral load, virulence, host resistance and extent of respiratory mucosal involvement [57].

The patient's age is also an important factor in the form and severity of infection; for example rhinovirus typically causes only coryza in immunocompetent adults, whereas it is a cause of croup, bronchitis, bronchiolitis and pneumonia in children. The attack rates for respiratory syncytial virus (RSV), parainfluenza virus types 1 and 3 and adenovirus are also severalfold higher in the first 2 years of life [57].

In the ICU, viral tracheobronchitis is usually seen in one of two situations: (a) primary viral infection usually acquired in the community, such as influenza, parainfluenza, adenovirus or RSV that is either severe or complicates underlying pulmonary disease or, (b) reactivation of a latent virus in the nosocomial setting, such as herpes simplex virus (HSV) or cytomegalovirus (CMV). Either situation can further be complicated by bacterial co-infection or superinfection [58].

35.4.1
Influenza Virus

The influenza viruses A, B, and C are the three most important genera of the Orthomyxoviridae, a group of single stranded RNA viruses. Hemagglutinin and neuraminidase are the major antigenic determinants of influenza A viruses and serve as the basis for their subtype classification [59]. A minor mutation in the anti-

genicity of hemagglutinin or neuraminidase leads to antigenic drift and explains the need for yearly changes in the influenza vaccine composition. On the other hand, genetic reassortment can result in the appearance of a novel hemagglutinin/neuraminidase combination called an antigenic shift which, due to lack of immunity in the human population, can lead to influenza pandemics.

Influenza virus infection usually involves only the upper respiratory tract, including trachea and major bronchi; however in a small percentage of patients, particularly the chronically ill or the elderly, it may be responsible for severe pneumonia. It can occur in pandemics, epidemics or sporadically. Almost all severe epidemics and all pandemics are caused by type A influenza. Typical winter outbreaks occur every year in temperate climates with a less predictable seasonal variation in tropical areas. Transmission occurs from person to person with an incubation period of 24–48 h and is highly contagious. Viral shedding and infectivity can persist for as long as 2 weeks in children, but probably less in adults [60]. Antibody formation to specific strains by either immunization or infection confers immunity for 1–2 years. Serologic studies have found a higher incidence of antibodies to influenza A and B in health care workers than controls [61]. The risk of developing a complicated course is increased in the older individuals, and those with a significant history of tobacco smoking, comorbidities and pregnancy [62–64]. Recent outbreaks of avian influenza virus infections in humans have been the source of concern for a potential influenza pandemic. Since 2004, the H5N1 influenza A virus has expanded from southern China to western China, Mongolia, Russia, and, more recently, Europe and Africa. Humans acquire avian influenza through direct contact of mucous membranes with infected secretions and excreta from infected birds or contaminated poultry. Human-to-human transmission of avian influenza has thus far only occurred sporadically and with low efficiency [65].

The clinical manifestations of human influenza are variable and depend on the virulence of the influenza virus strain, the underlying condition and response of the host. The flu-like syndrome with rapid onset of dry cough, myalgias, headache, chills and fever without major pulmonary complaints affects predominantly young adults. Another syndrome seen in influenza is bronchitis/tracheobronchitis with no radiographic abnormality but with more respiratory distress and sometimes associated with hemoptysis, exacerbation of underlying asthma or chronic obstructive pulmonary disease (COPD). In more severe cases, spread of the virus to the pulmonary parenchyma causes clinical worsening within 12–36 h with worsening dyspnea, tachypnea, cyanosis and hypoxemia [66, 67]. The radiographic abnormalities of influenza pneumonia include interstitial infiltrates, lobar consolidation with air bronchograms, and focal areas of atelectasis. Finally, it is well recognized that superinfection with *Staphylococcus aureus, Streptococcus pneumoniae, Hemophilus influenzae* or other bacteria can occur after influenza [68]. The clinical manifestations of avian influenza infection also depend on the viral subtype causing the disease. Conjunctivitis, with or without an influenza-like illness, occurs with the A/H7N7 and A/H7N3 strains. A/H5N1 strains lead to more severe presentations with frequent progression to pneumonia and a high fatality rate. Gastrointestinal complaints of abdominal pain, nausea, vomiting, and diarrhea are common. Lymphopenia and thrombocytopenia are common findings and prognostic indicators for ARDS and death [69].

