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Review

Bronchiolitis: what the clinician should know

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Abstract

Bronchiolitis is an acute infection of the lower respiratory tract affecting infants and young children, with Respiratory Syncytial Virus (RSV) being the most common pathogen. Bronchiolitis is generally a mild disease, but may present with severe signs and symptoms requiring hospitalization. Risk factors including prematurity, bronchopulmonary dysplasia, immunodeficiency and congenital heart defects may predispose patients to develop a severe disease. The diagnosis should be based on clinical evaluation, without supportive radiographic and laboratory studies. Etiological diagnosis may be helpful to decrease the hospital transmission of virus and to avoid inappropriate use of antibiotics.

The mainstay of therapy for bronchiolitis is supportive care, which should be directed at maintaining adequate oxygenation, ensuring a proper respiratory toilet, and meeting the requirements of fluids and nutrition. The use of nebulized hypertonic saline should be limited to hospitalized patients. Severe respiratory failure may require mechanical ventilatory support. Neither corticosteroids nor antibiotics offer consistent benefit in the treatment of bronchiolitis, and thus should not be used. A trial of a bronchodilator may be appropriate, but should be continued exclusively if a prompt favorable response occurs. Effective interventions to prevent the spread of RSV infection include hand washing or disinfection by caregivers and contact isolation. The use of palivizumab, a monoclonal antibody directed against RSV, is a

safe prophylactic option, but should be restricted to children at high-risk for severe RSV disease, during the epidemic period. Current evidence suggests that early RSV bronchiolitis predisposes children to recurrent wheezing and asthma in the first decade of life.

Keywords

Bronchiolitis, Respiratory Syncytial Virus, therapy, complications, infants, children.

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Introduction

Acute bronchiolitis is the most frequent lower respiratory tract infection (LRTI) in children aged less than 2 years, and is characterized by inflammatory obstruction of small airways. A UK Delphic process achieved a 90% consensus on the definition of bronchiolitis as "*a seasonal viral illness characterised by fever, nasal discharge and dry, wheezy cough. On examination there are fine inspiratory crackles and/or high pitched expiratory wheeze*" [1]. Acute bronchiolitis is an annual and primary cause of morbidity in infancy. By age 2 years, virtually all children have been infected at least once.

Etiology and Epidemiology

Bronchiolitis is primarily a viral disease. The most frequently identified infectious agent is Respiratory Syncytial Virus (RSV). However, other identified pathogens include Parainfluenza virus, Adenovirus, Influenza virus, Rhinovirus and Human Metapneumovirus.

RSV, a member of the Paramyxoviridae family, is an enveloped, single-stranded RNA virus. Two surface proteins, the F protein and the G protein, are the major antigens of RSV, and play a crucial role in the virulence of this pathogen. Two antigenic subtypes of RSV, A and B, are usually present during seasonal outbreaks.

The World Health Organization estimates that RSV is responsible for more than 60% of pediatric acute respiratory infections. Each year, seasonal outbreaks occur throughout the world, even though onset, duration and peak vary from year to year. Moreover, the epidemiology of RSV differs at different latitudes and is affected by meteorologic conditions (ambient temperature and absolute humidity) [2]. In temperate climates, RSV outbreaks generally occur between late fall and early spring [3]. In Italy, annual epidemics of RSV have been shown to begin in November, to peak in February or March, and to end in April [4].

The initial RSV infection typically occurs in the first 2 years of life and is usually the most severe. Previous infection only confers partial immunity, so subsequent infection with RSV is common, and can recur over the course of the same viral season. Most re-infections run a milder course, and are limited to the upper respiratory tract.

In previously well children, bronchiolitis is usually a self-limited infection and responds well to supportive care. However, young children and children with pre-existing medical conditions are a vulnerable population, who may require hospitalization due to severe clinical manifestations. Risk factors for severe RSV infection include current weight < 5 kg, premature birth (less than 35 weeks gestation), chronic lung disease, cyanotic congenital heart disease, neuromuscular disease, immunodeficiency, intrauterine exposure to tobacco smoke and low socioeconomic status [5, 6]. Age less than 12 weeks, male gender, lack of breastfeeding, and crowding are additional risk factors for severe RSV disease. Children aged less than 3 months and those born preterm have been shown to be at higher risk for apnea and severe respiratory distress [7].

