Ipersensibilità ai FANS: fenotipi clinici, meccanismi e gestione terapeutica

UNIVERSITÀ DEGLI STUDI DI BRESCIA

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CASA DI CURA BEATO PALAZZOLO
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Updating the classification and routine diagnosis of NSAID hypersensitivity reactions: A WAO Statement

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Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs)

Immediate (or acute)

1. NSAID-exacerbated respiratory disease (N-ERD),
2. NSAID-exacerbated cutaneous disease (NECD),
3. NSAID-induced urticaria/angioedema (NIUA),
4. Single NSAID-induced urticaria/ angioedema/anaphylaxis (SNIUAA).

Delayed

- AGEP Acute Generalized Exanthematous Pustolosis
- CD Contact Dermatitis
- PACD Photo Allergic Contact Dermatitis
- GBFDE Generalized Bullous Fixed Drug Eruption
- MDE Morbilliform Drug Eruptoption
- DRESS Drug Reactionwith Eosinophilia and Syistemic Symptoms
- FDE Fixed Drug Eruption
- SJS Steven Jhonson Syndtrome
- TEN Toxix Epidermal Necrolysis
- SSLR Serum Sicknes Like Reaction
- SV Systemic Vasculitis

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Delayed

- Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to non-steroidal anti-inflammatory drugs. Allergy. 2013;68(10):1219–1232 **(immediate < 24h)**
- Broyles AD, Banerji A, Barmettler S, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. J Allergy Clin Immunol Pract. **2020**;8(9S):S16– S116. **(immediate < 6h)**
- Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: a 2022 practice parameter update. J Allergy Clin Immunol. **2022**;150(6):1333–1393. **(immediate < 6h)**

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Immediate

Delayed

Phenotype	Clinical manifestation	Chronology[a]	Underlying disease	Pathogenic Mechanism	Cross-reactive phenotype
NSAID-exacerbated respiratory disease (N-ERD)	*Classical variant:* Nasal airway congestion, rhinorrhea, sneezing, nasal pruritus, ocular chemosis, and/or bronchospasm *Mixed variant:* Classical plus cutaneous or other non-respiratory symptoms	**Immediate** (≤6 h)	**Chronic rhinosinusitis with nasal polyps and/or asthma**	**COX-1 inhibition**	**Yes**
NSAID-exacerbated cutaneous disease (NECD)	*Classical variant:* Urticaria and/or angioedema *Mixed variant:* Classical plus respiratory symptoms	**Immediate** (≤6 h)	**Chronic spontaneous urticaria or recurrent urticaria**	**COX-1 inhibition**	**Yes**
NSAID-induced urticaria/ angioedema/ anaphylaxis (NIUAA)	Urticaria, angioedema, anaphylaxis	**Immediate** (≤6 h)	None	**COX-1 inhibition**	**Yes**
Single-NSAID-induced urticaria/ angioedema/ anaphylaxis (SNIUAA)	Urticaria, angioedema, anaphylaxis	**Immediate** (≤6 h)	None	**IgE-mediated**	**No**
NSAID-exacerbated/ induced food allergy (NEFA/ NIFA)	Urticaria, angioedema, anaphylaxis	**Immediate** (≤6 h)	**Food hypersensitivity/ sensitization**	**NSAID acts as aggravating factor (NEFA) or cofactor (NIFA)[b]**	
Single-NSAID-induced delayed hypersensitivity reactions (SNIDHRs)	CD, FDE, MDE, PACD, SDRIFE, SCARs (e.g., AGEP, DIHS/DRESS, GBFDE, SJS/TEN), systemic (allergic) CD, vasculitis	**Delayed** (>6 h)	None	**T-cell-mediated**	**No**

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Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs)

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In the current classifications of NSAID hypersensitivity, the reactions in which NSAIDs act as aggravating factors or cofactors in subjects with sensitization to foods are not included. Recently, this type of reactions has been defined as NSAID-exacerbated food allergy (NEFA) and NSAID- induced food allergy (NIFA), respectively. 16-18% of patients

There are small sub- groups of N-ERD patients who also report skin symptoms and, alternatively, NECD patients who report respiratory symptoms:

- mixed N-ERD
- mixed NECD

they are patients suffering from N-ERD or NECD **with anaphylaxis.**

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Chemical group	Drug
Salicylic acid derivatives	Acetylsalicylic acid (aspirin), sodium salicylate, salsalate, diflunisal, sulfasalazine
Propionic acid derivatives	Dexibuprofen, dexketoprofen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, piketoprofen
Acetic acid derivatives	Aceclofenac, diclofenac, etodolac, fentiazac, ketorolac, indomethacin, sulindac, tolmetin
Anthranilic acid derivatives (Fenamates)	Etofenamate, flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid, tolfenamic acid
Pyrazolone derivatives	Aminophenazone, dipyrone (metamizole, noramidopyrine), phenylbutazone, propyphenazone
Enolic acid derivatives (oxicams)	Lornoxicam, meloxicam[a], piroxicam, tenoxicam
Para-aminophenol derivatives	Paracetamol (Acetaminophen)[c]
Sulphonanilide derivatives	Nimesulide[a]
Coxibs[b]	Celecoxib, etoricoxib, parecoxib

Non-steroidal anti-inflammatory drugs (NSAIDs) classified according to the chemical structure. *[a]Meloxicam and nimesulide are preferential COX-2 inhibitors. [b]Selective COX-2 inhibitors. [c]Paracetamol is often included into the category of NSAIDs; however, it has little anti-inflammatory activity and COX-1 inhibition is only noted at cumulative doses >4 g per day.*

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NSAID-exacerbated respiratory disease (N-ERD)

CLINICAL EXPRESSION:

- Asthma
- Chronic rhinosinusitis with nasal polyps (CRSwNP)
- Respiratory reactions to cyclooxygenase (COX)-1 inhibitors.

