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To What Extent does a History of Viral Bronchiolitis Predispose a Patient to the Development of Other Illnesses?

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Abstract

Objectives: Viral Bronchiolitis is a seasonal respiratory infection predominant in children less than 2 years, commonly caused by the Respiratory Syncytial Virus (RSV). Typical symptoms of this infection include fever, cough, rhinorrhoea and wheezing. Most cases resolve with supportive measures however, there have been investigations on the post- infectious sequalae of this disease. This literature review aims to investigate what post- infectious sequalae have been reported in literature and how often are they present in patients diagnosed with viral bronchiolitis.

Methods: A literature review format was used for this paper with articles being collected from databases including PubMed, Google Scholar and the Cochrane Library. Free full text articles from 2010 onwards were acquired to obtain a wider range of articles and case reports to be accessed.

Discussion: Post-infectious sequelae can be divided into pulmonary and extrapulmonary manifestations. According to one study, 48% of the patients diagnosed with bronchiolitis presented with asthma, the most common pulmonary manifestation of this disease. Other, pulmonary manifestations included post-infectious bronchiolitis obliterans, spontaneous pneumopericardium, pneumorrachis and pneumomediastinum. Extrapulmonary manifestations included cardiac arrhythmias, apnea, seizures, hyponatremia and hepatitis.

Conclusion: Viral bronchiolitis can predispose a patient to developing both pulmonary and extrapulmonary complications. Pre-existing cardiovascular conditions can increase the predisposition of this infection and result in complications afterwards. Larger case control studies would be recommended to assess the statistical significance and the odds of developing post-infectious sequelae.

Keywords: Bronchiolitis • Pediatrics • Extrapulmonary manifestations • Reactive airway disease • Cardiological manifestations • Neurological manifestations • Gastrointestinal manifestations

Introduction

Acute viral bronchiolitis is considered one of the most common respiratory illnesses affecting infants and young children worldwide, with a peak in incidence among children during the first 2 years of life. It is considered a seasonal infection, with a usual peak in disease incidence twice per year during the months of January and February along with October and November. It is estimated that around 3.5 million children are admitted to hospitals every year due to bronchiolitis and it accounts for roughly 22% of all acute lower respiratory tract infections among children [1-7]. Fortunately, over the past 2 decades, the methods of diagnosing and treating bronchiolitis improved significantly, ultimately leading to a significant decline in the incidence of hospitalization among children due to bronchiolitis from the year 2000 up until 2016 [8].

Bronchiolitis is defined as an extensive inflammation and swelling of the bronchial tubes and their surrounding tissue. The most common cause of bronchiolitis is an infection with the Respiratory Syncytial Virus (RSV) however other viruses that may contribute include human bocavirus, rhinovirus and human metapneumovirus, followed by parainfluenza virus, adenovirus, coronavirus, and influenza virus [1]. There is evidence in existing literature that co-infection with 2 different types of viruses at the same time can also occur.

Respiratory syncytial virus, in particular, binds to respiratory epithelial cells in order to replicate as part of its pathogenesis, ultimately leading to necrosis of airway epithelial cells. The resulting edema from the inflammation and the increased mucus production within the bronchioles leads to obstruction and ultimately the production of symptoms such as cough and wheezing [1]. Viral bronchiolitis has a complex risk factor profile which includes prematurity, parental smoking, possession of atopic characteristics and a positive family history of allergies. Comorbidities such as gastro-esophageal reflux disease, cardiac abnormalities, and chronic lung diseases were also associated with bronchiolitis in children [8].

Viral Bronchiolitis is a clinical diagnosis based on history and physical examination. The American Academy of Pediatrics, in 2014, had established guidelines on diagnosis and management with clinical recommendations for diagnosis and its relative strength with regards to its related evidence, which is followed by the majority of practitioners, especially in North America [2]. Specific signs and symptoms include fever, rhinorrhea, cough, wheezing, rhonchi, dyspnea, tachypnoea, and respiratory distress in severe cases. Increased pulmonary translucency on chest imaging is also highly diagnostic. Oxygen saturation is an essential factor to aid the decision of whether hospital admission is necessary or not. The general condition of the affected child should also be considered, as their behavior may change to being easily irritable or lethargic in cases of severe disease, along with poor oral intake and signs of dehydration [1,5,6]. Figure 1 shows the key recommendations for practice [3].

