REVIEW
BRONCHIOLITIS

The use of β_2-adrenoreceptor agonists in viral bronchiolitis: scientific rationale beyond evidence-based guidelines

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ABSTRACT Despite scientific evidence proving that inhaled β_2-adrenergic receptor (β_2-AR) agonists can reverse bronchoconstriction in all ages, current guidelines advocate against the use of β_2-AR bronchodilators in infants with viral bronchiolitis because clinical trials have not demonstrated an overall clinical benefit. However, there are many different types of viral bronchiolitis, with variations occurring at an individual and viral level. To discard a potentially helpful treatment from all children regardless of their clinical features may be unwarranted. Unfortunately, the clinical criteria to identify the infants that may benefit from bronchodilators from those who do not are not clear. Thus, we summarised the current understanding of the individual factors that may help clinicians determine the highest probability of response to β_2-AR bronchodilators during viral bronchiolitis, based on the individual immunobiology, viral pathogen, host factors and clinical presentation.

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There are several factors that may help clinicians determine the highest probability of response to β_2-AR bronchodilators during viral bronchiolitis, based on the individual immunobiology, viral pathogen, host factors and clinical presentation https://bit.ly/30CoHcH

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Introduction

Viral bronchiolitis is the most important cause of lower respiratory tract infection (LRTI) in children during the first 2 years of life and is the leading cause of hospitalisation among infants younger than 1 year [1–3]. Despite the high incidence of viral bronchiolitis, there is not yet a unified definition nor international agreement on diagnostic criteria of the disease: while in North America the presence of wheezing in infants aged up to 24 months is usually a criterion used for defining bronchiolitis, in the UK, the presence of inspiratory crackles in infants aged up to 12 months is the diagnostic criterion [4]. The latter is a major issue because it makes comparison of therapeutic studies difficult.

β_2-Adrenergic receptor (β_2-AR) agonists are essential for the management of many conditions causing lower airway obstruction in adults and children [5, 6]. β_2-AR agonists prevent bronchial airway smooth muscle (ASM) constriction increasing the production of cyclic AMP, the primary mediator of relaxation in the ASM cell [5, 6]. Given that viruses and pro-asthmatic type 2 cytokines (*e.g.* interleukin (IL)-4/IL-13) directly elicit bronchial ASM constriction [7–14], β_2-AR agonists are primarily used as a "rescue" bronchodilator therapy during virus or allergen induced exacerbations of asthma, and other causes of episodic wheezing (*e.g.* exercise-induced ASM bronchoconstriction). Clinically, there is no doubt that with proper use of inhaler devices, β_2-AR agonists can deposit in the lower airways and can induce potent bronchodilation in all age groups, including newborns and infants [15–19].

Despite scientific evidence proving that the ASM is present and fully functional during early human life [20, 21], and that β_2-AR agonists can reverse bronchoconstriction in newborns and young children [15–19], clinical trials (all of them with albuterol by nebuliser but not by metered dose inhaler- MDI with a spacer) have failed to demonstrate an overall clinical benefit of β_2-AR agonists in infants with "viral bronchiolitis" [22]. As a result, viral bronchiolitis guidelines advocate against the use, or even a therapeutic trial, of bronchodilators [23, 24]. However, the presence of multiple viral bronchiolitis phenotypes [4] indicates that while β_2-AR agonists may be ineffective in some cases, bronchodilators are potentially useful in in infants with a phenotype in which bronchial ASM hyperreactivity is a primary component. Unfortunately, there are no criteria to identify infants with viral bronchiolitis that may benefit from β_2-AR agonists from those who do not. Thus, we aimed to perform a narrative review to summarise and analyse the current scientific evidence that may help to identify possible phenotypes or subgroups of responders to β_2-AR agonist bronchodilators among infants with "viral bronchiolitis".

