

# PRESCHOOL WHEEZING PHENOTYPES

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## ABSTRACT

Wheezing in preschool children is very common, with a wide differential diagnosis. It is essential to be sure of the exact sound that parents are describing; the term 'wheeze' is often applied to non-specific sounds. Structural airway disease such as vascular ring should be considered. Thereafter we propose that umbrella terms for preschool wheeze should be abandoned in favour of 'Hargreave phenotyping', in which the presence and extent of the components of infection, inflammation, variable airflow obstruction, and fixed airflow obstruction are determined as far as is possible, rather than using a general umbrella term such as 'asthma'. The justification for this approach is that it leads to a logical approach to treatment in the disparate airway diseases presenting in the preschool years, and should hopefully prevent over-treatment with inhaled corticosteroids. If, despite this approach, doubt remains as to the nature of the airway disease, then a therapeutic trial of treatment is permissible, but it should be for a short defined period only. In any event, such children should be reviewed regularly to see if treatments need to be changed.

**Keywords:** Asthma, airway inflammation, inhaled corticosteroid, phenotype, bacterial bronchitis, obliterative bronchiolitis, persistent airflow limitation, airway hyper-responsiveness, bronchomalacia.

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## BACKGROUND

Approximately one-third of children are diagnosed with wheeze in the first 3 years of life, making wheeze one of the commonest respiratory symptoms.<sup>1</sup> The differential diagnosis of wheeze is wide, and different management strategies are needed depending on the underlying phenotype.<sup>2</sup> Unfortunately, investigative strategies are crude in the extreme, hampering progress both in managing individuals and also in understanding disease groups. The aim of this review is to discuss the reasons as to why preschool children wheeze; to propose a logical, 'Hargreave-driven', clinically relevant approach to phenotyping;<sup>3,4</sup> and to discuss the consequences for management of these wheeze phenotypes (Table 1). There is no point at all in phenotyping or carrying out any other splitting exercise unless there are useful

consequences, such as a better understanding of disease or a change in treatment approach.

We will demonstrate that this Hargreave-driven approach to airway disease does have important consequences, and that the use of umbrella terms such as 'asthma' is about as useful as the old, long superseded 'diagnostic' labels of anaemia and arthritis. This approach means that airway disease is described in precise terms, and over-treatment of children with corticosteroids with no evidence of eosinophilic inflammation is avoided. Ideally, treatment in preschool children would be based on objective measurements of lung function and airway inflammation and infection, and this should be our aspiration; however, these tests are rarely available in current clinical practice.

## IS IT WHEEZE AT ALL?

The word 'wheeze' is used to describe many different sounds. In one study, there was <50% agreement between parents and clinicians on whether the child wheezed, and only 11% of parents mentioned 'whistling' as part of their description of wheeze.<sup>5</sup> Another study used objective transthoracic recordings of added sounds as the 'gold standard', and showed that there was only 32% agreement between parents and physicians; the objective recording correlated with the physician report. Nurses and parents were equally unreliable.<sup>6</sup> Another study, this time using a video questionnaire as the gold standard, reported that 30% of parents used words other than wheeze to describe wheeze, or wheeze to describe non-wheeze sounds.<sup>7</sup> This same video questionnaire was shown to help to identify upper airway abnormalities such as stridor-causing laryngomalacia, which had been misdiagnosed as wheeze.<sup>8</sup> Clearly if the noise reported is non-specific from the upper airway, management is completely different; and indeed, with the exception of snoring, which should prompt consideration of performing a sleep study, reassurance is all that is required. These findings call into question studies based on tick-box questionnaires, which may make no attempt to determine the sound that is actually heard.

Even if true wheeze is heard, this should not be automatically assumed to be due to bronchospasm. Airway narrowing by mucus will produce true wheeze but does not respond to bronchodilators. Similarly, airway malacia, either related to intrinsic airway wall defects or loss of alveolar tethering points, are also causes of bronchodilator-unresponsive wheeze; indeed, bronchodilators, by reducing airway smooth muscle tone, may actually worsen airway narrowing.<sup>9</sup>

## IS WHEEZE DUE TO STRUCTURAL AIRWAY DISEASE?

The differential diagnosis is extensive. Causes of fixed obstruction are summarised in [Table 2](#); a detailed discussion of these possibilities is beyond the scope of this article.

