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Management of NSAID hypersensitivity

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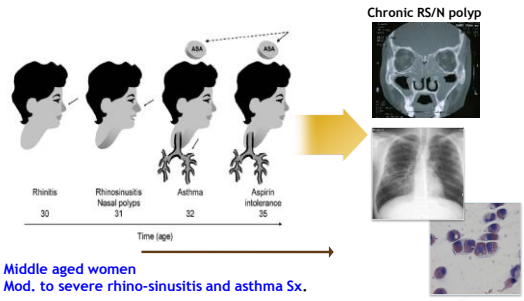
Clinical manifestations of ASA/NSAIDs hypersensitivity

Reaction time	Clinical manifestation	Type of reaction	Underlying disease	Putative mechanism
Acute (immediate to several hours)	Rhinitis/asthma (AERD)	Cross-reactive (ie, induced by multiple NSAIDs)	Asthma/RS /nasal polyps	Inhibition of COX-1
	Urticaria/angioedema (ASA intolerant chronic urticaria, AECD)	Cross-reactive	CU AR/atopy	Inhibition of COX-1 Unknown ?
	Urticaria/angioedema /Anaphylaxis ASA intolerant acute urticaria)	Multiple NSAID hypersensitivity	AR/atopy	Inhibition of COX-1 Unknown ?
	Urticaria/angioedema /anaphylaxis	Single NSAID hypersensitivity	Atopy /food allergy /drug allergy	Specific IgE ?
Delayed (>24 h)	Fixed drug eruption Severe bullous reaction Maculopapular eruption Contact and photocontact Dermatitis	Selective or cross-reactive	Usually none	T cells Cytotoxic T cells Natural killer cells Other

Kowalski ML et al. Allergy 2011;66:818; Park HS et al. Middleton's text of Allergy, 8th edition, 2012

Clinical characteristics of AERD



Chronic RS/N polyp

Middle aged women
Mod. to severe rhino-sinusitis and asthma Sx.

A Szczeklik A & Sanak M: Eur J of Pharm, 2006
Palikhe N & Park HS. J Allergy, 2012

Clinical characteristics of the AERD patients in a Korean cohort

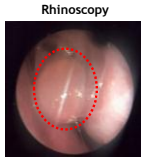
	AERD (n=267)	ATA (n=449)	p value
Atopy (positive)	114 (53.3%)	175 (60.8%)	0.101
Log total IgE	2.23±0.55	2.22±0.64	0.773
FEV1(% Pred)	79.65±26.07	84.89±21.67	0.018
Metacholine_PC20	4.35±7.66	6.76±8.94	0.003
Rhinosinusitis (positive)	127 (75.6%)	198 (58.2%)	<0.001
Nasal polyp (positive)	78 (48.4%)	14 (6.5%)	<0.001
Asthma duration (year)	6.15±5.85	4.9±5.97	0.045

ATA; aspirin-tolerant asthma, "24% of them were severe asthma"

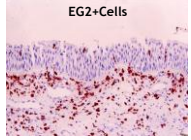
Palike N & Park HS. Yonsei Med J, 2009;50:744

AERD is highly associated with R-S/nasal polyp

Rhinoscopy



EG2+Cells

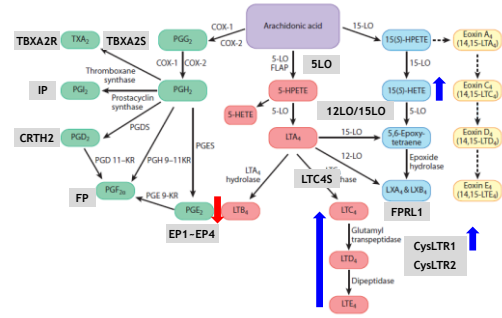


♣ Eosinophils were more activated in nasal polyp tissue from AERD patients

	AERD (n=10)	ATA (n=10)	p value
ECP(ng/mg)	366.5 ± 89.1	59.0 ± 14.0	0.01
MMP-9(ng/mg)	53.7 ± 21.1	27.8 ± 6.3	0.70
MMP-2(ng/mg)	134.1 ± 30.5	81.9 ± 14.1	0.29
TIMP-1(ng/mg)	42.7 ± 12.3	11.1 ± 4.1	0.02
MMP-9/TIMP-1	1.8 ± 0.6	4.6 ± 1.3	0.07
MMP-2/TIMP-1	6.4 ± 1.7	13.8 ± 2.2	0.02

