

DR. INMACULADA DOÑA (Orcid ID : 0000-0002-5309-4878)

DR. NATALIA PÉREZ-SÁNCHEZ (Orcid ID : 0000-0001-9399-8188)

DR. MARIA SALAS (Orcid ID : 0000-0002-0583-9492)

DR. MARÍA JOSÉ TORRES (Orcid ID : 0000-0001-5228-471X)

Article type : News & Views: Algorithms in Allergy and Clinical Immunology

TITLE: Medical Algorithm: Diagnosis and Treatment of NSAIDs Hypersensitivity

AUTHORS: Doña, Inmaculada^{1,2}; Pérez-Sánchez, Natalia^{1,2,3*}; Bogas, Gábor^{1,2}; Moreno, Esther^{4,5}; Salas, María^{1,2}; Torres, María José^{1,2,3,6}

AFFILIATIONS:

¹Allergy Unit, Hospital Regional Universitario de Málaga. Málaga, Spain.

²Allergy Research Group, Instituto de Investigación Biomédica de Málaga-IBIMA. Málaga, Spain.

³Departamento de Medicina, Facultad de Medicina, Universidad de Málaga. Málaga, Spain

⁴Allergy Service, Hospital Universitario de Salamanca, Salamanca, Spain

⁵Institute for Biomedical Research of Salamanca (IBSAL), Salamanca, Spain

⁶Nanostructures for Diagnosing and Treatment of Allergic Diseases Laboratory, Andalusian Center for Nanomedicine and Biotechnology-BIONAND. Málaga, Spain

*Both authors contributed equally.

CORRESPONDING AUTHOR:

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/all.14119](#)

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Inmaculada Doña, Allergy Unit, pabellón 6, primera planta, Regional University Hospital of Malaga (Pavillion C, Hospital Civil), Plaza del Hospital Civil, 29009 Malaga, Spain. Tel: +34 951290224. FAX: +34 951290302. E-mail: inmadd@hotmail.com

Abbreviations

AGEP, acute generalized exanthematous pustulosis; Basophil activation test, BAT; CI, cross-intolerant; CSU, chronic spontaneous urticaria; DIHS/DRESS, drug-induced hypersensitivity syndrome/drug reaction eosinophilia and systemic symptoms; FDE, fixed drug eruption; LTT, lymphocyte transformation test; MPE, maculopapular exanthema; NECD, exacerbated cutaneous disease; NERD, NSAIDs-exacerbated respiratory disease; NIUA, NSAIDs-induced urticaria/angioedema; NSAIDs, non-steroidal anti-inflammatory drugs; SNIDHRs, Single-NSAID-induced delayed hypersensitivity reactions; SNIUAA, Single-NSAID-induced urticaria/angioedema and anaphylaxis; SJS, Steven-Johnson syndrome; SR, selective responders; TEN, toxic epidermal necrolysis.

Diagnosis in suspected hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) is complex as different mechanisms are involved: specific (selective responders, SRs) and non-specific immunologically mediated (cross-intolerants, CIs) (1-3) (Table 1).

The clinical history is essential for diagnosis. Patients with repeated episodes to ≥ 3 different NSAIDs, including a strong COX-1 inhibitor, may be diagnosed as CIs (4). The symptomatology after NSAIDs-intake and the underlying diseases lead to their precise diagnosis: NSAIDs-exacerbated respiratory disease (NERD), NSAIDs-exacerbated cutaneous disease (NECD), NSAIDs-induced urticaria/angioedema (NIUA), and blended reactions (Figure 1, Table 1) (1,5). If < 3 episodes to different NSAIDs are reported, challenge tests are recommended to confirm/exclude the CI diagnosis; except if reactions involve airways in patients with underlying chronic respiratory disorders in which NERD diagnosis can be made by clinical history without performing challenge (6). After diagnosis confirmation, a challenge to find a safe alternative is required (Figure 1). Challenge tests are time- and cost-consuming, not risk-free, and should be performed after a risk-benefit analysis by trained personnel in an appropriate setting (1). Depending on the NSAID-administration route, the challenge can be intranasal, inhaled, or oral (1,6). Intranasal aspirin challenge is indicated if reactions involve airways. It is safer and faster than inhaled and oral, although less sensitive. It can be used initially in the most sensitive subjects and when oral and inhaled challenges are contraindicated. Intranasal challenge with ketorolac has a lower sensitivity and cannot substitute oral challenge (6). Inhaled challenge with lysine-aspirin is indicated for reactions involving airways; being as