Each component of the triad can develop over a span of months to many years.

PEAK INCIDENCE: in the third and fourth decade of life (possible also puberty onset and late onset).

SYMPTOMS: Nasal congestion, rhinorrhea, sneezing, nasal pruritus, ocular chemosis, and/or broncho- spasm within 30 min to 3 h of exposure.

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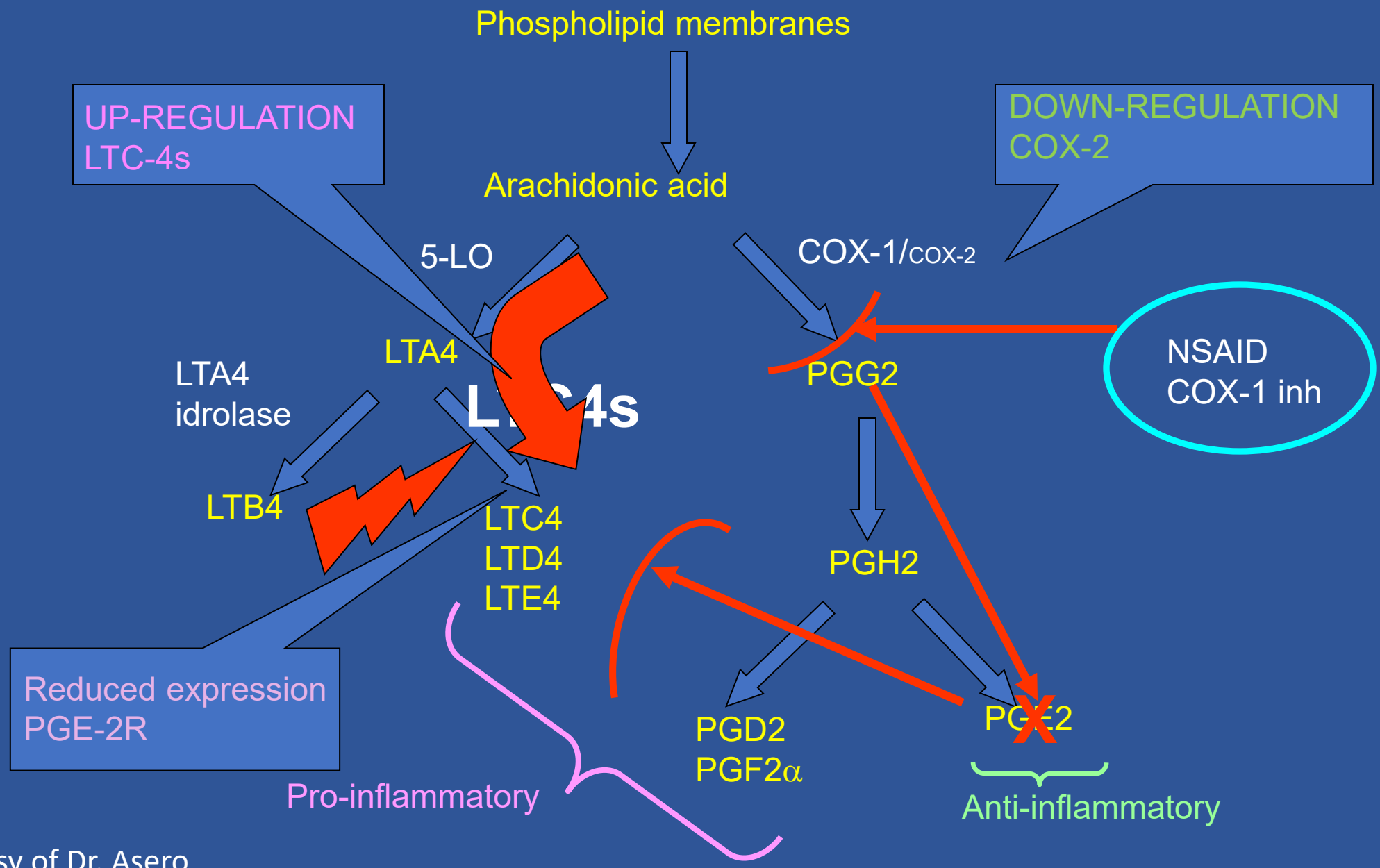
Common defects of eicosanoids methabolism in AERD e CU/ASA



Courtesy of Dr. Asero

N-ERD: Pathogenic mechanism

1. Disturbances in the COX pathways. (**<u>Down-regulation COX-2)</u>**

The inhibition of COX-1 by NSAIDs, and high- dose paracetamol (acetaminophen) in a minority of patients, precipitates respiratory tract reactions.

