WEBINAR

ALerMOLD PEDIÁTRICO 2021

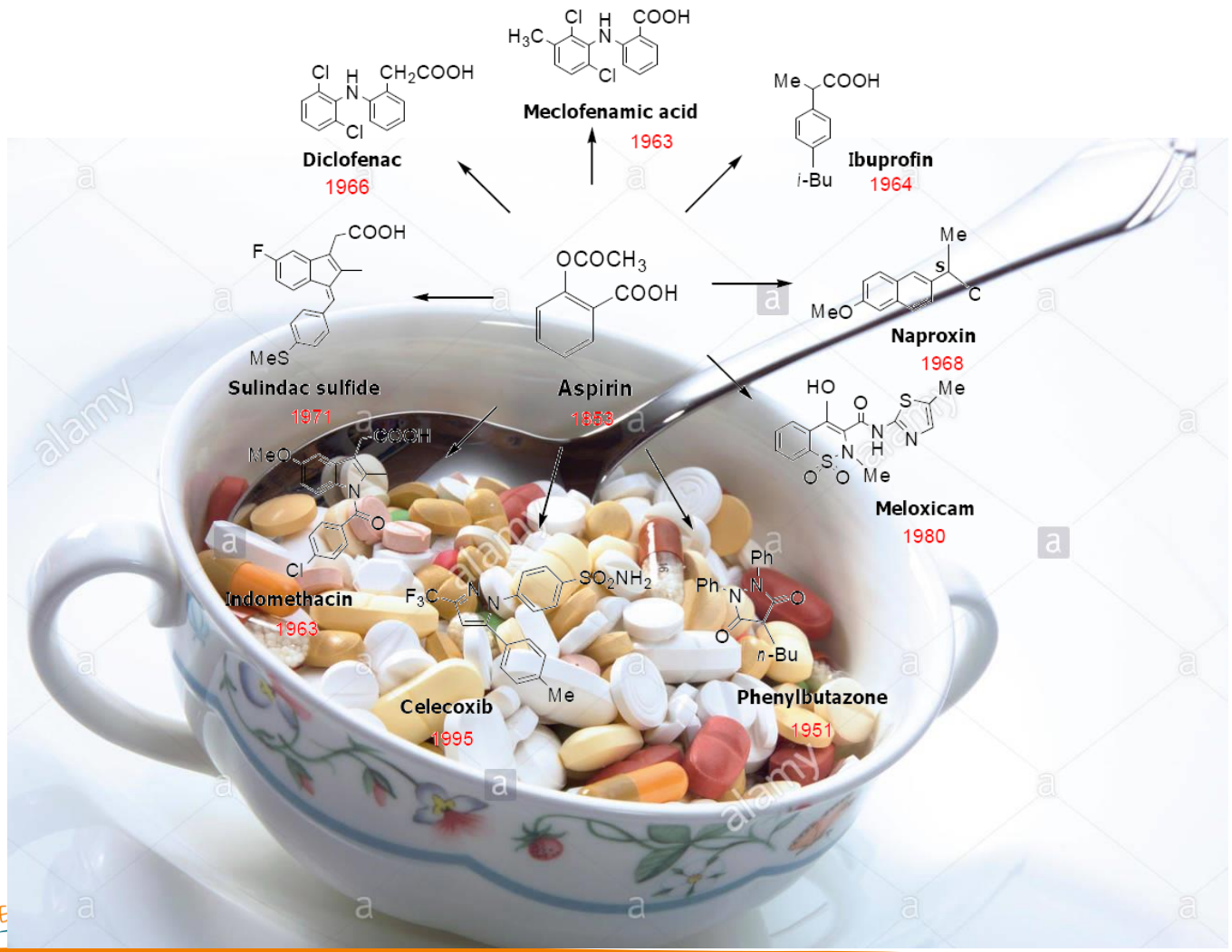
¿Qué hago con mi paciente alérgico a AINES?

Dr. Luis Moral Gil

Hospital General Universitario de Alicante

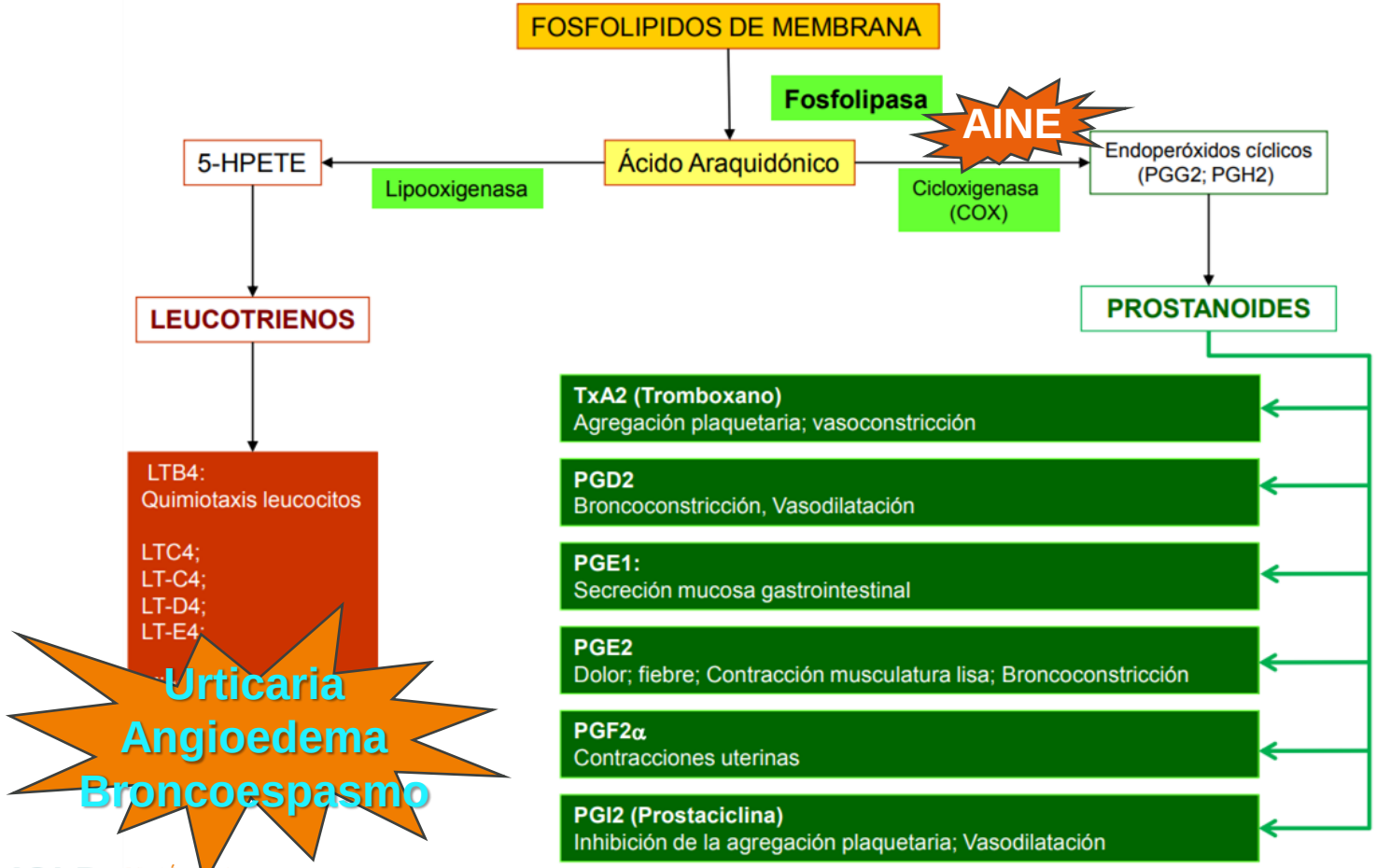
INMUNOTERAPIA MOLECULAR
la inmunización más precisa, a la dosis exacta

