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The impact of viral bronchiolitis phenotyping: Is it time to consider phenotype-specific responses to individualize pharmacological management?

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SUMMARY

Although recent guidelines recommend a minimalist approach to bronchiolitis, there are several issues with this posture. First, there are concerns about the definition of the disease, the quality of the guidelines, the method of administration of bronchodilators, and the availability of tools to evaluate the response to therapies. Second, for decades it has been assumed that all cases of viral bronchiolitis are the same, but recent evidence has shown that this is not the case. Distinct bronchiolitis phenotypes have been described, with heterogeneity in clinical presentation, molecular immune signatures and clinically relevant outcomes such as respiratory failure and recurrent wheezing. New research is critically needed to refine viral bronchiolitis phenotyping at the molecular and clinical levels as well as to define phenotype-specific responses to different therapeutic options.

Keywords

Bronchiolitis; Viral bronchiolitis phenotyping; Clinical practice guidelines; Phenotype-specific treatment

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APPENDIX A. SUPPLEMENTARY DATA

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THE CLINICAL AND ECONOMIC IMPORTANCE OF VIRAL BRONCHIOLITIS

Viral bronchiolitis is the most important cause of pediatric lower respiratory tract infection (LRTI), and is the leading cause of hospitalization among infants younger than 1 year [1]. Respiratory syncytial virus (RSV) is the most commonly identified virus, being responsible for approximately 60% of cases of bronchiolitis requiring hospitalization [2-4]. Recent reports have shown that RSV-related infection is an important cause of death in younger children, especially in those with comorbidities [5]. Rhinovirus (RV) has also been recognized as a top cause of bronchiolitis and is the second most common virus in infants requiring hospitalization [3,6]. Viral bronchiolitis is usually associated with a substantial clinical and economic burden, mainly in low- and middle-income countries (LMICs) [7], and is considered to be among the most incident and costly pediatric clinical conditions during the first years of life [8]. In addition to the obvious direct costs for healthcare systems, viral bronchiolitis is usually associated with substantial indirect costs for families and for society [9].

DEFINITIONS OF VIRAL BRONCHIOLITIS: LACK OF CONSENSUS AND THE SHORTCOMINGS OF GROUPING DIVERSE RESPIRATORY SYNDROMES AS A SINGLE CONDITION

It is unfortunate that although viral bronchiolitis is one of the most common conditions in infancy, and poses a significant clinical and economic burden, it does not have a unified definition. There is general agreement with respect to the pattern of the presentation of the disease, however, there are international differences in diagnostic criteria [10]. While in North America the presence of wheeze in infants aged up to 24 months is usually a criterion used for defining bronchiolitis [11], in the United Kingdom, the presence of inspiratory crackles in infants aged up to 12 months is the diagnostic criterion [12]. The latter is a major issue because there are age-related differences in disease severity, presence of wheeze and crackles, response to inhaled bronchodilators, progression to recurrent wheezing and asthma, virus predominance, and immune phenotypes [13-17]. The causative virus and the inclusion or exclusion of infants with previous presentations and/or various comorbidities are additional sources of variability [18]. In a recent survey of Spanish pediatricians, it was determined that the adherence to diagnostic criteria for viral bronchiolitis is heterogeneous, with high agreement on issues such as being the first episode of respiratory distress and the usefulness of virus identification in making a diagnosis, but poor agreement on other important issues such as the maximum age for diagnosis [19]. Notably, although there is overall consensus that the term viral bronchiolitis must be used only to describe the first/single episode of viral LRTI in infants, a recent study found that >60% of bronchiolitis cases requiring hospitalization are really recurrent wheezing cases [20]. On the other hand, all cases of recurrent wheezing and childhood asthma initially present as bronchiolitis during infancy (first episode), which makes the current definition of bronchiolitis problematic because it encompasses individuals with different respiratory phenotypes and outcomes that perhaps should not be grouped under the umbrella term of “viral bronchiolitis”.

In summary, the absence of a clear and unified definition of viral bronchiolitis makes the interpretation and comparison between clinical trials and epidemiological studies difficult and challenging, therefore hampering research progress and preventing the development of appropriate evidenced-based guidelines for this condition.