- Ying S. JACI 2006.
- Corrigan CJ. JACI. 2012.
- Cahill KN. AJRCMB. 2016.
- Machado-Carvalho L. Rhinology. 2016
- Mitsui C. JACI 2016.

2. Disturbance inthe 5-lipoxygenase (5- LO) pathways. (**<u>Up-regulation LTC4s</u>**)

Increased frequency of the allelic variant $_{-444}$C of LTC_4-synthase → overexpression of the enzyme

High **basal** levels of urinary LTE_4 ($uLTE_4$) that increase following the ingestion of ASA/NSAIDs

Correlation between $uLTE_4$ levels and severity of adverse reactions.

In some NSAID-intolerant, CU patients LRA prevent NSAID-induced exacerbations

- Cahill KN. IACI 2016.
- Mullol JACI. 2021.
- Boyce JA. JACI. 2019
- Kowalski ML. AJRCCM. 2000.
- Pérez-Novo CA. JACIAl. 2005.
- Roca-Ferrer J, JACI. 2011.
- Machado-Carvalho L. JACI.2016.
- Asero R. AAAAI 2000.
- PerezC. JACI 2001.

3. **Diminished expression of the anti-inflammatory EP2 receptor of PGE2**

By mechanisms still unknown, patients with N-ERD almost always tolerate selective COX-2 inhibitors during observed drug challenges (DCs).

- Li L. JACIP 2019.

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NSAID-exacerbated respiratory disease (N-ERD)

N-ERD variants

<u>Extra -respiratory signs and symptoms (About 20%):</u>

- Pruritic macular cutaneous eruption
- Urticaria
- Angioedema
- Angina-like chest pain
- Abdominal pain, nausea, vomiting, and diarrhea.

Prevalence was **0.1%–0.6%,** BUT:

According to a recent meta-analysis, prevalence is **7.2%** among adults with **asthma**, and up to **14.9%** among those with **severe asthma.**

Mixed N-ERD.

Hedman J, et al. Int J Epidemiol. 1999. Kasper Ł, et al. Pneumonol Alergol Pol.2009. Eriksson J, et al. Clin Exp Allergy. 2015.

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N-ERD: Diagnosis

Clinical history and exam

- Asthma
- CRSwNP
  - ❑ Eosinophilia (>300 cells/mL) and
  - ❑ elevated FeNo (>25 ppb) are common in N-ERD but are neither sensitive nor specific for the diagnosis of N-ERD.
  - ❑ Urinary LTE4 levels is useful, but not sufficient, for the diagnosis.
- COX-1 inhibitor hypersensitivity. The diagnosis requires the development of acute upper and/or lower respiratory symptoms (nasal congestion, rhinorrhea, sneezing, conjunctival irritation, ocular chemosis, pruritus, bronchospasm) **following ingestion of a therapeutic dose** of a COX-1 inhibitor.

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Oral **ASA challenge testing**: (325 mg ASA) sensitivety about 80-90%; and high specificity.

Additional options:

- bronchial (inhalation) challenge with soluble lysine acetylsalicylate
- nasal challenge with soluble lysine acetylsalicylate or ketorolac.

Sensitivity about 77–90%, but safer than the oral ASA challenge.

- Challenge must be performed **only if patient's FEV1 is >70%** of predicted value
- Treatment with b-blockers is contraindicate for DC
- **No in vitro tests are sensitive or reliable to be recommended in the diagnosis of N-ERD.**

NECD: NSAID-exacerbated cutaneous disease

- Up to 30% of patients with CSU, may experience a marked, acute, and short-lived exacerbation of their disease, including angioedema, within minutes to hours after taking chemically unrelated NSAIDs.
- Rare progression to anaphylaxis
- A small subgroup of patients with NECD who also report respiratory symptoms --> is called **mixed NECD**

In NECD, NSAID hypersensitivity is:

- Indipendent on the endotype of CSU
- Identically distributited in early-, slow- or non- responders to the anti-IgE Mab
- Non dependent on the presence or absence of autoreactivity.

The intensity of the reaction to NSAIDs depends on the activity of the underlying CSU
Patients can tolerate NSAIDs during periods of CSU remission.

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NECD: Pathogenic mechanism

- Reactions are clearly associated with the **COX-1 inhibiting activity** of the offending drugs. **General good tolerance to paracetamol, meloxicam and nimesulide or selective COX-2 inhibitors (ie, coxibs**).
- Pathogenic mechanism of NECD is identical or very similar to N-ERD and NIUAA patients.
- In some cases, **LT receptor antagonists** were able to prevent NSAID-induced exacerbations in NECD.
- Both SNIUAA and NIUAA patients may evolve into a NECD **(Controverse!)**
- Rather frequent association between CSU and NSAID hypersensitivity could be explaned by **genetic linke to the changes in eicosanoid metabolism** that also characterize patients with NIUAA.

