Respiratory type of Hypersensitivity to NSAIDs

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GA²LEN
Global Allergy and Asthma European Network
Network of Excellence

Adverse Drug Reactions

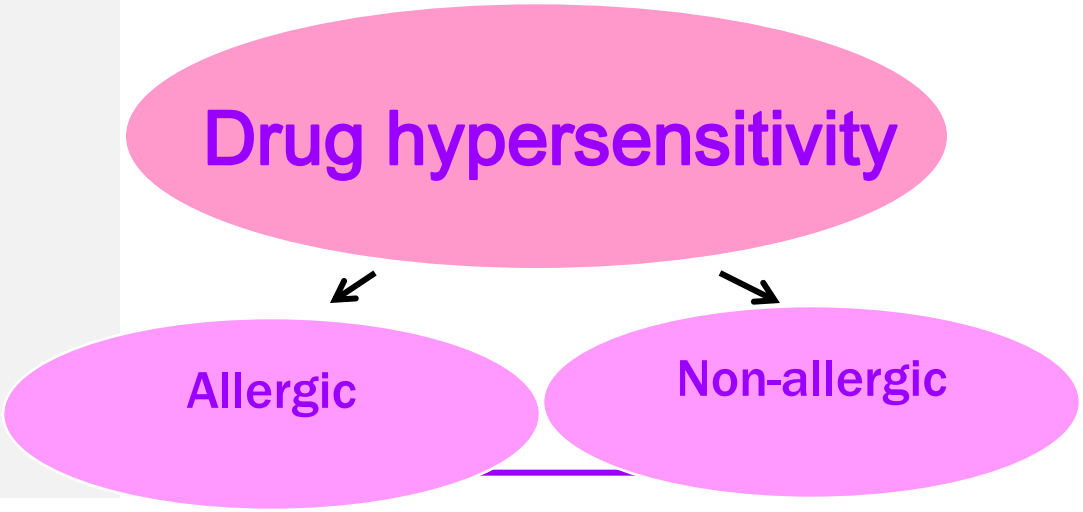
Type A (70-90%)

- Common and predictable
- In normal individuals
- Dose-dependant

- **NSAIDs:**
  Gastrointestinal
- **Renal**

Type B (10-30%)

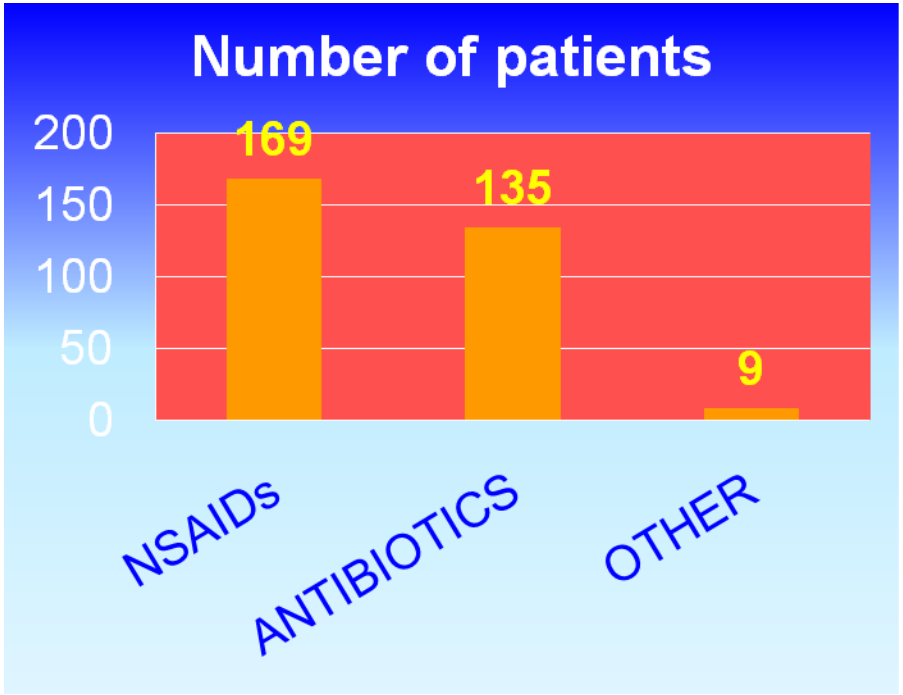
- Unpredictable
- In susceptible individuals



Drug hypersensitivity at the University Hospital Allergy Clinic in Lódź

In 2005 and 2006

- 4511 new patients were referred to the Clinic
- 313 patients (6.7%) reported drug hypersensitivity



