Etiology and clinical features of viral bronchiolitis in infancy

Andrew Fretzayas, Maria Moustaki
Athens, Greece

Background: **Bronchiolitis is a common lower respiratory tract infection in infancy. The aim of this review is to present the clinical profile of viral bronchiolitis, the different culprit viruses and the disease severity in relation to the viral etiology.**

Data sources: **Databases including PubMed and Google Scholar were searched for articles about the clinical features of bronchiolitis and its viral etiology. The most relevant articles to the scope of this review were analyzed.**

Results: **Currently there are two main definitions for bronchiolitis which are not identical, the European definition and the American one. The most common viral pathogen that causes bronchiolitis is respiratory syncytial virus which was identified in 1955; now many other viruses have been implicated in the etiology of bronchiolitis such as rhinovirus, adenovirus, metapneumovirus, and bocavirus. Several studies have attempted to investigate the correlation of bronchiolitis severity with the type of detected virus or viruses. However, the results were not consitent.**

Conclusions: **For the time being, the diagnosis of bronchiolitis remains clinical. The isolation of the responsible respiratory pathogens does not seem to confer to the prognosis of the disease severity.**

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Author Affiliations: 3rd Department of Pediatrics, Athens University, School of Medicine, Athens, Greece (Fretzayas A, Moustaki M)

Corresponding Author: Andrew Fretzayas, MD, PhD, 3rd Department of Pediatrics, "Attikon" University Hospital, Athens University, School of Medicine, 1 Rimini str, Haidari, 12462 Athens, Greece (Tel: +302105831299; Fax: +302105832229; Email: afretz@med.uoa.gr)

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Introduction

Viral bronchiolitis is a common lower respiratory tract infection in infancy. Although the term "bronchiolitis" implies the inflammation of bronchioles, the diagnosis of the disease is clinical and there is still debate regarding the most appropriate definition for the disease. Recent advances in laboratory diagnostic methods confer to the identification of different viruses as etiologic pathogens of bronchiolitis, although respiratory syncytial virus (RSV) remains the main culprit The aim of this review was to present the clinical picture of bronchiolitis as a whole entity irrespective of the virology as well as in relation to the particular viral parthogens that are incriminated as etiological factors.

Databases including PubMed and Google Scholar were searched for articles about the clinical features of bronchiolitis and its viral etiology. We searched the databases with the following key words: viral bronchiolitis, clinical features, definition, epidemiology, etiology, guidelines, severity score, adenovirus, bocavirus, coronavirus, influenza, metapneumovirus, parainfluenza, respiratory synchytial virus, and rhinovirus. Manual searching through cross-references was also performed to identify additional relevant studies. There was no chronological restriction. The most relevant articles to the scope of this review were analyzed.

Definition of viral bronchiolitis

The diagnosis of bronchiolitis is based on the history and the clinical findings. In 1973 it was shown by Court[1] that there was not sufficient agreement and reproducibility for the definitions that were used for the classification of acute respiratory illness including bronchiolitis in childhood by the clinicians even in the same country. Based on the clinical symptoms and signs he defined acute bronchiolitis as follows: "Illness mainly affecting infants, especially in the first 6 months of life. Rapid respiration, dyspnoea, wheezing, chest recession, cough, rhonchi and rales are very frequent. Visible distention of the chest and increased pulmonary translucency on the chest radiograph are frequent and of high diagnostic significance. Upper respiratory features, especially nasal discharge and a red pharynx are frequent. Fever is very frequent but high fever

uncommon". As it is evident in this definition there was not a specific upper limit for the age, the wheezing episode was not necessarily the first one in the infant's life and radiographic findings were also included in the definition. Ten years later in 1983, McConnochie[2] summarized the clinical criteria for the case definition of bronchiolitis. Bronchiolitis was considered as the first episode of wheezing of acute onset in children younger than 24 months of age with preceding signs of viral respiratory illness such as coryza, otitis or fever. Respiratory distress symptoms, pneumonia and atopy signs may or may not be present. According to this definition wheezing was a sufficient auscultatory finding and crackles were not mentioned in this classification as a necessary finding on auscultation.

