Article:
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Declarative Title: Quadrupling or quintupling inhaled corticosteroid doses to prevent asthma exacerbations – the jury's still out.

STUDY 1

STUDY DESIGN

Design: Double blind randomised control trial

STUDY QUESTION

Setting: United Kingdom

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 1 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.

	Quadrupling Group	Control Group	Adjusted Hazard Ratio (95% CI)
% of patients with severe asthma exacerbation	45%	52%	0.81 (0.71 to 0.92)
			Incidence Rate Ratio (95% CI)
Mean no of courses of systematic corticosteroid per patient	0.5	0.61	0.82 (0.7 to 0.96)
Mean no of unscheduled healthcare visits per patient	0.73	0.84	0.86 (0.75 to 0.99)

Table 1: Summary of asthma exacerbations for patients treated with quadrupled dose ICS vs usual dose ICS during the 12 month trial period. CI=confidence interval

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., Walker, S., Brightling, C., Skeggs, A., Pavord, I., Price, D., Duley, L., Thomas, M. and Bradshaw, L., 2018. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. New England Journal of Medicine, 378(10), pp.902-910.

STUDY 2

STUDY DESIGN
Design: Double blind randomised control trial

STUDY QUESTION
Setting: United States

Patients: 254 children aged 5-11 who had a diagnosis of asthma, were being treated with inhaled corticosteroid and had had at least 1 exacerbation requiring systemic glucocorticoid treatment in the preceding 12 months.

Intervention: Quintupling dose of inhaled corticosteroid at the early loss of asthma control (vs usual dose of inhaled corticosteroid; 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.

	Quintupling Group (95% CI)	Group (95% CI)	Treatment Effect (95% CI)
Mean no 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 no 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)

Table 2: Summary of asthma exacerbations for patients treated with quintupled dose ICS vs usual dose ICS during the 12 month trial period. *severe exacerbation defined as requiring systemic corticosteroid treatment. CI=confidence interval

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 decrease in linear growth.

ABSTRACTED FROM: Jackson, D.J., Bacharier, L.B., Mauger, D.T., Boehmer, S., Beigelman, A., Chmiel, J.F., Fitzpatrick, A.M., Gaffin, J.M., Morgan, W.J., Peters, S.P. and Phipatanakul, W., 2018. Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. New England Journal of Medicine, 378(10), pp.891-901.

Both studies abstracted by Dr Amanda J Friend, Department of Paediatrics, Leeds General Infirmary, Leeds, UK

A 2016 Cochrane review[1] concluded that there was no benefit in increasing ICS doses at the initial stages of deterioration in asthma control. However, they note a lack of robust evidence and wide confidence intervals 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 of adults appeared to show some benefit to increasing ICS dose, whilst the study in children didn't, 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 confidence intervals 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. 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 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 United States 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.

Commentary by Dr Amanda J Friend, Department of Paediatrics, Leeds General Infirmary, Leeds, UK

References:

1. Kew, K.M., Quinn, M., Quon, B.S. and Ducharme, F.M.,2016. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. The Cochrane Library

2. Beydon, N. and Delclaux, C., 2017. Digital action plan for asthma exacerbations (PANAME). Revue des maladies respiratoires, 34(9), pp.1026-1033.

3. Akhter, L.S., Monkman, J.L., Vang, G. and Pfeiffer, J.,2017. Improving Asthma Control through Asthma Action Plans: A Quality Improvement Project at a Midwest Community Clinic. Journal of community health nursing, 34(3), pp.136-146.

4. Simon, A.E. and Akinbami, L.J., 2016. Asthma action plan receipt among children with asthma 2–17 years of age, United States, 2002–2013. The Journal of pediatrics, 171,pp.283-289.