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EDITORIAL

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Asthma diagnosis in the community – time for a change?

This editorial discusses the findings of the paper in this issue by A. Manoharan et al. [20], pp. 1240–1245.

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Asthma is a very common long-term condition affecting over 5 million people in the UK, and the global prevalence continues to rise [1]. The scale of the asthma public health problem is such that the majority of patients are diagnosed and managed in the community by generalists rather than by respiratory specialists. The diagnosis of asthma can be complex, particularly in patients with alternative potential explanations for their symptoms, such as the elderly and the obese [2, 3]. How accurate is this diagnosis, and is asthma being over- or under-diagnosed against established gold standards? Similarly, how well is asthma being monitored to ensure that control is achieved and maintained and that medication is effectively titrated?

The pathology of asthma is characterized by abnormal airways, which constrict excessively in response to a wide range of exogenous and endogenous stimuli. Such bronchial hyperresposiveness (BHR) is a fundamental and defining feature of asthma, although it is rarely assessed in routine care. The clinical manifestations of asthma result from both airways inflammation and from the varying contributions of smooth muscle contraction, oedema and airways remodelling. Asthma is increasingly recognized as being highly heterogeneous in character [4, 5] and varies in severity, clinical expression and treatment response between individuals and within individuals over time. The symptoms of asthma – predominantly breathlessness, chest tightness, wheeze and cough – are non-specific and are shared by other acute and long-term conditions. These include other respiratory diseases, such as COPD, infections and fibrotic lung disease, and non-respiratory conditions such as cardiovascular, metabolic and even psychological/psychiatric conditions. There is a well reported disconnect between on the one hand patient experience (as measured by symptoms or quality of life impairment) and on the other 'objective' markers of disease severity and activity, including physiological, inflammatory and lung function measures [6–10]. As a consequence, making the diagnosis of asthma based on symptoms alone is fraught with potential error, and monitoring and treatment titration decisions may be more effective if assessments of symptom control are augmented by objective evidence of disease activity [11]. Simple physiological tests of reversible or variable airflow obstruction can confirm the diagnosis in some cases, although spirometry and peak expiratory flow rate (PEFR) monitoring have relatively low sensitivity and specificity [10, 12] so often do not permit these strategies to be definitive. In the absence of triggers, patients with mild or intermittent disease may have unobstructed spirometry and lack PEFR variability when assessed, so normal results cannot exclude the diagnosis. Lung function tests can be spuriously abnormal in patients with conditions other than asthma presenting with similar symptoms [12]. In cases of diagnostic uncertainty, more sophisticated tests are advised before the diagnosis of an incurable and usually lifelong condition is made and long-term treatment is instigated.

Further diagnostic tests centre on bronchial challenge testing to confirm BHR and on measures of airways

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inflammation, for example assessing the fraction of exhaled nitric oxide (FeNO) [13]. These tests are rarely performed in the community, and few primary care clinicians currently have access to them. More often than not, in 'real-life' practice, the diagnosis of asthma is made without even basic lung function tests being recorded, never mind more sophisticated tests being applied [14]. There is now a growing concern that many patients labelled and treated as having asthma have been misdiagnosed [11], so are receiving inappropriate and hence ineffective treatment. As asthma is very common and inhaled therapy expensive (inhaled medication products top the pharmacy costs list in many health economies), this potentially leads to resources being wasted, to patient exposure to ineffective medication with potential adverse effects, as well as to the consequences for the individual of the failure to make a correct diagnosis. We have known for some time that many patients can have their treatment reduced or even withdrawn without detriment [15], suggesting overtreatment is common and step-down underused. Worryingly, there are now a number of studies from different geographical settings and using different methodologies consistently suggesting that a significant minority of people labelled as having asthma have no objective evidence of the disease, with objective tests being normal. On detailed assessment, up to 1/3 of adults diagnosed and treated for asthma [9, 16–19] lack objective evidence, including a lack of abnormal physiology, of BHR or of airways inflammation. These cross-sectional studies involved assessment occurring some time after the diagnosis had been made. It is therefore possible that some patients would have had confirmatory tests at the time of the original diagnosis, with asthma subsequently resolving or with all metrics normalizing on treatment. However, in the absence of reliable 'incident' studies, it is equally (if not more) plausible that many never really had asthma at all. Demographic factors and symptom levels do not predict the presence or absence of BHR or airways inflammation in patients labelled with asthma [9], so without objective testing the problem would not be apparent, and long-term would treatment is likely to continue.