Bronchiolitis is the foremost cause of hospitalization in infants. In the USA, RSV causes approximately 125,000 hospitalizations and 250 infant deaths annually [2]. Bronchiolitis admission rates in infants younger than 1 year have been estimated from regional studies to be 31.2 per 1,000 in the USA [8] and 30.8 per 1,000 in the UK [9]. In a recent population-based birth cohort study, hospital admissions for bronchiolitis in England have been estimated to be 24.2 per 1,000 infants younger than 1 year, 15% of which were born preterm [10].

Pathophysiology

RSV infection is transmitted through the inoculation of nasopharyngeal or conjunctival mucosa with infected respiratory secretions. The virus invades the nasopharyngeal epithelium, then spreads rapidly by cell-to-cell transmission to the lower airways, and reaches the terminal bronchioles, where its replication is most efficient. Lytic viral replication leads to direct pathological consequences including the following: (a) sloughing of necrotic ciliated epithelial cells; (b) submucosal edema and swelling resulting from polymorphonuclear neutrophil influx initially, and then from peribronchiolar lymphomononuclear infiltration and increased microvascular permeability; (c) widespread mucous plugging as a result of the increase in quantity and viscosity of mucous secretions and the loss of ciliated epithelial cells. These acute inflammatory changes in the bronchioles cause airway obstruction and air trapping leading to wheezing, bilateral hyperinflation and patchy atelectasis [2].

The above mentioned pathological processes impair pulmonary gas exchange. Variable hypoxemia may be observed as a result of both the impairment of diffusion across blood-gas membrane and the ventilation-perfusion mismatch. Progressive hypercapnia and respiratory acidosis indicate evolving respiratory failure.

The severity and duration of RSV disease primarily depend on the host immune response: initially innate immunity, and subsequently specific humoral and cellular immunity, are critical barriers to infection.

Clinical manifestations

The clinical manifestations of RSV infection in children vary depending on the patient's age, previous health status and environmental exposures. Infants and young children affected by a primary infection generally present with signs or symptoms of bronchiolitis or pneumonia, including cough, fever, rhinorrhea, labored respiration, wheezing, and occasionally hypoxia [11]. Nasal flaring, grunting, and intercostal retractions are observed in children with more severe disease, reflecting increased respiratory effort.

Young infants with RSV infection may present with apnea, the incidence of which has been shown to be as high as 20% in infants aged less than six months who need hospitalization. Generally, apnea is an early event preceding signs and symptoms of lower respiratory tract involvement; this finding suggests a possible role of reflex neural activity originating in the upper respiratory tract. Premature infants and infants less than 1 month of age show the highest incidence of apneic events, probably due to an immature respiratory control.

Older children tipically manifest upper respiratory tract symptoms (coryza, rhinorrhea and cough), and conjunctivitis.

Diagnosis

The diagnostic workup of bronchiolitis may be divided into 2 phases: clinical diagnosis of bronchiolitis and identification of causative agent.

The diagnosis of bronchiolitis should be based exclusively on patient history and physical examination findings [12]. Abnormalities on chest radiography (bilateral hyperinfation, patchy atelectasis and infiltrates) are often observed in children with bronchiolitis. The count of white blood cells is generally normal, but a slight increase may be observed. However, these findings do not correlate to the severity of bronchiolitis and are not helpful in guiding therapy. Therefore, radiographic and laboratory studies are not routinely recommended [13, 14].

Chest radiography may be indicated in cases of suspected cardiac disease, suggesting a different diagnosis and treatment. The total and differential blood cell counts and the determination of C-reactive protein levels are advisable to assess a possible bacterial superinfection in young febrile children; moreover, the measurement of electrolyte serum levels may be helpful to monitor hydration and electrolyte balance.

