Clinical definition of respiratory viral infections in young children and potential bronchiolitis misclassification

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ABSTRACT

Viral respiratory infections are often grouped as a single respiratory syndrome named 'viral bronchiolitis', independently of the viral etiology or individual risk factors. Clinical trials and guidelines have used a more stringent definition of viral bronchiolitis, including only the first episode of wheezing in children less than 12 months of age without concomitant respiratory comorbidities. There is increasing evidence suggesting that this definition is not being followed by pediatric care providers, but it is unclear to what extent viral respiratory infections are currently misclassified as viral bronchiolitis using standard definitions. We conducted a retrospective analysis of hospitalized young children (≤3 years) due to viral respiratory infections. Bronchiolitis was defined as the first wheezing episode less than 12 months of age. Demographic variables and comorbidities were obtained by electronic medical record review. The study comprised a total of 513 hospitalizations (n=453). Viral bronchiolitis was diagnosed in 144 admissions (28.1%). Notably, we identified that the majority of children diagnosed with bronchiolitis (63%) were misclassified as they had prior episodes of wheezing. Many children with bronchiolitis misclassification had significant comorbidities, including prematurity (51%), neuromuscular conditions (9.8%), and congenital heart disease (9.8%). Misclassification of bronchiolitis is a common problem that may lead to inappropriate management of viral respiratory infections in young children. A comprehensive approach that takes into consideration viral etiology and individual risk factors may lead to a more accurate clinical assessment of this condition and would potentially prevent bronchiolitis misclassification.

Significance of this study

What is already known about this subject?

- Viral bronchiolitis is one of the most common respiratory illnesses in children less than 1 year.
- Previous studies and current guidelines do not recommend use of prior mainstay therapies such as nebulized beta-agonist therapy, nebulized racemic epinephrine, and corticosteroids.
- Guidelines are limited in patients with comorbidities such as prematurity, neuromuscular disease, cardiac disease, and recurrent wheezing.

What are the new findings?

- There is a potential disassociation between standard classification as shown in guidelines (ie, first episode of wheezing) and the definition of bronchiolitis used in practice.
- Most common factors leading to misclassification of viral respiratory infection in hospitalized children were the presence of prior wheezing and concomitant respiratory conditions, including prematurity and neuromuscular disease.
- These results may bring to light the misclassification and possible mistreatment of children diagnosed as bronchiolitis.

How might these results change the focus of research or clinical practice?

- The misclassification of viral bronchiolitis may affect the management of viral respiratory infections in young children.
- Consider alternative diagnoses and therapies for children with recurrent wheezing and/or comorbidities such as prematurity, neuromuscular disease, and congenital heart disease.
- Careful considerations must be made when instituting bronchiolitis guidelines as treatment pathways to not include the above population.

INTRODUCTION

Viral respiratory infections are the top cause of morbidity and mortality in the pediatric population and represent a major burden for healthcare utilization.[1] Prior to the widespread use of viral respiratory polymerase chain reaction (PCR) to identify specific viral respiratory pathogens, all viral respiratory infections were traditionally grouped together as a single respiratory

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syndrome named 'viral bronchiolitis',[2 3] which assumes a similar clinical picture independently of the viral etiology or individual host responses and risk factors. Randomized clinical trials have used a more stringent definition of viral bronchiolitis to narrow down the phenotype of interest, including only children with viral bronchiolitis defined as *the first episode of wheezing in children less than 12 months of age without concomitant respiratory comorbidities*.[2] Most guidelines have also adopted similar definitions of viral bronchiolitis to propose standardized recommendations for management and treatment for this condition.[4]

Importantly, there is increasing evidence suggesting that this definition of bronchiolitis is not being followed by several pediatric care providers. Fernández *et al* has recently reported that only 5% of general pediatricians agree with the standard definition of viral bronchiolitis.[5] This represents a significant problem because it limits the applicability of clinical trials findings and viral bronchiolitis guidelines. Of particular concern is the fact that many children with recurrent and multitrigger wheezing may be misclassified as viral bronchiolitis, preventing the use of therapies such as corticosteroids and bronchodilators, standard of care in young children with asthma,[6] but not recommended for the treatment of viral bronchiolitis.[4 7] Thus, it is crucial to understand to what extent respiratory viral infections are misclassified as viral bronchiolitis according to standard definitions. To address this important unanswered question, we conducted a retrospective study in children hospitalized ≤3 years of age with PCR-confirmed viral respiratory infection. Our study included a total of 513 hospitalizations (n=453 children). The overarching hypothesis was that a significant proportion of cases of viral respiratory infection are currently misclassified as viral bronchiolitis. In addition, we performed secondary analysis to investigate the specific reasons why cases are being misdiagnosed as viral bronchiolitis with the prediction that prior wheezing and concomitant respiratory conditions would be the most common reasons.

