Title:

European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5 to 16 years

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**Glossary**

AHR Airway hyperresponsiveness

BDR Bronchodilatator reversibility

BTS/SIGN British Thoracic Society/Scottish Intercollegiate Guidelines Network

ELF European Lung Foundation

EtD Evidence to Decision

FeNO Fractional exhaled Nitric Oxide

FEV1 Forced Expiratory Volume in the first second

FVC Forced Vital Capacity

FEV1/FVC Ratio of FEV1 over FVC

GINA Global Initiative for Asthma

GLI Global Lung Function Initiative

ICS Inhaled corticosteroids

LABA Long acting beta2 agonists

LLN Lower limits of normal

LTRA Leukotriene receptor antagonists

NICE National Institute for Health and Care Excellence

PC20 Provocative concentration leading to a fall of 20% in FEV1

PD20 Provocative dose leading to a fall of 20% in FEV1

ppb Parts per billion

PEFR Peak Expiratory Flow Rate

SABA Short acting beta2 agonists

TF Task Force

**Abstract**

Diagnosing asthma in children represents an important clinical challenge. There is no single gold standard test to confirm the diagnosis. Consequently, both over-, and under-diagnosis of asthma are frequent in children.

A Task Force (TF) supported by the European Respiratory Society has developed these evidence-based clinical practice guidelines for the diagnosis of asthma in children aged 5 to 16 years using nine PICO (Population, Intervention, Comparator and Outcome) questions. The TF conducted systematic literature searches for all PICO questions and screened the outputs from these, including relevant full text articles. All TF members approved the final decision for inclusion of research papers. The TF assessed the quality of the evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.

The TF then developed a diagnostic algorithm based on the critical appraisal of the PICO questions, preferences expressed by lay members and test availability. Proposed cut-offs were determined based on the best available evidence. The TF formulated recommendations using the GRADE Evidence to Decision framework.

Based on the critical appraisal of the evidence and the Evidence to Decision Framework the TF recommends spirometry, bronchodilator reversibility testing and FeNO as first line diagnostic tests in children under investigation for asthma. The TF recommends against diagnosing asthma in children based on clinical history alone or following a single abnormal objective test. Finally, this guideline also proposes a set of research priorities to improve asthma diagnosis in children in the future.

**239 of 250 words**

Twitter: International ERS clinical practice guidelines recommend a combination of objective tests including spirometry, bronchodilator reversibility, fraction of exhaled nitric oxide and bronchial challenge testing to diagnose asthma in children aged 5 to 16 years.

**Introduction**

Asthma is the commonest chronic respiratory condition affecting approximately 5.5 million children in the European Union. (1) In many European healthcare settings the diagnosis is based on clinical history and examination without further tests.

Several recent reports from Europe and North America have highlighted a high rate of asthma misdiagnosis, including over- and under-diagnosis. (2-10)

Misdiagnosis in children often arises because respiratory symptoms are common in this age group. These are frequently non-specific (11) and often represent episodes of viral respiratory tract infections (12,13). Some of these can be prolonged with clinical symptoms similar to asthma. Getting the correct diagnosis in children matters because over-diagnosis frequently results in over-treatment with corticosteroids (6,14) with implications for health care costs (15), the risk of unnecessary side-effects and, in some cases, delay in establishing an important alternative diagnosis. Under-diagnosis with under-treatment of asthma results in unnecessary morbidity, poor quality of life and increased mortality in low resource settings. (16,17)

Many asthma guidelines (18-20) recommend the use of objective tests to confirm the diagnosis in symptomatic patients. Spirometry, bronchodilator reversibility testing (BDR) and measurements of peak flow variability are recommended in some form by all the guidelines. UK National Institute for Health and Care Excellence (NICE) asthma guidelines also recommend the use of FeNO. (20) Recommendations on the hierarchy and timing of objective tests varies considerably between guidelines. This has resulted in variation of diagnostic tests used across Europe and across different healthcare settings within individual countries.

Importantly, to date there are no child focused evidence-based asthma diagnostic guidelines. The usual approach is to produce joint adult and paediatric asthma guidelines and this often results in extrapolation from adult data where there is a lack of evidence in children. However, tests employed in adults under investigation for asthma may not be appropriate in children and the best cut-offs for many of the tests may not be the same in children and adults. This makes child focused guidelines for the diagnosis of asthma essential.

The aim of this TF was to systematically review the evidence that supports the use of tests commonly used across Europe to diagnose asthma in children and to propose evidence-based clinical practice recommendations for the diagnosis of asthma in children aged five to 16 years.

**Methods**

The methods are described in detail in the supplementary material.

**TF composition**

The panel consisted of a multidisciplinary group including paediatricians, primary care physicians, researchers, patients and patient representatives. All members of the TF have either recognised clinical experience in the diagnosis of asthma practicing in various regions of Europe or personal experience with asthma as patients or are caregivers of children with asthma. Junior members and trainees affiliated with European paediatric asthma centres were active members of the committee (supplementary table 1).

Methodologists from the ERS provided expertise in guideline development following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach for diagnostic tests (21). Panel members disclosed potential conflicts of interest according to ERS policies at the start of the TF and prior to publication of this manuscript.

Patient and parent representatives recruited to the TF through the European Lung Foundation (ELF) were involved from the beginning. They commented on the selection and scope of the PICO questions, attended meetings, commented on the hierarchy of tests, contributed to the discussions relating to the Evidence to Decision (EtD) for each PICO question and approved the final diagnostic algorithm. All the recommended tests to support asthma diagnosis were acceptable to patients and carers.

The TF was organised into four core centres (Leicester, Zurich, Bern and Aberdeen), each with PICO leads and junior members. The core centres divided the PICO questions between themselves. The other members of the TF each aligned themselves to two or three PICO questions so that each PICO was supported by a TF subgroup consisting of a core centre and additional TF members. The numbers in each PICO TF subgroup were evenly distributed. Junior members performed the initial screening of the outputs from the systematic literature reviews, coordinated the final selection of research papers and performed the initial quality of evidence assessment for each selected research paper. The other PICO subgroup members supported the PICO groups and were involved in selecting and approving the included research papers and reviewing the quality of the evidence. The whole TF was involved in all the key decisions such as selection of PICO questions, agreed recommendations for each PICO question, and the drafting and agreement on the diagnostic algorithm.

**Formulation of the review questions**

Review questions were formulated using the **P**opulation, **I**ntervention, **C**omparator and **O**utcome (PICO) format. The chairs initially proposed eight PICO questions based on common clinical practice in Europe. Early on during the TF, members discussed each PICO question to evaluate whether it should be included. The PICO questions were discussed during several rounds of telephone conferences and email discussions. Nine PICO questions were finally agreed at the first face-to-face TF meeting in 2018 (table 1).

Table 1: The list of PICO questions that this TF sought to answer with their respective comparator or reference standard.

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| **PICO questions** | **Comparator/Reference standard** |
| ***PICO 1.***In children aged 5-16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma? | Doctor diagnosis of asthma **and** one of the following:Obstructive spirometry, bronchodilator reversibility, challenge testing, FeNO, two-week PEFR variability.  |
| ***PICO 2.*** *In children aged 5-16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?* | Doctor diagnosis of asthma **and** one of the following:Obstructive spirometry, bronchodilator reversibility, challenge testing, FeNO, two-week PEFR variability. |
| ***PICO 3.*** *In children aged 5-16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?* | Doctor diagnosis of asthma **and** one of the following:Challenge testing, bronchodilator reversibility, FeNO, two-week PEFR variability. |
| ***PICO 4.*** *In children aged 5-16 years under investigation for asthma, should bronchodilator reversibility (BDR) testing be used to diagnose asthma?* | Doctor diagnosis of asthma **and** one of the following:Challenge testing, FeNO, two-week PEFR variability. |
| ***PICO 5.*** *In children aged 5-16 years under investigation for asthma, should FeNO testing be used to diagnose asthma?* | Doctor diagnosis of asthma **and** one of the following:Obstructive spirometry, bronchodilator reversibility, challenge testing, two-week PEFR variability. |
| **PICO 6.** *In children aged 5-16 years under investigation for asthma, should peak expiratory flow rate (PEFR) variability be used to diagnose asthma?* | Doctor diagnosis of asthma **and** one of the following:Obstructive spirometry, bronchodilator reversibility, challenge testing, FeNO. |
| ***PICO 7.*** *In children aged 5-16 years under investigation for asthma, should allergy testing be used to diagnose asthma?\** | Doctor diagnosis of asthma **and** one of the following:Obstructive spirometry, bronchodilator reversibility, challenge testing, FeNO, two-week PEFR variability.  |
| **PICO 8.** *In children aged 5-16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?* | Doctor diagnosis of asthma **and** one of the following:Obstructive spirometry, bronchodilator reversibility, FeNO, two-week PEFR variability. |
| **PICO 9.** *In children aged 5-16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?* | Doctor diagnosis of asthma **and** one of the following:Obstructive spirometry, bronchodilator reversibility, FeNO, two-week PEFR variability. |

\*food allergens were not included

**Systematic literature review**

For each PICO question, a systematic literature review was carried out and eligible papers had to include the diagnostic test in question plus at least one other objective test. For each question, the outcomes were diagnostic accuracy; sensitivity and specificity.

