Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Asthma: The new NICE guideline on asthma – what's different?

NICE recently published new guidance on the diagnosis, monitoring and management of chronic asthma. This extended KINES Update discusses some recommendations made in this guideline, differences from the existing national guideline produced by British Thoracic Society/Scottish Intercollegiate Guideline Network, some changes in clinical practice that will be needed for healthcare professionals in England and Wales and reasons why these have been advised.

Key References:

- NICE guideline [NG80]. **Asthma: diagnosis, monitoring and chronic asthma management.** Nov 2017
- BTS/SIGN guideline: **British guideline on the management of asthma**. Latest Update: Sep 2016

Introduction

- Since 2003, national asthma guidance has been produced by the British Thoracic Society in collaboration with the Scottish Intercollegiate Guidelines Network (the 'BTS/SIGN guideline'). Their latest update was published in September 2016, and included substantial revisions to recommendations on diagnosis and pharmacological management, including dose categorisation of inhaled corticosteroids (ICS).
- In November 2017, NICE published a new guideline on asthma (NG80).
- Whilst the general principles used to develop NICE and BTS/SIGN guidelines are similar, some processes undertaken by NICE, including cost-effectiveness analyses, have provided new perspectives. Notable differences between the guidelines relate to:
    - Diagnosis using fractional exhaled nitrous oxide (FeNO) testing
    - Age ranges used to define treatment pathways
    - Use of leukotriene receptor antagonists (LTRAs) ahead of long-acting beta agonists (LABAs)
    - ICS dose categories for children and adolescents.
- The management of acute asthma, difficult asthma, asthma in pregnancy and occupational asthma is not covered in the NICE guideline, but guidance is available from BTS/SIGN. Advice on managing acute asthma is also available via the BNF.

> ***A note on NICE's terminology:***
> NICE uses direct instructions in its guidance where advice is expected to be followed. The term '***offer'*** reflects a strong recommendation, usually where there is clear evidence of benefit; ***'consider'*** reflects a recommendation where the evidence of benefit is less certain.

Diagnosis of Asthma

Objective tests and recording of an asthma diagnosis in clinical records

- NICE has produced algorithms summarising guidance on initial clinical assessment, and diagnostic testing for adults and children (5 to 16 years). The NICE guideline emphasises the need for a structured clinical history and examination, together with the use of **objective tests,** which should be done in all people (age 5 and over), if possible. The main tests are **spirometry**, with reversibility testing if indicated, and **FeNO**. If a person is acutely unwell, they should be treated immediately, with objective tests performed if possible or once symptoms are controlled.

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- There are some other tests that may have been used by healthcare professionals when asthma has been suspected (e.g. skin prick tests to aeroallergens; serum total and specific IgE; peripheral blood eosinophil count; exercise challenge tests). NICE advises against their use, although there may be a role for skin prick or specific IgE tests to identify triggers ***after*** a formal diagnosis of asthma. This advice is similar to that from BTS/SIGN.
- In children under 5 it is generally not possible to do objective tests. NICE recommends treating symptoms based on observation and clinical judgement, reviewing regularly and testing when the child reaches 5 (if incapable, try testing every 6 to 12 months.) If a child repeatedly cannot perform these tests and is not responding to treatment, it may be necessary to consider referral for specialist assessment.
- Recording the basis for an asthma diagnosis should be made in a single entry in medical records, alongside the coded diagnostic entry. This is recommended as it is good practice, will aid continuity of care and help assist audits.

