European Respiratory Society guidelines for the diagnosis of asthma in adults

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Shareable abstract (@ERSpublications)
Asthma diagnosis in adults still remains a challenge with over- and under-diagnosis. Spirometry with reversibility testing is essential. Nitric oxide, peak expiratory flow variability and bronchial challenge testing should also be considered. https://bit.ly/3ghCigm

Abstract

Although asthma is very common, affecting 5–10% of the population, the diagnosis of asthma in adults remains a challenge in the real world, which results in both over- and under-diagnosis. A taskforce was set up by the European Respiratory Society to systematically review the literature on the diagnostic accuracy of tests used to diagnose asthma in adult patients and provide recommendations for clinical practice. The taskforce defined eight Population, Index, Comparator and Outcome questions that were assessed using the Grading of Recommendations, Assessment, Development and Evaluation approach. The taskforce utilised the outcomes to develop an evidence-based diagnostic algorithm, with recommendations for a pragmatic guideline for everyday practice that was directed by real-life patient experiences.

The taskforce supports the initial use of spirometry followed by bronchodilator reversibility testing (if airway obstruction is present). If initial spirometry fails to show obstruction, further tests should be performed in the following order: exhaled nitric oxide fraction, peak expiratory flow variability, or, in secondary care, bronchial challenge. We present the thresholds for each test that are compatible with a diagnosis of asthma in the presence of current symptoms.

The taskforce reinforces spirometry as a priority and recognises the value of measuring blood eosinophils and serum immunoglobulin E to phenotype the patient. Measuring gas trapping by body plethysmography in patients with preserved forced expiratory volume in 1 s/forced vital capacity ratio deserves further attention. The taskforce draws attention to the difficulty of making a correct diagnosis in patients already receiving inhaled corticosteroids; the comorbidities that may obscure diagnosis; the importance of phenotyping; and the necessity of considering the patient experience in the diagnostic process.

Introduction

Asthma is the most frequent chronic inflammatory airway disease globally, with a prevalence reaching 5–10% [1], affecting 339 million people worldwide [2]. Asthma is defined by the cardinal symptoms of breathlessness, wheeze, chest tightness and cough, together with the presence of exaggerated expiratory airflow fluctuation that varies over time. This airways instability is usually ascertained by peak flow variability, reversibility to fast-acting bronchodilator drug or by bronchoconstriction following bronchial challenge [3]. However, population data consistently show that asthma is both under- and over-diagnosed; a phenomenon that may approach a false positive diagnosis of 30% [4], where the insufficient use of spirometry is fundamentally recognised to cause misdiagnosis, as the diagnosis is based primarily on symptoms alone. Misdiagnosis also occurs in specialist care, where patients labelled with and treated for severe asthma do not satisfy the classic criteria of asthma when thoroughly investigated and monitored over time [5]. Although there is no unanimous agreement upon an acceptable false positive rate, a 10% threshold represents a significant improvement in diagnostic accuracy.

When faced with the clinical challenge of diagnosing asthma, we must not forget that, at the centre, there is an individual patient struggling to manage their health. Patients describe feeling upset and frustrated when going through a series of tests that do not provide a definitive diagnosis, describing the process as "trial and error" [6–10]. Combining tests into a single appointment can make the process easier by reducing travel time, childcare costs and time off work [11]. However, patients do find certain diagnostic tests difficult to complete and may experience side-effects, such as breathlessness and anxiety [12, 13]. The requirement to stop asthma medications prior to a diagnostic test can cause anxiety [14], with lack of clear advance information on which medications to stop and for how long [12].

Although there are many asthma guidelines recommending objective testing to confirm the diagnosis in symptomatic patients, there is considerable variation between them with lack of consensus on the tests and their sequence. Yet, reports consistently reiterate the need to better diagnose asthma and the need to determine which of the commonly used tests are most helpful [15]. It is well recognised that adherence by healthcare professionals to guidelines is suboptimal [16], and this may reflect difficulty in access to the recommended tests or incorporating them in their everyday practice in diagnosing asthma within local patient pathways. Importantly, the patient's perspective is often not taken into account at the planning stage when developing guidelines [17].

In 2018, the European Respiratory Society (ERS) set up a task force to systematically review the literature on the diagnostic accuracy of tests used to diagnose asthma in adult patients using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology and provide recommendations for clinical practice. The taskforce specifically focused on developing an evidence-based pragmatic clinical guideline for everyday practice that was directed by patients' real-life experiences in their diagnosis of asthma (a patient-driven guideline), with a physician-centric practical approach to determine 1) which tests to use to diagnose asthma in primary care; 2) the transition point of referral to specialist care; and 3) which tests to undertake in the specialist setting.

Methods

The methods are described in detail in the supplementary material. The purpose of the taskforce was to assess the accuracy of tests used to diagnose asthma in well-resourced healthcare systems.

Taskforce composition

The panel consisted of a multidisciplinary group of healthcare professionals with expertise in asthma from both primary and specialist care settings and junior and senior clinicians, including a respiratory nurse, and with patient representation (supplementary table S1). The panel did not include respiratory technicians or primary care clinicians from low- or middle-income countries. Methodologists from the ERS provided expertise, overview and guidance on methodology, GRADEing and making recommendations for diagnostic tests [18]. Panel members disclosed potential conflicts of interest according to ERS policies at the start of the taskforce and prior to publication of this article.

Formulation of the PICO questions

Asthma is characterised by variable respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough and variable expiratory airflow limitation, and is usually associated with airway inflammation [3]. The taskforce initially met at the ERS 2018 congress and, importantly, agreed upon the operating definition of asthma to be used (table 1), which was close to the definition adopted by the Global Initiative for Asthma (GINA). We adopted the eight-question PICO framework and GRADE

TABLE 1 Operating definition of asthma

Typical symptoms including breathlessness, wheezing, cough, chest tightness and objective demonstration of excessive airway calibre fluctuation with at least one of the following define asthma both in primary and secondary care:

1) Peak flow variability ⩾20% or spontaneous variation in FEV_1 ⩾12% and 200 mL
2) Reversibility after bronchodilator inhalation with improvement in FEV_1 of ⩾12% and 200 mL
3) Airway hyperresponsiveness: PC_{20M} (or PC_{20H}) <8 mg·mL^{-1} (or 16 mg·mL^{-1} in ICS-treated patients), PD_{15} mannitol <635 mg or FEV_1 fall ⩾10% after exercise
4) Improvement in FEV_1 ⩾12% and 200 mL after a 2-week course of OCS or a 4–6-week course of ICS

FEV_1: forced expiratory volume in 1 s; PC_{20M}: provocative concentration causing 20% fall in FEV_1 with methacholine; PC_{20H}: provocative concentration causing 20% fall in FEV_1 with histamine; ICS: inhaled corticosteroid; PD_{15}: provocative dose causing a 15% fall in FEV_1; OCS: oral corticosteroid.

methodology to assess each individual diagnostic test, but no treatment interventions were evaluated (supplementary table S2).

Several discussions led to the finalisation of the eight review questions, formulated using the PICO format (table 2). PICO questions were designed to assess the diagnostic tests available in the primary and specialist care settings. Two PICO questions were externally commissioned. A pair of taskforce members (one senior, one junior) were allocated to address the PICO questions.

Literature search and application of the GRADE approach

An initial systematic literature search was performed by an experienced librarian based at Liege University (Public Health Dept, Liege, Belgium) for each PICO question covering the period from January 1946 to July 2019. Eligible papers had to compare the index test to a reference standard including at least one other objective test. For each question, the outcomes were diagnostic accuracy: sensitivity and specificity. Cross-sectional and retrospective studies were included. Case–control studies were excluded. Manuscripts where tests had been used in the monitoring of asthma or assessment of treatment response were excluded. A final literature review for the eight PICO questions was performed for new publications up until July 2020. While conducting the PICO analysis, we ensured that the index test was only in the index group and not in the gold-standard reference group as, in routine clinical care, current clinical symptoms with either peak expiratory flow (PEF) variability, bronchodilator reversibility or bronchial hyperresponsiveness are used to diagnose asthma, so it may seem that the index test is also part of the gold-standard reference operational definition.

Junior members performed the initial screening of the outputs (title, abstract and full-manuscript review) from the systematic literature search, coordinated the final selection of research papers, performed the quality-of-evidence assessment for each selected research paper and undertook a draft GRADE assessment for presentation to the whole taskforce, supported by their senior members. In addition to the PICO questions, important diagnostic themes were identified by the taskforce as additional considerations, each assigned to a senior member, including the patient representative's view about the diagnostic tests they had undergone and the physical, social or psychological impact of the diagnosis [19], reported as the patient perspective within each PICO.

