Oral and inhaled corticosteroids (ICS) do not work in asthma and should not be prescribed for that disease. A somewhat startling statement, since there can probably be hardly a clinician alive who has not used these medications, or at least seen first-hand the strikingly beneficial results of treatment. Yet in the 1950s, these were the conclusions of the MRC after their randomised controlled trial was negative.

Enter from Derby Dr Harry Morrow-Brown and his medical student microscope. Dr Morrow-Brown, who was as incredulous as today’s readership at this statement, showed that both were effective in patients with sputum eosinophilia, but not in those who were neutrophilic. Thus were salvaged two of the most effective treatments for any disease known to man, and an age of improved asthma outcomes was ushered in. The benefits of ICS have been recapitulated wherever they have been introduced. However, two subsequent developments, or rather lack of them, prompted the Lancet Asthma Commission:

• Despite the use of ICS, asthma outcomes have stalled; mortality has flatlined over the past decade and during this time we have had no real new innovations in terms of treatment (‘the blue inhaler and the brown inhaler’)
• Although personalised medicine is all the rage, in our enthusiasm for corticosteroids, we have forgotten about Harry Morrow-Brown’s decades-old lessons in personalised medicine, as a result of which we nearly consigned the anti-interleukin-5 monoclonal antibody mepolizumab to the therapeutic dustbin.

The seven major recommendations of the Commission are shown in Table 1; not all are relevant to primary care. We will discuss what asthma really means in the 21st century, the vexed question of asthma diagnosis and the importance of asthma attacks, with a particular focus on managing children with asthma. Given that UK asthma outcomes are among the worst in Europe, a wake-up call is more than overdue. As most
Asthma is diagnosed and treated in primary care, and most asthma deaths are in patients who are not under specialist care, the relevance to primary care is high.

What is this thing called asthma?

At present, things are quite a mess! Definitions for asthma that have been advanced in all seriousness in scientific manuscripts include “a Dr said so” and “someone once gave me an inhaler”. Guidelines vary, all stressing clinical symptoms, some insisting on variable airflow obstruction, others airway inflammation or combinations of the two. The late Richard Asher strongly charged clinicians to think clearly, and to keep clinical and pathological definitions separate, because almost always assumptions about the pathology underlying a clinical picture are proved wrong sooner or later.

So the Commission recommends that the term ‘asthma’ should be used to describe a constellation of clinical symptoms, namely wheeze, breathlessness and chest tightness sometimes with cough. It is an umbrella term, as is ‘arthritis’ for swollen painful joints and anaemia for a reduced haemoglobin. As with these latter two, the next step after diagnosing asthma should be to ask “what kind of asthma is this?” Thus ‘asthma’, as with anaemia and arthritis, is the start not the end of the patient’s diagnostic journey.

How does this work in primary care?

In particular for children, the questions arising are:

- Does the patient have eosinophilic airway inflammation, a trait treatable with ICS?
- Does the patient have intermittent bronchoconstriction, a trait treatable with beta₂-agonists and other bronchodilators?
- Does the patient have airway infection, a trait treatable with antibiotics?

Answering these questions does not require sophisticated tests. There is increasing evidence at all ages that a raised peripheral blood eosinophil count is a good surrogate for eosinophilic airway inflammation. Fractional exhaled nitric oxide (FeNO) is another increasingly available surrogate, and there is now compelling and consistent evidence that patients who have high blood eosinophil counts and FeNO are at particularly high risk of exacerbations, independent of traditional measures of asthma control.

In children, the absence of atopy is a pointer against airway eosinophilia. The presence and severity of symptoms, and the degree or pattern of impairment of lung function, do not relate to airway eosinophilia and cannot be used as surrogates. Of course, there is interest in these measures in their own right. Peak flow and indeed spirometry, at baseline and response to a short-acting beta₂-agonist, is achievable even in young children, as is a short period of home monitoring. Culture of sputum or cough swab can give a clue to airway infection.