Makowska J et al. 2008

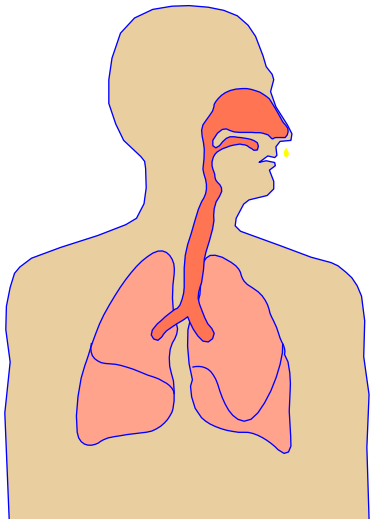
Classification of Hypersensitivity reactions to NSAIDs

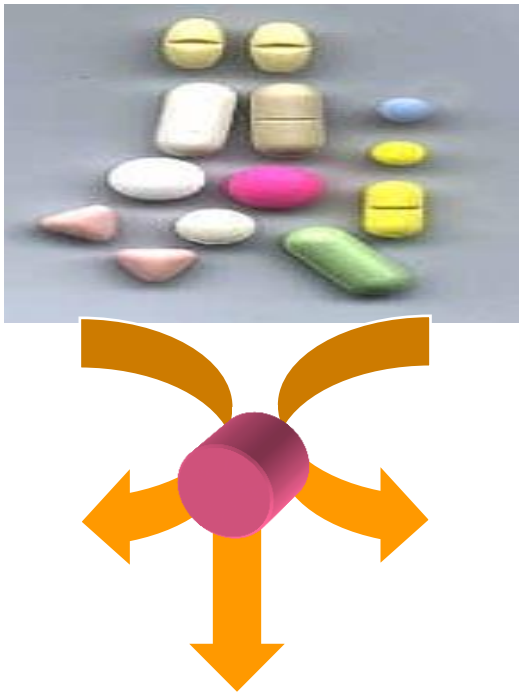
Clinical manifestation	Type of reaction	Underlying disease	Putative mechanism
Rhinitis/asthma	**Cross-reactive**	**Asthma/rhinosinusitis/ nasal polyps**	**Inhibition of COX -1**
Urticaria/angioedema	**Cross-reactive**	**Chronic urticaria**	**Inhibition of COX -1**
Urticaria/angioedema	**Multiple NSAIDs-induced**	**No underlying chronic disease.**	**Unknown . Presumably related to Cox-1 inhibition**
Urticaria /angioedema/anaphylaxis	**Single drug -induced**	**Atopy , Food allergy Drug allergy**	**IgE-mediated**
Blended			
DELAYED	**various**	**None or various**	**DTH, various**

D.D.Stevenson, A. Szczeklik. M. Sanchez-Borges 2000

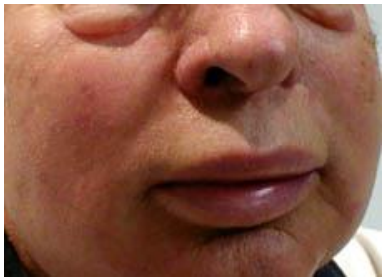
Acute hypersensitivity reactions to ASA and other NSAIDs

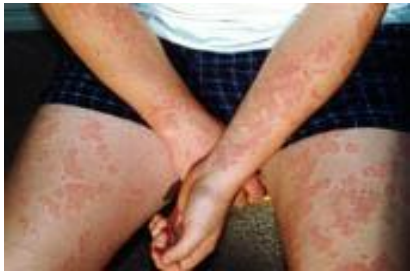
Respiratory





Cutaneous





cross-reacting

Anaphylaxis and/or cutaneous

cross-reacting

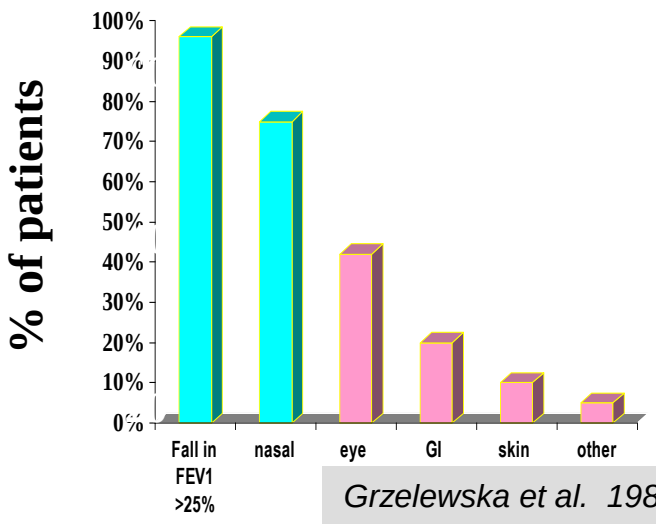
or

multiple drug

Single drug reactors

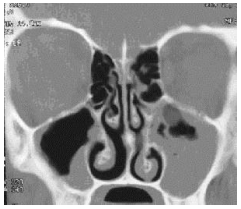
Respiratory type of hypersensitivity to NSAIDs

