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Severe bronchiolitis profiling as the first step towards prevention of asthma

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Abstract

Bronchiolitis is the most common respiratory infection leading to hospitalization and constitutes a significant healthcare burden. The two main viral agents causing bronchiolitis, respiratory syncytial virus (RSV) and rhinovirus (RV), have distinct cytopathic, immune response, and clinical characteristics. Different approaches have been suggested for subtyping bronchiolitis based on viral etiology, atopic status, transcriptome profiles in blood, airway metabolome, lipidomic data, and airway microbiota. The highest risk of asthma at school age has been in a subgroup of bronchiolitis characterized by older age, high prevalence of RV infection, previous breathing problems, and/or eczema. Regarding solely viral etiology, RV-bronchiolitis in infancy has been linked to a nearly three times higher risk of developing asthma than RSV-bronchiolitis. Although treatment with betamimetics and systemic corticosteroids has been found ineffective in bronchiolitis overall, it can be beneficial for infants with severe RV bronchiolitis. Thus, there is a need to develop a more individualized therapeutic approach for bronchiolitis and follow-up strategies for infants at higher risk of asthma in the future perspective.

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Introduction

Bronchiolitis is defined as a viral infection of bronchioles and surrounding tissue. It can present as a mild illness that is safely managed as an outpatient or as a severe illness requiring hospitalization, intensive care unit (ICU) admission, and/or invasive ventilatory support.¹ Bronchiolitis is the leading cause of hospitalization in children, accounting for approximately 1% of all children.² Moreover, it also has substantial chronic airway morbidity, such as recurrent wheezing and childhood asthma.² Depending on risk factors, approximately 30-80% of children will have subsequent asthma.^{3,4} Therefore, bronchiolitis and its long-term sequela has a considerable impact on the healthcare systems worldwide.^{5,6} Most guidelines, however, recommend only supportive care for bronchiolitis, even in the hospital setting.¹

The purpose of this brief review was to open the evidence supporting distinct entities of bronchiolitis. Moreover, we wanted to discuss how they are linked to compromised long-term outcomes and treatment responses.

Viral Etiology of Bronchiolitis

Based on the past and current evidence, respiratory viral infections are the main trigger of bronchiolitis and acute wheezing episodes in children. Epidemiological data might vary, but most observational studies have identified respiratory syncytial virus (RSV) and rhinovirus (RV) as the two dominant viral triggers.^{7,9} The overall prevalence of RSV and RV in children under 2 years old with bronchiolitis is estimated at approximately 60 and 20%, respectively.¹⁰ During infancy the most common etiologic factor is RSV, accounting for about 60-70% of the cases.¹¹ The hospitalization rates of RSV-induced bronchiolitis are the highest in those aged less than 3 months.¹² In comparison, RV is the second most common virus in infants older than 6 months.⁶ Other less commonly detected viruses in children with bronchiolitis under 2 years old include human bocavirus, adenovirus, metapneumovirus, parainfluenza virus, influenza virus, and coronaviruses.¹⁰

Before the COVID-19 pandemic in 2020, seasonality of RSV and RV infections was different. In Europe, the RSV wave started in December and continued until April (peaking between January and March).^{13,14} RV infections, on the contrary, were present throughout the year but with the greatest prevalence during the spring and autumn.¹⁵ During the COVID-19 pandemic, a deviation from that pattern was observed with a significantly reduced number of bronchiolitis hospitalizations in Europe during winter 2020/21.^{16-18,19} In the subsequent winter season (i.e., winter 2021/22), the bronchiolitis cases peaked in Europe earlier, starting in November, and was approximately 2-3 weeks shorter^{18,20} with a similar pattern in the current 2022/23 season.^{20,22} A recent study observed an increase in RSV infections needing hospitalization in the current season, increased medium age of hospitalized infants, a more extended hospital stay, a more frequent need for respiratory support, and a higher frequency of patients with a history of prematurity.²¹ At the same time, the rate of ICU admissions and mechanical ventilation did not increase.²¹ Overall,