In this edition of the journal, Manoharan et al. [20] report interesting findings from an observational cross-sectional survey on apparently representative UK adults diagnosed and treated for asthma in the community. Objective assessments were made of symptoms, airways physiology and of BHR using both a direct (methacholine) and an indirect (inhaled mannitol) inhalational challenge, with an assessment of airways inflammation using exhaled nitric oxide assessment (FeNO). BHR is fundamental to our concept of asthma, management strategies using BHR as a guide to dose titration have reported improved outcomes in comparison with guideline-based care [21, 22], and lack of a positive BHR test has been suggested as a marker for an incorrect diagnosis of asthma [23]. In agreement with previous work, the current study reports a heterogeneous pattern of dysfunction, but the most striking finding was that 30% of subjects were negative to both mannitol and methacholine BHR testing. Those testing negative were older, had less atopy, better lung function and less airways inflammation (FeNO), with the large majority being within normal limits for all these measures. They also had lower symptom scores. The authors conclude that asthma was either over-treated or misdiagnosed in these patients. Fourteen percent of methacholine responders were negative to mannitol, and 16% of mannitol responders negative to methacholine, showing that while broadly overlapping, direct and indirect BHR testing will produce subtly different results in unselected asthmatics. Methacholine testing requires a well-organized pulmonary function laboratory setting to be safely and accurately performed, but mannitol testing is feasible in community settings. Mannitol offer the advantage (as an indirect test requiring an intermediate inflammatory pathway) of correlating better with airways inflammation and the corticosteroid responsiveness. The authors call for studies to assess the clinical and cost-effectiveness of BHR testing (particularly with mannitol) in the community.

We would agree that the volume of evidence is now such that prospective controlled trials of 'enhanced' diagnostic and monitoring strategies incorporating biomarkers and testing diagnostic and management algorithms are required. Such implementation studies need to assess the acceptability of these strategies to patients and to clinicians and to include detailed health economic evaluations. The availability of simple and relatively inexpensive near-patient tests such as FeNO and mannitol, (as well as older potentially useful markers such as the blood eosinophil count that may not have been fully exploited), mean that if shown to be useful, enhanced testing strategies are feasible, and may save money. The most effective testing strategies and algorithms require further definition. Current guidelines are consistent with this approach, stressing the need for objective testing in cases of diagnostic uncertainty, but are not fully implemented in the community due to practical and logistic problems associated with making testing widely available. Different models of care are possible, ranging from investment in expanded open access hospital-based services to community based and run diagnostic clinics and to individual practices (or local groups) offering the services in-house.

Why is asthma being over-diagnosed? GPs may perceive a pressure to apply the label and commence empirical inhaled treatment in patients with non-specific symptoms, even when lacking objective confirma-

tion, due to well-publicized evidence of under-diagnosis in epidemiological surveys such as the ECRHS and ISAAC studies [24, 25]. These continue to suggest that there are many undiagnosed people in the community with persistent respiratory symptoms consistent with asthma. The only objective tests available to most primary care clinicians managing asthma are PEF monitoring and/or spirometry, but even these tests seem to have been under-used in diagnosis in 'real-life' practice, with many patients commenced on inhaled treatment with corticosteroids for 'asthma' before the diagnosis is objectively secured [14]. Subsequent improvements in symptoms, which may be non-causally related and due to spontaneous improvements or 'regression to the mean' in a symptomatic patient, are likely to be taken as confirmation of the diagnosis. Lack of response, on the other hand, may lead to increases in asthma medication, rather than triggering a diagnostic review.

As the era of stratified medicine evolves [26], better patient characterization will underpin the progression to a more personalized, patient-centred approach to care. Although much of the current focus is on severe, difficult to treat asthma, it may well be that the same considerations apply to milder, community treated disease. Any significant change to the way we diagnose and treat asthma that incorporates increased use of additional tests or biomarkers will need some degree of service reconfiguration and investment in setting up and maintaining services, as well as training issues for front-line staff. This will inevitably cost money at a time when resources are scarce. However, perhaps we are now approaching a time when we can not afford NOT to make more objective and accurate diagnoses and assessments in asthma and other long-term conditions.

Conflict of interest. The authors declare no conflict of interest.

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