The impact of this study in the field is that it may ultimately lead to improvements in healthcare by demonstrating the critical importance of proper clinical assessment of viral respiratory infections in young children. The latter must acknowledge prior history of wheezing illnesses, age of presentation, and known underlying respiratory conditions and risk factors. Our results may also impact the design of future clinical trials and guidelines for standardized management and treatment of viral respiratory infections in children, taking into consideration the heterogeneity and complexity of this common and potentially life-threatening pediatric condition.

MATERIALS AND METHODS

Study subjects

We conducted a retrospective cross-sectional analysis of a cohort of children ≤3 years of age admitted with viral respiratory infection, confirmed by PCR analysis, at Children's National Medical Center (CNMC) during 2014. Viral PCR was performed on subjects who presented to the hospital with suspected viral respiratory tract infection at discretion of clinician. We only included children with positive PCR for any of the viruses included in our panel, including rhinovirus (RV), respiratory syncytial virus (RSV), human metapneumovirus (HMPV), influenza A/B, parainfluenza 1–3, and adenovirus. This study was approved by the Institutional Review Board at CNMC.

Clinical and demographic variables

Clinical and demographic variables were obtained by reviewing electronic medical records (EMR) at CNMC. Demographic variables comprised gestational age in weeks, age, gender, and ethnicity. For the purpose of the study, clinical parameters were characterized as binary outcome for the presence of wheezing and the classification of severe prematurity defined a priori by a gestational age of less than 32 weeks to include extremely preterm and very preterm subjects based on WHO's definition of prematurity.[8] We used the most common definition of viral bronchiolitis according to what has been used in clinical trials and adopted clinical practice guidelines. 'Viral bronchiolitis' was defined as the first episode of wheezing in children <12 and <24 months of age without concomitant respiratory comorbidities.[4 9]

Statistical analysis

Data were analyzed using the software SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to calculate the prevalence of each virus and to present demographic information. Comparison of viral bronchiolitis definitions and recurrent wheezing misclassified as bronchiolitis were performed with a χ^2 test (categorical variables). Significance was taken at the $p<0.05$ level.

RESULTS

Demographics and epidemiology of viral respiratory infections

The study comprised a total of 510 hospitalizations in children aged 3 years or less who were positive for an identified virus using viral PCR. As shown in table 1, there were 320 males, which was 62.7% of the subject population, median age was 1.18 years (IQR 0.58–2.15). We identified RV as the predominant viral pathogen found in 280 of the subjects (55%). RSV was the second most common virus and found in 84 subjects (16.5%), HMPV in 56 subjects (11%), and adenovirus in 56

Table 1 Baseline characteristics

Demographics	
Male, n (%)	320 (62.7)
Age (years), median (IQR)	1.18 (0.58–2.15)
Black, n (%)	259 (50)
Viral pathogen	
RV, n (%)	280 (55)
RSV, n (%)	84 (16.5)
HMPV, n (%)	56 (11)
Adenovirus, n (%)	56 (11)
Influenza, n (%)	43 (8.4)
Parainfluenza, n (%)	39 (7.6)

Demographics for all study subjects (n=510). Influenza virus includes H1N1, H3N2, influenza A, and influenza B. Parainfluenza includes parainfluenza types 1–3.
HMPV, human metapneumovirus; RSV, respiratory syncytial virus; RV, rhinovirus.