Evidence-based medicine guidelines and the need for phenotype-specific treatments in viral bronchiolitis

For decades, the treatment of bronchiolitis has been mostly supportive, focussing only on observation, hydration and oxygen supplementation. Although prior evidence-based medicine clinical practice guidelines (CPGs), such as the 2006 American Academy of Pediatrics (AAP) bronchiolitis CPG, recommended the use of β_2-AR agonist bronchodilators on a trial basis [25], the latest evidence-based CPGs on viral bronchiolitis no longer recommend a trial of bronchodilators [23, 24]. The most commonly argued reasons for these new recommendations are the greater strength of the evidence demonstrating no benefit in the viral bronchiolitis population as a whole, and that there is no "objective method" of determining response [23]. However, the implicit assumption of these evidence-based medicine guidelines is that the group of infants with "viral bronchiolitis" is homogeneous, which is no longer considered true [4]. Recent studies have identified multiple viral bronchiolitis phenotypes with high heterogeneity in clinical presentation and molecular pathobiology, indicating that we also need to consider heterogeneity in the response to different therapeutic options (phenotype-specific treatment strategies) [4]. Despite this novel understanding of the disease, it is currently unknown which patients are most likely to benefit from the available respiratory therapies (*i.e.* β_2-AR agonist bronchodilators such as albuterol) [26]. Just as it is inappropriate to use β_2-AR agonist indiscriminately in all patients with the diagnosis of "viral bronchiolitis", we would contend that it is also inappropriate to not administer it to patients who could benefit from this medication. Indeed, inhaled β_2-AR agonists are effective inducing bronchodilation in newborns and infants according to objective clinical and functional respiratory parameters [15–19]. Thus, the lack of response in prior clinical trials might be related to issues with the study design (*e.g.* definition of bronchiolitis, inappropriate outcomes, nebulised normal saline treatment rather than placebo effect [27], and not trials with albuterol by MDI) and the fact that some infants with viral respiratory illnesses may have bronchial ASM hyperactivity but others do not. Using inhaled β_2-AR agonist based on specific patient characteristics or biomarkers, instead of a "one-size-fits-all" guideline-based approach [4] can lead to a more cost-effective treatment strategy centred on personalised and precision medicine, which may ultimately improve the outcomes of all subtypes of "viral bronchiolitis".

β_2-AR agonist responsiveness and virus-induced type 2 immune signatures

The most appropriate way to identify infants with viral bronchiolitis who may benefit from β_2-AR agonists from those who do not, is to conduct randomised clinical trials using stratified randomisation based on the

presence or absence of certain clinical characteristics or biomarkers that could be plausibly associated with a clinical response to β_2-AR agonists. In the meanwhile, current practice requires that clinicians integrate scientific evidence with individual clinical and molecular signatures to select the patient profile with the greatest likelihood of response to β_2-AR agonists. This profile could provide a scientific rationale for bronchodilator administration in a subset of patients with "viral bronchiolitis", at least on a therapeutic trial basis [28].

Notably, there is a strong scientific rationale to link the bronchiolitis profile characterised by ASM hyperactivity and responsiveness to β_2-AR agonists with the presence of T-helper cell type 2 (Th2 cell) responses, which are also defined as "type 2" to encompass other cells (*e.g.* innate lymphoid cells type 2 and the airway epithelium) [29]. Indeed, several studies have shown that Th2/type 2 cytokines such as IL-4/IL-13 can directly induce ASM alterations in calcium homeostasis [9–14], activation of the mitogen-activated protein kinases [9–14], changes in phosphodiesterase activity and cAMP metabolism [30–32], and activation/desensitization to β_2-AR and G protein-coupled receptor signalling [30–32].

Collectively, these Th2/type 2-driven molecular changes create an ASM "pro-asthmatic" phenotype that is hyperresponsive to contractile agonists and viruses [9–14]. In view of the latter mechanisms, Th2/type 2 inflammation, a common feature of the atopic and asthmatic condition [33], is often considered a molecular signature of β_2-AR agonist-responsive airway obstruction [34]. For example, Seumois *et al.* [34] found a significant association between bronchodilator reversibility post-albuterol and a Th2 transcriptional profile in adult asthmatics. The presence of bronchodilator reversibility has been associated with asthma in the paediatric population as well [15]. In addition, Debley *et al.* [17] identified that exhaled nitric oxide fraction, which is considered a biomarker of Th2/type 2 airway inflammation [35], predicts changes in lung function and risk of future wheezing in wheezy infants and toddlers.