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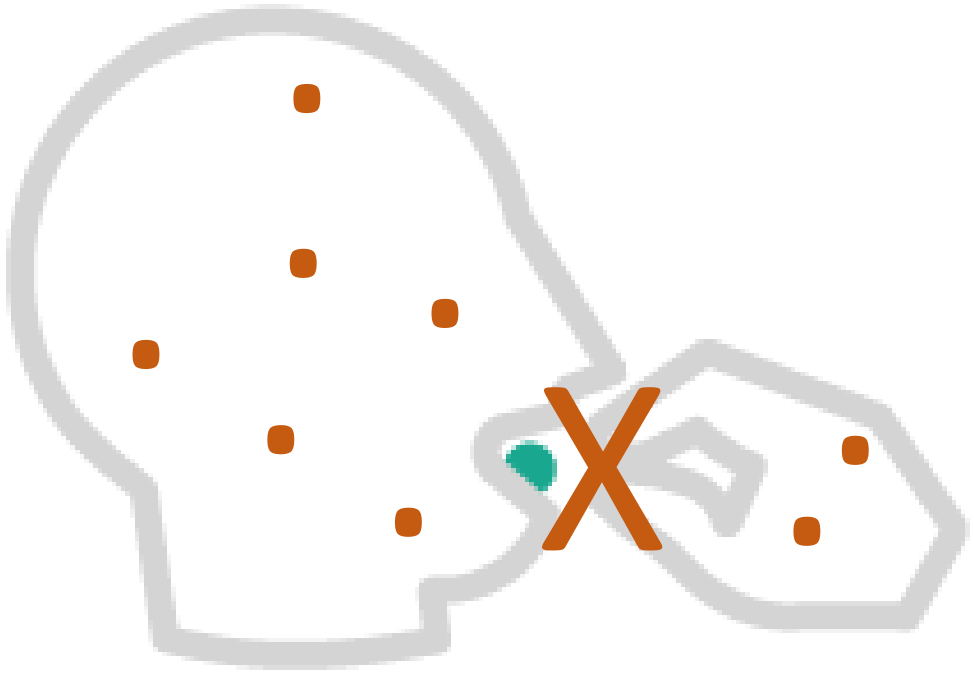
NECD: Diagnosis



- **Not advisable to perform a graded DC with ASA** in active CSU or recurrent urticaria
- Patients with uncontrolled urticaria are **unlikely to tolerate these NSAIDs** at any dose.
- **A history** of cutaneous reactions triggered by 2or> 2 chemically unrelated COX-1 inhibitors **confirms the NSAID cross-reactivity** observed in NECD.

Potential biomarkers such as LTE4 and the ratio LTE4/9a,11b-PGF2,
and **serum tryptase** have been proposed as in vitro diagnostic tests (data limited)!

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NIUAA: NSAID-induced urticaria/angioedema

- **The most common** NSAID hypersensitivity category for all age groups; > 40% in adults, and 45% and 60% in the pediatric population.
- More common in adult females (60– 65%)
- In the pediatric population there is a male predominance (70%).
- Controversies exist about whether **NIUAA can precede the appearance of CSU** (1/3 casese)
- Up to 60% of NIUAA are **atopic,** mainly sensitized to **dust mite** (peculiarity of this group)
- Symptoms are typically elicited by **strong COX-1 inhibitors**, but **high doses of weak COX-1** inhibitors (e.g.paracetamol) **can also induce symptoms in up to 20%** of adult patients.
- Most patients with cross-reactive NSAID hyper-sensitivity report isolated cutaneous symptoms involving urticaria and/or angioedema.
- **Blended** (Skin, Respiratory, GI) features or anaphylaxis are possible: **9% and 28% of adults** and up to **40% of children**

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NIUAA: Diagnosis

- **Basophil activation test (BAT):** utility unclear (lack of consistent results). It coul be used for the evaluation of cross-reactive types of NSAID hypersensitivity, including NIUAA.
- **Oral challenge protocols:** the gold standard for proving NSAID hypersensitivity.

In clinical practice:

- **Patients without CSU** who report recent (ie, that occurred <5 years before allergy testing) and well- documented urticarial/angioedematous/anaphylactic **reactions to > 2** chemically unrelated NSAIDs can be diagnosed as having NIUAA. Risk overdiagnosis of NIUAA
- **ASA challenge:** the best way **to discriminate** between NIUAA and SNIUAA, as well as to exclude NSAID hypersensitivity
- Test with **another NSAID** is possible

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NIUAA: Diagnosis- patients with reactions to multiple, but not all COX-1 inhibitors

- Subjects reacting to several NSAIDs: **cross-hypersensitive!**
- Subjects responding to only one NSAID with good tolerance of other chemically unrelated NSAIDs: **selective responders.**

In real life several cases of patients who had **reactions with several chemically unrelated NSAIDs but tolerated ASA (high doses of ASA: >500 mg).**

Hypothesis:

❑pharmacological **IgE-mediated response dose-dependent mechanism** related to COX-1 inhibition?

❑an to several chemically unrelated NSAIDs but not to other drugs?

Challenges with ASA in these patients: **High risk of reactions-->** to perform only if indication for aspirin therapy.

No biomarkers available!

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Is a confirmative provocation test with the offending drug **warranted** in subjects with a clear-cut history of NSAID-induced urticaria?

ANSWER...Probably → NO! ... Because:

1. In subjects with IgE-mediated sensitivity this might pose a risk of adverse, even life-threatening reactions (Ispano M et al. Drugs 1993; 46: 253)
2. The offending drug can in most instances be substituted with a number of equally effective but chemically distinct compounds

Don’t perform challenge with offending drug if History is clear!

