# Effect of increasing glucocorticoids on asthma exacerbations

Two multicentre, randomised trials assessed whether severe asthma exacerbations could be prevented by substantially increasing the daily dose of inhaled glucocorticoids at the first symptoms of loss of asthma control (the "yellow zone"). The results indicated that this common practice might not be helpful in preventing exacerbations in children but might be beneficial to some adults, although with increased adverse events.

In a double-blind study, Daniel Jackson (University of Wisconsin School of Medicine and Public Health, Madison, WI, USA) and colleagues enrolled 254 children (aged 5 to 11 years) with mild-to-moderate asthma who had had one or more asthma exacerbations treated with systemic glucocorticoids during the preceding year. All participants received low-dose inhaled glucocorticoids (fluticasone propionate, 44 µg per inhalation, two inhalations two times a day) for 4 weeks (adherence >75%) before, as well as throughout, the 48 week study. Additionally, participants were randomly assigned 1:1 to receive either low-dose or high-dose therapy (fluticasone propionate, 220 µg per inhalation, two inhalations twice a day) for 1 week at the first symptoms of loss of asthma control.

Results indicated that quintupling the inhaled glucocorticoid dose did not reduce the asthma exacerbation rate: the high-dose group had 0·48 (95% CI 0·33–0·70) exacerbations per year compared with 0·37 (0·25–0·55) for the low-dose group (relative rate 1·3, 95% CI 0·8–2·1, p=0·30). During the trial, children in the high-dose group had a 16% higher total exposure to glucocorticoids than that of children in the low-dose group, as well as a growth rate that was 0·23 cm per year lower.

Jackson summarised, "We found that for a child with persistent asthma taking low doses of inhaled corticosteroids, significantly increasing their dose of inhaled corticosteroids when they start to have symptoms of loss of asthma control does not prevent the development of severe asthma exacerbations." He added, "The study confirms the efficacy of low doses of inhaled steroids when taken on a regular basis to reduce risk for exacerbations, but also highlights the need to identify effective 'yellow zone' strategies for exacerbation prevention in children."

In an unblinded, pragmatic study, Tricia McKeever (University of Nottingham, Nottingham, UK) and colleagues enrolled 1922 participants (aged ≥16 years) with asthma, who had one or more asthma exacerbations treated with systemic glucocorticoids during the preceding year and were receiving any dose of inhaled glucocorticoids. All patients were given an identical self-management plan except for the action to be taken at the first signs of asthma control loss: participants were randomly assigned to either continue their normal dose of inhaled glucocorticoids or quadruple their dose of inhaled glucocorticoids temporarily.

The primary outcome analysis showed that, after 1 year, 420 (45%) participants in the quadrupling group had an asthma exacerbation compared with 484 (52%) in the non-quadrupling group (hazard ratio for time to first exacerbation 0.81, 95%CI 0·71–0·92, p=0·002). 50% of the quadrupling group and 42% of the non-quadrupling group had good adherence to their self-management plan at the time the symptoms of loss of asthma control appeared. The rate of drug-related side effects was higher in the quadrupling group, including oral candidiasis and dysphonia (36 occurrences in the quadrupling group *vs* nine in the non-quadrupling group).

Timothy Harrison (University of Nottingham, Nottingham, UK), senior author of the study in adults, said, "In one of the largest non-commercial asthma studies ever performed in the UK we have shown that severe asthma exacerbations can be reduced by about 20% by using a self-management plan that includes a four-fold increase in inhaled steroid dose at the first signs of asthma deteriorating. The plan was simple and evaluated under real-world conditions, giving it excellent external validity."

Chitra Dinakar (Stanford University, Stanford, CA, USA) commented, "Both are excellent publications, and highlight the important clinical problem of how to empower patients at home to overcome their asthma exacerbations so that they don't have to take systemic steroids or seek urgent medical care. The paediatric study had rigorous methodology and clinically relevant outcomes, but there are still some gaps suggesting that there may be children who need to be studied to see how they would respond; e.g., 43% of patients were excluded during the run-in phase… The strengths of the adult study are that it is more a real-life, patient-driven study that we can all relate to. On the other hand, patients are on other concomitant medications, and may not perceive their symptoms that well or start treatment late, affecting outcomes."

Jay Portnoy (Children's Mercy Kansas City, Kansas City, MO, USA) commented on the two reports, "In general, you shouldn't change practice based on one study." Portnoy said of the paediatric study, "Parents need an action plan to follow when their child is in the 'yellow zone' so that they're not too fast to move to oral corticosteroids and antibiotics. The study does not prove that there is harm to increasing inhaled steroids; the suppressed growth is probably from the oral steroids." He said of the adult study, "Increasing inhaled steroid was effective; more research is necessary to tease out what is going on. This is an intriguing study that raises a lot of questions."

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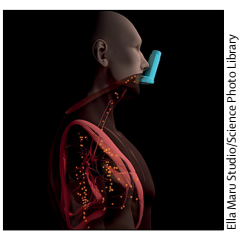

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For the **study in children** see *N Engl J Med* 2018; **378:** 891–901

For the **study in adults** see *N Engl J Med* 2018; **378:** 902–910