ERS pocket guidelines

From the ERS task force on Asthma Diagnosis in Children

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

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ERS TASK FORCE ON ASTHMA DIAGNOSIS IN CHILDREN

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Question #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)

- **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 and a referral for further investigations to exclude differential diagnoses should be considered.

Evidence on benefits and harms

- A detailed clinical history and examination are important in the diagnostic work-up for asthma. Wheeze heard by a health care professional has the best specificity (0.640.90) for the diagnosis of asthma of the classical symptoms wheeze, cough and breathing difficulty.
- There is evidence that using a history of symptoms including wheeze, cough and breathing difficulty alone results in misdiagnosis in a considerable number of children. However, by itself the sensitivity and specificity of a history of wheeze is too low for this to be diagnostic by itself and wheeze is usually absent when the patient is well.

Rationale of 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.

Implementation considerations

The health care practitioner obtains the clinical history of asthma signs and symptoms during the medical consultation. There are no additional costs involved. Unequal access to additional tests may result in less health equity in relevant populations. However using symptoms alone will

result in a delay in appropriate asthma treatment or in over-treatment and potentially missing the correct diagnosis in a considerable number of children.

Question #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

Evidence on benefits and harms

- Children correctly diagnosed with asthma may experience an improvement in their symptoms after a trial of preventer medication based on clinical experience and on treatment efficacy studies.
- The test on its own has no physical effect on the children because when it is being done it is only for a short period of time. There is a risk of over-treatment in children misdiagnosed with asthma.

Rationale of 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. 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. 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.

Implementation considerations

The intervention is widely used to diagnose asthma in children but carries the potential risk of misdiagnosis, resulting in unnecessary treatment of children misdiagnosed with asthma and potentially a delay in establishing the correct diagnosis. Unequal access to additional tests may result in less health equity in relevant populations.

Question #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 FEV_1/FVC < LLN or < 80%, or an FEV_1 < 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 FEV_1/FVC ratio
2. A normal spirometry result does not exclude asthma

Evidence on benefits and harms

- Spirometry testing is a non-invasive procedure. Abnormal spirometry and a positive reversibility test confirm the diagnosis. Abnormal spirometry has a moderate to good specificity (0.72 to 0.93) as a diagnostic test for asthma in children.
- Spirometry and BDR testing are well tolerated but time-consuming away from specialist services The test is generally well tolerated however a small number of children report light-headedness especially after repeated forced expiratory manoeuvres. In some children the repeated forced expiratory manoeuvres themselves can cause progressive airway obstruction and the number of manoeuvres should be limited in those children and a bronchodilator administered. Asthma is an episodic condition and spirometry is frequently normal when the child's asthma is well controlled or the child is asymptomatic.

Rationale 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. 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. Serial measurements may be required to confirm the diagnosis. Abnormal spirometry has good specificity for asthma.

Implementation considerations

Moderate cost for equipment and maintenance and training issues. Spirometry alone takes approximately 5 minutes, spirometry with BDR testing approximately 30 minutes of operator time. There is also training required to interpret the results. Acceptance may vary depending on resources, healthcare settings and travel times.

Question #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 $FEV_1 \geq 12\%$ 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

Evidence on benefits and harms

- Abnormal spirometry and a positive BDR confirm the diagnosis due to the high specificity of a positive BDR test. BDR testing is a non-invasive procedure and usable results are obtained in the majority of children from age 5 years.
- BDR testing is time-consuming. In addition, the test relies on the performance of spirometry and this requires training to perform the test and training to interpret the results. Minor side effects in the experience of the TF members are fleeting light-headedness following SABA administration and repeated forced expiratory manoeuvres. This however rarely results in the test not being performed as planned. One solution is for those children with light-headedness is to sit down for a few minutes and to perform the test with the child sitting

rather than standing. Due to moderate staff, equipment and training costs and low sensitivity the test is frequently not done in low resource and in primary care settings.

Rationale of recommendation

Variable airflow limitation is a defining feature of asthma 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. 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 FEV_1.

Implementation considerations

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. Similar to spirometry, acceptance may vary depending on resources, healthcare settings and travel times.

Question #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

Evidence on benefits and harms

- FeNO testing is a non-invasive procedure. The test is quick and easy to perform. A FeNO ≥ 25ppb has moderate specificity (moderate mean specificity 0.81) as a diagnostic test for asthma in children.
- However, FeNO has a relatively low sensitivity as a diagnostic test for asthma in children depending on the population studied, which can lead to underdiagnosis due to false negative results. On the other hand, as FeNO is also raised in other atopic conditions such as eczema and allergic rhinitis the moderate specificity may lead to overdiagnosis. It is important to

interpret FeNO in the context of the clinical picture. Normal FeNO values do not rule out a diagnosis of asthma.

Rationale 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. 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 table 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.

Implementation considerations

The test is non-invasive and easy to interpret. There are moderate cost for equipment and consumables. Relatively little training required to perform and interpret the test result. The acceptance by health care practitioners and commissioners may vary depending on resources and healthcare setting. Unequal access to FeNO may delay the diagnosis in relevant populations. This may result in a delay in appropriate asthma treatment. This would have a negative impact on health equity.