Management of patients with cross-reactive types of immediate NSAID hypersensitivity: administration of alternative agents

Relatively safe alternatives in patients with N-ERD, NECD, or NIUAA

- Selective COX-2 inhibitors NSAID: rofecoxib, celecoxib, parecoxib, valdecoxib, and etoricoxib
- Preferential COX-2 inhibitors NSAID: meloxicam and nimesulide.
- Paracetamolmg has COX-1 inhibiting effects at high doses--> test with low doses

Note

- ❑ Cross-reactivity higher with **meloxicam/nimesulide** than with the **coxibs**
- ❑ Respiratory symptoms may occor in 3.3%- 5.4%, of patients.
- ❑ Urticaria/ angioedema: higher
- ❑ A positive test can be repeated with **antihistamine premedication** (eg, rupatadine 10 mg, cetirizine 10 mg, or desloratadine 5 mg, **30 min to 6 h before the test**)

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SNIUAA

- Immediate reactions to a single NSAID or closely related drugs from the same chemical group, but tolerate other, non-chemically related NSAIDs
- **The reaction is independent of the strength of COX-1 inhibition**, pointing to a probable specific immunological mechanism.
- These reactions usually occur within the **first hour following drug intake**, although this interval can be longer (ie, up to 6 h)
- Symptoms may vary from skin reactions, such as urticaria/angioedema and generalized erythema, to anaphylaxis.
- **In adults** (15.9%- 47.2%); the most involved NSAIDs **were pyrazolones** (ie, metamizole/ dipyrone and propyphenazone) and **propionic acid derivatives** (ie, ibuprofen and ketoprofen).
- **In children** and adolescents (15.5%-33%). **Paracetamol and ibuprofen** were the most frequent elicitors of SNIUAA.

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SNIUAA: Diagnosis

History of well documented immediate urticarial/angioedematous/anaphylactic reactions to a single NSAID or to 2 NSAIDs belonging to the same chemical group in a patient without CSU.
The diagnosis is firmly established if a patient has a history of tolerance of chemically unrelated NSAIDs taken after the reaction(s).

Start performing oral tolerance test with an **alternative, chemically distinct non-selective COX-1 inhibitor**

WHY?

1. This is the only way to establish if a patient is monosensitized (i.e., may take any other NSAID) or if the reported reaction represents the first sign of multiple NSAID intolerance
2. **The anti-inflammatory and/or analgesic activity of selective COX-2 inhibitors** (nimesulide, meloxicam, paracetamol, etoricoxib) **is inferior to most non-selective drugs**.

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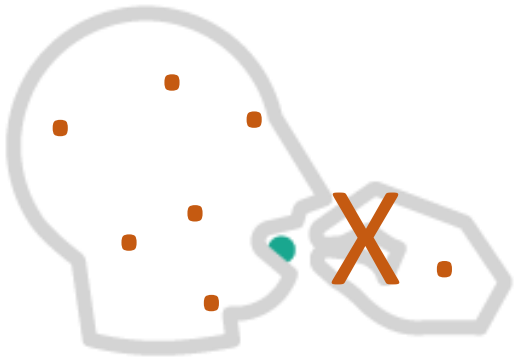
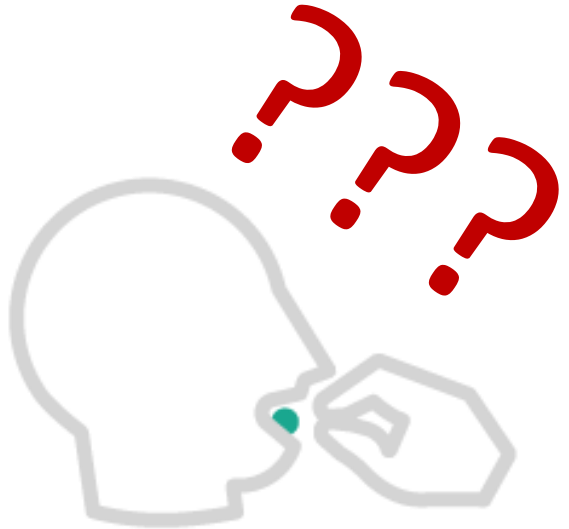
SNIUAA: Diagnosis

- **Skin tests (STs)** with the suspected NSAID may be helpful, if possible.
- **In vitro tests:** serum specific IgE assay and BAT, --> not widely available and their diagnostic and predictive values also not validated
- However, in patients with immediate reactions to <u>metamizole</u>, the BAT showed a sensitivity ranging from 42% to 65% and a specificity from 83% to 100%, proving to be complementary to STs.



DCs with the suspected NSAIDs are contraindicated in patients with severe anaphylaxis

Patients who report **equivocal/doubtful** and/or non-recent reactions are **referred to a DC with ASA**



