Evidence Table 17. Managing Exacerbations: Increasing the Dose of Inhaled Corticosteroids

Abbreviations used in table:

CI	**confidence interval**	**ITT**	**intent-to-treat analysis**
$FEF_{25\%–75\%}$	**forced expiration flow between 25% and 75% of vital capacity**	**LABA**	**long-acting beta-agonist**
FEV_1	**forced expiratory volume in 1 sec.**	**LD**	**low dose**
HD	**high dose**	**OS**	**oral steroid**
ICS	**inhaled corticosteroid**	**PEF**	**peak expiratory flow**
		PEFR	**peak expiratory flow rate**

*** indicates primary outcome**

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Citation (Sponsor)	Study Design	Study Population		
		Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if reported)
Garrett et al. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. Arch Dis Child 1998;79(1):12–17. (Otago Division of the New Zealand Asthma Society)	Randomized, double-blind, placebo-controlled, crossover trial	28 (18) Recruited from pediatric outpatient department, department of respiratory medicine, and a local general practice	**Recruited Sample** Age 6–14 yr, mean = 9.3 yr Gender 68% male, 32% female Ethnicity Not reported **Analysis Sample** Age 6–14 yr, mean = 8.2 yr Gender 67% male, 33% female	Mild to moderate severity On inhaled steroid prophylaxis not exceeding 800 mcg/day **Recruited Sample** PEFR % pred., mean = 100 FEV_1% pred., mean = 99 FVB % pred., mean = 110 $FEF_{25–75}$ % pred., 89 **Analysis Sample** PEFR % pred., mean = 99 FEV_1 % pred., mean = 99 FVB % pred., mean = 108 $FEF_{25–75}$ % pred., 93
Foresi et al. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group. Chest 2000:117(2):440–446. (Astra Farmaceutici, Italy)	Multicenter, randomized, double-blind, parallel-group study (14 outpatient clinics)	213 (191 completed study; 209 in intent-to-treat (ITT) analysis)	Age Mean = 38.5 yr Gender 47% male, 53% female Ethnicity Not reported Smoking 70% nonsmokers, 22% ex-smokers, 8% smokers	Moderate asthma Duration of asthma: 28%<5 yr, 22%5–10 yr, 50%>10 yr FEV_1 % pred. mean = 74 PEF % pred. = 75 41% taking salmeterol, 17% theophylline

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FitzGerald et al. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. Thorax 2004;59(7):550–556. (Astra Zeneca Canada Inc.)	Multisite, randomized, double-blind, placebo-controlled parallel-group trial (university affiliated teaching hospitals)	290 (98; analysis used "all patients treated" approach)	Age Mean = 32.2 yr Gender 29% male, 72% female Ethnicity Not reported Smoking 86% nonsmokers	Mean dose of budesonide 635 mcg FEV_1 mean = 2.8 PEF mean = 422.9 L/min Mean days from recent exacerbation to visit 1 = 130.6 Stable dose of inhaled corticosteroid (ICS) (<1200 mcg/day of beclomethasone or equivalent twice daily) for 1 month before visit 1
Harrison et al. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomized controlled trial. Lancet 2004;363(9405):271–275. (NHS Executive, UK)	Randomized controlled trial (recruited from local general practices and asthma research register)	390 (ITT; 207 for per protocol analysis)	Age ≥16 yr, mean = 49 yr Gender 33% male, 67% female Ethnicity Not reported Smoking 61% never smoked, 36% ex-smokers, 3% smokers	Mean ICS dose, 710 mcg 82% on low dose (LD) to moderate dose and 18% on high dose (HD) FEV_1 , mean = 2.4 L FEV_1 % pred., mean 80 PEFR, mean 384 L/min Symptom score (range 0–7), mean 0.5 35% on long-acting beta-agonist 55% took oral corticosteroids, 42% doubled inhaled corticosteroids, and 2% did both in previous 12 months to treat or prevent asthma exacerbation
Rice-McDonald et al. Doubling daily inhaled corticosteroid dose is ineffective in mild to moderately severe attacks of asthma in adults. Intern Med J 2005;35(12):693–698. (Asthma Foundation of Queensland)	Randomized, double-blind, placebo-controlled (double-dummy), triple crossover trial	35 (22)	Age 35–64 yr, median 46.5 yr Gender 41% male, 59% female Ethnicity Not reported	FEV_1 , median 2.15 L FEV_1 % pred., median 73; 36.4% were >80%; 31.8% were 60–80%, 31.8% were <60%