Management of RSV-induced bronchiolitis remains challenging. The current recommendations and guidelines for management of bronchiolitis

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SORT: KEY RECOMMENDATIONS FOR PRACTICE

CLINICAL RECOMMENDATION	EVIDENCE RATING	REFERENCES
Routine viral testing and chest imaging are not recommended for patients with presumed RSV bronchiolitis.	B	4, 15, 16
Bronchodilators, systemic or inhaled corticosteroids, and epinephrine should not be administered to infants and children with bronchiolitis.	A	4, 24, 28, 30
Antibiotics should not be administered to children with RSV bronchiolitis unless a bacterial infection is confirmed or suspected.	B	4, 37
Palivizumab (Synagis) should be given in the first year of life to infants born before 29 weeks' gestation or to infants born before 32 weeks' gestation who have chronic lung disease.	B	42

RSV = respiratory syncytial virus.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

Figure 1. American academy of paediatrics guidelines on diagnosis and treatment of viral bronchiolitis.

in children declare that the hallmark of therapy is supportive therapy, which includes hydration, suctioning, and chest physiotherapy to help expel mucus secretions. It is important to recognize the sequalae and potential complications after being diagnosed with bronchiolitis as it has been known to increase the likelihood of developing a reactive airway disease. This study aims to only investigate the likelihood of developing a respiratory complication as a sequelae of viral bronchiolitis but also to determine which other systems are involved and their respective manifestations.

Methods

A literature review format was adopted for the purpose of this research question to assess the pre-existing literature. The search strategy aimed at retrieving studies focusing on the incidence, epidemiology, risk factors, pathogenesis, clinical burden, and the routine clinical practice in the prevention and management of RSV-related bronchiolitis in children worldwide, along with its association with pulmonary and cardiac complications. Only articles published since the year 2010 until date were considered in this article. Data were extracted and confirmed from multiple databases including PubMed, Cochrane library, and Google Scholar. Thirty studies were included. The reference lists of the selected articles were searched for additional studies.

A combination of controlled key words were used including: "Bronchiolitis", "Respiratory syncytial virus", "RSV", "Pathophysiology", "Incidence", "Etiology", "Management", and "RSV-related pulmonary and cardiac complications". A comprehensive data collection sheet was designed to extract data from the selected articles. Relevant data were extracted and confirmed by multiple investigators. The method of communication used between the authors was through multiple virtual meetings using the Zoom application to plan, discuss, and analyze the papers, and collect relevant data for writing this article.

Impact of the COVID-19 Pandemic on Bronchiolitis

The COVID-19 pandemic, which originated in China in December 2019, was declared a pandemic in March 2020 by the World Health Organization (WHO) [9]. In a study conducted by Brusselen V, et al. [9] in 2021, there was a significant reduction in cases of bronchiolitis. Between 98% to 99% reduction in bronchiolitis cases were noted in Australia and New Zealand whereas in Brazil, a 70% reduction in bronchiolitis cases were noted.

Another study conducted by Rius-Peris JM, et al. [10] in 2021 also recorded a significant reduction in bronchiolitis cases and noted that there was a substantial reduction in the utilization of pediatric healthcare resources, specifically with pediatric viral communicable diseases. This may be due to the overshadowing of the COVID-19 pandemic itself. With the worldwide implementation of interventions such as facemasks, regular hand-washing and social distancing, Both Brusselen V, et al. [9] and Rius-Peris JM, et al. [10] suggested that this may have reduced the likelihood of transmission of viral upper airway and lower airway tract infections. This also leads to a point of view that continuing the interventions first established during the COVID- 19 pandemic can further reduce the healthcare burden with regards to infections such as bronchiolitis .