Recommendation development process and construction of a diagnostic algorithm

All taskforce members were presented with and discussed the results of the GRADE assessment. Using the Evidence to Decision framework, they agreed recommendations for each PICO question and documented the factors taken into account for each of them. Recommendations were described as strong or conditional. The strength of recommendations considers the balance of presumed outcomes as a result of diagnostic testing, the quality of the evidence, the uncertainty about values and preferences, and costs [20, 21] (tables 3 and 4). The algorithm was constructed based on the clinical practice of the taskforce members for the diagnosis of asthma in primary and specialist care, identifying when it is best for a primary care physician to refer to specialist care if doubt persists in the diagnosis of asthma. All taskforce members drafted and agreed the steps in the diagnostic algorithm.

Patient-relevant outcomes

The GRADE approach emphasises the importance of recommendations based on the impact on relevant patient outcomes [18]. Our patient taskforce member and the European Lung Foundation (ELF) were involved in every meeting of the taskforce, apart from the first one, and contributed to the Evidence to Decision process for every PICO. The ELF conducted a patient-centred literature review to identify relevant outcomes and patient experience of diagnostic testing. Although diagnostic accuracy studies do

TABLE 2 Population, Index (Test), Comparison and Outcome (PICO) questions	
PICO 1: Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
In patients with episodic/chronic symptoms suggestive of asthma	
Index test	FEV_1/FVC ratio
Gold standard	Excessive airway calibre fluctuation (see definition, table 1)
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Time	Depending on the gold standard chosen: 2 weeks for PEF recording, 6 months' follow-up with repeated spirometry tests for reversibility, 1 day for bronchial challenge
PICO 2: Can PEF variability testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
In patients with episodic/chronic symptoms suggestive of asthma	
Index test	Peak flow variability (minimum 2 weeks for peak flow recording as an index test)
Gold standard	Excessive airway calibre fluctuation (see definition, table 1)
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Time	Depending on the gold standard chosen: 2 weeks for PEF recording, 6 months' follow-up with repeated spirometry tests for reversibility, 1 day for bronchial challenge
PICO 3: Can measuring F_{eNO} help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
In patients with episodic/chronic symptoms suggestive of asthma	
Index test	F_{eNO}
Gold standard	Excessive airway calibre fluctuation (see definition, table 1)
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Time	Depending on the gold standard chosen: 2 weeks for PEF recording, 6 months' follow-up with repeated spirometry tests for reversibility, 1 day for bronchial challenge
PICO 4: Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
In patients with episodic/chronic symptoms suggestive of asthma	
Index test	Blood eosinophil count
Gold standard	Excessive airway calibre fluctuation (see definition, table 1)
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Time	Depending on the gold standard chosen: 2 weeks for PEF recording, 6 months' follow-up with repeated spirometry tests for reversibility, 1 day for bronchial challenge
PICO 5: Can measuring total serum IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
In patients with episodic/chronic symptoms suggestive of asthma	
Index test	Total or specific IgE (RAST) to common aeroallergens
Gold standard	Excessive airway calibre fluctuation (see definition, table 1)
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Time	Depending on the gold standard chosen: 2 weeks for PEF recording, 6 months' follow-up with repeated tests for reversibility, 1 day for bronchial challenge
PICO 6: Can combining F_{eNO}, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
In patients with episodic/chronic symptoms suggestive of asthma	
Index test	Combination of tests (blood eosinophils+F_{eNO}+IgE)
Gold standard	Excessive airway calibre fluctuation (see definition, table 1)
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Time	Depending on the gold standard chosen: 2 weeks for PEF recording, 6 months' follow-up with repeated tests for reversibility, 1 day for bronchial challenge
PICO 7: Can bronchial challenge testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
In patients with episodic/chronic symptoms suggestive of asthma	
Index test	Bronchial challenge tests (methacholine, histamine, mannitol, exercise)

Continued

TABLE 2 Continued	
Gold standard	Reversibility after bronchodilator testing (see definition, table 1)
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Time	Demonstration of reversibility before or during 6 months' follow-up
PICO 8: Can measuring of sG_{aw} and RV/TLC help in the diagnosis of asthma with episodic/chronic suggestive symptoms?	
In patients with episodic/chronic symptoms suggestive of asthma	
Index test	sG_{aw} and RV/TLC ratio (whole-body plethysmography)
Gold standard	Positive bronchial challenge (see definition, table 1)
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Time	1 day

PEF: peak expiratory flow; F_{eNO}: exhaled nitric oxide fraction; sG_{aw}: specific airway conductance; RV: residual volume; TLC: total lung capacity; FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; RAST: radioallergosorbent testing.

not provide direct evidence for the improvement of patient outcomes, the taskforce discussed each PICO and the Evidence to Decision framework in the context of patient-related outcomes including test acceptability, feasibility, how importantly a patient may value the test, and the potential for the test to have an impact on treatment (table 5).

Results

PICO 1: Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The taskforce recommends performing spirometry to detect airway obstruction as part of the diagnostic work-up of adults aged ⩾18 years with suspected asthma (strong recommendation for the test, low quality of evidence).

Remarks

- A forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio below the lower limit of normal (LLN) or <0.75, higher than the commonly utilised 0.70 threshold, should be considered supportive of an asthma diagnosis and should prompt further testing (see algorithm).
- Normal spirometry does not exclude asthma.

Background

Spirometry is a noninvasive physiological test, performed since the 19th century, that measures the volume and flow of air during inhalation and exhalation. A standardised procedure for performing spirometry has been published by the ERS and the American Thoracic Society (ATS) [12]. The FEV_1/FVC ratio is an index reflecting airway obstruction. The taskforce assessed the FEV_1/FVC ratio to determine whether it could help in the diagnosis of asthma.

TABLE 3 Understanding the strength of the recommendation, according to target group		
	Strong recommendations[#]	**Conditional (weak) recommendations**
Patients	Most people in your situation would want the recommended course of action and only a small proportion would not	The majority of people in your situation would want the recommended course of action, but many would not
Clinicians	Most patients should receive the recommended course of action	Recognise that different choices will be appropriate for different patients and that you must make greater effort to help each patient to arrive at a management decision consistent with their values and preferences; decision aids and shared decision are particularly useful
Policy-makers	The recommendation can be adopted as a policy in most situations	Policy-making will require substantial debate and involvement of many stakeholders

[#]: strong recommendations based on high-quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the unique features of individual patients and clinical circumstances.

TABLE 4 Recommendations on Population, Index (Test), Comparison and Outcome (PICO) questions

	Recommendation	Remarks
PICO 1: Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?	The taskforce recommends performing spirometry as part of the diagnostic work-up of adults aged ≥18 years with suspected asthma (strong recommendation for the test, low quality of evidence)	An FEV_1/FVC less than LLN or <0.75 should be considered supportive of an asthma diagnosis and should prompt a reversibility test. Normal spirometry does not exclude asthma
PICO 2: Can PEF variability testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?	The taskforce suggests not recording PEF variability as the primary test to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence)	Serial PEF may be considered if spirometry is normal and no other lung function test available, including spirometry and bronchial challenge. PEF should be monitored over a 2-week period and a variation of 20% considered supportive of asthma diagnosis. PEF variability <20% does not rule out asthma. PEF may be especially useful in case of suspicion of occupational asthma
PICO 3: Can measuring F_{eNO} help diagnose asthma in adults with episodic/chronic suggestive symptoms?	The taskforce suggests measuring F_{eNO} as part of the diagnostic work-up of adults aged ≥18 years with suspected asthma (conditional recommendation for the test, moderate quality of evidence)	A cut-off of 40 ppb offers the best compromise between sensitivity and specificity, while a cut-off of 50 ppb has a high specificity close to 90% and is therefore supportive of an asthma diagnosis. A F_{eNO} value <40 ppb does not rule out asthma. F_{eNO} values are markedly reduced by smoking and treatment with ICS and dupilumab
PICO 4: Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?	The taskforce suggests not measuring blood eosinophil count to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence)	Blood eosinophil count does not define asthma, but rather contributes to phenotyping
PICO 5: Can measuring total serum IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?	The taskforce suggests not measuring total serum IgE to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence)	Total serum IgE does not define asthma, but rather contributes to phenotyping
PICO 6: Can combining F_{eNO}, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?	The taskforce suggests not combining F_{eNO}, blood eosinophils and serum IgE to make a diagnosis of asthma (conditional recommendation against the test, moderate quality of evidence)	
PICO 7: Can bronchial challenge testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?	The taskforce suggests bronchial challenge testing should be performed in secondary care to confirm a diagnosis of asthma in adults when the diagnosis was not previously established in primary care (conditional recommendation for the test, low quality of evidence)	PC_{20M} or PC_{20H} <8 mg·mL^{-1} in steroid-naïve patients and <16 mg·mL^{-1} in patient receiving regular ICS supports a diagnosis of asthma. Indirect challenges such as mannitol or exercise may be considered in patients who remain negative with direct constricting agents
PICO 8: Can measuring sG_{aw} and RV/TLC help in the diagnosis of asthma with episodic/chronic suggestive symptoms?	The taskforce suggests not measuring sG_{aw} and RV/TLC by whole-body plethysmography to make a diagnosis of asthma (conditional recommendation against the tests, low quality of evidence)	sG_{aw} does not perform better than FEV_1/FVC ratio to predict a positive methacholine challenge in patients with normal baseline FEV_1. RV/TLC >130% predicted has a high specificity (>90%), but poor sensitivity (25%) to predict a positive methacholine challenge in patients with normal FEV_1/FVC

PEF: peak expiratory flow; F_{eNO}: exhaled nitric oxide fraction; sG_{aw}: specific airway conductance; RV: residual volume; TLC: total lung capacity; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal; ICS: inhaled corticosteroid; PC_{20M}: provocative concentration causing 20% fall in FEV_1 with methacholine; PC_{20H}: provocative concentration causing 20% fall in FEV_1 with histamine.