VIRAL BRONCHIOLITIS GUIDELINES: LACK OF ADHERENCE AND ISSUES WITH THE QUALITY OF CURRENT TREATMENT RECOMMENDATIONS

Although in most cases bronchiolitis is a self-resolved condition, some infants develop respiratory distress and pharmacological therapies may need to be considered. The 2006 American Academy of Pediatrics (AAP) bronchiolitis guidelines recommended a bronchodilator trial to treat the subset of infants with viral-induced bronchoconstriction [21]. This approach is no longer recommended in the latest AAP viral bronchiolitis guidelines in 2014 [11,22], a change that has generated controversy in the field [23-25]. Bronchodilators may be useful in some infants with bronchiolitis [23], and clinical studies reporting lack of efficacy have mostly used nebulizer administration instead of metered-dose inhaler with a valved holding chamber (MDI + VHC). This is a major flaw because, as demonstrated by a meta-analysis including six clinical trials (n = 491) [26], bronchodilator via MDI + VHC is more effective than nebulized therapy decreasing hospitalization and improving clinical scores in young children with wheezing, many of them suffering their first episode [26]. In addition, the AAP 2014 bronchiolitis guideline's assertion that clinicians are unable to adequately observe clinically relevant responses to bronchodilator is not congruent with the evidence [27]. A systematic review of all available instruments to evaluate severity of bronchiolitis identified a total of 32 tools, some of them considered to have adequate "responsiveness" [28,29], defined as the ability of a score to detect clinically important changes over time in response to interventions such as bronchodilators [27].

The controversy generated by the minimalist approach of the 2014 AAP bronchiolitis guidelines has resulted in an overall lack of adherence by pediatric care providers [30,31]. The lack of adherence to medical guidelines is strongly linked to the quality of the guidelines themselves [32,33], which may be the case in viral bronchiolitis [34]. The latter is supported by a systematic and rigorous quality evaluation of the AAP 2014 bronchiolitis guidelines using the Appraisal of Guidelines for Research & Evaluation (AGREE) II Instrument [34]. Based on AGREE II criteria these guidelines are sub-optimal and "recommended with modifications" with the lowest score in the "applicability domain", a marker of failure to identify facilitators and barriers for bridging the gap between research and clinical practice [34]. As further detailed below, we feel that one of the critical gaps between research and clinical practice leading to disagreements in current viral bronchiolitis definitions and guidelines is the lack of consideration of different respiratory phenotypes and potential phenotype-specific responses to different therapeutic options.

NOT ALL BRONCHIOLITIS CORRESPONDS TO THE SAME CLINICAL CONDITION: VIRAL BRONCHIOLITIS RESPIRATORY PHENOTYPING

An important issue to be considered when treatment recommendations from bronchiolitis guidelines are critically analyzed is the implicit assumption that we are treating a homogeneous group of patients with the same clinical condition. The guidelines group all acute viral respiratory infections as a single respiratory syndrome named “viral bronchiolitis”, assuming a similar clinical picture independent of the viral etiology or individual host responses and risk factors [20]. Reynolds and Cook stated more than half a century ago that “Much of the confusion about the management of bronchiolitis results from the fact that there are probably two groups of patients: (1) those with obstructive disease resulting entirely from infection, thickening of the bronchiolar walls, and intrabronchiolar secretions and (2) those with a predisposition to asthma who develop obstruction as a result of both inflammation and bronchospasm” [35]. They also mentioned that these two groups cannot readily be distinguished on clinical grounds and need to be clarified by further studies. Nowadays, there is increasing and convincing evidence showing that not all “viral bronchiolitis” corresponds to the same clinical condition, and that affected patients have high heterogeneity in their clinical presentation, immune responses, molecular immune signatures, and probably distinct response to different therapeutic options (phenotype-specific treatment strategies). Dumas et al. identified several distinct clinical profiles (phenotypes) in two multicenter studies of children hospitalized for bronchiolitis [36]. Using a clustering approach, the authors identified the following four profiles: profile A, patients characterized by history of wheezing and eczema, wheezing at the emergency department (ED) presentation and rhinovirus infection; profile B, children with wheezing at the ED presentation, but, in contrast to profile A, most did not have history of wheezing or eczema; profile C, the most severely ill group, with a longer hospital stay and moderate-to-severe retractions; and profile D, the least severely ill group, including non-wheezing children with a shorter length-of-stay. Notably, profile B infants had the largest probability of RSV-infection [36], and Profile A infants had higher eosinophil counts, higher cathelicidin levels, and increased *Haemophilus*-dominant or *Moraxella*-dominant microbiota profiles. Additionally, compared with profile B infants, those with profile A had a significantly increased risk of recurrent wheezing [37].