In 2006 American Academy of Pediatrics (AAP) published a clinical practice guideline for bronchiolitis,[3] that was updated in 2014[4] according to which bronchiolitis is "a constellation of signs and symptoms including children younger than 2 years including a viral upper respiratory tract prodrome followed by increased respiratory effort and wheezing". This definition is in accordance with the abovementioned of McConnochie[2] regarding the upper limit of age and the presence of wheezing as a constitutional finding for the diagnosis of bronchiolitis. According to AAP, rales are among the possible signs of bronhiolitis on auscultation.[3] However, in Europe[5,6] and Australia,[7,8] till recently it was considered that the hallmark for the diagnosis was fine crackles on auscultation and that wheezing is not a prerequisite for the diagnosis. The most recent guidelines from the United Kingdom[9,10] state that the presence of fine inspiratory crackles and/or high pitched expiratory wheeze on auscultation lead to a diagnosis of bronchiolitis for children under two years of age.

The discrepancy of these definitions regarding the hallmark auscultatory finding for the diagnosis of bronchiolitis has been highlighted by other reviews,[11-13] and it had as a result different definitions to be used by the investigators. Some researchers sometimes limit their population to the age of 12 months, in an attempt to minimize the possibility to include in their studies children with early onset virus induced wheezing instead of bronchiolitis. However, these different approaches do not facilitate the comparison of the results from different studies as well as the generability of their results.

Etiology

RSV is the most common viral agent that causes bronchiolitis in infancy. RSV was first identified in 1955 as causing chimpanzee coryza[14] and one year later it was recovered from infants with respiratory illness in the USA.[15] Since then, with the evolution of different laboratory techniques, RSV was found to be a culprit viral agent for the majority of bronchiolitis cases in infancy.[16] Epidemiological studies revealed that the average annual rate of RSV-associated hospitalizations was 32 per 1000 infants in the USA[17] for the period 1997-2006 indicating the high burden of morbidity due to RSV.

During the same period (1953), adenovirus was also first isolated from human adenoids.[18] It affects respiratory system as well as other organs. In different series of children with upper and/or lower respiratory illness due to adenovirus, 5%-24% had bronchiolitis.[19-21] The prevalence of adenovirus infection in children with bronchiolitis ranges from 1% to 9%.[22-25]

Rhinovirus which is known as the common cold virus, also first isolated in 1956[25] was found to be implicated as a viral pathogen in bronchiolitis cases in 8%-29% of infants with bronchiolitis.[22,26-32] It is of interest that children with a history of bronchiolitis caused by rhinovirus are at increased risk for developing recurrent wheezing later[33,34] without its precise role having being clarified. However, it is beyond the scope of this paper to analyze further this issue.

Influenza virus was first obtained and identified from patients with influenza disease in 1933. This virus can also cause bronchiolitis, less frequently however, as it was identified as the primary pathogen or as a co-pathogen in 0.5%-5% of children with bronchiolitis in different cohorts.[24,26,29,30,32]

Parainflueza virus was first isolated in patients with respiratory disease in 1956. In different bronchiolitis cohorts it was identified as the causative agent either primary or as a co-pathogen in 2.6%-6% of children.[24,28,30,32]

The availability of modern molecular techniques and the identification of new viruses such as human metapneymovirus (hMPV) and human bocavirus (HBoV) made possible the characterization of the viral culprit agent in about one third of bronchiolitis which used to be simply considered in the past as non RSV bronchiolitis. hMPV was characterized for the first time in 2001 in the Netherlands.[35] However, serological studies confirmed the circulation of the virus in humans for at least since 1950s.[35] The frequency of its detection in infants with bronchiolitis ranged from 1.7% to 16.8%.[27-29,32,36-38]

HBoV was first described by Allander et al[39] in 2005 in children with respiratory tract infection. Since then, its prevalence in children with respiratory infections worldwide was corroborated by many studies.[28,29,40] However, high rates of co-infections have been described that question to some extent the role of HBoV alone as a causative agent of lower respiratory tract infections.[37] It was isolated in 0.6%-27% of infants[22,24,26,28-30,38,41,42] with bronchiolitis, with most studies identifying it in about 10% of children.[22,26,29]

