

Is asthma overdiagnosed?

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Martin Luther likened human reason to a drunken man on horseback, alternately falling off to the left and then to the right.¹ The same is true of diagnosing asthma; undoubtedly in the past it was underdiagnosed, but have we gone too far in the opposite direction? The evidence is that we have; for example, in an Australian paper, in which more than 100 children with chronic cough were investigated intensively, including with bronchoscopy (which we do *not* recommend as a routine diagnostic test!), half were given a diagnosis of asthma prior to investigation; the number actually thought to have asthma had dwindled to 5% at the end of testing.² Although cough-variant asthma exists, it is overdiagnosed; isolated cough in the community is rarely, if even, due to asthma,³ and even in a tertiary centre, atopic children with cough only infrequently have eosinophilic inflammation.⁴ Key to diagnosing asthma correctly is being confident in making that most difficult diagnosis of all, normal child; and this requires detailed knowledge of the range of symptoms with upper respiratory infections in the normal child.⁵

Overdiagnosis of asthma clearly matters. The fiscal cost of asthma medications is not trivial. Inhaled corticosteroids (ICS), when properly used, drastically improve quality of life and reduce the risk of asthma attacks and mortality. However they have side effects, including adrenal failure and growth suppression, with increasingly worrying evidence (mainly in adults) that they cause mucosal immunosuppression and an increased risk of respiratory infections.⁶ There is also evidence that systemic absorption of ICS depends not just on the prescribed dose, but is greater if the dose is inappropriately high for the degree of airway inflammation.⁷ The National Review of Asthma Deaths⁸ highlights another reason why we need to get the diagnosis right. It is an intensely depressing document which shows that no lessons have been learnt over the last 15 years, and children still

die because of failures in basic management. We propose that one contributing factor is that the diagnosis of asthma has been trivialised and inhalers dispensed for no good reason, and have become almost a fashion accessory. The result is the fact that asthma is a killing disease, if not correctly managed, is overlooked.

On this background, the National Institute for Health and Care Excellence (NICE) has put out a consultation paper recommending that we should seek more objective evidence before making a diagnosis of asthma.⁹ Disappointingly, the idea that asthma may be overdiagnosed and objective tests should be performed has not been uniformly welcomed. We have previously proposed a practical algorithm based on NICE's recommendation for the diagnosis of asthma incorporating objective tests.¹⁰ We know that the word wheeze, the hallmark symptom of asthma, is used imprecisely by parents and professionals.¹¹ Is there any other chronic disease in the world in which children are committed to potentially hazardous, long-term therapy without every effort being made objectively to document the diagnosis? Of course, recommendations must be practical; it is unlikely that primary care and much of secondary care will be measuring exhaled nitric oxide (FeNO) any time soon, and it would be absurd to draw the conclusion that only tertiary care can diagnose paediatric asthma. However what should not be controversial are two principles:

- A. We must seek evidence of variable airflow obstruction, at least in school-age children, before contemplating an asthma diagnosis.
- B. If therapeutic trials of treatment are to be performed, then they should be focused, and children should not be left on an unproven treatment *ad infinitum*.

Objective tests broadly relate to the diagnosis of variable airflow obstruction, and the characterisation of any airway inflammation that may be present. Physiological testing in the school-age child is available at all levels of care. The easiest is to measure peak flow at the point of care, and measure the acute response to a short-acting β -2 agonist (SABA). There will be none if peak flow is normal, but a simple exercise challenge test could be considered, although with the realisation

that such field tests may lack specificity.¹² Home peak flow meters are notoriously underused by children in the long term, but a two-week trial should be practical.¹³ It is totally legitimate for the child to have access to SABAs via an appropriate device during this period, and this provides an opportunity to see if there is fluctuation in peak flow either spontaneously or with SABA. Such testing is known to be specific but lacks sensitivity; the harder the paediatrician tries to demonstrate variable airflow obstruction, and the more this is not seen, the less likely is a diagnosis of asthma.

Thus far physiology has been addressed, but what about airway inflammation? ICS are an excellent treatment for eosinophilic airway inflammation, but if this is not present, should they be prescribed? Where does FeNO fit into the picture, if the measurement is available? First, atopy without asthma causes an elevation of FeNO;¹⁴ it is not an asthma diagnostic test. Knowledge of whether the child is atopic is useful; if a school-age child is not atopic, eosinophilic airway inflammation is unlikely, but not impossible. However, FeNO is not needed to diagnose atopy; skin prick tests to common aeroallergens are more than sufficient. Second, in ICS-naive patients with asthma, FeNO correlates with airway eosinophilia.¹⁵ Hence if FeNO is available and normal, this means a diagnosis of asthma characterised by eosinophilic airway inflammation, and therefore being ICS-responsive, is unlikely. If FeNO is elevated, then ICS-responsive asthma *may* be present, but this is not certain.