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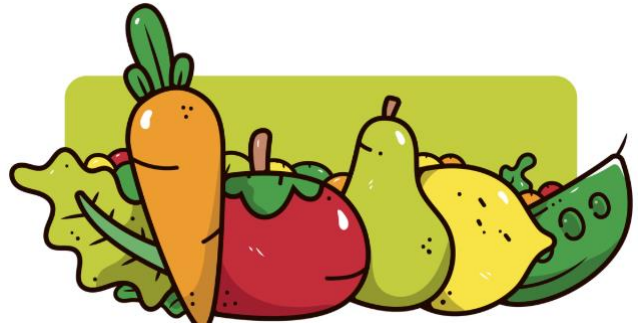
NSAIDs	Skin prick tests	Intradermal tests	Patch tests[a]	Photopatch tests
Acetylsalicylic acid			10% pet[b]	
Dexketoprofen				1% pet[197]
Ibuprofen			10% pet[b] - 30%[d],[198]	5% pet[197]
Ketoprofen	5 mg/mL[138]	5 mg/mL[138]	2.5% pet[b]- 30%[183]	1% pet[b],[197]
Piketoprofen				1% pet[197]
Diclofenac	2.5 mg/mL[138]	2.5 mg/mL[138]	5% pet[b]	5% pet[b],[197]
Ketorolac	1 mg/mL[143]	1 mg/mL[143]		
Etofenamate			30% pet[183]	2% pet[197]
Niflumic acid			Pure (gel)[198]	
Metamizole	400 mg/mL[15,137]	40 mg/mL[15,137]	10% water[137] – pet[203]	
Other pyrazolones	0.1 mg/mL[139]	0.1 mg/mL[139]		
Piroxicam	2 mg/mL[140]	2 mg/mL[140]	1% pet[b]	1% pet[b],[197]
Other injectable NSAIDs	0.1 mg/mL[139]	0.1 mg/mL[139]		
Paracetamol	10 mg/mL[15]	1 mg/mL[15],[138]	10% pet[b]	
Celecoxib			30% pet[c],[198]	

Table 3. Highest nonirritating concentrations of NSAIDs recommended for skin and patch testing [a]*In accordance with international guidelines,[199,200] the test material obtained from trade products is used at concentrations of 10% or 30% in petrolatum (see text).* [b]*Available as ready-to-use material (see text).* [c]*100-mg tablet.* [d]*400-mg tablet, diluted in water, petrolatum, or alcohol.*

NEFA/NIFA Clinical presentation

- NSAIDs can act as exacerbating factors or cofactors of hypersensitivity reactions to food allergens, most of which are anaphylaxis.
- **Patient may fully tolerate a food if ingested alone**, but experience a systemic reaction after its ingestion in combination with NSAIDs.
- These phenomena have been termed **NEFA** and the latter **NIFA.**
- In individuals with food sensitization, exercise and alcohol also act as aggravating factors and/or cofactors, often in association with NSAIDs. **Food-dependent exercise-induced anaphylaxis (FDEIA**)



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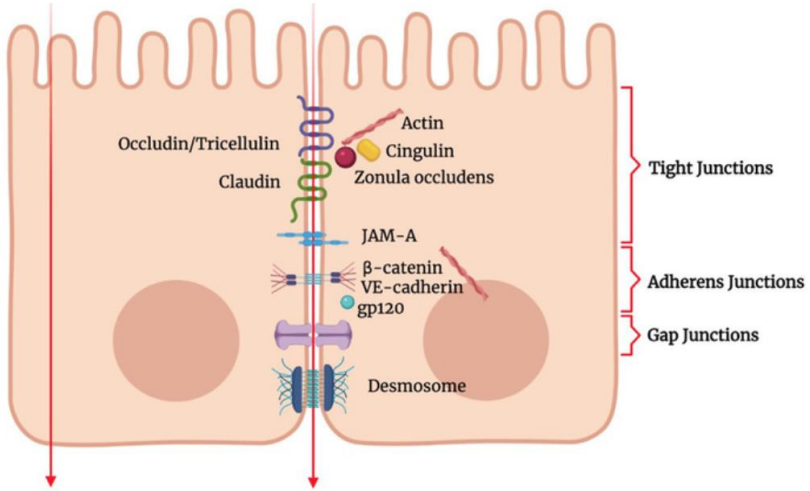
NEFA/NIFA and FDEIA: Pathogenic mechanism

NSAIDs increase the absorption of allergens:

- 5 omega gliadin (Tri a 19)
- Non-specific lipid transfer proteins (LTPs), mainly Pru p 3.



Mechanism:

-**an impaired tight junction barrier** secondary to diminished COX-1 dependent PG production in enterocytes.

Long- lasting or high-intensity exercise can also alter intestinal permeability.

-Another hypothesis: **redistribution of blood flow during exercise** might result in an ischemia/ reperfusion cycle that causes epithelial damage.

- NSAIDs and exercise have a **direct effect on mast cells and basophils**, amplifying their activation.

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NEFA/NIFA and FDEIA: Diagnosis

- Allergy tests to detect sensitization to food allergens (ie, skin prick tests and serum specific IgE assays)
- **In case of positive results, DCs with the suspected NSAIDs.**

NEFA/NIFA and FDEIA: Menagement

- **Avoid NSAIDs**, including ASA at anti-platelet doses, **for 4 h before and after a meal containing foods** that have been found to be **positive** in the allergy workup.
- This precaution allows all NEFA/ NIFA patients to **continue taking NSAIDs,** including those involved in hypersensitivity reactions, without any reaction.