In the context of viral bronchiolitis, it is important to mention that several studies have described that respiratory syncytial virus (RSV) and rhinovirus, the most common causes of bronchiolitis [36], are more likely to elicit Th2/type 2 airway responses and bronchial ASM hyperactivity in neonatal mice than in mature animals [35, 37]. Similarly, studies in human infants have reported that early-life rhinovirus infections are associated with robust Th2/type 2 airway responses [38, 39], and that RSV-infected infants with severe disease exhibit a Th2 polarisation in their respiratory secretions [40, 41].

Causative virus, viral bronchiolitis seasonality, and potential implications for β_2-AR agonist responsiveness

Respiratory viruses can promote Th2/type 2 responses during early life [35, 37–41], but the degree in which this occurs seems to be modified by the virus type. Studies suggest that rhinovirus-infected infants display a different acquired immunological response compared to infants with RSV bronchiolitis, with a stronger predominance of Th2 polarisation (Th2/Th1 ratios) [42]. There are also reported differences in the airway transcriptomic profiles of infants with rhinovirus and RSV infections [43]. Using network analysis, Turi *et al.* [43] identified that type-2 and type-17 cytokines were central to the immune response to RSV, whereas growth factors and chemokines were central to the immune response to rhinovirus. Hasegawa *et al.* [44] demonstrated that infants with rhinovirus have higher levels of nuclear factor (NF)-κB signalling responses and type-2 cytokines compared to those with RSV infection.

In the same line, there is evidence showing that RSV and rhinovirus bronchiolitis are associated with significantly different nasopharyngeal metabolome, and bacterial metagenome [45, 46]. For instance, Stewart *et al.* [45] demonstrated that RSV and rhinovirus are associated with different metabolic pathways and that the associated bacterial functional capacity is derived primarily from *Streptococcus pneumoniae* in RSV bronchiolitis and from *Haemophilus influenzae* in rhinovirus bronchiolitis. In addition to these airway molecular differences, prior studies have also found that rhinovirus and RSV infections exhibit distinct clinical features in young children [47, 48]. In comparison to infants with RSV bronchiolitis, those infected with rhinovirus are more likely to be older, to have a prior history of eczema, to be treated with systemic corticosteroids [48]; have a significantly shorter length of stay [49]; and have an increased risk of subsequent development of childhood asthma [50, 51]. However, it is worth mentioning that respiratory viral testing could not be available for routine clinical use, especially for patients with mild to moderate bronchiolitis. This fact could limit the clinical utility of the knowledge of the causative virus as a potential predictor of response to β_2-AR agonists.

These data indicate that young children with rhinvirus-bronchiolitis are more likely than their counterparts with RSV infection to have asthma-like characteristics (*i.e.* wheezing, atopic characteristics, Th2/type 2 signatures) [47, 48], which in turn may be associated with a greater component of ASM hyperreactivity and responsiveness to β_2-AR agonists bronchodilators.

Closely related to the causative virus, another factor that modifies the interplay between early viral infection and the development of airway hyperreactivity is the season of presentation. Cangiano *et al.* [52]

divided infants according to hospitalisation during the peak months or non-peak months (with RSV infections predominating during the peak months) and found significant differences in terms of risk factors for respiratory diseases. They found that infants hospitalised during peak months had a lower family history of asthma, more smoking mothers during pregnancy, were slightly more breastfed, had a lower number of blood eosinophils, and had higher clinical severity scores [52]. The authors hypothesised that infants hospitalised during the peak months of bronchiolitis epidemics and those hospitalised in non-peak months might reflect two different populations of infants [52]. The same group performed additional analyses aimed at testing the hypothesis that the balance of type 1/type 2 immune responses differs between these two populations of infants. They found that infants hospitalised 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 interferon γ, and a significantly higher Th2 polarisation than infants hospitalised during the peak months. In addition, other studies have estimated a population-based 25% increased risk of early childhood asthma following infant bronchiolitis occurring during rhinovirus-predominant months compared to asthma following infant bronchiolitis during RSV-predominant months [53]. Taking together, these studies suggest two different bronchiolitis phenotypes: previously healthy full-term infants hospitalised with RSV bronchiolitis during the peak months, and infants with a possible genetic predisposition to atopy, hospitalised during the non-peak months [53].