Also, within this context, Abrams et al. argues that non-epidemic coronaviruses are commonly found in children, exhibiting exacerbation of asthma including bronchial hyperreactivity and eosinophilic inflammation which can also play a symbiotic role in the development of bronchiolitis. However, during the COVID-19 pandemic we see a paradoxical decrease in asthma exacerbations, which can be attributed to greater attention being paid in relation to hygiene measures in this population. Obviously, the impact of the generalized lockdowns must be considered as a confounding factor [11].

Further Development of Other Respiratory Illnesses

There are fundamental differences seen between the anatomy and physiology of the neonate, pediatric, and adult airways. The pediatric airway is smaller in diameter and shorter in length than an adult, size being the obvious key disparity. This size difference has a greater impact on the mechanism of flow in the neonate/pediatric airway. Turbulent flow increases resistance to the fifth power as the radius is reduced which further exacerbates the airways. Thus, the effect of a minor airway narrowing in the neonate as a result of a bronchoconstriction or respiratory infection has a disproportional impact on airflow resistance leading to a more severe airway obstruction [12].

Bronchiolitis is a risk factor for chronic respiratory morbidity, particularly recurrent wheezing and asthma effecting approximately one-third of children with RSV infections [13]. Other risk factors that induce wheezing include

prematurity; heart, lung, and immune system abnormalities; and being 2-6 months of age during the winter RSV season. There is definitive evidence that RSV-induced bronchiolitis occurring in early life, damage airways promoting airway obstruction and recurrent wheezing which influence respiratory health in infants for years [14,15].

A controlled study done in Borås, Sweden, Sigurs et al. found a 30% cumulative incidence of asthma among 7-year-old children who had been hospitalized in infancy with severe RSV bronchiolitis, compared to 3% in the control group. In addition, 23% of physician-diagnosed asthma was found in post-RSV children compared to 2% of controls. Showing an increased prevalence of recurrent wheeze/asthma post RSV infection compared to controls [16].

About 48% of infants who are hospitalized for severe RSV-associated bronchiolitis go on to develop asthma during their childhood [17,18]. A retrospective cohort study including more than 95,000 infants showed that infants born three months before the RSV season had the greatest risk for hospitalization due to lower respiratory tract illness and subsequent asthma development between ages four and five years [14].

Along with RSV, it is important to consider the relationship between rhinovirus-induced bronchiolitis and the development of asthma. Bergroth E, et al. [19] conducted a study that examined this association and found that between 40%-50% of children under the age of 2 that were diagnosed with rhinovirus-induced bronchiolitis had to use asthma medication at an earlier age which continued even 4 years after the initial infection. It was also found that the highest risk of development of asthma was found in those infected with rhinovirus (type C) bronchiolitis, presented with a fever and a history of atopic dermatitis. Although it was suggested that RSV induces a greater amount of damage to respiratory epithelial in comparison to rhinovirus, the degree of damage to the epithelium prior to infection can correlate directly with the severity of the rhinovirus infection, especially when atopy and decreased levels of interferon responses are present [19]. It has also been established that rhinovirus can also decrease interferon responses and increase cytokine levels which can further exacerbate wheezing and obstruction in the airway.

In 2009, a study conducted by Carroll et al analyzed administrative data and reported a dose- response relationship between increasing severity of bronchiolitis (i.e., outpatient, emergency department, and hospitalization) and higher odds of developing childhood asthma. Infant RSV infection precedes asthma and is associated with severity-dependent odds of asthma development [20,21]. It is also imperative to note that the age at which a child develops RSV-induced bronchiolitis as well as their baseline pulmonary function correlates with how early they may develop asthma and other respiratory illnesses [19].

Many studies have suggested theories of genetic predispositions to RSV infections and its effect on developing asthma later in life. Polymorphic changes in several genes, mainly related to immune regulation, have been associated with increased risk for both RSV-induced bronchiolitis and asthma. The resulting effects of the mutations include imbalances between type 1 and 2 immune responses, declining T-cell functions in CD4 and CD8 T cells, reduced expressions of interferon-gamma factors in PBMCs (peripheral blood mononuclear cells) and airway cells. This can potentially result in airway inflammation, edema and obstruction which demonstrate a positive correlation with disease severity and development of long-term asthma [14,22]. Interestingly, the role of interferon has been shown to contribute towards the development of asthma. Low levels of interferon at birth were linked to an increased risk of developing asthma and wheezing later in life however, increased levels of interferon were observed during active asthma exacerbations. There has been contradictory evidence with regards to the relationship between interferons and viral bronchiolitis. Although some studies have described as both being independent variables, some evidence suggests that both RSV and rhinovirus-induced bronchiolitis increase levels of type 3 interferon subtypes which can correlate with the severity of the disease.

