

Supplement Table 1 Summary of the characteristics of included studies

Trials	Location	Study design	Medication/dose and usage	Concurrent treatment	Duration (weeks)	Number of Randomized/Completed patients		Inclusion criteria		Concurrent disease	Major exclusions
						Intervention group	Control group	Asthma diagnosis	GERD Diagnosis		
Ford 1994	UK	Crossover	Omeprazole 20 mg, qd	ICS 80%, ipratropium 10%	4	Total: 11/10		Doctor's diagnosis; reversibility PEFR after bronchodilator use: $\geq 15\%$; nocturnal asthma attack	Abnormal pH in 24-h pH monitoring; upper gastrointestinal endoscopy; history of esophagitis	Not stated	Not specified
Meier 1994	America	Crossover	Omeprazole 20 mg, bid	Asthma medications (lack of type), theophylline 11/15	6	Total: 15/15		ATS; reversibility of FEV ₁ and/ or PEF after bronchodilator use: $>15\%$	Abnormal pH in 24-h pH monitoring; manometry; esophagogastroduodenoscopy; acid-perfusion (Bernstein) test	Not stated	≤ 18 years old; pregnancy, female unwilling to use birth contraception; unable to give informed consent
Teichtahl 1996	Australia	Crossover	Omeprazole 40 mg, qd	Other asthma medications; $\beta 2A$	4	Total: 25/20		Doctor's diagnosis; positive HIT; diurnal variation of PEFR $\geq 20\%$; reversibility of FEV ₁ and/ or PEF after bronchodilator use: $>15\%$	Abnormal pH in 24-h pH monitoring; endoscopy	Not stated	Other significant respiratory disease; respiratory tract infection; significant systemic, esophageal stricture
Boeree 1998	The Netherlands	Parallel	Omeprazole 40 mg, bid	ICS 0.4 mg/day used in all	12	18/16	18/14	Doctor's diagnosis; FEV ₁ >1.25 L, PC20 <2 mg/mL	Abnormal pH in 24-h pH monitoring, increased GER was defined as $>4\%$ of 24 h registration, or $>3\%$ during the supine position	COPD	Upper and/or lower respiratory tract infection, other concomitant lung diseases
Levin 1998	America	Crossover	Omeprazole 20 mg, qd	Inhaled β -agonists used in all	8	total: 11/9		Doctor's diagnosis; $\geq 15\%$ reversibility in FEV ₁ after bronchodilator treatment; asthma medication used daily	Symptoms of heartburn or regurgitation at least once weekly without therapy; manometry, ambulatory 24-h esophageal pH monitoring	Not stated	COPD, URTI, prior gastroesophageal surgery, acute PUD, use of omeprazole or URTI within previous 30 days
Kiljander 1999	Finland	Crossover	Omeprazole 40 mg, qd	$\beta 2A$ 91%; ICS 89%	8	total: 57/52		Doctor's diagnosis; ATS	24-h pH monitoring and manometry	Not stated	Not specified
Littner 2005	multi-center, North America	Parallel	Lansoprazole 30 mg, bid	ICS, stable doses of asthma medications for at least 4 wks	24	99/85	108/88	Doctor's diagnosis; FEV ₁ pred $> 50\%$ and $< 85\%$; $\geq 12\%$ improvement in FEV ₁ (in liters) after the inhalation of 180 ug of albuterol; five or more nocturnal asthma awakenings and receiving stable doses of asthma medications within previous 4 wks	Investigator judgement based on symptomatic acid reflux and acid-suppressive therapy; 24-h esophageal pH monitoring	Not stated	Smoking; receiving ipratropium bromide, immunotherapy; URTI; uncontrolled medical condition; receiving PPI within 14 days
Størdal 2005	Norway	Parallel	Omeprazole 20 mg, qd	ICS: Int n=17, Cont n=17; long acting bronchodilators: Int 10, Cont 12	12	19/18	19/18	Doctor's diagnosis; at least two episodes of asthma symptoms requiring medication within previous six months	24-h pH monitoring; A reflux index ≥ 5.0 was considered abnormal	Not stated	Previously known or treated GERD
Kiljander 2006	GERD+/NOC+ (Kiljander-1) Europe, North America, South America	Parallel	Esomeprazole 40 mg, qd	ICS: 98.6%; LABAs: 49.8%	16	112/105	107/105	FEV ₁ % pred: 50 to 80%, $\geq 12\%$ (and ≥ 0.20 L) reversibility; PEF pred $< 80\%$; symptom of nighttime awakening with related respiratory symptoms; or PEF	Heartburn ≥ 2 times/wk; acid regurgitation \geq once /wk within previous 3 month. erosive esophagitis or Barrett's esophagus (without dysplasia) documented in the previous	Not stated	Smoking; esophageal or gastric surgery; glucocorticosteroids < 30 days; erosive esophagitis ≤ 16 wks and PPI use < 14 days before enrollment;
		Parallel	Esomeprazole 40 mg, bid	ICS: 97.7%; LABAs: 34%	16	174/174	176/171				