The diagnosis can be confirmed by culturing the virus from respiratory secretions, a throat swab, or a nasopharyngeal aspirate. More rapid diagnostic methods available consist of direct immunofluorescence assay (DFA), polymerase chain reaction (PCR) or the rapid assays that detect activity of influenza neuraminidase or viral nucleoproteins [70]. The currently commercially available test kits do not distinguish human from avian influenza or their subtypes. The sensitivity of these kits for detecting A/H5N1 infection ranges from 33 % to 86 % [69, 71].

Influenza vaccination is the mainstay of protection against the disease. The older drugs available for the prevention and treatment of influenza are amantadine and rimantadine. However, their use is limited by lack of activity against influenza B, rapid emergence of resistance and, especially with amantidine, central nervous system toxicity. Agents available for the treatment of influenza A and B include the neuraminidase inhibitor zanamivir that is delivered by inhalation (10 mg bid) and oseltamivir (75 mg PO bid) [72]. Controlled clinical trials on the efficacy of neuraminidase inhibitors for the treatment and prophylaxis of human avian influenza infections have not been performed.

35.4.2
Parainfluenza Virus

In adults, parainfluenza is responsible for pharyngitis and coryza; in infants and children it is the predominant cause of severe croup. Immunocompromised individuals are at increased risk for more severe presentations. Parainfluenza type 1 and 2 occur predominantly in the autumn and early winter. Parainfluenza type 3 occurs in the spring and is an important cause of bronchiolitis or pneumonia in infants and children. Lower respiratory tract involvement in adults is uncommon.

The parainfluenza viruses cause a spectrum of respiratory illnesses similar to those caused by *Mycoplasma* infection and respiratory syncytial virus (RSV) (see below). Most are upper respiratory tract infections of

which 30–50% are complicated by otitis media. In infants, about 15% of parainfluenza virus infection involves the lower respiratory tract. Croup is the signature clinical manifestation and chief cause of hospitalization in children 2–6 years of age [61].

The clinical manifestations in adults are acute pharyngitis and tonsillitis or the aggravation of an underlying cardiopulmonary problem. When complicated by pneumonia it is indistinguishable from other viral or *Mycoplasma* infection. The radiographic findings are nonspecific. The organism can be isolated by culture of sputum or nasopharyngeal secretions. Immunofluorescent antibody is useful for rapid identification.

There are currently no available antiviral agents with proven effectiveness against parainfluenza virus. Ribavirin is active against the virus in vitro, but there have been no randomized controlled trials in humans.

35.4.3
Rhinovirus

Rhinovirus causes approximately 40–50% of the common cold cases. Clinically significant lower respiratory tract infection in adults is uncommon but includes acute bronchitis, bronchiolitis and pneumonia. Perhaps more important is the indirect effect that such an infection may have in patients with asthma, COPD or other medically debilitating states. Rhinovirus infection has been associated with exacerbation of COPD and respiratory failure [73].

35.4.4
Adenovirus

Adenovirus can cause pharyngitis, pharyngoconjunctivitis, laryngotracheo-bronchitis, bronchiolitis, pneumonia or a non-specific acute respiratory syndrome; there is also some evidence that it may cause some cases of bronchiectasis, bronchiolitis obliterans and hyperlucent lung syndrome [74]. Infections can occur sporadically or in epidemics. Localized nosocomial outbreaks have also been reported.

The adenoviruses are the most common cause of the *acute respiratory disease syndrome,* a poorly defined condition consisting of fever, pharyngitis, cough, hoarseness, chest pain, and conjunctivitis. Chills and myalgias may be present. In some cases, tracheobronchitis is prominent and may be indistinguishable from the classic whooping cough caused by *Bordetella pertussis*. When pneumonia occurs it is typically mild and associated with upper respiratory symptoms. However, a few fatal cases have been seen with autopsy studies revealing extensive areas of hemorrhagic consolidation with alternating areas of atelectasis and hyperinflation. The airways frequently show marked airway congestion with mucopurulent or hemorrhagic material.

In most cases the infection is self-limited and the treatment is supportive.