Review of the evidence

Our literature search identified 11 potentially relevant studies, of which four were suitable to be included (supplementary tables S3a and b) [27–30], all performed in secondary care, that assessed the accuracy of the FEV_1/FVC ratio to predict the probability of asthma ascertained by either bronchodilator reversibility of 12% and 200 mL improvement or 15% reversibility, methacholine bronchial hyperresponsiveness (provocative concentration causing a 20% fall in FEV_1 with methacholine (PC_{20M}) <8–16 mg·mL^{-1}) or 20% PEF variability over a 2-week period (supplementary table S4).

TABLE 5 Patient perspectives of asthma diagnosis: patient advice to health professionals and illustrative quotes

Patient advice to health professionals	Communicate clearly with patients that there is no single test to diagnose asthma and that several steps may be needed Be responsive to the patient's needs and preferences on how many tests to complete within a single visit Consider rest periods between tests to improve the patient experience Consider seasonal and work-related variation in asthma if test results do not appear to match the patient's experience of their symptoms Explain the risks of stopping medication and the procedures in place if the patient experiences increased symptoms
Getting a diagnosis	"My experience has been that there is a great deal of guesswork involved and I'm sure most people would just walk away with whatever diagnosis they are offered, no matter how little it resembles their experience. You just have to keep being a thorn in the side of your doctor get to the bottom of it. It's a hassle for both you and your doctor, but getting your condition under control is well worth it." [7]
Phasing of tests	"Well, yes, in my case it is necessary [to test] because the complaints come back every summer every spring. So most probably there is something more behind it." [6]
Stopping medications	"Had my first ever [lung] function test done this evening. F_{eNO} was fine at 13. Kind of frustrating as I was told to continue using my inhalers when I checked, yet turns out I should have stopped them [...] As I had taken my inhalers this morning she wasn't going to do reversibility and then decided why not yet reversibility was only 13.5% [...] now left really confused and annoyed. I was told to continue meds when I was meant to stop them." [8] "I have done one histamine (negative, due to stupid instructions on stopping medications), one mannitol (positive, I checked the medications instructions myself) [...] my input would just be to triple-check you're stopping all the meds at the right time as I find it's complex with different types at different times before, and they don't always give helpful instructions." [6]
Understanding their results	"I always have to ask for my [spirometry] results and … feel like I'm being a nuisance asking for them. I have no understanding of the context of my results, *i.e.* how I compare to others of my age with my condition? Are my results viewed as good or bad?" [22] "Saw nurse this morning who told me she doesn't think I have asthma because although the preventer inhaler I was given has made my peak flows go up, I get symptoms when my peak flow is above the average for my age height weight *etc.* (450) and I don't feel I'm my normal self until I'm like 470–500. See specialist in Feb. More confused than ever". [9]
Trial of treatment	"I had to ask, I had to go back several times with my condition deteriorating [...] But one day I had such a lot of chest pain and I just couldn't breathe that I just made myself an emergency appointment and said to her, 'Look I think it's asthma, I've got this family history, of very severe asthma in several family members I'm in such pain, would you not think it appropriate to try and prescribe me some asthma medication and let's just see if that improves my condition'. So in a sense I diagnosed myself, but [the doctor] did agree to that and that's when I started on some fairly low doses of Ventolin plus a Beclazone inhaler and that did help me." [23] "The doctor had given me a blue inhaler, but kind of hadn't shown me how to use it." [23]
Experiences of being diagnosed later in life	"I just assumed people got it as young children and kept it or got rid of it, 'cause I know children now can reduce or get rid of their symptoms, but I hadn't realised that you could be diagnosed as an adult with it." [24] "I was actually diagnosed with asthma round about my 47th birthday [...] Probably looking back I didn't actually manage things terribly well, when you first are diagnosed, especially the sort of age that I was diagnosed at, there was just that feeling of, well, just why me?" [23]
Psycho-social impact of diagnosis	"I would say that it's really important to listen to your patients. Because they are the experts in how they're feeling. And to see asthma as more than something that affects our airways. It actually affects us as people, it affects our lives. There's a huge adjustment that you have to make when you're first diagnosed. I went from seeing myself as a healthy person with no health worries and problems at all to somebody who might have an asthma attack tomorrow that they don't survive. Or even this afternoon. And that's a huge adjustment that you have to make. [...] I would ask health professionals to talk to us about how it's affecting us not just how it's affecting our breathing." [25] "There was say five minutes after I'd actually left the GP, after the chat with the doctor, there was five minutes before I went and collected my prescription where I was kind of depressed. You know, there was a [...] slump but then I decided, you know, 'This isn't going to be a big thing and I'm going to get out. I'm going to train harder. It's not going to affect my lifestyle'." [24] "Just been diagnosed with asthma by the nurse after 3 months of issues [...] New to this to be honest and I'm finding it quite a challenge to adapt to. I'm 38. It seems pretty bleak outlook to be honest constantly battling to breathe easy." [10] "I don't want to be different and I don't want my health to deteriorate, but going in there with that attitude isn't going to get me anywhere. And I think for those people who are newly diagnosed that is almost impossible, to go in there and be calm and clear-headed about it. You can't in the beginning, especially before diagnosis, because you haven't, you might have no idea why you're ill. Why you feel like you have no energy, why you can't do certain things, why you can't do certain jobs. Your career can be affected by it. Your home life is affected by it. Your social life is affected by it. And I think people who are newly diagnosed have got to give themselves time to come to terms with it. And that doesn't necessarily mean accepting it. For some people accepting you're ill will never happen. But it doesn't mean that you can't get your head round it and deal with it. [26]

In their cross-sectional study, HUNTER et al. [28] recruited 89 patients (baseline FEV_1 >65% predicted) from primary care with a prior label of asthma, but 20 patients were found to have an alternative explanation for their asthma. Of those diagnosed with asthma (n=69), 46% were receiving concomitant inhaled corticosteroids (ICS) while undergoing diagnostic testing. Asthma was diagnosed based on symptoms combined with at least one of the following: bronchodilator reversibility of 15% after 200 µg salbutamol, PC_{20M} <8 mg·mL^{-1}, or PEF variability of 20% over a 15-day period. A pre-determined cut-off of the FEV_1/FVC ratio at 77% based on the 95% LLN found in healthy subjects yielded a sensitivity and specificity of 61% and 60%, respectively [28]. STANBROOK et al. [30] retrospectively analysed lung function tests of 500 patients referred to secondary care and found a FEV_1/FVC cut-off value of <90% pred had 53% sensitivity and 28% specificity to identify a positive methacholine test (PC_{20M} <8 mg·mL^{-1}).

Two retrospective studies conducted in secondary care investigated the best threshold by constructing receiver operating characteristic (ROC) curves. In 270 patients, of whom half were treated with ICS, BOUGARD et al. [27], found an area under the curve (AUC) of 0.62 and a FEV_1/FVC ratio cut-off value at 0.77 in the training cohort and an AUC of 0.68 with a FEV_1/FVC cut-off value of 0.79 in the validation cohort. NEKOEE et al. [29] recruited steroid-naïve patients (n=702) with symptoms suggestive of asthma, including 19% of current smokers, and displaying an average baseline FEV_1 of 95% pred, and found sensitivity of 0.51 with specificity of 0.76 (GRADE table 6, supplementary table S3b).

Justification of the recommendation

Physiological airflow obstruction and fluctuation of airway calibre that is usually reversible are recognised as hallmarks of asthma. Though the quality of evidence was low, the taskforce recommends spirometry as the first test to be conducted in the diagnostic work-up. Over-diagnosis, which occurs in ~30% of patients with asthma diagnosed in primary care, occurs in part because spirometry is not performed and has a substantial risk of harm due to inappropriate treatment side-effects, costs and lack of proper diagnosis [4]. Therefore, a strong recommendation can be made despite low quality of evidence. Spirometry is readily available both in primary and secondary care, even though it might not be used sufficiently in primary care. Our research found that the FEV_1/FVC ratio cut-off providing the best combination of sensitivity and specificity is close to 0.75, a threshold well above the 0.70 generally recognised as a marker of airway obstruction. However, sensitivity at a cut-off of 0.75 is close to 50%, and much too low to rule out asthma. Likewise, at this cut-off, specificity remains <80%, making spirometry alone insufficient to rule in asthma with confidence.