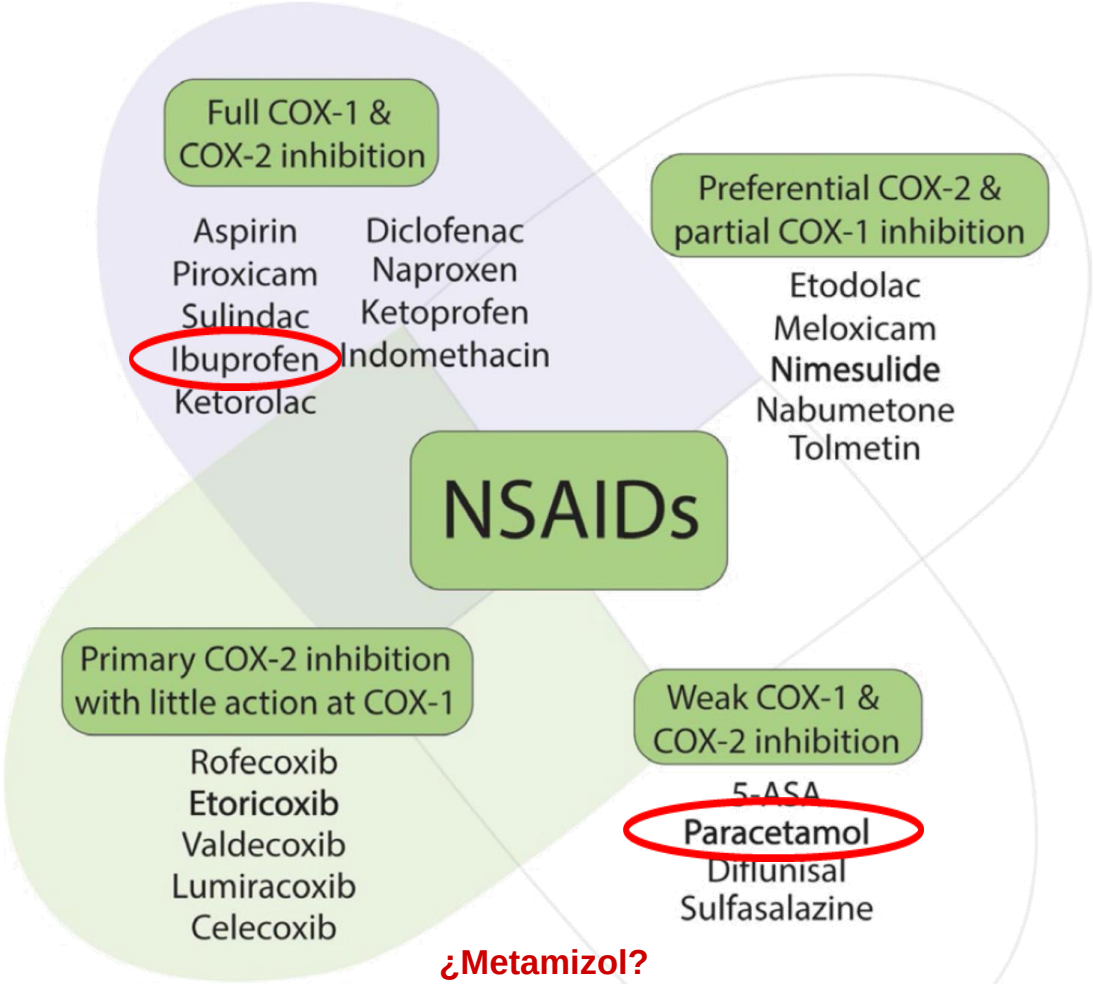
DIATER


Diclofenac
1966
Meclofenamic acid
1963
Ibuprofin
1964
Sulindac sulfide
1971
Aspirin
1853
Naproxin
1968
Meloxicam
1980
Indomethacin
1963
Celecoxib
1995
Phenylbutazone
1951

Chemical group	Drug	Chemical group	Drug
Salicylic acid derivatives	Aspirin (Acetylsalicylic acid)	Enolic acid derivatives	Pyrazolones
	Sodium Salicylate		Phenylbutazone
	Salsalate		Dipyrone (metamizole)
	Diflunisal		Oxicams
	Sulfasalazine		Piroxicam
Para-aminophenol	Paracetamol (acetaminophen)		Meloxicam
			Tenoxicam
Propionic acid derivatives	Ibuprofen		Lornoxicam
	Naproxen	Fenamic acid derivatives	Mefenamic acid
	Flurbiprofen		Meclofenamic acid
	Ketoprofen		Flufenamic acid
	Fenoprofen		Tolfenamic acid
	Oxaprozin	Sulfonanilide derivatives	Nimesulide
Acetic acid derivatives	Diclofenac	Selective COX-II inhibitors	Celecoxib
	Etodolac		Etoricoxib
	Ketorolac		Rofecoxib
Indole acetic acid derivatives	Indomethacin		
	Sulindac		
	Tolmetin		
Non-acid derivatives	Nabumetone		

Classification of NSAIDs according to their chemical structure

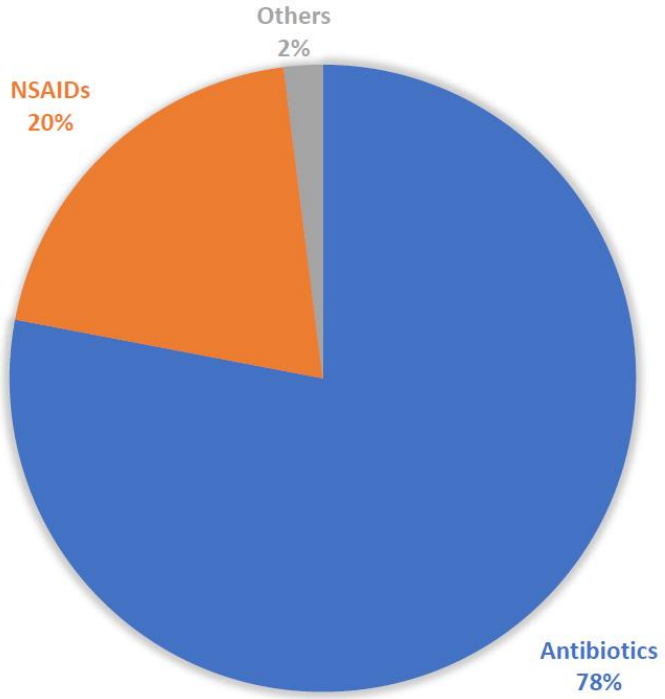

FOSFOLIPIDOS DE MEMBRANA
Fosfolipasa
AINE
5-HPETE
Lipooxigenasa
Ácido Araquidónico
Cicloxigenasa (COX)
Endoperóxidos cíclicos (PGG2; PGH2)
LEUCOTRIENOS
PROSTANOIDES
LTB4:
Quimiotaxis leucocitos
LTC4;
LT-C4;
LT-D4;
LT-E4;
TxA2 (Tromboxano)
Agregación plaquetaria; vasoconstricción
PGD2
Broncoconstricción, Vasodilatación
PGE1:
Secreción mucosa gastrointestinal
PGE2
Dolor; fiebre; Contracción musculatura lisa; Broncoconstricción
PGF2α
Contracciones uterinas
PGI2 (Prostaciclina)
Inhibición de la agregación plaquetaria; Vasodilatación
Urticaria
Angioedema
Broncoespasmo


