



Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Asthma or recurrent wheeze: preventing exacerbations in pre-school children using inhaled corticosteroids

A meta-analysis of 15 studies found that, compared with placebo, daily inhaled corticosteroids (ICS) prevented severe exacerbations requiring systemic corticosteroids in pre-school children with asthma or recurrent wheeze. When subgroups of children were considered, no statistically significant benefits were seen in children without a diagnosis of persistent asthma (for example those with mixed wheezing phenotype or unclear diagnosis). Meta-analysis of 5 studies found that intermittent ICS statistically significantly reduced the risk of severe exacerbations in children with intermittent asthma or viral-triggered wheeze. However, when 3 studies at high risk of bias were excluded, the difference was no longer significant. Health care professionals should continue to follow BTS/SIGN guidance on managing asthma. The NICE guideline on asthma management (which includes the pharmacological management of chronic asthma) is expected to be published in June 2017.

Overview and current advice

The [British Thoracic Society and Scottish Intercollegiate Guidelines Network \(BTS/SIGN\) guideline on the management of asthma](#) (2016: [NICE accredited](#)) includes advice on diagnosing asthma in adults and children. Diagnosis is based on the recognition of a characteristic pattern of respiratory symptoms, signs and test results, and the absence of any alternative explanation for these. Almost all children with asthma have intermittent cough, wheeze or exercise induced symptoms, but only about a quarter of children with these symptoms have asthma.

The BTS/SIGN guideline states that in some children, particularly pre-school children, there is insufficient evidence at the first consultation to make a firm diagnosis of asthma, but no features to suggest an alternative diagnosis. Furthermore, there are several possible approaches to reaching a diagnosis in these children, depending on the frequency and severity of symptoms. These approaches include watchful waiting with review, and monitored initiation of treatment.

If a monitored treatment approach is selected, the choice of treatment depends on the severity and frequency of symptoms. The BTS/SIGN guideline recommends that treatment should be monitored for 6 to 8 weeks and if there is clear evidence of clinical improvement, the child should be regarded as having asthma and treatment should be continued. The guideline adds that it may be appropriate to consider a trial of withdrawal of treatment at a later stage.

In children with mild intermittent wheeze and other respiratory symptoms that occur only with viral infections, BTS/SIGN states that it is often reasonable to give no maintenance treatment and to plan a

review after an interval agreed with the parents or carers. Many children under 5 years old with recurrent episodes of viral wheeze do not go on to have chronic atopic asthma and the majority do not require treatment with regular inhaled corticosteroids (ICS).

For children under the age of 5 years who have been diagnosed with asthma, BTS/SIGN recommends that regular 'preventer' treatment with ICS should be considered for children with any of the following features: using inhaled beta₂ agonists 3 times a week or more, symptomatic 3 times a week or more, or waking 1 night a week.

NICE guidelines on [asthma: diagnosis and monitoring](#) (publication date to be confirmed) and [asthma management](#) (which includes the pharmacological management of chronic asthma; expected publication June 2017) are currently underway. The NICE pathway on [asthma](#) brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.

New evidence

A [systematic review and meta-analysis](#) of 22 [randomised controlled trials](#) (RCTs) in children aged 6 years and under with asthma or recurrent wheeze (classed as 2 or more episodes in the previous year) aimed to assess the evidence on the effectiveness of daily ICS, intermittent ICS and montelukast as treatment strategies for preventing severe exacerbations¹. Studies which only included children under the age of 2 years were excluded due to a potential overlap between asthma and bronchiolitis.

The RCTs included several different ICS delivery systems and different ICS at a range of doses. The primary outcome for the meta-analysis was severe exacerbations, which were defined as severe wheezing exacerbations requiring systemic corticosteroids.

Daily ICS compared with placebo (15 RCTs)

[Meta-analysis](#) of the 15 RCTs that compared daily ICS with placebo (n=3278, age range 4 to 72 months; study duration 6 weeks to 5 years) showed a [statistically significant](#) reduction in severe exacerbations with daily ICS compared with placebo (12.9% compared with 24.0% respectively, risk ratio [RR] 0.70, 95% [confidence interval](#) [CI] 0.61 to 0.79, $p < 0.001$). The authors noted that this translates into a [number needed to treat](#) (NNT) of 9 children who would need to be treated with daily ICS to prevent 1 child having a severe exacerbation (NNT 9, 95% CI 7 to 12). However, treatment duration varied widely from 6 weeks to 5 years, so this value is difficult to interpret.