Lee YM & Park HS. J Kor Med Sci, 2003;18:97

Pathogenic mechanisms of ASA/NSAIDs hypersensitivity

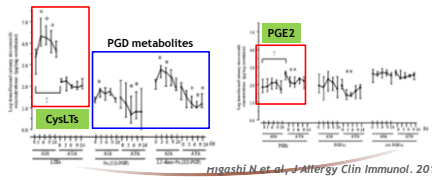


Profile of eicosanoid generation in AERD and anaphylaxis

** Urinary eicosanoid concentrations at baseline in AIA, ATA and anaphylaxis groups

Group	AIA	ATA	Anaphylaxis
LTE4	2275 (449-3495)*,‡	156 (152-209)	183 (124-197)
2,3-Dinor-9a,11b-PGF2	161 (96.3-200)	92.5 (58.9-116)	160 (29.0-249)
9a,11b-PGF2	21.6 (18.1-31.0)	31.6 (13.7-100)	16.4 (16.0-75.4)
PGE2	71.9 (43.0-161)†	313 (228-504)	202 (103-384)
PGF2a	89.8 (40.5-307)	87.1 (68.6-146)	71.1 (30.1-241)
ent-PGF2a	405 (356-676)	480 (359-657)	411 (290-494)

** Changes of CysLTs, PGD & PGE2 after ASA challenges



Higashi N et al, J Allergy Clin Immunol. 2010;125:1084

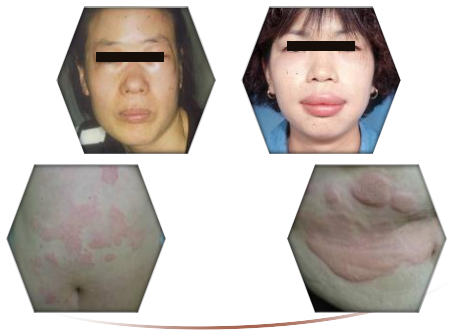
Molecular genetic mechanisms in AERD

1. HLA and LT related genes : HLA class II, 5-LO, LTC4S, CysLTR1, CysLTR2, P2RY12
2. COX-1/PG related genes : PGE2R, PGE4R, TXA2R
3. Mast cell activation genes : FceRIß, ADORA
4. Eosinophil activation genes : CCR3, CRTH2, IL13, 15-LO, IL5/IL5R
5. Others : IL10, TGFß1, TLR3

Palike N & Park HS. Yonsei Med J, 2009;50:744
Palike N & Park HS. J Allergy, 2012; Kim SH & Park HS. Clin North America, 2012

ASA intolerant urticaria (AIU)

Chronic (AICU, AECD) and acute (AIAU, multiple NSAID hypersensitivity)



Clinical characteristics of chronic urticaria according to the ASA hypersensitivity

- 1/ 3 of CU patients had ASA hypersensitvity- mostly reacting to multiple NSAIDs
- Clinically more severe course : higher drug requirement including OCS
- Pathogenesis : CysLT overproduction and mast cell activation
- Pre-disposing factor : atopy

Table 1. Comparison of clinical features between two groups

	AICU (n=81)	ATCU (n=146)	P value
Sex (M/F)	36/45	70/76	NS
Age (years)*	34.68±11.4	39.36±11.7	0.004
Duration (months)*	25.40±42.6	31.39±58.4	NS
Atopy (%)	62/81 (76.5)	133/227 (58.6)	<0.001

*These values are presented as mean±standard deviation. AICU = aspirin intolerant chronic urticaria; ATCU = aspirin tolerant chronic urticaria; NS = not significant.