Use of Spirometry

- Spirometry is advocated in all people who can perform this test, moving away from the measurement of peak expiratory flow (PEF). This is similar to the establishment several years ago of spirometry testing in primary care to help diagnose chronic obstructive pulmonary disease.
- The recommendations regarding spirometry are:
    - to offer spirometry to all people (age 5 and over) when an asthma diagnosis is being considered.
        - A forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio < 70% (or below the 'lower limit of normal' if this value is available) should be regarded as a positive test, indicating 'obstructive spirometry'.
    - to offer bronchodilator reversibility (BDR) testing to adults (17 and over) with obstructive spirometry (FEV1/FVC ratio < 70%).
        - An improvement in FEV1 of ≥ 12%, together with an increase in volume of ≥ 200 ml, should be regarded as a positive test.
    - to consider BDR testing in 5 to 16 year olds with obstructive spirometry (FEV1/FVC ratio < 70%).
        - An improvement in FEV1 of ≥ 12%

Comment: The BTS/SIGN guideline advice on spirometry is similar but places greater emphasis on 'lower limit of normal'. Concerns have been raised about how this wider use of spirometry will be funded, the training needs, and also the capacity of primary care to take on this extra work.

Use of FeNO tests

Comment: NICE's recommendations on FeNO have caused some controversy, with concerns about the test's validity, source of funding, and lack of experience in primary care. NICE has acknowledged it will take the NHS time to implement these recommendations and that additional infrastructure and training is needed. NICE recommends ***considering*** establishing **asthma diagnostic hubs** to achieve economies of scale and improve the practicality of implementation.

- NICE has previously considered FeNO testing in diagnostic guidance published in 2014.
    - The advice in the latest NICE guideline is to ***offer*** a FeNO test to all adults (17 and over) alongside spirometry if an asthma diagnosis is being considered.
        - For adults, a FeNO level of ≥ 40 ppb should be regarded as a positive test.
        - Levels between 25 to 39 ppb are equivocal and require further investigation.
    - It is noted that a person's current smoking status can lower FeNO levels both acutely and cumulatively but a high level remains useful in supporting a diagnosis of asthma.
    - A FeNO test should be ***considered*** in all children and young people (5 to 16 years) if there is diagnostic uncertainty after initial assessment and where there is either normal spirometry or obstructive spirometry with a negative BDR test.
        - In children, a FeNO level of ≥ 35 ppb should be regarded as a positive test.

Comment: The BTS/SIGN guideline refers to FeNO as potentially useful in probable asthma, but does not give it the same prominence as NICE. It notes there are no research data from primary care populations.

Recommendations on unclear tests or poor symptom control

- If there is still diagnostic uncertainty after an initial assessment and FeNO, spirometry and BDR testing, NICE recommends that peak flow variability should be assessed for 2 to 4 weeks (see the guideline for details and thresholds). A value of more than 20% variability is regarded as a positive test.
- If a person with symptoms suggestive of asthma cannot perform a particular test, the advice is to try to perform at least 2 other objective tests. It may be necessary to diagnose suspected asthma based on symptoms and any positive objective test results that are available.
- A direct bronchial challenge test with histamine or methacholine is an option if uncertainty remains. This test is rarely performed in primary care and referral to a specialist centre may be indicated.
- A diagnosis other than asthma should be considered and referral made for specialist assessment in patients with symptoms suggestive of asthma but where tests remain equivocal or negative.
- Other diagnoses should not be ruled out if symptom control remains poor after treatment, with a recommendation to review the diagnosis after 6 weeks by repeating any abnormal tests and reviewing symptoms.

Pharmacological Management of Asthma

- NICE has produced 3 treatment pathways for the following age groups:
    - adults (aged 17 and over)
    - children and young people (ages 5 to 16)
    - children < 5 years.