studies show that compared to pre-pandemic years, hospital admissions due to bronchiolitis significantly decreased during the pandemic.^{16,18,23} The most likely reason is that children and caregivers did not contract respiratory viral illnesses in view of “stay at home” measures that were followed by the entire families. Other reasons focus on the possibly successful implementation of non-pharmacological interventions, the reduced use of daily care facilities, and school closures during the COVID-19 pandemic.²⁰ Following this period of reduced bronchiolitis hospitalizations, we observed a spike in bronchiolitis cases (hospitalized or not) the subsequent year. This increase in disease severity may be related to the “immunity debt” phenomenon. This phenomenon is more prevalent in children who were raised in areas of restrictive measures and were suddenly exposed to extensive social interactions and viral infections.²¹

Hence, being on top of epidemiological evidence, around RSV and RV-induced infections can possibly inform healthcare services’ design and can also introduce impactful public health interventions, changing respiratory viral epidemiology should affect the distribution of healthcare resources and future public health policies.²⁴

Clinical Characteristics and Their Link to Asthma

Expiratory breathing difficulty is a characteristic symptom of bronchiolitis and asthma. The diagnosis of bronchiolitis is made clinically. The constellation of clinical symptoms of bronchiolitis typically includes cough and signs of dyspnea as tachypnea, accessory respiratory muscles usage, and/or nasal flaring with possible decreased oxygen saturation.¹¹ Among the other bronchiolitis features, adventitious breath sounds such as expiratory wheezing, crackles, rhonchi, and rales, hyperinflation and displaced liver may be observed in severe cases.^{1,25} Prodromal signs, occurring between 2 and 4 days before, usually include rhinitis, nasal congestion, and rhinorrhea.¹

RV-bronchiolitis is mainly caused by species A and C. Overall, in this disease, the odds ratios (ORs) for school-age asthma are in the range of 3-10. However, allergic sensitization (OR 45) and eczema have been associated with an enhanced risk for atopic asthma inception later in childhoods, OR up to 5.1.²⁶⁻²⁸ Conversely, the risk factors for a nonatopic phenotype of asthma by the age of 7 were RSV-induced bronchiolitis, the first episode of wheezing before the age of 1, and parental smoking ORs up to 8.1.²⁷

Viral-dependent Pathogenesis of Bronchiolitis

For decades bronchiolitis was regarded as a single disease based solely on the clinical presentation; however emerging data have recently demonstrated that the underlying pathomechanism of bronchiolitis is associated with specific viral etiology. Its two most common viral triggers, RSV and RV, were shown to engage a distinct host immune response and are associated with different airway injuries.²⁹ However, with regard to asthma development, it remains unclear whether it is the early-life respiratory viral infection that initiates the abnormal chronic immune reactions

in the airways or whether it is the viral-induced bronchiolitis that can serve as the marker of the underlying personal predisposition to asthma development. Most of the data supports the latter (Figure 1).²⁵

Respiratory syncytial virus-induced bronchiolitis

Following an incubation period lasting about 4-6 days, the virus starts to replicate in the nasal mucosa, resulting in nasal congestion, rhinorrhea, irritability, and poor feeding.²⁹ Further involvement of the epithelial cells of the lower respiratory tract induces secretion of antiviral interferons type I and III.²⁵ Subsequent infiltration of immune cells (NK cells, helper CD4+, cytotoxic CD8+, and granulocytes) leads to edema, hypersecretion of mucus, sloughing of infected epithelial cells, and impaired ciliary action resulting in obstruction of bronchioles. Typical cytopathic features are syncytiums and multinuclear giant cells when infected superficial epithelial cells merge with neighboring cells before apoptosis. Cell debris and mucus make a mechanical obstruction in the airways. Inhaled air is trapped behind occluded bronchioles, leading to hyperinflation. Intraluminal obstruction causes decreased perfusion and oxygen saturation.²⁹

