

## CASE REPORT OPEN

## The challenge of objective confirmation of asthma diagnosis in primary care

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Asthma represents one of the most common chronic conditions encountered in primary care and diagnosis should be confirmed objectively with the demonstration of variable airflow obstruction. As many asthmatics have normal lung function at the time of clinical presentation, objective confirmation of airflow limitation may be challenging. Fluctuations in airflow obstruction can be documented with simple office spirometry after bronchodilator challenge, home monitoring of peak expiratory flow and bronchoconstriction induced by spasmogens such as methacholine. We present a case highlighting the challenge of objective confirmation of asthma diagnosis in primary care and provide a critical review of the diagnostic approaches highlighted above. Our aim is to provide a pragmatic interpretation of the available literature with a view to assisting clinicians in selecting the diagnostic test best suited for individualised patient encounters.

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## CASE PRESENTATION

A 48-year-old woman with no smoking history reported cough and feeling short of breath with exertion beginning several months before her clinic visit. It was not clear whether she experienced any episodes of wheezing or chest tightness in association with her shortness of breath. She also reported longstanding nasal congestion and throat irritation, which are symptoms consistent with postnasal drip syndrome. She did not complain of chest pain or respiratory symptoms associated with nocturnal or early-morning awakening.<sup>1</sup>

Her past medical history included eczema and a single episode of generalised hives. She reported sensitivities to trimethoprim and sulfamethoxazole as well as to metronidazole. Skin prick testing revealed positive responses to house dust mites. There was no family history of atopy or asthma. She did not report a history of cardiovascular illness. On physical examination, the blood pressure was 130/90 bilaterally, heart rate was 76 beats/min and regular, with a respiratory rate of 10 breaths/min. Her body mass index was 32 kg/m<sup>2</sup>. Air entry was equal bilaterally with no audible wheeze. There was mild nasal mucosal oedema and erythema without evidence of nasal polyps. Simple spirometry was carried out in the clinic for further assessment according to the American Thoracic Society Criteria.<sup>2</sup> A chest X-ray and 12-lead electrocardiogram obtained at the initial visit were both normal.

## INTRODUCTION

Asthma is a complex disease associated with airway inflammation, hyper-responsiveness and variable airflow obstruction that may not all co-exist in many patients.<sup>1</sup> The criteria for spirometric diagnosis of asthma include an improvement in forced expiratory volume in 1 s (FEV<sub>1</sub>) of 12% and 200 ml after bronchodilator challenge.<sup>1</sup> This latter approach is often recommended as a first-line strategy for asthma diagnosis in the asthma guidelines.<sup>1</sup>

Simple spirometry can be carried out in the physician's office in a timely manner, and it provides useful information about the relationship between flow and volume. There are few clinically relevant risks associated with performing simple spirometry tests. However, the test's accuracy and reproducibility depends on maximal effort by the patient. The assessor must have the expertise to coach the patient, address language barriers and recognise unacceptable efforts, as poorly performed manoeuvres can mimic various disease patterns.<sup>3,4</sup> Measurement of peak expiratory flow rate (PEFR) is simple, convenient and can be done either in the clinic or in the home settings.<sup>1</sup> PEFR variability has been linked to airway hyper-reactivity and is recognised as a useful diagnostic aid that is well suited for adoption in primary care.<sup>1</sup>

More sophisticated testing such as methacholine challenge is recommended among patients who present with clinical features compatible with asthma but normal spirometric findings on initial testing. Methacholine challenge testing (MCT) includes inhalation of methacholine, a substance that is intended to induce bronchoconstriction in susceptible airways and may be associated with some risks. To our knowledge, there have been no reported deaths from MCT.<sup>5</sup> Some reports indicate that MCT is quite safe, even in patients with severe obstruction.<sup>6</sup> To date, the role of MCT as a first-line test for asthma diagnosis in the primary care setting has not been clearly delineated and has yet to be recommended by any agency or guideline outside of a specialty care facility.

The importance of objective confirmation of asthma diagnosis in the community setting has been discussed by Aaron *et al.*<sup>7</sup> They describe that about one-third of obese and non-obese individuals with physician-diagnosed asthma did not have asthma when objectively assessed. These findings raise awareness of the importance of objective confirmation of asthma diagnosis, and have stimulated considerable debate around which test to consider first by primary care physicians in the office setting.<sup>8,9</sup>

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**Table 1.** Initial spirometry assessment: spirometry performed during the initial clinic visit

Spirometry indices	PRE		POST		% Change
	Best	% Pred	Best	% Pred	
FVC	3.8	98	3.82	99	1
FEV <sub>1</sub>	2.85	91	2.96	95	4
FEV <sub>1</sub> /FVC	0.75		0.77		

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; % Pred, % predicted.