Full COX-1 & COX-2 inhibition
Aspirin
Piroxicam
Sulindac
Ibuprofen
Ketorolac
Diclofenac
Naproxen
Ketoprofen
Indomethacin
Preferential COX-2 & partial COX-1 inhibition
Etodolac
Meloxicam
Nimesulide
Nabumetone
Tolmetin
NSAIDs
Primary COX-2 inhibition with little action at COX-1
Rofecoxib
Etoricoxib
Valdecoxib
Lumiracoxib
Celecoxib
Weak COX-1 & COX-2 inhibition
5-ASA
Paracetamol
Diflunisal
Sulfasalazine

¿Metamizol?

Results 2008-2018 Alicante (3 hospitales)

- 1185 reactions
- 1093 children (55 with more than one reaction)



Others
Local anesthetics
Vaccines
Radiological contrasts
Perianesthetic reactions
Cytostatics
Chlorhexidine

Results 2008-2018 Alicante (3 hospitales)

- 1185 reactions
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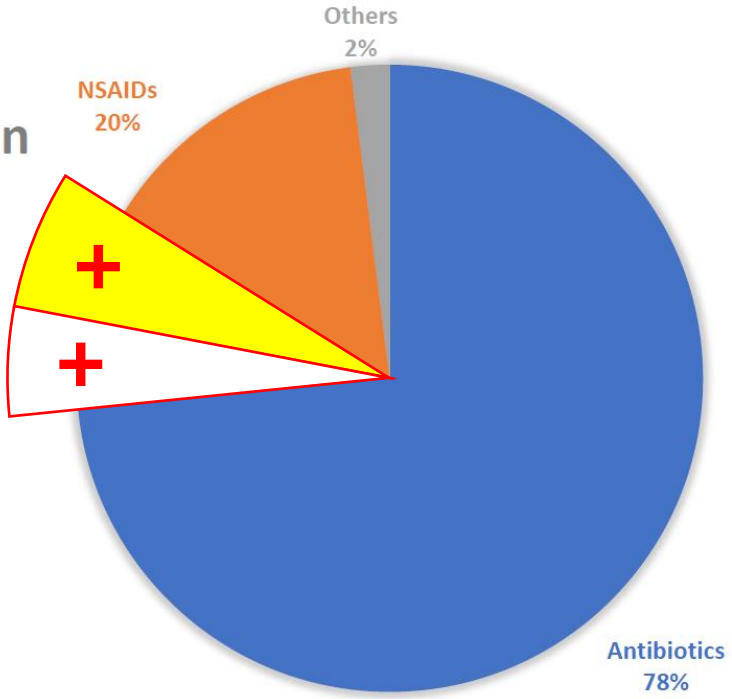

Others
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Vaccines
Radiological contrasts
Perianesthetic reactions
Cytostatics
Chlorhexidine

Phenotypes of NSAID-H according to the EAACI/ENDA/GA²LEN classification

Classification according to ENDA/GA²LEN	Type of the reaction	Timing of the reaction	Underlying disease	Clinical manifestation
SNIUAA	Non–cross-intolerant	Usually immediate (within minutes up to 1 h)	None	Urticaria, angioedema, and/or anaphylaxis
SNIDR	Non–cross-intolerant	Usually more than 24 h after exposure	None	Fixed drug eruption Maculopapular exanthema Severe bullous reactions Contact/photocontact dermatitis Pneumonitis, nephritis Aseptic meningitis
NIUA	Cross-intolerant	Within 1 h up to several hours	None	Urticaria/angioedema
NECD	Cross-intolerant		Chronic urticaria	Urticaria/angioedema
NERD	Cross-intolerant		Asthma/rhinosinusitis nasal polyposis	Asthma/rhinosinusitis

NECD, NSAID-exacerbated cutaneous disease; NECD, NSAID-exacerbated respiratory disease; NIUA, NSAID-induced urticaria and/or angioedema; SNIDR, single NSAID-induced delayed reaction; SNIUAA, single NSAID-induced urticaria, angioedema, and/or anaphylaxis.

Phenotypical characterization of children with hypersensitivity reactions to NSAIDs

Mathias Cousin[1], Anca Chiriac[1,2], Nicolas Molinari[3], Pascal Demoly[1,2] & Davide Caimmi[1,2]

PAI Pediatric Allergy and Immunology 2016

107 of 635 (**16.9%**) comprobados por PEOC

POSITION PAPER

WILEY

EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents

Mona Kidon[1] | Natalia Blanca-Lopez[2] | Eva Gomes[3] | Ingrid Terreehorst[4] | Luciana Tanno[5,6,7] | Claude Ponvert[8] | Chiang Wen Chin[9] | Jean Christoph Caubet[10] | Ozge Soyer[11] | Francesca Mori[12] | Miguel Blanca[13] | Marina Atanaskovic-Markovic[14]

CLASIFICACIÓN DE LAS REACCIONES DE HIPERSENSIBILIDAD A AINE EN MENORES DE 10 AÑOS

Tipo de reactividad	Tipo de reacción	Manifestación clínica	Intervalo entre administración y síntomas	Mecanismo	Cofactores implicados
Cruzada (reacción no alérgica) **85.1 %**	Hipersensibilidad no alérgica inducida por AINE (NERD, NECD, NIUAA)	Urticaria. AE. Disnea. Rinitis. Conjuntivitis. Anafilaxia	Inmediata (habitualmente entre minutos y varias horas)	Inhibición de COX1	Posible
No Cruzadas (Alérgicas) **14.0 %**	Reacciones selectivas producidas por un AINE: urticaria. AE Anafilaxia (SNIUAA)	Urticaria. AE. Anafilaxia	Inmediata (<1 hora)	Mediada por IgE	Desconocido
0.9 %	Reacción selectiva tardía inducida por AINE (SNIDR)	Varios síntomas y órganos involucrados (exantema fijo, nefritis, SJS-TEN)	Tardía (habitualmente > de 24 horas)	Mediada por linfocitos T	Desconocido

AE: angioedema; **SJS:** síndrome de Stevens Johnson; **TEN:** necrólisis epidérmica tóxica; **NERD:** *NSAIDs-exacerbated respiratory disease*; **NECD:** *NSAIDs-exacerbated cutaneous disease*; **NIUAA:** *NSAIDs-induced urticaria/angioedema, anafilaxia*; **SNIUAA:** *selective NSAID-induced urticaria, angioedema, and/or anaphylaxis*; **SNIDR:** *selective NSAID-induced delayed type HS reactions.*

