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Viral bronchiolitis in children: A common condition with few therapeutic options ☆

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ABSTRACT

Even though bronchiolitis is a disease that has been recognized for many years, there are still few therapeutic strategies beyond supportive therapies. Bronchiolitis is the most frequent cause of hospital admission in children less than 1 year of age. The incidence is estimated to be about 150° million cases a year worldwide, and 2–3% of these cases require hospitalization.

It is acknowledged that viruses cause bronchiolitis, but most of the studies focus on RSV. The RSV causes a more severe form of bronchiolitis in children with risk factors including prematurity, cardiovascular disease and immunodeficiency. Other viruses involved in causing bronchiolitis include RV, hMPV, hBoV and co-infections. The RV seems to be associated with a less severe acute disease, but there is a correlation between the early infection and subsequent wheezing bronchitis and asthma in later childhood and adulthood.

The supportive therapies used are intravenous fluids and oxygen supplement administered by nasal cannula or CPAP in most complicated patients. Additional pharmacological therapies include epinephrine, 3% hypertonic saline and corticosteroids. The Epinephrine seems to have the greatest short-term benefits and reduces the need of hospital admission, whereas hypertonic saline and corticosteroids seem to reduce the length of hospital stay.

As bronchiolitis is such a prevalent disease in children and RV seems to play an important role, perhaps more studies should center around the RV's contribution to the initial disease and following pathology.

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1. Introduction

Bronchiolitis is the leading reason for hospitalization in infants younger than 1 year of age [1,2]. The incidence peaks between December and March. The most common cause of bronchiolitis is respiratory syncytial virus (RSV) infection [3]. Although most children have only mild bronchiolitis, some manifest more severe respiratory symptoms that require intensive care. Risk factors for severe bronchiolitis include prematurity, cardiovascular disease, chronic pulmonary disease and immunodeficiency.

Bronchiolitis in young infants is caused also by respiratory viruses other than RSV: one of the most common is rhinovirus (RV), the major cause of the common cold. It often affects children with a family history of atopy and blood eosinophilia [4].

The therapy for bronchiolitis is mainly supportive [5], with supplemental oxygen, nasal washing, and intravenous (IV) fluids. Clinical trials, testing β 2-agonists [6,7], glucocorticoids [8], epinephrine [9], recombinant human DNase [10,11], and hypertonic saline [12] in bronchiolitis report highly controversial results.

2. Definition

Bronchiolitis is the first acute lower respiratory tract viral infection affecting terminal and respiratory bronchioli in infants less than 12 months of age and resulting from bronchiole obstruction. First-time bronchiolitis is a clinical diagnosis based on runny nose, sometimes accompanied by fever, cough, mild-to-severe respiratory distress, and diffuse rales at auscultation [13].

The differing opinions on how to define bronchiolitis clinically (North American vs European) make it difficult to interpret clinical, therapeutic and epidemiological studies. Including wheezing in infants less than 24 months in the diagnostic criteria (North American definition) might cause an overlap between bronchiolitis and an early wheezing bronchitis [14].

3. Epidemiology

Bronchiolitis is the most frequent disease in children less than 12 months of age, and is the leading cause of hospitalization in this group of infants (mainly in children younger than 6 months). Seasonal bronchiolitis epidemics peak between December and March. Each year 150 million new cases of bronchiolitis are reported worldwide, and 2–3% of infants affected require hospitalization [15].

4. Etiology

Bronchiolitis is a viral disease. The most common virus involved in the pathogenesis of bronchiolitis, and one that seems to cause more severe disease, is RSV. Other viruses causing bronchiolitis include RV, human metapneumovirus (hMPV) [16], human bocavirus (hBoV) [17], enterovirus, adenovirus, influenza virus, human coronavirus and parainfluenza virus [18]. Sometimes these viruses manifest as a co-infection [18–23], mainly RSV+hBoV and RSV+RV [18]. The severity of bronchiolitis correlates also with the viral load [24,25]. Bacterial co-infections are rarely described in infants with bronchiolitis, despite the antibiotic prescription [26–29].

5. Risk factors

In most cases bronchiolitis can be safely managed at home by parents adequately educated to recognize the clinical signs indicating deterioration [26]. The risk of severe bronchiolitis is highest in premature infants, aged younger than 3 months, small weight, male sex, low socio-economic conditions, maternal smoking, RSV infection, and underlying comorbidities (cardiovascular diseases, immunodeficiency, chronic respiratory disease, bronchopulmonary dysplasia). Only 2% of these infants, mainly those with risk factors, need admission to the intensive care unit (ICU) [26].