Patient perspective

Spirometry is noninvasive and generally well accepted by the patient. However, the reproducibility of the measure depends on the skill of the operator and the participation of the patient. Indeed, the role of the operator is crucial in putting patients at ease and guiding them through each step [22], which patients value: "a sympathetic, helpful and considerate nurse can do wonders during this test". In addition, patients are interested in knowing about their breathing performance and individual test results, and how they relate to averages for their age, height and weight.

Key unanswered questions

We know that FEV_1/FVC ratio declines with age, so fixing a threshold is inappropriate to apply across a population with varying ages [31]. We did not find any study that expressed the FEV_1/FVC ratio as <LLN and calculated its prediction value. There is an urgent need for prospective studies in both primary and secondary care that would combine specific symptoms with spirometry indices expressed as LLN to make a diagnosis of asthma.

PICO 2: Can PEF variability testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The taskforce suggests not recording PEF variability as the primary test to make a diagnosis of asthma diagnosis (conditional recommendation against the test, low quality of evidence).

Remarks

- PEF may be considered if no other lung function test is available, including spirometry at rest and bronchial challenge testing.
- PEF should be monitored over a 2-week period and a variation of >20% considered as supportive of asthma diagnosis.
- PEF variability <20% does not rule out asthma.
- PEF may be especially useful to support a diagnosis of occupational asthma.

Background

PEF measurement over a few weeks has been advocated as a test to diagnose asthma for several decades as the tool to evidence airway calibre fluctuation associated with poor asthma control [32].

Review of the evidence

Our literature search identified 15 potentially relevant studies, of which six (one retrospective, five prospective) met the inclusion criteria (supplementary tables S5a and b) [28, 33–37]. Five studies (three in primary care, two in specialist care referred from primary care) addressed symptomatic patients without any prior investigations or diagnosis, and one study included patients diagnosed with asthma in primary care, but referred to secondary care (supplementary table S4).

All the studies assessed the diagnostic performance of pre-specified thresholds of PEF variability with thresholds most often set at 15% or 20% over a 2-week period. The way to calculate the PEF variability has a great impact on diagnostic performance with the greatest sensitivity when variability is the difference between the greatest and the lowest value divided by the lowest [34]. Overall, PEF variability provided a highly variable sensitivity ranging from 5% to 93%, while the specificity ranged from 75% to 100% (GRADE table 7, supplementary table S5b). The lower the variability required to define asthma, the greater the sensitivity.

Justification of the recommendation

Results from studies on PEF variability demonstrate a highly variable sensitivity, with lower sensitivities in studies where the prevalence of asthma was low. The most common method used to calculate PEF variability is the average daily amplitude percentage mean with a cut-off of 20%; however, alternatives such as the percentage amplitude highest PEF may just be as accurate and not require calculating the daily mean PEF [34, 38]. Completion of accurate peak flow diaries was poor, with results as low as 50% in one study [34], challenging the reliability, accuracy and feasibility of home PEF recordings. In addition, reliability of PEF measurement may be even lower in real life than in a research setting. A very recent study has shown that measurement over 5 days compared to 14 days improved diary completion rate from 15% to 94% with no loss of accuracy [38]. In the absence of spirometry-defined obstruction and significant bronchodilator reversibility, PEF can be monitored over a 2-week period, particularly if access to bronchial challenge is limited. In the context of a patient with symptoms suggestive of asthma, a positive PEF variability of >20%, that is reliably performed, has a high positive predictive value. Lowering the cut-off at 15% to 10% would increase the sensitivity at the expense of specificity. Thus, PEF monitoring may be of higher value to diagnose asthma in patients with highly variable day-to-day symptoms, where variable airflow obstruction might be easily detected, or in patients with suspected occupational asthma. However, we caution that lack of PEF variability does not rule out asthma and further objective testing should always be performed. Spontaneous and ICS-induced FEV_1 variability over time could also have been considered. However, we decided not to conduct a separate PICO due to the limitation of the ERS framework to eight PICO questions, and the low number of longitudinal studies that have evaluated FEV_1 variability over time. Nonetheless, we mention a recent study looking at between-visit FEV_1 variability, that provided similar results to PEF, with a poor sensitivity but a high specificity in order to diagnose asthma [39].

Patient perspective

PEF variability testing has advantages of being cheap and easy to perform, even in low-resource settings. Although no undesirable effects of PEF testing were documented, the taskforce recognises that for some patients performing home PEF twice daily for at least ⩾2 weeks may become unrewarding and time-consuming, reinforcing the need for proper education and training. Patients may prefer a one-stop bronchodilator reversibility test undertaken in 15 min, which if positive would potentially prevent delay in diagnosis and potential treatment. Hence, if available, the taskforce advises bronchodilator reversibility testing above PEF testing, particularly in primary care.

Key unanswered questions

PEF variability between 15% and 20% clearly lacks sensitivity to diagnose asthma compared to bronchial challenge and we advocate prospective studies to establish the threshold of variability that best correlates to a positive bronchial challenge test.

PICO 3: Can measuring exhaled nitric oxide fraction help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- In patients suspected of asthma, in whom the diagnosis is not established based on the initial spirometry combined with bronchodilator reversibility testing, the taskforce suggests measuring

exhaled nitric oxide fraction (F_{eNO}) as part of the diagnostic work-up of adults aged ⩾18 years with suspected asthma (conditional recommendation for the intervention, moderate quality of evidence).

Remarks

- A cut-off value of 40 ppb offers the best compromise between sensitivity and specificity, while a cut-off of 50 ppb has a high specificity close to 90% and is supportive of a diagnosis of asthma.
- A F_{eNO} value <40 ppb does not rule out asthma; similarly, high F_{eNO} levels themselves do not define asthma.
- F_{eNO} values are markedly reduced by smoking, impaired airway calibre, treatment with ICS or anti-interleukin (IL)4/IL13-receptor-α antibody.

Background

Nitric oxide is a gas measurable in exhaled air by chemoluminescence or an electrochemical method, where the measurement has been standardised and endorsed by the ERS/ATS [40]. The fraction of exhaled nitric oxide (F_{eNO}) measures allergic airway inflammation mediated through allergen-driven IL-4 and IL-13 effects on airway epithelial cells and is associated with the extent of airway eosinophilic inflammation [41]. F_{eNO} is dependent on height, gender, atopy and smoking status and airway calibre [42]. F_{eNO} is raised in patients with asthma compared to healthy subjects, and in asthma patients with allergic rhinitis compared to those without rhinitis. F_{eNO} is exquisitely sensitive to ICS, with a sharp decrease in levels a few days after starting treatment [43]. Certain biological treatments, which can be given for diseases other than severe asthma, e.g. nasal polyposis, also reduce F_{eNO} [44].

Review of the evidence

Our literature search identified 31 potentially relevant studies, of which 21 met the inclusion criteria (supplementary tables S6a and b) [13, 22, 29–64]. We exclusively selected studies that measured F_{eNO} at an expiratory flow of 50 mL·s^{-1} (supplementary table S7), thus excluding two studies where F_{eNO} was measured at a higher flow [65, 66]. Optimal F_{eNO} cut-off values for a diagnosis of asthma in adults ranged from 15 ppb to 64 ppb, with sensitivity values ranging from 29% to 79% and specificity values ranging from 55% to 95%. The high variability observed across the studies reflected differences in patient inclusion criteria in demographics, such as smoking and atopy status, or concurrent ICS treatment during assessment.

KATSOULIS et al. [54] found a F_{eNO} cut-off of 32 ppb for the whole population of patients with symptoms suggestive of asthma (n=112), but a low cut-off of 11 ppb when selecting actively smoking asthma patients. NEKOEE et al. [29] (n=702) found that a F_{eNO} cut-off value of 36 ppb yielded a sensitivity of 30% and a specificity of 85%. The taskforce derived the sensitivity and specificity for fixed F_{eNO} cut-offs where it was provided by the study authors. A lower cut-off of 25 ppb provided sensitivity and specificity of 0.53 (95% CI 0.33–0.72) and 0.72 (95% CI 0.61–0.81), respectively (GRADE table 8a), where a higher 50 ppb cut-off value ranged from 0.19 to 0.56 and 0.77 to 0.95, respectively (GRADE table 8c). A cut-off of 40 ppb yielded a sensitivity of 0.61 (95% CI 0.37–0.81) and a specificity of 0.82 (95% CI 0.75–0.87) (GRADE table 8b).