## WHEEZE IN THE FIRST YEAR OF LIFE

Wheeze in the first year of life is common throughout the world, at least as determined by

questionnaires, with all the caveats set out above. In one international study of >30,000 infants, 45.2% had at least one episode of 'wheeze', and 20.3% had recurrent 'wheeze'.<sup>9,10</sup> The nature of the noise and the pathophysiology was unclear. However, a study of 53 infants aged 3–26 months, who were investigated with infant pulmonary function tests and rigid bronchoscopy for severe respiratory symptoms including wheeze, had no evidence of eosinophilic airway inflammation or remodelling.<sup>11</sup> This was true even in the subgroup that was atopic and had airflow obstruction acutely reversible with short-acting  $\beta$ 2 agonist. Given that this group of infants must have been the most severe tip of the iceberg, and yet had no airway eosinophilia, prescribing inhaled corticosteroids (ICS) to wheezy children in this age group does not seem logical. Despite this, 46.1% of the 30,000 infants reported above were prescribed ICS. The Hargreave phenotype is non-inflammatory, likely variable due to bronchoconstriction and possibly fixed airflow obstruction, triggered by viruses; the role of bacteria is unclear, but the finding in the COPSAC data that early bacterial colonisation of the nasopharynx is associated with later wheeze suggests that there may be a role for bacteria.<sup>12</sup> Indeed, in older children bacterial infection may be at least as common as viruses in triggering acute asthma attacks.<sup>13</sup> However, as yet there is no evidence to deploy antibiotics in preschool children, except in the presence of clear-cut evidence of a bacterial infection.

## MULTIPLE TRIGGER WHEEZE AND EPISODIC VIRAL WHEEZE

Approximately 30% of all children have at least one episode of wheeze in the first 3 years of life. The paper from Tucson delineating the patterns of transient, persistent, and late-onset wheeze<sup>1</sup> has to some extent been superseded by more detailed data from the ALSPAC group,<sup>14</sup> confirmed in the PIAMA<sup>15</sup> and Southampton birth cohorts<sup>16</sup> in which more temporal phenotypes have been described. This combination of birth cohorts has been a powerful tool in genetic and other studies, and will undoubtedly lead to more discoveries, but as yet it has not told us much about how to treat these infants. What we do know is that no treatment prevents progression from early wheeze to school-age atopic asthma; three well-conducted randomised controlled trials have shown that early use of ICS does not modify disease progression.<sup>17–19</sup>

**Table 1: Components of the proposed Hargreave phenotypes.**

Note that inflammation may be a beneficial response to infection, or may be exaggerated and detrimental to the host.

Component	Extramural	Intramural	Intraluminal
Fixed airflow obstruction	Loss of alveolar tethering	Reduced airway calibre (developmental or environmental)	-
Variable airflow obstruction	Loss of alveolar tethering	Airway smooth muscle (bronchospasm) Airway oedema	Mucus and other airway secretions
Inflammation	Role poorly explored	Cellular pattern: eosinophilic, neutrophilic, both, neither: likely many pathways Neurogenic Other	Cellular pattern: eosinophilic, neutrophilic, both, neither: likely many pathways Neurogenic Other
Infection	-	Latent viral in particular	Any combination of bacterial, viral, fungal

**Table 2: Differential diagnosis of wheeze and other sounds that may be confused with wheeze.**

Upper airway disease - adenotonsillar hypertrophy, rhinosinusitis, postnasal drip, subglottic stenosis, laryngomalacia, vocal cord paresis.
Congenital structural bronchial disease - complete cartilage rings, cysts, webs.
Bronchial/tracheal compression - vascular rings and sling, enlarged cardiac chamber, lymph nodes enlarged by tuberculosis or lymphoma.
Endobronchial disease - foreign body, tumour.
Oesophageal/swallowing problems - reflux, incoordinate swallow, laryngeal cleft, or tracheoesophageal fistula.
Causes of pulmonary suppuration - cystic fibrosis, primary ciliary dyskinesia, persistent bacterial bronchitis, any systemic immunodeficiency.
Miscellaneous - bronchopulmonary dysplasia, congenital or acquired tracheomalacia, pulmonary oedema.