Ye YM et al, J Asthma Allergy Clin Immunol 2005; 25: 194

What are differences between AIAU and AICU ?

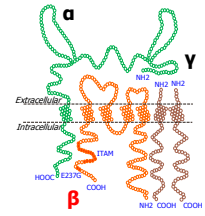
	AIAU (n=232)	AICU (n=244)	NC (N=232)	P value		
				AIAU vs. AICU	AIAU vs. NC	AICU vs. NC
Log[MPO] (log(ng/mL))*	2.10±0.53	1.84±0.43	1.87±0.73	0.007†	0.029†	NS
Log[IL-8] (log(pg/mL))*	1.35±0.43	1.23±0.37	1.30±0.37	NS	NS	NS
Log[IL-18] (log(pg/mL))*	2.29±0.24	2.23±0.23	2.03±0.60	NS	<0.001†	<0.001†
TGF-β1 (pg/mL)*	30.8±7.40	32.5±9.18	23.1±11.4	NS	<0.001†	<0.001†
Specific IgE antibody to SEA**	13/78 (16.7%)	15/115 (13.0%)	6/83 (8.1%)	NS	NS	NS
Specific IgE antibody to SEB**	12/78 (15.4%)	22/114 (19.3%)	2/75 (3.0%)	NS	NS	NS
Specific IgE antibody to TSST-1**	16/78 (20.5%)	37/115 (32.2%)	2/86 (2.6%)	NS	0.005‡	<0.005‡

→ Atopy was significantly higher in both AIAU and AICU than in NC.

Kim JE et al. J Asthma Allergy Clin Immunol 2010

Mast cell as a key effector cell in chronic urticaria

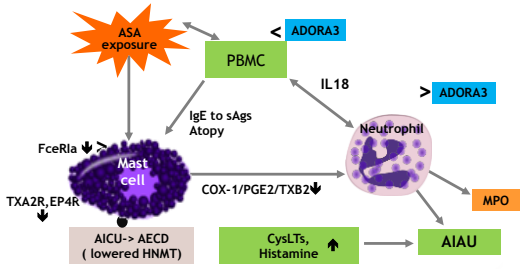
- α>> ß, γ chain of FcεRI
- ADRB2 at 46 A>G
- EP4 -1254 G> A
- TXA2R- 4684 T>C
- HNMT ; promoter and 3'UTR



No significant differences were noted in H1R and H2R among AICU, ATCU and NC patients.

Kim SH et al. J Kor Med Sci 2005, Bae JS et al. J Allergy Clin Immunol, 2008
Kang YM et al. Allergy 2009, Palike N et al. Clin Exp Allergy 2011

Molecular genetic mechanisms of AIU



Acoustic rhinometry and ASA nasal challenge in the diagnosis of AERD

Table 1. L-ASA nasal challenge schedule

	Likert scale	Symptoms VAS	Acoustic rhinometry	nNO	Pulmonary functions test
Baseline	×	×	×	×	×
Diluent					
30 min	×	×	×	×	
L-ASA					
15 min	×	×	×	×	
30 min	×	×	×	×	
60 min	×	×	×	×	
90 min	×	×	×	×	×

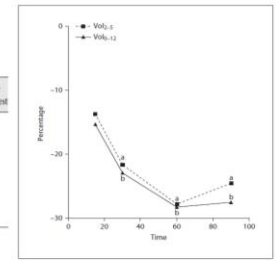


Fig. 1. Volume decrease (%) in Vol_{2-5} and Vol_{5-12}. Differences in volume decrease in Vol_{2-5} between diluent at 30, 60 and 90 min (* $p < 0.05$). Differences in volume decrease in Vol_{5-12} between diluent at 30, 60 and 90 min (b $p < 0.05$).

* Nasal challenge test has a low sensitivity

R. Munoz-Cano et al. Int Arch Allergy Immunol 2012;16:307

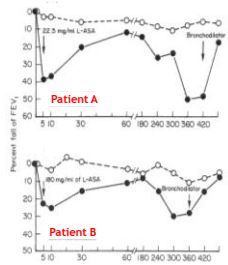
Lysine ASA bronchoprovocation test for AERD

The protocol

Conc. of L-ASA (M)	No. of inhalations	Inhaled dose of ASA (mg)	Cumulative dose of ASA (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 has a low sensitivity

Early and late asthmatic responses are noted.



