

# **Prevention and management of ASA/NSAID hypersensitivity**

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# Clinical manifestations of **ASA/NSAIDs** hypersensitivity

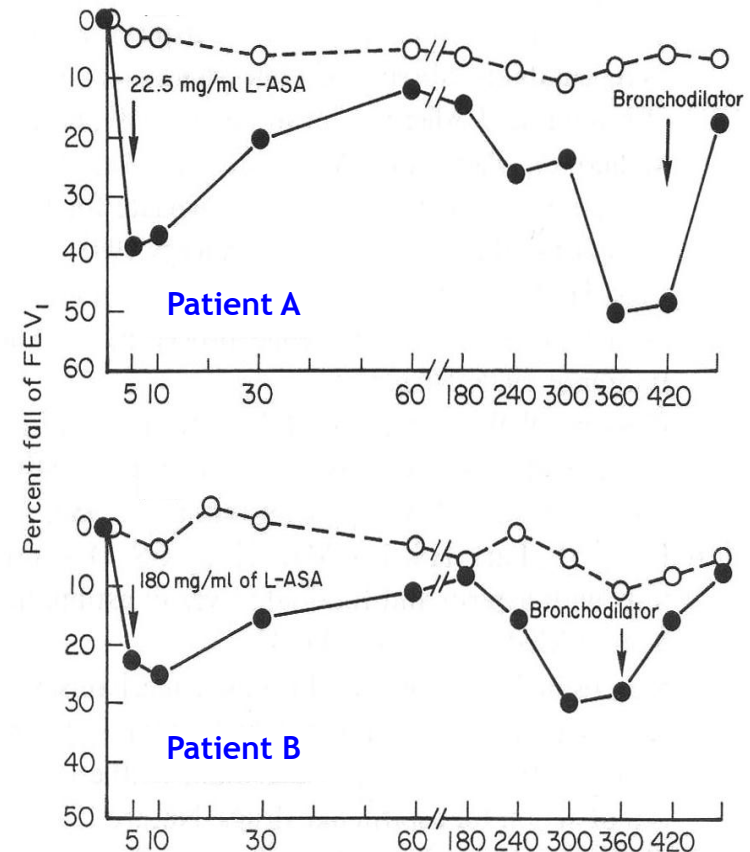
Reaction time	Clinical manifestation	Typ of reaction	Underlying disease	Putative mechanism
Acute (immediate to several hours)	Rhinitis/asthma ( <b>AERD</b> )	Cross-reactive (ie, induced by multiple NSAIDs)	Asthma/RS/nasal polyps	Inhibition of COX-1
	Urticaria/angioedema (ASA intolerant chronic urticaria, <b>AECD</b> )	Cross-reactive	CU AR/atopy	Inhibition of COX-1 Unknown ?
	Urticaria/angioedema/ Anaphylaxis <b>ASA intolerant acute urticaria</b> )	Cross-reactive	AR/atopy	Inhibition of COX-1 Unknown ?
	Urticaria/angioedema/a naphylaxis	<b>Selective</b> (induced by a single NSAID)	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

# 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

Early and late asthmatic responses are noted.



# Oral ASA challenge test in AERD and AIU patients

For AERD patients

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	<b>ASA 325-650 mg</b>

- 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 bronchoconstrictions

**For AIU patients, open single oral ASA challenge test with 500 to 650 mg**

# 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

# Cross reacting NSAIDs in AERD and AIU

Table . NSAIDs tolerance in patients with acute, cross-reactive type of aspirin hypersensitivity

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

\* Urticaria / angioedema type

- Acetaminophen, meloxicam, nimesulide

- **selective COX-2 inhibitors (celecoxib, rofecoxib)**

**Group C : NSAIDs well tolerated by all hypersensitive patients\***

Rhinitis/asthma type

- selective cyclooxygenase inhibitors (celecoxib, parvcoxib) , trisalicylate, salsalate