Hence it is logical to consider only symptoms when planning treatment, and to this end the ERS Task Force<sup>2</sup> has proposed the use of two categories:

- Episodic viral wheeze (EVW) - the child wheezes only at the time of a usually clinically diagnosed viral upper respiratory tract infection and is symptom-free between viral colds
- Multiple trigger wheeze (MTW) - the child wheezes at the time of viral colds, but also between colds, for example with excited behaviour, aeroallergen exposure, and cold, smoky atmospheres

Of note, the atopic status of the preschool child does not help predict response to ICS. These phenotypes have limitations, but these have been

exaggerated. There are objective differences between them: MTW has worse airflow obstruction and gas mixing, and evidence of eosinophilic airway inflammation as judged by exhaled nitric oxide (eNO), compared with EVW.<sup>20</sup> There is evidence of fixed airflow obstruction, as well as bronchial hyper-responsiveness, in preschool wheeze phenotypes, although often studies do not discriminate between EVW and MTW.<sup>1,21-24</sup> It is true that they are not fixed, and may change over time,<sup>25</sup> but in this case the treatment approach changes, and this is standard in paediatric conditions as the child develops. It is also true that an infant may have interval symptoms that the family do not appreciate and are only recognised when they are treated. Despite this, they are useful to guide treatment,

accepting that regular review and possible change of treatment in the future may be necessary.

## EPISODIC VIRAL WHEEZE

Invasive studies including bronchoalveolar lavage (BAL) and endobronchial biopsy have shown no evidence of eosinophilic airway inflammation.<sup>11</sup> Indeed, BAL studies have demonstrated that non-atopic, EVW infants have predominantly neutrophilic inflammation.<sup>26,27</sup> There is likely to be neutrophilic inflammation at the time of acute viral infection, but this is likely to be a beneficial response. Non-invasive studies have shown that there is less airway obstruction, less impairment of gas mixing, and lower fractional eNO than in MTW.<sup>28</sup> No study has shown that prophylactic ICS has prevented episodic symptoms, and treatment should therefore be intermittent; trials of inhaled  $\beta_2$  agonists and anticholinergics are the first line if therapy is needed at all.<sup>29</sup> The data on the intermittent use of leukotriene antagonists are controversial, and although two early trials showed benefits from this approach,<sup>30,31</sup> two significantly larger studies failed to confirm these findings.<sup>32,33</sup> Nonetheless, anecdotally some children respond; however, parents must be warned about the behavioural side effects of montelukast. Intermittent ICS just at the time of viral colds may be indicated; there are proof-of-concept studies supporting this approach, but the dose and duration of therapy are unclear. The frequency of viral colds needs to be considered; if very high doses of ICS are given, then the cumulative dose over the winter may be considerable. A trial of continuous ICS should only be given if the paediatrician suspects that interval symptoms are being underplayed by the family. The Hargreave phenotype of EVW is non-inflammatory (or at least non-eosinophilic), possible fixed airflow obstruction, with variable airflow obstruction that may be due to bronchospasm, but could be due to airway oedema or mucus. The acute triggers are viral and likely bacterial infection.

## MULTIPLE TRIGGER WHEEZE

The presumption from invasive studies is that these children have classical eosinophilic inflammation and should be treated along the same lines as school-age children.<sup>11</sup> However, other than in a research context, objective measurement of response is difficult to measure, and a three-stage therapeutic trial is recommended (below).

The Hargreave phenotype of MTW is eosinophilic inflammation, likely some fixed but also variable airflow obstruction, the latter due to bronchoconstriction but likely also a component of airway oedema and mucus, with acute viral and likely bacterial triggers.

## POST-BRONCHIOLITIS WHEEZE

Infants who are admitted to hospital with respiratory syncytial virus (RSV) bronchiolitis are especially likely to have prolonged cough and wheeze afterwards. There is controversy over whether in fact RSV causes asthma, or if severe RSV bronchiolitis is a sign that the infant had preceding risk factors that are a marker for risk of asthma onset, or in fact that the symptoms regress.<sup>34</sup> Prospective data from Perth, Australia, showed impaired lung function in babies who went on to develop bronchiolitis, and this tracked into mid-childhood.<sup>35</sup> We also know that none of the myriad studies showed any evidence of benefit from ICS either in the acute phase of the illness or after discharge from follow-up.<sup>36,37</sup> The best evidence is that, for most infants, symptoms gradually regress over time, but those who are at high risk of asthma due to preceding factors such as a strong atopic history and maternal smoking may obviously develop asthma.<sup>38</sup> Hence, the Hargreaves phenotype is fixed airflow obstruction, with no evidence of chronic inflammation. There may be episodes of variable airflow obstruction due to any or all of bronchospasm, airway oedema, and mucus triggered by viral and possibly bacterial infection. There is no reason to treat with ICS; if it is thought that the child is developing true eosinophilic asthma, then a therapeutic trial of ICS should be at least considered, but only using the three-step protocol discussed below.