Rhinovirus-induced bronchiolitis

Rhinoviruses and RSV are spread via direct contact or aerosol particles and target respiratory epithelial cells of the upper and lower airways.²⁵ RV enhances the production of epithelial-derived cytokines such as²⁵ interleukin (IL)-25 and

IL-33, inducing type-2 immune response. Activated type-2 innate lymphoid (ILC2) cells secrete type-2 cytokines such as IL-5, IL-9, and IL-13, which generate the recruitment of eosinophils, mast, and goblet cells, and increased mucus production.³⁰

In addition, RV has been reported to elucidate increased production of molecules involved in remodeling, fibrosis of airways, and reduction of preventive factors such as tissue inhibitor metalloproteinases (TIMPs) *in vitro*.^{31,32} A recent study reports that during a severe RV-induced bronchiolitis episode, there is an upregulated secretion of remodeling factors (e.g., TGF α , HGF, and MMP-2) in nasal washings from children below 24 months old. Thus, data indicate that RV infection in early childhood may induce a pro-remodeling milieu in airways and may result in permanent obstruction later in life.³³ Moreover, RV-induced bronchiolitis in infancy has been associated with lower lung function at ages 7-9. Children with a sequel of RV infection before the age of 24 months had significantly lower z-score FEV1 values (-0.64) at ages 7-9 years than those with past RSV bronchiolitis (-0.13, P = 0.04).³⁴

There are three RV species (A, B, C), and species C and A have been linked with more severe illness and wheezing compared to species B.³⁰ The single nucleotide polymorphism in the CDHR3 gene (a unique receptor for RV-C) has been associated with a phenotype of more severe asthma exacerbations³⁰ and an increased risk of childhood asthma.^{35,36} Additionally, variants at the 17q21 locus in children with an episode of RV bronchiolitis in infancy have been linked with a greater risk of childhood asthma OR 26.1.³⁷ Factors predisposing to RV-wheeze in infants include aeroallergen sensitization and other atopic features such as eczema or eosinophilia.³⁸

