Aspirin-Exacerbated Respiratory Disease

2017. 9. 23.

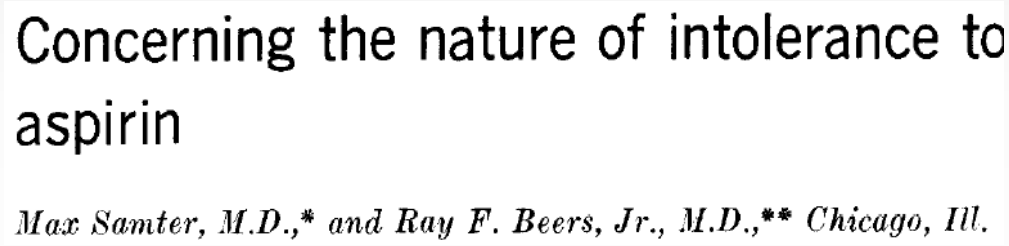
고려대학교 안암병원
김병근

KOREA UNIVERSITY MEDICAL CENTER

Adverse reaction to aspirin

- Mitteilungübereinen Fall von Nebenwirkung des Aspirin
  - “Communication of a case of the side effects of aspirin”

- Samter disease



Concerning the nature of intolerance to aspirin

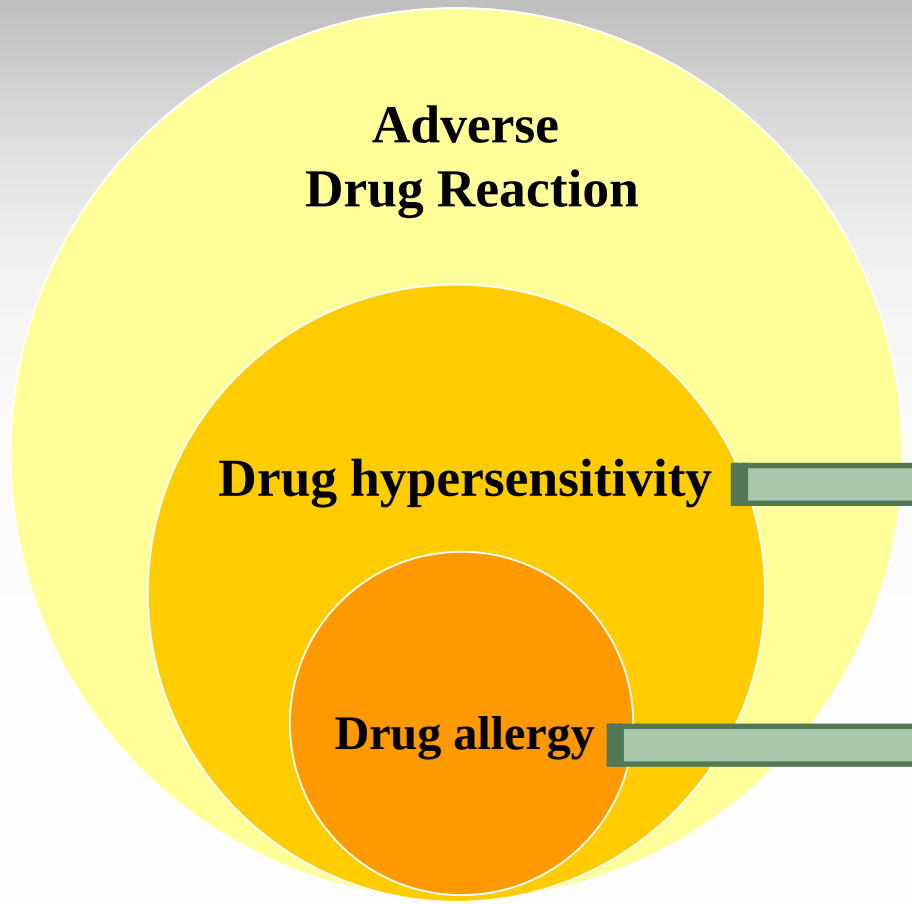
Max Samter, M.D., and Ray F. Beers, Jr., M.D.,** Chicago, Ill.*

- Samter’s triad (=Triad asthma, ASA triad)
  - Asthma
  - Nasal polyp
  - Aspirin intolerance

Dtsch Med Wochenschr 1902;28:416.

J Allergy 1967;40:281-93.

Concept of drug hypersensitivity



- Non-allergic hypersensitivity
- Pseudoallergy
- Idiosyncrasy
- Intolerance

ADRs including non-immunologic reactions (e.g. aspirin) to susceptible host

ADRs by immunologic reactions e.g. Type I (IgE), Type IV (T cell)

NSAID hypersensitivity and AERD

Table 1 Classification of hypersensitivity reactions to ASA and other nonsteroidal anti-inflammatory drugs (NSAIDs) (Modified from [3])

Timing of reaction	Clinical manifestation	Type of reaction	Underlying disease	Putative mechanism
Acute (immediate to several hours after exposure)	Rhinitis/asthma	Cross-reactive	Asthma/rhinosinusitis/ nasal polyps	Inhibition of COX-1
	Urticaria/angioedema	Cross-reactive	Chronic urticaria	Inhibition of COX-1
	Urticaria/angioedema	Multiple NSAIDs-induced	No underlying chronic disease (in some patients, the reaction to NSAIDs may precede development of chronic urticaria)	Unknown Presumably related to COX-1 inhibition
	Urticaria/angioedema/ anaphylaxis	Single drug-induced	Atopy Food allergy Drug allergy	IgE-mediated

KOREA UNIVERSITY MEDICAL CENTER

Allergy 2011;66:818–829

Aspirin-Exacerbated Respiratory Disease

- Typical ASA triad
  - Chronic rhinosinusitis complicated by polyp formation
  - Moderate to severe bronchial asthma
  - Hypersensitivity reactions in response to aspirin and other NSAIDs
    - Acute dyspnea accompanied by nasal symptoms

- Aspirin-exacerbated respiratory disease (AERD)
  - Main mechanism: NSAID-induced acute respiratory reaction
  - Development of chronic intractable inflammation
    - Both lower and upper airway mucosa
    - Underlies chronicity of disease
    - Even in the absence of exposure to NSAID

Prevalence of AERD

- Varies depends on diagnostic method and patient factors
  - Widely underdiagnosed
  - Diverse diagnostic method: history, provocation test (oral / nasal / bronchial)
- Among Asthma
  - 4.3% ~ 12% in various populations
  - 7% of adults with asthma, 14% of patients with severe asthma
  - 21.1% for adult, 5% for children in systematic review of 15 studies
- 30 ~ 40% among CRS and/or NP