An alternative surrogate for eosinophilic airway inflammation is peripheral blood eosinophilia.¹⁶ Careful interpretation is needed; blood eosinophilia may be driven by extrapulmonary atopic disease such as eczema, but a normal blood eosinophilia is another pointer that airway eosinophilia is unlikely.¹⁷

Blind therapeutic trials are another trap for the unwary. We suggest they should only be carried out when objective measurements cannot be made, and then too in a very focused manner. There is no evidence base, but we suggest a trial period of a moderate dose of ICS (eg, 200 μ g beclomethasone equivalent twice daily) for no more than 6 weeks, at the end of which, irrespective of the clinical state, treatment is stopped. If there has been no response, and (a big if!) if treatment has really been given, the diagnosis of asthma with eosinophilic inflammation can be discarded. If symptoms have disappeared and only if they subsequently reappear

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and again respond to ICS should a diagnosis of asthma be made, and ICS treatment titrated to the lowest effective dose. This staged trial avoids the paediatrician mistaking spontaneous improvement for therapeutic benefit.¹⁸

A further safeguard is to consider the diagnosis of asthma as dynamic—many children outgrow their symptoms, and many professors frequently get things wrong. No matter who has made the diagnosis, always consider whether it was actually correct in the first place, or whether it is still relevant. Asthma therapy should not be escalated heedlessly if there is no response—for most children, the plateau of the ICS dose-response curve is as low as 100 µg fluticasone twice daily.¹⁹ Oliver Cromwell's advice is still apposite: 'I beseech you, in the bowels of Christ, think it possible that you may be mistaken'.²⁰

The present proposals by NICE are welcome in principle, but there are still many gaps which we should not tolerate. We need to move the diagnostic process forward in a number of ways. First, we need to bring objective testing into the preschool years; off-line FeNO, multiple breath washouts²¹ and even induced sputum²² can all be performed, and surely should be performed, in non-straightforward airway disease in this age group. Second, we should be more objective about therapeutic trials; they should be placebo-controlled, cross-over, N of 1 trials, during which neither the paediatrician nor the family know whether the active canister is being used. If we can obtain placebo inhalers for randomised-controlled trials and for Respiratory Nurses to demonstrate inhaler technique, why not for therapeutic trials? Electronic monitoring of adherence and peak flow measurements is surely the 21st century gold standard, and adherence monitoring should move beyond whether the device has been activated to measuring whether someone has actually inhaled adequately from the device. Finally, we need to go

beyond umbrella labels for airway diseases such as asthma, and move to phenotyping childhood airway diseases in terms of parameters such as fixed and variable airflow obstructions, presence or otherwise, and nature of, airway inflammation, and whether there is chronic infection. The aim is not to split and phenotype for the sake of it, but to identify treatable characteristics and treat them appropriately.²³ But that is another story.

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REFERENCES

- Martin Luther. Werke 1883;54:111.
- Marchant JM, Masters IB, Taylor SM, *et al.* Evaluation and outcome of young children with chronic cough. *Chest* 2006;129:1132–41.
- Kelly YJ, Brabin BJ, Milligan PJ, *et al.* Clinical significance of cough and wheeze in the diagnosis of asthma. *Arch Dis Child* 1996;75:489–93.
- Ferreira Fde A, Filho LV, Rodrigues JC, *et al.* Comparison of atopic and nonatopic children with chronic cough: bronchoalveolar lavage cell profile. *Pediatr Pulmonol* 2007;42:857–63.
- Thompson M, Vodicka TA, Blair PS, *et al.* TARGET Programme Team. Duration of symptoms of respiratory tract infections in children: systematic review. *BMJ* 2013;347:f7027.
- Sabroe I, Postma D, Heijink I, *et al.* The yin and the yang of immunosuppression with inhaled corticosteroids. *Thorax* 2013;68:1085–7.