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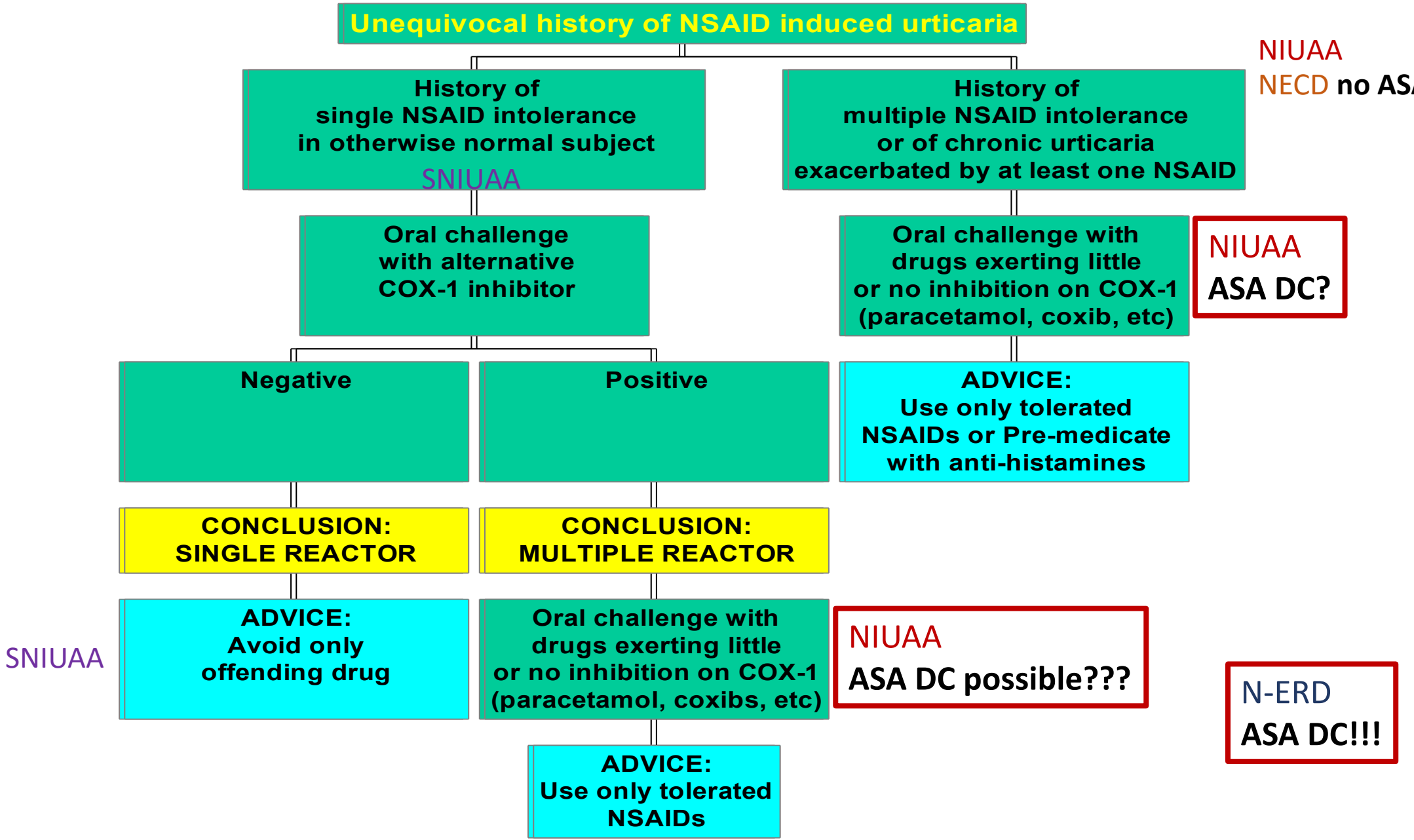
Clinical management of patients with a history of NSAID-induced urticaria (Asero R. Allergy 1998, AAAI 1998; CEA 2005; AAAI 2006; AACI 2007)



SINGLE-NSAID-INDUCED DELAYED HYPERSENSITIVITY REACTIONS (SNIDHRS)

- Prevalence not known
- The least common type of NSAID hypersensitivity in patients diagnosed by allergy testing.
- The pathogenic mechanism involves the stimulation of drug specific CD4þ and CD8þ T cells and does not differ from that of delayed reactions to other drugs.
- Cross- reactions between NSAIDs are observed within the same chemical group of drugs.