Etiological diagnosis can be determined by *antigen detection tests* (immunofluorescence, enzyme immunoassay), currently being replaced by *genome detection* using *polymerase chain reaction* (PCR) *assays*. Nasal swabs and nasal lavage followed by nasopharyngeal aspirate ensure the most effective detection of causative agents.

The identification of etiological agent is usually not recommended in clinical practice [12] because the management of the patient with bronchiolitis does not change. Nevertheless, etiological diagnosis may be helpful, particularly in hospital settings, to avoid inappropriate use of antibiotics and to reduce the risk of nosocomial infections by "cohorting"; additionally, the identification of virus may have epidemiological relevance [15].

Therapy

Multiple therapeutic interventions such as bronchodilators, corticosteroids, antibacterials, antiviral agents, nasal suction, nasal decongestant drops and chest physiotherapy have been used for treating bronchiolitis. Nevertheless, none of these interventions have been shown to have a significant impact on severity of clinical course, duration of illness, or clinical outcomes [16].

Currently, the treatment of bronchiolitis is based on supportive care and pharmacologic therapy.

Supportive care

To date, supportive care measures remain the most effective management of bronchiolitis. They include essentially respiratory support and appropriate management of fluids and nutrition.

Nasal toilet. The toilet of the nasopharynx with normal saline drops and nasal suctioning is a common practice in infants with bronchiolitis. Superficial nasal aspiration may temporarily relief nasal congestion and upper airway obstruction, and seems to be the most beneficial before feeding. Current data are not sufficient to make a recommendation about suctioning.

Oxygen supplementation. Bronchiolitis is characterized by variable levels of hypoxemia, and thus oxygen supplementation is a key intervention in the treatment of this illness. Warm, humidified oxygen should be given to children with oxygen saturations persistently below 90% at room air [12, 15].

Scheduled spot checks of pulse oxymetry are appropriate for patients with bronchiolitis. Continuous pulse oxymetry monitoring is not necessary as a routine intervention, and should be reserved for infants and children who previously needed continuous oxygen supplementation, had apnea, or have underlying cardiopulmonary conditions [5].

Patients with hypoxemia refractory to oxygen supplementation, with persistent respiratory distress or respiratory failure, need either support with nasal continuous positive airway pressure (nCPAP) or tracheal intubation and mechanical ventilation.

High Flow Nasal Cannula (HFNC) is a new modality of non-invasive ventilatory support for infants and children with respiratory failure. The use of HFNC to deliver humidified, heated oxygen or blended oxygen with air has been shown to improve respiratory effort and to generate CPAP. Furthermore, there is evidence that it decreases work of breathing [17, 18] and may reduce need for intubation [19, 20]. At present, the efficacy of HFNC is not definitively demonstrated, precluding specific recommendations on its use [21].

Mechanical ventilatory support and, occasionally, extracorporeal membrane oxygenation may be required in the case of severe respiratory failure.

Nebulized hypertonic saline. Nebulization of 3% saline solution seems to improve ciliary clearance of mucus, and to reduce both airway edema and respiratory secretion viscosity [22]. It has been reported that nebulized hypertonic saline is able to reduce hospitalization and to provide symptomatic relief in infants and children with bronchiolitis; however, it is not effective in reducing length of hospital stay when used in emergency settings. No significant adverse events related to hypertonic saline nebulization have been observed. According to the current evidence, the administration of hypertonic saline should be limited to hospitalized patients with bronchiolitis.

Chest physiotherapy. It has been often used in an effort to mobilize secretions and to reexpand atelectatic pulmonary segments. Currently, this practice should be discouraged because there is no evidence to support its use in infants and children with bronchiolitis [23].