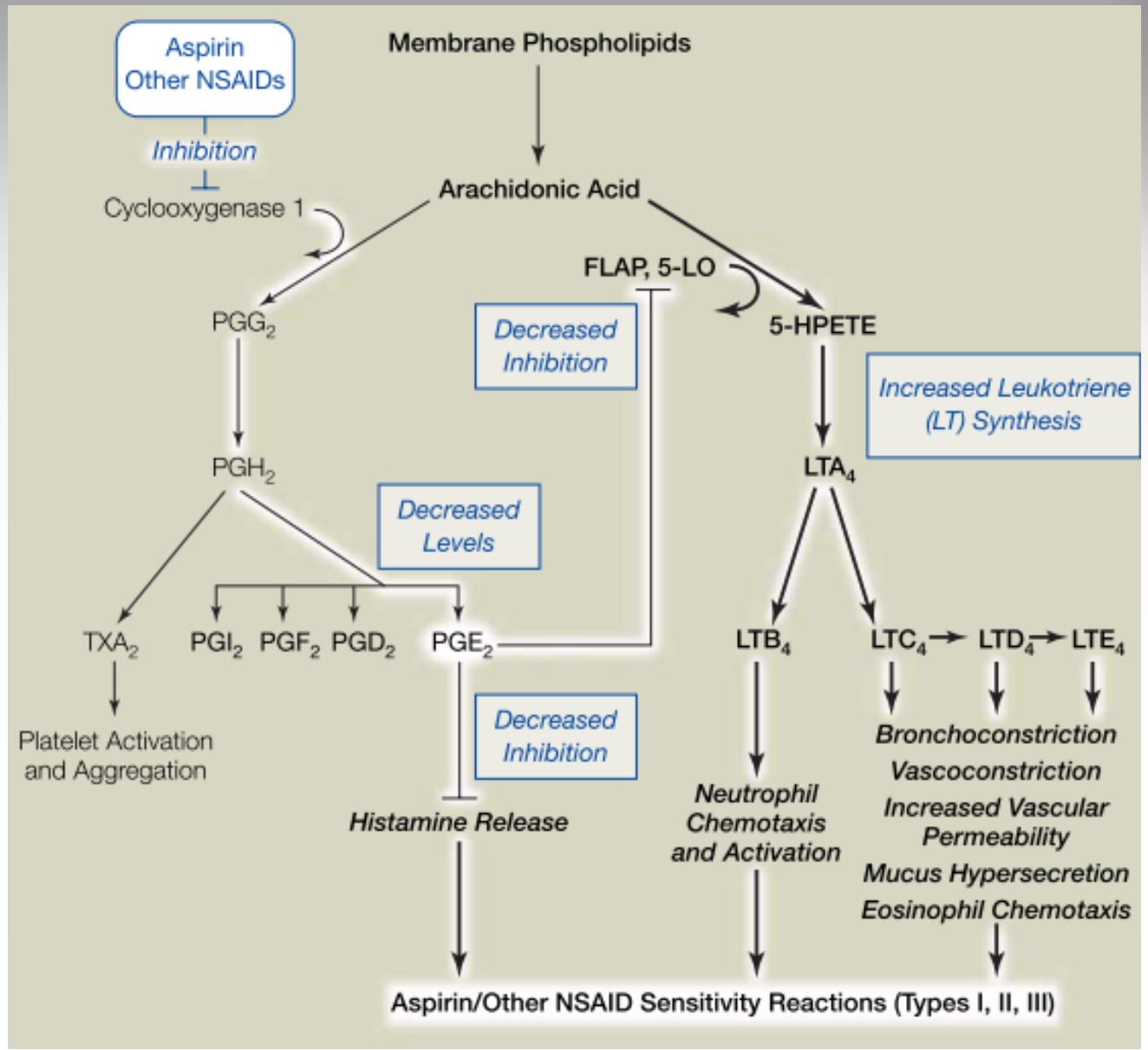
Allergy 2003;58:1064-6.
Thorax 2002;57:569-74.
NEJM 2016;374;5
BMJ 2004;328:434.
Am J Rhinol 1987;1:119-26

Pathogenesis of AERD

- Cyclooxygenase pathway
  - Dysregulated function of 5-Lipoxygenase
  - Cysteinyl-leukotrienes → bronchoconstriction, vascular leak, and mucous secretion
  - Amplify eosinophilic inflammation and mast cell activation

- Mediators involved in AERD
  - Both the blood and sinonasal tissues
  - Nasal and bronchial secretion