Cangiano et al. analyzed the epidemiological characteristics of infants with bronchiolitis over 10 consecutive seasons and evaluated whether there are any clinical differences between infants hospitalized for bronchiolitis during peak epidemic months and those hospitalized in non-peak months. They found that infants hospitalized during peak months had a lower family history for asthma, more smoking mothers during pregnancy, were slightly more breastfed, had a lower number of blood eosinophils, and had a higher clinical severity score, and hypothesized that infants hospitalized for bronchiolitis during peak months and those hospitalized during non-peak months might reflect two different populations of children [38]. The same group reported differing Th1/Th2 response in these patients. Those infants hospitalized during the non-peak months had a significantly higher percentage of CD4 T cells producing IL-4, a slightly lower percentage of CD8 T cells producing IFN γ , and a significantly higher Th2 polarization than infants hospitalized during

the peak months. They hypothesized that there are at least two different bronchiolitis phenotypes: previously healthy full-term infants hospitalized with RSV bronchiolitis during the peak months, and infants with a possible genetic predisposition to atopy, hospitalized during the non-peak months [39]. Recently, the same group went further in their work, reporting different disease courses in infants hospitalized for acute RSV bronchiolitis, depending on the RSV genotype. The authors prospectively enrolled 312 previously healthy term infants less than 1 year old hospitalized for bronchiolitis over 12 epidemic seasons and found that on stratifying data according to genotypes NA1, ON1, and BA, NA1-infected infants were the youngest and had the most severe clinical course. Conversely, BA infected infants had less severe symptoms and more frequently had eosinophilia and a family history of asthma. Infants with the ON1 genotype had a milder clinical course than those with NA1 and more risk factors for asthma, despite having the highest viral loads [40]. Similarly, Bhavnani, S. K. et al. aimed to identify inherent hostspecific genetic and immune mechanisms in children under two years of age with influenza or RSV infections that develop severe disease resulting in hospitalization despite having no identifiable clinical risk factors, through the use of bipartite networks. The analysis revealed three clusters of cases common to both types of infection: core cases with high expression of genes in the network core implicated in hyperimmune responsiveness; periphery cases with a lower expression of the same set of genes indicating medium-responsiveness; and control-like cases with a gene signature resembling that of the controls, indicating normal responsiveness [41].

Viral etiology adds further complexity, because it has been reported that demographic characteristics and clinical severity of bronchiolitis may depend on the number of viruses or on the specific virus detected [42,43]. Relative to infants with RSV bronchiolitis, those with RV bronchiolitis have a shorter hospital length of stay [44], are more likely to be treated with systemic corticosteroids [45], and have an increased risk of asthma [46-48]. Bronchiolitis occurring during RV-predominant months has been associated with an estimated 25% increased risk of early childhood asthma compared with RSV-predominant months [49]. Multi-omic analysis of nasopharyngeal airway samples shows pathobiological differences between RSV and RV bronchiolitis, with different mechanisms that involve a complex interplay between virus, microbiome, and host [50]. RSV and RV infections have different nasal airway microRNA profiles associated with a nuclear factor kappa-light-chain-enhancer of activated B cell (NF- κ B) signaling [51]. In addition, recent evidence shows that compared to infants with RSV bronchiolitis, those with RV bronchiolitis display a predominant Th2 oriented immune response, with significantly higher Th2 cells frequencies, Th2 index [52], and increased airway interferon lambda receptor 1 (IFNL1R) transcript levels [53]. Although replication is needed, all this evidence collectively demonstrates that bronchiolitis is a heterogeneous condition with multiple phenotypes and endotypes (i.e. specific pathobiological mechanisms that underlie the observable properties of different phenotypes) [54]. Current phenotypes/endotypes of bronchiolitis are shown in Table 1. The multiple faces of the umbrella term “viral bronchiolitis” are depicted in Fig. 1.