Citation (Sponsor)	Study Characteristics			Findings		
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Severity/ Admissions	Safety
Garrett et al. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. Arch Dis Child 1998;79(1):12–17. (Otago Division of the New Zealand Asthma Society)	**Purpose/Objective:** To determine the effect of an increased dose of inhaled steroids on acute exacerbations of asthma in children, within the context of an asthma self-management plan			Mean morning and mean evening PEFR were similar for steroid and placebo in the two weeks following an exacerbation: AM PEFR days 1–3, p=0.31; days 4–10, p=0.51; days 11–14, p=0.48. PM PEFR days 1–3, p=0.61; days 4–10, p=0.41; days 11–14, p=0.13. There was no difference between treatments for any of the spirometric parameters measured.	There was no difference between treatments for any of the symptom scores, except for days 11–14 in the activities score (0.06 vs. 0.24, p=0.05) that favored placebo.	Two children required oral steroids when study inhaler contained steroid. No children were hospitalized during the study.
	Sequence 1 Placebo then beclomethasone **Sequence 2** Beclomethasone then placebo	The dose of beclomethasone varied across children but was equivalent to the child's daily maintenance dose.	6 months or until 4 exacerbations; 2-week run-in period Children continued with usual maintenance therapy. Child received 3-zone action plan and when entry into "orange zone" occurred, child used study inhaler in addition to maintenance ICS for 3 days. Only those with pairs of exacerbations (n=18) were analyzed.			

Citation (Sponsor)	Study Characteristics			Findings		
	Treatment	Dose	Duration of Active Treatment; Duration of Postintervention/ Off-Treatment Followup	Lung Function	Severity/ Admissions	Safety
Foresi et al. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group. Chest 2000:117(2): 440–446. (Astra Farmaceutici, Italy)	**Purpose/Objective:** To compare the effect of prolonged treatment with a low dose of inhaled budesonide in controlling symptoms and maintaining optimal pulmonary function, and ascertain whether exacerbations could be treated by early intervention with a short-term increase in daily dose of inhaled budesonide			PEF was higher in HD group vs. LD + budesonide ($p<0.05$) and vs. LD + placebo ($p <0.05$) after 6th month.	*There was no difference between groups in number of days with wheeze, cough, and shortness of breath. The majority of patients recorded no exacerbations: 84% in HD, 82% in LD + budesonide, 68% in LD. There was significance between HD and LD ($p <0.04$) with IIT analysis and $p <0.015$ for per-protocol analysis. There was significance between LD + budesonide vs. LD ($p <0.025$) with per-protocol analysis.	
	Arm 1 HD budesonide + placebo (n=67)	400 mcg bid	6 months following 4-week run-in during which patients inhaled budesonide 800 mcg bid Inhaled $beta_2$-agonists allowed on as-needed basis; treatment with LABA or theophyllines kept constant			
	Arm 2 LD budesonide + budesonide (n=67)	100 mcg bid + 200 mcg qid				
	Arm 3 LD budesonide + placebo (n=75)	100 mcg bid				

Citation (Sponsor)	Study Characteristics			Findings		
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FitzGerald et al. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. Thorax 2004;59(7):550–556. (Astra Zeneca Canada Inc.)	**Purpose/Objective:** To investigate whether doubling the dose of maintenance inhaled budesonide early in an asthma exacerbation prevents worsening and the need for systemic corticosteroid				*40% MD and 41% DD with treatment failure, p=0.94 Mean number of exacerbations = 6 of 35 in MD vs. 5 of 34 in DD, p=0.92 Patients with ICS <400 mcg/day were less likely to have treatment failure vs. those receiving ICS dose >400 mcg/day (28% vs. 50%).	
	Arm 1 Maintenance dose (MD) (n=148; 52 treated) **Arm 2** Double dose (DD) (n=142; 46 treated)	Maintenance inhaler + inhaler with placebo for 2/day use Maintenance inhaler + inhaler with budesonide to double dose of ICS at time of exacerbation	Patients with asthma exacerbation during the study period (6 months) who were stable at the end of the 14-day additional treatment course were followed for a 3-month surveillance period. Terbutaline sulphate inhaler as rescue medication, theophylline, anticholinergics, and nasal steroids allowed throughout			