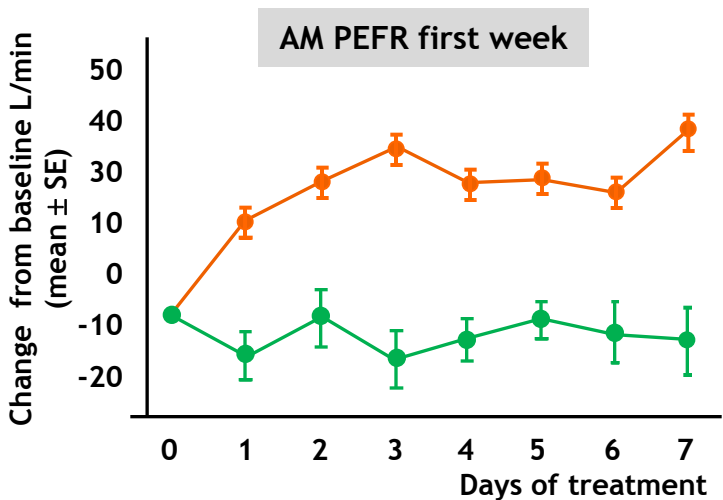
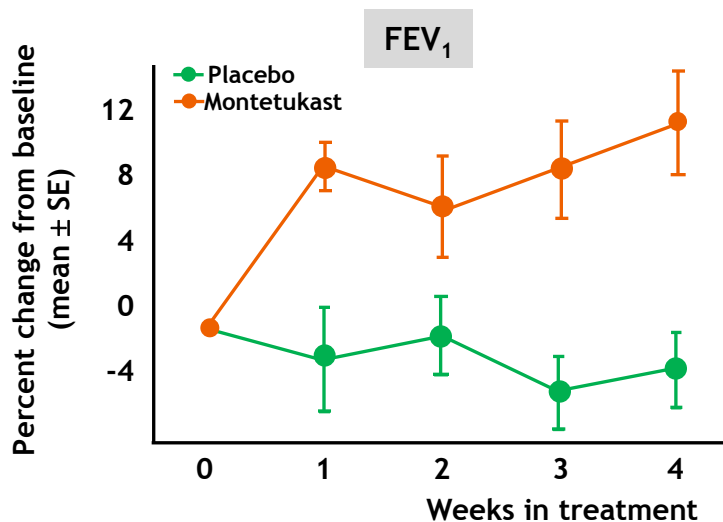
Urticaria/angioedema type

- new selective COX-2 inhibitors (etoricoxib, pavocoxib)

**\*Single cases of hypersensitivity have been reported**

**should recommend to avoid for both AERD and AIU patients**

# The effect 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 <sub>1</sub> values:	24.8	24.6	NS†
Mean ASA provoking does, mg (bronchial)	60.4 (30-150)	70.3 (30-325)	NS†
Upper respiratory reactions only	49 (51%)	53 (32%)	0.004*

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



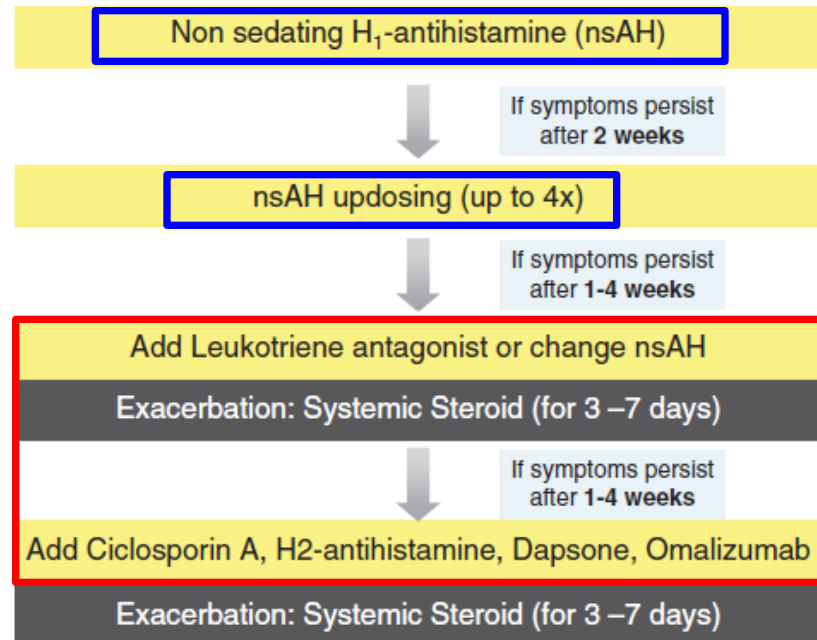
# Therapeutic implications for AERD patients with chronic rhino-sinusitis

Therapeutic implications	Potential therapies
<ul style="list-style-type: none"><li>✓ Surgery</li><li>✓ Nasal saline irrigation</li><li>✓ Topical (intrasinus) CS</li><li>✓ Aspirin desensitization</li><li>✓ Leukotriene modifier</li></ul>	<ul style="list-style-type: none"><li>✓ Eosinophil-targeting modalities(anti-IL-5/anti-IL-5 receptor)</li><li>✓ Anti-IgE antibody</li><li>✓ IL-4/signal transducer and activator of transcription 6 antagonists</li><li>✓ Role of Staphylococcus species/staphylococcal superantigen-targeting approaches</li></ul>

## Benefits of surgery :

Remove the hyperplastic tissues & eosinophil burden, but high recurrence rate

# Step wise treatment of AECD



*Allergy 2009; 64: 1427-1443*

Comments on procedure on algorithm for chronic urticaria

- **Present more severe form( higher UAS >13)**  
-> require higher dose of anti histamines and immunomodulators
- **Most patients can be controlled by pharmacologic treatment, but some patients have to maintain the medications for many years**
- **ASA desensitization** is not performed for AIU patients

# THANK YOU

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