WORLD ALLERGY TRAINING SCHOOL

DRUG ALLERGY: PATHOPHYSIOLOGY, DIAGNOSIS AND MANAGEMENT

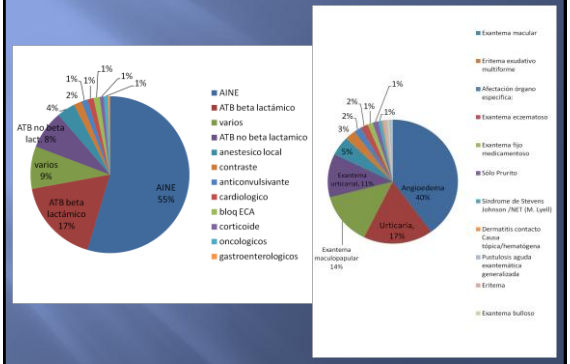
Mario Sánchez-Borges

Hyderabad, India
December 9th, 2012

sanchezbmario@gmail.com

EPIDEMIOLOGY

- In the USA ADR 15.1 % and serious ADR 6.7 % (Lazarou et al. J Am Med Assoc 1998; 279: 1200-5)
- Responsible for 3.1 to 6.2 % of hospitalizations
- Inpatient ADRs responsible for 106,000 deaths annually
- 4th to 6th leading cause of death
- In outpatients 17 to 25 %, serious 13 %
- Most common offenders: Antibiotics, NSAIDs, diuretics, anticonvulsivants



Jares E, Sánchez-Borges M, Gómez M, et al. AAAAI 2013

Main triggering agents for severe allergic reactions according to the age of patients registered in the Online Latin American Survey on Anaphylaxis

Agents	Age (years)				
	<2 31 (16.3%)	2-5 28 (14.7%)	6-11 57(29.9%)	12-18 75(39.2%)	Total N=191 (%)
Food - total	***16 (53.3)***	***16 (56.5)***	***17 (30.5)***	***20 (26.2)***	***69 (36.1)***
Cow's milk	7 (22.6)	7 (25.0)	4 (7.0)	-	*18 (9.4)*
Egg	8 (25.8)	5 (17.9)	-	1 (1.3)	*14 (7.3)*
Fish/seafood	-	1 (3.6)	4 (7.0)	9 (12.0)	*14 (7.3)*
Peanuts	-	1 (3.6)	2 (3.5)	2 (26.7)	*5 (2.6)*
Nuts	-	-	2 (3.5)	2 (26.7)	*4 (2.1)*
Manioc	-	-	1 (1.8)	-	*1 (0.5)*
Corn	-	-	-	1 (1.3)	*1 (0.5)*
Fruits	1 (3.2)	2 (7.1)	2 (3.5)	2 (26.7)	*7 (3.7)*
Wheat*	-	-	2 (3.5)	2 (26.7)	*4 (2.1)*
Soy	-	-	-	1 (1.3)	*1 (0.5)*
Drugs - total	***6 (20.0)***	***-***	***14 (24.5)***	***33 (44.0)***	***53 (27.7)***
NSAID	2 (6.5)	-	9 (15.8)	25 (33.3)	*36 (18.9)*
Antibiotics	4 (12.9)	-	3 (5.3)	6 (8.0)	*13 (6.8)*
Others	-	-	-	2 (2.7)	*2 (1.0)*
Insects - total	***8 (26.7)***	***11 (39.1)***	***17 (30.5)***	***15 (19.7)***	***51 (26.2)***
Bee	-	1 (3.6)	10 (17.5)	8 (10.7)	*19 (10.0)*
Ants	7 (22.6)	9 (32.1)	4 (7.0)	3 (4.0)	*23 (12.0)*
Wasp	1 (3.2)	1 (3.6)	3 (5.3)	4 (5.3)	*9 (4.7)*
Immunotherapy	-	-	***6 (10.2)***	***5 (6.6)***	***11 (5.8)***
Latex	-	***1 (3.6)***	***1 (2.0)***	***2 (3.3)***	***4 (2.1)***
Exercise/cold	-	-	***1 (2.0)***	***2 (3.3)***	***3 (1.6)***