VIRAL BRONCHIOLITIS PHENOTYPING: THERAPEUTIC IMPLICATIONS

Although most bronchiolitis guidelines recommend an approach called “minimal handling” based on the best available evidence, the compelling data showing that not all cases of viral

bronchiolitis correspond to the same clinical condition (Table 1) indicates that not all patients should be treated in the same way. It sounds plausible to consider pharmacological treatment (e.g. bronchodilators or corticosteroids) in infants with progressive disease that may require hospitalization for viral bronchiolitis and patients with recurrent wheezing illnesses, given that some of them likely have a phenotype with pro-asthmatic immune responses (Fig. 1). A conservative approach would be to consider performing a trial of bronchodilators via MDI + VHC [26], at least in patients with moderate to severe respiratory distress, with the recommendation to continue their use only if there is a documented positive clinical response to the trial using a validated clinical system of evaluation [27].

Along the same line, a systemic (oral or parenteral) “asthma burst” type therapy could be considered in some infants with moderate to severe respiratory distress, particularly in those who improve significantly after a trial of bronchodilators or have other individual factors suggesting an asthmatic phenotype. Al-Shawwa demonstrated that in non-RSV cases with a positive family history of asthma and/or allergic rhinitis, the use of systemic corticosteroids helps to reduce hospitalization rates [55]. Furthermore, Alansari et al. reported that dexamethasone with salbutamol shortened the time for readiness for inpatient discharge during bronchiolitis episodes in patients with eczema or a family history of asthma in a first-degree relative [56]. Notably, individualized therapeutic considerations in viral bronchiolitis are already widely used by pediatric providers [31,57]. There are studies reporting that physicians, probably intuitively or perhaps even instinctively, use albuterol and other therapeutic options not recommended for routine use in current bronchiolitis guidelines, based on several patient characteristics such as age, presence of wheezing, and atopic dermatitis [31,57].

DIRECTIONS FOR FUTURE RESEARCH

In summary, the failure of clinical studies investigating therapies for all cases of “viral bronchiolitis” have led to a potentially dangerous “minimal handling” approach endorsed by AAP bronchiolitis guidelines because no therapy can be recommended for all cases of this condition. The latter likely reflects the heterogeneity of the multiple faces of the umbrella term “viral bronchiolitis”, and not really lack of responsiveness to all pharmacological therapies. Before embarking in more clinical trials and guidelines updates, we believe there is a critical need to re-define this condition considering phenotype-specific mechanisms of disease as an essential notion to individualize therapeutic recommendations. We totally agree with Alvarez Paggi and Polack that “the syndrome we have been calling bronchiolitis for eighty years may evolve into a discrete group of disease endotypes with specific diagnostic tests, finer prognostic tools, and tailored therapeutics. And the search for the panacea will be finally abandoned” [24]. Cutting-edge studies are now using computational biology integrating multi-omic data to describe the main viral bronchiolitis subsets and hypothesize molecular mechanisms for each of them. The introduction of models of the human infant airway is likely the next step to rigorously validate and refine the postulated mechanism(s) for each disease subset. This translational approach may lead to new ways to diagnose and treat viral respiratory illnesses in young children based on individual molecular pathobiology. The latter would be a major milestone to: 1) re-define viral bronchiolitis based on standardized phenotyping at the molecular and clinical levels; and 2) allow the design of

new clinical trials to establish the best phenotype-specific responses to different therapeutic options. Then we will be ready to develop guidelines that truly help clinicians treat this common and potentially serious respiratory condition.