Recently, human coronaviruses (HCoV) NL63 and HKU1 have been linked to bronchiolitis. HCoV NL63 was first isolated from a child with bronchiolitis and conjunctivitis in 2004.[43] And the presence of this virus worldwide in individuals with respiratory illness was confirmed by different investigators.[44-46] It was isolated from children with bronchiolitis from several patient cohorts,[26,38,45,46] but in low percentages either as the primary pathogen or as a co-pathogen. HCoV HKU1 was first detected in 2005 in a adult with pneumonia[47] and it was also isolated from children with bronchiolitis.[48,49]

It is of interest to mention that in infants with bronchiolitis not fully vaccinated for pertussis, bordetella pertussis was isolated along with RSV or other viruses in 8%-16% of infants, indicating the need to consider the possibility of pertussis in young infants with clinical signs of bronchiolitis and even positive virology tests for RSV or other respiratory viruses.[50,51] Furthermore, atypical bacteria such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Chlamydophila trachomatis* were isolated in infants with viral bronchiolitis in a cohort from Thailand[52] indicating that the identification of a virus in infants with viral bronchiolitis does not necessarily precludes the possibility of bacterial co-infection at least with atypical bacteria.

Clinical features (symptoms and signs)

Viral prodrome symptoms of upper respiratory tract such as nasal obstruction and/or coryza and cough usually precede bronchiolitis findings, lasting 1-3 days.[3,4,10] The main symptoms/signs of bronchiolitis are wheezing and/or crackles on auscultation and increased respiratory effort characterized by tachypnoea and/or chest wall retractions and/or nasal flaring. It is important for the clinicians to determine the clinical severity of the disease so that the affected infant is given the appropriate care as outpatient or inpatient. Although the diagnosis of the disease and the assessment of the disease severity is clinical, there are no universally used validated clinical scores of disease severity.

According to the AAP definition[3,4] wheezing is a prerequisite for the characterization of bronchiolitis, a finding that is not considered obligatory according to the National Institute for Health and Care Excellence (NICE) guidelines.[10] Wheezing may be present at the end or throughout expiration or it may be also present during inspiration. However, hypoventilation may occur due to severe obstruction when wheezing is not audible. Crackles may be present over one or more lung fields and their presence was associated with the severity of the disease using as a surrogate for the disease severity the requirements for oxygen;[53] in this study,[53] wheezing was considered as a prerequisite for the diagnosis of bronchiolitis, signs of respiratory distress such as tachypnoea and chest wall retractions were not related to the disease severity. However, according to NICE guidelines,[10] respiratory rate over 60 breaths/minute is considered as an indicator for referral to the hospital. Marlais et al[54] suggested that that respiratory rate as well as heart rate were among the clinical predictors of admission in infants with bronchiolitis.

Respiratory effort should be also evaluated assessing the degree of chest wall retractions and nasal flaring. According to the NICE guidelines[10] marked chest wall retractions is an indicator for admission to the hospital.

A rather uncommon but alarming symptom of bronchiolitis, which is an indicator for admission to the hospital, is apnoea. Recent prospective studies estimated that the rate of apnea among the hospitalized infants with bronchiolitis is about 5%.[30,55,56] There is not an excess risk for apnea for any type of isolated viral pathogen, whereas prematurity and younger corrected age seem to confer to an excess risk.[56] A systematic review[57] of apnea in hospitalized infants with RSV bronchiolitis found the rates ranged widely from 1.2% to 23.8%; but the majority of the studies were retrospective and included infants with serious underlying conditions. Infants with bronchiolitis may also have hypoxemia and SaO_2 is considered an indicator of disease severity.[10,54,58,59] An SaO_2 lower than 92% was considered an indication for admission to the hospital.[10]