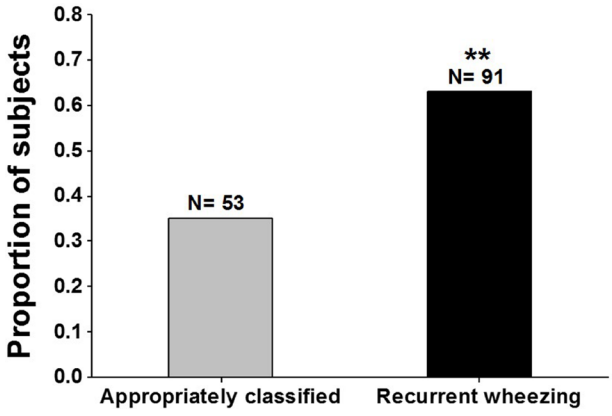

Figure 1 Comparison of viral bronchiolitis definitions. Subjects diagnosed with viral bronchiolitis (n=144) were subdivided into those appropriately classified as first wheezing episode plus age criteria of <24 months (n=53) and those misclassified due to at least one prior episode of wheezing, which was the most common category (recurrent wheezing; n=91; p<0.01**).

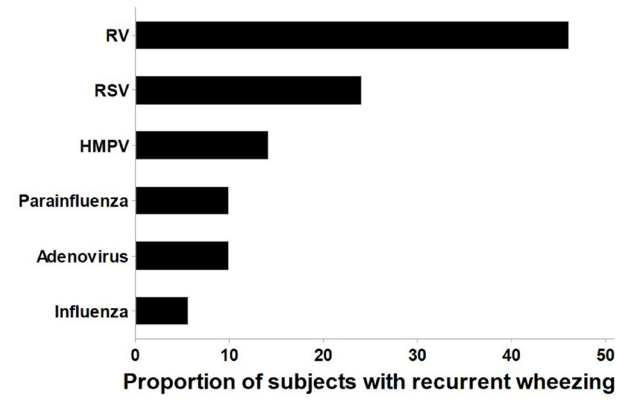

Figure 2 Viruses implicated in subjects with recurrent wheezing. Data for all subjects with recurrent wheezing (n=91). RV, rhinovirus; RSV, respiratory syncytial virus; HMPV, human metapneumovirus. RV was the most prevalent virus in the recurrent wheezing group (46%).

subjects (11%). Influenza virus, which includes H1N1, H3N2, influenza A, and influenza B, was implicated in 43 subjects (8.4%). Parainfluenza includes parainfluenza types 1–3 in 39 subjects (7.6%).

Comparison of viral bronchiolitis definitions

To compare the varying definitions of bronchiolitis based on the American Academy of Pediatrics of children less than 24 months with first wheezing episode[4] and the European guidelines definition of bronchiolitis as a seasonal virus infection of the lower respiratory tract in infants less than 12 months,[9] we combined all subjects less than 12 or 24 months, as shown in figure 1. Of the subjects diagnosed with viral bronchiolitis (n=144), we selected for those *appropriately classified* as having a first-time wheezing episode plus two different age criteria to include both the American and the European definitions. We identified 41 subjects who met the above-mentioned criteria and were less than 12 months (definition 1; n=41; 29%). There were 53 subjects who met criteria and were less than 24 months (definition 2; n=53; 37%, which included the <12 months patients). There were 91 subjects (63%) *misclassified* due to at least one prior episode of wheezing which either bronchiolitis definition was applicable.

Table 2 Characteristics of subjects with recurrent wheezing misclassified as bronchiolitis

Male, n (%)	57 (63)
Age (years), median (IQR)	1.01 (0.62–1.51)
Black, n (%)	45 (49)
Wheezing in current episode, n (%)	80 (89)
Prior albuterol use, n (%)	77 (85)
Prior inhaled steroids, n (%)	62 (69)

Data for all subjects with recurrent wheezing (n=91).

Characteristics of subjects with recurrent wheezing misclassified as bronchiolitis

Taking a further look into the subpopulation of subjects with recurrent wheezing misclassified as bronchiolitis, we characterized gender, age, race, wheezing during current episode, prior use of albuterol, and inhaled steroids in table 2. Males outnumbered females at 63% (n=57), and median age was 1.01 years (IQR=0.62–1.51). Almost half of the subjects were black at 49% (n=45). The vast majority of subjects at 89% (n=80) wheezed during the current studied episode.