Another pulmonary complication of bronchiolitis that was seen in children was noted to be PIBO (Post-infectious Bronchiolitis Obliterans). Bronchiolitis obliterans is described as an irreversible obstructive lung disease that is characterized by subepithelial inflammation and fibrotic narrowing of the bronchioles [23] and it leads to damage and inflammation of the bronchiolar epithelial and subepithelial cells [16]. "The cellular infiltrate of the lung was mainly composed of CD3+ T cells with a predominance of the CD8+ T-cell subtype" in children with PIBO [24]. A prospective study conducted by Li et al at the first hospital of Jilin University in Northern China looked at a population of forty-two patients below the age of 14 years old and were diagnosed in the hospital with PIBO [16]. The criteria used for confirming PIBO in these patients was:

1. Acute respiratory tract infection in an otherwise healthy child
2. High-resolution CT scan findings such as "mosaic ground-glass pattern, bronchiectasis or pulmonary atelectasis."
3. Pulmonary function tests that show a persistent obstruction pattern
4. Exclusion of other chronic lung diseases

Follow-up visits 6 months later were conducted after a confirmed diagnosis of PIBO during which pulmonary function tests were conducted [16]. The study confirmed that the most common pathogen associated with PIBO was adenovirus, followed by Mycoplasma Pneumoniae and measles. The prevalence of PIBO was seen to be more common in boys than in girls. The definitive treatment for PIBO is currently unknown; however, a suggested therapeutic strategy involved oral azithromycin and glucocorticoids paired with supportive care and mechanical ventilation in cases with severe breathing difficulties. The study's results showed "that mechanical ventilation was needed in 40.5% of children in the acute phase and 7.1% of children during follow-up" [16], however the benefits of azithromycin and corticosteroids were not replicated in subsequent studies [16].

Spontaneous pneumopericardium, pneumorrachis and pneumomediastinum were rare complications of viral bronchiolitis reported in a case report by Fantacci C, et al in 2017 [25]. One of the cases examined a 3-year-old boy presenting with fever and cough of one-day duration, which clinically deteriorated and was admitted to the pediatric intensive care unit. A chest CT scan was done, which confirmed the presence of both pneumomediastinum and pneumorrachis. A diagnosis of RSV infection was confirmed for this patient and he was on non-invasive ventilation in addiction to this the patient was given intravenous fluids, antipyretics, intravenous antibiotics, and cough sedatives. Another case involved a 2-year-old boy who presented with non-productive cough and dyspnea. A chest X-ray was done for this patient who confirmed the presence of extensive subcutaneous emphysema involving his neck. The patient was admitted to the pediatric intensive care unit and received non-invasive ventilation, intravenous antibiotics and fluids and a cough sedative. The presence of RSV was confirmed by a nasopharyngeal swab and the presence of pneumopericardium and pneumomediastinum were confirmed on a chest x-ray. As per the Fantacci C, et al. [25] study, it is uncommon to see spontaneous PM, PP, or PR as a complication of RSV infection; however, they stated that it might represent "a diagnostic and therapeutic challenge for pediatricians" [25]. Patients must be closely monitored and given the appropriate therapy as it was noted that with viral bronchiolitis whether due to Influenza A virus or RSV virus the patient presents "with a more violent cough which would explain the high incidence of rupture of the respiratory tract" in an otherwise previously healthy child.

Extrapulmonary Manifestations and Sequelae of Bronchiolitis

Sequelae of a common respiratory illness such as bronchiolitis tend to typically present as pulmonary manifestations as described in the previous section. However, there are studies that have investigated the extrapulmonary manifestations as a consequence of bronchiolitis due to RSV, of which one of the most frequently described manifestations are that of the cardiovascular system.