Cyclooxygenase pathway



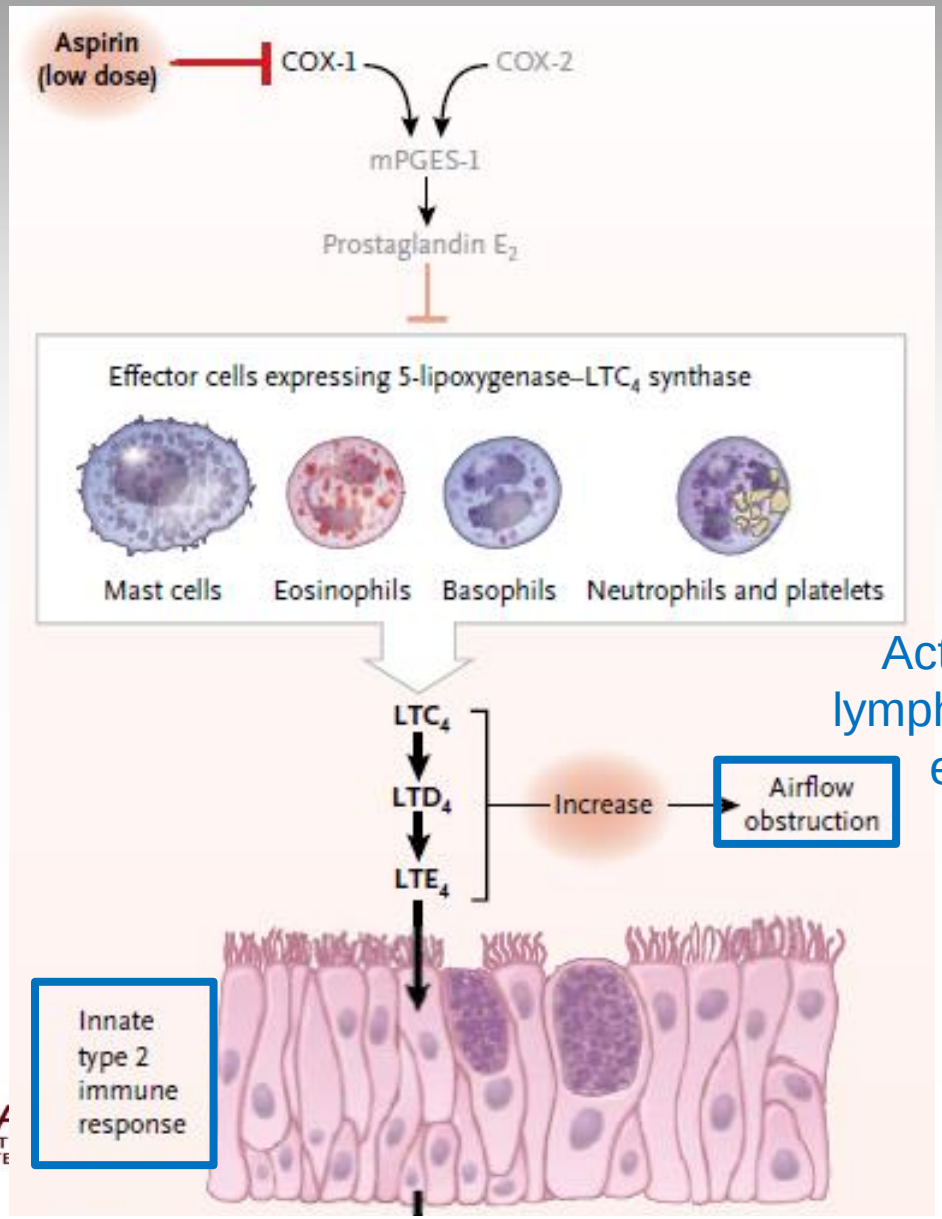
- Local deficiency in PGE_2 synthesis in NP epithelial cells and bronchial fibroblasts
- Inhalation of PGE_2 or oral misoprostol → prevents ASA-induced bronchoconstriction

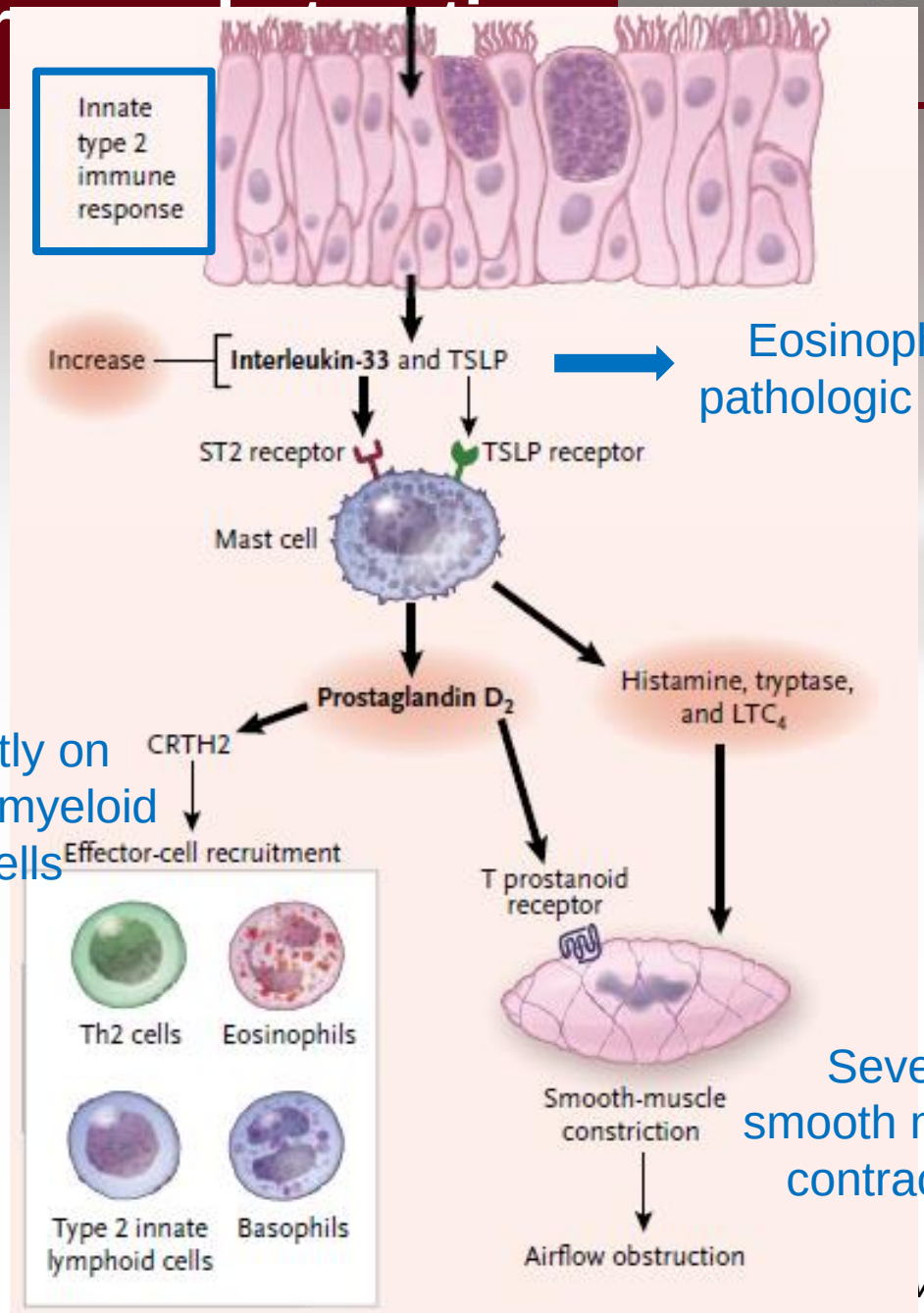
JAMA 2004;292;24:3017-3023

Am J Respir Crit Care Med 2000;161:391-8.