Allergy 2007;62:1111-1118

Park HS et al. Clin Exp Allergy 1995;25:38

Single - blind 3 - day oral ASA challenge for AERD

Time	Day 1	Day 2	Day 3
First dose	Placebo	ASA 30 mg	ASA 100-150 mg
Second dose after 3 hrs	Placebo	ASA 45-60 mg	ASA 150-325 mg
Third dose after 6 hrs	Placebo	ASA 60-100 mg	ASA 325-650 mg

1) Schedule and dose may be altered by doctors depending upon patient profile, lung function, degree of previous reaction, etc.
2) induce cutaneous, nasal and GI symptoms as well as bronchoconstricions

In AIU patients, a single blinded oral provocation test with ASA 500 mg is commonly applied → 500 * 2 /d every 12 hrs for two days-> > 92% sensitivity

Ann Allergy Asthma Immunol 2002;89:474-78; Blanca M et al, Clin Allergy, 2012
Sang Ha Kim et al. Clin Exp Allergy, 35: 339, 2005

In vitro test : Basophil activation test in ASA hypersensitivity

Useful

- ✓ In vitro aspirin stimulation on basophils in patients with AERD. *Clin Exp Allergy 2009*
- ✓ Flow cytometry-assisted BAT as a safe dx tool for NSAID hypersensitivity. *Allergy Asthma Immunol Res. 2012;4:137*
- ✓ Basophil activation test for the in vitro diagnosis of NSAID hypersensitivity. *Allergy Asthma Proc. 2008 May-Jun;29:241*
- ✓ Basophil tesponsiveness and clinical picture of ASA intolerance. *Int Arch Allergy Immunol 2011;155:257*
- ✓ A new combined test with flow cytometric basophil activation. *Int Arch Allergy Immunol. 2005;136:58-72.*
- ✓ The flow-cytometric determination of basophil activation is useful for in vitro dx of NSAID hypersensitivity. *Clin Exp Allergy. 2004;34:1448*

Partly useful

- ✓ NSIAD hypersensitivity syndrome: Basophil activation by NSAID. *J Investig Allergol Clin Immunol 2010;20:39*
- ✓ NSIAD hypersensitivity syndrome: A multicenter study I. *J Investig Allergol Clin Immunol 2009;19:355*
- ✓ Comparison of CD63 up regulation induced by NSAIDs in patients with NSAID hypersensitivity. *J Allergy 2012*
- ✓ The values of NPT and BAT in the different patterns of ASA/NSAID hypersensitivity. *Allergol immunopathol. 2012;40:156*

Not reliable

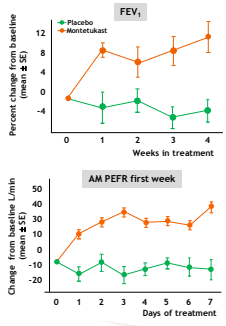
- ✓ Up regulation of CD63 or CD203c alone or in combinations in the dx of NSAID intolerance.
- ✓ *Int Arch Allergy Immunol 2009;1580:261*
- ✓ The BAT in drug allergy. *Revue francaise d'allergologie 51(2011)192*
- ✓ Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol 2011;127:567*
- ✓ Diclofenac induces basophil degranulation without increasing CD63 expression. *Clin Exp Immunol. 2007;147:99*

* Low sensitivity -43%

Management of AERD

1. Avoidance from ASA and cross reacting drugs of COX-1
2. LTRA, ICS with or without LABA inhaler
3. Intranasal steroid, anti-histamine for RS / nasal polyp
4. Nasal polypectomy, ASA desensitization
5. Biologics : anti-IgE or anti-IL5 antibodies