6. Pathophysiology

Viral respiratory infection causes respiratory epithelium necrosis, loss of ciliated epithelial cells, collection of desquamated airway epithelial cells, lymphocyte and neutrophil infiltration within terminal and respiratory bronchioli, and edema around the airway. Widespread cellular debris, inflammatory cells and fibrin could cause airway obstruction and the development of mucus plugs that can partially or totally occlude the bronchioli. A "ball-valve" mechanism induces air trapping in the respiratory tract distal to the partially occluded bronchioli, and atelectasis when the bronchioli are completely occluded [30]. Because the bronchiolar smooth muscles have a minor role in obstruction, bronchodilator therapy achieves a limited benefit in acute bronchiolitis [28]. Atelectasis and air trapping cause an altered ventilation/perfusion (V/Q) ratio [28] clinically resulting in hypoxemia and increased CO_2.

Both anatomical and functional alterations increase airway resistance and decrease dynamic lung compliance. The increased work of breathing causes respiratory distress. Many children reduce their fluid intake, resulting in mild-to-severe dehydration with metabolic acidosis.

7. Diagnosis and symptoms

The diagnosis of acute bronchiolitis should be supported by a careful medical history and a physical examination.

Bronchiolitis diagnosis requires epidemiological data, age younger than 12 months, a previous upper respiratory tract infection with runny nose, cough and rarely fever, and diffuse rales [3,31,32]. Bronchiolitis is a "dynamic disease" characterized by a worsening clinical picture over the first 72 h. Most children have respiratory distress with tachypnea, retractions or nasal flaring, low O_2 saturation, and dehydration. In infants born preterm, the first symptom could be apnea. In more severe cases bronchiolitis could be complicated by metabolic acidosis, inappropriate antidiuretic hormone secretion, and bacterial superinfection.

The current guidelines do not recommended chest X-ray and blood tests [33–35], and infants should undergo these diagnostic procedures only if suggested by their clinical conditions with severe presentation, and worsening clinical condition.

The criteria for hospital admission include respiratory distress, apnea, respiratory rate greater than 70 per minute, oxygen requirement, dehydration, oral liquid intake lower than 50% of the total 24 hour requirement, and low family compliance. Heart rate, respiratory rate, and percutaneous oxygen saturation (SpO_2) should be monitored during the first 24 h after hospitalization [15]. Discharge criteria are decreasing respiratory rate, no evidence of respiratory distress, adequate family education, oxygen saturation remaining stable at >94% in room air, and adequate oral feeding [15].

8. Therapy

In infants with mild bronchiolitis general management includes therapies intended to reduce the work of breathing and restore clinical stability. In these cases the recommended measures are upper airway clearance (nasal suctioning), prone position to improve diaphragmatic function, hydration and oxygenation. Breast feeding with small volume and frequent feeding should be encouraged. If the infant's clinical conditions worsen (respiratory rate over than 70 per minute, oral liquid intake reduced more than 50% over 24 h, and signs of dehydration) then treatment should include IV hydration [15].

Oxygen should be administered via nasal cannulae or a head box. In the UK, supplemental oxygen therapy is usually administered for oxygen saturations of less than 95% in air, whereas the American Academy of Pediatrics recommends its use only if oxygen saturations fall persistently below 90% in previously healthy infants. In the USA, the introduction of routine measurement of oxygen saturations led to a 2.5-fold increase in hospitalizations for bronchiolitis without any significant change in mortality. Hence there is probably little to be gained in administering oxygen to infants with oxygen saturations of greater than 90% in the absence of respiratory distress. Accepting lower oxygen saturation thresholds before administering supplemental oxygen might decrease the rate and length of hospital stay [15].

Oxygen can now be given by heated, humidified, high-flow nasal cannula (HFNC) therapy, a modality suggested to improve tolerability and decrease the need for mechanical ventilation [15]. This device can deliver oxygen heated, humidified and at high flow (up to 8 L/min) with nasal cannulas, and supplies oxygen mixtures containing a known inspired O_2 concentration (from 21% to 100%). HFNC has the advantage that O_2 flow can be set to values greater than the child's inspiratory peak. This adjustment minimizes inhaled ambient air, and maintains a constant FiO_2. Equally important, high flows, humidified and heated oxygen minimize the adverse effects related to inhaling cold and anhydrous gas (mucosal dehydration, reduced ciliary clearance, increased bronchobstructive stimulus). Finally, the continuous positive airway pressure (CPAP) effect, caused by high flow gases, keeps the airway patent in all respiration phases. The efficiency of HFNC depends on cannulae adhesion to the nostrils, and an adequate flow setting according to the patients. In infants with severe respiratory distress, $PO_2 < 60$ mm Hg and $PCO_2 > 50$ mm Hg, or in infants with apnea, CPAP is indicated [15].