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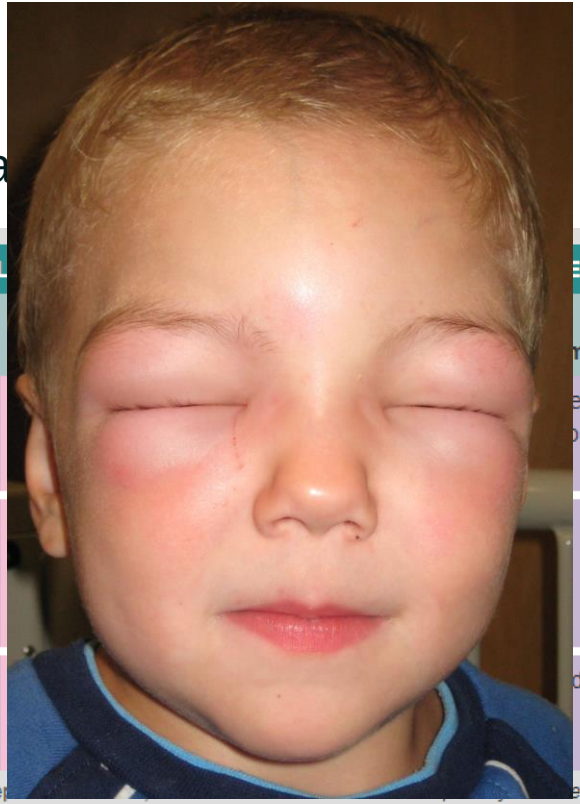

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CLASIFICACIÓN DE L… EN MENORES DE 10 AÑOS

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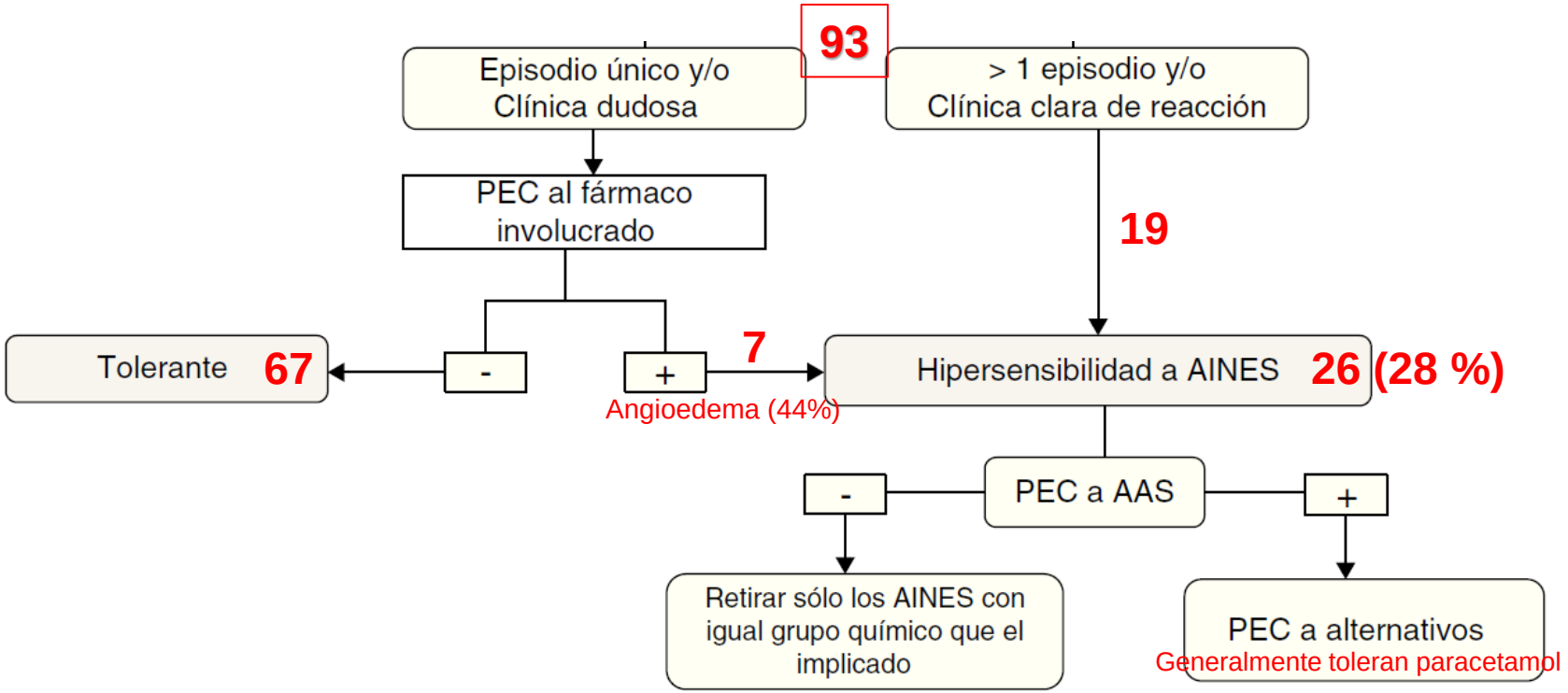
Reacciones de hipersensibilidad a antiinflamatorios no esteroideos y su tolerancia a fármacos alternativos☆

analesdepediatría 2016

K. Calvo Campoverde, M.T. Giner-Muñoz, L. Martínez Valdez, M. Rojas Volquez, J. Lozano Blasco, A. Machinena y A.M. Plaza*