## PERSISTENT BACTERIAL BRONCHITIS

This condition is poorly understood but was the commonest cause of cough in one large series investigated in a tertiary hospital; nearly 40% of >100 children were given this diagnosis after investigation. Of note, half had received an initial diagnosis of asthma, which was the final diagnosis in only about 5%.<sup>29</sup> Persistent bacterial bronchitis (PBB) is largely a disease of preschool children, and is characterised by neutrophilic airway inflammation and chronic infection with organisms such as *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*.<sup>39,40</sup>

It is a diagnosis of exclusion; more serious conditions such as bronchiectasis and aspiration syndromes must be considered. The pathophysiological basis is not known but it presumably reflects a local defect in mucosal defence because there is no systemic infection.<sup>41</sup> It is interesting to speculate how much may be iatrogenic; ICS are widely used in children with respiratory symptoms, and are known to increase the risk of pneumonia,<sup>42</sup> tuberculosis,<sup>43</sup> and atypical mycobacterial infection in adults.<sup>44</sup> Could it be that the treatment of non-specific respiratory symptoms with ICS promotes mucosal immunosuppression and low-grade infection?

Whatever the pathophysiology, the Hargreave phenotype of PBB is neutrophilic inflammation and airflow obstruction due to mucus. If PBB is suspected clinically, it is reasonable to give a 2-week trial of co-amoxiclav.<sup>45</sup> If there is no response or a rapid relapse after treatment, then it is wise to consider further investigations to exclude bronchiectasis or another underlying cause.<sup>46</sup> The presumption that PBB is a precursor of idiopathic bronchiectasis has not been tested, but aggressive treatment with antibiotics (courses may need to be prolonged and repeated) and airway clearance should be instituted until the problem resolves.

## CYSTIC FIBROSIS, PRIMARY CILIARY DYSKINESIA, BRONCHIECTASIS

These conditions are included because the same phenotypic considerations apply to their management, and also because, in the case of cystic fibrosis (CF) and primary ciliary dyskinesia (PCD), they would likely still be categorised under the same non-specific umbrella as PBB and probably other causes of preschool respiratory symptoms because the diagnosis is made from specific tests.<sup>47,48</sup> The detailed management is beyond the scope of this article, but the Hargreave phenotype is neutrophilic inflammation, chronic bacterial infection, and fixed and variable airflow obstruction, and antibiotics and airway clearance are the mainstays of treatment.

CF and PCD point the way towards that which we should aspire to for other infant and preschool respiratory diseases. Even Hargreave phenotyping is at best crude, albeit a lot better than categorising conditions together under the same umbrella. CF and PCD are diagnosed using very specific tests, and this is needed for other conditions. The use of the terms EVW and MTW

may represent an advance, but they can hardly be considered 21<sup>st</sup>-century diagnostic terms.

## OBLITERATIVE BRONCHIOLITIS

In preschool children, this is usually the result of a preceding severe infection, usually adenovirus or *Mycoplasma pneumoniae*.<sup>49</sup> The Hargreave phenotype is fixed airway obstruction with no reversibility or inflammation unless coincidentally the child has a second airway disease such as coincident atopic asthma.

## SICKLE CELL ANAEMIA

Sickle cell anaemia (SCD) is another condition in which asthma is said to be common, but without much evidence of clarity of thought about what the nature of the airway disease is. The nature of SCD airway disease is controversial. One recent study in SCD children with only very mild pulmonary vascular disease demonstrated that they had mild airway obstruction, but no evidence of variable airflow obstruction or eosinophilic inflammation (at least as shown by eNO) when compared with ethnically matched controls.<sup>50</sup> Other studies have shown increased airway responsiveness in SCD, including acute bronchodilator responsiveness, but no convincing evidence of eosinophilic airway inflammation.<sup>51,52</sup> As with obliterative bronchiolitis, these children may have another coincident airway disease such as atopic asthma that should be treated on merit, but pure SCD airway disease appears not to have the Hargreave phenotype of eosinophilic airway inflammation. There is certainly fixed obstruction; the data on variable airflow obstruction are controversial.