RISK FACTORS

- **Drug**: structure, molecular weight, dose, route of administration, duration of Tx, repetitive exposure, concurrent illnesses.
- **Host**: age, sex, atopy, specific genetic polymorphisms, inherent predisposition to react to multiple unrelated drugs (multiple drug allergy syndrome), underlying diseases, and specific genetic polymorphisms

CLASSIFICATION OF ADVERSE REACTIONS TO DRUGS

Type	Characteristics	Reactions
TYPE A: PREDICTABLE (80%)	**Dose dependent, related to known pharmacologic action, in healthy individuals**	**TOXICITY (OVERDOSE)** **SIDE EFFECTS** **SECONDARY EFFECTS** **INTERACTIONS**
TYPE B: UNPREDICTABLE (20%)	**Dose independent, unrelated to pharmacologic action, in susceptible individuals**	**INTOLERANCE** **IDIOSINCRASY** **ALLERGY** **PSEUDOALLERGY**

DRUG ALLERGY PRACTICE PARAMETERS 2010

Drug Reactions

Predictable

Reaction	Example
Overdose	Acetaminophen -induced liver necrosis
Side effect	Albuterol-induced tremor
Secondary effect	*C. difficile* colitis (clindamycin)
Drug interactions	Cardiac arrhythmia from terfenadine/ erythromycin

Unpredictable

Reaction	Example
Intolerance	Tinnitus from ASA
Idiosincrasy	Dapsone-induced HA in def of G6PD
Allergy (6-10%)	Anaphylaxis due to PCN
Pseudoallergy	Anaphylactoid reaction from RCM

UNPREDICTABLE REACTIONS

- **INTOLERANCE**: Occurs at low and sometimes subtherapeutic doses without underlying abnormalities of metabolism, excretion, or bioavailability of the drug
- **IDIOSINCRASY**: Abnormal or unexpected effect unrelated to the intended pharmacologic action.

UNPREDICTABLE REACTIONS

- **ALLERGY**: Immunologically mediated response resulting in the production of drug-specific antibodies, T cells, or both.
- **PSEUDOALLERGY**: Mimic IgE-mediated allergic reactions but are due to direct release of mediators from mast cells and basophils. Do not require previous sensitization (opiates, colloid volume expanders, polymyxin B, ACTH, RCM,excipients, vancomycin)

DRUG ALLERGY: MECHANISMS AND CLINICAL PICTURE

	Clinical picture	Drugs
Type I: IgE-mediated	Urticaria, angioedema, bronchospasm, anaphylaxis	β-lactam antibiotics, platinum, perioperative agents
Type II: Cytotoxic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinidine, α-methyldopa, sulfonamides
Type III: Immune complex	Serum sickness	Penicillin, infliximab, thymoglobulin, procainamide, phenylpropanolamine
Type IV: Delayed hypersensitivity	Contact dermatitis, exanthema	Neomycin, bacitracin, glucocorticoids, penicillin, sulfonamides, local anesthetics, antihistamines

According to **temporal relationship**:
- IMMEDIATE (< 1 hour)
- ACCELERATED (1 hour to 3 days)
- DELAYED (> 3 days)

Hypersensitivity Reactions Mediated by Antibodies (I-III) and Delayed Hypersensitivity Reactions (IV a-d)

	Type I	Type II	Type III	Type IV a	Type IV b	Type IV c	Type IV d
Immune reactant	IgE	IgG	IgG	IFNγ, TNFα (T$_H$1 cells)	IL-5, IL-4/IL-13 (T$_H$2 cells)	Perforin/ GranzymeB (CTL)	CXCL-8, GM-CSF, IL-17 (?) (T-cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation
Effector	Mast-cell activation	FcR$^+$ cells (phagocytes, NK cells)	FcR$^+$ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction, contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis, maculo-papular exanthema with eosinophilia	Contact dermatitis, maculopapular and bullous exanthema, hepatitis	AGEP, Behçet disease

Pichler W.J. Delayed drug hypersensitivity reactions, Ann Int Med 2003

p-i concept
(Pharmacologic interaction with immune receptors)

- A drug binds noncovalently to a T-cell receptor, leading to an immune response via interaction with a major histocompatibility complex receptor.
- No sensitization required.
- Direct stimulation of memory and effector T cells.