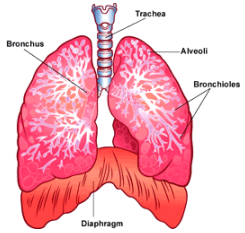
ASA-induced symptoms



Grzelewska et al. 1981

Clinical phenotype





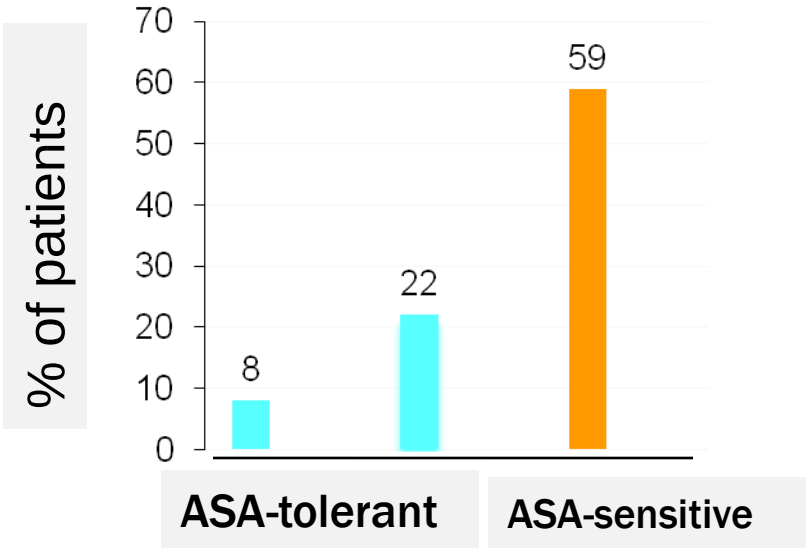
CRS with nasal polyps

Severe asthma

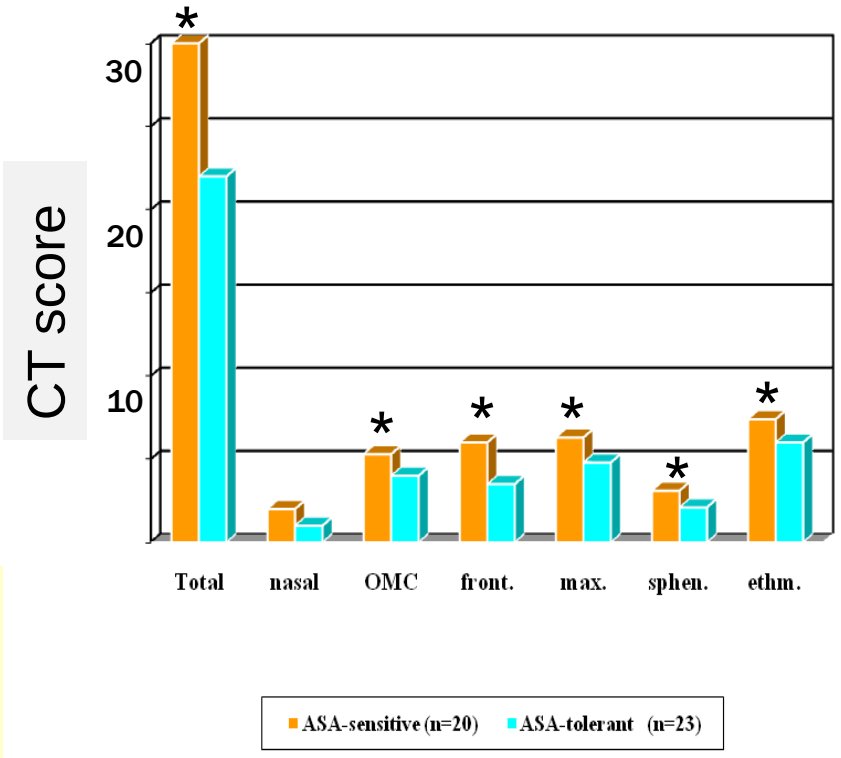
Aspirin Exacerbated Respiratory Disease (AERD)
NSAIDs Exacerbted Respiratory Disease (NERD)

Severity of CRS in ASA-tolerant and ASA-sensitive patients

Recurrence of nasal polyps after polypectomy (follow-up period of 4 years)