Viruses implicated in subjects with recurrent wheezing

In the 91 subjects who have recurrent wheezing as seen in figure 2, RV was the most prevalent at 46% followed by RSV 24%, HMPV 14%, and adenovirus 9.8%. Parainfluenza, which includes parainfluenza types 1–3, was in 9.8% of subjects. Influenza was found in 5.5% of subjects and includes H1N1, H3N2, influenza A, and influenza B.

Comorbidities of subjects with recurrent wheezing misclassified as bronchiolitis

To further describe the population of subjects misclassified as bronchiolitis with recurrent wheezing, we took a closer look at comorbidities. We found that about half (n=47, 51%) of the subjects had history of prematurity with 77% of those falling under the category of very premature with gestational age of <32 weeks. Other comorbidities prevalent in these subjects were congenital heart disease (n=9, 9.8%), airway/respiratory abnormalities (n=12, 13%), genetic disorders (n=11, 12%), and neuromuscular diseases (n=9, 9.8%)

DISCUSSION

Viral respiratory infections are the top cause of hospitalization in children around the world.[10] Respiratory viruses are also a major burden for healthcare utilization due to multiple emergency department visits, prolonged hospitalizations, and recurrent respiratory symptoms in outpatient follow-up visits.[11] Despite increasing evidence demonstrating that the pathogenesis of viral respiratory infections is highly

Table 3 Comorbidities of subjects with recurrent wheezing misclassified as bronchiolitis

Prematurity, n (%)	47 (51)
<37–33 weeks GA, n (%)	11 (12)
≤32 weeks GA, n (%)	36 (39)
Congenital heart disease, n (%)	9 (9.8)
Airway/respiratory abnormalities, n (%)	12 (13)
Genetic disorders, n (%)	11 (12)
Neuromuscular disease, n (%)	9 (9.8)

Data for all subjects with recurrent wheezing (n=91). GA, gestational age.

complex and heterogeneous,[12–15] they are often grouped as a single respiratory syndrome named 'viral bronchiolitis'.[2 3] This assumes that different respiratory viruses will cause the same clinical picture independently of the individual host response and risk factors. Clinical trials and guidelines have narrowed down the definition of viral bronchiolitis to include only the first episode of wheezing in children under 12 months of age and have specifically excluded individuals with respiratory comorbidities.[6] Nonetheless, there is evidence that many pediatric care providers do not follow this narrowed definition,[16] which limits the applicability of the scientific evidence generated by viral bronchiolitis research. The latter represents a significant clinical problem because bronchiolitis misclassification may lead to inappropriate decisions in treatment and need for additional work up and/or follow-up. Given the importance of this issue, we set a study to investigate the frequency and causes for viral bronchiolitis misclassification in young children hospitalized with viral respiratory infections. Specifically, we determined the proportion of cases of hospitalization due to respiratory viruses in which the term viral bronchiolitis was inappropriately used. We also conducted additional analyses to investigate the specific reasons why this bronchiolitis definition was incorrect, with particular focus on the presence of conditions that may significantly change the management of viral respiratory infections in children (eg, recurrent/multitriggered wheezing).

The main finding of our current study is that among the population of young children hospitalized with PCR-confirmed viral infection, we identified that 65% where mistakenly diagnosed as viral bronchiolitis, according to the most accepted definition of this condition.[4 9] Our study included a representative sample of 513 hospitalizations (n=453 children) caused by several respiratory viruses, including RV, RSV, HMPV, influenza A/B, parainfluenza types 1–3, and adenovirus. The impact of the misclassification of viral bronchiolitis is that it may affect the management of viral respiratory infections in young children. This is particularly concerning given that multiple clinical trials have failed to identify beneficial effects for many treatments, including bronchodilators, corticosteroids, hypertonic saline, and epinephrine, among others.[17–19] Accordingly, it is critically important to avoid misusing the term viral bronchiolitis as it may lead to withholding therapies that may be beneficial for specific groups of young children. For instance, there is compelling evidence, based on randomized controlled clinical trials,[20–22] that corticosteroids are beneficial in young children with multiple-trigger wheezing, which is often triggered by respiratory viruses. Despite the implications of the identification of recurrent/multitrigger wheezing, our study identified that the top reason to misclassify respiratory infections as viral bronchiolitis was the prior presence of wheezing episodes. We believe an explanation for these findings is that some providers still prefer to use the term viral bronchiolitis instead of childhood asthma in children with recurrent/multitrigger wheezing given the potential controversy of diagnosing asthma in young children. This contradicts the latest National Asthma Education and Prevention Programme guidelines (Expert Panel Report III) specifically describing a category for the identification and management of asthma in children 0–4 years old.[6]