DIAGNOSIS

- History and physical examination: previous and current use, previous reactions, temporal sequence
- Most frequent in the skin.
- Complementary tests: chest X-ray, EKG, CBC with differential, ESR, CRP, ANA, ANCAs, tryptase.
- IgE-mediated: skin testing, sIgE *in vitro*.
- Basophil activation test.
- Patch testing.
- Skin biopsy.

DIAGNOSIS
CLINICAL CRITERIA

1. Symptoms compatible with unpredictable drug reaction
2. Temporal relationship
3. Class and structure of the drug have been associated with reactions
4. Previous exposure
5. There is no other clear cause
6. STs, laboratory tests compatible

DRUG ALLERGY: DIAGNOSTIC METHODS

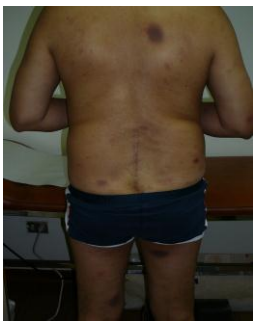
	Diagnostic methods
Type I: IgE-mediated	Skin tests, in vitro IgE, tryptase, 24-hour urine histamine or N-methylhistamine
Type II: Cytotoxic	Direct and indirect Coombs test
Type III: Immune complex	Cryoglobulins, C1q binding, Raji cell assay, complement
Type IV: Delayed hypersensitivity	Patch testing, lymphocyte proliferation assays, skin biopsy

CUTANEOUS MANIFESTATIONS

Clinical picture	Drugs
Maculopapular eruption	Allopurinol, aminopenicillins, cephalosporins, antiepileptic, sulfonamides
Fixed drug eruptions	Tetracyclines, NSAIDs, carbamazepine
Urticaria and angioedema	Penicillins, NSAIDs, ACE inhibitors
Photoallergic reactions	Oxicams
Lichenoid eruptions	ACE inhibitors, furosemide, NSAIDs, proton pump inhibitors, imatinib
Palmar-plantar erythrodysesthesia	Doxorubicin
Acne, AGEP	Glucocorticoids, androgens, lithium, phenytoin, isoniazid, sirolimus, antibiotics, calcium channel blockers
Sweet syndrome	GM-CSF, sulfonamides, minocycline
Pemphigus	Captopril, penicillamine
Pemphigoid	ACE inhibitors, furosemide, penicillin, sulfasalazine
Purpura and petechiae	Antibiotics, NSAIDs, diuretics
Erythema multiforme	
Exfoliative dermatitis	

Maculopapular rash induced by NSAID

FIXED DRUG ERUPTION (MEFENAMIC ACID)



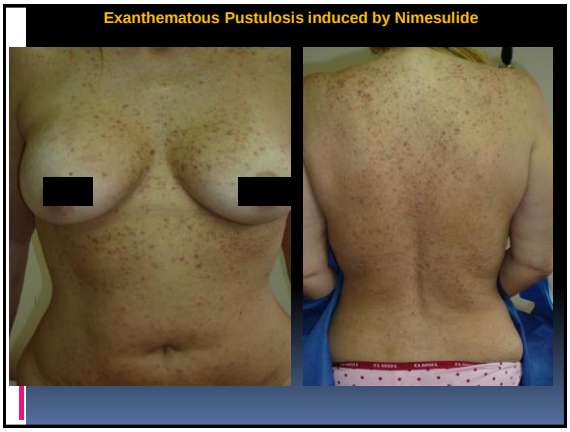
Sánchez-Borges M, González-Aveledo A. Allergol Immunopathol (Madr). 2011; 39: 246-7.