CT staging of chronic rhinosinusitis in ASA-sensitive and ASA-tolerant patients



- **Patients with AERD had history of 10 times as many previous FESS procedures as had the patients without aspirin sensitivty**
- **ASA triad mean: 5.2**
- **ASA (-) mean 0.53; ($p < 0.001$)**

Kowalski ML et al. WAJ 2003

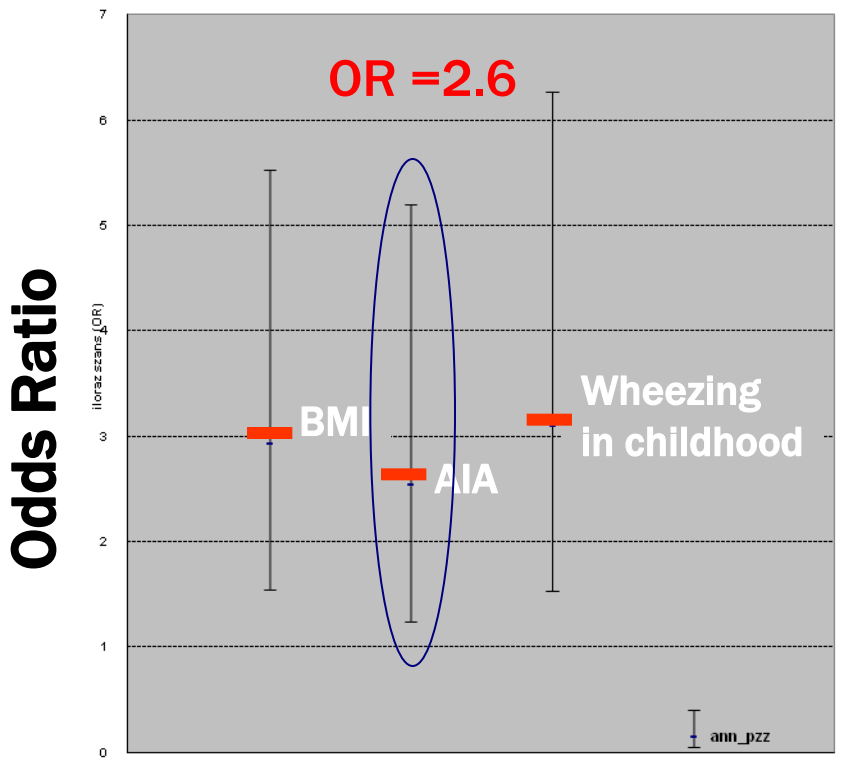
Jantti-Alanko S. et al. Rhinology 1989,8.59

Kim JE Ear Nose Throat J. 2007 Jul;86(7):396-9.

AERD - a severe asthma phenotype

- Higher medication requirements, including dependence on oral GCS *(Szczeklik A. et al. 2000)*
- Irreversible airway obstruction
- More likely to have been intubated and to have a steroid burst in the previous three months *(**Mascia K et al . 2005**)*
- Frequent exacerbations
  (Koga T. Et al. 2006)
- Association with near fatal asthma
  (Plaza W. et al. 2002)

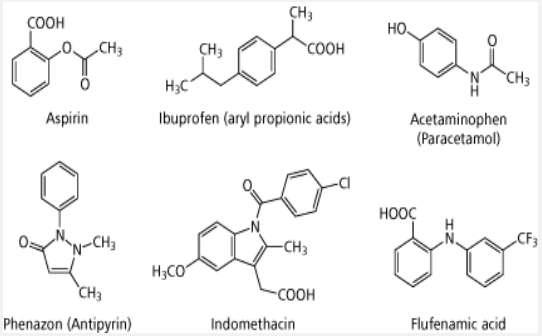
Risk factors for severe asthma



ML Kowalski et al. Allergy 2010 ,in press

The mechanism of sensitivity to NSAIDs in patients with AERD

- **Mechanism – non immunological**
  - Cross-reacting drugs have diverse chemical structure
  - No specific immunoglobulins
  - No specific T-cells



- **Mechanism related to pharmacological activity of NSAIDs**
  - Only Cox inhibitors cross-react with ASA
  - COX-1 >>> COX-2 inhibitors

- **Biochemical abnormalities**
  - Several – related to AA metabolism e.g. decreased PGE2 generation , elevated urinary LTE4
  - Identified only in some patients