  These age categories differ from those used by BTS/SIGN, which are: adults and adolescents >12 years; children 5 to 12 years; children < 5 years. The full NICE guideline indicates that the guideline development committee felt that the new categories provided a better match to clinical trials that have informed the guideline.
- NICE has acknowledged the new clinical pathways will entail a change in practice; however people whose asthma is well controlled on current treatment **should not have their treatment altered purely to follow the guidance**.
- The recognition of 'uncontrolled asthma' is important to guide when to step up (or down) treatment. The NICE guideline uses the following pragmatic thresholds to define uncontrolled asthma:
    - 3 or more days a week with symptoms **or**
    - 3 or more days a week with required use of a short-acting beta$_2$ agonist (SABA) for symptomatic relief **or**
    - 1 or more nights a week with awakening due to asthma.
- NICE uses different ICS dose categories compared with BTS/SIGN, and currently (*see comment below*) makes the following recommendations on how to categorise ICS dose:
    - For **adults** (17 and over), consider budesonide (or equivalent):
        - ≤ 400 µg daily as low dose
        - > 400 to 800 µg as a moderate dose
        - > 800 µg as high dose
    - For **children** (16 and under), consider budesonide (or equivalent):
        - ≤ 200 µg as paediatric low dose
        - > 200 to 400 µg paediatric moderate dose
        - > 400 µg paediatric high dose.

Comment: **Update on ICS dose categorisation**
NICE originally suggested that the tables presented in the full NICE guideline (page 30), which placed ICS drugs into low, medium and high dose categories for the purposes of reviewing the evidence, may also help guide ICS dosage within clinical practice. **This wording has now been removed from the guideline** and we have been advised that NICE is currently working on the production of new ICS dose categorisation tables. When this new information becomes available, we will provide an update via a future KINES publication.

Pharmacological management for adults (17 and over)

Early therapy: SABAs and the introduction of first-line maintenance therapy

- NICE recommends offering of a SABA as reliever therapy to all adults with newly diagnosed asthma. For people with infrequent, short-lived wheeze and normal lung function, consideration may be given to SABA reliever therapy alone.
- Regarding the introduction of maintenance therapy, a low dose ICS should be offered to those with symptoms at presentation that clearly indicate the need for maintenance therapy (for example, asthma-related symptoms 3 times a week or more, or causing waking at night) **or** asthma that is uncontrolled with a SABA alone.

> ***Comment***: The BTS has issued feedback that NICE's recommendations on SABAs and the introduction of ICS maintenance therapy differ from the 2016 update to the BTS/SIGN guideline, with a change in the latter "*making it explicit that patients should not be given SABA alone (except in the few with very occasional short-lived wheeze)*". This change was in response to the National Review of Asthma Deaths, which demonstrated a high number of deaths in people using a SABA alone. However, NICE's recommendations are similar to the advice provided within the **full text** of the BTS/SIGN guideline, which list reasons for introducing ICS that include: use of a SABA ≥ 3 times a week; symptomatic ≥ 3 times a week and waking ≥ 1 night a week. Additional reasons suggested by BTS/SIGN are an asthma attack in the last 2 years requiring oral corticosteroids or using > 1 SABA inhaler in a month.

Further Treatment – LTRAs ahead of LABAs

- If asthma is uncontrolled on low dose ICS, NICE recommends offering an **oral leukotriene receptor antagonist (LTRA) in addition to the ICS,** reviewing the patient's response after 4 to 8 weeks.

> ***Comment***: The above recommendation is a major change from established clinical practice, which had been to step-up treatment by introducing a LABA at this stage. Feedback from BTS indicates there is disagreement with NICE on this matter, commenting that head-to-head comparisons of LABA/ICS *and* LTRA/ICS favour the LABA/ICS for effectiveness in adults, but are inconclusive in children. BTS also cites previous evidence that found a quarter of people commenced on LTRA therapy either switched to or were given LABAs, with none switching from the LABA strategy. Other concerns related to problems with adherence (use of a daily inhaler plus an evening tablet; additional prescription cost for a patient).
>
> That LABA/ICS is more effective was also the conclusion of the evidence review in the full NICE guideline. However, the reason why NICE recommends use of an LTRA is that it is more cost-effective, as generic LTRA plus ICS is inexpensive compared with LABA/ICS inhalers.
>
> BTS has also suggested that failure to obtain asthma control in some people may lead to avoidable acute asthma, and associated costs through emergency attendances and possibly hospital admissions. A December 2017 press release suggests BTS will meet with NICE again shortly to discuss next steps.
>
> Feedback on the guideline from the Primary Care Respiratory Society UK (PCRS-UK) notes that the use of combination inhalers can prevent non-adherence with ICS. PCRS-UK is of the view that given cost is a key consideration for the NHS, unless there is good reason to the contrary, an LTRA should be tried as first-line add-on therapy to ICS. They note the importance of withdrawing the LTRA if it is ineffective, as adding LABA to an LTRA would obviate the cost advantage of this approach. PCRS-UK also suggests that clinicians consider factors such as patient preference, compliance, concomitant diseases (e.g. rhinitis), and exacerbation risk when deciding the best option for a patient, with decisions made after discussion between the clinician and patient.