Current clinical evidence shows that bronchodilators (albuterol, ipratropium bromide and epinephrine), produce small short-term improvements in clinical scores. A trial with albuterol is justified and recommended only in patients with a family history of atopy. If inhaled albuterol improves the patients' clinical status then this therapy should be continued [15,36].

Among all bronchodilators, epinephrine appears to have the greatest short term benefits. It provides better short-term improvement in the clinical score than placebo or albuterol, particularly in the first 24 h, significantly reducing the risk of admission on day 1, but has no effect on length of hospital stay [37]. These benefits are related to its combined α and β adrenergic properties, and thus potentially greater vasoconstrictor effects and edema reduction [38–40].

Nebulised 3% hypertonic saline is believed to improve airway hydration through osmosis (it causes water to move from the interstitium into the airway thereby decreasing interstitial edema mucosal viscosity), resulting to improvement in mucociliary clearance of airway secretions and effectively reduces the hospitalization stay among infants with non-severe acute viral bronchiolitis. It appears efficacious and

safe if combined with a bronchodilator, and it improves clinical severity score in outpatient and inpatient populations [39,41].

Current evidence demonstrates that neither duration of hospitalization nor severity of symptoms is improved by inhaled or systemic corticosteroids [42,43]. A single study shows that combined therapy with dexamethasone and epinephrine may significantly reduce hospital admission compared with placebo [40]. According to the literature, RV infants who receive oral corticosteroid therapy during the acute severe viral episode, are less likely to have recurrent wheezing over the following year [44].

Scarce evidence supports the use of antibiotics for bronchiolitis [45,46]. Antiviral drugs have no benefits in acute bronchiolitis [47]. Caffeine is rarely used, and only in very young ex-preterm infants who have bronchiolitis with apnea [48].

9. From bronchiolitis to wheezing bronchitis

Mild respiratory symptoms may last about 3 weeks after bronchiolitis and children can be discharged when parents are informed about home care management (airway clearance, position, feeding, and aerosol therapy). Many studies showed that infants with early and severe bronchiolitis needing hospital admission (about 50%), are at significantly higher risk for both recurrent wheeze and subsequent asthma [49] in later years. This correlation can be explained by the combined factors related to viral pathogenic role, host genetic predisposition, and environmental factors. The viral role implicates multiple mechanisms. First, infection might cause direct damage to the respiratory epithelium, in incompletely developed lungs [50]. Equally well known is the crucial role of viral infections in asthma exacerbations by altering the Th1/Th2 response. Viruses can also activate specific molecular pathways that induce the synthesis of many factors that regulate remodeling and alveolar development (vascular endothelial growth factor (VEGF), nitric oxide (NO), transforming growth factor β (TGF), amphiregulin and fibroblast growth factor (FGF)). Viral infection seems also to upregulate neurotrophins, substances that can remodel neuronal connections, thus promoting non-specific bronchial hyperresponsivity [51–53].

Bronchial hyperresponsivity might be lasting and could explain wheezing later in life whether viral infections predispose selected individuals to asthma causing a host Th2 immune response, or whether respiratory viruses only identify infants who are already predisposed to a Th2 response, and to asthma development [54].

Ample evidence now documents cytokine dysregulation [55–59], but the specific biological, therapeutic and prognostic significance in infants with bronchiolitis remains poorly understood. This cytokine imbalance leads to interleukin (IL) overexpression (IL 4, IL 5, and IL 13), and seems to depend not only on host factors (genetic predisposition or immune system immaturity) but also on environmental factors.

The role of environmental factors is highlighted by the "hygiene hypothesis". The increasing incidence of allergic disease depends on vaccination, decrease in infections due to antibiotics use, and changing family models. All these events impair maturation and weaken Th1-mediated host immunity, to viral infections [60]. All these factors join in the "two hit hypothesis" theory: bronchial hyperresponsivity and asthma develop after viral infections only in predisposed children, or in those who have a family history for atopy, and a dysregulated cytokine response (with imbalance towards Th2 pathways) [61]. Evidence in more recent years shows that the various viral infections causing bronchiolitis differ in the risk of wheezing and asthma developing in childhood.