Question #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

Evidence on benefits and harms

- The test is non-invasive and quick to perform and should not cause harm. It is a widely available test as peak flow meters are easily obtainable and cheap. However, the test only detected asthma in half of the cases in the one study included.
- Sensitivity is low (0.50) and a negative test does not rule out a diagnosis of asthma. Repeated forced blows can result in light-headedness in a small number of children. There is a risk of misdiagnosis and this has the potential to adversely affect health outcomes. The test is rarely performed in secondary/tertiary care. There is little evidence on the use of the test in primary care and in low resource settings.

Rationale 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. 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 but is offset by decreasing adherence to the test by children and their families. The use of electronic meters and diaries may help to overcome some of the adherence issues.

Implementation considerations

The test is cheap and peak flow meters are widely available and cheap to buy. The test results need to be reviewed and PEFR variability calculated. The staff time needed has resource implications. In low resource settings, the test could improve health equity as this objective tests would improve diagnostic accuracy compared to no tests. The intervention would be relatively easy to implement, with the caveat that currently only < 50% of PEFR diaries are returned to the medical team.

Question #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

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**

Evidence on benefits and harms

- There is evidence that positive allergy tests have moderate to good sensitivity but low specificity for the diagnosis of asthma. Allergy tests are not useful to make a diagnosis of asthma, but for further phenotyping and management in order to identify triggers of poor asthma control or exacerbations, to distinguish between asthma phenotypes, to predict prognosis, to plan individualised prevention measures (e.g. mattress covers)
- There is evidence that positive allergy tests have low specificity for the diagnosis of asthma. Reliance on allergy tests to diagnose asthma leads to a risk of asthma overdiagnosis, particularly in children with allergic rhinitis. There is also a risk of underdiagnosis of non-allergic asthma. Both skin prick tests and taking blood are slightly disagreeable to children, but not associated with relevant side effects.

Rationale 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. Sensitivity is moderate to high, but may have been artificially boosted by the fact that research studies tend to include mainly children with allergic asthma, so biasing the sensitivity upwards. Considering the low specificity, the TF recommends against allergy testing as a diagnostic test for asthma in children

Implementation considerations

Both types of tests can be implemented in all care settings. Skin prick tests need experienced examiners (training) and adequate storage of ingredients (in fridge, timely replacements). There are moderate cost for RAST testing also requiring access to relevant laboratory facilities. SPT is time consuming and limited to a relatively small number of allergens.

Question #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 of 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

Evidence on benefits and harms

- There is evidence that a positive direct bronchial challenge test has moderate sensitivity and specificity to confirm the diagnosis of asthma in children. Direct bronchial challenge testing is a non-invasive procedure. Bronchial hyper-reactivity is a cornerstone of asthma pathophysiology.
- Despite moderate sensitivity and specificity of direct bronchial challenge tests, there are significant numbers of children returning false positive or false negative tests. Direct bronchial challenge tests are time consuming and require a specialist setting. Therefore, children need to be referred to a specialist setting if bronchial challenge tests are not available. This can be bothersome for children and families. The tests can be uncomfortable for children.

Rationale of recommendation

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.
The TF emphasises the importance of interpreting direct challenge testing as part of a wider clinical assessment.
Direct bronchial challenge testing with methacholine should be reserved for patients where the diagnosis was not confirmed with first line objective tests.

Implementation considerations

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.
Equipment and maintenance costs and costs for consumables, training costs to perform the test and interpret the test results have to be considered. A barrier for implementation may be the need for referral to specialist setting if bronchial challenge testing is not available at the setting. The TF and lay members of TF found this acceptable in carefully selected children where asthma diagnosis could not be confirmed

Question #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 of 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

Evidence on benefits and harms

- Indirect bronchial challenge testing, particulary the treadmill exercise test is a non-invasive procedure. Bronchial hyper-reactivity is a cornerstone of asthma pathophysiology. Despite sensitivity of indirect bronchial challenge testing being very low to moderate depending on the test used, specificity is moderate to good making this a good test to confirm the diagnosis.
- Indirect bronchial challenge tests are time consuming and require a specialist setting. Therefore, children may need to be referred to a specialist laboratory. Exercise tests are tiring and can be considered bothersome by some children. As a result some

children do not complete the test. Children often find the mannitol challenge test unpleasant.

Rationale of recommendation

A positive indirect bronchial challenge test confirms the diagnosis of asthma with a moderate sensitivity and high specificity. Based on the evidence 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. Indirect bronchial challenge testing should be reserved for patients where the diagnosis was not confirmed with first line objective tests.

Implementation considerations

Indirect bronchial testing is time consuming and formal tests require a specialist setting. Children referred for indirect direct bronchial challenge testing require careful selection. Equipment and maintenance costs and costs for consumables in addition to training costs to perform the test and interpret the test results have to be considered. A barrier for implementation may be the need for referral to specialist setting if bronchial challenge testing is not available at the setting.
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