Librarians experienced with systematic reviews based at University Hospitals Leicester (UK) performed the systematic literature searches for all PICO questions covering the period from 1st January 1980 to 31st August 2019. They searched the Medline (via OVID), Cochrane and Embase databases. Supplementary searches were undertaken by checking the references of included papers and by asking TF members if they were aware of additional papers not identified by the searches. The full details of all the searches are provided in the supplementary material.

**Screening of search results**

At least two TF members from each core group reviewed all the titles and abstracts identified by each of the literature searches. They agreed on the inclusion of full-text manuscripts. The screening results were shared with the TF PICO group for comments. The whole TF discussed and agreed the final selection of studies included for each PICO question during a face-to-face meeting. Research papers were only included if all the TF members agreed that they fulfilled the *a priori* inclusion criteria. PRISMA flow diagrams showing the search process for each PICO question are available in supplementary figure 1A-H. Tables listing all the full-text articles, which were screened, are shown in in the supplementary material.

*Study designs:* In clinical practice, caregivers bring children with respiratory symptoms to the doctor. These symptoms may be compatible with a diagnosis of asthma. Confirming or refuting the diagnosis represents a clinical challenge due to the absence of a gold standard test. Therefore, we only included studies that replicated this clinical scenario and included studies that had followed consecutive patients with relevant respiratory symptoms referred for asthma diagnosis. The diagnosis was then either confirmed or excluded using objective tests. This approach also allowed us to calculate the sensitivity and specificity of the index test. We excluded case control studies for this reason. We included cohort studies.

**Reference standard**

In the absence of a universally accepted reference standard for the diagnosis of asthma, the TF agreed to accept a “doctor diagnosis of asthma” supported by at least one abnormal comparator test as the standard with which to compare the index test of interest for each PICO. This standard was chosen for the following reasons: A diagnosis made by a doctor following a careful medical history and clinical examination is an important criterion for a diagnosis of asthma. However, studies have shown that a diagnosis of asthma based on this approach results in considerable rates of misdiagnosis in children (3). Therefore, a doctor diagnosis had to be supported by at least one abnormal objective test. The TF agreed on the following comparator tests: Spirometry, BDR, FeNO, two-week PEFR variability test, direct and indirect bronchial challenge tests.

The TF agreed not to include “trial of treatment” and “allergy testing” as comparator tests but to evaluate the usefulness of a “trial of treatment” and “allergy testing” to diagnose asthma in children as separate PICO questions instead.

We have addressed important aspects relating to asthma diagnosis such as hierarchy and timing of objective tests, cut off points of objective tests and confounders. Because we did not formally assess the evidence for these aspects, we present the results based on the Delphi process and discussions using the Evidence to Decision (EtD) tables without making formal recommendations.

**Quality of evidence and strength of recommendations**

We used the GRADE approach through the entire process, from grading the quality of the evidence, to determining the strength of the recommendations. GRADE represents a rigorous methodology to evaluate the quality of evidence and is considered the gold standard for grading the strength of evidence-based recommendations in health care due to its structured approach and transparency. In keeping with the GRADE approach, we formulated from the outset clear clinical PICO questions. TF members assessed the quality of the evidence by evaluating risk of bias, indirectness, inconsistency, imprecision, and other factors (22-26).

The TF based recommendations for the asthma diagnostic algorithm on the strength of the evidence, test availability and factors such as sensitivity and specificity of the index test. Using the EtD framework (27) the TF considered additional factors such as test availability, feasibility and patient and caregiver acceptability and access to specialist tests. The GRADE and EtD tables for all the PICO questions are shown in the online supplement.

**Patient and caregiver important perspectives**

The GRADE approach emphasises the importance of recommendations based on the impact on patient-important outcomes (25). The patient representatives of the TF fully endorsed that an accurate diagnosis was an important outcome, because it leads to a better recognition of their child’s problems by physicians. Patient representatives stated that this would lead to treatment that is more effective, would reduce overtreatment in some children and generally improve health and quality of life. However, diagnostic accuracy studies do not provide direct evidence for the improvement of patient-important outcomes; consequently, the confidence in results of test accuracy studies can be judged, at best, as moderate.

**Development of recommendations and the diagnostic algorithm**

The TF used the EtD framework (27) as well as an informal consensus development method (28) to agree each recommendation and to build the diagnostic algorithm. This involved a face-to-face meeting where the whole TF discussed and agreed the recommendations and the tests recommended to support a diagnosis of asthma in children, based on the literature searches, the ‘GRADEing’ of the evidence and the EtD framework.

Once the provisional recommendations and the building blocks of the diagnostic algorithm were agreed, the TF used free discussion to reach consensus and agree a provisional hierarchy of tests and a prototype diagnostic algorithm.

In order to obtain the most reliable consensus of opinion of our expert group we employed a modified Delphi process using repeated iterative online voting (29). All the recommendation statements and all the steps of the diagnostic algorithm that had been developed and discussed at the face-to-face meeting were listed in an online questionnaire and circulated to the whole TF. In each round, panel members were asked to mark “agree” or “disagree” beside each statement, and provide comments. Recommendation statements and the diagnostic algorithm were modified after each round. The whole TF finally approved the final version after three rounds of online voting. Responses were not anonymous and the TF defined consensus *a priori* as agreement by 75% or more of the participants.

**Results**

**Results of literature reviews and TF recommendations**

*Definition of asthma:* Several definitions exist. (18,30,31) The TF agreed on the following definition of asthma: Asthma is a disease that includes the symptoms of wheeze, cough and breathing difficulty together with reversible airways obstruction, airway inflammation and bronchial hyper-responsiveness. However, asthma is a heterogeneous and variable condition and frequently not all of the above are present in each individual patient at the same time.

The TF emphasizes that the words to describe asthma symptoms vary considerably depending on language, culture, education and age of the patient. In addition, young children may describe pain in the abdomen due to difficulty pinpointing the lungs. The results of the evidence assessment gave rise to the recommendations listed in table 2.

Table 2: Evidence-based recommendations for the use of each of the tests considered for asthma diagnosis in children aged 5-16 years in primary, secondary or tertiary care.

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| ***PICO 1:*** *In children aged 5-16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?** The TF recommends against diagnosing asthma based on symptoms alone (strong recommendation against the intervention, moderate quality of evidence)

Remarks:1. Recurrent wheeze, cough and breathing difficulty are key symptoms of asthma. The TF considers a history of recurrent reported wheeze or wheeze on auscultation as the most important symptom of asthma
2. Children with chronic cough (i.e. cough for more than 4 weeks) as the only symptom are unlikely to have asthma and should be investigated according to the ERS guidelines for chronic cough in children (32) and a referral for further investigations to exclude differential diagnoses should be considered
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| ***PICO 2:*** *In children aged 5-16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?** The TF recommends against using an improvement in symptoms after a trial of preventer medication alone to diagnose asthma (conditional recommendation against the intervention, based on clinical experience)

Remarks:1. The TF did not find any evidence for or against a trial of preventer medication to diagnose asthma in children aged 5 to 16 years
2. Despite the lack of evidence, based on clinical experience, the TF members agreed that a trial of preventer medication can be considered; but only in symptomatic children with abnormal spirometry and negative bronchodilatator response. In such cases, the objective tests spirometry and, if indicated, BDR should be repeated after 4 to 8 weeks
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| ***PICO 3:*** *In children aged 5-16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?** The TF recommends to perform spirometry as part of the diagnostic work-up of children aged 5-16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

Remarks:1. An FEV1/FVC < lower limit of normal (LLN) or < 80%, or an FEV1 < LLN, or < 80% predicted should be considered supportive of an asthma diagnosis. It is important to be aware that not all children are able to perform a sufficient FVC manoeuvre resulting in a false normal FEV1/FVC ratio
2. A normal spirometry result does not exclude asthma
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| ***PICO 4:*** *In children aged 5-16 years under investigation for asthma, should bronchodilator reversibility (BDR) testing be used to diagnose asthma?** The TF recommends BDR testing in all children with FEV1 < LLN or < 80% predicted and/or FEV1/FVC < LLN or < 80% predicted (strong recommendation for the intervention, based on clinical experience)

Remarks:1. Consider an increase in FEV1 ≥ 12% and/or 200 ml following inhalation of 400 micrograms of a short acting beta2-agonist as diagnostic of asthma
2. A BDR < 12% does not exclude asthma
3. Most TF members consider BDR testing when baseline spirometry is normal if the clinical history is strongly suggestive of asthma
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| ***PICO 5:*** *In children aged 5-16 years under investigation for asthma, should FeNO testing be used to diagnose asthma?** The TF recommends to measure FeNO as part of the diagnostic work-up of children aged 5 to 16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

Remarks:1. A FeNO value ≥ 25ppb in a child with asthma symptoms should be considered as supportive of a diagnosis of asthma
2. A FeNO value < 25ppb does not exclude asthma
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| ***PICO 6:*** *In children aged 5-16 years under investigation for asthma, should peak expiratory flow rate (PEFR) variability be used to diagnose asthma?** The TF recommends against PEFR variability testing as the primary objective test on its own to diagnose asthma in children aged 5-16 years (conditional recommendation against the intervention, moderate quality of evidence)

