NICE National Institute for Health and Care Excellence

2018 exceptional surveillance of asthma: diagnosis, monitoring and chronic asthma management (NICE guideline NG80)

Surveillance report

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Surveillance decision

We will update the guideline on asthma.

The update will focus on recommendation 1.11.2:

'Within a self-management programme, consider an increased dose of inhaled corticosteroids (ICS) for 7 days for children and young people (aged 5 to 16) who are using an ICS in a single inhaler, when asthma control deteriorates. Clearly outline in the person's asthma action plan how and when to do this, and what to do if symptoms do not improve. When increasing ICS treatment:

- consider quadrupling the regular ICS dose
- do not exceed the maximum licensed daily dose.'

Reasons for the decision

Assessing the evidence

The purpose of this exceptional review was to examine any impact on NICE's guideline on asthma following publication of the Step up yellow zone inhaled corticosteroids to prevent exacerbations (STICS) trial. No additional evidence published since the publication of NICE's guideline on asthma in November 2017 was considered by the exceptional review.

Methods of the new study

The STICS trial is a US, double-blind, multicentre, randomised controlled trial (RCT) of 254 children, aged 5 to 11 years, with mild-to-moderate persistent asthma, and at least 1 asthma exacerbation treated with systemic corticosteroids in the previous year. For 48 weeks, all children received maintenance low-dose ICS (fluticasone propionate 44 micrograms per inhalation, 2 inhalations twice daily). At the early signs of loss of asthma control ('yellow zone'), a low-dose group continued the same dose of ICS, whereas a high-dose group used a 5-fold dose (fluticasone 220 micrograms per inhalation, 2 inhalations twice daily) for 7 days.

Yellow-zone episodes were identified by any of the following: using 2 doses of rescue salbutamol in 6 hours, using 3 doses of rescue salbutamol in 24 hours, or 1 night awakening due to asthma and treated with salbutamol.

The primary outcome was the rate of severe asthma exacerbations treated with systemic

corticosteroids.

Results of the new study

Of the 254 children randomised, 62 did not complete the trial (25 were lost to follow-up or did not wish to continue, 18 had treatment failure, 12 were unable to continue, 5 were dissatisfied with asthma control, and 2 did not have asthma). In total, 94 children in the high-dose group and 98 in the low-dose group completed the final trial visit. The rate of yellow-zone episodes was similar in the high-dose and low-dose groups (2.01 and 1.96 episodes per year respectively; p=0.90).

For the primary outcome, the number of children experiencing at least 1 severe asthma exacerbation during the trial was 38 in the high-dose group (rate 0.48 per year) and 30 in the low-dose group (rate 0.37 per year). The exacerbation rate was not significantly different between the groups (p=0.30).

There was no significant difference between groups for the following secondary outcomes: time to the first exacerbation; rates of emergency department visits, urgent care visits or hospitalisations for asthma; rate of treatment failure; symptom scores; salbutamol use during yellow zones; or adverse events reported by the participants. There were no deaths.

In terms of safety, exposure to inhaled corticosteroids and total corticosteroids during the trial was significantly greater in the high-dose than the low-dose group. The growth rate was numerically lower in the high-dose group (5.43 cm per year) than the low-dose group (5.65 cm per year), but was not significantly different (p=0.06).

An exploratory outcome of mean percentage of days of asthma control was 95% in the high-dose group and 96% in the low-dose group for overall control, dropping to 72% and 74% control respectively during yellow-zone episodes.

Guideline development

One RCT published in 2012, directly relevant to increasing ICS in children and young people during exacerbations, was evaluated during guideline development (though recommendations in this area were considerably influenced by extrapolation from adult data). In the single trial of children and young people examined by the guideline, 197 participants aged 2 to 17 years were randomised to a 12-day treatment protocol for acute asthma exacerbation at doses of ICS that were 2, 4 or 8 times their maintenance ICS dose. The total duration of the trial was unclear.

From a 3-armed comparison of the 3 different multiples of maintenance ICS dose (4-fold versus

2-fold, 8-fold versus 2-fold, and 8-fold versus 4-fold), there was a suggestion of increased benefit with increased dose. Although the effects were not statistically significant and the quality of the evidence was considered very low due to risk of bias and imprecision of the results, the guideline committee felt there were clinically important benefits of 4-fold and 8-fold increases in the dose. The committee also felt that the short-term increase in ICS dose was unlikely to have significant adverse events, and when compared with the potential exposure to the alternative (oral steroids), it would be safer.