The general condition of the affected infant should be also evaluated. The behavior may be normal indicating mild disease, or the infant may be irritable or lethargic in cases of moderate or severe disease. If the general appearance is toxic, the infant should be carefully evaluated for other causes that could possibly explain the situation. It should be noted that infants with bronchiolitis may have fever or history of fever although very high temperature is rather uncommon. In a series of 90 infants with bronchiolitis, fever was identified in about 1/3 of them, however temperature >40ºC was recorded in only 2/90 children of the study.[60] The investigators[60] found that infants with fever had a more severe clinical course compared to the afebrile counterparts, a finding that was not corroborated by other investigators.[30,54] It was also shown that the risk of sepsis was extremely low even in febrile infants with bronchiolitis younger that 3 months of age, whereas the risk of urinary tract infection was low but not negligible.[61,62] The type of isolated virus was not associated with the presence and duration of fever, as it was shown by studies that compared the clinical characteristics of bronchiolitis in relation to the detected viruses.[26,30,38,52]

Another indicator of infant's general condition is its ability for feeding and the degree of hydration. Poor oral

fluid intake, inability or indifference for eating due to breathlessness are indicators of moderate or severe disease and the affected infant should be referred to the hospital.[10] The clinicians should make the diagnosis of bronchiolitis on the basis of the history and physical examinations and evaluate the clinical severity of the disease in order to decide outpatient or inpatient care for the patient.

Although there are not universally used validated clinical scores of disease severity, different scores have been used for the assessment of bronchiolitis severity in clinical studies. In 1972, Wood et al[63] introduced a clinical scoring system for the diagnosis of respiratory failure that has been also used for bronchiolitis since then. The score includes the following parameters: arterial oxygen tension or cyanosis, type of inspiratory breath sounds, usage of accessory muscles, presence of expiratory wheezing and level of cerebral function. In 1983, Tal et al[64] used a score in order to evaluate the clinical changes in bronchiolitis severity in relation to the type of treatment. This score has been also used in other clinical studies since then and it includes the following parameters: respiratory rate, accessory muscle use, degree of wheezing and cyanosis. In 1987 the respiratory distress assessment instrument (RDAI) was first used by Lowell et al[65] to evaluate the response of bronchiolitis to treatment. RDAI includes the following items: presence of wheezing on expiration, inspiration, location of wheezing, presence of retractions (supraclavicular, intercostals, subcostal). In 1992, Wang et al[66] used another score (respiratory rate, retractions, wheezing, general appearance) for the evaluation of lower respiratory infection severity in infants. In 2004, Liu et al[67] evaluate another clinical score with the following components: respiratory rate, presence and location of retractions, presence and degree of dyspnea, presence and type of wheezing. There are several limitations for the usage of severity scores in everyday practice but it is beyond the scope of this paper to analyze further this issue.

Severity of bronchiolitis and types of viral pathogens

Many studies attempted to investigate the relation of the disease severity with the number and the type of detected viruses, although only a few of these studies were initially designed to answer this question. Their results are controversial. This would not be unexpected as the studies differ regarding the eligibility criteria of patients with bronchiolitis and the indicators of the disease severity.

Although viruses other than RSV have been implicated as etiologic agents of viral bronchiolitis, it is not clarified whether the type of carried virus confers to the disease severity. When wheezing alone was not considered sufficient for the characterization of bronchiolitis, the clinical severity score on admission was higher among infants with RSV bronchiolitis compared to those with rhinovirus or HBoV bronchiolitis.[29] Bamberger et al[22] also showed that patients infected solely with rhinovirus had a lower severity score on admission as well as during hospitalization compared to RSV bronchiolitis. Additionally, they found that only RSV bronchiolitis patients had a significantly higher severity scores on admission and during hospitalization compared to any type of non-RSV bronchiolitis. This observation is of interest as bronchiolitis is a dynamic situation and disease severity on admission can not necessarily predict the severity during hospitalization. When the length of hospitalization was used as a surrogate for the disease severity it was also found that rhinovirus only or rhinovirus plus any other non-RSV pathogen had a significantly shorter length of stay at the hospital.[32] Similarly, other researchers[27,28] found that RSV bronchiolitis was associated with a longer length of hospital stay, whereas rhinovirus as well as hMPV bronchiolitis with a shorter one.[26] However, when admission to pediatric intensive care unit (PICU) was used as a surrogate for bronchiolitis severity Richard et al[23] did not find any difference in RSV or rhinovirus prevalence among infants hospitalized either in the short term unit or in the PICU. In contrast to these observations, it was also shown that rhinovirus bronchiolitis indicated an excess risk for having a significantly higher clinical severity score on admission.[30,31] It is obvious that all these findings are not necessarily comparable as different indicators of severity were used by the investigators as well as different bronchiolitis definitions with the main difference in the inclusion criteria the age up to 12 or up to 24 months, sufficiency of wheezing alone or not as a hallmark for bronchiolitis.