- Brutsche MH, Brutsche IC, Munawar M, *et al.* Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in patients with asthma and healthy volunteers: a randomised crossover study. *Lancet* 2000;356:556–61.
- <https://www.rcplondon.ac.uk/projects/national-review-asthma-deaths>
- <http://www.nice.org.uk/guidance/gid-cgwave0640/resources/asthma-diagnosis-and-monitoring-draft-nice-guideline2>
- Bush A, Fleming L. Diagnosis and management of asthma in children. *BMJ* 2015;350:h996.
- Levy ML, Godfrey S, Irving CS, *et al.* Wheeze detection: recordings vs. assessment of physician and parent. *J Asthma* 2004;41:845–53.
- Powell CV, White RD, Primhak RA. Longitudinal study of free running exercise challenge: reproducibility. *Arch Dis Child* 1996;74:108–14.
- Redline S, Wright EC, Kattan M, *et al.* Short-term compliance with peak flow monitoring: results from a study of inner city children with asthma. *Pediatr Pulmonol* 1996;21:203–10.
- Franklin PJ, Taplin R, Stick SM. A community study of exhaled nitric oxide in healthy children. *Am J Respir Crit Care Med* 1999;159:69–73.
- Piacentini GL, Bodini A, Costella S, *et al.* Exhaled nitric oxide and sputum eosinophil markers of inflammation in asthmatic children. *Eur Respir J* 1999;13:1386–90.
- Price DB, Rigazio A, Campbell JD, *et al.* Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849–58.
- McKeown S, Saglani S, Bush A, *et al.* The relationship between invasive and non-invasive measures of inflammation in children with severe, therapy-resistant asthma. *Thorax* 2015;70(Suppl 3):A124–5.
- Bush A. Diagnosis of asthma in children under five. *Prim Care Respir J* 2007;16:7–15.
- Lemanske RF Jr, Mauger DT, Sorkness CA, *et al.* Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975–85.
- Carlyle T, ed. *Oliver Cromwell's letters and speeches 1*. New York: Harper, 1855:448.
- Ahmad F, Irving S, Alton E, *et al.* Multiple breath washouts in children can be shortened without compromising quality. *Eur Respir J* 2015;46:1814–16.
- Zar HJ, Hanslo D, Apolles P, *et al.* Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* 2005;365:130–4.
- Bush A, Kleinert S, Pavord ID. The asthmas in 2015 and beyond: a Lancet Commission. *Lancet* 2015;385:1273–5.

ARCHIVES OF DISEASE IN CHILDHOOD

Childhood asthma overdiagnosed, argue leading respiratory doctors

Inhalers often dispensed for no good reason and have “almost become a fashion accessory”

Doctors are overdiagnosing asthma, with inhalers frequently dispensed for no good reason, to the point that they have “almost become a fashion accessory,” argue two leading respiratory doctors in a leading article published online in the ***Archives of Disease in Childhood***.

In the past asthma was undoubtedly underdiagnosed, but the evidence now is that the pendulum has swung too far in the opposite direction, insist Professor Andrew Bush and Dr Louise Fleming of Imperial College and Royal Brompton & Harefield NHS Foundation Trust, in the journal.

It matters, not only because of the cost of inhalers, but also because of their side effects, which are more likely to occur in patients who are prescribed an inappropriate dose, they say.

“Inhaled corticosteroids, when properly used, dramatically improve quality of life and reduce the risk of asthma attacks and mortality,” they write.

But there are potential side effects associated with their use, they point out. These include growth suppression and the dampening down of immune cell activity in the airways and the subsequent heightened risk of respiratory infections.

“There is also evidence that systemic absorption of [inhaled corticosteroids] depends not just on the prescribed dose, but is greater if the dose is inappropriately high for the degree of airway inflammation,” they caution.

Key to diagnosing asthma correctly is a detailed knowledge of normal respiratory symptoms in healthy children, they say. But as the National Review of Asthma deaths shows, children who have asthma still die because of failures in basic management, including not taking inhalers that they really need.

“We propose that one contributing factor is that the diagnosis of asthma has been trivialised and inhalers dispensed for no good reason, and have become almost a fashion accessory,” they write.

“The result is, the fact that asthma is a killing disease if not correctly managed, is overlooked,” they say.

All too often, the hallmark symptom of asthma—wheeze—is used imprecisely by both parents and healthcare professionals. More objective evidence, such as simple breathing tests, is required before a diagnosis is made, they suggest.

“Is there any other chronic disease in the world in which children are committed to potentially hazardous, long term therapy without every effort being made objectively to document the diagnosis?” they ask.

They outline various approaches to aid correct diagnosis, including the need to remember that many children outgrow asthma symptoms, and that treatment shouldn't simply be

stepped up if the child fails to respond, because there's a chance the diagnosis might not be right in the first place.

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