Am J Respir Crit Care Med 1996;153:567-71

Cyclooxygenase pathway and air





Eosinophil-rich pathologic changes

Acting directly on lymphoid and myeloid effector cells

Severe smooth muscle contraction

Mediators involving AERD

- Release of both mast cell and and eosinophil-specific mediators
  - Tryptase, histamine, PGD_2
  - Eosinophil cationic protein (ECP)

- After aspirin challenge
  - Release of cysteinyl leukotrienes into nasal secretions or induced sputum
  - PGD_2 metabolite from mast cell increase in urine after aspirin challenge
  - Mobilization of eosinophil progenitor cells from BM

Chronic airway inflammation in AERD

- Eosinophilic inflammation
  - High degree of tissue eosinophilia and increased ECP release
  - Increased IL-5, GM-CSF, RANTES

    → Increased eosinophil activation and survival

- Mast cell activation
  - Increased mast cell density in NP mucosa
  - Greater number of CD45RO+ T cell

Chronic inflammation in the airways

- Arachidonic acid metabolites
  - PGE2 deficiency / overproductions of Leukotriene

Abnormality	PBMC	Urine	Exhaled Air	Saliva	Tissue
Decreased production of PGE_2	±	—	—	—	NPEC± BF+
Decreased expression of PGE_2 receptors	—	—	—	—	NP±
Decreased expression of COX-2	No	—	—	—	NP± BEC+
Increased generation of cysteinyl leukotrienes	±	+	±	+	NP±
Increased expression of Cys-LT1 receptors	—	—	—	—	NP+
Increased LTC_4 synthase expression	+	—	—	—	BM+ NP+
Increased 5-LO expression	—	—	—	—	NPEC+
Decreased lipoxin generation	±	—	—	—	NPEC+

Middleton's Allergy, 8th Ed.

Genetic mechanisms

Gene	SNP(s)	Clinical Phenotype	Mechanism
LTC4S	–444A>C	High genotype frequency of C allele compared with A allele	C allele may be the risk allele owing to overproduction of cys-LTs
CYSLTR1	–634C>T, –475A>C, –336A>G	ht2(TCG) showed higher frequency in AERD and higher promoter activity	Higher *CysLTR1* mRNA expression may be responsible for pathogenesis
CYSLTR2	—	Frequencies of rare allele increased in AERD, with decrease in FEV_1 after aspirin provocation	Elevation of cys-LT production
CRTH2	—	–466T allele had higher frequency in AERD and increased serum and cellular eotaxin-2 production and lower mRNA expression	–466T allele may be the risk allele by activation of eosinophils
CCR3	–520T>C	Frequencies of rare genotypes were higher in AERD, and –520G allele showed higher promoter activity	Higher mRNA expression of CCR3 may cause eosinophil activation
MS4A2R	E237G	FcER1b –109T allele had higher frequency and high promoter activity	Increased mRNA expression of –109T allele may cause mast cell activation mediated by MS4A2R receptor
ACE	–262A>T, –115T>C	Frequencies of the rare alleles were higher in AERD; –262T had lower promoter activity; and reduction in FEV_1 was seen after aspirin provocation	Downregulation of ACE expression
IL4	–589T>C	The frequency of rare alleles was higher in AERD; –589C had enhanced promoter and transcriptional activity induced by aspirin	Enhanced IL-4 activity with aspirin exposure

Middleton's Allergy, 8th Ed.

Environmental trigger

- Role of environment
  - Airway disease precedes development of hypersensitivity to ASA.
  - Complete avoidance of NSAIDs does not lead to clinical improvement.
  - Cross-reactive respiratory-type hypersensitivity reactions to ASA do not occur in healthy persons without rhinosinusitis / asthma

- Suggested mechanism
  - Human rhinovirus
  - Staphylococcal enterotoxin

Am J Respir Crit Care Med 2008;177:1082-9
Clin Exp Allergy 2004;34:1270-5.

Clinical feature

- More common in women
- Non-atopic status is more prevalent
- Usually begins during adulthood
  - Rhinosinusitis, commonly with polyposis → Asthma → Aspirin hypersensitivity

- Symptom and signs
  - Moderate to severe asthma with chronic persistent rhinosinusitis with nasal polyps
    - Intense eosinophil infiltrations in upper and lower airway mucosa
  - NSAIDs intolerance
    - Bronchospasm of variable severity accompanied by rhinitis symptoms and ocular injection.
    - Can be combined with chronic urticaria with or without angioedema and/or anaphylaxis.
    - Nausea and stomach pain occur only occasionally

Yonsei Med J 50(6): 744-750, 2009

Allergy 2011;66:818–829

Ann Allergy Asthma Immunol 2002;89:474-8

What matters?

- Aggressive, persistent nature of the disease

- Requirement for high-dose glucocorticoids to manage the asthma
- Frequent recurrence of nasal polyps after surgery

NEJM 2016;374;5

AERD and severity of asthma

- Significant risk factor for severe chronic asthma and near-fatal asthma

	Non–aspirin-sensitive asthma (n = 2848)	AERD (n = 459)	*P* value*
Physician assessment of "severe" asthma, % (n)	49 (1378)	66 (304)	<.001
History of intubation, % (n)	11 (322)	20 (92)	<.001
Unscheduled office visit in previous 3 mo, % (n)	44 (1264)	54 (249)	.001
Emergency department visit in previous 3 mo, % (n)	13 (372)	18 (81)	.017
Hospitalized in previous 3 mo, % (n)	5 (131)	6 (29)	.068
Corticosteroid burst in previous 3 mo, % (n)	46 (1319)	56 (258)	<.001
Use of high-dose inhaled corticosteroids, % (n)	26 (727)	34 (157)	<.001
Use of leukotriene modifier, % (n)	57 (1615)	67 (308)	<.001