IBUPROFENO, metamizol, AAS



Non-steroidal anti-inflammatory drug hypersensitivity in children

C. Alves[a,*], A.M. Romeira[a], C. Abreu[b], P. Carreiro-Martins[a,c], E. Gomes[b], P. Leiria-Pinto[a,c]

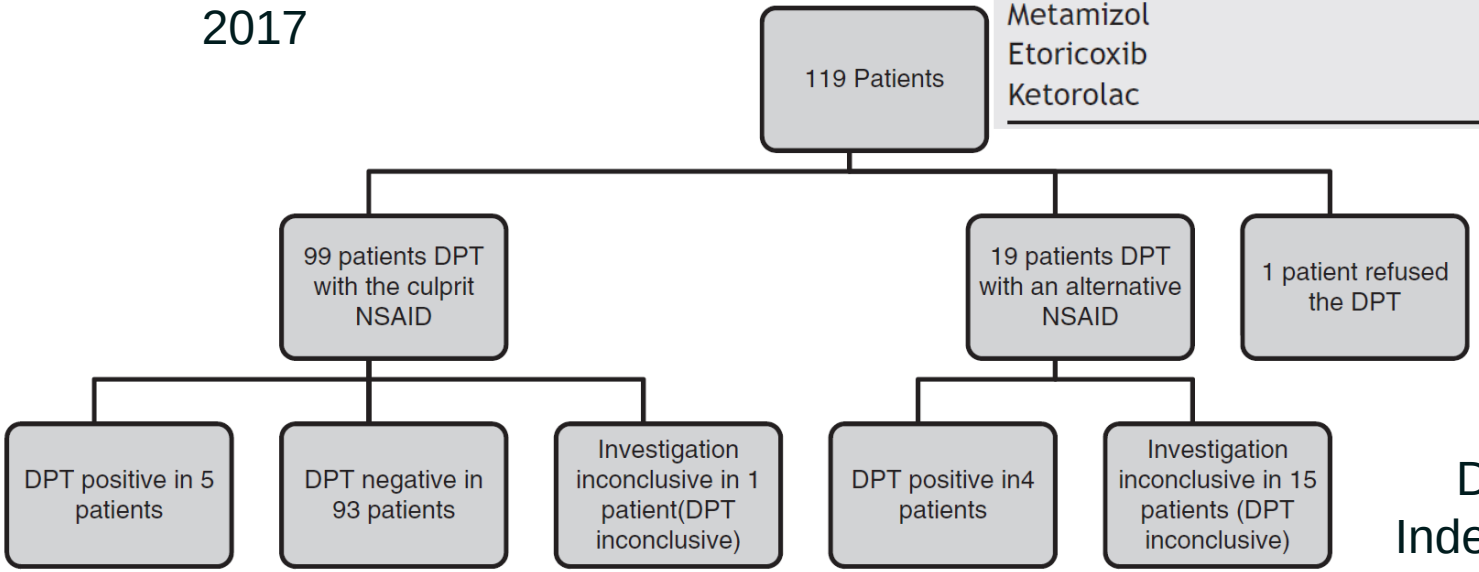
Allergologia et immunopathologia

SEICAP

2017

119 niños (Lisboa y Oporto)

Implicated NSAID	Number of patients
Ibuprofen	94
Paracetamol	20
ASA	7
Nimesulide	4
Metamizol	1
Etoricoxib	1
Ketorolac	1



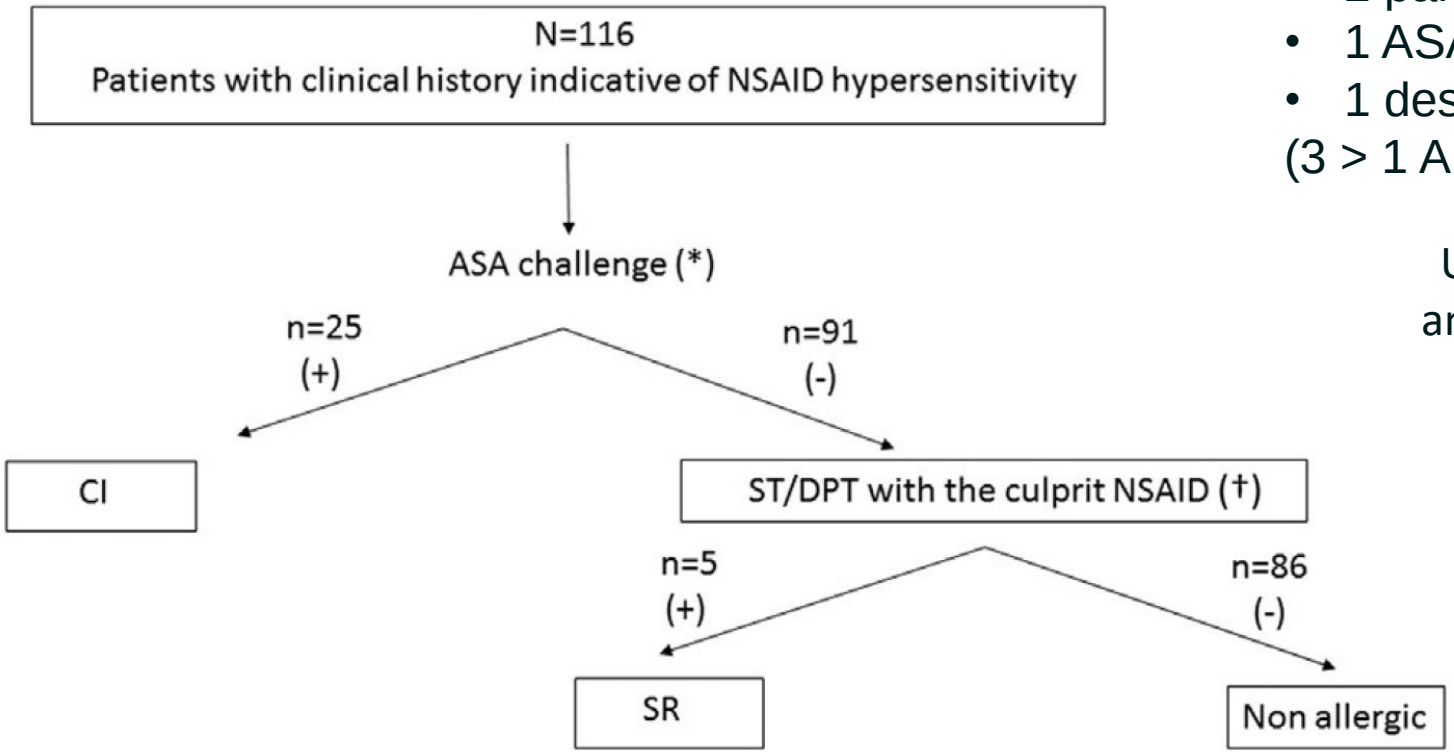
Confirmado: **8 %**
Descartado: 78 %
Indeterminado: 14 %

Acetyl Salicylic Acid Challenge in Children with Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs Differentiates Between Cross-Intolerant and Selective Responders

Natalia Blanca-López, MD, PhD[a], Elisa Haroun-Diaz, MD[a], Francisco Javier Ruano, MD, PhD[a], Diana Pérez-Alzate, MD[a], María Luisa Somoza, MD[a], María Vázquez de la Torre Gaspar, MD, PhD[a], Francisco Rivas-Ruiz, PhD[b], Elena García-Martin, PhD[c], Miguel Blanca, MD, PhD[a], and Gabriela Canto, MD, PhD[a] *Madrid, Málaga, and Cáceres, Spain*

JACI: **In Practice**

2018



HS demostrada: 30 (**26 %**)

- 26 ibuprofeno
- 5 metamizol
- 2 paracetamol
- 1 ASA
- 1 desketoprofeno

(3 > 1 AINE)

Urticaria o angioedema 57 %

Results of NSAID provocation tests and difficulties in the classification of children with nonsteroidal anti-inflammatory drug hypersensitivity

Annals of Allergy, Asthma & Immunology
OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF ALLERGY, ASTHMA & IMMUNOLOGY

2020

Ozge Yilmaz Topal, MD*; Ilknur Kulhas Celik, MD*; Irem Turgay Yagmur, MD*; Muge Toyran, MD*; Ersoy Civelek, MD*; Betul Karaatmaca, MD*; Can Naci Kocabas, MD†; Emine Dibek Misirlioglu, MD*

243 pacientes:

- 69 % ibuprofeno
- 86 % reacción cutánea

47 confirmados (**20 %**)

12 no comprobados (5 %)

Difícil de clasificar:

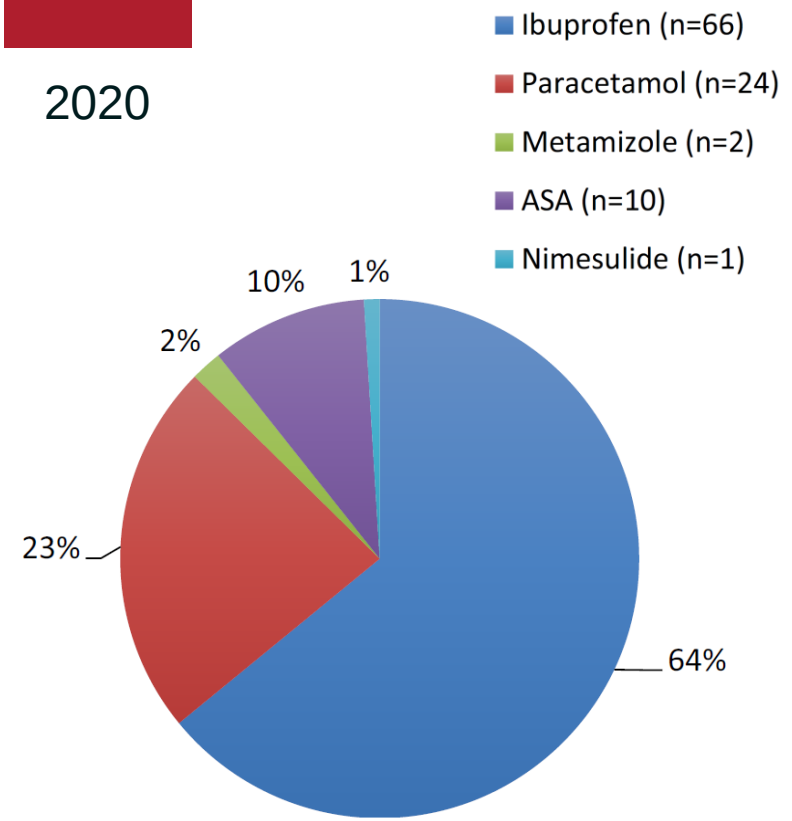
- Coexistencia de síntomas cutáneos y respiratorios
- Necesidad de multiples pruebas (no consentimiento)

A Multicenter Retrospective Study on Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Children: A Report from the European Network on Drug Allergy (ENDA) Group

JACI: In Practice

2020

Francesca Mori, MD, PhD[a], Marina Atanaskovic-Markovic, MD, PhD[b], Natalia Blanca-Lopez, MD, PhD[c], Eva Gomes, MD[d], Francesco Gaeta, MD[e], Lucrezia Sarti, MD[a], Marcel M. Bergmann, MD[f], Vladimir Tmusic, MD[b], Rocco L. Valluzzi, MD[g], and Jean-Christoph Caubet, MD[f] *Florence and Rome, Italy; Belgrade, Serbia; Madrid, Spain; Porto, Portugal; Geneva, Switzerland; and Rome, Vatican City*



Estudio restrospectivo 6 centros europeos
693 niños, 526 pruebas de exposición:
20 % positivas

Diferencias entre los centros:

- Duración de la prueba de exposición
- Uso de pruebas cutáneas
- Prueba oral con aspirina (solo en un centro)

Risk factors for positive paracetamol drug provocation testing and procedure optimization

Dunya Nohra[a,b,*], Rik Schrijvers, MD, PhD[c,*], Nidhal Touati, MD[a], Olga Nahas, MD[a], Najah Ben Fadhel, MD[a,d], Laetitia Ferrando[a], Pascal Demoly, MD, PhD[a,b], and Anca-Mirela Chiriac, MD, PhD[a,b]

JACI: **In Practice**

2019

498 pacientes estudiados por prueba de exposición en 22 años: 55 positivos (**11 %**), 16 en niños.

Todos los pacientes con historia inicial de anafilaxia fueron negativos para la prueba cutánea.

Behind the scene: Paracetamol hypersensitivity in children

PAI Pediatric Allergy and Immunology

Sevgi Sipahi Cimen[1] | Esra Yucel[1] | Deniz Ozceker[2] | Ayse Suleyman[1] | Zeynep Hizli Demirkale[1] | Ugurcan Sayili[3] | Nermin Guler[1] | Cevdet Ozdemir[1,4] | Zeynep Ulker Tamay[1]

2021

60 pacientes estudiados en 4 años: 8 confirmados (**13 %**)

- 4 selectivos
- 3 no selectivos, toleraron COX-2
- 1 no determinado

Solo 1 paciente con pruebas cutáneas positivas, pero toleró la prueba oral

Allergic Reactions to Metamizole: Immediate and Delayed Responses

International Archives of Allergy and Immunology

2016

Natalia Blanca-López[a] Natalia Pérez-Sánchez[b] José Augusto Agúndez[d]
Elena García-Martin[d] María José Torres[b] José Antonio Cornejo-García[c]
James R. Perkins[c] Miguel Angel Miranda[e] Inmaculada Andreu[e]
Cristobalina Mayorga[c] Gabriela Canto[a] Miguel Blanca[b] Inmaculada Doña[b]

[a]Allergy Service, Infanta Leonor Hospital, Madrid, [b]Allergy Unit and [c]Research Laboratory, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, [d]Department of Pharmacology, University of Extremadura, Caceres, and [e]Chemical Technology Institute, UPV-CSIC, Polytechnic University of Valencia, Valencia, Spain

922 reacciones con metamizol en adultos:

- Reacciones cruzadas: 678 (74 %)
- Reacciones selectivas: 137 (15 %)
  - No confirmado: 107 (12 %)

→
- 85 (62 %) pruebas cutáneas positivas
- 96 % reacciones de tipo inmediato
- 60 % anafilaxia

Metamizole-induced reactions as a paradigm of drug hypersensitivity: Non-allergic reactions, anaphylaxis, and delayed-type allergy

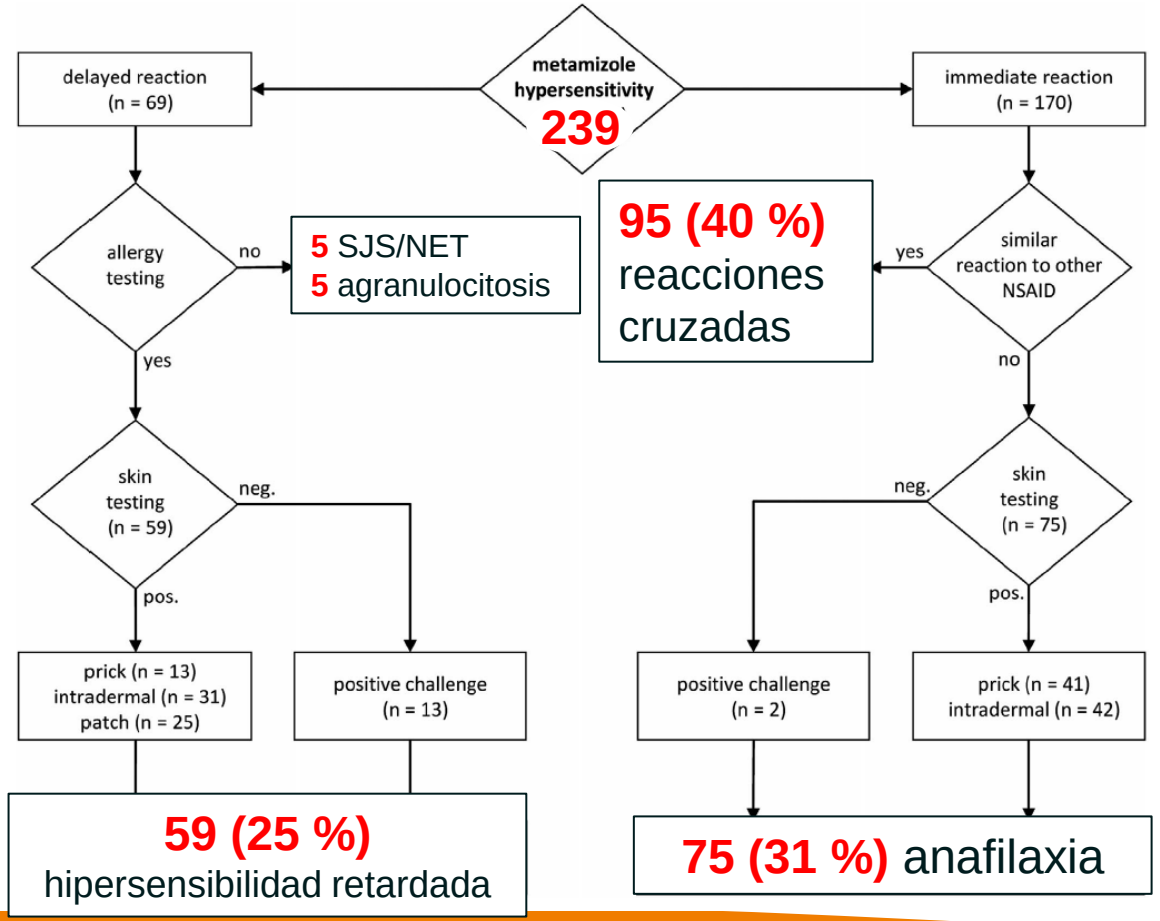
Axel Trautmann[1]
Knut Brockow[2]
Johanna Stoevesandt[1]