We also identified several cases of recurrent wheezing misclassified as viral bronchiolitis in which there was previous use of inhaled corticosteroids, bronchodilators, and/or diagnosis of asthma (table 3). Due to the retrospective nature of our study, we could not ascertain that this misclassification altered the management and/or outcome of the acute viral-induced wheezing episode. However, our current data suggest some asthmatic children may have been treated as viral bronchiolitis, which highlights the importance of educating clinicians on how to interpret bronchiolitis studies and guidelines[4 9] and how to differentiate viral bronchiolitis from recurrent viral-induced wheezing illnesses in this age group. Given that viral infections are by far the most common cause of asthma exacerbation in young children,[23] the misuse of the term viral bronchiolitis in this population is highly inappropriate and may lead to the mistaken idea that corticosteroids and bronchodilators are not clinically indicated in this setting of viral respiratory infection.

Another finding of our study was the presence of concomitant respiratory comorbidities that are not part of the standard definition of the viral bronchiolitis. Of particular interest was the high number of young children admitted under the umbrella of viral bronchiolitis, who were born severely premature. It is important to mention that most bronchiolitis clinical trials have specifically excluded premature children given the unique host factors that greatly increase the risk for severe respiratory disease.[13 24 25] In this connection, we and others have described dysfunctional airway immune responses in premature babies during respiratory infections caused by RV, RSV, and HMPV.[26–30] This evidence indicates that the pathogenic mechanisms causing respiratory disease during viral respiratory infection in premature infants are distinct and may influence the clinical presentation, prognosis, and management.[31–33] Similarly, in our current study, we identified that many children hospitalized due to viral respiratory infections had the concomitant diagnosis of neuromuscular disease, which put them at high risk for severe respiratory distress due to a myriad of factors, including poor airway clearance, aspiration, and sleep breathing disorders,[34] all of which need treatment approaches not typically considered in the therapeutic algorithm for viral bronchiolitis.[4] Collectively, these new data highlight the importance of taking into account concomitant respiratory conditions before using the term viral bronchiolitis to guide the management of viral respiratory infections in hospitalized children.

The misclassification of viral bronchiolitis identified in our study occurred independently of the viral pathogen, and it was particularly common in cases triggered by RV infection. In this regard, it is important to mention that several studies have highlighted the importance of determining the

specific viral pathogen causing respiratory disease in young children as it may impact the clinical presentation[28 35] and short-term or long-term prognosis.[36] Perhaps the strongest evidence of this comes from the childhood origins of asthma study, which assessed the long-term consequences of viral respiratory infections in early life. This seminal study identified that RV-induced wheezing illnesses in children under 3 years of age increases dramatically the likelihood (10 times OR) of developing asthma beyond childhood.[37] At the molecular level, RV is increasingly recognized to enhance the secretion of T helper 2 pro-asthmatic cytokines,[29] which is now considered one of the most important risk factors for the development of asthmatic condition[38 39] and the most common trigger of asthma exacerbations.[38 39] Accordingly, many of the young children labeled as viral bronchiolitis, who have RV-induced wheezing, may need careful evaluation and follow-up as they are at high risk of recurrent wheezing and asthma development later in life.[38 39] Taken together, these data suggest that using a broad categorical definition to include all viruses as a single respiratory syndrome (viral bronchiolitis) is likely to omit important clinical information that may impact not only the current management but also the short-term and long -term prognosis of viral respiratory infections in young children.