Patomechanisms of Aspirin Exacerbated Respiratory Disease

I. The acute reaction precipitated by ASA and NSAIDs

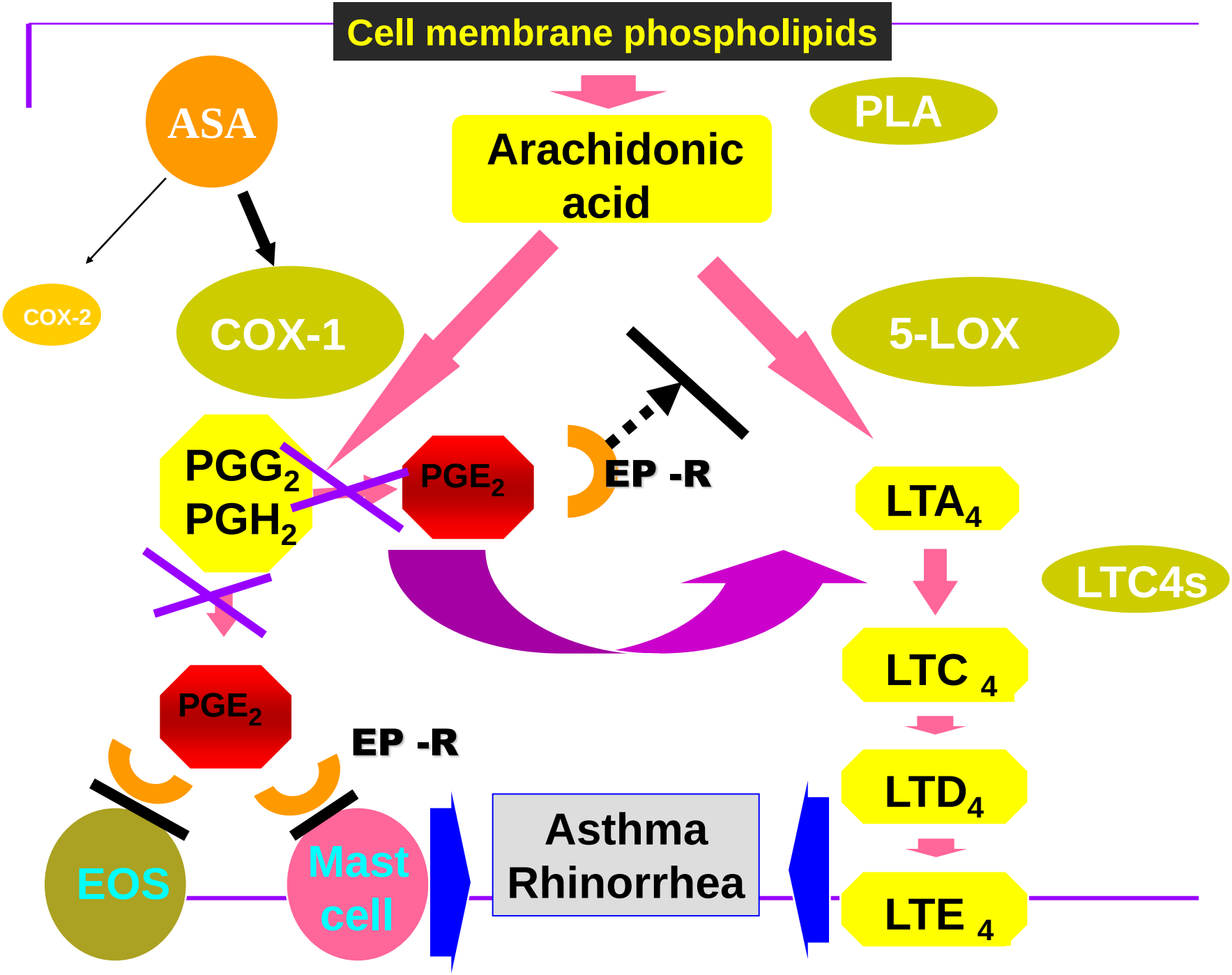
I I. Chronic symptoms and underlying airway inflammation

?

