

Quadrupling or quintupling inhaled corticosteroid doses to prevent asthma exacerbations: the jury's still out

STUDY 1

Study design

Double blind, randomised controlled trial.

Study question

Setting: UK.

Patients: 1871 adults and adolescents (mean age 57 years) who had a diagnosis of asthma, were being treated with inhaled corticosteroid (ICS) and had had at least one exacerbation requiring systemic glucocorticoid treatment in the preceding 12 months.

Intervention: Quadrupling dose of ICS at the early loss of asthma control (vs usual dose of ICS; both groups increased bronchodilator as required).

Outcomes: Rates of asthma exacerbation requiring treatment with systemic glucocorticoids or an unscheduled healthcare visit.

Main results

The study's main results are summarised in [table 1](#).

Conclusion

Temporary quadrupling of ICS dose at the early signs of loss of asthma control results in a lower rate of severe asthma exacerbations than when ICS dose is not quadrupled.

Abstracted from: McKeever T, Mortimer K, Wilson A, *et al.* Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. *New England Journal of Medicine* 2018; 378(10), 902–910.

STUDY 2

Study design

Double-blind, randomised controlled trial.

Study question

Setting: USA.

Patients: 254 children aged 5–11 who had a diagnosis of asthma, were being treated with inhaled corticosteroid (ICS) and had had at least one exacerbation requiring systemic glucocorticoid treatment in the preceding 12 months.

Intervention: Quintupling dose of ICS at the early loss of asthma control (vs usual dose of ICS; both groups increased bronchodilator as required).

Outcomes: Rates of asthma exacerbation requiring treatment with systemic glucocorticoids.

Secondary outcomes: Number of emergency care visits; linear growth.

Main results

The study's main results are summarised in [table 2](#).

Conclusion

Quintupling of ICS at the early signs of loss of asthma control does not reduce the rates of severe exacerbations and is associated with a decrease in linear growth.

Abstracted from: Jackson DJ, Bacharier LB, Mauger DT, *et al.* Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. *New England Journal of Medicine* 2018;378(10), 891–901.

Table 1 Summary of asthma exacerbations in patients treated with quadrupled dose of ICS vs usual-dose ICS during the 12-month trial period

	Quadrupling group	Control group	Adjusted HR (95% CI)
Patients with severe asthma exacerbation (%)	45	52	0.81 (0.71 to 0.92)
			Incidence rate ratio (95% CI)
Mean number of courses of systemic corticosteroid per patient	0.5	0.61	0.82 (0.7 to 0.96)
Mean number of unscheduled healthcare visits per patient	0.73	0.84	0.86 (0.75 to 0.99)

ICS, inhaled corticosteroid.

Table 2 Summary of asthma exacerbations in patients treated with quintupled dose of ICS vs usual-dose ICS during the 12-month trial period

	Quintupling group (95% CI)	Group (95% CI)	Treatment effect (95% CI)
Mean number of severe exacerbations* per patient	0.48 (0.33 to 0.70)	0.37 (0.25 to 0.55)	1.3 (0.8 to 2.1)
Mean number of emergency department or urgent care visits per patient	0.64 (0.42 to 0.96)	0.47 (0.31 to 0.72)	0.86 (0.75 to 0.99)
Growth (cm/year)	5.43 (5.26 to 5.60)	5.65 (5.48 to 5.81)	−0.23 (−0.47 to 0.01)

*Severe exacerbation defined as requiring systemic corticosteroid treatment.

ICS, inhaled corticosteroid.

A 2016 Cochrane review¹ concluded that there was no benefit in increasing inhaled corticosteroid (ICS) doses at the initial stages of deterioration in asthma control. However, the authors note a lack of robust evidence and wide CIs for several outcomes, meaning potential benefit cannot be excluded. These two studies go some way to improving the evidence base which was lacking in 2016.

The study in adults appeared to show some benefit to increasing ICS dose, while the study in children did not, even though both had similar inclusion criteria with the exception of age. Additionally, children treated with increased ICS exhibited decreased linear growth. Both studies, however, generated results which had wide CIs and were close to the line of no effect. Paediatricians are unlikely to change their practice on the basis of these results.

Across both studies, there was only one death and no asthma-related deaths. The overall rates of severe asthma exacerbation and hospitalisation were relatively low, so it may be that, as a result of strict inclusion/exclusion criteria, overall asthma control was better in these studies than in the real-world population.

These studies do not provide robust evidence that increased ICS doses improve asthma control. All study patients in both groups, however, received a written asthma action plan detailing how patients could assess their asthma control and what to do in the event of any deterioration. There is strong evidence that the use of a written asthma action plan is associated with improved asthma-related morbidity and mortality.^{2,3} However, half of children with asthma in the USA had not received a written plan as recently as 2013.⁴

It is too soon to say whether or not patients should be increasing their ICS dose at the early signs of exacerbation, but it remains essential that patients and carers are provided with written asthma action plans and are aware of how to recognise that their control is deteriorating.

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