Justification of the recommendation

Measuring F_{eNO} is a point-of-care method that may be particularly useful in both primary and secondary care [67], although it is not yet considered for reimbursement in most European countries. A cut-off value above 40–50 ppb yields a high specificity (0.75–0.95), to rule in a diagnosis of asthma with confidence. However, the poor sensitivity (0.19–0.81) does not allow asthma to be ruled out, for values <40 ppb. Although the taskforce recommends using F_{eNO} to help in the diagnosis of asthma, we make it clear that high F_{eNO} levels do not define asthma. High F_{eNO} levels may be observed in patients with eosinophilic chronic bronchitis, allergic rhinitis or eczema who may deny any asthma symptoms and do not show bronchial hyperresponsiveness [3]. Additional factors such as training, cost of device and sensors, and local reimbursement policies may limit its use in primary care.

Patient perspective

F_{eNO} is a noninvasive, quick and relatively cheap measurement well accepted by the patient. It is worth noting that some patients are unable to adequately control their expiratory flow to provide a value. Given the strong influence of ICS on F_{eNO} level it is better to measure it when patients have not taken this medication, whenever possible. The cost of paying for F_{eNO} by patients in settings where reimbursement is not available may limit its use.

Key unanswered questions

Given the many factors influencing F_{eNO} values, prospective studies are needed defining the best cut-off in different categories of patients, taking into account smoking and atopic status.

PICO 4: Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The taskforce suggests not measuring blood eosinophil count to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence).

Remarks

- Blood eosinophil count does not define asthma, but rather contributes to phenotyping.

Background

Eosinophilic inflammation is a feature often found, but not specific to, asthma, irrespective of atopic status [68], which may contribute to asthma exacerbation [69]. Although analysis of the airway compartment by sputum or bronchoalveolar lavage is preferred, measuring the systemic component of eosinophilic inflammation by blood sampling may be a practical alternative. We investigated whether measuring blood eosinophil count (BEC) may help in the diagnosis of asthma.

Review of the evidence

Our search identified 24 potentially relevant studies, of which five (four prospective, one retrospective) were suitable for analysis (one in primary care, four in specialist care) (supplementary tables S8a,b and S9). HUNTER et al. [28] assessed the value of a BEC cut-off of 6.3%, taken as the upper limit of the normal range. POPOVIĆ-GRLE et al. [70] investigated 195 patients with symptoms of dyspnoea where asthma was diagnosed in 141 subjects based on a symptom questionnaire and significant bronchodilator reversibility (no threshold was provided) and assessed the value of eosinophilia without providing any cut-off. In a prospective observational study, YURDAKUL et al. [71] included 123 participants, of whom 60 had asthma, 40 had pseudo-asthma and 23 were healthy. Asthma was diagnosed based on reported symptoms associated with either bronchodilator reversibility of 15%, PC_{20M} <8 mg·mL^{-1} or PEF diurnal variation of $\geqslant$20%. Nearly half (48%) of the patients with asthma were receiving ICS before testing. No cut-off for BEC was provided. Two studies constructed ROC curves to determine the performance of BEC and the best BEC cut-offs. TILEMANN et al. [62] prospectively investigated 210 patients recruited in primary care with symptoms suggestive of asthma, of whom 5% were receiving ICS treatment. Asthma was confirmed in patients with bronchodilator reversibility of 12% and 200 mL improvement, or PC_{20M} <16 mg·mL^{-1}. The AUC (95% CI) for BEC was 0.60 (0.52–0.68) with an optimal cut-off of 4.1% in the TILEMANN et al. study, and 0.58 (0.54–0.62) with a cut-off of 4.4% in the NEKOEE et al. [29] study. Overall, sensitivity ranged between 0.15 and 0.59 while specificity was between 0.39 and 1 (GRADE table 9, supplementary table S8b). A 95% specificity was obtained for a BEC cut-off of 5.9% in the NEKOEE et al. study.

Justification of the recommendation

BEC lacks sensitivity to diagnose asthma, with sensitivities ranging between 21% and 59% in the reported studies. A BEC does not provide immediate results at the time of the consultation in order to directly help the clinician, although, as blood leukocyte differential is a test frequently performed for several indications in routine practice, it may be that a previous test is available at the time of the consultation. BEC cut-offs >4% and >6% have a specificity >80% and >95%, respectively, and may help the clinician to be confident in their diagnosis in patients with suggestive symptoms.

Patient perspective

Performing a blood leukocyte differential is relatively cheap and minimally invasive, although some patients may be anxious about venepuncture.

PICO 5: Can measuring total serum IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The taskforce suggests not measuring total serum IgE to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence).

Remarks

- Total serum IgE does not define asthma, but rather contributes to phenotyping.

Background

Immunoglobulin E is a key component in mediating type 1 hypersensitivity reactions resulting in degranulation of mast cells and basophils, which can lead to symptoms of asthma [72]. There are

non-IgE mediated events that can also trigger symptoms. IgE mediated mechanisms can also occur in nonatopic patients [73, 74], in whom elevated levels of total serum IgE have been reported [75]. We investigated whether assessing total serum IgE could help in the diagnosis of asthma.

Review of the evidence

Our search identified 26 potentially relevant studies, of which four were considered suitable for analysis (supplementary tables S10a,b), described earlier (supplementary table S8) [29, 62, 70, 71]. Popović-Grle *et al.* [70] and Yurdakul *et al.* [71] assessed the value of a pre-determined (but not provided) cut-off, while Tilemann *et al.* [62] and Nekoee *et al.* [29] constructed ROC curves. The AUC-ROC (95% CI) was 0.58 (0.50–0.66) with a cut-off of 90 kilounits (ku)·L^{-1} in the Tilemann *et al.* [62] study, and 0.57 (0.53–0.61) with a cut-off value of 132 ku·L^{-1} in the Nekoee *et al.* [29] study. Overall, sensitivity ranged between 0.33 and 0.51 and specificity between 0.72 and 0.85 (GRADE table 10, supplementary table S10b). Using a cut-off of 584 ku·L^{-1}, 95% specificity was obtained [29].

Justification of the recommendation

Total serum IgE should not be used for the diagnosis of asthma, because of consistently poor sensitivities across the studies, reaching at best 51%. This is in line with the existence of a significant proportion of non-IgE-mediated asthma, also called "intrinsic" asthma. Measuring total serum IgE does not provide immediate results at the time of the consultation. If specificity is better than sensitivity, it remains limited at the cut-offs provided by the ROC curves, ranging from 72% to 85%. The value of measuring IgE may vary according to the population of patients investigated, the seasonal manifestations of the symptoms and the coexistence of allergic rhinitis, and is likely to be more valid in young patients, as IgE levels decline with age [76–78].

Patient perspective

Measuring total IgE is relatively cheap and minimally invasive, although some patients may be anxious about venipuncture. Patients are often keen to know their possible allergies and, although skin tests are the gold standard to define allergic status, measuring total and specific serum IgE may represent a useful approach to assess allergy in primary care.

PICO 6: Can combining F_{eNO}, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The taskforce suggests not combining F_{eNO}, blood eosinophils and serum IgE to make a diagnosis of asthma (conditional recommendation against the combination of tests, moderate quality of evidence).

Background

Total serum IgE, BEC and F_{eNO} represent facets of the type 2 (T2) asthma phenotype, although the molecular mechanisms behind these biochemical and cellular variables may be different, and eosinophils and IgE dissociated [79, 80]. Therefore, we investigated whether the combination of these variables could improve their diagnostic value.

Review of the evidence

Our search identified 10 potentially relevant studies, of which only one was suitable to be included (supplementary tables S11a,b). Combination of the three tests provided an AUC-ROC of 0.6 (95% CI 0.56–0.64), while the AUC for individual tests were 0.58 (0.54–0.62), 0.57 (0.53–0.61) and 0.58 (0.54–0.62) for F_{eNO}, IgE and BEC, respectively [29]. Overall, sensitivity of the combination was 0.46 (95% CI 0.37 to 0.52) while specificity was 0.74 (95% CI 0.64 to 0.69) (GRADE table 11, supplementary table S11b).

Justification of the recommendation

Although it was a large study, the only study that met the criteria was a single-centre secondary-care assessment. Combining blood eosinophils, total serum IgE and F_{eNO} does not seem to improve diagnostic accuracy compared to performing a single test. Further studies are needed, particularly in primary care.

Patient perspective

Although all the tests are easy to undertake, if one test performs as well as the combination of tests, there is no utility in combining them.

PICO 7: Can bronchial challenge testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The taskforce suggests that bronchial challenge testing should be performed in secondary care to confirm a diagnosis of asthma in adults when the diagnosis was not previously established in primary care (conditional recommendation for the test, low quality of evidence).

Remarks

- A provocative concentration of methacholine (PC_{20M}) or histamine <8 mg·mL^{-1} in steroid-naïve patients and <16 mg·mL^{-1} in a patient receiving regular inhaled corticosteroids supports a diagnosis of asthma.
- Indirect challenges such as mannitol or exercise may be considered in patients who remain negative with direct constricting agents.