Cross-sensitivity between ASA and NSAID's and prostaglandin inhibition

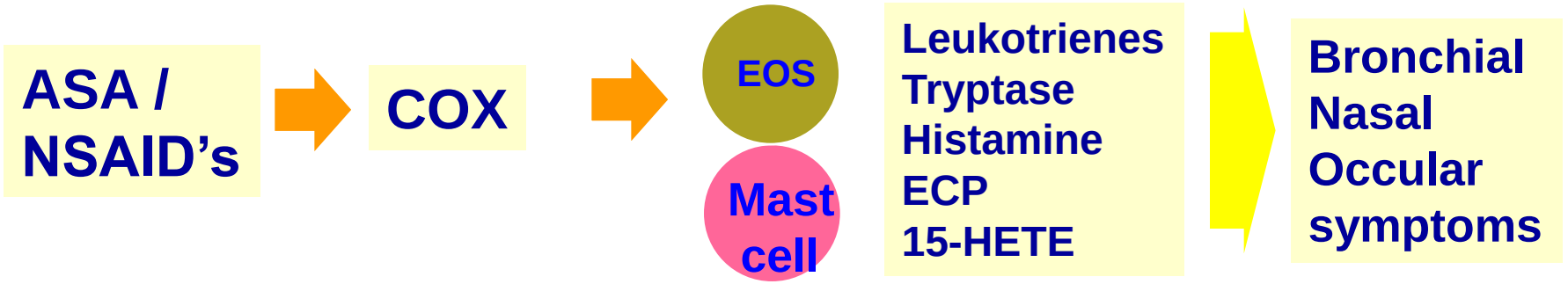
A.Szczeklik 1975/modified

Generic name	PG's inhibition	Cross-sensitivity
Aspirin **Indomethacin** **Ibuprofen** **Piroxicam** **Naproxen**	**Strong**	**High - 50 - 90%**
Phenylbutazon **Acetaminophen**	**Weak**	**Low < 5%**
Na Salicylate	**No**	**none or rare cases reported**


Cell membrane phospholipids
ASA
PLA
Arachidonic acid
COX-2
COX-1
5-LOX
PGG2
PGH2
PGE2
EP -R
LTA4
LTC4s
LTC 4
PGE2
EP -R
LTD4
EOS
Mast cell
Asthma
Rhinorrhea
LTE 4

Patomechanisms of Aspirin Exacerbated Respiratory Disease

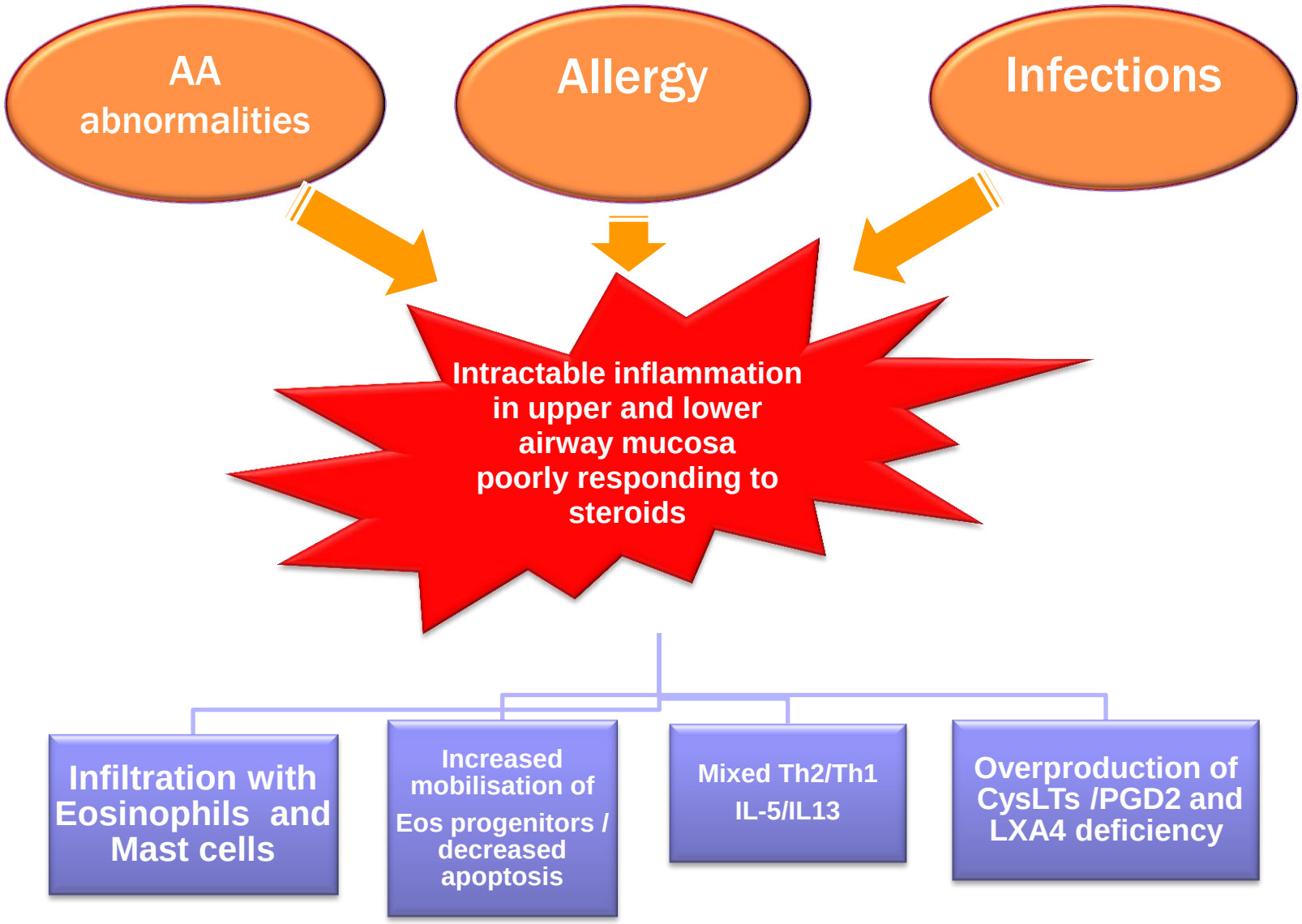
I. Acute symptoms precipitated by ASA and NSAIDs