Cardiovascular System

A study conducted by Horter T, et al. [26] in 2017 investigated the degree of cardiac morbidity in children that required hospitalization and intensive care as

a result of an RSV infection. It is plausible to note that symptoms of respiratory distress as well as cardiac malfunction can present similarly and may be difficult to distinguish. Existing literature has noted that children who have been diagnosed with an RSV infection have been known to have increased s-troponin levels with the etiology possibly being linked to increased pulmonary circulation pressure resulting in increased work of the right ventricle. Horter T, et al. [26] investigated the cardiac function by measuring the s-troponin levels and via echocardiography in patients admitted with an RSV infection. With regards to the left ventricular function, an increase cardiac output was noted and a positive correlation between the heart rate and cardiac output was seen. Right ventricular output was noted to be increased than the reference range in this cohort of patients as well. When assessing capillary refill time, a prolonged time was noted in those requiring supplementary oxygen.

Interestingly, Ivey KS, et al [27] mentioned a study that showed 54.5% (of 22 patients admitted due to RSV) displayed elevated levels of troponin, findings similar to the study by Horter T, et al. [26] which showed 60% (out of 26 patients due to admitted due to RSV). When examining the pathophysiology of how RSV may cause cardiovascular illnesses, a study from Japan was quoted as finding raised levels of interleukin-6 in patients with RSV that corresponded to an increased risk of sudden cardiac death. Another rare sequela of viral bronchiolitis from RSV includes myocarditis.

This study warrants the use of cardiac biomarkers and echocardiography as part of a thorough cardiological evaluation in patients with viral bronchiolitis. However, it is pertinent to assess the need for this in all patients as Horter T, et al. [26] concluded only a small percentage of patients diagnosed with viral bronchiolitis presented with cardiological sequalae. The potential pathophysiology behind this was suggested to be an autoregulation mechanism. To further assess cardiological implications from viral bronchiolitis, it would be imperative to conduct a large case control study to assess the odds of developing a cardiac pathology.

In a systematic review conducted by Eisenhut M [28] in 2006 cardiac manifestations such as atrial flutter, second-degree heart blocks, ventricular arrhythmias and cardiac tamponade have been described in patients who had viral bronchiolitis earlier. Another study demonstrated patients exhibiting heart blocks with concurrent positive RSV infections.

Sinoatrial blocks, were identified in 26/34 RSV-positive patients (76.5%) and 1/35 RSV- negative patients (2.9%) ($p < 0.0001$) showing a significant relationship between RSV infection and development of heart blocks. Frequency of blocks were seen in the children with an RSV load of ≥100,000 copies/mL than in those with a lower viral load ($p < 0.0001$) [29]. Results of this study showed RSV induced bronchiolitis to be frequently associated with the development of sinoatrial blocks, an increase in absolute heart rate, and an increase in the low frequency component of heart rate variability (possible marker for cardiac damage); findings which were not seen in RSV negative patients or bronchiolitis caused by a different infectious agent. However, these changes are transient and reversible once the respiratory disease clears.

When considering the cardiovascular manifestations in pediatric patients, one of the common risk factors for lower respiratory tract infections and their severity has been noted to be pre-existing cardiopulmonary disease. A study conducted by Ivey KS, et al in 2018 [27] described the presence of underlying congenital heart disease has been showed to increase the severity of illness from RSV which was reflected by factors such as length of hospitalization, rates of intensive care admission and the use of mechanical ventilation. Higher mortality was also described in patients who had contracted RSV and also had underlying congenital cardiopulmonary illnesses.

It is worthy to note at this time that guidelines by the American Academy of Pediatrics [30] suggests that infants with co-morbidities such as underlying significant heart disease should receive the monoclonal antibody Palivizumab, which has shown to reduce hospital admissions. This guideline has been perceived to be backed with moderate strength in recommendation.