Background

Bronchial challenge testing demonstrates bronchial hyperresponsiveness, one of the key pathophysiological features of asthma, and are divided into direct and indirect challenges on the basis of the mechanism leading to airway constriction [81–83]. Challenges with methacholine or histamine are considered direct tests, as these mediators bind directly to airway smooth muscle, leading to constriction. Exercise or mannitol challenge are considered indirect airway challenges, as they involve local release of constricting mediators such as cysteinyl-leukotrienes in the vicinity of smooth muscle. Indirect challenges are better correlated with the extent of airway inflammation than direct challenges [82, 84]. We investigated whether bronchial challenge could identify patients with asthma diagnosed by bronchodilator reversibility and we compared the performance of both tests to confirm a diagnosis of asthma.

Review of the evidence

Our search identified 18 potentially relevant studies, of which six were suitable for inclusion (supplementary table S12a,b) (five prospective cross-sectional [28, 34, 37, 71, 85], one retrospective [86]). Three studies assessed the value of bronchial challenge to identify patients diagnosed as being asthmatic based on both suggestive symptoms and positive bronchodilator reversibility test. ULRIK et al. [37] performed a survey in a large population including 609 adolescents and young adults and compared the value of histamine challenge and bronchodilator reversibility testing to identify asthma patients diagnosed by a validated questionnaire suitable for an epidemiological study. PORPODIS et al. [85] prospectively investigated 88 steroid-naïve subjects where 67 patients were diagnosed as having asthma, based on suggestive symptoms and bronchodilator reversibility of 12% and 200-mL FEV_1 improvement. LOUIS et al. [86] assessed 194 steroid-naïve patients retrospectively with symptoms suggestive of asthma and baseline FEV_1 >70% predicted, and found 39 patients with a bronchodilator reversibility of 12% and 200-mL FEV_1 improvement. Other studies have compared the performance of bronchodilator reversibility and bronchial challenge in patients with symptoms suggestive of asthma (supplementary table S13). Of the six studies, three were selected for the final PICO analysis as it was methodologically feasible to directly compare against the gold standard BDR. Overall, sensitivity ranged between 0.63 and 1.00 while specificity ranged between 0.07 and 0.95 (GRADE table 12, supplementary table S12b). The specificity was highly variable as there were many more positive bronchial challenge tests in those who were BDR negative. Interpretation of such cases requires clinical judgment as in specific situations many physicians would consider this scenario to be consistent with asthma.

Justification of the recommendation

In making a conditional recommendation the taskforce balanced the desirable effects of making a diagnosis against any undesirable effects, risks to patients and the resources required to implement and make bronchial challenge testing a feasible test. Although methacholine, histamine and mannitol are very safe, these tests require additional equipment, reagents, time in the laboratory, air source and trained staff, with access to resuscitation facilities and medical personnel in rare cases of severe bronchoconstriction. This will undoubtedly increase the costs in comparison to bronchodilator reversibility testing. Mannitol challenge appeared to be slightly more specific than methacholine challenge, in all but one study.

Patient perspective

Patients may feel uncomfortable during bronchial challenge testing, as using histamine may cause unpleasant facial flushing and headache, and mannitol can induce cough. In addition, prior to bronchial challenge tests, patients on inhaled and oral treatment, including antihistamines (for histamine challenge) will need to be withdrawn in order to reduce the risk of a false negative test. However, some patients, particularly those who may been previously diagnosed as moderate or severe asthma, may find treatment

withdrawal difficult or unacceptable. Therefore, the taskforce recommends careful discussion with patients about medication withdrawal for the purpose of testing.

Key unanswered questions

Several types of bronchial challenge have been validated to confirm the diagnosis of asthma when reversibility of airway obstruction cannot be demonstrated. Whether prognosis, natural evolution and response while on treatment are similar, irrespective of the method that has been used to make the diagnosis, is largely unknown. Prospective trials are needed to answer this important clinical question.

PICO 8: Can measuring specific airway conductance and residual volume/total lung capacity help in the diagnosis of asthma with episodic/chronic suggestive symptoms?

Recommendation

- The taskforce suggests not measuring specific airway conductance (sG_{aw}) and residual volume (RV)/total lung capacity (TLC) by whole-body plethysmography to make a diagnosis of asthma (conditional recommendation against the tests, low quality of evidence).

Remarks

- sG_{aw} does not perform better than FEV_1/FVC ratio to predict a positive methacholine challenge in patients with normal baseline FEV_1.
- RV/TLC >130% predicted has a high specificity (>90%), but poor sensitivity (25%) to predict a positive methacholine challenge in patients with normal FEV_1/FVC.

Background

Temporal fluctuation in airway calibre is linked to variation in airways resistance. sG_{aw} is a sensitive index to measure airway resistance related to lung volume and does not require the patient to perform a forced effort-dependent manoeuvre. TOPALOVIC et al. [87] observed that 21% of asthma patients may display abnormally low specific airway conductance (<0.63 1/kPa·s) despite FEV_1/FVC >LLN. Emphasis has been placed on the role of distal airway narrowing and gas trapping in asthma that can be measured by the ratio RV/TLC [88, 89]. We undertook to investigate whether sG_{aw}, a sensitive marker of airway obstruction, and the ratio of RV/TLC, an index of lung hyperinflation measured by whole-body plethysmography, could help in the diagnosis of asthma when baseline spirometry appears to be normal.

Review of evidence

Our literature search identified 11 potentially relevant studies, of which only two were suitable for inclusion (supplementary table S14a). Both were retrospective and performed in secondary care, where only one undertook a direct comparison between FEV_1/FVC, sG_{aw} and RV/TLC (supplementary table S4) [27, 30]. STANBROOK et al. [30] analysed the lung function results of 500 patients with asthma, COPD, bronchitis and bronchiectasis, of whom 169 patients had no baseline airway obstruction, defined by FEV_1/FVC >90% predicted. The authors investigated the relationship between gas trapping, measured by the change in functional residual capacity ($\Delta FRC_{bodyplethysmography} - FRC_{helium}$) and RV/TLC with a positive PC_{20M} <8 mg·mL^{-1}. However, no details were provided on the symptom status of the patients, so it is difficult to ascertain if all patients with a positive PC_{20M} were actually patients with asthma. The authors investigated the diagnostic performance of pre-determined values of $\Delta FRC_{bodyplethysmography} - FRC_{helium}$ and RV/TLC. BOUGARD et al. [27] assessed the lung function indices of sG_{aw} and RV/TLC to predict a positive bronchial methacholine challenge (PC_{20M} <16 mg·mL^{-1}) by constructing ROC curves in 270 patients referred to a secondary care asthma clinic. All patients had whole-body plethysmography prior to their visit at the asthma clinic for the methacholine challenge and were divided into a training cohort (n=129, baseline FEV_1 95% predicted) and a validation cohort (n=141, baseline FEV_1 91% predicted), indicating no substantial lung function impairment. Among all plethysmography indices measured, RV/TLC provided the best AUC-ROC in both training and validation cohorts with values reaching 0.74 and 0.75, respectively while AUC-ROC reached 0.69 and 0.62 for sG_{aw} in the training and validation cohorts, respectively. A model combining RV/TLC and F_{eNO} provided an AUC that rose up to 0.79. Overall, sensitivity for sG_{aw} ranged from 0.50 to 0.86 and specificity from 0.50 to 0.71 (GRADE table 13, supplementary table 14b). Sensitivity for RV/TLC ranged from 0.28 to 0.71 while specificity ranged from 0.68 to 0.86 (GRADE table 14, supplementary table 14b). Patients having an RV/TLC >135% predicted and an FEV_1/FVC >90% predicted, had 95% specificity in the STANBROOK et al. study [30].

Justification of the recommendation

The current evidence with RV/TLC is too limited to recommend using it to ascertain a diagnosis of asthma. The two studies suggest that a high RV/TLC might be a useful physiological index to consider asthma diagnosis. Whole-body plethysmography can provide sophisticated lung function measurements

including the early physiological sign of hyperdistention as a consequence of small-airway obstruction, not revealed by spirometry. While RV/TLC may hold some promise, measuring sG_{aw} does not bring additional value to the measurement of FEV_1/FVC ratio by spirometry. However, whole-body plethysmography requires technical expertise from laboratory personnel and the cost and relatively limited access, even in specialist secondary care, may preclude the use of this test on a large scale.

Patient perspective

Patients are usually keen to know about their lung function and respiratory performance. Body plethysmography is sophisticated and requires both technical expertise and patient collaboration, and some manoeuvres may be unpleasant and possibly induce anxiety when the patient is forced to breathe while airflow is suppressed.

Key unanswered questions

Prospective studies are needed to further assess the value of RV/TLC, potentially combined with F_{eNO} in patients with normal baseline spirometric indices.