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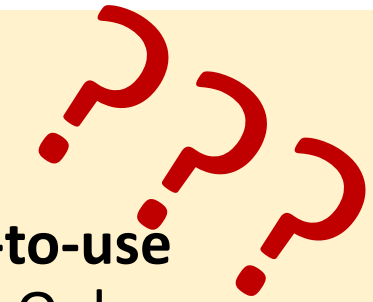
Reaction type	Main responsible NSAIDs[a]	Time interval[b]	Patch tests	dSPTs	dIDTs	Drug challenges
Morbilliform drug eruption	Metamizole;[142] metamizole, ketoprofen[182]	4–14 days	Useful	Limited value	Useful	After negative skin tests in mild/moderate reactions
Contact dermatitis	Ketoprofen[183]	4 days-weeks	Useful	Unknown value	Unknown value	Unknown value
Systemic (allergic) contact dermatitis	Reports of <5 positive cases[205,209]	4 days-weeks	Useful	Limited value	Unknown value	After negative skin tests
SDRIFE	Reports of <5 positive cases[180,205]	Up to 7 days	Useful	Limited value	Useful	After negative skin tests
Photoallergic contact dermatitis	Ketoprofen, dexketoprofen, etofenamate;[204] ketoprofen, etofenamate, piroxicam[210]	Days-years	Photopatch tests with low concentrations (≤5% in petrolatum) with a 5 J/cm^{-2} UVA irradiation	No value	No value	No value without exposure to UV
Fixed drug eruption[c]	Metamizole;[142] metamizole, ketoprofen;[182] piroxicam;[206] mefenamic acid, piroxicam;[207] etoricoxib[208]	30 min-8 h after readministration	Useful if applied on the area of eruption (see text)	Not useful	Not useful	At full dose when patch tests or repeated application tests are negative
GBFDE	Reports of <5 positive cases	4 days-weeks	May be useful	Contraindicated	Contraindicated	Contraindicated
AGEP	Reports of <5 positive cases[180]	1–12 days	Useful	Limited value	Potentially useful	Contraindicated with suspected drugs and cross-reactive ones
DRESS/DIHS	Reports of <5 positive cases[180]	2–8 weeks	Useful recommended 6 months after healing	Limited value	Reading at 24 h	Contraindicated with suspected drugs and cross-reactive ones
SJS/TEN	Reports of <5 positive cases[180,211]	4–28 days	Low sensitivity	Unknown value	Contraindicated with suspected drugs	Contraindicated with suspected drugs and cross-reactive ones
Vasculitis/SSLR		7–21 days	No value	No value	No value	Contraindicated

SINGLE-NSAID-INDUCED DELAYED HYPERSENSITIVITY REACTIONS (SNIDHRS): Diagnosis

- Clinical history

- In vivo tests:



- Patch tests (PTs) --> **the material for testing NSAIDs not available as ready-to-use reagents has to be prepared in-house** from the drugs used by the patients. Only a limited number of molecules marketed by Chemotechnique (Velinge, Sweden) and SmartPractice Europe GmbH (Greven, Germany) are available as ready-to-use material at concentrations ranging from 1% to 10% in petrolatum
- STs, namely skin prick tests and delayed-reading intradermal tests (dIDTs)

- **In vitro methods:**

- LTT: Lymphocyte transformation test (diagnostic value not yet been reached).
- ELISPOT: Enzyme-linked immunosorbent spot assay (diagnostic value not yet been reached).

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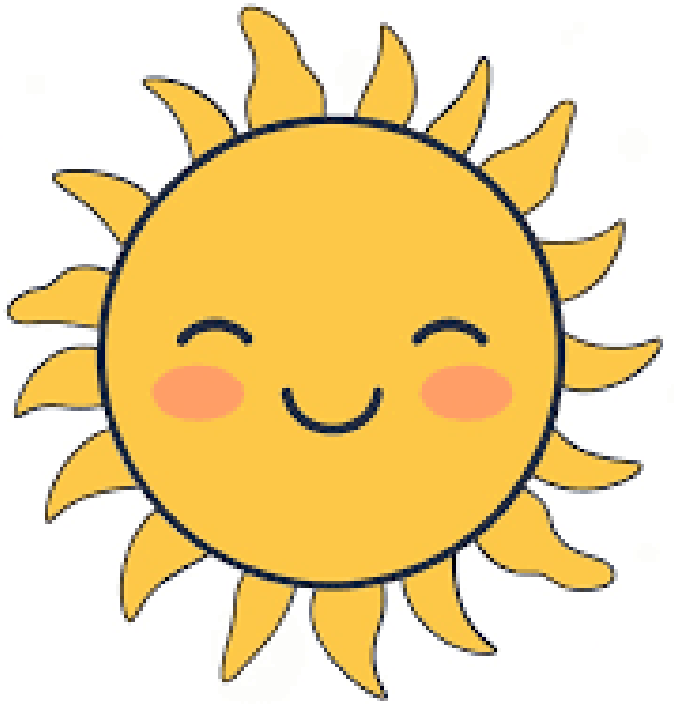
SINGLE-NSAID-INDUCED DELAYED HYPERSENSITIVITY REACTIONS (SNIDHRS): Management

Avoid the responsible drugs and prudently also those belonging to the same chemical group.

- Ketoprofen photoallergies are due to the chemical **benzophenone structure**. This structure can be found in other drugs such as **fenofibrate** and **tiaprofenic acid**, and in many chemical sunscreens such as **oxybenzone or mexenone.**
- The sensitizing photometabolite of piroxicam is thiosalicylic acid. **Cross-allergy** is constant with **thiomersal**, which is partly composed of thiosalicylic acid.
- In **piroxicam** photoallergy, **other oxicams are well tolerated**.
- Patients with photosensitization to **diclofenac** cross react with **aceclofenac.**
- The use of high sun protection factor (SPF) mineral sunscreens is recommended to prevent photo-remanence.



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???...Open questions...

- Timing: Immediate or Delayed...6- 24 h?
- N-ERD: Oral ASA challenge testing or alternative drug?
- NECD: role of serum tryptase as in vitro diagnostic tests (CSU patients!)
- NIUAA: Oral ASA challenge testing or alternative drug?
- NEFA/NIFA: DCs with the suspected NSAIDs?
- SNIUAA: SPT and ID in real life?
- SNIDHRS: Patch Test in real life?

Grazie!!!