ENALAPRIL

Sánchez-Borges M, González-Aveledo L. Allergy Asthma Immunol Res. 2010; 2:195-8.

Sánchez-Borges M, González-Aveledo LA.
J Eur Acad Dermatol Venereol. 2011 May;25(5):621-2.

Sánchez-Borges M, González-Aveledo LA.
J Eur Acad Dermatol Venereol. 2011 May;25(5):621-2.



Pustuloderma induced by Amoxicillin/clavulanic acid

PANTOPRAZOLE

Sánchez-Borges M, González-Aveledo L. Allergol Immunopathol (Madr); 2012; 40: 194-5.

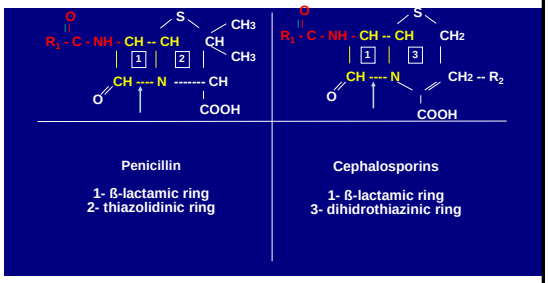
PANTOPRAZOLE

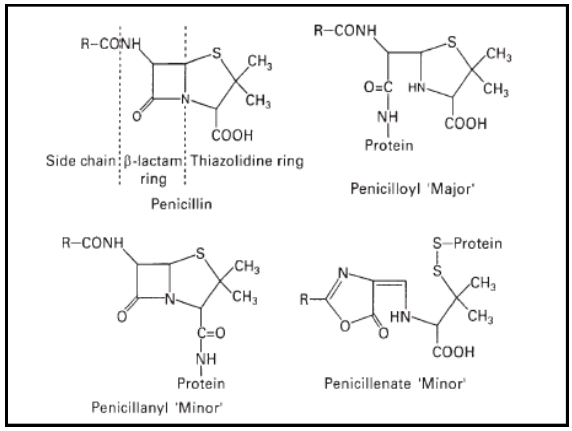
Sánchez-Borges M, González-Aveledo L. Allergol Immunopathol (Madr); 2012; 40: 194-5.

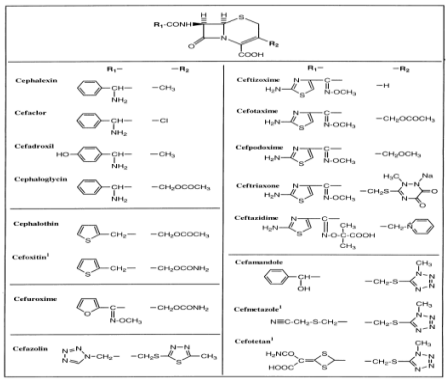
β-LACTAM ANTIBIOTICS

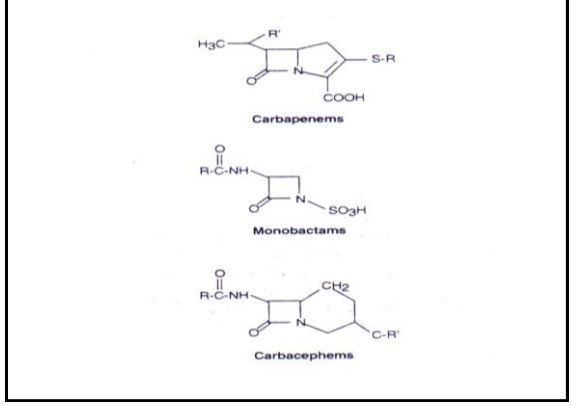
- Self-reported allergy 10 %, up to 90 % tolerate PCNs
- Anaphylaxis 1-2 per 10,000 treated patients
- ST with major and minor determinants (NPV 100 %, PPV 40-100 %)
- In vitro testing has uncertain predictive value (specificity 97-100 %, sensitivity 29-68 %)
- Ampicillin and amoxicillin induce IgE to R-group side chain
- Aztreonam does not cross react with other β-lactams except for ceftazidime
- Patients with positive PCN STs: administer carbapenems via graded challenge