## CASE UPDATE

Spirometry performed during the initial clinic visit revealed a pre-bronchodilator forced vital capacity (FVC) of 3.80 l (98% predicted), FEV<sub>1</sub> of 2.85 l (91% predicted) and FEV<sub>1</sub>/FVC ratio of 0.75. The results are shown in Table 1. After bronchodilator challenge with salbutamol, the FVC was 3.82 l (99% predicted) and FEV<sub>1</sub> was 2.96 l (95% predicted), with an improvement of 4% and 110 ml from baseline. The FEV<sub>1</sub>/FVC ratio was 0.77 (Table 1). After discussion about the possible causes of her symptoms, including asthma, a management plan including watchful waiting of her mild symptoms was decided upon, including repeat spirometry during a follow-up visit in 1 month's time or sooner to evaluate interval change in clinical status.

The patient did not return until 6 months after the initial clinic visit. Spirometry revealed a pre-bronchodilator FVC of 4.13 l (105% predicted), FEV<sub>1</sub> of 3.02 l (97% predicted) and FEV<sub>1</sub>/FVC ratio of 0.75 (Table 2). After bronchodilator challenge with salbutamol, the FVC was 4.13 l (107% predicted), FEV<sub>1</sub> was 3.00 l (95% predicted); with an improvement of 0% and reduction of 20 ml from baseline), and the FEV<sub>1</sub>/FVC ratio was 0.73 (Table 2). Since her previous clinic visit, she described her symptoms as somewhat worse with increased cough, mucus production and shortness of breath with activity. Salbutamol was prescribed for as-needed use and an MCT was ordered. The results of baseline spirometry conducted ~2 months later and just before MCT and after reversal of methacholine-induced bronchoconstriction are shown in Table 3. Although baseline spirometry was normal and comparable to the previous measurements, mentioned above, the provocative concentration of methacholine resulting in a 20% reduction in FEV<sub>1</sub> (PC20) from baseline was 3.37 mg/ml, a finding that would support a positive hyper-bronchial test. Treatment with regular inhaled corticosteroid and as-needed salbutamol resulted in a marked improvement in symptoms.

## CLINICAL CONSIDERATIONS

In this case, several attempts with simple spirometry failed to identify FEV<sub>1</sub> changes that would meet the bronchodilator reversibility criteria for asthma diagnosis outlined in national and international guidelines.<sup>1,10</sup> Lusardi *et al.*<sup>11</sup> reveal that most patients in primary care have mild asthma and well-preserved lung function and that airflow obstruction—defined as a reduction in the ratio of FEV<sub>1</sub>/FVC < 0.70—was observed in only 21% of patients diagnosed with asthma. They were not able to demonstrate a significant advantage of office spirometry in improving the diagnosis of asthma and COPD in standard general practice.<sup>11</sup>

Goldstein *et al.*<sup>12</sup> were among the first to report that variability in PEF and postbronchodilator FEV<sub>1</sub> responses are poor substitutes for methacholine inhalation challenge in the assessment of patients with suspected asthma with normal findings on lung examination, chest radiography and spirometry. The reports

**Table 2.** Follow-up spirometry assessment

Spirometry indices	Pre		Post		% Change
	Best	% Pred	Best	% Pred	
FVC	4.04	105	4.13	107	2
FEV <sub>1</sub>	3.02	97	3.00	96	0
FEV <sub>1</sub> /FVC	0.75		0.73		

Spirometry performed six months after the initial clinic visit.

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; % Pred, % predicted.

**Table 3.** Methacholine challenge test

Methacholine concentration (mg/ml)	FVC (l)	FVC (%Ctrl)	FEV <sub>1</sub> (l)	FEV <sub>1</sub> (%Ctrl)
Baseline	3.85	96	2.98	97
Control (Ctrl)	4.01	100	3.06	100
0.125	3.23	81	3.04	99
0.500	3.10	77	2.91	95
2.000	3.25	81	2.77	91
4.000	3.17	79	2.3	75
Reversal	3.68	92	2.8	92

Baseline spirometry prior to methacholine challenge test and after reversal of methacholine-induced bronchoconstriction.