## POST PREMATURE BIRTH

A description of the early pathophysiology of neonatal lung disease of prematurity is beyond the scope of this review. There is ample evidence that infant survivors of premature birth have evidence of fixed airflow obstruction, even if they do not require ventilation.<sup>53,54</sup> The decrements with prematurity are improving as intensive care becomes more sophisticated. These babies at follow-up into childhood have increased respiratory symptoms, acute bronchodilator responsiveness, and may have airway reactivity.<sup>55</sup> However, they have no evidence of airway inflammation; exhaled breath temperature and eNO are both normal.

**Table 3: Phenotyping preschool paediatric wheezing disorders.**

There are multiple different paediatric pathways to wheeze, and the approaches should be pathway-specific.

Disease	Inflammation?  (Eosinophilic, neutrophilic, both)	Variable airflow obstruction?  (Bronchospasm, oedema, mucus, loss of tone, loss of alveolar tethering)	Fixed airflow obstruction	Infection?  (Bacterial, viral, both)	Treatment
Wheeze in the first year of life	No	+/-	+/-	Likely viral and bacterial triggers	Trial bronchodilators, discontinue if ineffective
Multiple trigger wheeze	Eosinophilic	Yes, bronchoconstriction	+/-	Likely viral and bacterial triggers	Inhaled steroids, bronchodilators
Episodic viral wheeze	None chronic	Yes, bronchoconstriction, airway oedema, mucus	+/-	Likely viral and bacterial triggers	Bronchodilators. Inhaled steroids ineffective
Post-bronchiolitis wheeze	None chronic	Probably, nature unclear	+/-	Likely viral and bacterial triggers	Bronchodilators. Inhaled steroids ineffective
Persistent bacterial bronchitis	Neutrophilic, bacteria	Mucus	No	Bacterial, viral	Antibiotics, Airway clearance
Cystic fibrosis, primary ciliary dyskinesia, bronchiectasis	Neutrophilic	Yes, mucus obstruction	Usually	Bacterial predominant	Antibiotics, mucolytics, airway clearance
Obliterative bronchiolitis	No	Mucus	Yes	No	Airway clearance
Obliterative bronchiolitis	None	No	Yes	No	Supportive
Sickle cell anaemia	None	Yes, bronchoconstriction	Yes	Not known	Bronchodilators
Post-premature birth	None	Yes, bronchoconstriction	Yes	Not known	Bronchodilators
Primary airway malacia	None	Yes, loss of airway wall tone	+/-	Secondary	Airway clearance, CPAP, antibiotics, mucolytics, tracheostomy
Post-NEHI wheeze	None	Yes, bronchoconstriction	Yes	Not known	Bronchodilators

NEHI: neuro-endocrine cell hyperplasia; CPAP: continuous positive airway pressure.

There may be evidence of oxidative stress.<sup>56</sup> There is no evidence that these babies respond to ICS, and the Hargreave phenotype is fixed and variable airflow obstruction, with no inflammation.

These children may, of course, have more than one cause of airway obstruction, and iatrogenic large airway disease must not be disregarded. Repeated or prolonged intubation may lead to subglottic

stenosis, and damage to the left recurrent laryngeal nerve during surgery to ligate a patent ductus arteriosus may leave the child with a vocal cord palsy.

The importance of phenotyping is illustrated by the problems of the so-called late-preterm delivery. There is evidence of persistent and fixed airflow obstruction in babies born as late as 32 weeks

gestation and an increased burden of asthma even in babies delivered at 37-38 weeks gestation.<sup>57</sup> This begs the question as to what sort of asthma is being diagnosed; the evidence that these babies have eosinophilic inflammation as a result of late prematurity is missing, but there is a real risk that ICS will be prescribed indiscriminately, especially to these late-premature babies whose Hargreave phenotype is the same as for the more preterm infants.

## AIRWAY MALACIA

Airway malacia may be primary, related either to loss of airway wall tone or reduction in the number of alveolar attachments holding open the airways; it may be part of a syndrome, such as Ehlers-Danlos; or it may be secondary to airway compression by blood vessels or a mass, and persist even after relief of the external pressure. In any event, the Hargreave phenotype is just variable airflow obstruction with no inflammation. There may be a secondary infection and inflammation as a result of poor distal airway drainage that may need treatment, but asthma medications are ineffective.