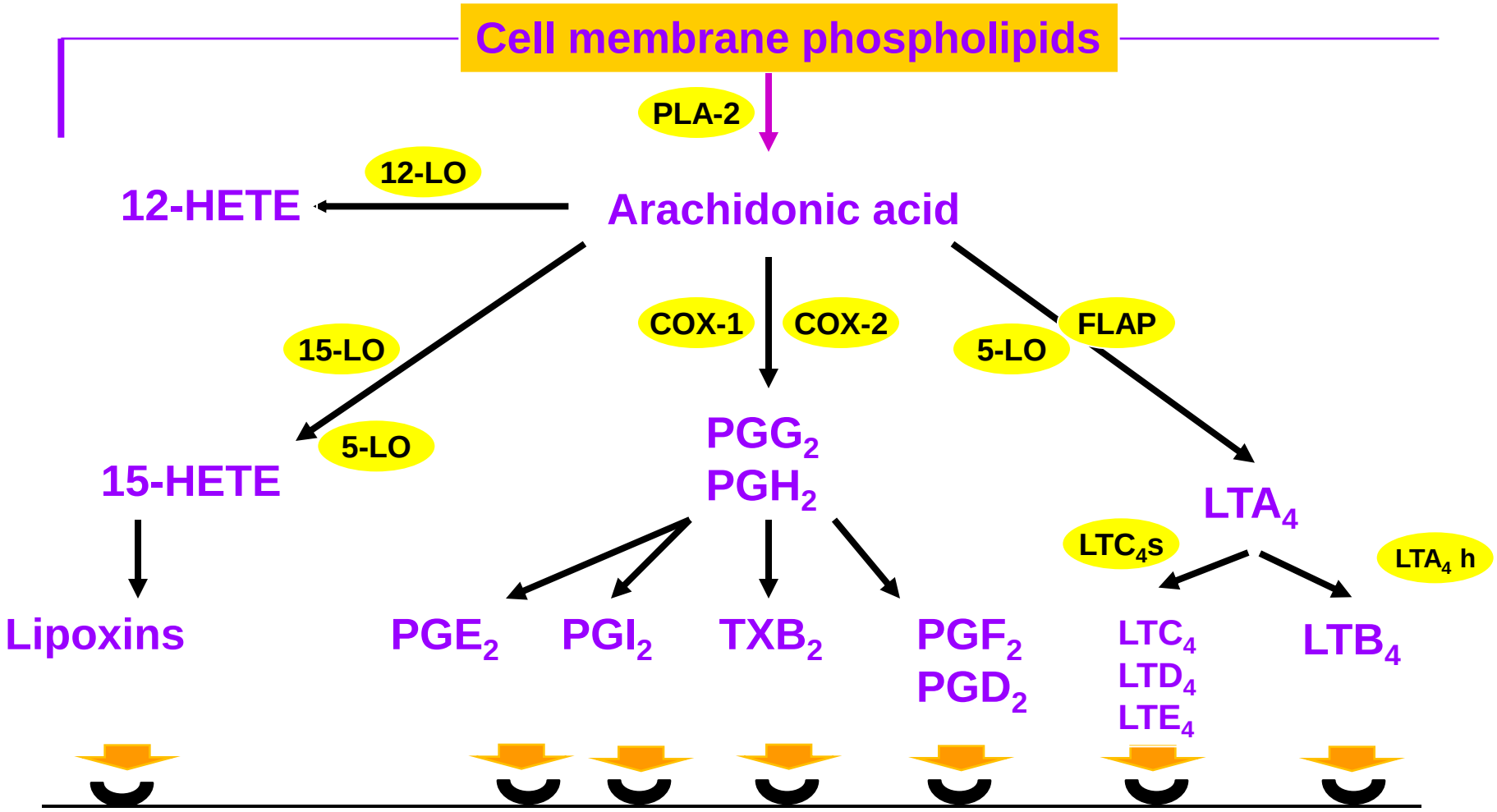


I I. Chronic symptoms and underlying airway inflammation

Unrelated to intake of ASA or other NSAIDs !!!