Our study has a number of strengths and some limitations. We included a relatively large cohort of children hospitalized due to viral respiratory infections. We were able to investigate clinical manifestations and definitions (viral bronchiolitis) and correlate these with viral-specific pathogens (determined by PCR). The main limitation of the present study is perhaps the retrospective collection of clinical data. We acknowledge the inherent bias in only including patients who had a viral PCR ordered. Because the clinical guidelines for viral bronchiolitis do not have any targeted therapy, a provider may choose to not order a viral PCR as it may not change management. However, because the data were taken from EMR, and the key variables analyzed are hard variables, it is unlikely that retrospective collection significantly compromised the validity of the results due to misclassifications of disease status. In addition, it is important to emphasize that the study was conducted in a specialized, tertiary referral hospital, which makes it likely that the patients included represent the extreme of the spectrum of severity of all patients with viral respiratory infection, which could limit the generalization of results to other contexts.

In conclusion, our current study identified that a significant portion of children admitted with diagnosis of viral bronchiolitis do not meet the standard definition criteria of this condition. The most common factors leading to misclassification of viral respiratory infection in hospitalized children were the presence of prior wheezing and concomitant respiratory conditions, including prematurity and neuromuscular disease. Given that several clinical trials have used a standard definition of viral bronchiolitis that exclude recurrent wheezing and comorbid conditions, it is critically important for clinicians to understand the applicability and limitations of the evidence generated in viral bronchiolitis research. A comprehensive approach that takes into consideration the heterogeneity and complexity of the pathobiology of viral respiratory infections in young children may lead to a more accurate clinical assessment of this condition and would potentially prevent bronchiolitis misclassification.

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REFERENCES

1 Lambert SB, Allen KM, Carter RC, *et al*. The cost of community-managed viral respiratory illnesses in a cohort of healthy preschool-aged children. *Respir Res* 2008;9:11.
2 Nicolai A, Ferrara M, Schiavariello C, *et al*. Viral bronchiolitis in children: a common condition with few therapeutic options. *Early Hum Dev* 2013;89(Suppl 3):S7–11.
3 Øymar K, Skjerven HO, Mikalsen IB. Acute bronchiolitis in infants, a review. *Scand J Trauma Resusc Emerg Med* 2014;22:22–3.
4 Ralston SL, Lieberthal AS, Meissner HC, *et al*. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2015;136:782.
5 Fernandes RM, Andrade MG, Constant C, *et al*. Acute viral bronchiolitis: physician perspectives on definition and clinically important outcomes. *Pediatr Pulmonol* 2016;51:724–32.
6 National Asthma Education and Prevention Program. *Expert Panel Report III: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: US Department of Health and Human Services, 2007.
7 Iqbal SM. Management of acute viral bronchiolitis in children: evidence beyond guidelines. *Sudan J Paediatr* 2012;12:40–8.
8 World Health Organization. 2013. http://www.who.int/mediacentre/factsheets/fs363/en/
9 National Institute for Health and Care Excellence (NICE). Bronchiolitis in children: diagnosis and management, 2015.
10 Nair H, Simões EA, Rudan I, *et al*. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* 2013;381:1380–90.
11 Meissner HC. Viral bronchiolitis in children. *N Engl J Med Overseas Ed* 2016;374:62–72.
12 Rossi GA, Colin AA. Infantile respiratory syncytial virus and human rhinovirus infections: respective role in inception and persistence of wheezing. *Eur Respir J* 2015;45:774–89.
13 Jackson DJ, Gangnon RE, Evans MD, *et al*. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008:178:667–72.
14 Melendi GA, Laham FR, Monsalvo AC, *et al*. Cytokine profiles in the respiratory tract during primary infection with human metapneumovirus, respiratory syncytial virus, or influenza virus in infants. *Pediatrics* 2007;120:e410–5.
15 Perez GF, Pancham K, Huseni S, *et al*. Rhinovirus infection in young children is associated with elevated airway TSLP levels. *Eur Respir J* 2014;44:1075–8.
16 Ralston SL, Garber MD, Rice-Conboy E, *et al*. Value in inpatient pediatrics network quality collaborative for improving hospital compliance with