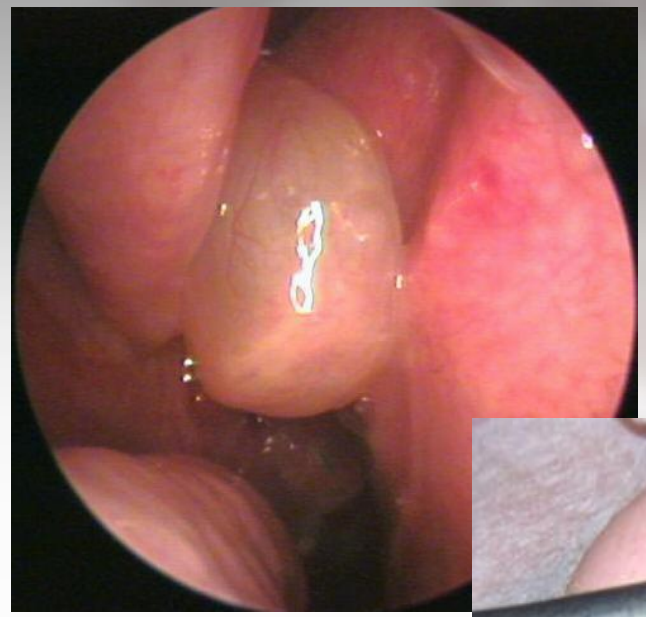
	Non–aspirin-sensitive asthma (n = 2848)	AERD (n = 459)	*P* value
Unadjusted results*			
Prebronchodilator	Mean (SD)	Mean (SD)	
FEV_1 (%)	75.2 (22.5)	70.7 (21.2)	<.001
FVC (%)	86.1 (20.0)	82.6 (19.5)	.001
FEV_1/FVC	0.71 (0.11)	0.70 (0.12)	.107
Postbronchodilator	Mean (SD)	Mean (SD)	
FEV_1 (%)	79.9 (22.0)	75.3 (21.0)	<.001
FVC (%)	90.2 (19.1)	86.7 (19.2)	<.001
FEV_1/FVC	0.72 (0.12)	0.71 (0.12)	.085
Adjusted results†			
Postbronchodilator	Mean (SE)	Mean (SE)	
FEV_1 (%)	80.0 (0.4)	75.3 (1.0)	<.001
FVC (%)	90.2 (0.3)	87.2 (0.9)	.002
FEV_1/FVC	0.72 (0.002)	0.71 (0.005)	.005

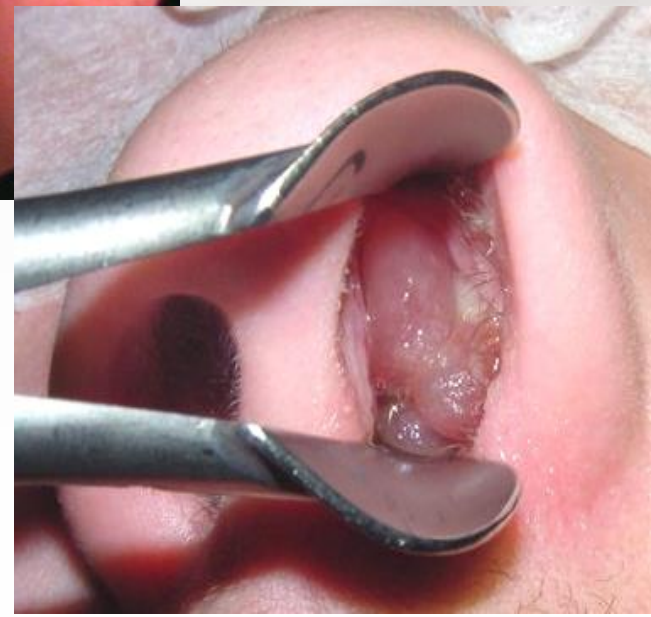
J Allergy Clin Immunol 2005;116:970-5.

AERD and severity of CRS

- More severe..
  - Polypoid hypertrophy of sinus mucosa
  - Severity of inflammation

- Nasal polyps undergo rapid regrowth
  - 5~6 fold more sinus infection per year
  - 3 fold more sinus surgery or polypectomies per patients

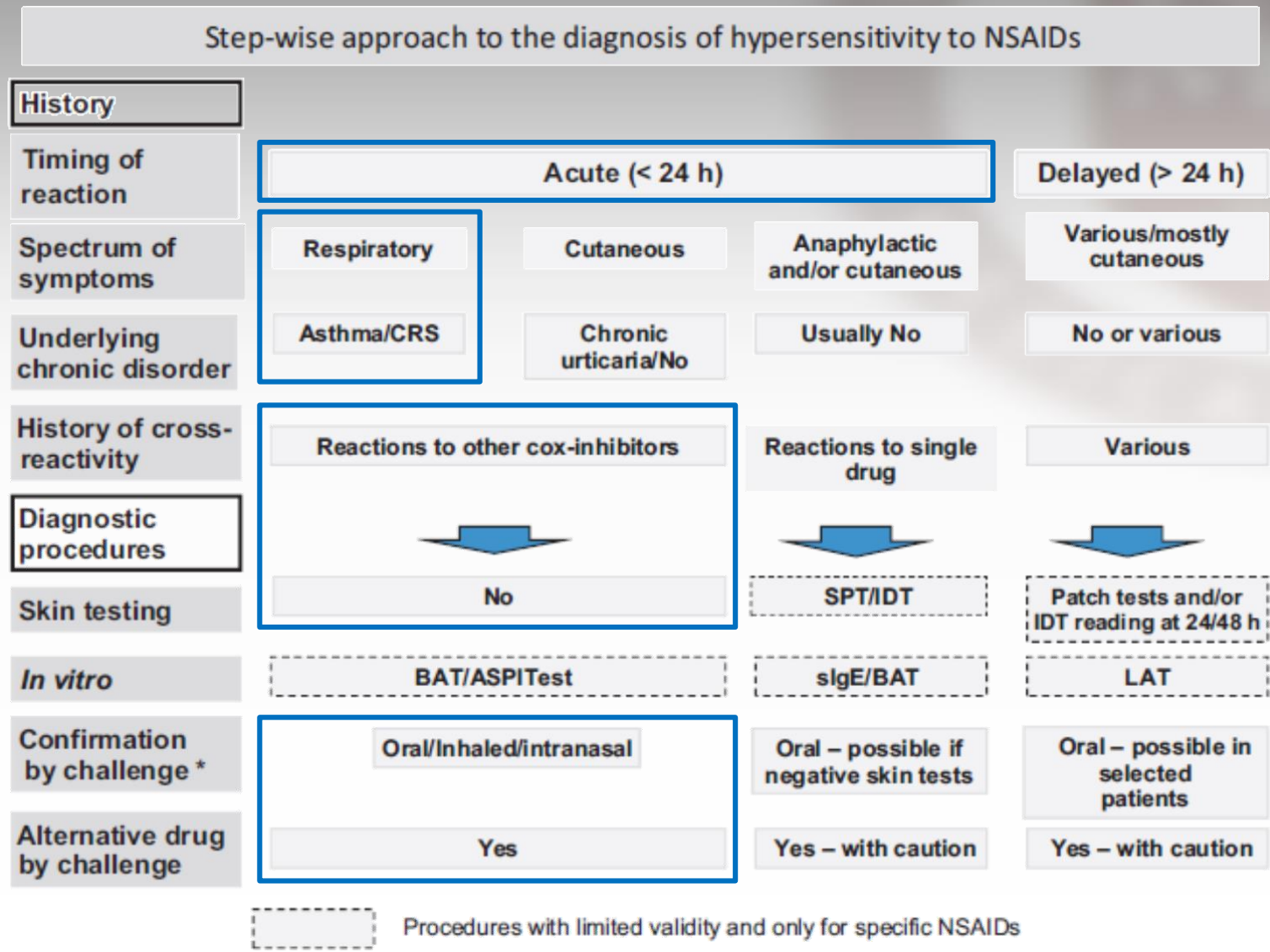




Allergy 2011;66:818–829

Ann Allergy Asthma Immunol 2002;89:474-8.