- If asthma is still uncontrolled on a low dose of ICS with an LTRA, NICE recommend ***offering*** **a LABA in combination with low dose ICS**, and review LTRA treatment (*discuss with the person whether or not to continue LTRA treatment; take into account the degree of response to LTRA treatment.*)
- If control is still not achieved, the advice is as follows:
    - If uncontrolled on a low dose ICS and a LABA, with or without an LTRA, *offer* to change the person's ICS and LABA maintenance therapy to a **Maintenance and Reliever Therapy (MART) regimen with**

a low maintenance ICS dose. (*MART involves use of a combined ICS/fast-acting LABA inhaler used as both daily maintenance therapy and 'as required' for relief of symptoms. Inhalers licensed for MART include Symbicort and its branded generic equivalents, and Fostair.)*

- If uncontrolled on a MART regimen with a low maintenance ICS dose, with or without an LTRA, ***consider*** **increasing the ICS to a moderate maintenance dose** (either continuing a MART regimen or changing to fixed-dose ICS and LABA, with a SABA as reliever therapy).
- If asthma is uncontrolled on a moderate maintenance ICS dose with a LABA (either MART or a fixed-dose regimen), with or without an LTRA, *consider*:
  - increasing the ICS to a high maintenance dose (this should only be offered as part of a fixed-dose regimen, with a SABA used as a reliever therapy) **or**
  - a **trial of an additional drug** (e.g. long-acting muscarinic receptor antagonist or theophylline) **or**
  - seeking advice from a healthcare professional with expertise in asthma.

Comment: The above elements of the NICE guideline are somewhat similar to BTS/SIGN, although the latter advocates MART as an alternative to moderate dose LABA/ICS. Both NICE and BTS/SIGN agree that the evidence for optimal treatment options beyond LABA/ICS combinations is limited.

Pharmacological treatment in children and young people aged 5 to 16

Initial treatment

- NICE's recommendations on initial treatment in children and young people (aged 5 to 16) are similar to that for adults but with paediatric ICS doses.
  - A SABA should be *offered* when asthma is diagnosed. NICE advises there will be some children with mild asthma who can be given a SABA alone. See the guideline for the full details.
  - The next step is to *offer* paediatric low dose ICS as maintenance therapy. If symptoms are uncontrolled with SABA, or there is a clear need for maintenance therapy, an ICS should be offered at the outset.
  - As with adults, if asthma is uncontrolled on a paediatric low dose ICS, an LTRA should be *considered* in addition to the ICS (NB: not all LTRAs are licensed for use in people aged under 18). The response to treatment should be reviewed in 4 to 8 weeks.

Further step-up

- If asthma is uncontrolled on a paediatric low dose ICS plus LTRA, *consider* stopping the LTRA and starting a LABA in combination with the ICS (NB: not all LABA/ICS inhalers are licensed for children).
- If still uncontrolled, *consider* changing to a MART regimen with a paediatric low ICS dose, ensuring that the child/young person is able to understand and comply with the MART regimen.
- As for adults, if asthma is uncontrolled on a MART regimen with paediatric low ICS dose, *consider* increasing the ICS to a paediatric moderate maintenance dose (either continuing on MART or changing to a fixed-dose of an ICS and LABA, with SABA as reliever therapy).
- If still uncontrolled, *consider* seeking advice from a healthcare professional with expertise in asthma and *consider* either: increasing the ICS dose to paediatric high maintenance dose (only as part of a fixed-dose regimen, with a SABA used as a reliever therapy) or a trial of an additional drug (for example, theophylline).