These tests need to be interpreted critically. Most children who have eosinophilic airway inflammation are atopic, but many atopic children do not have any airway disease. FeNO is elevated in atopic eosinophilic asthma, but it is also elevated in atopy without airway disease. Blood eosinophil count correlates with airway eosinophilia and thus likely ICS responsiveness, but it may also be elevated in non-airway atopic disease, eg eczema, and also with parasitic infections. The goal of these investigations is to build up a picture of mechanisms (or ‘treatable traits’) that might be driving current morbidity and/or future risk of adverse outcomes, paving the way for more individualised, precision management.

There is no single ‘asthma test’ but the more tests that give normal results in a symptomatic child, the less likely is the diagnosis of asthma.

Asthma diagnosis

The Commission, as well as the NICE guidelines, have stressed the importance of objective testing before making a diagnosis. Indeed, it is difficult to think of any chronic condition in which patients are committed to long-term treatment without the performance of simple tests when these are readily available. Recent studies have clearly demonstrated that asthma diagnosis in adults and children is a lottery, with overdiagnosis.

Table 1. The seven recommendations of the Lancet Asthma Commission

<table>
<thead>
<tr>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Revolutionise airway disease, deliver precision medicine</td>
</tr>
<tr>
<td>Move beyond asthma control to prevention and cure</td>
</tr>
<tr>
<td>Emerge from age- and discipline-associated silos</td>
</tr>
<tr>
<td>Test before treatment</td>
</tr>
<tr>
<td>Zero tolerance of asthma attacks</td>
</tr>
<tr>
<td>Maximise treatment opportunities in severe disease</td>
</tr>
<tr>
<td>Better research – especially basic and epidemiological</td>
</tr>
</tbody>
</table>

At no age should you rely just on a subjective history!

- Wheeze
  - Have you or any other doctor actually heard wheeze?
- Is there any evidence of reversible airflow obstruction?
  - Acute peak flow or spirometry response to inhaled short-acting beta₂-agonist
  - Peak flow variability on home monitoring for two weeks
  - Drop in peak flow after vigorous exercise (can also be a home test)
- Is there evidence of airway inflammation?
  - Is the child atopic (eosinophilic airway inflammation very rare in non-atopics)
  - Measure FeNO if you have access to it
  - Consider measuring blood eosinophil count (and if you do, IgE and specific IgE to aeroallergens)
- Is airway infection the problem?
  - Perform sputum culture if any produced, otherwise cough swab

Table 2. Measure before you treat: what the Commission means for asthma diagnosis in children in primary care
A standard three- or five-day course of prednisolone without assessing response has no place in the 21st century – check the child has got better by seeing them quickly after an attack, and also follow up within (say) four weeks to ensure improvement is maintained.

A child who has had an asthma attack will have another one unless something is done; and the next attack may kill that child. Does the family understand that something really serious has happened?

Does the family understand the importance of regular check-ups or do they just bring the child in at crisis time?

Review the asthma plan – does it exist? Was it followed, and if so does it need changing? If it was not followed, is there a need for education?

Review adherence: at a minimum, what has been the prescription uptake from your computerised records? This may be an imperfect measure, but it is better than asking the family! Also check if there is a pattern of excessive prescriptions for beta₂-agonists.

Is the medication delivery device correct and being correctly used?

Generally multiple teaching sessions are needed.

Are there issues in the environment that need addressing, e.g. smoking, vaping or exposure to allergens to which the child is sensitised?

Should the child be referred to secondary care?

**Table 3.** Asthma attacks should be a never-event: what the Commission means in practice for primary care

<table>
<thead>
<tr>
<th>Child with suspected asthma</th>
<th>Objective evidence of variable airflow obstruction and/or eosinophilic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Consider diagnosis</td>
</tr>
<tr>
<td>Yes</td>
<td>No further action</td>
</tr>
</tbody>
</table>

**Response to beta₂-agonists**

- Yes: No further action
- No: Reconsider diagnosis

**Response to inhaled corticosteroids (beclometasone equivalent 200µg twice daily)**

- Yes: No further action
- No: Reconsider diagnosis

**Response to addition of one other controller**

- Yes: No further action
- No: Go to non-treatment responsive algorithm (see Figure 2)