Citation (Sponsor)	Study Characteristics			Findings		
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Harrison et al. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. Lancet 2004;363(9405): 271–275. (NHS Executive, UK)	**Purpose/Objective:** To investigate whether doubling the dose of inhaled corticosteroids when asthma control starts to deteriorate reduces the number of patients needing prednisolone, and to establish the effect on the severity and duration of the subsequent exacerbation			There was a small reduction in mean maximum fall in peak flow between active and placebo (mean diff. –10 L/min, 95% confidence interval (CI) –21 to 0.8, p=0.07). There was no difference in lowest peak flow recorded. There was no difference in time for peak flow to return to baseline for active vs. placebo (6.8 days vs. 7.0 days).	*11% of active and 12% of placebo group started prednisolone (risk ratio 0.95, 95% CI 0.55 to 1.64, p=0.80). Of those who started study inhaler, 17% of active group and 23% of placebo group started prednisolone (risk ratio 0.80, 95% CI 0.45 to 1.4, p=0.53). In low- to moderate-dose group, 8% of active group and 10% of placebo group started prednisolone (risk ratio 0.8, 95% CI 0.4 to 1.6, p=0.66). In per-protocol analysis, 12% of active group and 22% of placebo group started prednisolone (risk ratio 0.63, 95% CI 0.31 to 1.27, p=0.27).	
	Arm 1 Active study inhaler (n=192; 175 completed; 110 started study inhaler) **Arm 2** Placebo study inhaler (n=198; 178 completed; 97 started study inhaler)	Active and placebo study inhalers matched patient's type of inhaler; active inhaler also matched patient's regular ICS and dose. Participants were to use study inhaler for 14 days in addition to usual treatment when peak flow or symptoms deteriorated.	Up to 12 months; 2-week run-in period Participants continued usual treatment throughout the study and received a 10-day course of prednisolone (30 mg/day) to be taken if asthma control deteriorated to the point they would usually start oral corticosteroids or if peak flow fell by 40% from mean run-in value.			

Citation (Sponsor)	Study Characteristics			Findings		
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Rice-McDonald et al. Doubling daily inhaled corticosteroid dose is ineffective in mild to moderately severe attacks of asthma in adults. Intern Med J 2005;35(12): 693–698. (Asthma Foundation of Queensland)	**Purpose/Objective:** To examine the comparative effectiveness and side effects of doubling ICS (fluticasone propionate) versus two other treatment strategies: (i) as required rescue short acting (SA) beta-agonist while continuing usual ICS dose; and (ii) as required rescue SA beta-agonist while continuing usual ICS dose accompanied by oral steroid (OS; dexamethasone)			Only treatment with OS improved PEF by a significant and clinically relevant amount (p=0.006). Median PEF at endpoint as a percentage of run-in best was 78.3% for placebo, 77.9% for double ICS, and 90.5% for OS.	*There were treatment failures for 62% receiving placebo, 58% receiving doubled ICS, and 25% receiving OS. Failure was lower for OS vs. placebo (p=0.02), with no difference between ICS and placebo (p=0.66) or OS and ICS (p=0.07). When doubling ICS, treatment failure was more common if fluticasone dose was <2000 mcg vs. >2000 mcg. With OS, treatment failure was more common with increased age (p=0.01) and presence of upper respiratory tract infection (p=0.04).	Side effects were more common for OS (52.6%) than with ICS (42.1%) or placebo (19.1%). Most common side effects with OS were mood change (36.8%), insomnia (31.6%), and change in appetite (26.3%) and these were more frequent than when doubling ICS (5.3%, 5.3%, and 10.5%, respectively).
	Placebo Arm Placebo inhaler for 14 days and placebo OS for 7 days (placebo are) (n=21 completed arm) **Double ICS Arm** Double daily ICS dose for 14 days and placebo OS for 7 days (n=19 completed arm) **OS Arm** Placebo ICS for 14 days and oral steroid for 7 days (n=19 completed)	All were treated with as required rescue SABA and usual ICS dose. Dexamethasone dose set at 0.1 mg/kg/day rounded to nearest 2 mg using a 4-mg strength tablet administered daily	Endpoint was assessed at 7 days if no treatment failure or at time of treatment failure, in the event of failure. Participants allowed a 4-week run-in period and 4 week washout period after any exacerbation, whether either treatment or rescue prednisolone was administered.			