sensitive as oral challenge, but less risky and time-consuming (6). Oral challenge is considered the gold standard (1,6) and recommended with aspirin to distinguish between CIs and SRs, to verify negative results of inhaled or intranasal tests, and with the culprit when aspirin is tolerated to confirm the SR-diagnosis (Figure 1). Inhaled and oral challenges are contraindicated in life-threatening reactions (i.e., anaphylaxis, drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, or toxic epidermal necrolysis) (1,6).

Skin tests are only useful for SR-diagnosis (Figure 1). For immediate SRs, prick and intradermal tests have only shown usefulness for pyrazolones, although sensitivity is not optimal and there is a risk of systemic responses after intradermal tests (1). For delayed SRs, patch tests, although not sufficiently standardized, can be useful. Delayed-reading intradermal tests, particularly metamizole, are more sensitive than patch tests; both have low sensitivity, but high specificity (1).

Regarding *in vitro* tests, specific IgE has been quantified by immunoassay in 60% of pyrazolone immediate SRs, however, its availability is limited (7). Basophil activation test (BAT) has proved validity for these patients, with sensitivity 42%-55% and specificity 86%-100% (7). As skin tests and BAT sensitivity decreases over time, an early assessment is required (1,7). The lymphocyte transformation test (although not routinely recommended as sensitivity and specificity are highly variable) may be useful for delayed SR diagnosis (7) (Figure 1).

After diagnosis confirmation, SRs must avoid the culprit and chemically related drugs, whereas CIs must avoid all NSAIDs although weak COX-1 inhibitors (paracetamol), preferential (meloxicam, nimesulide), and selective COX-2 inhibitors (etoricoxib, celecoxib) can be indicated after a tolerance assessment (1,8). In NIUA, if paracetamol is tolerated, selective COX-2 inhibitors can be indicated without previous oral challenge (8) (Figure 1).

In NERD patients that do not respond to standard therapy, need to reduce chronic oral corticosteroids, or have undergone repetitive nasal polypectomies; desensitization followed by aspirin treatment may be indicated (7). For NIUA, patients must be re-evaluated 6 years after the initial diagnosis, or after a shorter interval in non-atopics, if reactions appear >1 hour after NSAIDs-intake, and if the reaction is manifested as isolated urticaria, as more than 50% tolerate NSAIDs over time (9) (Figure 1).

FIGURE AND TABLE LEGENDS:

Figure 1. Algorithm for diagnosing and managing patients with suspected hypersensitivity reactions to NSAIDs. [†]NERD can be diagnosed with high probability if >1 reaction occurred, reactions to ≥2 different NSAIDs have been reported, the latest reaction occurred within the last 5 years and underlying chronic

respiratory disorders exist. *When the history of respiratory symptoms is not convincing of NERD, intranasal or inhaled challenge is recommended. **ST with metamizole: 40-400 mg/ml for skin prick test, 0.4-4 mg/ml for intradermal test (use diluted 10-fold or lower if severe reactions due to the risk for developing systemic reactions). *Contraindicated if severe reactions.

Table 1. Classification of hypersensitivity reactions to NSAIDs and indications of the methods used for their diagnosis.

ACKNOWLEDGEMENTS

The present study has been supported by the Institute of Health Carlos III of the Ministry of Economy and Competitiveness (grants cofounded by European Regional Development Fund (ERDF): RETIC ARADyAL RD16/0006/0001, RD16/0006/0019 and RD16/0006/0021 and PI 17/1593) and the Spanish Society of Allergology (Fondo de Investigación de la Fundación de la SEAIC 2016). I Doña is a Clinical Investigator (B-0001-2017) from Consejería de Salud of Junta de Andalucía. N Pérez-Sánchez holds a Rio Hortega research contract (CM17/0014) and G Bogas a Juan Rodes research contract (JR18/00054), both from the Institute of Health Carlos III, Spanish Ministry of Economy and Competitiveness (grants cofounded by European Social Fund, ESF).

