Guideline topic: Pharmacological management of asthma
Evidence table 4.21: Aspirin intolerant asthma

Author	Year	Study type	Quality rating	Population	Outomes measured	Effect size	Confidence intervals / p values	Comments
Adults								
Dahlen[1]	1998	Randomised, double-blind placebo-controlled, cross-over study 6 week study of zileuton vs. placebo	++	40 AIA mean age 44 yrs 28 females and 12 males Mean FEV1 2.5L 38/40 on inh. Corticosteroids (mean dose 1030 mg/day) and 35? On oral steroids	1] Increase in FEV1 at 4h and 6 weeks vs placebo 2] Urinary (LTE4 3] Nasal symptoms 4] beta2-agonist use 5] PD20 LTD4	1] 7.5% at 4 hr 0.19L at 6 weeks 2] 36% reduction 3] reduced 4] reduced 5] unchanged	P<0.01 P <0.01 P< 0.01 P<0.05 P <0.05 NS	Despite the fact theat zileuton treatment achieved only a 36% reduction in leukotiene synthesis, zileuton treatment improved FEV1 and PEF acutely and over 6 weeks. In addition, this treatment was associated with an improvement in sense of smell and rhinorheoa. Bronchoconstriction caused by LTD4 inhalation was unaffected.
Robuschi[2]	1997	Randomised, double-blind, placebo-controlled, cross-over study. Single	+	10 AIA ages 20-65 (mean 46) yr FEV1> 70% pred. (mean 80%	1] Fall FEV1 over 195 minutes post aspirin inh.	1] Placebo - 42% Nedocromil - 18%	1] vs placebo p<0.001 both treatments	In this small study 4 mgs odium nedocromil and 10 mg sodium chromoglycate

		dose nedocromil or chromoglycate or placebo 30 minutes before aspirin challenge		On 200-2000 mg inh. Corticosteroids	2] Increase Straw over 195 minutes post aspirin inh.	Chromoglycate - 20% 2] Placebo - 143 Nedocromil - 79 Chromoglycate - 69	ns between active treatments 2] vs placebo p< 0.01 both treatments ns between active treatments	were equally effective in attenuating aspirin-induced bronchoconstriction following a known inhalation of aspirin in AIA on inh. corticosteroids.
Szczeklik[3]	1998	Randomised, double-blind placebo-controlled, cross-over study. Single 50mg inhaled dose of salmeterol prior to inhaled aspirin challenge.	+	10 AIA aged 34 - 64 years. 7 females and 4 males. Mean FEV1 x .5L (89% pred.) 9/10 on inh. Corticosteroids (mean dose 960mg/day) 6 on oral steroids (mean dose 6.3mg/day)	1] PD 20 aspirin 2] Urinary (LTE4) post-aspsirin 3] Aspirin-induced bronchoconstriction 4] Urinary (PGD-M) post aspirin	1] Increased from 8.3 mg to 68.5mg 2] Aspirin-induced increase prevented by salmeterol 3 Prevented by salmeterol 4] Aspirin-induced increase prevented by salmeterol	P = 0.02 P<0.05 Not given P=0.008	This small trial studies the effect of a single dose of inhaled salmeterol 50mg inh on inhalational aspirin challenge in known AIA. Pre-treatment with salmeterol effectively attenuated aspirin-induced bronchoconstriction and leukotriene synthesis in aspirin sensitive asthmatics.
Szczeklik[4]	1995	2 phases, 1] Randomised double-blind placebo controlled cross-over trial into effect of pre-treatment with GPE2, salbutamol or misopropstol on aspirin induced brochoconstriction	+	Phase 1] 11 AIA, non-smoker FEV1>70% pred. 5/11 on 5-15 mg/day oral predn. Phase 2] 12 AIA mean age 42 yrs, FEV1 75% pred. 10/12 on oral	1] Aspirin PC20 30 mins after treatment (mg lysine aspirin) 2] More prolonged bronchodilation after salbutamol in ATA than AIA 3] PGE2 caused bronchodilation which was more marked and	Placebo - 1.8 PGE2, - 5.4 Salbutamol - 8.4 Misoprostol - 4.0	P vs placebo = 0.04 = 0.06 - 0.25	Inhaled PGE 2 and inhaled salbutamol inhibited aspirin induced bronchoconstriction to a similar degree, Oral misoprostol attenuated aspirin induced bronchoconstriction to a lesser degree. Inhaled PGE2 causes caugh and

		in AIA 2] Randomised, cross-over, double-blind, placebo controlled trial into bronchial response to inhaled PGE2 PGE1, + salbutamol or placebo over 120 minutes in AIA vs aspirin tolerant asthma (ATA)		pred. (mean 8mg) 10 ATA mean age 38 yres, FEV1 78% pred. 2/10 on oral predn. (mean 5mg) All patients showed > 15% reversibility to beta2-agonists	persistent in ATA than AUAI 3] PGE1 caused bronchodilation followed by bronchoconstriction in ATA but had no effect on FEV1 in AIA			retrosternal pain which subsides during treatment but can be dose limiting. The study on the effect of these agents on bronchial tone shows that both PGE2 and salbutamol cause less marked and less persistent bronchdilation in AIA than ATA. The poor bronchodilatory effect of PGE2 in AIA suggests that the attenuation of aspirin-induced bronchoconstriction by PGE2 is not medicated purely airway muscle tone.
Wasiak[5]	1999	Randomised double-blind, placebo-controlled cross-over 6 weeks oval misoprostol	++	17 Adults aged 26-68 years 13 females and 4 males. EV1 83% pred. 15% reversibility to beta2 agonist 15/17 on inh. Corticosteroid	1] 1m and pm PEFR, FEV1/FVC, asthma symptom scores, beta2-agonist use, preipheral blood eosinophils 2] Reduction in rhinorrhoea score 3] Defecation symptom score	1] All nil 2] from 1.0 to 0.36 points/day 3] Minimal increase	All ns P = 0.03 P = 0.004	Oral misoprostol, an oral PGE1 analogue, a either 800 to 1600 mg per day failed to improve asthma symptoms or asthma control in this small study of aspirin sensitive asthmatics.

1. Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. Am J Respir Crit Care Med 1998;157(4 Pt 1):1187-94.

2. Robuschi M, Gambaro G, Sestini P, Pieroni MG, Refini RM, Vaghi A, et al. Attenuation of aspirin-induced bronchoconstriction by sodium cromoglycate and nedocromil sodium. Am J Respir Crit Care Med 1997;155(4):1461-4.
3. Szczeklik A, Dworski R, Mastalerz L, Prokop A, Sheller JR, Nizankowska E, et al. Salmeterol prevents aspirin-induced attacks of asthma and interferes with eicosanoid metabolism. Am J Respir Crit Care Med 1998;158(4):1168-72.
4. Szczeklik A, Nizankowska E, Serafin A, Dyczek A, Duplaga M, Musial J. Autoimmune phenomena in bronchial asthma with special reference to aspirin intolerance. Am J Respir Crit Care Med 1995;152(6 Pt 1):1753-6.
5. Wasiak W, Szmidt M. A six week double blind, placebo controlled, crossover study of the effect of misoprostol in the treatment of aspirin sensitive asthma. Thorax 1999;54(10):900-4.