Pathogenesis of eosinophylic inflammation in patients with AERD





- Specific release of 15-HETE upon ASA challenge
- Abnormal lipoxins generation

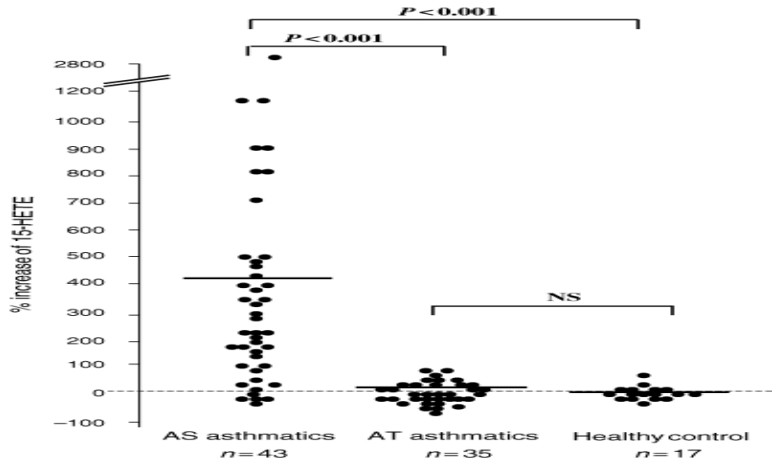
- Decreased production of PGE2
- Downregulation of Cyclooxygenase-2 Cyclooxygenase-1(?)

- Increased generation of cysLTs (urine , BAL, EAC)
- Overexpression of LT receptors

Diagnosis of respiratory type of hypersensitivity to NSAIDs

- **History**
- **Aspirin challenge**
  - Oral
  - Inhaled
  - Intranasal
- **In vitro testing**
  - Cellular activation tests
    - BAT
    - ASPITest (15-HETE)
  - Urinary LTE4
- **Genetic testing**

Aspirin-Sensitive Patients Identification Test (ASPITest)



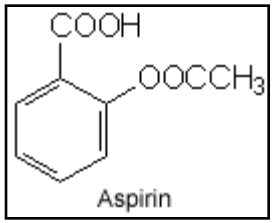
Sensitivity	**82%**	**PPV**	**79%**
Specificity	**83%**	**NPV**	**86%**

M.L.Kowalski et al. Allergy 2005,60,1139-45

Arachidonic acid

COX-1

COX-2

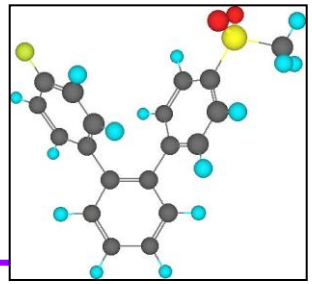


Aspirin

Celecoxib

PGE, PGI2, TXB2

Prostaglandins



Cytoprotection Regulation

Inflammation

Allergy

REVIEW ARTICLE

Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAACI/ENDA# and GA2LEN/HANNA*

M. L. Kowalski[1], J. S. Makowska[1], M. Blanca[2], S. Bavbek[3], G. Bochenek[4], J. Bousquet[5], P. Bousquet[6], G. Celik[3], P. Demoly[7], E. R. Gomes[8], E. Niżankowska-Mogilnicka[4], A. Romano[9], M. Sanchez-Borges[10], M. Sanz[11], M. J. Torres[2], A. De Weck[11], A. Szczeklik[12,*] & K. Brockow[13,#]

Allergy 2011; 66, 6 (June), 818- 829

Tolerance of NSAIDs by sensitive patients: ENDA/GA2LEN classification

- **Group A. NSAIDs cross-reacting in majority of hypersensitive patients (60 -100%)**
- **Group B . NSAIDs cross- reacting in minority of hypersensitive patients (2-10%)**
- **Group C. NSAIDs well tolerated by all hypersensitive patients***

M.L. Kowalski et al. Allergy 2011

Management of AERD

Avoidance of NSAIDs

- **Recommendations for selective COX-2 inhibitors**

Pharmacologic treatment

- **Intranasal /inhaled/oral glucocorticosteroids**
- **Leukotriene antagonists**

Sinus surgery / polypectomy

- **Less effective in ASA-sensitive**

Aspirin desensitization

- **Clinical effects: risks / benefits**

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