[1]Department of Dermatology and Allergy, University Hospital Würzburg, Würzburg, Germany
[2]Department of Dermatology and Allergy, Technical University of Munich, Munich, Germany

CLINICAL & EXPERIMENTAL ALLERGY TRUSTED EVIDENCE IN ALLERGY

2020

239 pacientes (> 12 años)



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	Formulation	Skin test	Intradermal test
Acetaminophen	Perfalgan®	10 mg/mL	1 mg/mL
Metamizole sodium	Novalgin®	40-400 mg/mL 400 mg/mL	0.4-4 mg/mL 40 mg/mL


Ibuprofen
Pain Relief Fever Reduction
NSAID
200 Tablets 200 mg
Extra Strength
Acetaminoph
Pain Reliever/ Fe
200 Capsules

REVIEW ARTICLE

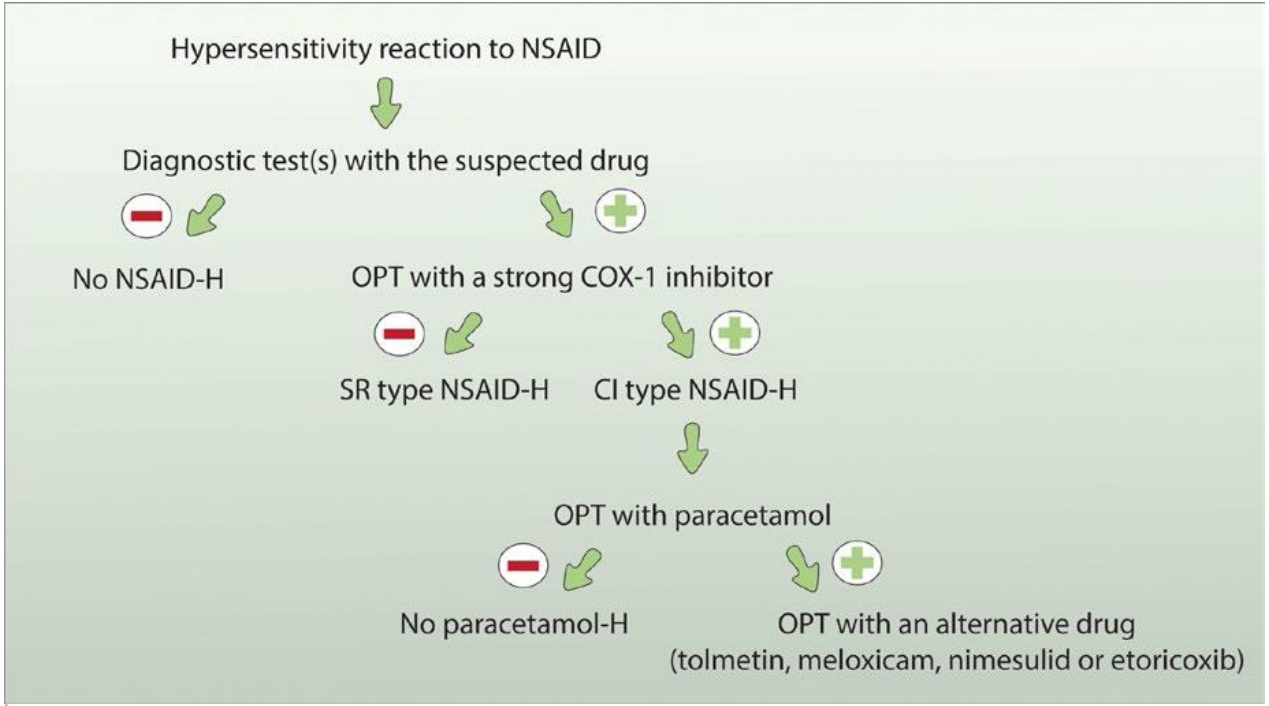
WILEY

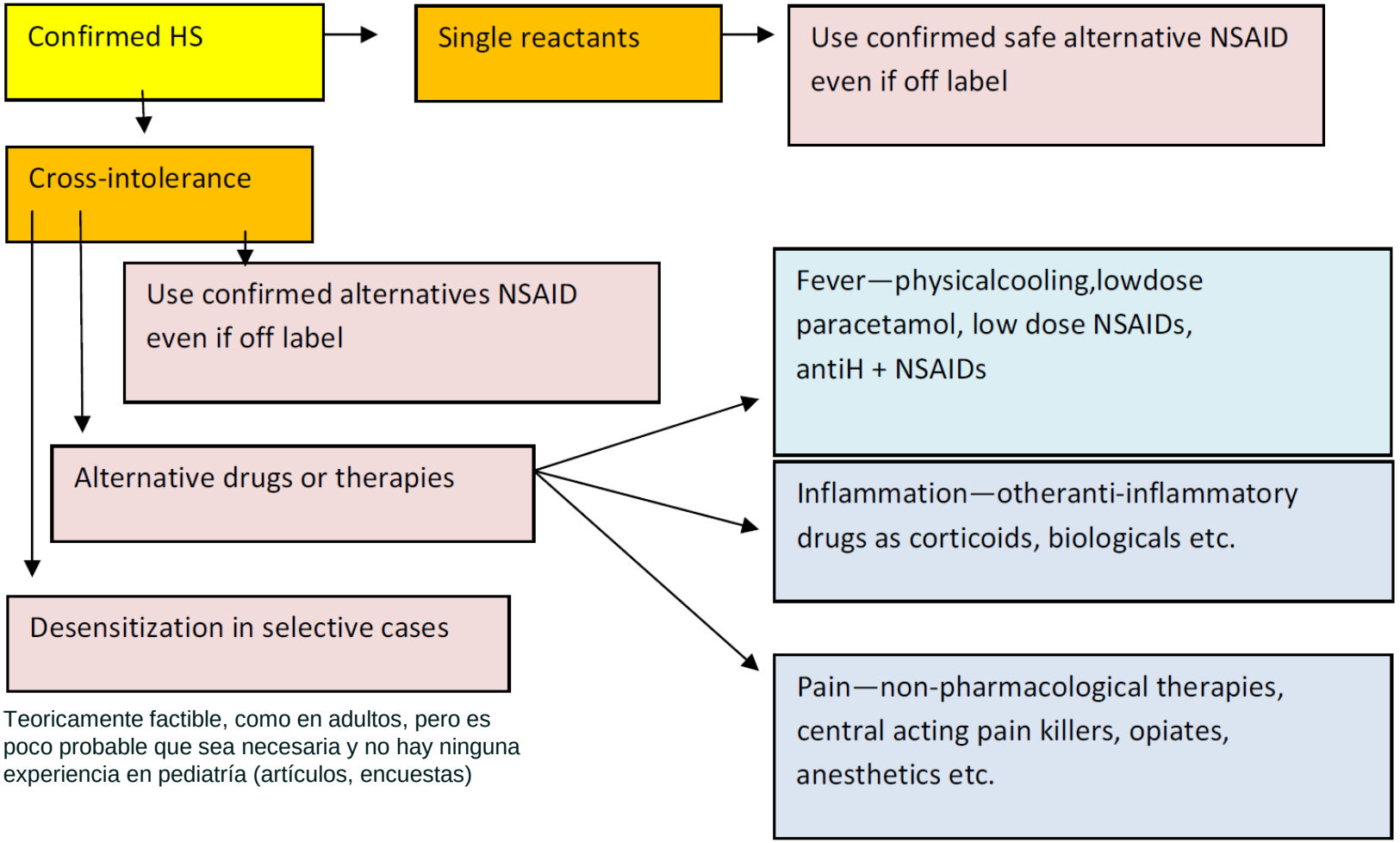
Characteristics of NSAID-induced hypersensitivity reactions in childhood

