

Quadrupling inhaled glucocorticoid dose for deteriorating asthma control reduced severe exacerbations

Clinical impact ratings: ★★★★★☆ ★★★★★☆ ★★★★★☆

Question

Does a self-management plan for deteriorating asthma control that includes quadrupling the dose of inhaled glucocorticoids (ICSs) reduce exacerbations compared with a plan without dose escalation?

Methods

Design: Pragmatic randomized controlled trial. ISRCTN15441965.

Allocation: Concealed.*

Blinding: Blinded* (trial management group, statistician, and chief investigator).

Follow-up period: 12 months.

Setting: Primary and secondary care in the UK.

Patients: 1922 adults and adolescents ≥ 16 years of age (mean age 57, 68% women) who had asthma treated with any dose of ICSs, with or without add-on medication, and ≥ 1 exacerbation requiring systemic glucocorticoids in the past 12 months. Exclusion criteria included maintenance and relief treatment with a combination glucocorticoid plus long-acting bronchodilator inhaler; maintenance with oral glucocorticoids (OCSs); or history akin to smoking-related chronic obstructive pulmonary disease.

Intervention: When asthma control deteriorated (≥ 1 of needing bronchodilator more than usual, difficulty sleeping due to asthma, or peak flow $< 80\%$ of normal level), use of a self-management plan with guidance to increase bronchodilator medication and quadruple the dose of ICSs until symptom resolution, peak flow returned to normal, or 14 days ($n = 965$) or guidance to increase bronchodilator medication without ICS dose escalation ($n = 957$).

Outcomes: Primary outcome was severe asthma exacerbation (systemic glucocorticoid use or unscheduled health care visit for asthma). Secondary outcomes included components of the primary outcome.

Patient follow-up: 97% (intention-to-treat analysis).

Main results

1114 patients (58%) had deteriorating asthma control. The time to first exacerbation was later for the glucocorticoid-quadrupling group than the nonescalation group (hazard ratio 0.81, 95% CI 0.71 to 0.92). Other results are in the Table. Over 12 months, the estimated mean total dose of ICSs was 385 mg in the quadrupling

McKeever T, Mortimer K, Wilson A, et al. **Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations.** *N Engl J Med.* 2018; 378:902-10.

group and 328 mg in the nonescalation group; mean total dose of systemic glucocorticoids was 121 mg and 151 mg, respectively.

Conclusion

A self-management plan for deteriorating asthma control that quadrupled the dose of inhaled glucocorticoids reduced exacerbations compared with a plan without dose escalation.

*See Glossary.

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Commentary

Guidelines recommend OCSs for 5 to 7 days for acute asthma (1). This treatment, although effective, is associated with adverse effects. As a result, other options have been considered. Transiently increasing the dose of ICSs is an attractive alternative: It is easy to deliver, potentially has fewer systemic effects, and is more directly delivered to the target tissue.

The trial by McKeever and colleagues is the largest to date exploring the effects of increasing ICSs during the initial stages of acute asthma. This pragmatic, randomized, open-label trial showed that temporarily quadrupling the dose of ICSs to treat early worsening asthma symptoms reduced severe exacerbations and the need for systemic corticosteroids compared with standard care. These findings are consistent with those of a previous study that showed reduced need for OCSs with ICS quadrupling compared with placebo (21% vs 50%, relative risk reduction 57%, CI 22 to 76) (2).

Risk for serious adverse events, including pneumonia, was low in both groups. However, nonserious adverse events—mostly oral candidiasis and dysphonia—were more frequent in the quadrupling group. Although the results of this trial further support temporary quadrupling of ICSs during acute asthma, the reduction in severe exacerbations was modest. Additionally, the median dose of ICSs was 0.8 mg/d, and quadrupling this dose was equivalent to 3.2 mg/d of beclomethasone. Because absorbed ICSs from the lung do not undergo first-pass metabolism, this dose might have the same systemic effects as OCSs. Therefore, it is difficult to determine a definitive risk-benefit ratio for patients on medium- or high-dose ICSs until future studies provide additional evidence.

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Self-management plan for deteriorating asthma control that includes quadrupling dose of inhaled glucocorticoids vs plan without dose escalation†

Outcomes	Event rates		At 12 mo	
	Glucocorticoid quadrupling	No dose escalation	RRR (95% CI)	NNT (CI)
Severe exacerbations‡	45%	52%	13% (5 to 20)	15 (10 to 39)
Use of systemic glucocorticoids	33%	40%	17% (7 to 26)	15 (10 to 36)
Unscheduled health care visit	41%	47%	14% (5 to 22)	16 (10 to 43)

†Abbreviations defined in Glossary. RRR, NNT, and CI calculated from control event rates and risk ratios in article appendix.

‡Composite of systemic glucocorticoid use or unscheduled health care visit for asthma.

References

1. **Global Initiative for Asthma.** Global strategy for asthma management and prevention, 2018. <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/> (accessed 19 Apr 18).
2. **Oborne J, Mortimer K, Hubbard RB, et al.** Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. *Am J Respir Crit Care Med.* 2009;180:598-602.