Comment: A caveat is that the MART regimen is not licensed for children under 12. The BTS/SIGN guideline does not make a recommendation on MART for this age group because of the absence of a licence, although there is agreement that there is some evidence to support its use.

A further discrepancy between the guidelines is that BTS/SIGN recommend children under 12 needing a medium dose of ICS should be under the care of a specialist paediatrician.

There are also differences in the ICS dose categories for children:

- NICE refers to paediatric 'high', 'moderate' and 'low' ICS dose categories for all children 16 years and under
- BTS/SIGN doses for children over 12 are considered the same as for adults, whereas for under 12s they are categorised as 'very low', 'low' and 'medium' dose.

Feedback from BTS also pointed out some discrepancies in the relative potencies used by NICE for some ICS drugs, with associated concerns about the potential for over-dosage of ICS. As stated above, we are aware that NICE is updating information on ICS dose categorisation.

Pharmacological treatment in children under 5

An 8-week trial of ICS therapy

- It can be difficult to confirm asthma diagnosis in young children, therefore NICE's recommendations apply to children with 'suspected' asthma. Diagnosis should be confirmed once the child is able to undergo objective tests. Also, many under 5s have recurrent episodes of viral-induced wheeze but will not go on to have chronic asthma.
- The advice from NICE for this age group is:
    - *offer* SABA reliever therapy. This should be used for symptom relief alongside maintenance therapy.
    - ***consider* an 8-week trial of a paediatric moderate dose ICS** where symptoms at presentation clearly indicate the need for maintenance therapy (for example, asthma-related symptoms ≥ 3 times a week or causing waking at night) or symptoms are uncontrolled with SABA alone. After 8 weeks, ICS treatment should be **stopped** and the child's symptoms monitored:
        - if symptoms did not resolve during the trial, review whether an alternative diagnosis is likely
        - if symptoms resolve then reoccur within 4 weeks of stopping, restart ICS at a paediatric low dose
        - if symptoms resolve but reoccur beyond 4 weeks after stopping ICS, repeat the 8-week trial of paediatric moderate dose ICS.
    - If suspected asthma is uncontrolled in children under 5 on paediatric low dose ICS, ***consider* an LTRA** in addition to the ICS (NB. not all LTRAs are licensed in children).
- If uncontrolled on paediatric low dose ICS and an LTRA, stop the LTRA and refer the child to a healthcare professional with expertise in asthma for further investigation and management.

Comment: The advice for this age group is similar to that in the BTS/SIGN guideline, which advises a trial of ICS with the starting dose appropriate to the severity of the disease and careful down-titration to the dose where control is maintained. BTS/SIGN also advises a trial of LTRA with ICS where control is poor. The evidence base for NICE and BTS recommendations, both for ICS use and 'add on' therapy, is very limited, so much of this guidance is based on expert opinion and clinical experience.

Other topics covered by the NICE guideline

The NICE guideline also includes further sections covering:

- **Adherence:** The recommendation is to see the NICE guideline on medicines adherence.
- **Self-management:** For people using a single ICS inhaler, this includes advice to temporarily increase their ICS dose when asthma control deteriorates, which should be outlined in their asthma plan.
    - The recommendation to ***offer*** an increased ICS dose for 7 days to adults, and to ***consider*** an increased dose for 7 days for children ages 5 to 16. Quadrupling of dose may be considered, but should not exceed the maximum dose.
- **Decreasing maintenance therapy**: Consider 'stepping down' maintenance therapy when asthma has been controlled on current therapy for at least 3 months
- Risk stratification
- **Monitoring asthma control:** The Asthma Control Test and Asthma Control Questionnaire are examples suggested for use in adults.
- Please see the NICE guideline for further details.

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