In a prospective study of 206 children less than 12 months of age hospitalized for severe RSV bronchiolitis followed through a 6-year-follow-up, Castro et al. showed that RSV bronchiolitis is a risk factor for persistent wheezing and asthma in the first six years of life, and symptoms generally persist in school age [61]. They also detected increased expression of chemokine CC motif ligand 5 (CCL5), a chemoattractant for inflammatory cell β-chemokine, in the nasal epithelium of children during the episode of bronchiolitis. An increased CCL5 value was highly predictive for the development of asthma in school-age. Its over-expression

during bronchiolitis seems to be genetically determined, and possibly linked to an increased severity of clinical manifestation during RSV acute infection, and persistent wheezing during follow-up.

Hereditary susceptibility to lower respiratory tract infections receives support from Goetghebuer [62], and Janssen [63] who detected the genes related to innate immunity (such as the vitamin D receptor, inducible nitric oxide synthase [NOS2A] and interferon-α5 [IFNA5]) closely associated with development of bronchiolitis.

A study conducted in recent years in a small series of infants with early severe RSV bronchiolitis, showed that RSV infection was an important risk factor for the development of asthma, clinical allergy and sensitization to common allergens also at the age of 18 [65]. Bronchiolitis caused by RSV, parainfluenza virus and influenza virus seems to have a similar long-term prognosis, whereas many studies suggest that children with RV bronchiolitis appear to be at higher risk for the development of persistent wheezing and asthma in adulthood [66–69].

Based on this evidence, our group tested nasal aspirates from 182 infants with bronchiolitis for 14 respiratory viruses, using a panel of real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) or nested PCR assays. The panel identified a virus in only 57.2% of patients. Among these, we identified three groups, according to the viral agent. We observed that infants with RSV bronchiolitis (41.2%) were younger, had been breastfed for a shorter time and had a more severe bronchiolitis with prevalent diffuse air trapping on the chest X-ray. Conversely, infants with hBoV bronchiolitis (12.2%) were the oldest, had been breastfed for longer and had a mild clinical form with patchy infiltrates on the chest X-ray. Conversely, infants with RV bronchiolitis (8.8%) had moderately severe bronchiolitis, and more frequently had a family history for atopy and higher blood eosinophil counts than the other infants. These findings seems to suggest that RV preferentially infects infants who are predisposed to asthma, as others have confirmed [18,70–73].

In a more recent paper, we evaluated "recurrent wheezing" (two or more physician-verified wheezing episodes) during a one-year follow-up, in 262 infants hospitalized for bronchiolitis in the first year of life. We found that the major risk factors for wheezing episodes after acute bronchiolitis are RV infection and a positive heredity for asthma. We also confirmed a higher blood eosinophil count, a lower blood CRP concentration and fewer radiologically-documented lung consolidations in infants with recurrent wheezing than in non-wheezing infants [74]. These results receive support from other studies [75,76]. Particularly the COAST (Childhood Origins of Asthma) study, started in 1998, investigated the interaction between genetic predisposition to the development of atopic diseases, viral infections and environmental factors in a cohort of 289 newborns with a high risk for allergic diseases. They showed that the combination of genetic predisposition (family history for atopy), and RV-induced wheezing before the age of three years was associated with a higher risk of asthma developing at the age of 6 years [75].

Other studies conducted on children with bronchiolitis, divided into RSV and non-RSV etiology, showed that recurrent wheezing develops at substantially higher rates in children hospitalized with bronchiolitis caused by viruses other than RSV [77]. Unfortunately the study by Koponen et al. lacked further details about non-RSV bronchiolitis, but RV might have played an important role [78–84].

In vitro findings seem to confirm that RV preferentially affects the lower airways causing bronchiolitis in atopic children prone to wheeze [85,86]. In a study designed to investigate the balance between type 1 and type 2 immune response to RV, Papadopoulos et al. found that peripheral blood mononuclear cells (PBMCs) incubated with RV from atopic subjects produced interleukin-10 whereas PBMCs from nonatopic subjects produced interferon-γ and interleukin-12. This defective type 1 immune response to RV in predisposed patients with asthma may contribute to the development of acute asthma exacerbation by promoting type 2 inflammation and diminishing viral clearance through deficient type 1 antiviral immune response [84].

10. Conclusion

Bronchiolitis is an old disease, but one that still has few therapeutic strategies. Long-standing evidence underlines the correlation between bronchiolitis and wheezing bronchitis. Although RSV remains the most common pathogen associated with bronchiolitis emerging evidence documents RV as risk factor for the subsequent wheezing bronchitis. The precise mechanism predisposing children to wheezing remains controversial. To answer this question research efforts should now switch from RSV to RV.

Conflict of interest

All authors disclose that they have no financial and personal relationships with other people or organisations that could inappropriately influence their work.

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