PC20 (FEV<sub>1</sub>) = 3.37 mg/ml, where PC20 is the provocative concentration of methacholine resulting in a 20% reduction in FEV<sub>1</sub> from baseline.

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1 s (predicted value = 3.11 l); FVC, forced vital capacity (predicted value = 3.85 l); % Pred, % predicted.

of Hunter *et al.*<sup>13</sup> indicate that methacholine responsiveness is more than twice as sensitive as bronchodilator reversibility for FEV<sub>1</sub> and variability in PEF as a marker of mild asthma. Furthermore, Schneider *et al.*<sup>14</sup> highlight that the sensitivity for diagnosing airway obstruction in asthma with simple spirometry was only 29%. The data described by Ulrik *et al.*<sup>15</sup> suggest that airway responsiveness to histamine, diurnal peak-flow variability and bronchodilator reversibility cannot be used interchangeably as objective markers of asthma in epidemiologic studies. They suggest on the basis of their findings that airway hyper-responsiveness to a nonspecific bronchoconstrictor is recommended as the objective marker of asthma-related airway lability. Yurdakul *et al.*<sup>16</sup> also describe a much higher sensitivity for MCT compared with FEV<sub>1</sub> reversibility and PEF variability for asthma diagnosis among patients attending an outpatient asthma clinic. Furthermore, the data described by Aaron *et al.*<sup>7</sup> suggest that asthma diagnosis could be confirmed in only 16% of patients by means of postbronchodilator spirometry at the time of testing (at least 15% and at least 200 ml) and in 72% of patients by means of bronchial challenge testing with methacholine. Finally, Luks *et al.*<sup>17</sup> suggest that only 10.8% of patients were diagnosed with asthma using simple pre- and postbronchodilator spirometry at the time of testing, while MCT resulted in a confirmation rate of 61.7% and an exclusion rate of 27.3% among individuals whose lung function was reported to be in the normal range at clinical presentation. It is important to note that, among asthma patients identified in an administrative database with lower lung function compared with the studies cited above, Macy *et al.*<sup>18</sup> found that 62% of asthmatics were identified with FEV<sub>1</sub> reversibility.

These findings<sup>18</sup> may suggest that baseline lung function and asthma control in general may influence bronchodilator responsiveness.

The findings highlighted above underscore the lower sensitivity of bronchodilator reversibility and PEFV variability as confirmatory tests compared with MCT for asthma diagnosis in primary care among patients with mild disease. Repeated testing with simple spirometry at different visits is advised in order to obtain objective confirmation of asthma diagnosis.<sup>19</sup> To date, there are no studies describing how many simple spirometric tests or trials of PEFV monitoring would be required to demonstrate bronchodilator responsiveness and airflow variability in a given patient in whom asthma is suspected. Guidelines do not clearly highlight how bronchodilator reversibility and PEFV variability testing might be implemented in primary care, including how patients with normal lung function on repeat testing should be managed during the interval between clinical suspicion of asthma and objective confirmation, particularly as treatment might reduce the odds of detecting meaningful improvements in FEV<sub>1</sub> after bronchodilator challenge or documentation of PEFV variability. Although MCT is safe and perhaps the most sensitive test for diagnosis of mild asthma, its role as a first-line test in primary care remains to be determined and it is not without deficiencies as a confirmatory test. For example, a provocative concentration of methacholine causing a 20% fall in FEV<sub>1</sub> of < 8 mg/ml may lack specificity and sensitivity.<sup>20</sup> False-positive results are seen in patients with other diseases, including COPD, allergic rhinitis and sarcoidosis. Because MCT has a high negative predictive value, it is more useful in ruling out asthma (if the result is negative) than in ruling it in (if the result is positive). A negative methacholine challenge test nearly always rules out asthma; however, a positive test result needs to be interpreted cautiously if the patient is not experiencing symptoms.<sup>21–23</sup>

## SUMMARY AND CONCLUSIONS

The case presented here and the series of studies highlighted above underscore the challenge of asthma diagnosis in primary care where there is a high probability of normal lung function at the time of testing in many patients. This clinical scenario calls for more studies dealing with the evaluation of asthma diagnostic and management strategies that are pragmatic, sensitive and cost-effective. Understanding the benefits and limitations of reversibility testing, PEFV variability measurements and MCT may help primary care physicians to better tailor their diagnostic approach among individuals with suspected asthma.

## CONTRIBUTIONS

All authors contributed to the development of this article.

## COMPETING INTERESTS

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