(Kiljander-2)								overnight variability $\geq 15\%$	12 months; abnormal 24-h esophageal pH	recurrent moderate or severe GERD symptoms	
dos Santos-2007	Brazil	Parallel	Pantoprazole 40 mg, qd	long-acting β_2 -agonists (%): Int 45%, Cont 64%; oral corticoids: Int 9%, Cont 18%	12	total: 44 (Int n=22, Cont n=22)/35		Asthmatic clinical history and symptoms for at least two months; airflow obstruction (FEV_1/FVC) < 90% of predicted; the methacholine bronchoprovocation test (+), obstruction reversibility: $FEV_1 > 200$ mL and 7% of predicted	24-h esophageal pH monitoring; manometry	Not stated	Smoking; receiving PPI and H-2 receptor blocker; systemic arterial hypertension
Susanto-2008	Indonesia	Crossover	Esomeprazole 40 mg, qd	inhaled budesonide 400 μ g bid, salbutamol 100 mg/puff	8	18/16	18/16	GINA 2002	Endoscopy and or esophageal histopathologic examination; typical GERD symptoms	Not stated	Not specified
Mastronarde-2009	Multicenter, North America	Parallel	Esomeprazole 40 mg, bid	ICS in all	24	61 /61	62 /62	Doctor's diagnosis; positive methacholine challenge test; 12% increase in FEV_1 after bronchodilator treatment	24-h pH monitoring, mean % time with pH < 4 (range): total >5.8%, upright >8.2%, supine <3.5%	Not stated	Smoking; $FEV_1\%$ pred <50%; surgery; acid-suppression treatment
Kiljander-2010	Multicenter, Europe, North America, South America	Parallel	Esomeprazole 40 mg, qd/bid	ICS and LABA in all	26	40 mg, qd: 313/273; 40 mg, bid: 320/272	328/283	Doctor's diagnosis; ATS	The validated Reflux Disease Questionnaire, esophageal 24-h pH monitoring	Not stated	Alarm symptoms presented, smoking, esophageal or gastric surgery, Barrett esophagus
Holbrook 2012	America	Parallel	Lansoprazole, children <30 kg: 15 mg/d; children ≥ 30 kg: 30 mg/d	ICS in all	24	29 /29	20 /20	Doctor's diagnosis; $\geq 12\%$ in FEV_1 after bronchodilator treatment; $PC20 \leq 16$ mg/mL; positive exercise bronchoprovocation test	Ambulatory esophageal pH monitoring: time of pH <4 in 6- to 11-year-old for $\leq 6\%$, in 12- to 17-year-old for $\leq 4\%$	Not stated	Receiving PPI or other reflux medications; anti-reflux surgery or trachea-esophageal fistula repair; $FEV_1\%$ pred <60%

Abbreviations: LABA, long-acting β_2 -agonists, FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity; $PC20$, provocative concentration of methacholine bromide causing a $\geq 20\%$ fall in forced expiratory volume in 1 second; β_2A , inhaled β_2 -agonists, ICS, inhaled corticosteroid; mPEF, morning peak expiratory flow; PEF, morning peak expiratory flow; pred, predicted; PUD, peptic ulcer disease; URTI, upper respiratory tract infection; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GINA: Global Initiative for Asthma; ATS: American Thoracic Society; Int, intervention; Cont, control; wks, weeks; qd, once daily; bid, twice daily; PPI, proton pump inhibitor, NOC, nocturnal respiratory symptoms; SD, standard deviation; HIT histamine bronchoprovocation test; NA, not available