CONFLICT OF INTEREST STATEMENT

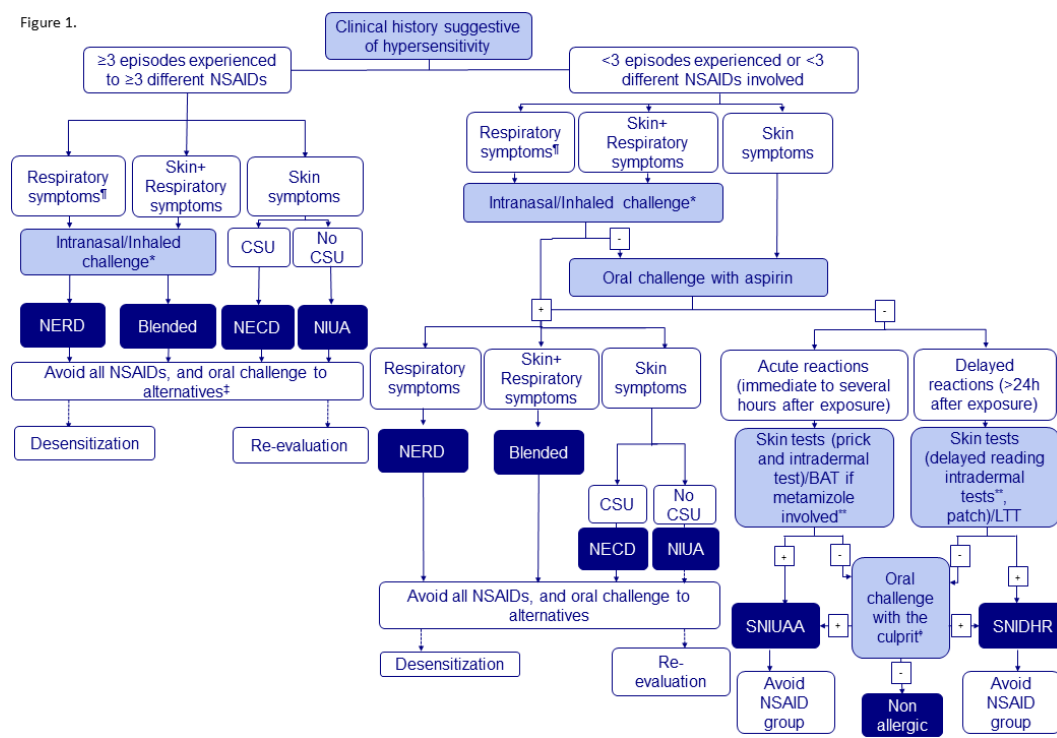
None of the authors have any conflict of interest and all authors had full access to the manuscript.

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Figure 1.



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Table 1.

Group	Clinical entity	Symptoms	Underlying disease	Diagnostic methods						Avoid
				Skin test	In vitro test		Challenge test			
					BAT	LTT	Nasal	Inhaled	Oral	
CI (Non-specific immunologically mediated mechanism)	NERD	Rhinitis/ Asthma	Chronic rhino-sinusitis/ Asthma/ Nasal polyps	Not indicated			If upper and/or lower airways involved*	If lower airways involved*	With aspirin, if other tests are negative or not available	All NSAID
	NECD	Urticaria/ AE	CSU				Not indicated			
	Blended	Rhinitis/ Asthma+ Urticaria/ AE+ Gastro-intestinal	Rhinitis/ Asthma/ Nasal polyps/ Atopy				If upper and/or lower airways involved	If lower airways involved	With the culprit, if aspirin tolerated*	
	NIUA	Urticaria/ AE	Atopy							
SR (Specific immunologically mediated mechanism)	SNIUAA	Urticaria/ AE/ Anaphylaxis	None	Only validated for metamizole		Not indicated	Not indicated			Only NSAID group
	SNIDHR	MPE, FDE, contact dermatitis, DRESS, AGEP, SJS/TEN	None	Low sensitivity	Not indicated	Highly variable sensitivity and specificity				