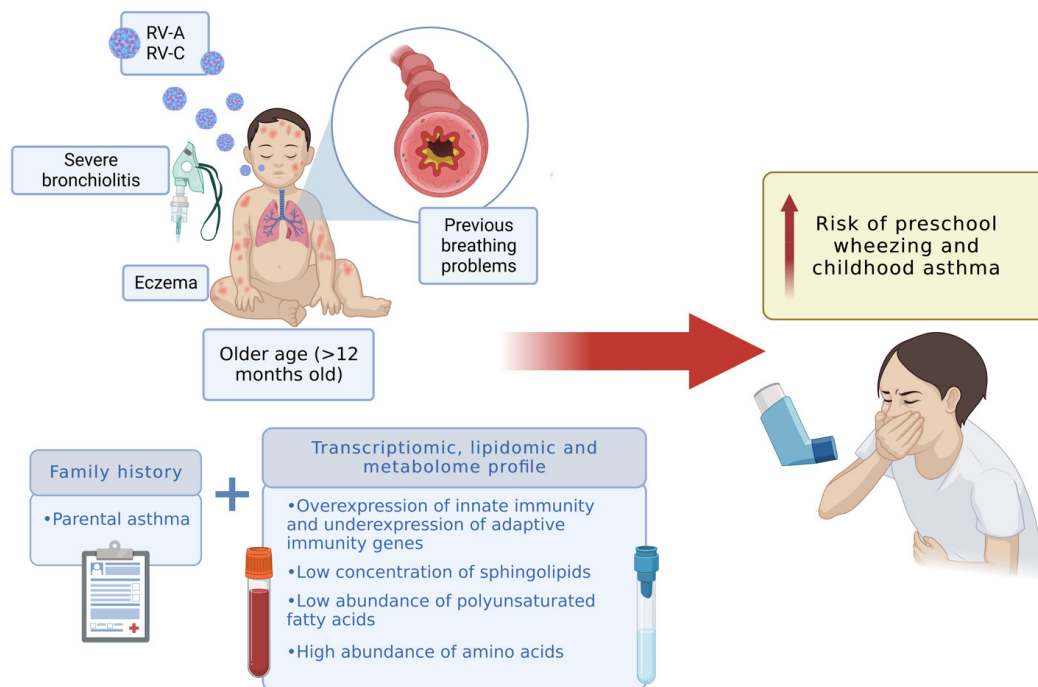


Figure 1 Summary of personal traits, family history, metabolome, and lipidomic profile associated with a higher risk of preschool wheezing and childhood asthma. Created with BioRender.com.

Risk Factors for Developing a Severe Course of the Disease

About 19% of hospitalized infants with bronchiolitis need intensive care treatment.³⁹ The risk factors for a severe course of bronchiolitis include age below 6 weeks, prematurity, underlying chronic lung disease, congenital heart disease, immunodeficiency, and neurological disease.¹¹ The higher risk of bronchiolitis in preterm infants is partially explained by insufficient transplacental passage of RSV-specific maternal antibodies, as it predominately occurs during the third trimester.⁴⁰ Very preterm infants born before 30 weeks of gestation were found to have significantly higher hospitalization rates than late preterm (born >30 weeks of gestation) or term infants. Still, other factors can explain this, for example, increased prevalence of chronic lung disease and congenital heart defects that can add to the increased susceptibility to invasive respiratory pathogens.^{12,41}

Severe Bronchiolitis Profiling (Molecular Differences between RSV and RV)

With the advances in high-throughput sequencing technology, attempts are underway to dissect the different populations of children with severe bronchiolitis. Differences in host immune responses to RSV and RV in infants with bronchiolitis have been first studied based on the analysis of the whole-blood RNA sequencing.⁴²⁻⁴⁴ RSV blood transcriptional profile was characterized by the upregulation of genes related to inflammation and innate immunity with simultaneous suppression of modules regulating adaptive immunity (such as T cells, B cells, and natural killer (NK) cells) and antimicrobial responses. In subjects with RV bronchiolitis, the downregulation of adaptive immunity genes was significantly less pronounced.⁴³ The degree of host immune suppression genes was linked with disease severity and younger age in infants with RSV bronchiolitis.⁴³ Interestingly, changes in transcriptome profile (overexpression of innate immunity and underexpression of adaptive immunity genes) were significant in infants who tested positive for RV but only in symptomatic subjects, in contrast with those with asymptomatic RV infection.⁴⁴ RV is frequently detected in the absence of symptoms of infection in young children, varying from 14 to 50%.⁴⁵⁻⁴⁸ These findings suggest that asymptomatic RV detection likely represents the detection of viral RNA without significant activation of systemic host responses. Therefore, whole-blood transcriptional profiling of children may serve as a useful diagnostic tool to discriminate between active infection and incidental pathogen detection.⁴⁴

Emerging evidence has demonstrated the contributions of the respiratory viral trigger, airway microbiome, and transcriptome in infants with bronchiolitis, mainly in the *single*-element “omic” approaches (such as proteomic or metabolomic analysis).⁴⁹⁻⁵⁴ Studies using nasopharyngeal airway metabolome data from inpatients with severe bronchiolitis identified their distinct metabolotypes. The metabolic profile characterized by a high abundance of inflammatory amino acids and low abundance of PUFAs was associated with a higher risk for the development of recurrent wheezing and childhood asthma.⁵⁵ Based on analysis