## WHEEZE AND CHILDHOOD INTERSTITIAL LUNG DISEASE

The presentation of childhood interstitial lung disease is non-specific, but interestingly, wheeze was reported at presentation in >20% of nearly 200 children.<sup>58</sup> Neuroendocrine cell hyperplasia of infancy typically presents with respiratory distress and oxygen dependency in the early weeks of life. High-resolution computed tomography shows typical appearances of ground-glass opacification in the lingula and right middle lobes, and also in a perihilar distribution.<sup>59</sup> Lung biopsy appearances are usually normal, except for increased numbers of cells positive for the neuropeptide bombesin in the distal airways.<sup>60</sup> Infant lung function shows hyperinflation. The prognosis is good, although some may have prolonged oxygen dependency. However, a small follow-up series showed that six of nine children had non-atopic asthma and those tested had some evidence of variable airflow obstruction.<sup>61</sup> Despite an absence of evidence of inflammation, prescriptions of ICS/long acting  $\beta$ 2 agonists were given to 50%. Not enough is known to Hargreaves phenotype these children, but given that they present with airflow obstruction early on, at a time when there is little if any evidence

of airway inflammation, the presumption must be that this is non-inflammatory, fixed, and possibly variable airflow obstruction.

## DOES IT MATTER?

**Table 3** summarises the various wheezing syndromes, and, more importantly, shows how lines of treatment can and should be determined by the Hargreave phenotype.<sup>62</sup> Of course, there may be some overlap, and it may also be difficult to differentiate between, for example, post-bronchiolitis, episodic viral, and multiple trigger wheeze. The cardinal principle when starting a treatment for any child with a wheezing disorder is to constantly re-evaluate whether there is any response to treatment, whatever it is, and discontinue it if there is any doubt about benefit.

It is wise to use a three-stage protocol for any trial of medium-term (i.e. non-acute) treatment since the natural history of many airway diseases is spontaneous remission. So, for example, if a trial of ICS is being given to a child with a presumptive diagnosis of MTW,<sup>63</sup> the steps would be:

1. Commence treatment at a relatively high dose (e.g. fluticasone 150  $\mu$ g b.i.d. via an appropriate spacer); if the child does not respond to this dose, then the airway disease is unlikely to be steroid-responsive. If a low dose is used, then time may be wasted by going on to a higher dose before steroid insensitivity is diagnosed
2. After a fixed (arbitrary) period, around 4-8 weeks, stop treatment. If the child has not improved, do not escalate ICS therapy but reconsider the diagnosis. If the child appears to have improved, then it is unclear at this stage if this is spontaneous or treatment-related
3. Only restart ICS treatment if symptoms return, and then keep titrating the dose to the minimum needed to control symptoms; regular review is mandatory

Clearly in older children, who can perform lung function testing, objective documentation of response is mandatory. However, in preschoolers this protocol, which is of course not evidence-based, will avoid the error of labelling children as having a steroid-sensitive airway disease and continuing treatment, whereas in fact they had merely spontaneously improved.

## SUMMARY AND CONCLUSION

Here we have proposed a framework for the assessment, and more importantly treatment, of preschool airway disease. We propose that the components of airway diseases are considered separately and that each are treated on merit, rather than applying umbrella terms such as 'asthma'. We accept that studies are needed to confirm that this is a useful approach in routine clinical practice. In particular, the phrase 'Dr-diagnosed asthma' should vanish from the literature, particularly for preschool children. It is clear that our means of assessing airway disease in the clinic are very crude; in particular, airway inflammation and airway obstruction are usually not measured at all, and upper airway surrogates

are used for lower airway infection. Clearly an infant who has a clear clinical picture and responds to appropriate therapy does not need elaborate testing, but for more problematic cases we should deploy existing tests, such as induced sputum for lower airway inflammation and infection, eNO, and peripheral blood eosinophil count. There is also an urgent need to put our assessments of these infants on a more scientific basis by developing new, clinically applicable tests, to bring the ideas of Freddie Hargreave<sup>64</sup> into the preschool years. Clearly his ideas are the start of a process, and in the future, refinements of his thinking will be introduced, but these ideas are far better than the current lumping of wheezing syndromes. The ultimate aim of all of this is, of course, improved outcomes for these infants, to which we all aspire.

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