Remarks:1. Other objective tests are preferred but a PEFR variability test can be considered in healthcare settings lacking other objective tests
2. If a PEFR variability test is used the result should be based on two weeks of measurements, ideally using electronic peak flow meters
3. A cut-off of ≥ 12% in PEFR variability should be considered a positive test
4. A PEFR variability of <12% does not exclude asthma
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| ***PICO 7:*** *In children aged 5-16 years under investigation for asthma, should allergy testing be used to diagnose asthma?** The TF recommends against the use skin prick tests to aeroallergens as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)
* The TF recommends against the use of serum total and specific IgE tests as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)
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| ***PICO 8:*** *In children aged 5-16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?** The TF recommends a direct bronchial challenge test using methacholine in children aged 5-16 years under investigation for asthma where asthma diagnosis could not be confirmed with first line objective tests. (conditional recommendation for the intervention, low quality evidence)

Remarks:1. A provocative concentration of methacholine that results in a 20% drop in FEV1 (PC20) value of 8 mg/ml or less should be considered as a positive test
2. The TF found no evidence for or against performing histamine challenge tests in children under investigation for asthma
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| ***PICO 9:*** *In children aged 5-16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?** The TF recommends an indirect bronchial challenge test using a treadmill or a bicycle in children aged 5-16 years under investigation for asthma with exercise related symptoms where asthma diagnosis could not be confirmed with first line objective tests. (conditional recommendation for the intervention, moderate quality evidence)

Remarks:1. A fall in FEV1 of > 10% from baseline should be taken as a positive test
2. A mannitol challenge can be considered as an alternative to exercise challenge. However due to its limited availability in most countries, and the fact that children often find the test unpleasant, mannitol challenge should be best avoided in favour of other challenge tests
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**Results of the literature reviews and TF recommendations for PICO 1 to 9**

**PICO 1 -** *In children aged 5-16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?*

*Recommendation*

* The TF recommends against diagnosing asthma based on symptoms alone (strong recommendation against the intervention, moderate quality of evidence)

*Remarks*

1. Recurrent wheeze, cough and breathing difficulty are key symptoms of asthma. The TF considers a history of recurrent reported wheeze or wheeze on auscultation as the most important symptom of asthma
2. Children with chronic cough (i.e. cough for more than 4 weeks) as the only symptom are unlikely to have asthma and should be investigated according to the ERS guidelines for chronic cough in children (32) and a referral for further investigations to exclude differential diagnoses should be considered

*Background*

Asthma symptoms vary over time and may respond to bronchodilator treatment. Wheeze is a key feature of asthma but the term is poorly understood by clinicians and patients (33). Wheeze is a soft polyphonic noise or whistling sound heard mainly during expiration and is caused by turbulent airflow occurring simultaneously in many airways of different calibre. Parents often describe stridor and rattles as wheeze. Moreover, the word wheeze does not have an equivalent in many languages (34). Other symptoms that caregivers often report are cough and breathing difficulty with or without exercise. Most asthma definitions include the presence of respiratory symptoms such as wheeze, cough, breathing difficulty and others.

*Review of evidence directly addressing PICO 1*

We included four observational published studies (from Switzerland, Inner Mongolia, Netherlands and Brazil) that fulfilled inclusion criteria (supplementary table 2). All four reported the relationship between reported wheeze and subsequent asthma diagnosis (table 3). (35-38). Wheeze, cough and breathing difficulty was by parental/caregiver report in all four studies. Any prior ICS treatment was withheld for three days before lung function testing in one study (35), ≥ one month in a second study (36) and not mentioned in the remaining two. Overall, the sensitivity of wheeze to correctly identify a child with asthma ranged between 0.55 and 0.86 and the specificity between 0.64 and 0.90 (supplementary table 3 and 5). Cough and breathing difficulty were much less specific for asthma ranging from very low to low depending on the study. Results for breathing difficulty were variable and this symptom generally was very non-specific.

*Justification of the recommendation*

Overall, the sensitivity of wheeze to correctly identify a child with asthma ranged between 0.55 and 0.86 and the specificity between 0.64 and 0.90. Using the presence of the symptoms wheeze, cough and breathing difficulty alone results in misdiagnosis in a considerable number of children. The Task Force agreed that sensitivity and specificity of wheeze was not strong enough to confirm a diagnosis of asthma on its own.

Cough and breathing difficulty are non-specific symptoms and should not be used to diagnose asthma (supplementary table 4 and 5).

*Key unanswered questions and future research needs*

Further studies are needed that combine symptoms with other predictors of asthma such as the presence of other atopic features, family history etc. to test whether this increases the sensitivity and /or specificity of symptoms to diagnose asthma. Further studies are also needed investigating the diagnostic accuracy of wheeze heard by a medical doctor and video recordings of wheezing children made by parents or carers.

**PICO 2 –** In children aged 5-16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?

*Recommendation*

* The TF recommends against using an improvement in symptoms after a trial of preventer medication alone to diagnose asthma (conditional recommendation against the intervention, based on clinical experience)

*Remarks*

1. The TF did not find any evidence for or against a trial of preventer medication to diagnose asthma in children aged 5 to 16 years
2. Despite the lack of evidence, based on clinical experience, the TF members agreed that a trial of preventer medication can be considered; but only in symptomatic children with abnormal spirometry and negative bronchodilatator response. In such cases, the objective tests spirometry and, if indicated, BDR should be repeated after 4 to 8 weeks

*Background*

A trial of preventer medication with inhaled corticosteroids (ICS), either alone or in combination with a long-acting beta-2 agonist (LABA), or leukotriene receptor antagonist (LTRA) is widely used by clinical practitioners to evaluate the response in children with suspected asthma. The treatment trial consists of starting ICS or LTRA treatment empirically in a child presenting with symptoms of asthma, without performing additional objective tests. The child is reviewed after a period of 4 to 8 weeks and the diagnosis of asthma is then often made based on symptom improvement alone at clinical review.

*Review of evidence directly addressing PICO 2*

We found no study where children with asthma symptoms but no confirmed diagnosis received a trial of treatment and investigation with at least one objective test. Most studies did not meet the inclusion criteria because they investigated the effectiveness of the trial medication in children already diagnosed with asthma.

*Justification of the recommendation*

Despite the lack of evidence to support a recommendation, the TF members are well aware that a trial of preventer medication is widely employed by clinicians to evaluate the response in children with symptoms of asthma. The main reason for this is remaining diagnostic uncertainty and because spirometry and FeNO confirm asthma only in a minority of children seen during routine clinical reviews in children (39-41). The TF discussed and agreed that a trial of treatment with ICS can be considered, but only in steroid-naïve or non-adherent children with asthma symptoms in whom initial tests have not been able to confirm the diagnosis. Objective tests should be repeated after 4 to 8 weeks. (18,42-44)

The difference in our diagnostic approach is that the TF does not recommend to diagnose asthma on the basis of improvements in reported symptoms alone following the treatment trial but to base the diagnosis on a significant improvement in lung function and symptoms after completion of the trial of treatment. This recommendation is supported by the GINA 2020 strategy document. (18) GINA in addition proposes a supervised stepping down of preventer medication in conjunction with lung function tests to confirm or refute the presence of (active) asthma (supplementary table 6).

*Key unanswered questions and future research needs*

There is a need for validation studies investigating the diagnostic accuracy and limitations of preventer medication treatment trials in preventer naïve school-age children. Studies need to assess the type, dosage and the length of the treatment trial period, taking into account factors such as proper inhaler technique, adherence to medication and the season during which the trial is conducted.

**PICO 3 -** In children aged 5-16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?

*Recommendation*

* The TF recommends to perform spirometry as part of the diagnostic work-up of children aged 5-16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

*Remarks*

1. An FEV1/FVC < LLN or < 80%, or an FEV1 < LLN or < 80% predicted should be considered supportive of an asthma diagnosis. It is important to be aware that not all children are able to perform a sufficient FVC manoeuvre resulting in a false normal FEV1/FVC ratio
2. A normal spirometry result does not exclude asthma

*Background*

Spirometry is a non-invasive physiological test, which measures the volume and flow rate of air during inhalation and exhalation. The most commonly reported parameters are FEV1 (forced expiratory volume in 1 second) and FVC (forced vital capacity) and the ratio of FEV1 to FVC (FEV1/FVC). The FEV1 represents the volume of air (litres) expired in the first second and the FVC (litres) is the total volume of air expired from the start of the manoeuvre to the end. A reduced FEV1 to FVC ratio indicates airway obstruction.

A standardised procedure for performing spirometry has been published jointly by the European Respiratory Society (ERS) and American Thoracic Society (ATS) (45).

*Cut-offs:* The TF strongly recommends the use of LLN to define abnormal spirometry but the panel agreed to accept a fixed cut-off for FEV1/FVC and FEV1 < 80% where LLN is not available because this cut-off reasonably closely approximates LLN. In a large recent UK study using a fixed cut-off of 80% for FEV1/FVC and FEV1 % predicted, airflow obstruction was falsely identified in 6.4% of children aged 5 to 16 years (41) compared to using LLN.