of lipidomic data from upper airways of the same study group, a lower concentration of sphingolipids (e.g., sphingomyelins, ceramides) was linked with a significantly higher risk of asthma at the age of six.⁵⁶ Again, based on the MARC cohort studies, the distinct endotypes within the infants with RSV and RV-induced bronchiolitis were recognized by integrating multi-“omics” data on the clinical presentation, nasopharyngeal airway microbiome, and immune response (level of expression of INF- α and IFN- γ response).^{57,58} Regarding RSV endotypes, the highest risk of asthma by the age of 5 years was in profile with a high percentage of parental asthma, IgE sensitization, RV coinfection, codominance of *Streptococcus pneumoniae*/*Moraxella catarrhalis* in the lung microbiome, and high epithelial INF- α and IFN- γ responses.⁵⁸ In contrast, an endotype with the highest risk for asthma and recurrent wheeze among RV profiles was characterized by the high (>300 cells/mm³) serum eosinophilia, IgE sensitization, genotype RV-C infection, a predominance of *M. catarrhalis* in the microbiome and high type-2 cytokine response.⁵⁷

A recent study showed that the airway microbiome could modify host immune responses and influence metabolic pathways associated with a higher risk of asthma. The most significant changes in host metabolic pathways (such as fatty acid and carbohydrate metabolism) in children that developed asthma 6 years after a bronchiolitis episode were driven by three major bacteria species (*S. pneumoniae*, *Haemophilus influenzae*, *M. catarrhalis*).⁵⁹ Second, airway colonization with *S. pneumoniae* in infants was related to a significantly higher risk of asthma in infants with non-RV bronchiolitis, suggesting a synergistic effect of viral trigger and microbiome.⁵⁹ Third, in line with previous findings, downregulated INF- α and IFN- γ host response was associated with the disease severity and long-term respiratory sequela such as asthma development.⁵⁹

Moreover, another bronchiolitis research integrated the interrelations between the host response, microbial composition with its function in the airway, and their integrated role in the disease severity in infants with bronchiolitis.⁵¹ Fujiogi et al. identified several modules linked with illness severity.⁵¹ The host-type I interferon, *S. pneumoniae*/*Staphylococcus aureus* abundance, neutrophil/IL-1, T-cell regulation, microbial-branched-chain amino acid metabolism, and nicotinamide adenine dinucleotide hydrogen were the modules significantly associated with risks of positive pressure ventilation use in these infants. However, the mechanisms involved in these complex interactions still need to be further elucidated, especially as they are not reciprocally exclusive.⁵¹

These studies support the notion of bronchiolitis as a heterogeneous disease with distinct underlying mechanisms and risk for long-term sequelae (Table 1).

Severe Bronchiolitis Phenotypes (Clinical Differences)

Up to 30% of children with the first wheezing episode will later be diagnosed with childhood asthma and require asthma control medications.³ Clinically, the exciting profiling of bronchiolitis patients based on multi-“omic” approaches is currently unreachable to large-scale usage.

Table 1 Summary of differences in prevalence, clinical presentation, treatment responses and molecular distinctions between two major viral agents causing bronchiolitis—respiratory syncytial virus (RSV) and rhinovirus (RV).