Shaping the clinical practice algorithm

Historically, asthma is defined by an episode of airway obstruction that reverses either spontaneously or following treatment, and this is why our algorithm starts with spirometry (figure 1). However, in clinical practice, the majority of patients with symptoms suggestive of asthma do not present with spirometric airway obstruction, hence reducing the likelihood of identifying significant bronchodilator reversibility. We observed that the T2 biomarkers differed in their sensitivity to make a diagnosis of asthma, while displaying an acceptable specificity. We decided to recommend F_{eNO} as an aid to diagnose asthma in our algorithm, in contrast to blood eosinophil count and total serum IgE, as F_{eNO} is noninvasive and provides an immediate result at the time of the consultation. F_{eNO} values >50 ppb (or >40 ppb) have a low false positive rate (<10%; <20% at 40 ppb), which gives confidence to rule-in asthma. However, where a high F_{eNO} is supportive of a diagnosis of asthma it does not define the disease itself, as high F_{eNO} without asthma is observed in other conditions such as allergic rhinitis or chronic eosinophilic bronchitis. With respect to lung function testing in secondary care, our conditional recommendation for bronchial challenge is justified by its high sensitivity to demonstrate excessive airflow variation, which is far superior to bronchodilator reversibility or PEF variability over a 2-week period. In addition, PEF monitoring requires a 2-week observation period that may result in a lack of patient adherence with incomplete recording.

Additional considerations

How to investigate patients already receiving regular maintenance medication to make an asthma diagnosis?

In patients receiving ICS maintenance therapy as monotherapy or in combination with a long-acting β-agonist (LABA), the demonstration of variable airway obstruction may be challenging. Where the influence of LABA disappears in a few days, long-term ICS use may reduce airway responsiveness and normalise airway calibre for longer [90, 91]. For patients established on maintenance therapy, GINA recommends making the diagnosis by the classic criteria of reversibility testing or bronchial challenge testing, being less stringent for the latter and accepting a PC_{20M} <16 mg·mL^{-1} as valid diagnostic criterion. In patients with a negative bronchodilator reversibility (FEV_1 does not improve by 12% and 200 mL) and a negative methacholine challenge (PC_{20M} <16 mg·mL^{-1}), ICS maintenance treatment is gradually tapered, and if symptoms do not worsen nor do spirometry or PEF values decline significantly, a bronchial challenge test can be repeated [3, 90].

Objective testing of airflow variability and airway hyperresponsiveness over 12 months is important to address seasonal and occupational asthma or intermittent increases in airway hyperresponsiveness from respiratory infections, and asthma is usually excluded if these are normal [92]. Patients should be encouraged to present to the physician if they experience any worsening of respiratory symptoms during this period, and alternative diagnoses should of course be considered and investigated.

How may comorbidities obscure the diagnosis of asthma?

Asthma frequently coexists with comorbidities that not only affect the control and management of asthma [93], but need to be considered during the diagnostic phase. Some comorbidities can be supportive in diagnosing asthma. The presence of atopy and atopic conditions such as allergic rhinitis or atopic dermatitis increase the probability of the diagnosis of allergic asthma when patients present with respiratory symptoms [94]. The presence of atopy is not specific for asthma [95], nor does its absence rule out asthma, since atopy is not present in all asthma phenotypes. It should be noted that the relevance of allergen exposure in relation to symptoms requires a positive test (skin-prick test or serum-specific IgE) confirmed by a corresponding history.
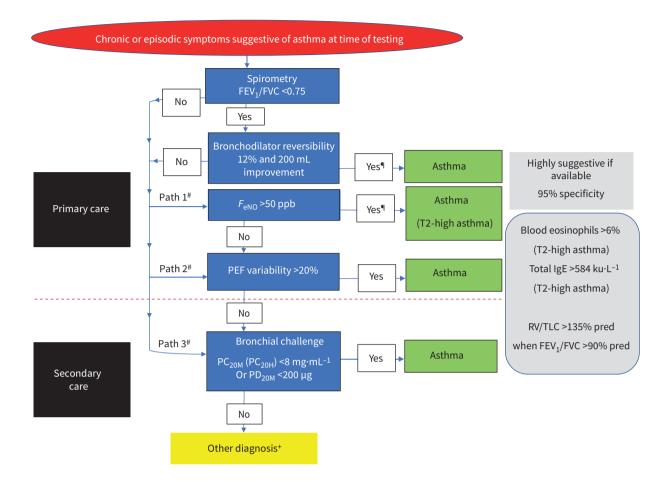
FIGURE 1 Algorithm for asthma diagnosis in adults with current symptoms. The algorithm was constructed by distinguishing primary from secondary care testing. It was constructed based on both the literature evidence and clinical experience of the taskforce members. Three paths to diagnosis were defined. All the paths place spirometry as the key starting investigation, which was accepted by all taskforce members. If spirometry with reversibility to bronchodilators cannot confirm the diagnosis, we propose three paths, dependent on the local resources and healthcare organisation available. A vote among the taskforce members (n=17) on the preferred path gave nine votes for path 1 and four votes for both path 2 and path 3. While the majority of the taskforce members recognised the benefit of using exhaled nitric oxide fraction (F_{eNO}) as a support to asthma diagnosis, the best threshold for F_{eNO} was debated and subjected to a written vote after each member had received the Grading of Recommendations, Assessment, Development and Evaluation tables. The threshold at 50 ppb received 10 votes and 40 ppb received five votes. Two taskforce members were not able to participate. Peak expiratory flow (PEF) variability is assessed over a 2-week period. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PC_{20M}: provocative concentration causing 20% fall in FEV_1 with methacholine; PC_{20H}: provocative concentration causing 20% fall in FEV_1 with histamine; PD_{20M}: provocative dose causing a 20% fall in FEV_1 with methacholine; T2: type 2; RV: residual volume; TLC: total lung capacity. #: options dependent upon access to testing and previous testing; order of tests agreed by taskforce members; ¶: allergic rhinitis, eosinophilic bronchitis and atopic dermatitis may be associated with raised F_{eNO} without asthma; +: gastro-oesophageal reflux disease, chronic rhinosinusitis, dysfunctional breathing, vocal cord dysfunction, tracheobronchomalacia.

Chronic rhinosinusitis and nasal polyposis are more often associated with the late-onset eosinophilic asthma subtype, characterised by onset of disease in adulthood, absence of atopy, airway obstruction without a smoking history and eosinophilic inflammation [96, 97]. In this respect, the presence of chronic rhinosinusitis or nasal polyposis in patients with respiratory symptoms usually alerts physicians to consider the diagnosis of asthma, with the late-onset phenotype.

COPD is the other most common chronic obstructive airway disease. The diagnosis of asthma and COPD may not be mutually exclusive, given that many patients with asthma smoke [98] or are exposed to noxious gases, and it is common to observe irreversible airway obstruction in moderate-to-severe asthmatics [99]. Gastro-oesophageal reflux disease (GORD) can cause laryngeal or pharyngeal irritation,

chest tightness and dry cough, symptoms that can easily be misinterpreted as asthma [3], and are often more problematic at night. The diagnosis of GORD may be considered, particularly in patients presenting with nonproductive cough as their main symptom, and current consensus suggests an empirical treatment of antireflux medication may be used where there is objective evidence of reflux or a history suggestive of reflux symptoms [52].

A particular challenge is the diagnosis of asthma in people with obesity. Obesity itself can cause shortness of breath, wheezing due to breathing at lower volume and reduced exercise tolerance, and may be accompanied by GORD or obstructive sleep apnoea, which in turn can cause asthma-like symptoms. People with obesity are shown to be at risk of both over- and under-diagnosis of asthma [100], and need an objective diagnosis of asthma to prevent unwanted over- or under-treatment.

Inducible laryngeal obstruction, hyperventilation and dysfunctional breathing all may cause asthma-like symptoms and lead to an incorrect asthma diagnosis. Patients with inducible laryngeal obstruction have a transient, reversible narrowing of the larynx in response to diverse triggers [101], that may result in inspiratory breathing difficulties, sometimes with coarse to high-pitched inspiratory breath sounds, and repetitive attacks of acute dyspnoea (mimicking exacerbations of asthma). Dysfunctional breathing is characterised by irregular breathing patterns and patients with this condition often present with dyspnoea or "air hunger", together with nonrespiratory symptoms such as dizziness and palpitations [102]. Valid, accessible and quantifiable tests for diagnosing dysfunctional breathing are missing, making it difficult to distinguish from asthma, although continuous laryngoscopy during exercise is considered a reliable test to diagnose or rule out exercise-induced laryngeal obstruction [103]. In these patients, symptoms do not improve on asthma medication and it is preferable to consider alternative options, such as breathing exercises, speech therapy, biofeedback strategies or psychological support.

Does lung imaging help in the work-up of asthma diagnosis?