PAI Pediatric Allergy and Immunology

2019

Ozlem Cavkaytar[1] | George du Toit[2] | Davide Caimmi[3,4]





Teoricamente factible, como en adultos, pero es poco probable que sea necesaria y no hay ninguna experiencia en pediatría (artículos, encuestas)

Prevention of nonsteroidal inflammatory drug-induced urticaria and/or angioedema

Audrey Nosbaum, MD[*,†,‡]; Marion Braire-Bourrel, MD[*]; Rolande Dubost, MD[§]; Amélie Faudel, PharmD[‖]; Stéphanie Parat, PharmD[‖]; Jean-François Nicolas, MD, PhD[*,†,‡]; and Frédéric Bérard, MD, PhD[*,†,‡]

Annals of Allergy, Asthma & Immunology
Official Publication of the American College of Allergy, Asthma & Immunology

2013

65 pacientes adultos,
6 confirmados (9 %)

Characteristics of the patients who reacted to NSAIDs without premedication

Sex/age, y	Underlying diseases	Culprit NSAID	Time to onset of the reaction, min	Type of final premedication	Tolerance of final NSAID challenge
F/35	Atopy/CU	Aspirin	30	AntiH1 and LTA	Yes
F/41	Atopy	Aspirin	60	AntiH1 and LTA	Yes
M/44	0	Aspirin	30	AntiH1	Yes
F/21	0	Aspirin	240	AntiH1 and LTA	No
F/42	0	Flurbiprofen	120	AntiH1 and LTA	Yes
M/28	0	Aspirin	30	AntiH1	Yes

mi (humilde) opinión…

- Historia clínica
- Prueba de provocación con ibuprofeno
- Paracetamol, metamizol…
- Si no tolera, alternativa sencilla

No veo la necesidad de clasificar ni buscar tolerancia a fármacos que no sean imprescindibles

PROTOCOLO DE LA PRUEBA DE EXPOSICIÓN CONTROLADA

- 1/10 de dosis plena
- 1/4 de dosis plena
- Dosis plena

Intervalos de 1 hora y espera final de 1-2 horas

Natural evolution in patients with nonsteroidal anti-inflammatory drug-induced urticaria/angioedema

I. Doña[1] | E. Barrionuevo[1] | M. Salas[1] | J. A. Cornejo-García[2] | J. R. Perkins[2] | G. Bogas[1] | A. Prieto[1] | M. J. Torres[1]

EAACI Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMUNOLOGY
2017

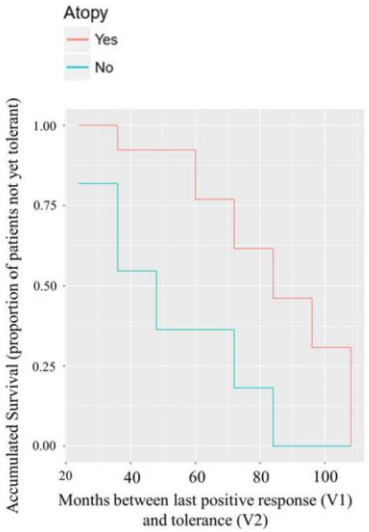
38 pacientes 14-60 años de edad

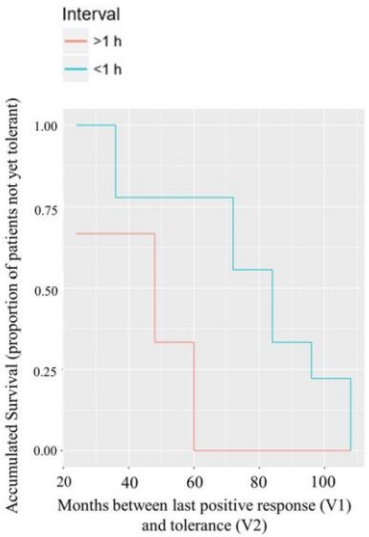
63 % acabaron tolerando AINE

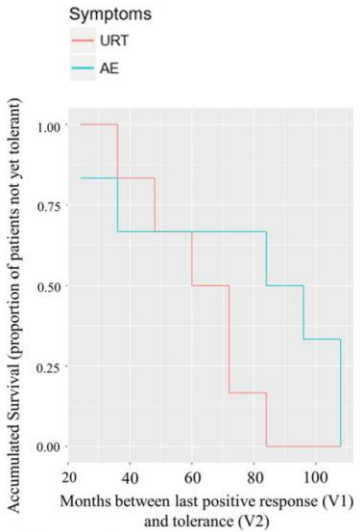
La edad no influyó en la evolución

- Ibuprofeno: 50 %
- Paracetamol: 75 %

p = 0,2







ALerMOLD PEDIÁTRICO

DIATER PIONEERING IMMUNOTHERAPY

¿ES POSIBLE LA REEXPOSICIÓN CONTROLADA EN REACCIONES ADVERSAS CUTÁNEAS GRAVES?

Pediatric Allergy and Immunology

EAACI

DRUG RE-EXPOSURE IN CHILDREN WITH SEVERE CUTANEOUS ADVERSE REACTIONS

27 AL 29 DE MAYO DE 2021

SEICAAP

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14 REACCIONES MUCOCUTÁNEAS GRAVES ASOCIADAS AL USO DE FÁRMACOS: ¿PUEDE PLANTEARSE LA PRUEBA DE EXPOSICIÓN?

A Sánchez Sánchez, A Gilabert Mayans, L Moral Gil, T Toral Pérez, FM Marco de la Calle, JF Silvestre Salvador
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