**Figure 1.** Proposed algorithm for approaching the diagnosis and treatment of children with suspected asthma in primary care

Asthma attacks

An asthma attack should be a never-event, like cutting off the wrong leg during surgery. The feeble word ‘exacerbation’, implying a transient inconvenience, should not be used. The strongest risk factor for a further attack, and death from asthma, is a previous attack, especially in the month following discharge from hospital. Furthermore, asthma attacks are associated with worse subsequent airway growth. It is not acceptable practice to prescribe a short, fixed-dose course of oral prednisolone (eg three to five days) without evaluating the patient: (a) to ensure recovery is complete; (b) to determine what went wrong and what can be done to prevent it happening again; and (c) to try to modify risk factors. Specifically, there needs to be a review of the asthma plan – was it followed (or does it even exist?) and should it be modified?

It is well known that respiratory viruses are an important driver of asthma attacks, and beyond influenza immunisation, there seemed little in the way of preventing attacks that was possible. However, recent studies have challenged this therapeutic nihilism. One study showed that the combination of allergen sensitisation, allergen exposure and respiratory virus infection in children aged 3–17 years was very strongly predictive of admission to hospital with acute wheeze, underscoring and a lack of any attempt to make objective measurements common. Overdiagnosis is important, not just for the waste of medication costs and risk of unnecessary side-effects, but because the diagnosis is trivialised, leading to a lack of focus on those at real risk.

A frequently encountered proposition is that asthma cannot be diagnosed until a particular age. The Commission contends that this is untrue. The question really should be: how do we determine the presence or otherwise of the above treatable traits at any given age? Of course, this is most challenging in young children, but even then, physician diagnosis of wheeze and auscultatory response to a beta₂-agonist is useful in determining bronchodilator responsiveness.

A question of little meaning in the view of the Commission is: do children with disease X (either pulmonary, such as chronic lung disease of prematurity, or systemic, such as sickle cell anaemia) also have asthma? The question needs to be re-phrased. Assuming the child really has an airway disease (and in the general population, around half of all those complaining of breathlessness are in fact deconditioned), then what treatable traits does the child with a specified other condition have? So survivors of preterm delivery have fixed and variable airflow obstruction, but no evidence of eosinophilic airflow inflammation, and thus should be treated with bronchodilators but not ICS. The airway disease of sickle cell anaemia is fixed airflow obstruction with no bronchial hyper-responsiveness or airflow inflammation. Neglect of these principles leads to inappropriate prescribing of ICS to children with chronic airway infection, which may in fact actually increase the tendency to infection.

Table 2 summarises the Commission’s recommendations on asthma diagnosis in primary care.
the importance of interactions between type 2 inflammation and viruses in causing attacks. Of these three factors, allergen exposure alone can be modulated.

In another study, children in the same age range who had been admitted at least once to hospital with an asthma attack and who were sensitised to house dust mite were randomised to mite-impermeable bed covering or placebo covers. Fewer children in the active group attended hospital with an attack in the subsequent 12 months, although there were only trends for total number of attacks and prednisolone usage. This study nicely gives proof of concept that something can be done to modify risk, but perhaps it was too narrowly focused. For example, many of the children were pet sensitised and exposed, but nothing was done about this, and a more broadly-based intervention might be more effective. Certainly, evaluation of allergen exposure, as well of course as irritants like tobacco smoke, should be part of the assessment of the child who has suffered an asthma attack.