35.4.5
Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections (bronchiolitis and pneumonia) among young children, resulting in an estimated 51,000–82,000 hospitalizations annually in the United States. Infection occurs predominantly during the winter months and early spring. Transmission occurs by airborne droplets or hand-to-hand contact. The disease is highly contagious and there is evidence that health care workers are at increased risk for infection [61].

In adults, the disease is usually mild and limited to the upper respiratory tract. However, in the elderly, chronically ill, immunocompromised or hospitalized patient, lower tract involvement can occur [75]. Rarely, RSV can cause acute pneumonia with rapid progression to ARDS [76]. A recent prospective surveillance study of healthy elderly patients, high-risk adults, and patients hospitalized with acute cardiopulmonary conditions found RSV in 10.6% of hospitalizations for pneumonia, 11.4% for chronic obstructive pulmonary disease, 5.4% for congestive heart failure, and 7.2% for asthma [76].

The clinical manifestations reflect the extent of airway involvement. Nasal congestion and discharge usually precede the cough and wheezing by 2–3 days, but may occur simultaneously. In contrast to influenza infection, RSV is associated with relatively little risk of bacterial superinfection. The radiological findings usually reflect a disparity between the severity of respiratory symptoms and a paucity of abnormalities. However, bronchial wall thickening, peribronchial infiltrates or lobular consolidation may occur.

RSV can be cultured from nasopharyngeal or lower respiratory secretions. In adults and transplant patients, bronchoalveolar lavage is more sensitive than throat swabs [77]. The shell-vial culture has been shown to be a rapid and sensitive method. PCR and immune based assays including antigen detection by immunofluorescence or enzyme-linked immunosorbent assay (ELISA) are available for rapid diagnosis with a sensitivity and specificity of 80–90% [61].

In addition to supportive care, severe cases of RSV infection have been treated with aerosolized ribavirin (6 g reconstituted in 300 ml of sterile water to a final concentration of 20 mg/ml and administered 12–18 h/day for 3–7 days); although no clinical trials have been conducted in this patient population. There is no data regarding the use of oral ribavirin. Intravenous and inhaled human immunoglobulin RSV hyperimmune globulin and monoclonal antibody have been used to

treat limited numbers of patients with RSV infection. The therapeutic effect has been marginal [61].

35.4.6
Herpes Simplex Virus

Herpes simplex virus (HSV) was first recognized as a pulmonary pathogen by Morgan and Finland almost a half century ago [78]. Stern and associates [79] first focused attention on the possibility of herpetic involvement of the trachea and its transmission via contaminated secretions from an infected patient to a healthcare worker, causing herpetic whitlow. Later reports of herpetic respiratory infections have included patients with underlying diseases [80, 81], extensive burns [82], underlying malignancy, chemotherapy and radiation therapy [83], and critically ill patients with adult respiratory distress syndrome (ARDS) [84–87].

Herpetic tracheobronchitis has also been reported in immunocompetent patients without history of chronic lung disease [88–90], in patients after extracorporeal circulation for cardiac surgery [91], and following general surgery [92–94].

Despite the apparent increasing prevalence of pulmonary HSV, the relationship between respiratory HSV isolation, pulmonary function, and clinical outcome is not well documented. HSV type 1 in lower respiratory secretions has been associated with unresolved acute bronchospasm [88], prolonged requirement for mechanical ventilation [88–94], tracheal stenosis, and increased mortality [94, 95]. However, asymptomatic viral shedding of HSV also occurs in approximately 1–5% of asymptomatic normal individuals [96].

The concept of airway injury leading to viral reactivation has been reported previously in autopsy series [82, 97, 98] and in patients who have undergone surgery [88, 94]. One reason for this susceptibility of "traumatized" epithelium to viral colonization and potential subsequent inflammation may be that HSV typically infects squamous epithelium [99]. Thus, factors that promote squamous metaplasia, such as trauma, smoking, radiation therapy, or chemotherapy, may predispose the patient to lower respiratory tract infection with HSV [99].

At the present time, there are no defined criteria for the diagnosis or treatment of herpetic tracheobronchitis. Simple isolation of HSV from respiratory secretions is clearly insufficient to make this diagnosis, since HSV can be asymptomatically shed in up to 5% of asymptomatic adults, and the incidence of reactivation or shedding is increased in patients with airway injury. Thus, one usually makes the diagnosis based on a combination of the viral cultures, direct bronchoscopic examination of the endobronchial tree, cytological examination of tracheal or bronchial washings, and the clinical status of the patient.