The guideline committee also checked for studies in a 2010 Cochrane review of 'Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children'. The Cochrane review included a single RCT in children, but this was excluded from the NICE guideline on asthma because its primary outcomes were lung function parameters rather than patient-centred outcomes such as exacerbations. The Cochrane review was updated in 2016 and included 2 further RCTs in children. One of these did not examine increasing ICS in the way the NICE guideline considered it, and the other did not have any published data. Neither trial was therefore considered by the guideline committee when making its recommendation on increasing ICS. The 2016 Cochrane review excluded the 2012 RCT included by the NICE guideline because it did not have a comparator arm in which ICS dose was stable. The Cochrane review also looked for ongoing trials and found only the STICS trial (on which this exceptional review is based). The Cochrane review concluded that current evidence does not support increasing the dose of ICS as part of a self-initiated action plan to treat exacerbations.

A cost-effectiveness analysis was not conducted for the NICE guideline on asthma, and no economic evaluations were identified. However, the cost implications of self-administered increases in ICS were considered, leading to the decision that self-administered dose increases would mean fewer unscheduled GP appointments, which would offset the increased medication costs.

Views of topic experts

In this exceptional review, we engaged with topic experts who were members of the guideline committee involved in the development of NICE guideline NG80, and also a topic expert not involved in the guideline but with expertise in paediatric respiratory medicine.

Topic experts stated that the data added to what was available during guideline development, and that there are now 2 studies showing lack of a significant benefit of increasing ICS for exacerbations in children and young people.

Experts had some reservations about the evidence. A topic expert noted that children in the new study probably had very mild asthma, based on the high level of asthma control (even during yellow-zone episodes), and lower than expected exacerbation rates. They questioned whether the trial reflected the reality of how a population with such mild disease would be managed.

There was also some uncertainty among experts about the clinical significance of the adverse effect of increasing ICS on growth. They expressed caution in interpreting the result, noting that the difference in growth was fairly small and not statistically significant, it was measured over a single year, and that the numerically higher (though not statistically significant) severe exacerbation rate among the high-dose group may have affected growth.

However overall, experts stated that the study provides important new data that should be taken into consideration by the guideline.

Impact

Recommendation 1.11.2 currently states:

'Within a self-management programme, consider an increased dose of ICS for 7 days for children and young people (aged 5 to 16) who are using an ICS in a single inhaler, when asthma control deteriorates. Clearly outline in the person's asthma action plan how and when to do this, and what to do if symptoms do not improve. When increasing ICS treatment:

- consider quadrupling the regular ICS dose
- do not exceed the maximum licensed daily dose.'

This recommendation was based partly on 1 study in children and young people of very low quality (which showed a slight but insignificant dose response effect), and also extrapolation from adult data from several studies.

The new evidence showed that a 5-fold increase in regular ICS dose at early signs of loss of asthma control does not reduce the rate of severe asthma exacerbations in children with mild-to-moderate persistent asthma. There is also a suggestion of adverse effects on growth.

Strengths of the STICS trial are that it is larger than the single study in children examined by NICE guideline NG80, and includes fewer treatment arms, therefore more individuals were exposed to each of the interventions. There are also some limitations. Particularly, that the level of withdrawal of participants was higher than the investigators expected, and the exacerbation rates observed

were lower than expected. This meant that the trial did not achieve the desired power of 90%; however, the steering committee allowed the trial to proceed with an anticipated power of 80%.

Following consideration of the results published in the STICS trial, as well as topic expert feedback, the new evidence may have an impact on the current recommendation to consider increasing (such as quadrupling) the regular ICS dose within a self-management programme for children and young people when asthma control deteriorates.

Other clinical areas

This exceptional surveillance review did not search for new evidence relating to other clinical areas in the guideline.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

See how we made the decision for further information.

How we made the decision

Exceptionally, significant new evidence may mean an update of a guideline is agreed before the next scheduled check of the need for an update. The evidence might be a single piece of evidence, an accumulation of evidence or other published NICE guidance.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence

This surveillance report provides an overview of 1 study published since the end of the search period for the guideline (September 2016). The results of this study were considered in detail to determine if there is an impact on guideline recommendations.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline.

Views of stakeholders

Because this was an exceptional surveillance review, we did not consult on the decision.

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