Step-wise approach to NSAID hypersensitivity



Allergy 2011;66:818–829

Diagnosis of AERD

- Diagnosis of Asthma, CRS with/without NP, NSAID intolerance
- History of adverse reactions precipitated by ASA or other NSAIDs
  - 50% do not have a definitive history of adverse reaction to ASA or NSAID
- The diagnosis of AERD can be definitively established only through aspirin-provocation challenges
  - Oral / Bronchial inhalation / Nasal inhalation
  - Intravenous (?)

Yonsei Med J 2009;50(6):744-750

Aspirin challenge test (provocation test)

- Instruction
  - Hospital setting and emergency resuscitative equipment
    - Direct supervision of a physician experienced in the performance of such testing.
    - Patients should have an open intravenous line in place
  - Asthma should be stable.
  - Withdrawal of antiasthma drugs is needed
    - Regular OCS <10mg prednisolone or equivalent
    - The dose of bronchial and nasal corticosteroids should be as low as possible
  - Skin tests are not indicated
  - (Should be preceded by a placebo challenge)

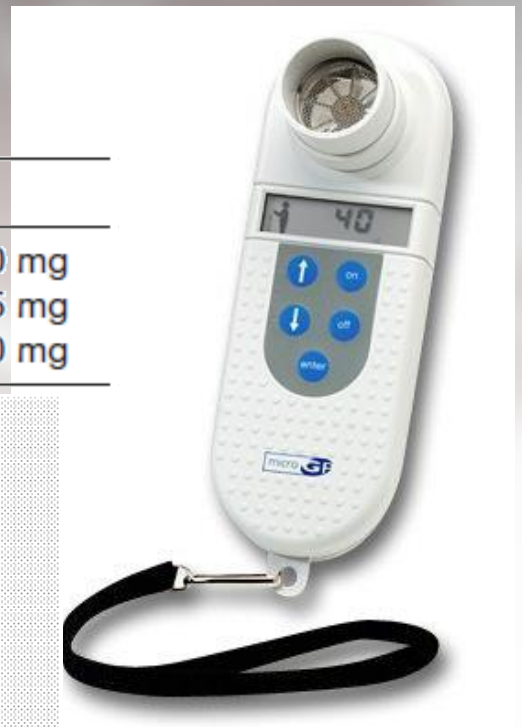
- Contraindication (relative)
  - Oral and inhalation challenges in patients with unstable asthma
  - FEV1 < 70% or 1.5L

Oral challenge test

- Gold standard for diagnosis of AERD
  - Time- and labor-intensive

Table 1. Single-blind 3-Day Oral ASA Challenge*

Time	Day 1	Day 2	Day 3
7:00 AM	Placebo	ASA 30 mg	ASA 100–150 mg
10:00 AM	Placebo	ASA 45–60 mg	ASA 150–325 mg
1:00 PM	Placebo	ASA 60–100 mg	ASA 325–650 mg



  - Criteria for positive response

Table 2. Types of Respiratory Responses to Oral ASA Challenges

Classic reaction: decline of 20% or more in FEV_1 values and a naso-ocular reaction

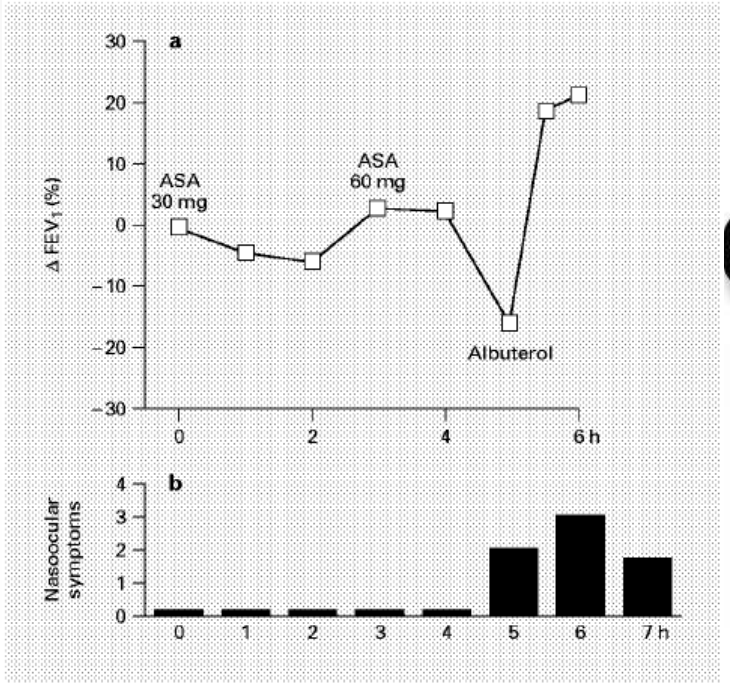
Pure lower: decline of 20% or more in FEV_1 values without naso-ocular reaction

Upper airway only: naso-ocular reaction alone

Partial asthma: declines in FEV_1 between 15 and 20% combined with naso-ocular reaction

Laryngospasm: crowing sounds in neck (flow volume curve: inspiratory loop flat and notched)

Negative: if up to ASA 650 mg was administered without any respiratory reaction



Cardiology 1999;91:8-13

Ann Allergy Asthma Immunol 2002;89:474-8.