Host factors potentially linked to ASM hyperactivity and β_2-AR agonist responsiveness during viral bronchiolitis

There are multiple viral bronchiolitis phenotypes characterised by distinct host factors [54], and likely different probability of ASM hyperactivity and response to β_2-AR agonists. Dumas *et al.* [54] analysed data from two prospective, multi-centre cohorts of children younger than 2 years hospitalised with viral bronchiolitis to define individual profiles using latent class analysis based on clinical factors and viral aetiology. Among the four clinical profiles (phenotypes) identified, it is worth highlighting the "profile A": patients characterised by history of wheezing and eczema, wheezing at presentation and rhinovirus infection. Children in this profile were also more often boys, older (>6 months), and had more often a parental history of asthma [54]. These results suggest that there is a subset of viral bronchiolitis characterised by early signs of asthma/atopy and older age that may have increased probability of response to β_2-AR agonists. In support of this notion, a classical study that measured the respiratory resistance and the thoracic gas volume before and after nebulised salbutamol therapy in 32 wheezing children, using a modification of the forced oscillation technique and total body plethysmograph, found that while no child under 18 months of age showed a greater than 5% fall in resistance or any fall in thoracic gas volume, the majority of children over 20 months showed a fall in resistance greater than 20% [55]. Additionally, a previous meta-analyses of the efficacy of bronchodilator therapy in viral bronchiolitis showed modest short-term improvements in older infants (>12 months) [56, 57]. Unfortunately, more recent meta-analysis have failed to include age subgroup analyses to confirm these previous findings [22, 58]. However, when analysing the results of studies included in the National Institute for Health and Care Excellence (NICE) guidance on the diagnosis and management of bronchiolitis that recruited children 24 months or younger (as compared to those studies that included younger infants) [59], β_2-AR agonists use was associated with significant improvements in outcomes such as accessory muscle score, oxygen saturation, respiratory rate [60], clinical respiratory scores [61, 62] and respiratory distress [63]. It is worth mentioning that two independent studies aimed at better understanding of predictors of prescription of albuterol in viral bronchiolitis identified age as an independent predictor, with the older patients being more likely to be prescribed with this β_2-AR agonist therapy [64, 65]. Altogether, these results indicate that the older the patient with viral bronchiolitis, the higher the probability of obtaining clinical benefit with β_2-AR agonists.

Atopy (*e.g.* eczema) is another host factor that may be associated with a higher probability of airway hyperactivity and β_2-AR agonist responsiveness during viral bronchiolitis. Alansari *et al.* [66] reported that dexamethasone with salbutamol shortened the time for readiness for infirmary discharge during viral bronchiolitis episodes in patients with eczema or a family history of asthma in a first-degree relative. Additionally, eczema was identified as an independent predictor of inappropriate use of diagnostic test and management of bronchiolitis, defined as not following the recommendations given in the main CPGs on how to diagnose and manage patients with viral bronchiolitis. Notably, the lack of adherence to these recommendations was mainly due to the use of β_2-AR agonists (in 89.4% of patients) [67]. There is also evidence showing that atopic dermatitis aggravates allergic airway inflammation in patients with acute viral bronchiolitis [68]. Notably, there is strong evidence suggesting that the interplay between early viral infection and the development of airway hyperreactivity and asthma is also influenced by the individual genetic background. Indeed, genome-wide association studies (GWAS) have shown that the ORMDL3