The prevalence of COVID-19 in pediatric patients is much lower than that of adults as previously stated. Along with respiratory complications COVID-19 has shown cardiovascular implications across pediatric patients, though the numbers are scant, literature has shown the heart as a potential target for complications especially in children with a preexisting or comorbid condition. In a small case series of eight critically ill patients infected by SARS- CoV-2, the case of a 13-month male child who developed heart failure, septic shock, coagulopathy, and multiple organ failure was described. In a study by Xia et al., Seven children out of the twenty enrolled were affected by a pre-existing congenital or acquired pathology leading to similar cardiac outcomes after COVID-19 infection [31].

Other Extrapulmonary Manifestations

Eisenhut M [28] in 2006, conducted a systematic review to outline the extrapulmonary manifestations and sequalae of RSV bronchiolitis. The central nervous system (CNS) was identified as producing extrapulmonary manifestations which included seizures, central apnoeas, lethargy and abnormalities in the muscle tone. Eisenhut M [28] reported that among the studies utilized in this systematic review, the incidence of seizures was 1.8% in one of them, whereas neurological complications in total were reported in 1.2% in another study that involved a larger population with a wider inclusion criterion of patients. A particularly noteworthy CNS manifestation was the development of apnea in patients who were admitted due to RSV bronchiolitis. An important risk factor identified for the development of this complication was being under the age of 2 months. This complication was found to be present in 16% to 21%, 26 of children admitted with RSV bronchiolitis. It is however important to note that the etiology of the apnea may be difficult to ascertain as whether it is stemming from the CNS or from the immature development of the larynx in infants.

Hyponatremia has also been identified in patients with RSV bronchiolitis, with up to 33% of patients reported as having isolated hyponatremia [32]. Hyponatremia has been known to manifest as seizures and when investigating the underlying cause of hyponatremia, 4% of patients diagnosed with RSV Bronchiolitis had been shown to have syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) as well. It is very intriguing to note that up to 10% of patients have been reported to develop encephalopathy as well due to RSV infections however the underlying mechanism of this manifestation has yet to be understood properly. Picone et al [32] has also described that two studies have reported strabismus as a neurological complication of RSV bronchiolitis.

Cases of RSV Bronchiolitis resulting in an extrapulmonary manifestation of hepatitis have been seldom reported in current literature. The study by Eisenhut M [28] in 2006 and a case study by Kirin K, et al. [33] in 2013 explored the development of hepatitis after an infection with RSV. Eisenhut M [28] suggested that around 46% to 49% of patients with RSV bronchiolitis receiving mechanical ventilation had elevated transaminase enzymes with an even higher prevalence in those with underlying cardiopulmonary disease. It was suggested that the respiratory syncytial virus is able to hematogenously spread to other organs and increases the production of reactive oxygen species. These reactive oxygen species can cause a transient elevation in transaminase enzymes reflecting hepatocyte damage. It is also suggested that recovery for the elevated liver enzymes can take weeks after the RSV infection has been diagnosed [34].

From this study and interpretation of the extrapulmonary manifestations, there are multiple manifestations of RSV outside the respiratory system but there is no uniform pattern of presentation. It can be postulated that from the review of the existing literature, underlying congenital heart disease is a major risk factor in the development of extrapulmonary manifestations including cardiovascular and otherwise. Since most cases have been described as either case reports or studies involving a small number of patients, a large sample size would be required to establish whether there is a clear association between RSV bronchiolitis directly causing extrapulmonary manifestations with minimal to no confounding factors. This, in turn, would aid in suggesting if screening protocols would need to be set in place for patients diagnosed with RSV bronchiolitis, especially those with moderate to severe symptoms.

Conclusion

Bronchiolitis is a condition that can be commonly observed in children especially under the age of 2. Although there is still debate with regards to the management strategies for this condition, it has been seldom investigated whether there are significant complications and sequelae as a result of acquiring this infection. From this study, it is deducible that not only can bronchiolitis result in residual respiratory illnesses but extrapulmonary manifestations within cardiovascular, metabolic, neurological and gastrointestinal systems can be observed in patients who have bronchiolitis and it is imperative for clinicians to be aware of such sequelae. Most of the existing literature with regards to this topic has been covered within case reports, case series and systematic reviews. Conducting large case-control studies would provide a more accurate depiction of the incidence and importance of post-bronchiolitis sequelae.

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