*Review of evidence directly addressing PICO 3*

Our search strategy was designed to identify studies addressing the diagnostic accuracy of spirometry using the lower limit of normal (LLN) or a fixed cut-off for FEV1 and/or FEV1/FVC to diagnose asthma in children aged 5-16 years. Three studies fulfilled the inclusion criteria (supplementary table 7) (35,46,47). All were observational, cross-sectional studies comparing the diagnostic accuracy of spirometry in school-aged children against a second objective test.

Studies using a fixed cut-off for FEV1 % predicted of < 80% or FEV1/FVC < 80% to diagnose asthma in children showed low sensitivity (0.12 to 0.52) and moderate to high specificity (0.72 to 0.93) (35,46,47) (supplementary tables 8 and 9). Only one study utilised Global Lung Function Initiative (GLI) reference equations to determine predicted values (35). This study reported the diagnostic accuracy of FEV1 z-score ≤ 0.8 with a sensitivity of 0.44 and specificity of 0.77

*Justification of recommendation*

Good quality spirometry can detect airway obstruction, the hallmark of asthma. Obstructed spirometry with positive BDR confirms the diagnosis. Spirometry testing is fairly quick and non-invasive and an experienced operator can obtain good quality data from the majority of children ≥ 5 years (41,48). The equipment is portable and the test is widely available, however availability in primary care is variable. It is important to emphasise that spirometry as a one-off measurement has a low sensitivity and is therefore poor at ruling out asthma. Because of the variable nature of the condition, when the asthma is controlled, spirometry is frequently normal (40,41). Serial measurements may be required to confirm the diagnosis (19). Abnormal spirometry has good specificity for asthma (supplementary table 9).

*Key unanswered questions and future research needs*

There is an urgent need for studies in children assessing the ideal timing and the frequency of spirometry measurements to improve the sensitivity of the test.

**PICO 4 –** In children aged 5-16 years under investigation for asthma, should bronchodilator reversibility (BDR) testing be used to diagnose asthma?

*Recommendation*

* The TF recommends BDR testing in all children with FEV1 < LLN or < 80% predicted and/or FEV1/FVC < LLN or < 80% predicted (strong recommendation for the intervention, based on clinical experience)

*Remarks*

1. Consider an increase in FEV1 ≥ 12% and/or 200 ml following inhalation of 400 micrograms of a short acting beta2-agonist as diagnostic of asthma
2. A BDR < 12% does not exclude asthma
3. Most TF members consider BDR testing when baseline spirometry is normal if the clinical history is strongly suggestive of asthma

*Background*

The bronchodilator reversibility (BDR) test measures changes in lung function following inhalation of a short acting bronchodilator. BDR is a test of bronchial lability, the hallmark of asthma. ERS/ATS test procedure and interpretation of results have been published (45,49).

*Review of evidence directly addressing PICO 4*

We found no studies directly addressing the diagnostic accuracy of BDR testing in school-aged children using a second objective test, which were the inclusion criteria. However, variable airflow limitation is the hallmark of asthma and the presence of variable airflow limitation demonstrated by BDR testing is part of the definition of asthma stated in all major international asthma guidelines such as GINA and BTS/SIGN. (18-20,30,31) The literature searches revealed that most studies, including most of those included in these clinical practice guidelines, used the presence of BDR as evidence to confirm the diagnosis of asthma. (35,36,46,47,50).

*Additional evidence:* The main uncertainty about BDR relates to its low sensitivity, and in children there is no direct evidence to support a robust cut-off for BDR. A change in FEV1 (L) of ≥ 12% and/or 200 ml is the widely used cut-off in children to define the presence of BDR. This cut-off is however derived from adult studies. Paediatric studies reported the mean change in FEV1 (L) post-bronchodilator to be 2.2-2.7% from baseline in healthy children (51,52) compared with 8.6-10.7% in those with a history of asthma. The reported values for sensitivity and specificity using a 12% cut-off in children is 0.35-0.36 and 0.90-0.98 respectively (52,53). Despite providing important information, we excluded these studies from the evidence synthesis because they did not fulfil inclusion criteria, namely a second objective test within the reference standard.

*Justification of recommendation*

Even though we did not find any studies investigating the diagnostic accuracy of BDR testing we recommend BDR testing in all children with abnormal spirometry. Variable airflow limitation is a defining feature of asthma as stated in major international asthma guidelines such as GINA and BTS/SIGN and a positive BDR in conjunction with obstructed spirometry has a high accuracy at confirming the diagnosis in children with relevant clinical signs and symptoms. Most studies included in these guidelines use a positive BDR test as the reference standard to support the diagnosis of asthma. In a child with relevant clinical symptoms, abnormal spirometry and positive BDR test treatment can be started immediately. Importantly, a child with abnormal spirometry and no evidence of BDR could have a restrictive lung disease or fixed airways obstruction and referral should be considered to specialist care for further investigations. The TF agreed with the cut-off for BDR of 12% in children, in agreement with previous studies in children (52,53) and existing international asthma guidance (18-20,49). The TF acknowledges that BDR testing has low sensitivity especially at the 12% threshold but good specificity for a diagnosis of asthma in children (52). The TF acknowledges that there are resource implications, but based on the high specificity of the test, its non-invasive nature and its availability, the TF recommends BDR testing in children with obstructed spirometry and/or low FEV1(supplementary table 10).

The TF considered that BDR testing is a non-invasive procedure and usable results are obtained in the majority of children. Spirometry and BDR can be performed in any health care setting and the results are immediately available. Equipment and consumables costs are moderate but the test is time consuming and there are training requirements. Reversible airflow obstruction is the hallmark of asthma and it would make little sense to perform spirometry but not BDR in cases where spirometry is abnormal/obstructed.

*Key unanswered questions and future research needs*

We need validation studies in children to investigate the diagnostic accuracy and limitations of BDR testing in asthma using different cut-offs, compared with an appropriate reference standard, which includes a second objective test. Different studies need to assess the type and dosage of short acting bronchodilator used, and when to perform BDR testing (i.e. for all children, or only when FEV1 or FEV1/FVC is < LLN).

**PICO 5 –** In children aged 5-16 years under investigation for asthma, should FeNO testing be used to diagnose asthma?

*Recommendation*

* The TF recommends to measure FeNO as part of the diagnostic work-up of children aged 5 to 16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

*Remarks*

1. A FeNO value ≥ 25ppb in a child with asthma symptoms should be considered as supportive of a diagnosis of asthma
2. A FeNO value < 25ppb does not exclude asthma

*Background*

FeNO was first measured in exhaled air by Gustafsson et al. in 1991 (54), and subsequently has been shown to be increased in asthma and regarded as an indirect marker of eosinophilic airway inflammation (55). Measurement is non-invasive, can be obtained in most children ≥ 5 years and results are available in a few minutes using portable, desktop equipment. Success in the routine clinical setting is variable in children aged 5 to 7 years (48).

International guidelines describe a standardized methodology and provide clinical interpretation of FeNO measurements (55). FeNO has been recommended as a useful test to support a diagnosis of asthma in adults and children. (20)

Multiple factors have been reported to influence the measurement (55) including subject related factors, such as age, height and ethnicity, lifestyle factors, such as smoking, diet and exercise, and environmental exposures such as to pollen (55). Atopy is associated with elevated FeNO, independent of asthma (55). Asthma treatments including ICS (56) and LTRA reduce FeNO by between 25% and 50% (57).

*Review of evidence directly addressing the question*

Four recent systematic reviews investigated the accuracy of FeNO in the diagnosis of asthma in children (58-61). Four observational studies in children fulfilled the inclusion criteria (35,46,47,50). Unpublished data were provided by the authors of a fifth study (36). A summary of this published evidence on FeNO is shown in table 5.

The overall diagnostic accuracy of the test is moderate since conclusions are based on non-weighted average FeNO values without 95% confidence intervals. FeNO values of 19 parts per billion (ppb) and 25 ppb showed the equal highest Youden’s index (sensitivity+specificity-100) shown in supplementary table 13.

The influence of inhaled corticosteroid (ICS) treatment on the results was considered;

participants in the study reported by Brouwer et al (36) had withheld any ICS for four weeks. In contrast, in the study reported by Sivan et al, one third of cases finally categorized as asthma were using ICS at the time of testing (46). Woo et al (50) included only steroid naïve children and finally, in the study by Grzelewski et al, 11% and in the study by de Jong et al, 19% of children were on controller medication at the time of FeNO measurement (35,47).

The TF explored whether there might be sub-groups of children where FeNO may be particularly suited to diagnosing/excluding asthma and one study showed that children with allergy show better accuracy for FeNO testing (50).

The five studies fulfilling the criteria for inclusion (35,36,46,47,50) reported sensitivity and specificity results for different cut-points for FeNO. These are shown in supplementary table 11.