Fluid intake and nutrition. Infants hospitalized with bronchiolitis require the assessment of hydration status since decreased nutritional intake and increased insensible losses are common. In these infants, continued oral feeding may increase the risk of aspiration if tachypnea and respiratory distress are significant. Therefore, patients unable to tolerate oral feeding should receive adequate fluid intake and nutrition by nasogastric feeding tube, or by intravenous route if enteral nutrition is not safe.

Pharmacological therapy

Bronchodilators. Available literature data show that inhaled β_2-agonists are not effective in the treatment of bronchiolitis, as they do not improve O_2 saturation levels and do not reduce need for and lenth of hospitalization nor duration of symptoms [24]. A brief therapeutic trial with inhaled salbutamol may be considered, especially

when there is a family history of allergy, atopy and/or asthma. This therapy should be discontinued if no documented clinical improvement occurs, due to the potential adverse effects [2].

Nebulized adrenaline. Adrenaline has been shown to be associated with a slightly better clinical response compared to albuterol [25]. This effect is likely caused by the α-adrenergic-mediated vasoconstriction, which may contribute to decreasing nasal congestion. The use of nebulized adrenaline in the treatment of bronchiolitis has been assessed in a recent meta-analysis. The results of this study show that adrenaline might be effective in reducing need for hospitalization in infants and children presenting to the emergency room, while it has not been shown to be effective in reducing length of hospital stay in hospitalized patients [26]. Moreover, a subsequent multicenter randomized trial has found that, in infants hospitalized with bronchiolitis, inhaled adrenaline is not more effective than inhaled 0,9% saline in terms of length of hospital stay, improvement in the clinical score and need for supportive care [27]. These findings suggest that adrenaline should not be used in patients hospitalized for bronchiolitis, although it could have a potential use as a rescue agent in the case of severe disease [21]. Nebulized adrenaline is not deemed safe for use at home or in other settings where cardiopulmonary monitoring cannot be ensured.

Corticosteroids. Neither systemic nor nebulized corticosteroids have been shown to provide clinically relevant benefits in terms of incidence and duration of hospitalization, and prognosis. These findings might be explained by the fact that bronchiolitis is characterized by a marked neutrophilic inflammation of airways. In a recent Cochrane systematic review, no significant association between therapy with systemic or inhaled corticosteroids and improved outcomes has been found in either outpatient or inpatient settings [28]. In addition, the safety of corticosteroids during the first year after birth, when a critical phase of lung growth occurs, is virtually unknown. Therefore, based on current evidence, the routine use of corticosteroids in the treatment of bronchiolitis is not recommended.

Antibiotics. Antibiotics should be used in cases of acute bronchiolitis with documented or strongly suspected bacterial co-infection [21], and in patients with severe bronchiolitis requiring to be admitted to the Intensive Care Unit [29]. Indeed, bacterial co-infections are uncommon. The routine use of antibiotics in the treatment of bronchiolitis must be avoided due to possible side effects, potential development of antibiotic resistance, and relevant costs.

Antivirals. Ribavirin is the only antiviral agent used for the treatment of severe RSV bronchiolitis. Ribavirin therapy is not recommended by current guidelines [12], although it may be considered in immunocompromised individuals.

Other agents. A variety of other therapeutic agents (nebulized DNase, methylxanthine, surfactant, Heliox and antileukotrienes) has been tested, but the available evidence supporting the clinical use of any of these agents is insufficient.

Prevention

In this section, we will make only brief remarks on major preventive interventions as they are exhaustively discussed in a dedicated article in this issue.

Prevention of bronchiolitis in infants and children includes environmental prophylaxis, active prophylaxis and passive prophylaxis.

Environmental prophylaxis. It is essential to reduce viral shedding in hospital settings, at outpatient clinics, and at home. In fact, the virus is spread primarily by direct contact with contaminated surfaces and objects (hands, medical instruments, toys, garments etc.), and rarely by droplet inhalation. Disinfection with alcohol-based rubs, and hand decontamination with alcohol-based rubs or soap-and-water washing are highly effective in decreasing the spread of RSV and other causative agents of acute bronchiolitis. The use of gloves and gowns may also be helpful in limiting viral transmission.