Structure of ß-lactamic Antibiotics









CEPHALOSPORINS

- Reaction rate ~ 10-fold lower than it is to PCN
- Most HRs directed at the R-group side chains
- Avoid cephalosporins with similar R-group side chains
- 2 % of PCN skin test-positive patients react to cephalosporins
- Most patients with history of PCN reaction and negative skin tests for PCN may receive cephalosporins.
- If PCN STs are positive: 1. Use alternate non-β lactam ATB, 2. Graded challenge with cephalosporin, or 3. Rapid tolerance induction

CEPHALOSPORINS

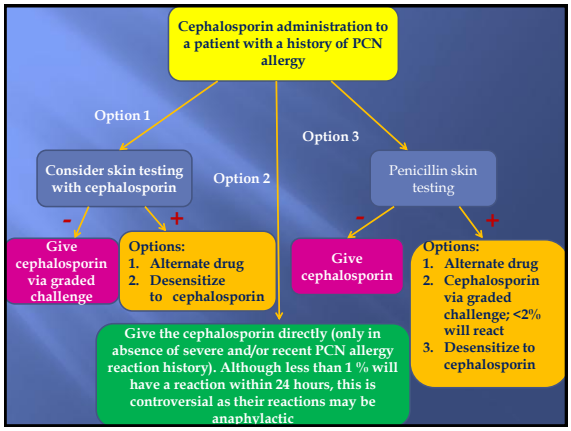
- Allergic to amoxicillin avoid Cephalosporins with identical R-group side chains (cefadroxil, cefprozil, cefatrizine)
- Allergic to ampicillin avoid Cephalosporins and carbacephems with identical R-group side chains (cephalexin, cefaclor, cephradine, cephaloglycin, loracarbef)

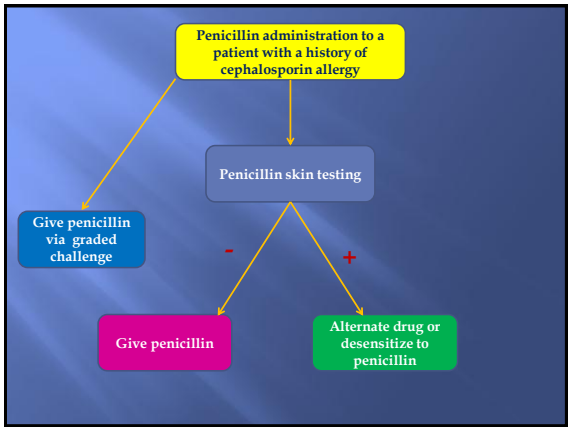
β-LACTAM ANTIBIOTICS THAT SHARE IDENTICAL R1-GROUP SIDE CHAINS

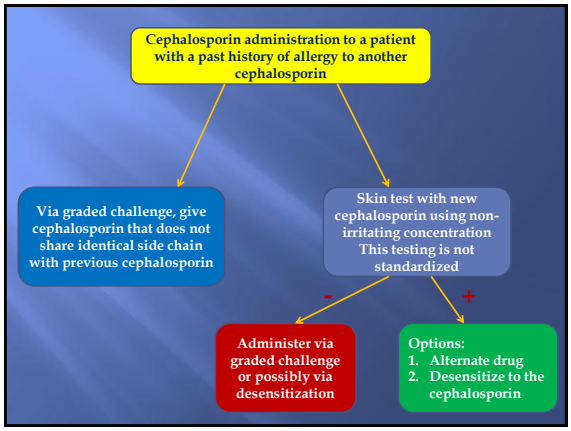
• Amoxicillin • Cefadroxil • Cefprozil • Cefatrizine	• Ampicillin • Cefaclor • Cephalexin • Cephradine • Cephaloglycin • Loracarbef	• Ceftriaxone • Cefotaxime • Cefpodoxime • Cefditoren • Ceftizoxime • Cefmenoxime
• Cefoxitin • Cephaloridine • Cephalotin	• Cefamandole • Cefonicid	• Ceftazidime • Aztreonam