*Justification of recommendation*

Although the diagnostic accuracy of FeNO is moderate the results of our review show that evidence exists to support FeNO as a useful test to diagnose asthma in children (supplementary table 14). FeNO testing is a relatively simple, non-invasive test that is highly acceptable to children and their caregivers. There are equipment and consumables costs that need to be considered. The TF panel agreed that a single recommended cut-off value was essential. The panel agreed that 25 ppb was the best cut-off value based on the mean sensitivity (0.57) and specificity (0.81) values (supplementary tables 12 and 13) at this cut-point. To reach this decision the panel considered the harm from over-treatment arising from false positive results and the remit of the TF, which was to provide recommendations on diagnosing asthma and not on excluding asthma. The TF acknowledges that any cut-off relating to continuous variables such as FeNO are to some extent arbitrary and confidence into the result increases with greater distance from the cut-off value. The TF also emphasises the importance of interpreting FeNO as part of a wider clinical assessment.

*Key unanswered questions and future research needs*

We need studies investigating the sensitivity and specificity of FeNO in ICS naïve child populations presenting with symptoms of asthma and studies, which further explore the role of FeNO in non-atopic children with asthma symptoms. Studies are also required to establish the “wash out” time after cessation of ICS or LTRA before FeNO can be used for diagnostic testing. We also need better technology to routinely test FeNO in children ≤ 5 years.

**PICO 6 -** In children aged 5-16 years under investigation for asthma, should peak expiratory flow rate (PEFR) variability be used to diagnose asthma?

*Recommendation*

* The TF recommends against PEFR variability testing as the primary objective test on its own to diagnose asthma in children aged 5-16 years (conditional recommendation against the intervention, moderate quality of evidence)

*Remarks*

1. Other objective tests are preferred but a PEFR variability test can be considered in healthcare settings lacking other objective tests
2. If a PEFR variability test is used the result should be based on two weeks of measurements, ideally using electronic peak flow meters
3. A cut-off of ≥ 12% in PEFR variability should be considered a positive test
4. A PEFR variability of <12% does not exclude asthma

*Background*

PEFR is a physiological measurement of the largest flow of exhalation that can be achieved from maximal inspiration, expressed in L/min. PEF should be recorded as the best of three forced expiratory blows immediately after a full inspiration with the patient either standing or sitting. The PEF variability is calculated as the difference between the highest and lowest PEF expressed as a percentage of the average PEF. PEF variability as a diagnostic test is supported by the BTS/SIGN and the UK NICE guidelines and the GINA 2020 asthma strategy document. (18-20)

*Review of evidence directly addressing PICO 6*

One study met our inclusion criteria (supplementary table 15). Brouwer et al. studied the usefulness of home spirometry and PEFR variability in diagnosing asthma in children consecutively referred to secondary care with nonspecific respiratory symptoms (36). Children performed home spirometry and peak flow measurements using an electronic device, twice daily for two weeks. Using a pre-defined cut-off of 12.3% (based on above 95% confidence interval of normal values in children) the sensitivity and specificity of PEFR variability was 0.5 and 0.72 respectively (supplementary tables 16 and 17).

*Justification of recommendation*

PEFR variability has been included as an optional test in the diagnostic algorithm however spirometry (with BDR where appropriate) and FeNO are preferred first line diagnostic tests. There is limited evidence to support PEFR variability as an asthma diagnostic tool (supplementary table 17). The only evidence to support its use is as a PEFR diary with twice-daily measurements for at least two weeks. More frequent testing may have greater sensitivity (62) but is offset by decreasing adherence to the test by children and their families (63). The use of electronic meters and diaries may help to overcome some of the adherence issues (64).

*Key unanswered questions and future research needs*

We need more studies to assess the diagnostic use and accuracy of PEFR variability in children. Future research should involve larger numbers of treatment naïve children referred with asthma symptoms who are investigated by means of PEFR variability and other objective tests.

**PICO 7 –** In children aged 5-16 years under investigation for asthma, should allergy testing be used to diagnose asthma?

*Recommendations*

* The TF recommends against the use skin prick tests to aeroallergens as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)
* The TF recommends against the use of serum total and specific IgE tests as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)

*Background*

Allergic sensitisation to aeroallergens is common among all children and even more common among children with asthma. Aeroallergens are common triggers of asthma symptoms. Common aeroallergens are house dust mites, animal dander, pollens and moulds. Allergic sensitisation to aeroallergens can be measured in several ways, but the most commonly used are skin prick test, or specific IgE measurement.

*Skin prick tests*

Skin prick tests (SPT) use the presence and degree of cutaneous reactivity as a marker for allergic sensitisation. A wheal size of ≥ 3 mm compared to negative control is considered a positive test (65). SPT is not practical in patients who have extensive eczema, dermographism, urticaria, or who are taking antihistamines or other medications, which interfere with the proper interpretation of the test results (65,66).

*Allergen-specific IgE tests*

The allergen specific IgE can be detected by a Radio-Allergo-Sorbent Tests (RAST) or by an Enzyme-Linked Immuno-Sorbent Assays (ELISA). (67) Different systems can measure allergen specific IgE. The cut-off for a positive test to diagnose allergic sensitisation in children is commonly defined as <0.35 kU/l.

*Review of evidence directly addressing PICO 7*

Four observational studies met our inclusion criteria (supplementary table 18) (35,36,47,50). However, only one study directly assessed allergy tests as an index test (35), even though it was possible to calculate the diagnostic accuracy of allergy tests from the other three studies as well. Most studies were excluded because they assessed prevalence and patterns of allergic sensitization in children with a prior asthma diagnosis or in healthy populations. Skin prick test had a sensitivity of 0.77-0.90 and specificity of 0.23-0.40 for one positive test and sensitivity of 0.79 and specificity of 0.53 for two positive tests (supplementary tables 19 and 21). Specific IgE measurements had a sensitivity of 0.58-0.90 and a low specificity of 0.56-0.65 (supplementary tables 20 and 21).

*Justification of recommendation*

Evidence from the available studies suggests that skin prick tests and specific IgE measurements have a limited value to diagnose asthma. The low specificity is likely to lead to an over-diagnosis of asthma, particularly in children with other atopic diseases. Non-allergic asthma, in contrast, will be under-diagnosed if physicians rely on allergy tests for asthma diagnosis.

However, after diagnosis, allergy tests can be useful for asthma management, in particular to describe the phenotype and to plan individualised prevention measures.

Considering the low specificity, the TF recommends against allergy testing as a diagnostic test for asthma in children (supplementary table 21).

*Key unanswered questions and future research needs*

Allergy tests are useful in patients already diagnosed with asthma, to determine measures of tertiary prevention, i.e. avoidance of clinically relevant allergens that trigger asthma attacks or maintain chronic symptoms. Carefully designed clinical studies in children with suspected asthma are essential to provide more evidence on their role in diagnosing asthma.

**PICO 8 –** In children aged 5-16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?

*Recommendation*

* The TF recommends a direct bronchial challenge test using methacholine in children aged 5-16 years under investigation for asthma where asthma diagnosis could not be confirmed with first line objective tests (conditional recommendation for the intervention, low quality evidence).

*Remarks*

1. A PC20 value of 8 mg/ml or less should be considered as a positive test
2. The TF found no evidence for or against performing histamine challenge tests in children under investigation for asthma

*Background*

One of the hallmarks of asthma is airway hyperresponsiveness (AHR), which is characterized by an increased sensitivity and exagerated response to stimuli resulting in airway obstruction (68). Direct bronchial challenge testing is performed with different chemical substances to test non-specific bronchial responsiveness to a variety of stimuli such as meatacholine (a neurotransmitter substance) or histamine (a mediator substance) directly interacting with receptors on airway smooth muscle. In individuals with asthma the response occurs at a lower dose and to a greater degree compared to children without AHR. An ERS TF recently revised the recommendations for methacholine bronchial challenge tests (69). The results are based on the concentration (PC20) causing a 20% fall in FEV1 or the delivered dose of methacholine resulting in a 20% fall in FEV1 (provocative dose (PD20)). As results are comparable between different protocols and devices, the latter is the preferred method (69). No studies using histamine challenge fulfilling inclusion criteria were identified by the literature searches.

Some parents/carers and patients have concerns about challenge tests due to the risk of creating a potentially severe asthma response. Health professionals should be mindful of these concerns when explaining the risks and benefits of challenge testing.

*Review of evidence directly addressing PICO 8*

Three studies directly addressed the PICO question and were included in the quantitative analysis (supplementary table 22) (35,70,71). Histamine for bronchial challenge was not tested in any of the studies fulfilling inclusion criteria.

We were unable to pool the accuracy data for these studies because sensitivity and specificity differed too much between studies, and therefore calculated the absolute effects of tests using the range of results. Sensitivity and specificity ranged from 0.66 to 0.91 and from 0.63 to 0.82 respectively (supplementary table 23).

*Justification of recommendation*

Direct bronchial testing is time consuming, requires a specialist setting and tests can be unpleasant for children. Children referred for direct bronchial challenge testing therefore require careful selection. However, the TF agreed that direct bronchial challenge testing should be offered to children where diagnostic uncertainty remains after repeated first line tests have not confirmed the diagnosis, the child remains symptomatic and other diagnoses have been considered. (supplementary table 24). The TF emphasises the importance of interpreting direct challenge testing as part of a wider clinical assessment. A positive challenge test may be present in the absence of asthma.