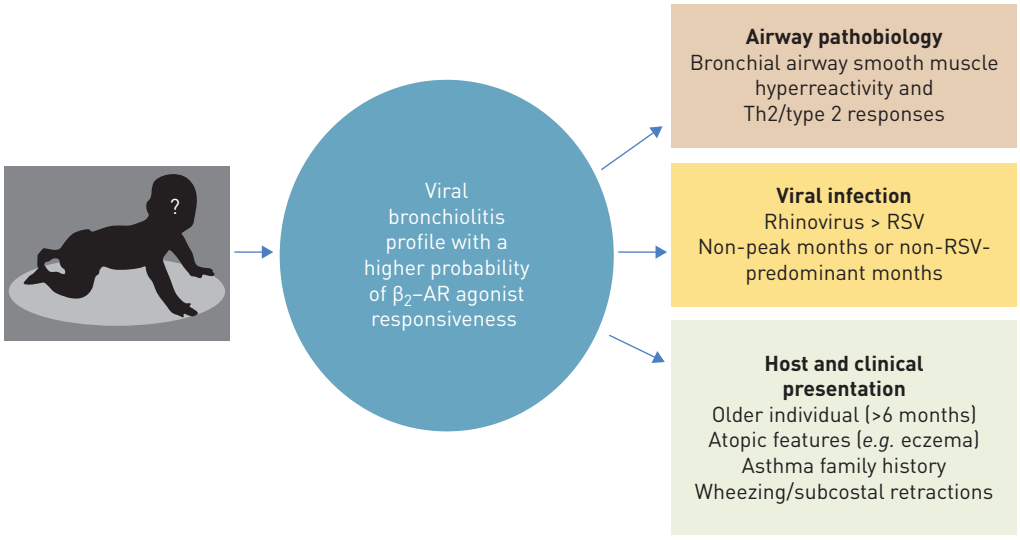

FIGURE 1 Viral bronchiolitis profile with a higher probability of β_2-adrenergic receptor (β_2-AR) agonist responsiveness. Th2: T-helper cell type 2; RSV: respiratory syncytial virus.

locus in chromosome 17q, the most highly replicated GWAS finding for asthma to date, seems to exert its effects by increasing susceptibility to rhivovirus wheezing illnesses in early life [69].

Bedside parameters and viral bronchiolitis respiratory phenotypes

The clinical presentation of viral bronchiolitis is heterogeneous and individual bedside parameters may also be used to assess airway hyperactivity and possible β_2-AR agonist responsiveness. Specifically, while wheezing and sub-costal retractions most likely represent underlying bronchial ASM hyperactivity (airway obstruction and hyperinflation/diaphragm flattening, respectively) [70, 71], hypoxaemia is primarily a clinical manifestation of ventilation/perfusion mismatching and/or diffusion abnormalities due to lung parenchyma compromise, particularly in the absence of wheezing and sub-costal retractions [72]. This concept was recently investigated by Arroyo *et al.* [72] using a weighted score system to integrate cardinal bedside parameters of viral bronchiolitis (wheezing, sub-costal retractions, hypoxaemia). Notably, this weighted scored system predicted the risk of recurrence of virus-induced LRTI illnesses, suggesting that bedside clinical parameters may help to identify the presence of recurrent virus-induced bronchial ASM hyperreactivity [72]. In addition, wheezing and family history of asthma showed the best predictive model for recurrence after viral LRTI hospitalisation [72], and young children with recurrent viral-induced wheezing had higher nasal airway levels of type 2 cytokines (IL-4/IL-13) [73].

Concluding remarks

Despite the CPGs recommendation against the use of β_2-AR agonist bronchodilators in infants with viral bronchiolitis, even on a trial basis [23–25], there is evidence that this has not had a major impact on physicians' behaviour [74, 75]. The rates of bronchodilator use in viral bronchiolitis range from 18% to 90% with substantial differences between countries and even among hospitals in the same country [64, 67, 76]. At first glance these data may be interpreted simply as inappropriate compliance with the bronchiolitis CPGs. However, the real issue is more complex and likely reflects the lack of criteria to identify infants with viral bronchiolitis that may benefit from bronchodilators from those who do not.

Accordingly, although acknowledging some speculation (due to the fact that responsiveness to β_2-AR agonists does not automatically imply improvement in clinically important outcomes, and to the lack of current randomised data to fully support their routine usage), based on our review and analysis of the literature we propose the following features (figure 1) to identify the subset of infants with viral bronchiolitis that most likely will benefit from β_2-AR agonist: 1) older infants (>6 months) with rhinovirus-bronchiolitis, 2) viral bronchiolitis occurring during non-peak months or during non-RSV-predominant months, 3) viral bronchiolitis presenting predominantly with wheezing/subcostal retractions, and 4) infants with viral bronchiolitis and atopic features (*e.g.* eczema) or a family history of asthma in a first-degree relative. Although at the moment this patient's profile could serve as a basis for rational administration of bronchodilators in patients with viral bronchiolitis, at least on a therapeutic trial basis, we believe that this β_2-AR agonist-responsive profile, in combination with robust airway biomarkers,

could be the starting point for future targeted randomised clinical trials to rationalise the use of bronchodilators and improve outcomes in all the subsets of infants with viral bronchiolitis.

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