The most frequent clinical manifestations exhibited by the patients are fever, productive cough, and dyspnea. Frequency of these symptoms does not differ between the immunocompromised and immunocompetent patients. However, immunocompetent patients have significantly more bronchospasm. These data imply that the pathogenicity of HSV in the respiratory tract may vary depending on underlying immune status and the host response [100].

In addition, the role of primary infection versus reactivation in the spectrum of clinical manifestations of tracheobronchitis is unclear. One could speculate that respiratory HSV isolation in the immunocompromised patients most often represents "asymptomatic" shedding, perhaps due to reactivation, with less airway inflammation and, consequently, less bronchial hyperactivity. For unclear reasons, the clinical manifestations of HSV infection are more severe in the immunocompetent population; this may represent a more exuberant local immune response.

Whether to treat critically ill patients with lower respiratory tract HSV isolation with acyclovir is uncertain and controversial at this time. At the present time, it seems reasonable to treat with intravenous acyclovir (8 mg/kg every 8 h for 10 days) those patients with HSV isolation from lower respiratory secretions if, in addition, they have a clinical syndrome or bronchoscopic findings consistent with tracheobronchitis. However, future prospective, randomized trials that assess the impact of treatment on the outcome of both the apparently asymptomatic HSV "carrier" and those patients with clinical HSV tracheobronchitis are needed to clarify this issue. In addition, given the risk of horizontal transmission of HSV-1 to health-care workers, full compliance with infection control measures, including use of gloves and goggles when there is any potential for contact with secretions, is recommended [101].

35.4.7
Cytomegalovirus

Cytomegalovirus (CMV) has been cultured with increasing frequency from patients on prolonged mechanical ventilatory support [102]. Similarly to the case of HSV, the clinical spectrum of CMV can range from asymptomatic viral shedding to a severe disease with profound immunosuppression, pneumonitis and multi-organ dysfunction syndrome. In contrast to HSV where the predominant involvement occurs in the airways, CMV typically involves the pulmonary parenchyma, leading to interstitial pneumonitis or diffuse alveolar damage. CMV infection has been shown to potentiate effects of bacterial infections, possibly through impairment of neutrophil migration or macrophage activation, and has been implicated in promoting bacterial translocation [94]. Cardiac surgery patients with CMV

infection complicating mediastinitis have been shown to have persistence of local infection, prolonged hospitalization and increased mortality [103]. Trauma patients with HSV or CMV reactivation have also been shown to have increased ventilator dependence and increased superimposed bacterial pneumonias [104].

As with other organisms, several techniques are available to detect CMV. The virus can be isolated from various body fluids (e.g., blood, urine, respiratory secretions) and buffy coat culture may be useful. Use of shell-vial technique yields results within 24–36 h. Additional, even more sensitive techniques including immunoglobulin-labeled immunomagnetic beads, fluorescent antibody staining, in situ hybridization, and PCR have also been utilized to identify CMV antigens. However, a major limitation of these tests is that they do not differentiate infection from disease. Thus, it is sometimes necessary to obtain tissue in order to assess the cytopathic effects.

The drugs effective against CMV are ganciclovir and foscarnet. However, the decision to treat an individual patient has to balance the risk of the patient, the evidence of disease and the potential toxicity associated with treatment.

35.5
Noninfectious Etiologies

Several noninfectious processes can initiate and/or perpetuate tracheobronchitis. Potential causes include nebulized medications (*N*-acetylcysteine, colistin, tobramycin, ribavirin, and dornase alfa), microaspiration of gastric contents, prolonged exposure to high concentrations of oxygen, and repeated trauma caused by airways suctioning or procedures.

35.6
Summary

Tracheobronchitis is increasingly recognized as a distinct syndrome in the intensive care unit. The most common etiology is infection caused by bacterial, fungal, or viral pathogens. The clinical manifestations are variable and not specific for individual pathogens. The clinical distinction between incidental airway colonization and significant infection is difficult but carries important therapeutic and prognostic implications. A high index of suspicion with the appropriate diagnostic and treatment intervention can lead to an improved outcome.

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