*Key unanswered questions and future research needs*

We need clinical studies to answer the question as to which children benefit most from direct bronchial challenge testing in order to make recommendations on the most appropriate referrals.

**PICO 9 –** In children aged 5-16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?

*Recommendation*

* The TF recommends an indirect bronchial challenge test using a treadmill or a bicycle in children aged 5-16 years under investigation for asthma with exercise related symptoms where asthma diagnosis could not be confirmed with first line objective tests. (conditional recommendation for the intervention, moderate quality evidence)

*Remarks*

1. A fall in FEV1 of > 10% from baseline should be taken as a positive test
2. A mannitol challenge can be considered as an alternative to exercise challenge. However due to its limited availability in most countries, and the fact that children often find the test unpleasant, mannitol challenge should be best avoided in favour of other challenge tests

*Background*

Indirect bronchial challenge tests trigger airway obstruction via endogenous pathways that are involved in the pathophysiology of asthma (72). Therefore, they are considered to be more specific for asthma compared to direct challenge tests but may be less sensitive at detecting AHR. Several methods exist for indirect bronchial challenge testing including exercise, eucapnic voluntary hyperpnoea, cold air challenge and the inhalation of osmotic substances such as hypertonic saline, mannitol or adenosine monophosphate. An ERS TF recently revised the recommendations for indirect bronchial challenge testing (73).

Exercise testing using a cycle ergometer or a motorized treadmill is the preferred test (73,74). Exercise induced bronchoconstriction is defined as a decrease in FEV1 ≥ 10% from baseline, but some studies use the criterion of 15%, which results in a higher specificity (73,75).

The mannitol challenge test is performed with the alcohol sugar mannitol, an osmotic agent, using a dry powder inhaler device. Increasing doses of mannitol are inhaled and FEV1 is measured repeatedly between the inhalation steps (76).The test is considered positive if there is a fall of 15% or more in FEV1 from baseline in response to the cumulative total dose or a 10% decrease between two consecutive doses of mannitol (77).

As above, some parents/carers and patients have concerns around challenge testing and potential adverse events.

*Review of evidence directly addressing the question*

We only found studies using either exercise challenge test or the mannitol challenge test that fulfilled our inclusion criteria. Three studies directly answered the review question and were included in the quantitative analysis (supplementary table 25) (35,70,71). All three studies provided accuracy data for indirect bronchial challenge tests using either exercise or mannitol.

Anderson et al. provided data for mannitol inhalation in children as a subsample of a larger study in adults (70). Zaczeniuk et al. reported the diagnostic accuracy of exercise testing by treadmill (71) as did De Jong et al. who also included bicycle (35). We were not able to pool the accuracy data of these studies because of the range of the results. Zaczeniuk et al. defined a positive test by a ≥10% decrease in FEV1 and reported a sensitivity of 0.77 and a specificity of 0.68 with de Jong et al. reporting sensitivity and specificity data for ≥10% and ≥12% FEV1 cut-off. Sensitivity was 0.47 and 0.37 respectively and specificity was 0.77 for both cut-offs (supplementary table 26).

We were unable to pool the mannitol challenge test data due to the range of values. For mannitol challenge testing, Anderson et al. reported a sensitivity of 0.63 and specificity of 0.81, and de Jong et al. reported a sensitivity and specificity of 0.39 and 0.97 respectively (supplementary table 27).

*Justification of recommendation*

Indirect bronchial testing is time consuming and formal tests require a specialist setting. Children referred for indirect direct bronchial challenge testing require careful selection. A positive indirect bronchial challenge test however confirms the diagnosis of asthma with a moderate sensitivity and high specificity. Based on the evidence (supplementary table 28), the TF agreed that indirect challenge testing during the diagnostic work-up with treadmill or bicycle is recommended in children where the diagnosis could not be confirmed using first line diagnostic tests and particularly for children with exercise induced symptoms.

The TF emphasises the importance of interpreting indirect challenge testing as part of a wider clinical assessment. A positive challenge test may be present in the absence of asthma.

*Key unanswered questions and future research needs*

There is uncertainty regarding the best approach with respect to challenge testing in children and it is unclear whether indirect or direct challenge tests should be prioritized in the asthma diagnostic pathway. Younger children especially were under-represented in the selected studies and should be included in future studies.

**Development of the diagnostic algorithm**

The TF agreed on the recommended diagnostic tests and a draft diagnostic algorithm during a meeting of the whole TF based on the results of the literature reviews, the recommendations for each PICO question and the EtD framework.

The TF used a modified Delphi process to decide on the hierarchy of the diagnostic tests.

Using the Delphi process described in the methods’ section, the TF members agreed that no single test on its own is currently sufficient to confirm the diagnosis of asthma. The TF agreed that two positive, evidence-based tests, are required to confirm the diagnosis in children aged 5-16 years. Spirometry, BDR testing and FeNO are the most widely available objective tests performed in patients under investigation for asthma. Major international asthma guidelines variously recommended these as first line tests. In addition, the tests are non-invasive, the equipment is portable, feasible in all healthcare settings, and have high acceptability by children and families (41). The evidence supporting the proposed objective tests was frequently sparse and in some places relied on a single research publication fulfilling inclusion criteria. In addition there is no study that tested a hierarchy of tests to diagnose asthma in children, or adults. No test was recommended for which there was no evidence. This means that a ‘trial of preventer medication’ is not included as a diagnostic test. Whilst it has been included as a step in the algorithm, the diagnosis of asthma depends entirely on a significant improvement in lung function after the trial of treatment. No studies were found investigating BDR as a test for asthma. However, there is substantial indirect evidence. Variable airflow obstruction is universally accepted as the key feature of asthma and most studies included in this TF report used the presence of BDR as a reference standard to measure other tests against. This approach is pragmatic and there is no evidence underpinning it. The diagnostic algorithm is shown in the figure.

*Application of the algorithm*

This algorithm applies to all children and adolescents presenting with symptoms of asthma irrespective of whether they are treatment naïve or had a prior diagnosis of asthma and are currently on treatment including ICS.

Where children are symptomatic despite ICS treatment, the algorithm can also be applied because in children with current symptoms but normal lung function and a normal FeNO value alternative diagnoses should be considered. Asymptomatic children on ICS should be reviewed at regular intervals (6 to 12 monthly) and treatment stepped down. If symptoms recur, the algorithm should be applied to confirm the diagnosis of asthma.

The algorithm is valid across the paediatric age group of 5 to 16 years. We did not conduct separate reviews for children 5 to 11 years and adolescents (12-16 years) because most included studies had recruited children across school age and adolescence and did not stratify their analyses by age. The whole Task Force agreed that the algorithm applies to children from age 5 to 16 years. Future studies could test whether the algorithm can be refined by adapting it to different age-groups, although every diversification will have to be gauged against the increasing complexity of its use in clinical practice.

**Discussion**

This document presents the first European evidence-based clinical practice guidelines for the diagnosis of asthma in children. We reviewed the literature for the last 40 years and found adequate evidence to support our recommendations in some areas but limited or no data in others.

*Key recommendations:* The TF recommends to diagnose asthma in children only when at least two objective test results are abnormal. The TF recommends that spirometry, BDR and FeNO are first line tests in the asthma diagnostic pathway. The TF also recommends against trials of treatment where an improvement of symptoms alone after a period of empiric asthma preventer medication is used to confirm the diagnosis.

We are not aware of any national or international guidelines that focus entirely on the diagnosis of asthma in children. The most widely cited asthma guidelines make statements or recommendations for diagnosis whilst focussing on the management of asthma, and cover children and adults in one document. The guideline development is different between all major asthma guidelines resulting in considerable variability of recommendations. These are summarised in table 3.

Table 3: Summary of the key recommendations for the diagnosis of asthma in children from three frequently cited current asthma guidelines

|  |  |
| --- | --- |
| **Major asthma guidelines** | **Diagnostic recommendations for children** |
| The Global Initiative for Asthma (GINA) 2020 strategy document (18) | Recommends Spirometry and Bronchodilator reversibility (BDR) testing or two weeks of twice-daily PEFR variability measurements to investigate for asthma.  |
| British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guideline 2019 (19) | States that asthma is a clinical diagnosis. Lung function tests influence the probability of an asthma diagnosis and BTS/SIGN recommend comparing the results of lung function tests undertaken whilst a patient is asymptomatic with that undertaken when the patient is symptomatic to detect variation over time to aid diagnosis. |
| UK National Institute for Health and Care Excellence guideline 2017 (20) | The guideline stipulates that two positive objective tests are required in children aged 5-16 years to confirm the diagnosis of asthma. Spirometry (and BDR if spirometry is obstructed) and FeNO are recommended as 1st line tests. |

Our guidelines differ from the GINA strategy document and the BTS/SIGN guidelines in that neither proposes a clear diagnostic pathway for either a sequence or timing of investigations. The BTS/SIGN guideline (19) does not recommend any tests for the routine diagnosis of asthma. Neither guideline recommends FeNO testing to diagnose asthma. The UK National Institute for Health and Care Excellence (NICE) recently developed asthma guidelines using GRADE methodology and systematic literature searches similar to our approach. (20) These guidelines included a diagnostic algorithm for children aged 5-16 years presenting with symptoms of asthma. Key differences between this and the UK NICE guideline include a) downgrading of the use of PEFR variability testing because the evidence to support this test in children is not strong. The cut-off for PEFR variability testing is also different based on the available evidence (12% vs 20%), b) the FeNO cut-off is lower (25ppb vs 35ppb) based on recent evidence that was not available to NICE, c) challenge testing in children was not recommended by NICE based on insufficient evidence. The TF recommends challenge testing in children as part of the diagnostic algorithm due to new evidence not available to NICE (35) and two studies not identified by the NICE searches. (71,76)

The TF strongly recommends the use of lower limits of normal (LLN) derived from the Global Lung Function Initiative (GLI) (78) as the reference standard for spirometry cut-off values. We have included fixed cut-offs only as a close approximation to be used in exceptional circumstances where LLN are not available either due to the spirometry equipment not displaying LLN values or where there is no GLI data due to the ethnicity of the patient.