In a subgroup analysis in children with persistent asthma^a (8/15 RCTs, n=2505), there was a statistically significant reduction in severe exacerbations with daily ICS compared with placebo (8.7% compared with 18% respectively, RR 0.56, 95% CI 0.46 to 0.70, $p < 0.001$). However, there was no statistically significant difference in severe exacerbations with daily ICS compared with placebo in the subgroup analysis of children with mixed wheezing phenotype or unclear diagnosis (6/15 RCTs, n=732; 30.8% compared with 40.1% respectively, RR 0.86, 95% CI 0.73 to 1.02, $p = 0.08$). There were also no significant differences between daily ICS and placebo in 1 small study of children with intermittent asthma^b or viral-triggered wheeze (n=41; percentages not reported, RR 1.05, 95% CI 0.16 to 6.76).

Intermittent ICS compared with placebo (6 RCTs)

Meta-analysis of the 6 RCTs (5 in children with intermittent asthma or viral-triggered wheeze) that compared intermittent ICS with placebo (n=588, age range 12 to 72 months; study duration 12 to 52 weeks) showed a statistically significant reduction in severe exacerbations with intermittent ICS compared with placebo (24.8% compared with 41.6% respectively, RR 0.64; 95% CI 0.51 to 0.81, $p < 0.001$). However, when 3 studies with a high risk of bias were excluded from this analysis,

comparison of intermittent ICS with placebo was no longer statistically significant for this outcome (RR 0.61, 95% CI 0.35 to 1.07, p value not reported).

Other comparisons

Meta-analysis of the 2 RCTs that compared daily ICS with intermittent ICS (n=498, study durations 12 weeks and 52 weeks) showed no statistically significant difference between the 2 interventions for severe exacerbations (25.7% vs 28.1% respectively, RR 0.91, 95% CI 0.71 to 1.18, p=0.49). Both of these studies were in children with intermittent asthma or viral-triggered wheeze and used high doses of ICS. The 2 RCTs which compared ICS with montelukast were both assessed to be at high risk of bias.

^a Children with symptoms on more than 2 days a week, waking once or twice a month, using short acting beta₂ agonists on more than 2 days a week, or minor limitations with normal activity.

^b Intermittent asthma was defined as symptoms on 2 days or less each week, no night-time awakenings, short acting beta₂ agonists on 2 days or less each week, or no limitation with normal activity.

Commentary

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This US based meta-analysis looked at the effects of daily ICS, intermittent ICS and montelukast for preventing severe exacerbations (defined as exacerbations requiring systemic corticosteroids) in children aged 6 years and under with asthma or recurrent wheeze. Unfortunately, there are no studies comparing montelukast with placebo and only 2 studies at high risk of bias comparing montelukast and ICS. Therefore, this review does not add to the evidence for montelukast in pre-school children with asthma, or help to determine the role of montelukast in pre-school children with recurrent wheeze.

Data from 15 studies that assessed daily ICS show a 30% relative risk reduction in severe exacerbations (NNT 9) compared to placebo. The evidence to support the use of daily ICS was found to be strongest in children with persistent asthma; daily ICS did not significantly reduce severe exacerbations in pre-school children without a diagnosis of persistent asthma. The findings support recommendations in [BTS/SIGN guidelines](#) and [Global initiative for asthma \(GINA\) guidelines](#).

Five studies of children with intermittent asthma or viral-triggered wheeze suggest that intermittent ICS reduce the relative risk of severe exacerbations by 35% compared with placebo, but this analysis included 3 studies that were at high risk of bias. In all 5 studies, ICS were used at high doses, which BTS/SIGN guidance recommends should only be used after referral of the child to secondary care. The GINA guidelines do suggest that episodic ICS may be considered for children with frequent viral-induced wheezing and episodic asthma but a trial of regular ICS should be undertaken first.

The conclusions of this meta-analysis on the use of daily ICS or intermittent ICS should be tempered by the fact that some of the patients in the viral-triggered wheezing groups had features of atopic disease, leading to the possibility that they actually had asthma. Analysis of subgroups where the phenotype was mixed or uncertain showed no benefit of daily ICS or intermittent ICS, compared with placebo.

In summary, this meta-analysis confirms the benefit of prescribing regular daily ICS in pre-school children with persistent asthma. In children where the diagnosis is uncertain then a 6 to 8 week trial of medium dose might be indicated. Insufficient safety data is presented to ascertain the role of high dose intermittent ICS in these children.

Declaration of interests:

Dr Kevin Gruffydd-Jones has spoken on behalf of and acted as a consultant to GSK, Astra Zeneca, Teva, Chiesi, Pfizer, NAPP, Mundipharma and Boehringer Ingelheim.

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References

1. Kaiser SV, Huynh T, Bacharier LB et al. (2016) [Preventing exacerbations in pre-schoolers with recurrent wheeze: a meta-analysis](#) Pediatrics 137 DOI: 10.1542/peds.2015-4496

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