The exposure to secondhand cigarette smoke must be avoided since it increases the risk of developing respiratory infections [12].

Active prophylaxis. Both the global burden of RSV infection in young children [30] and the highly contagious nature of this infection highlight the need for vaccination. Currently, no vaccine is available for active prophylaxis against RSV. Since the 1960s, a vast array of experimental approaches (attenuated or inactivated virus, purified capsid proteins etc.) have failed to yield a safe and effective vaccine.

Passive prophylaxis. The development of polyclonal intravenous immunoglobulin first, and monoclonal antibodies for intramuscular administration later, has been an important advance in the war against RSV infection. The use of palivizumab, a humanized monoclonal antibody directed against RSV, is a safe prophylactic option, but should be restricted to children at high risk for severe RSV disease, during the epidemic period.

Complications

Bronchiolitis has often a favorable course, but severe complications may develop. A retrospective study by Willson et al. [31] investigated complications in 684 infants hospitalized for bronchiolitis or RSV pneumonia. The authors found one or more complications in 79 percent of patients, with 24 percent of patients having severe complications. Higher rates of complications were documented in former premature infants (87%), infants with congenital heart defects (93%) or other congenital abnormalities (90%). The most common complications were found to be respiratory complications (hyperinflation, atelectasis, respiratory failure, apnea etc.) and infectious complications (otitis media, bacterial pneumonia, sepsis etc.), but were also observed cardiovascular complications (hypotension, cardiac arrhythmias etc.), electrolyte imbalance, anemia, seizure, etc. Complications were associated with longer length of stay and higher hospital costs.

Several reports have revealed the ability of RSV to spread from airways to various host tissues including heart, brain and liver, accordingly resulting in different clinical manifestations such as cardiopathy, encephalitis and hepatitis [32-34].

Children admitted to the intensive care unit with severe bronchiolitis have been found to exhibit more frequently extra-pulmonary manifestations including cardiovascular failure with hypotension requiring inotrope support, in association with myocardial damage, arrhythmias and pericardial tamponade [32]. Moreover, fatal interstitial myocarditis and second-degree heart block during RSV infection have been reported. Severe hepatitis with elevated levels of alanine aminotransferase has been also observed in association with RSV LRTI [35]. Endocrine alterations resulting in hyponatremia have been described in infants affected by severe RSV bronchiolitis, with elevated levels of antidiuretic hormone being found in hyponatremic patients [36].

Epidemiological studies have shown that approximately 1.2-1.8% of children hospitalized with severe RSV bronchiolitis can manifest some type of CNS disorder [33, 37], including seizures, central apnea, lethargy, tone abnormalities, strabismus, feeding or swallowing difficulties, encephalopathy and abnormalities in the CSF [37-41]. The most frequent neurological manifestations in the course of RSV infection are central apnea and seizures [42]. In a highly selected population of 21 newborns and young infants admitted to the Intensive Care Unit with severe bronchiolitis, acute encephalopathy was frequently observed (n = 10), with 6 patients (28.6%) developing seizures. Nevertheless, the results of this study suggest that the short- and long-term prognosis of bronchiolitis-associated encephalopathy is excellent [41]. To date, the mechanisms involved in the pathogenesis of neurological manifestations remain largely unknown.

Prognosis

Generally, RSV bronchiolitis is a self-limiting pathological condition. Most infants who experience this LRTI recover uneventfully within 2 weeks. However, approximately 40% of infants with bronchiolitis develop subsequent wheezing episodes through five years of age, while 10% have subsequent wheezing episodes beyond this age [43]. Currently, the relationship between RSV bronchiolitis and subsequent wheezing is unclear. The question remains whether RSV is a causative factor or rather a marker or trigger of an underlying intrinsic predisposition to develop asthma. Only randomized controlled trials with specific prophylaxis may conclusively establish whether preventing or delaying the first infection by RSV decreases the incidence and severity of asthma in later life.

Declaration of interest

The Authors have nothing to disclose.

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