The short and long term effects of LTRA in AERD patients



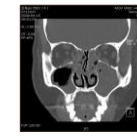
Types of reactions.	Treated with LTRA	Not treated with LTRA	P values
Classic (upper and lower)	19 (20%)	64 (39%)	0.001*
Pure lower respiratory	3 (2%)	4 (2%)	NS*
Partial asthma	15 (13%)	16 (9%)	NS*
All bronchospastic reactions	37 (39%)	84 (51%)	0.05*
% decline in FEV_1 values:	24.8	24.6	NS†
Mean ASA provoking	60.4	70.3	NS†
does, mg (bronchial)	(30-150)	(30-325)	
Upper respiratory reactions only	49 (51%)	53 (32%)	0.004*

-> The upper and lower airway symptoms could be suppressed by LTRA .

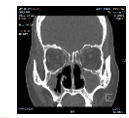
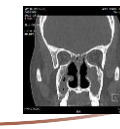
Am J Respir Crit Care 2002 *Clin Exp Allergy 2002;32:1491-6*

The benefits of nasal polypectomy

- Remove other potential causes (if relevant) :
  - Allergens
  - ETS &/or Diesel smoke
  - Infectious agents (S. aureus, fungi)
- Remove the hyperplastic tissues :
  - Surgery : eosinophilectony



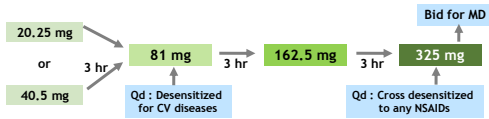
High recurrence rate after nasal polypectomy,
Then, consider the medications and ASA desensitization

Indication for oral ASA desensitization

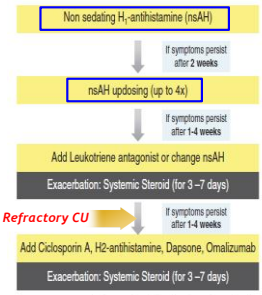
ASA desensitization can improve both
upper and lower respiratory symptoms in AERD

- Requirement for daily or frequent courses of systemic corticosteroids to control nasal symptoms and/or asthma
- Additional medical indication for ASA-coronary disease
- Medical indication for other COX-1 enzyme inhibiting medication
  (ex, arthritis refractory to acetaminophen)



Spirometry every 90min, Positive response : > 15% FEV_1 decrease

Step wise treatment of CU(= AECD)



Comments on procedure on algorithm for chronic urticaria

Allergy 2009: 64: 1427-1443

First level: High quality evidence
- Low cost (worldwide availability also in developing countries mostly cheaper than old sedating Antihistamines)
- Very good safety profile
- Very good evidence for efficacy

Second level: Low quality evidence
- Low cost
- Good safety profile
- Good evidence for efficacy

Third level: Very low quality evidence
- Low –to medium-low cost
- Good safety profile
- Insufficient or no evidence for efficacy in high quality RCT

Fourth level:
- *Ciclosporin A:*
  - Medium to high cost
  - Moderate safety profile
  - Moderate level of evidence for efficacy
- *H2-Antihistamine:*
  - Low cost
  - Good safety profile
  - Very low level of evidence for efficacy
- *Dapsone:*
  - Low cost
  - Medium level of side effects
  - Low level of evidence for efficacy
- *Anti-IgE:*
  - High cost
  - Good safety profile
  - Low level evidence for good efficacy

Effect of anti-IgE in refractory CU

Table. Association between ASA intolerance and severe CU

	Urticaria Activity Score (> 13)		
	Severe	Not-severe	P value
ASA intolerant CU	33 (44%)	42 (56%)	0.013
ASA tolerant CU	40 (27.4%)	106 (72.6%)	

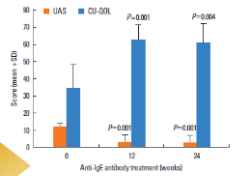


Fig. Change of urticaria activity score (UAS) and chronic urticaria-specific quality of life (CU-QOL) scores during anti-IgE antibody treatment (omalizumab)

Nam YH & Park HS et al. AAIR 2012

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WISC2012, Hydrabad, India

Thank you

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