We have included fixed cut-off values for other tests including BDR, FeNO, PEFR variability and challenge testing. These cut-offs are based on the evidence available to the TF and the research papers included in the quantitative analysis for each PICO. We used the Youden’s index for pooled data where more than one research paper was available. The TF is aware that these cut-offs represent arbitrary thresholds and that the likelihood that a child has asthma increases with decreasing FEV1, increasing BDR, increasing PEFR variability, increasing FeNO, and greater BHR.

We did not include children <5 years in these guidelines, because diagnostic tests for asthma on young children are rarely performed and there is insufficient evidence to support an evidence based diagnostic algorithm. We recognise that many children <5 years are treated for asthma-like symtpoms and families can't understand why asthma can't be diagnosed sooner but their child has to take asthma treatment. We refer the interested reader to a recent ERS TF report on the management of children with preschool wheeze (79).

There are no randomised controlled trials, which used diagnostic tests to diagnose asthma and the proposed diagnostic algorithm is based on pragmatic decisions including access to test equipment, clinicians’ familiarity with the tests and acceptability by children and families. All these factors and decisions are clearly documented in the EtDs in the supplementary material. In addition, we have not undertaken a health economic analysis because this was beyond the scope of this TF. Because of this lack of evidence to support a diagnostic sequence every diagnostic algorithm will be open to criticism. A recent study from Switzerland confirms the limited use of individual tests and applying the NICE and GINA algorithm retrospectively to a series of diagnostic tests showed variable sensitivity and specificity between the NICE and GINA algorithms (80). The TF is aware that diagnostic algorithms involving multiple tests are challenging especially in the primary care setting. Moreover, spirometry is frequently normal in patients with asthma during stable disease (40,41). Where this is the case and if the child is relatively asymptomatic a ‘watchful waiting approach’ can be considered. Repeat spirometry testing should then be performed with comparison of test results over time. Spirometry testing is likely to be most useful when the child is symptomatic, especially when wheezing is present, and a comparison is made with spirometry obtained during disease stability as suggested by the BTS/SIGN asthma guidelines (19).

We have highlighted areas of research need in the individual PICO sections. Future studies require careful planning with respect to study designs to improve the evidence base of paediatric asthma diagnosis and focus on affordable and scalable tests to diagnose asthma. Better strategies to diagnose childhood asthma in primary care are of particular importance in order to avoid large numbers of secondary and tertiary care referrals for asthma diagnostic tests, in particular challenge tests. More research is urgently needed in this area.

Invariably, regional differences exist in Europe in relation to asthma incidence and severity, availability of tests and the approach to asthma diagnosis. Given the resources and timeframe of this clinical practice guideline it was not possible to evaluate all the tests described in the literature for the diagnosis of asthma but instead to focus on the most commonly used tests and approaches. The ERS TF clinical practice guidelines closely align to other major international asthma guidelines. (18-20) All recommend some form of spirometry testing in patients with suspected asthma, usually from five years of age. Where this guideline differs is in the recommendation of a diagnostic algorithm that should ultimately allow us to diagnose or refute the diagnosis of asthma in all children presenting with relevant respiratory symptoms.

*In summary:* We present the first European guidelines for the diagnosis of asthma in children aged 5-16 years. The TF recommends spirometry, BDR and FeNO as first line tests to diagnose asthma in children and to diagnose asthma only when two test results are abnormal.

**Acknowledgements**

We would like to thank the library staff of University Hospitals Leicester in particular Sarah Sutton for refining the search strategies for each PICO and for conducting the systematic literature searches, and Pip Divall and Coral Pepper who supported her. We would also like to thank Kerri Jones, Steph Ayre, David Supple, Alex Supple, Kelly Lycett, Line Bednarczyk and Jasmine Parkinson who represented patients and parents on the TF and Courtney Coleman and Barbara Johnson from the European Lung Foundation.

**References**

(1) van den Akker-van Marle ME, Bruil J, Detmar SB. Evaluation of cost of disease: assessing the burden to society of asthma in children in the European Union. Allergy 2005;60:140-149.

(2) Aaron SD, Boulet LP, Reddel HK, Gershon AS. Underdiagnosis and Overdiagnosis of Asthma. Am J Respir Crit Care Med 2018;198:1012-1020.

(3) Danvers L, Lo DKH, Gaillard EA. The role of objective tests to support a diagnosis of asthma in children. Paediatr Respir Rev 2020;33:52-57.

(4) Kuprys-Lipinska I, Elgalal A, Kuna P. The underdiagnosis and undertreatment of asthma in general population of the Lodz Province (Poland). Pneumonol Alergol Pol 2010;78:21-27.

(5) Luks VP, Vandemheen KL, Aaron SD. Confirmation of asthma in an era of overdiagnosis. Eur Respir J 2010;36:255-260.

(6) Heffler E, Pizzimenti S, Guida G, Bucca C, Rolla G. Prevalence of over-/misdiagnosis of asthma in patients referred to an allergy clinic. J Asthma 2015;52:931-934.

(7) Kaur B, Anderson HR, Austin J, Burr M, Harkins LS, Strachan DP, et al. Prevalence of asthma symptoms, diagnosis, and treatment in 12-14 year old children across Great Britain (international study of asthma and allergies in childhood, ISAAC UK). BMJ 1998;316(7125):118-124.

(8) Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2009;64:476-483.

(9) Looijmans-van den Akker I, van Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. Br J Gen Pract 2016;66(644):e152-7.

(10) Yang CL, Simons E, Foty RG, Subbarao P, To T, Dell SD. Misdiagnosis of asthma in schoolchildren. Pediatr Pulmonol 2017;52:293-302.

(11) Jurca M, Ramette A, Dogaru CM, Goutaki M, Spycher BD, Latzin P, et al. Prevalence of cough throughout childhood: A cohort study. PLoS One 2017;12:e0177485.

(12) Rakes GP, Arruda E, Ingram JM, Hoover GE, Zambrano JC, Hayden FG, et al. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. IgE and eosinophil analyses. Am J Respir Crit Care Med 1999;159:785-790.

(13) Costa LD, Costa PS, Camargos PA. Exacerbation of asthma and airway infection: is the virus the villain? J Pediatr (Rio J) 2014;90:542-55.

(14) LindenSmith J, Morrison D, Deveau C, Hernandez P. Overdiagnosis of asthma in the community. Can Respir J 2004;11:111-116.

(15) Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. BMC Med 2016;14:113-016-0657-8.

(16) Neffen H, Baena-Cagnani CE, Malka S, Solé D, Sepúlveda R, Caraballo L, et al. Asthma mortality in Latin America. J Investig Allergol Clin Immunol 1997;7:249-253.

(17) Chua KL, Soh SE, Ma S, Lee BW, ia Pacific Association of Pediatric Allergy, Respirology & Immunology (APAPARI). Pediatric asthma mortality and hospitalization trends across Asia pacific: relationship with asthma drug utilization patterns. World Allergy Organ J 2009;2:77-82.

(18) <https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf> accessed 13th February 2021

(19) <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/> accessed 13th February 2021

(20) <https://www.nice.org.uk/guidance/ng80> accessed 13th February 2021

(21) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ 2016;353:i2089.

(22) Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-394.

(23) Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011;64:395-400.

(24) Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-406.

(25) Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008;336(7653):1106-1110.

(26) Gopalakrishna G, Mustafa RA, Davenport C, Scholten RJ, Hyde C, Brozek J, et al. Applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) to diagnostic tests was challenging but doable. J Clin Epidemiol 2014;67:760-768.

(27) Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ 2016 Jun 28;353:i2016.

(28) Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CF, Askham J, et al. Consensus development methods, and their use in clinical guideline development. Health Technol Assess 1998;2:i-iv, 1-88.

(29) Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900-20; quiz 1943.

(30) <https://www.who.int/respiratory/asthma/definition/en/> accessed 12th February 2021

(31) <http://www.globalasthmareport.org/> <https://ginasthma.org/gina-reports/> accessed 12th February 2021

(32) Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J 2020;55:10.1183/13993003.01136-2019.