Risk of oral challenge test for aspirin in AERD

TABLE I. OAC reactions

	n (%)
Naso-ocular	188 (90)
Bronchial	74 (35)
15% to 19% decrease in FEV_1	27 (13)
20% to 29% decrease in FEV_1	28 (13)
≥30% decrease in FEV_1	19 (9)
Gastrointestinal	49 (23)
Cutaneous	20 (10)
Laryngeal	16 (8)
Negative OAC	17 (8)

- Total 210 patients
- 1.4% (3 patients) experienced systemic reactions including hypotension
- Safe: Improves after proper treatment
- Should be cautious in outpatient setting

TABLE II. Relationship of OAC bronchial reaction severity to historical aspirin/NSAID reaction treatment location

	Historical reaction treatment location		
OAC bronchial reaction severity	**Home (n = 63), n (%)**	**ED (n = 101),* n (%)**	**Hospital (n = 46),† n (%)**
<20% decrease in FEV_1	53 (84)	79 (78)	31 (67)
20% to 29% decrease in FEV_1	5 (8)	14 (14)	9 (20)
≥30% decrease in FEV_1	5 (8)	8 (8)	6 (13)

J Allergy Clin Immunol 2007;120:273-7.

Diagnosis: Other challenge test

- Bronchial challenge test

Conc. of L-ASA (M)	No. of Inhalations	Inhaled ASA Dose (mg)	Cumulative ASA Dose (mg)
0.1	1	0.18	0.18
0.1	2	0.36	0.54
0.1	5	0.90	1.44
0.1	13	2.34	3.78
1	4	7.20	10.98
1	9	16.2	27.18
2	11	39.60	66.78
2	32	115.20	181.98

- Nasal challenge test
- Intravenous challenge test

Middleton's Allergy, 8th Ed.

Management

- Asthma
  - Should follow asthma guidelines
  - Leukotriene antagonist
    - Montelukast, zafirlukast, pranlukast
    - Improved asthma control and pulmonary function
    - Also attenuated nasal reactions

- CRS and Nasal polyposis
  - Difficult to treat: less response to medical & surgical treatment
  - High dose INS + prn) broad-spectrum antibiotics
  - Burst of systemic corticosteroid: “medical polypectomy”
  - Leukotriene antagonists
  - Decongestants and antihistamines

Am J Respir Crit Care Med 2002;165:9-14.

Prevention

- Alternative analgesics
  - Cross reactivity
    - Paracetamol 7%, 400mg ibuprofen 98%, 100mg naproxen 100%, 40mg diclofenac 93%
  - Education is utmost important !!

Group A: NSAIDs cross-reacting in majority of hypersensitive patients (60–100%)	
Ibuprofen	Etololac
Indomethacin	Diclofenac
Sulindac	Ketoprofen
Naproxen	Flurbiprofen
Fenoprofen	Piroxicam
Meclofenamate	Nabumetone
Ketorolac	Mefenamic acid

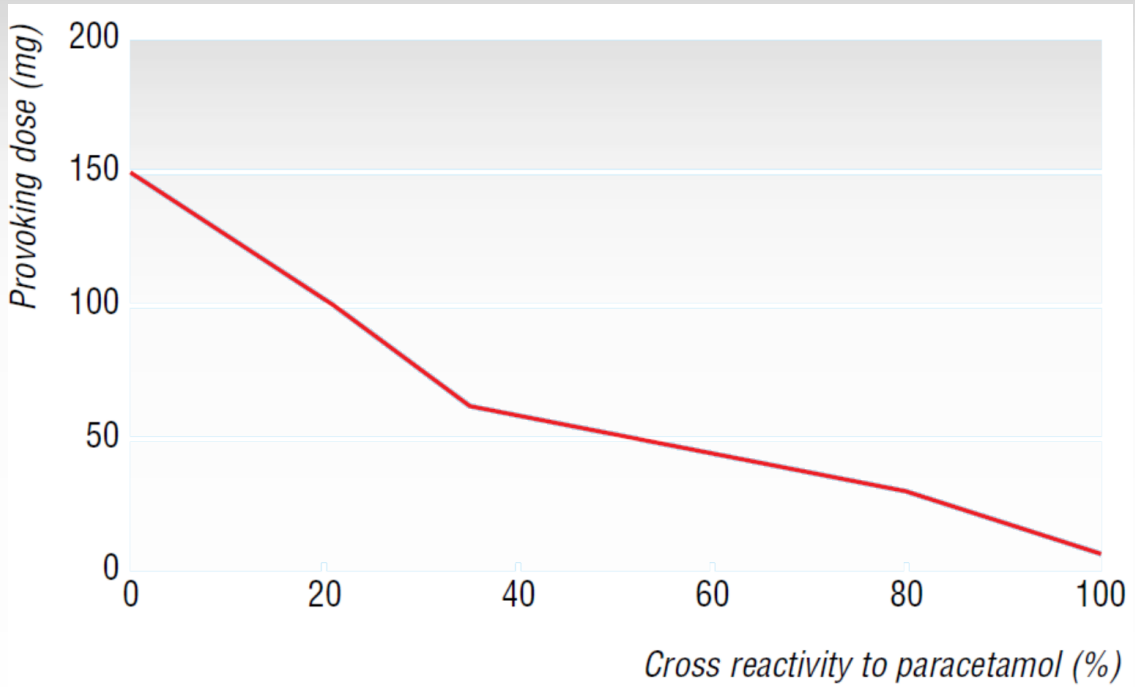
Group B: NSAIDs cross-reacting in minority of hypersensitive patients (2–10%)
Rhinitis/asthma type
acetaminophen (doses below 1000 mg)
meloxicam
nimesulide

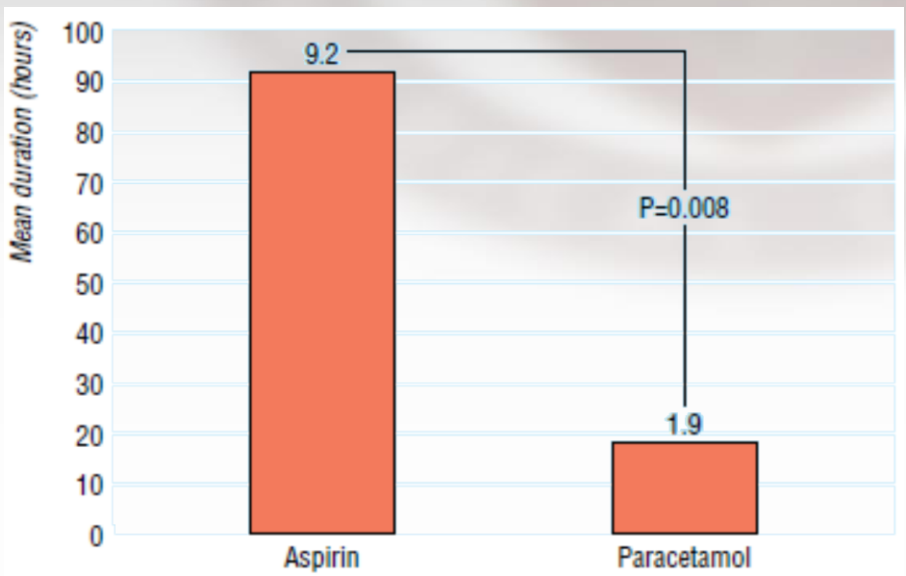
Group C: NSAIDs well tolerated by all hypersensitive patients*
Rhinitis/asthma type
selective cyclooxygenase inhibitors (celecoxib, parvocoxib)
trisalicylate, salsalate