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Educational aims

The reader will be able:

- To understand the shortcomings of the umbrella term “viral bronchiolitis” and the minimalist approach of the 2014 AAP bronchiolitis guidelines.
- To identify the distinct bronchiolitis phenotypes based on clinical presentation, molecular immune signatures, viral pathogen and clinically relevant outcomes.
- To discuss the potential therapeutic implications of viral bronchiolitis phenotyping.

Fig. 1.

The multiple faces of the umbrella term “viral bronchiolitis” RV: rhinovirus; RSV: respiratory syncytial virus, LOS: length of stay.

Table 1

Different potential phenotypes/endotypes of bronchiolitis.

Author	Year	Country	Phenotypes/endotypes of bronchiolitis
Reynolds E.O. et al. [35]	1963	United States	<ul style="list-style-type: none"> Patients with obstructive disease resulting entirely from infection, thickening of the bronchiolar walls, and intrabronchiolar secretions. Patients with a predisposition to asthma who develop obstruction as a result of both inflammation and bronchospasm.
Dumas O. et al. 36,37]	2016, 2018	United States, France	<ul style="list-style-type: none"> Profile A: children with history of wheezing and eczema, wheezing at the ED^a presentation and RV^b infection. Children with the higher eosinophil counts, higher cathelicidin levels, and increased proportions of Haemophilus-dominant or Moraxella-dominant microbiota profiles. Profile B: children with wheezing at the ED presentation, without history of wheezing or eczema, and the largest probability of RSV^c infection. Profile C: the most severely ill group, with longer hospital stay and moderate-to-severe retractions. Profile D: the least severe illness, including non-wheezing children with shorter length-of-stay.
Cangiano G. et al. 38], Nenna R. et al. [39]	2016, 2018	Italy	<ul style="list-style-type: none"> Infants hospitalized during peak months: lower family history for asthma more smoking mothers during pregnancy, higher breastfed, lower number of blood eosinophils, higher clinical severity score, and a higher probability of RSV infection.
Midulla F. et al. 40]	2018	Italy	<ul style="list-style-type: none"> Infants hospitalized during non-peak months: significantly higher percentage of CD4 T cells producing IL-4, a slightly lower percentage of CD8 T cells producing IFNγ, and a significantly higher Th2 polarization. Genotype NA1: the youngest patients and those with the most severe clinical course.
Bhavnani, S. K. et al. 41]	2014	United States	<ul style="list-style-type: none"> Genotype BA: patients with less severe symptoms and more frequently eosinophilia and a family history of asthma. Genotype ON1: patients with a milder clinical course than those with NA1 and more risk factors for asthma, despite having the highest viral loads. Core cases: high expression of genes in the network core implicated in hyperimmune responsiveness. Periphery cases: lower expression of the same set of genes indicating medium-responsiveness. Control-like cases: with a gene signature resembling that of the controls, indicating normal responsiveness.
Mansbach J.M. et al., [44,45], Jackson D.J. et al. [46], Rubner F.J. et al. [47], Frassanito A et al. 48, Carroll K.N. et al. 49, Stewart C.J. et al. [50], Hasegawa K. et al. [51], Fedele G., et al. [52], Pierangeli A. et al. 53]	2008-2018	United States, Italy	<ul style="list-style-type: none"> RV-bronchiolitis: Compared to infants with RSV-bronchiolitis, patients with RV-bronchiolitis have shorter hospital length of stay, are more likely to be treated with systemic corticosteroids, have an increased risk of asthma, display a predominant Th-2 oriented immune response, with significantly higher Th2 cells frequencies, Th2 index, and increased airway interferon lambda receptor 1 (IFNL1R) transcript levels. Also infants with RV-bronchiolitis have upregulation of NFκB family (RelA and NFκB2), downregulation of inhibitor κB family, and higher levels of NFκB-induced type-2 cytokines (IL-10 and IL-13). RV-bronchiolitis is associated with increased levels of essential and nonessential N-acetyl amino acids and with a high relative abundance of Haemophilus influenzae. RSV-bronchiolitis: associated with metabolites from a range of pathways and with a microbiome dominated by Streptococcus pneumoniae.

RSV: Respiratory syncytial virus

RV: Rhinovirus

ED: Emergency department

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