(33) Saglani S, McKenzie SA, Bush A, Payne DN. A video questionnaire identifies upper airway abnormalities in preschool children with reported wheeze. Arch Dis Child 2005;90:961-964.

(34) Pasterkamp H, Brand PL, Everard M, Garcia-Marcos L, Melbye H, Priftis KN. Towards the standardisation of lung sound nomenclature. Eur Respir J 2016;47:724-732.

(35) de Jong CCM, Pedersen ESL, Mozun R, Goutaki M, Trachsel D, Barben J, et al. Diagnosis of asthma in children: the contribution of a detailed history and test results. Eur Respir J 2019;54:10.1183/13993003.01326-2019.

(36) Brouwer A.F.J., Visser C.A.N., Duiverman E.J., Roorda R.J., Brand PLP. Is home spirometry useful in diagnosing asthma in children with nonspecific respiratory symptoms? Pediatr Pulmonol 2010;45:326-332.

(37) Santos M.C., Cunha AA. A brief questionnaire for screening asthma among children and adolescents in Rio de Janeiro, Brazil. Allergol Immunopathol 2005;33:20-26.

(38) Ma TT, Zhuang Y, Gong HY, Yii AC, Wang XY, Shi HZ. Predictive value of respiratory symptoms for the diagnosis of pollen-induced seasonal asthma among children and adults in Inner Mongolia. Ther Clin Risk Manag 2017;13:967-974.

(39) Murray CS, Foden P, Lowe LA, Durrington H, Custovic A, Simpson A. Diagnosing asthma in children using spirometry: Evidence from a birth cohort study. Thorax 2016;71:A179.

(40) Murray C, Foden P, Lowe L, Durrington H, Custovic A, Simpson A. Diagnosis of asthma in symptomatic children based on measures of lung function: an analysis of data from a population-based birth cohort study. The Lancet Child and Adolescent Health 2017;1:114-123.

(41) Lo DK, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, et al. Lung function and asthma control in school-age children managed in UK primary care: a cohort study. Thorax 2020;75:101-107.

(42) Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Götz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy 2008;63:5-34.

(43) Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol 2005;115:233-242.

(44) Bush A, Fleming L. Diagnosis and management of asthma in children. BMJ 2015;350:h996.

(45) Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J 2005;26:153-161.

(46) Sivan Y., Gadish T., Fireman E., Soferman R. The Use of Exhaled Nitric Oxide in the Diagnosis of Asthma in School Children. J Pediatr 2009;155:211-216.

(47) Grzelewski T, Witkowski K, Makandjou-Ola E, Grzelewska A, Majak P, Jerzynska J, et al. Diagnostic value of lung function parameters and FeNO for asthma in schoolchildren in large, real-life population. Pediatr Pulmonol 2014;49:632-640.

(48) Lo D, Beardsmore C, Roland D, Richardson M, Yang Y, Danvers L, et al. Spirometry and FeNO testing for asthma in children in UK primary care: a prospective observational cohort study of feasibility and acceptability. Br J Gen Pract 2020: 29;70:e809-e816.

(49) Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-968.

(50) Woo S, Lee J, Kim H, Kang J, Sun Y, Hahn Y. Utility of fractional exhaled nitric oxide (F(E)NO) measurements in diagnosing asthma. Respir Med 2012;106:1103-1109.

(51) Galant SP, Morphew T, Amaro S, Liao O. Value of the bronchodilator response in assessing controller naive asthmatic children. J Pediatr 2007;151:457-462.

(52) Tse SM, Gold DR, Sordillo JE, Hoffman EB, Gillman MW, Rifas-Shiman S, et al. Diagnostic accuracy of the bronchodilator response in children. J Allergy Clin Immunol 2013;132:554.

(53) Dundas I, Chan EY, Bridge PD, McKenzie SA. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. Thorax 2005;60:13-16.

(54) Gustafsson LE, Leone AM, Persson MG, Wiklund NP, Moncada S. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. Biochem Biophys Res Commun 1991;181:852-857.

(55) Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602-615.

(56) Beck-Ripp J, Griese M, Arenz S, Koring C, Pasqualoni B, Bufler P. Changes of exhaled nitric oxide during steroid treatment of childhood asthma. Eur Respir J 2002;19:1015-1019.

(57) Montuschi P, Mondino C, Koch P, Barnes PJ, Ciabattoni G. Effects of a leukotriene receptor antagonist on exhaled leukotriene E4 and prostanoids in children with asthma. J Allergy Clin Immunol 2006;118:347-353.

(58) Guo Z, Wang Y, Xing G, Wang X. Diagnostic accuracy of fractional exhaled nitric oxide in asthma: a systematic review and meta-analysis of prospective studies. J Asthma 2016;53:404-412.

(59) Wang Z, Pianosi PT, Keogh KA, Zaiem F, Alsawas M, Alahdab F, et al. The Diagnostic Accuracy of Fractional Exhaled Nitric Oxide Testing in Asthma: A Systematic Review and Meta-analyses. Mayo Clin Proc 2018;93:191-198.

(60) Tang S, Xie Y, Yuan C, Sun X, Cui Y. Fractional Exhaled Nitric Oxide for the Diagnosis of Childhood Asthma: a Systematic Review and Meta-analysis. Clin Rev Allergy Immunol 2019;56:129-138.

(61) Karrasch S, Linde K, Rucker G, Sommer H, Karsch-Volk M, Kleijnen J, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax 2017;72:109-116.

(62) D'Alonzo GE, Steinijans VW, Keller A. Measurements of morning and evening airflow grossly underestimate the circadian variability of FEV1 and peak expiratory flow rate in asthma. Am J Respir Crit Care Med 1995;152:1097-1099.

(63) Chowienczyk PJ, Parkin DH, Lawson CP, Cochrane GM. Do asthmatic patients correctly record home spirometry measurements? BMJ 1994;309(6969):1618.

(64) Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. Thorax 2001;56:180-182.

(65) Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test - European standards. Clin Transl Allergy 2013;3:3-7022-3-3.

(66) Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. Allergy 2009;64:1498-1506.

(67) Ricci G, Capelli M, Miniero R, Menna G, Zannarini L, Dillon P, et al. A comparison of different allergometric tests, skin prick test, Pharmacia UniCAP and ADVIA Centaur, for diagnosis of allergic diseases in children. Allergy 2003;58:38-45.

(68) Sterk PJ. Bronchial hyperresponsiveness: definition and terminology. Pediatr Allergy Immunol 1996;7(9 Suppl):7-9.

(69) Coates AL, Wanger J, Cockcroft DW, Culver BH, Bronchoprovocation Testing Task Force: Kai-Hakon Carlsen, Diamant Z, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests Eur Respir J. 2018;52:1801033. doi: 10.1183/13993003.01033-2018. PMID: 30361249.

(70) Anderson S.D., Charlton B., Weiler J.M., Nichols S., Spector S.L., Pearlman DS. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Respir Res. 2009;10:4. doi: 10.1186/1465-9921-10-4. PMID: 19161635.

(71) Zaczeniuk M., WoickaKolejwa K., Stelmach W., Podlecka D., Jerzynska J., Stelmach I. Methacholine challenge testing is superior to the exercise challenge for detecting asthma in children. Ann Allergy Asthma Immunol. 2015;115:481-4.

(72) Van Schoor J, Joos GF, Pauwels RA. Indirect bronchial hyperresponsiveness in asthma: mechanisms, pharmacology and implications for clinical research. Eur Respir J 2000;16:514-533.

(73) Hallstrand TS, Leuppi JD, Joos G, Hall GL, Carlsen KH, Kaminsky DA, et al. ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing. Eur Respir J. 2018;52:1801033. doi: 10.1183/13993003.01033-2018. PMID: 30361249.

(74) Anderson SD, Brannan JD. Methods for "indirect" challenge tests including exercise, eucapnic voluntary hyperpnea, and hypertonic aerosols. Clin Rev Allergy Immunol 2003;24:27-54.

(75) Backer V, Ulrik CS. Bronchial responsiveness to exercise in a random sample of 494 children and adolescents from Copenhagen. Clinical and Experimental Allergy 1992;22:741-747.

(76) Anderson SD, Brannan J, Spring J, Spalding N, Rodwell LT, Chan K, et al. A new method for bronchial-provocation testing in asthmatic subjects using a dry powder of mannitol. Am J Respir Crit Care Med 1997;156:758-765.

(77) Brannan J.D., Anderson S.D., Perry C.P., FreedMartens R., Lassig A.R., Charlton B., et al. The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: A phase 3 comparison study with hypertonic (4.5%) saline. Respir Res. 2005;6:144. doi: 10.1186/1465-9921-6-144. PMID: 16336673.

(78) Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40:1324-1343.

(79) Brand PL, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. Eur Respir J 2014;43:1172-1177.

(80) de Jong CC, Pedersen ES, Mozun R, Müller-Suter D, Jochmann A, Singer F, et al. Diagnosis of asthma in children: findings from the Swiss Paediatric Airway Cohort. Eur Respir J 2020 doi: 10.1183/13993003.00132-2020. PMID: 32499334.