BMJ 2004;328:434

Allergy 2011;66:818–829

Aspirin and acetaminophen





BMJ 2004;328:434

Aspirin desensitization

- Initial desensitization with incremental doses of aspirin followed by daily high dose therapy
  - Nearly all patients with AERD can be desensitized to aspirin
  - Clinically very effective
  - Cost-effective and safe
  - Produce definite improvement in both upper and lower respiratory tract symptom

- Indication
  - Intractable symptoms despite medical treatment
  - Recurrent nasal polyps requiring multiple surgeries
  - Frequent or daily systemic corticosteroids are required to control nasal symptoms and/or asthma
  - Additional medical indication for aspirin
    - Coronary disease, Rheumatic diseases,, etc

Yonsei Med J 2009;50(6): 744-750

Allergy Asthma Immunol Res. 2011;3(1):3-10.

Allergy Asthma Immunol Res. 2016;8(4):298-304

Effect of aspirin desensitization in AERD

TABLE I. Analysis of changes in markers of clinical disease during the first 6 months of treatment with aspirin desensitization (n = 126)

TABLE II. Analysis of changes in markers of clinical disease after greater than 1 year of treatment with aspirin desensitization (n = 126)

TABLE III. Analysis of treatment with corticosteroids before, at 6 months after, and greater than 1 year after starting aspirin desensitization therapy

TABLE IV. Number of patients who were taking systemic corticosteroids and LTMDs at baseline, at 6 months, and during the last year of aspirin desensitization treatment (n = 126)

	Baseline	6 mo after aspirin treatment	*P* value	Last year of aspirin treatment	*P* value
Not receiving prednisone	39 (31%)	62 (49%)	<.0001	84 (66%)	<.0001
Bursts of prednisone	55 (44%)	37 (29%)	<.0001	17 (13%)	<.0001
Alternate-day prednisone	2 (1%)	1 (1%)	NS	1 (1%)	NS
Daily prednisone	30 (24%)	26 (21%)	NS	24 (19%)	.03
Not receiving any LTMDs	102 (81%)	88 (70%)	.001	63 (50%)	<.0001
Zafirlukast use	7 (6%)	16 (13%)	.001	20 (16%)	<.0001
Montelukast use	13 (10%)	18 (14%)	.01	40 (32%)	<.0001
Zileuton use	4 (3%)	4 (3%)	NS	3 (2%)	NS

J Allergy Clin Immunol 2003;111:180-6

Aspirin desensitization protocols

- Target dose: 325mg or 650mg twice daily

Time (mins)	Dosage	Cumulative dosage
0		
30		
60		
90		
120		

Table 1
Sample oral

Time
8 AM
11 AM
2 PM

	Indications	Doses of aspirin [mg]	Dose inte
Silber et al. [			
Szczel			
Steve			
Wong			
Schafer, Gore [9]			
Stevenson, Simon 'Scripps Clinic' [24]	AERD	20.25, 40.5, 60, 75, 81, 101.25, 162.5, 325	3 h
Hope et al. [25]	AERD	30, 45, 60, 100, 150, 325, 650	3 h

Protocol	Hypersensitivity Type	Dosing Interval	Aspirin Dose, mg	Success Rate, n (%)[a]
Silberman[27]				
protocol 1	I, III, IV, V	30 min	1, 2, 4, 8, 16, 32, 64, 100	6/7 (86)[b]
protocol 2				
Wong[22]				
protocol 1[c]				
protocol 2				
protocol 3				

Patient No.	Dose (mg)*										
1	0.1	0.3	1	3	10	30	40	81	162	243	
2	0.1	0.3	1	3	10	20	40	81			
3	0.1	0.3	1	3	10	30	40	81	162		
4	0.1			3	10	20	40	81	162		
5					10	20	40	81	162		
6	0.1	0.3	1	3	10	20	40	81	162	325	
7†			1	3	10						
8-11	0.1	0.3	1	3	10	20	40	81	162	325	
P‡	0.1	0.3	1	3	10	20	40	81	(162)§	(325)§	

Aspirin desensitization protocol.

Time (min)	Aspirin dose (mg)	Cumulative aspirin dose (mg)
0	1	1
30	2	3
60	4	7
90	8	15
	16	31
	32	63
	64	127
	125	252
	250	502

Aspirin Dose (mg)
1
5
10
20
40
100

90
210
330

KOREA UNIVERSITY MEDICAL CENTER

Novel agents in AERD

- Anti-IgE monoclonal antibody
  - Several case reports and small study: Improve AERD symptoms
  - Mechanism of action is not clear: lowers LTE_4 activity?
- Anti-IL-5 monoclonal antibody
  - Although not a central mediator of AERD
  - Decrease nasal polyposis
- Anti-IL-4/IL-13, Anti-IL-33 monoclonal antibody / Anti-TSLP
  - Mediators of demonstrated role in AERD
  - No reports for now
- Immunotherapy
  - Not effective

Allergy Asthma Immunol Res. 2016;8(4):298-304
Journal of Asthma and Allergy 2016:9
J Allergy Clin Immunol. 2011;128(5):989–995

Summary

- Definition and prevalence
- Pathophysiology
- Clinical feature and importance
- Diagnosis
  - Challenge test
- Treatment options
  - Guideline-based therapy
  - Leukotriene antagonist
  - Aspirin desensitization
- Prevention

KOREA UNIVERSITY GLOBAL PRIDE

감사합니다

KOREA UNIVERSITY MEDICAL CENTER