	Respiratory syncytial virus (RSV)	Rhinovirus (RV)
Prevalence in children under 2 years old hospitalized with bronchiolitis	Around 60% ¹⁰	Around 20% ¹⁰
Clinical presentation		
Requirement of oxygen supplementation	More infants hospitalized with RSV bronchiolitis require oxygen ^{7,8,64,65}	-
Personal history of eczema	-	More infants hospitalized with RV bronchiolitis have a personal history of eczema ^{61,62,65,67,68}
Wheezing at admission	No difference has been found ^{7,8,61-65}	-
Fever at admission	No difference has been found ^{8,66}	-
Parental atopy	No difference has been found ^{7,61,67,68}	-
Ventilation support and ICU transfer	No difference has been found ^{7,8,61,63-65,69}	-
Risk of asthma following bronchiolitis episode		
Risk of asthma following severe bronchiolitis	Lower risk of recurrent wheeze and childhood asthma ⁴	Higher risk of the development of recurrent wheezing and childhood asthma compared to RSV (OR 4.1 vs 2.7) ⁴
Factors associated with higher risk of asthma by the age 5	Parental asthma IgE sensitization, RV coinfection Codominance of <i>Streptococcus pneumoniae</i> / <i>Moraxella catarrhalis</i> in the lung microbiome High epithelial INF- α and IFN- γ responses	High (>300 cells/mm ³) serum eosinophilia IgE sensitization RV-C infection Predominance of <i>M. catarrhalis</i> in microbiome High type-2 cytokine response
Molecular profiles		
Analysis of the whole-blood RNA sequencing	Upregulation of inflammation and innate immunity genes Suppression of modules regulating adaptive immunity ⁴³	Downregulation of adaptive immunity genes less pronounced ⁴³
Analysis of microbe's and host transcriptome	Enriched nucleic acid metabolism ⁸³	Enriched acylation/acetylation function ⁸³
Treatment	Systemic steroids not effective	Systemic steroids and beta 2-agonists found effective in short-term and long outcomes ^{7,8,80,81}

Therefore, there are other attempts to stratify the children with bronchiolitis into endotypes based on the accessible clinical features to easily identify those at higher risk of subsequent asthma in daily practice.

Evaluation of a prospective multicenter cohort (MARC-30 USA) and its validation in another two cohorts (MARC-30 Finland, MARC-35), altogether with over 3000 infants, identified distinct bronchiolitis profiles (A, B, C, D). Latent class analysis investigating factors of clinical presentation such as a history of breathing problems or eczema and virological data was used. Profile A assembled older infants between 6 and 12 months with previous breathing problems, eczema, high prevalence of RV infections, and less than 1% of RSV cases. Profile B was compared to “classic bronchiolitis” characterized by low percentage of previous breathing problems, a high proportion of children with wheezing at presentation, and a high detection rate of RSV. Profile C had the most severe clinical course with significantly longer hospitalization, younger age (2-6 months old), and inadequate

oral intake, while profile D had the least severe disease with no wheeze or retractions. Based on the follow-up assessment, these bronchiolitis profiles were found to be associated with different risks of developing long-term outcomes. Profile A had a higher chance of asthma development by age 6-7 years compared with profile B (38% vs 23%). No differences in risk for subsequent asthma were found between profiles C and D.⁶⁰ Furthermore, the researchers developed and validated a four-predictor model (RSV infection, history of breathing problems, history of eczema, and parental history of asthma), which helped to identify infants from the high-risk profile.⁶⁰

The Clinical Impact of Severe Bronchiolitis Profiling

The primary clinical objective of severe bronchiolitis profiling is to identify characteristics associated with the onset

or progression of later airway morbidities. Understanding the complex interplay between viral triggers, airway microbiome, host immune response, allergic status, and their contribution to childhood asthma is crucial. For example, colonization by *S pneumoniae* and non-rhino viral infection in infants correlated with a significantly higher risk of asthma at the age of 6 years.⁵⁹ A recent meta-analysis comparing between virus differences in the magnitude of preschool wheeze and childhood asthma showed that the RV-bronchiolitis group was over four times more likely to develop recurrent wheeze (OR 4.1) and nearly three times more likely to develop asthma (OR 2.7) than the RSV-bronchiolitis group.⁴ Hence, the viral etiology of early LTRIs has a vital role in the stratification of bronchiolitis patients, which could lead to more personalized management and preventive strategies in the future perspective.⁶⁰ Unfortunately, data from observational studies suggest that RSV- and RV-induced lower respiratory tract infections (LTRIs) in children under 2 years old are indifferent in terms of the clinical features present upon hospital admission, such as wheezing^{7,8,61-65} or fever,^{8,66} parental atopy,^{7,61,67,68} as well as ventilation support^{7,61,63} or ICU transfer.^{8,61,64,65,69} However, the requirement of oxygen supplementation^{7,8,64,65} seemed more common in the RSV-induced LTRIs, while a personal history of eczema was more frequently linked to the RV-induced LTRIs.^{61,62,65,67,68} In light of these reports, there is lacking evidence to differentiate the etiology of LTRIs between RSV and RV LTRIs based solely on patients' clinical presentation. Thus, the more widespread rapid respiratory virus testing of children with bronchiolitis is highly anticipated, especially for RV active infection.