As co-infection with two or even more than two viruses was found in a substantial proportion of children with viral bronchiolitis in different series, researchers studied the possible impact, if any, of co-infection on disease severity. Using as a surrogate for disease severity the need of admission to PICU, Richard et al[23] found that infants with viral co-infection were about three times more likely to be admitted to PICU even after adjusting for other factors that in univariate analyses increased the likelihood of admission to PICU. Similarly, another research group[68] also showed that children with dual infection with hMPV and RSV have a ten-fold increased relative risk of admission to PICU for mechanical ventilation. It should be noted, however, that in this study the term bronchiolitis was restricted to children younger than 2 years of age

with bilateral inspiratory crackles on auscultation. In the ward settings it was shown[32] that longer stay at the hospital was more likely among children with RSV/rhinovirus co-infection, whereas children with rhinovirus in combination with other than RSV viruses had a significantly shorter stay at the hospital. Therefore, it seems that it is not only the number of the viruses but also their type that confers or not to the severity of the bronchiolitis course. These findings were not corroborated by Marguet et al[27] who found that RSV infants had longer duration of hospitalization even in comparison with RSV/rhinovirus infants with bronchiolitis. As these results do not point to the same direction it can be speculated that in some cases of co-infections there may be a cumulative pathogenic effect but this is not always the case as in some infants co-infection may be a result of successive or concomitant infections whereas some infants may be simply carriers of one or more of the co-pathogens.

Another issue that was raised in the literature is whether viral load is related to the disease severity. A few studies were designed to address this issue. Scagnolari et al[69] indicated that there was a correlation of RSV viral load with duration of hospitalization in children with RSV bronchiolitis as well as with the clinical score severity index. In this study, the term "bronchiolitis" was restricted to children with diffuse crackles on auscultation whereas infants with wheezing alone were excluded. However, similar results were found by other investigators, relating RSV load with disease severity upon presentation at the emergency department[70] or with the need for mechanical ventilation.[71] Nevertheless, there are also results that support the view that viral load does not predict the severity of the disease either on admission or during hospitalization.[72] However, the population of the latter study included a significant proportion of infants with serious underlying diseases. A positive correlation of disease severity score with RSV load was also found in non-hospitalized infants with bronchiolitis[73] a finding that was not corroborated in the rhinovirus bronchiolitis group.

It seems therefore that heterogeneity of the population of different bronchiolitis cohorts as well as heterogeneity of the parameters that depict the disease severity among the studies do not allow the extraction of reliable conclusions regarding the correlation of the type of the virus or the viral load with the severity of viral bronchiolitis.

Management of bronchiolitis

Although there is controversy regarding the management of bronchiolitis there are certain guidelines of AAP (2014)[4] and NICE (2015)[10] that address this issue thoroughly. Management of bronchiolitis is not within the scope of this paper, however it should be mentioned that there are no official guidelines that correlate the management of bronchiolitis with the type of the viral pathogen. The type of management depends on the disease severity but not on the disease viral etiology, at least till now.

Conclusions

Many viruses are implicated in the etiology of viral bronchiolitis in infancy. However, it is not clear whether and to what extent different viruses confer to the degree of the disease severity or to the disease phenotype. The identification of the carried viruses in infants with bronchiolitis is not therefore necessary in the every day clinical practice. However, for research purposes it is important, using a universal definition for bronchiolitis and introducing a standardized severity score to clarify further whether the type of the culprit viruses confer to the bronchiolitis prognosis.

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