Beyond the physiological abnormalities defining asthma, additional investigations may be worthwhile to demonstrate comorbidities that may be contributing to the symptom burden of the patient. High-resolution computed tomography (HRCT) of the lungs provides a diagnosis of additional conditions in 40% of cases in patients with severe asthma, including bronchiectasis, emphysema and lung nodules [104]. HRCT can identify classical radiopathological patterns of airway wall thickening, airway distensibility, bronchiectasis, lung distension and air trapping, where most of these changes can coexist with each other and be present in varying proportions. The radiological presence of emphysema (or "pseudo-emphysema") increases the complexity of differentiating asthma from COPD, and air trapping can be challenging to discriminate from emphysema. Assessing HRCT lung changes before and after treatment (bronchodilation, anti-inflammatory treatment) or airway challenge (bronchoconstriction) are potentially insightful [105–108]. However, it appears that an increasing number of radiological features are being detected incidentally (*e.g.* interstitial lung abnormalities), which may make the diagnosis of asthma a challenge. Beyond an alternative diagnosis, additional studies are needed to assess whether HRCT is able to identify particular phenotypes and predict treatment response [106, 107], and potentially whether radiological features can predict future risk of disease exacerbation and lung function decline. Note that sinus computed tomography can not only identify asthma-related comorbidities such as nasal polyposis, but also has the potential to support phenotypic characterisation.

Do we need to phenotype airway and systemic inflammation in the patient with asthma?

Asthma is a heterogeneous disease that encompasses different clinical phenotypes and endotypes that share excessive airflow fluctuation [109, 110]. In particular, there is now clear evidence of differing patterns of airways inflammation in people with asthma. Although not applicable in the primary care setting, the development of the induced sputum technique has been pivotal to airway inflammatory phenotyping in asthma [111–113]. When available in secondary care, induced sputum may complement the diagnostic work-up in patients with severe asthma [3]. Some authors have advocated classifying patients based on granulocytic airway content [114–116]. In large cohorts of patients across the whole severity spectrum, paucigranulocytic and eosinophilic asthma were found to be the two most frequently encountered phenotypes where the proportion of eosinophilic asthma increases with disease severity [114, 115, 117]. In contrast, paucigranulocytic asthma is the most prevalent inflammatory phenotype in mild asthma [86, 114, 118], even if sputum analysis suggests that paucigranulocytic asthma is actually low-grade eosinophilic airway inflammation [119]. Although sputum eosinophils were shown to provide acceptable accuracy to diagnose asthma [28], the main interest of identifying airway cell content is that it may provide valuable information regarding several clinical asthma outcomes beyond the diagnosis [120]. Sputum eosinophilia predicts a good response to ICS or to a course of oral corticosteroid [111]. The persistently mixed granulocytic profile is associated with lung function decline and relative resistance to ICS in contrast to the

pure highly variable eosinophilic pattern, which shows propensity to disease exacerbation, but generally a good response to corticosteroids and less decline in lung function [121]. Biomarkers such as blood eosinophils and F_{eNO} have shown consistent relationship with sputum eosinophil counts and found to be good predictors of the response to ICS in steroid-naïve patients [59, 122–124], making them suitable tools to phenotype asthma in the primary care setting. We currently lack user-friendly biomarkers to identify neutrophilic asthma, a phenotype found to be associated with signs of innate immunity activation [125, 126], often induced by dysbiosis [127, 128] and resistant to ICS [129]. Analysis of volatile organic compounds has shown some promise in this respect [130].

Categorisation of asthma according to the inflammatory profile has proved to be invaluable in the appropriate targeting of expensive biological treatments in difficult asthma, where use of T2 biomarkers differentiates those likely to respond from those unlikely to benefit [131]. Furthermore, the growing recognition of the need for personalised [132] precision medicine, based on categorisation and appropriate response to the variety of drivers of disease at an individual level, has led to the proposal for a "treatable traits" strategy in airways disease [133]. There is preliminary evidence that this is a successful strategy in hospital-based care [134], with calls from the ERS for more research into wider clinical implementation of this approach [135].

What are the patient perspectives of asthma diagnosis in adults?
A review of published and grey literature explored patient experiences of adult asthma diagnosis. Details of the search strategy are available in the supplementary material.

Patients are often uncertain about starting treatment without first having a definitive diagnosis [6]. In the absence of a diagnosis, some patients may want to trial treatment to check if they experience any benefit (table 5). Patients describe the surprise of being diagnosed later in life as an adult. They often considered asthma to be a childhood illness, and thought it was possible to "grow out" of asthma. Patients express frustration at not knowing why they develop asthma at this point in life (table 5).

Patients describe the psychosocial impact of diagnosis where for some, getting a diagnosis can be positive, finally pinpointing the underlying cause of their poor health and providing tools to manage it. Depression, feeling scared and having anxiety about how asthma will affect other aspects of their life are common. Patients have complex emotions about how their condition impacts their loved ones, and how their relationships have changed as a result. Overall, patients describe coming to terms with the diagnosis, accepting it as something they have to live with long-term, recognising that asthma can be life-threating, and their role in self-management. Professionals have an important role in supporting their patients with the psychosocial impact (table 5). If a diagnostic test is done in hospital, results need to be communicated to the family doctor and ideally followed-up in community care [136].

Patients would benefit from further research on the actual diagnostic pathways of asthma patients. Professionals have an important role in improving the patient experience of diagnostic testing and supporting individuals to manage the wider impact of diagnosis. The diagnostic process can be long and confusing for adult patients who would benefit from clear patient-centred information which takes into account variation in access to diagnostic testing across Europe.

Conclusion
The remit of this taskforce was to produce a pragmatic guideline for clinicians focusing on the best current strategy for making a secure diagnosis of asthma in both primary and secondary care. The taskforce did not select symptoms in the list of PICO questions, as it was thought we needed more than symptoms alone to improve diagnostic accuracy, even if we recognise there are currently valuable symptom diaries approved by regulatory authorities to assess the clinical status of the patient with asthma [137]. However, we believe there is more research to be undertaken on the value of each symptom, and of their combinations, to predict an accurate diagnosis of asthma, as key asthma symptoms such as breathlessness, chest tightness, cough and wheeze can be present in other diseases than asthma. The taskforce emphasises the need to establish a correct diagnosis of asthma in patients with suggestive symptoms and reinforce performing spirometry on a much larger scale than is currently undertaken in primary care. Whether measuring F_{eNO} or monitoring PEF should be implemented in primary care, in the absence of significant bronchodilator reversibility, depends on the availability and access to bronchial challenge. Both direct and indirect bronchial challenges detect airway hyperreactivity in patients with symptoms, which make these tests optimal to eventually diagnose asthma in secondary care.

The main advantage of this guideline is that it has been developed with input from patients, the ELF, generalists and specialists in both primary and secondary care and a respiratory nurse specialist. We have adopted a methodological approach using the PICO and GRADE system. In so doing, we have generated and evaluated the evidence using strict inclusion and exclusion criteria and then used a standardised evidence-to-decision framework to make a recommendation.

A consistent problem encountered by the taskforce in the PICO questions was the paucity of well-designed studies and the difficulties of defining a "gold reference standard" comparator to confirm or refute the binary "yes–no" question of "is this asthma?". There is growing recognition of the heterogeneity and complexity of asthma, and evidence that within the broad diagnostic label, it is possible to further categorise patients into distinct groups that have differing responses to treatment and differing risk profiles. During the literature analysis, the taskforce found several manuscripts that addressed the issue of phenotyping patients with asthma using the index tests discussed herein. A phenotype is defined as the "observable properties of an organism that are produced by the interactions of the genotype and the environment", which can be identified by biomarkers discussed in this article, and which may have a role in prognosis and therapeutic decision-making.

In less well-resourced healthcare systems and low- and middle-income countries (LMIC), some of these diagnostic tests may not be available and a pragmatic empirical treatment trials protocol may be used instead. However, we hope that this guideline becomes an impetus for change against such practices. Large population-based studies like the Prospective Urban Rural Epidemiology Study (which involved studying 225 000 participants in detail including spirometry from >1000 urban and rural communities in 27 high-, middle- and low-income countries [138]), or the Global Burden of Disease study [139] have demonstrated the feasibility of performing spirometry using cheap handheld devices in countries in LMICs such as Brazil, Tanzania, Kenya, Palestine and India. With salbutamol being freely available, we believe that bronchodilator testing can be performed in most parts of the world.

With this rapidly changing and evolving background, and on the basis of the literature searches performed, the taskforce highlights that a more nuanced and individualised diagnostic approach may be needed in the near future, to inform accurate prognostic and therapeutic clinical practice. We conclude with the words "Asthma is like love, everybody says that they know what it is, but nobody has the same definition" [140]. We hope the taskforce has helped clarify some of the mystery … in the diagnosis of asthma [26].

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