Treatment

Currently, most guidelines recommend limiting bronchiolitis management only to supportive care, even at the hospital setting.¹ However, in some international guidelines, there is permission to perform a trial of salbutamol treatment and continue the therapy in case of good clinical response.⁷⁰⁻⁷³ Despite being discouraged, salbutamol and systemic corticosteroids are reported to be used against the guidelines in managing bronchiolitis in both the hospital and emergency department settings, indicating an urgent need for the revision of current guidelines.^{74,75} The available evidence shows that inhaled beta₂-mimetics are ineffective in terms of impact on oxygen saturation, length of hospital stay, and hospitalization rate.^{76,77} Systemic corticosteroids failed to prove efficacy in bronchiolitis and preschool wheezing management.

However, with the growing knowledge of the heterogeneity of bronchiolitis illness, it should be noted that the majority of the studies that were conducted investigated the interventions with the one-size-fits-all approach, regardless of its viral etiology or atopic status.⁷⁷ Interestingly, a more personalized approach and asthma-like treatment (with systemic corticosteroids and beta₂-agonists) in infants with RV-induced bronchiolitis have improved short- and long-term outcomes. However, a robust data is still lacking.^{68,78,79}

In a randomized clinical trial of children with bronchiolitis, treatment with prednisolone was associated with less

recurrent wheezing but only in subjects with a history of eczema or RV infection.⁸⁰ The researchers supported this finding in their second study, which showed that children with a high rhinovirus load particularly benefitted from prednisolone.⁸¹ In a post-hoc analysis of two clinical trials with high-dose salbutamol, it has been found that it could be more effective in a subgroup of children with bronchiolitis. The study noticed shortened hospitalization in the RV-induced bronchiolitis group who received high-dose salbutamol compared to on-demand salbutamol or placebo.⁷⁸ In addition, high-dose salbutamol combined with prednisolone was associated with a longer time to the new physician-confirmed wheezing episode than prednisolone alone or placebo.⁷⁸ A post-hoc analysis of two clinical trials assessing the efficacy of high-dose salbutamol alone and high-dose salbutamol combined with oral prednisolone showed that the latter treatment was associated with a longer time to the new physician-confirmed wheezing episode than prednisolone alone or placebo. Therefore, suggesting a positive long-term effect of the interaction of salbutamol with oral steroids in infants with RV bronchiolitis.⁷⁸

A recent study revealed that factors predicting the administration of albuterol prior to hospital admission included older age (6-12 months), previous salbutamol use, and wheezing.⁸²

Conclusion

In summary, the modern view of bronchiolitis assumes early subtyping into at least 2-3 major entities depending on the viral etiology, lung microbiome, and type of immunologic response, as they have different pathogenetic mechanisms and slightly different clinical pictures. Bronchiolitis subtypes are associated with different risks of subsequent asthma and may have a different response to treatment (systemic corticosteroids, beta 2-agonists). Thanks to the COVID-19 pandemic, early general virological diagnosis has gained attention and become possible, significantly supporting bronchiolitis subtyping.

Therefore, we suggest a more individualized approach to patients with bronchiolitis, such as an earlier therapeutic trial with beta 2-agonists, regardless of etiology. In the case of severe rhinovirus-induced wheezing, also consider systemic corticosteroids. However, further research is needed to adjust individualized treatment for specific subtypes and develop strategies to follow up with patients at higher risk of asthma.

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None.

Conflict of Interest

The authors declare that there are no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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