β-LACTAM ANTIBIOTICS THAT SHARE IDENTICAL R2-GROUP SIDE CHAINS

• Cephalexin • Cefadroxil • Cephradine	• Cefotaxime • Cephalotin • Cephaloglycin • Cephapirin	• Cefuroxime • Cefoxitin
• Cefotetan • Cefamandole • Cefmetazole • Cefpiramide	• Cefaclor • Loracarbef	• Ceftibuten • Ceftizoxime







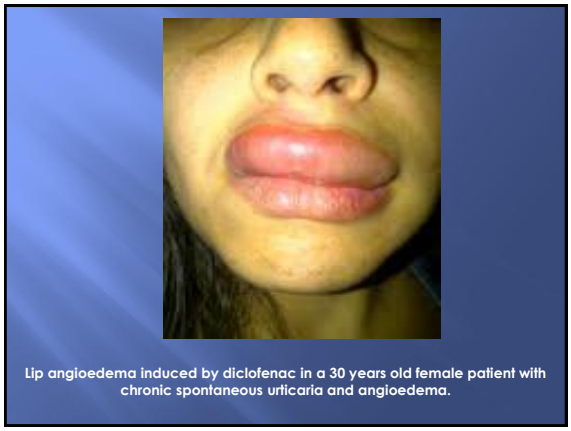
NONIRRITATING CONCENTRATIONS OF 15 ANTIBIOTICS

Drug	Full-strength concentration	Dilution	Nonirritating concentration
Azithromycin	100 mg/mL	10^{-4}	10 µg/mL
Cefotaxime	100 mg/mL	10^{-1}	10 mg/mL
Cefuroxime	100 mg/mL	10^{-1}	10 mg/mL
Cefazolin	330 mg/mL	10^{-1}	33 mg/mL
Ceftazidime	100 mg/mL	10^{-1}	10 mg/mL
Ceftriaxone	100 mg/mL	10^{-1}	10 mg/mL
Clindamycin	150 mg/mL	10^{-1}	15 mg/mL
Cotrimoxazole	80 mg/mL	10^{-2}	800 µg/mL
Erythromycin	50 mg/mL	10^{-3}	50 µg/mL
Gentamicin	40 mg/mL	10^{-1}	4 mg/mL
Levofloxacin	25 mg/mL	10^{-3}	25 µg/mL
Nafcillin	250 mg/mL	10^{-4}	25 µg/mL
Ticarcillin	200 mg/mL	10^{-1}	20 mg/mL
Tobramycin	80 mg/2mL	10^{-1}	4 mg/mL
Vancomycin	50 mg/mL	10^{-4}	5 µg/mL

Classification of Hipersensitivity reactions to ASA and NSAIDs

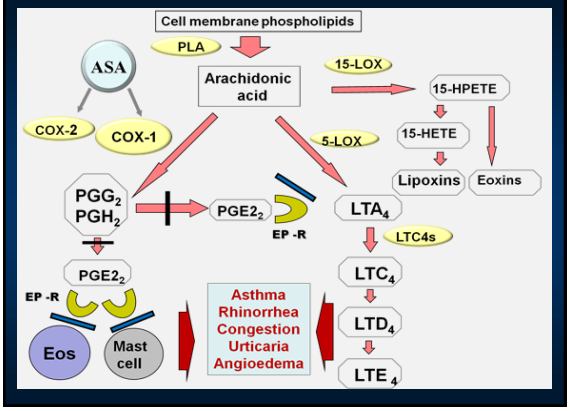
Reaction time	Clinical picture	Type of reaction	Underlying disease	Putative mechanism
Acute (immediate to several hours)	Rhinitis/asthma (AERD)	CR	Asthma/RS/NP	Inhib. COX-1
	Urticaria/AE (AECD)	CR	CSU	Inhib. COX-1
	Urticaria/AE/ anaphylaxis	Induced by multiple NSAIDs	None	Unknown Inhib. COX-1?
	Urticaria/AE/ anaphylaxis	Induced by a single drug	Atopy Food allergy Drug allergy	Specific IgE
Delayed (>24h)	- FDE - Severe bullous reaction - Maculopapular eruption - Pneumonitis - Aseptic meningitis - Nephritis - Contact and photocontact dermatitis	Induced by one or multiple drugs	Generally no	T Cells Cytotoxic T cells NK cells Other

Kowalski ML et al . Allergy 2011


Lip angioedema induced by diclofenac in a 30 years old female patient with chronic spontaneous urticaria and angioedema.