Another approach to the prevention of asthma attacks is the use of the injected anti-IgE monoclonal antibody omalizumab, a secondary or tertiary care medication. Everyone knows that when children return to school in September, winter respiratory viruses wreak havoc in terms of asthma attacks. To what extent poor adherence to medication during the holiday period, when the child is well, is a contributing factor is unclear. However, the use of omalizumab in the run-up to the return to school has been shown to eliminate the peak of asthma attacks. Omalizumab worked best in those who were on step 5 treatment, and who had an asthma attack during the run-in period. For all others, increasing ICS therapy was an equally effective strategy. In general, those having attacks and responding best to omalizumab were those with evidence of uncontrolled eosinophilic inflammation (high FeNO, high blood eosinophil count). Indeed, a Cochrane review suggested that a strategy to normalise FeNO in adults and children reduced asthma attacks, and in adults, a strategy based on normalising sputum eosinophil counts also reduced attacks; the evidence is less clear for the latter in children.

Table 3 summarises the Commission’s recommendations for primary care on the management of a child following an asthma attack.

The end of the affair: back to basics
It must be remembered that treating asthma is very simple in the vast majority of patients, if treatment is regularly and appropriately given. Low-dose ICS with possibly the addition of one additional controller will be effective in virtually all children. The plateau of the dose-response curve is the equivalent of 200µg daily fluticasone dipropionate. Few children derive any benefit from higher ICS doses, and few require sophisticated monitoring of biomarkers, if the basics are got right. A proposed treatment algorithm for children with suspected asthma in primary care is provided in Figure 1. So, if the child is not responding to simple measures, the answer is not to scale up treatment but to ask the question: why not? Figure 2 outlines the approach to management of the child

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### Table 3: Commission’s Recommendations for Primary Care

<table>
<thead>
<tr>
<th>Consider the child’s treatment:</th>
<th>What about the environment?</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Are inhaled corticosteroid prescriptions being collected?</em></td>
<td><em>Parental smoking and vaping</em></td>
</tr>
<tr>
<td><em>Is there excess use of beta₂-agonist?</em></td>
<td><em>Outdoor pollution</em></td>
</tr>
<tr>
<td><em>Is the inhaler device appropriate?</em></td>
<td><em>Allergen exposure</em></td>
</tr>
<tr>
<td><em>Does the child know how to use it?</em></td>
<td></td>
</tr>
<tr>
<td><em>Is treatment supervised?</em></td>
<td></td>
</tr>
</tbody>
</table>

### Consider co-morbidities:

- Hyperventilation, exercise-induced laryngeal obstruction
- Obesity
- Allergic rhinitis

### Psychosocial morbidity?

- Anxiety
- Depression
- Failure to engage with routine care
- Hidden gain from bad symptoms

### Escalate inhaled corticosteroid dosage

Add other medications

Refer to secondary care if still a problem

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**Figure 2. Approach to the child with asthma apparently not responding to low-dose asthma therapy**
with asthma that is not responsive to treatment. Questions to consider are:

- Does the child have asthma at all? For example, is breathlessness due to deconditioning?
- Are the symptoms due to asthma? For example, exercise-induced laryngeal dysfunction caused by vocal cord adduction during exercise commonly co-exists with asthma. 2, 3
- Is the medication being taken regularly with good technique through an appropriate device?

Co-morbidities such as obesity, and social and environmental factors are also important:

- Are there adverse environmental factors such as a high-allergen burden to which the child is sensitised, or exposure to tobacco or vaping?
- Are there important psychological factors – depression, denial or disorganisation?

Very few children referred to the Royal Brompton severe asthma clinic actually turn out to need beyond-guidelines therapy. Simple treatment if accessed works well for the vast majority; if it does not, improved access to simple treatment, not more ICS, is likely the answer. 4

Impact on practice

Finally, to what extent has the Commission influenced practice? The proposal for the renewal of the Asthma UK Centre for Applied Research focused on zero tolerance for asthma attacks – something we strongly advocated – but we are a long way from achieving this. NICE in particular has focused on making asthma diagnosis more objective – again a Commission recommendation. However, we are still a long way from objective, 21st century diagnosis, risk assessment and management of asthma. Complacency is probably the biggest barrier to progress.

References


Declaration of interests

Andrew Bush is an NIHR Senior Investigator and additionally was supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London; Ian D Pavord is an NIHR Senior Investigator and additionally is supported by the Oxford NIHR Respiratory Biomedical Research Centre.

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