AAP Bronchiolitis Guideline (BQIP). A multicenter collaborative to reduce unnecessary care in inpatient bronchiolitis. *Pediatrics* 2016;137:e20150851.
17 Skjerven HO, Rolfsjord LB, Berents TL, *et al*. Allergic diseases and the effect of inhaled epinephrine in children with acute bronchiolitis: follow-up from the randomised, controlled, double-blind, bronchiolitis all trial. *Lancet Respir Med* 2015;3:702–8.
18 Silver AH, Esteban-Cruciani N, Azzarone G, *et al*. 3% Hypertonic saline versus normal saline in inpatient bronchiolitis: a randomized controlled trial. *Pediatrics* 2015;136:1036–43.
19 Smith M, Iqbal S, Elliott TM, *et al*. Corticosteroids for hospitalised children with acute asthma. *Cochrane Database Syst Rev* 2003;(2):CD002886.
20 Lehtinen P, Ruohola A, Vanto T, *et al*. Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema. *J Allergy Clin Immunol* 2007;119:570–5.
21 Grigg J. Role of systemic steroids in acute preschool wheeze. *Arch Dis Child* 2010;95:491–2.
22 Zeiger RS, Mauger D, Bacharier LB, *et al*. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med Overseas Ed* 2011;365:1990–2001.
23 Tan WC. Viruses in asthma exacerbations. *Curr Opin Pulm Med* 2005;11:178–83.
24 Drysdale SB, Lo J, Prendergast M, *et al*. Lung function of preterm infants before and after viral infections. *Eur J Pediatr* 2014;173:1497–504.
25 Melville JM, Moss TJ. The immune consequences of preterm birth. *Front Neurosci* 2013;7:79.
26 Pancham K, Perez GF, Huseni S, *et al*. Premature infants have impaired airway antiviral IFNγ responses to human metapneumovirus compared to respiratory syncytial virus. *Pediatr Res* 2015;78:389–94.
27 Pancham K, Sami I, Perez GF, *et al*. Human metapneumovirus infection is associated with severe respiratory disease in preschool children with history of prematurity. *Pediatr Neonatol* 2016;57:S1875–9572.
28 Rodríguez DA, Rodríguez-Martínez CE, Cárdenas AC, *et al*. Predictors of severity and mortality in children hospitalized with respiratory syncytial virus infection in a tropical region. *Pediatr Pulmonol* 2014;49:269–76.
29 Perez GF, Pancham K, Huseni S, *et al*. Rhinovirus-induced airway cytokines and respiratory morbidity in severely premature children. *Pediatr Allergy Immunol* 2015;26:145–52.
30 Pancham K, Perez GF, Huseni S, *et al*. Premature infants have impaired airway antiviral IFNγ responses to human metapneumovirus compared to respiratory syncytial virus. *Pediatr Res* 2015;78:389–94.
31 Greenough A. Long-term respiratory consequences of premature birth at less than 32 weeks of gestation. *Early Hum Dev* 2013;89(Suppl 2):S25–7.
32 Kotecha SJ, Edwards MO, Watkins WJ, *et al*. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. *Thorax* 2013;68:760–6.
33 Drysdale SB, Lo J, Prendergast M, *et al*. Lung function of preterm infants before and after viral infections. *Eur J Pediatr* 2014;173:1497–504.
34 Birnkrant DJ, Bushby KM, Amin RS, *et al*. The respiratory management of patients with duchenne muscular dystrophy: a DMD care considerations working group specialty article. *Pediatr Pulmonol* 2010;45:739–48.
35 Hong JY, Bentley JK, Chung Y, *et al*. Neonatal rhinovirus induces mucous metaplasia and airways hyperresponsiveness through IL-25 and type 2 innate lymphoid cells. *J Allergy Clin Immunol* 2014;134:429–39.
36 Feldman AS, He Y, Moore ML, *et al*. Toward primary prevention of asthma. Reviewing the evidence for early-life respiratory viral infections as modifiable risk factors to prevent childhood asthma. *Am J Respir Crit Care Med* 2015;191:34–44.
37 Lemanske RF. The childhood origins of asthma (COAST) study. *Pediatr Allergy Immunol* 2002;13(Suppl 15):38–43.
38 Liu L, Pan Y, Zhu Y, *et al*. Association between rhinovirus wheezing illness and the development of childhood asthma: a meta-analysis. *BMJ Open* 2017;7:e013034.
39 Lukkarinen M, Koistinen A, Turunen R, *et al*. Rhinovirus-induced first wheezing episode predicts atopic but not nonatopic asthma at school age. *J Allergy Clin Immunol* 2017;140:988–95.