Chronic urticaria exacerbated by sodium diclofenac

♀ 15 years old, ibuprofen

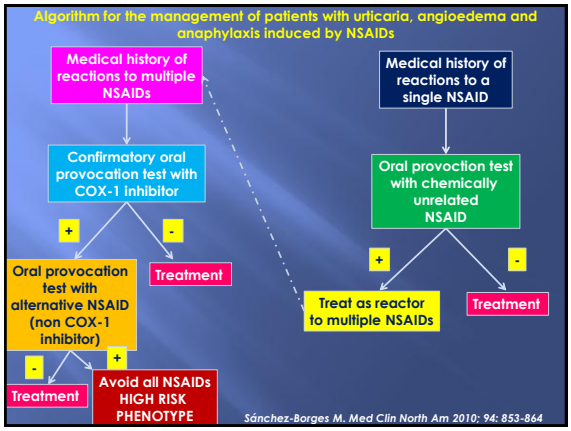


Tolerance to NSAIDs in patients with acute cross-reactive hypersensitivity to ASA

Group A. NSAIDS cross-reactive in most patients (60-100%)	
•Ibuprofen •Indomethacin •Sulindac •Naproxen •Fenoprofen •Meclofenamate •Ketorolac	•Etodolac •Diclofenac •Ketoprofen •Flurbiprofen •Piroxicam •Nabumetone •Mefenamic acid

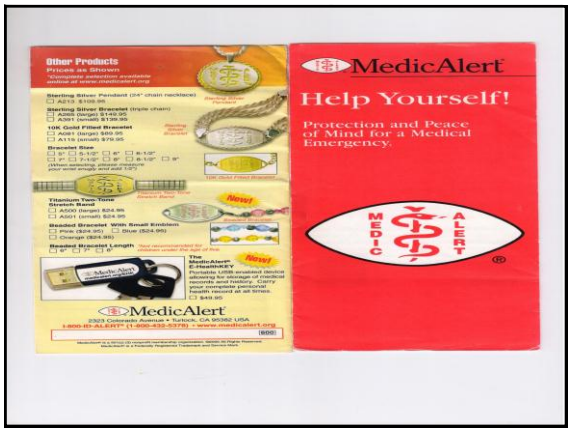
Group B. NSAIDs cross-reactive in a minority of patients (2-10%)	
Rhinitis/asthma	Urticaria/angioedema
•Acetaminophen (<1000 mg) •Meloxicam •Nimesulide	•Acetaminophen (<1000 mg) •Meloxicam •Nimesulide •Selective COX-2 inhibitors

Group C. NSAIDs well tolerated by all patients	
Rhinitis/asthma	Urticaria/angioedema
•Selective COX-2 inhibitors •Trisalicylate	•New selective COX-2 inhibitors (etoricoxib, parecoxib)



DRUG ALLERGY: PREVENTION AND MANAGEMENT

1. Careful history to determine host risk factors
2. Avoidance of cross-reactive drugs
3. Use of predictive tests, when available
4. Proper and prudent prescribing of drugs
5. Use oral route when possible
6. Documentation of ADR in the medical record
7. Medic Alert tags and bracelets
8. Induction of drug tolerance: where an alternate non-cross reacting drug cannot be used
9. Graded challenge: cautious introduction in patients who are unlikely to be allergic


Other Products
Prices as Shown
MedicAlert
Help Yourself!
Protection and Peace of Mind for a Medical Emergency.
MEDIC ALERT
MedicAlert


Thank you!!!