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Medical algorithm: Diagnosis and treatment of nonsteroidal antiinflammatory drugs hypersensitivity

Diagnosis in suspected hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) is complex as different mechanisms are involved: specific (selective responders, SRs) and nonspecific 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

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

<table>
<tr><th rowspan="3">Group</th><th rowspan="3">Clinical entity</th><th rowspan="3">Symptoms</th><th rowspan="3">Underlying disease</th><th colspan="6">Diagnostic methods</th><th rowspan="3">Avoid</th></tr>
<tr><th rowspan="2">Skin test</th><th colspan="2">In vitro test</th><th colspan="3">Challenge test</th></tr>
<tr><th>BAT</th><th>LTT</th><th>Nasal</th><th>Inhaled</th><th>Oral</th></tr>
<tr><td rowspan="5">CI (Non-specific immunologically mediated mechanism)</td><td>NERD</td><td>Rhinitis/ Asthma</td><td>Chronic rhino-sinusitis/ Asthma/ Nasal polyps</td><td rowspan="4" colspan="3">Not indicated</td><td>If upper and/or lower airways involved*</td><td>If lower airways involved*</td><td rowspan="5">With aspirin, if other tests are negative or not available
With the culprit, if aspirin tolerated*
With alternative, if positive intranasal, inhaled or oral challenge to aspirin</td><td rowspan="4">All NSAID</td></tr>
<tr><td>NECD</td><td>Urticaria/ AE</td><td>CSU</td><td colspan="2">Not indicated</td></tr>
<tr><td>Blended</td><td>Rhinitis/ Asthma+ Urticaria/ AE+ Gastro-intestinal</td><td>Rhinitis/ Asthma/ Nasal polyps/ Atopy</td><td>If upper and/or lower airways involved</td><td>If lower airways involved</td></tr>
<tr><td>NIUA</td><td>Urticaria/ AE</td><td>Atopy</td><td rowspan="2" colspan="2">Not indicated</td></tr>
<tr><td rowspan="2">SR (Specific immunologically mediated mechanism)</td><td>SNIUAA</td><td>Urticaria/ AE/ Anaphylaxis</td><td>None</td><td colspan="2">Only validated for metamizole</td><td>Not indicated</td><td rowspan="2">Only NSAID group</td></tr>
<tr><td>SNIDHR</td><td>MPE, FDE, contact dermatitis, DRESS, AGEP, SJS/TEN</td><td>None</td><td>Low sensitivity</td><td>Not indicated</td><td>Highly variable sensitivity and specificity</td></tr>
</table>

* When the history of respiratory symptoms is not convincing of NERD, intranasal or inhaled challenge is recommended.ᵠ Contraindicated if severe reactions.

Abbreviations: AGEP, acute generalized exanthematous pustulosis; BAT, basophil activation test; CI, cross-intolerant; CSU, chronic spontaneous urticarial; 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, nonsteroidal anti-inflammatory drugs; SJS, Steven-Johnson syndrome; SNIDHRs, single-NSAID-induced delayed hypersensitivity reactions; SNIUAA, single-NSAID-induced urticaria/angioedema and anaphylaxis; SR, selective responders; TEN, toxic epidermal necrolysis.

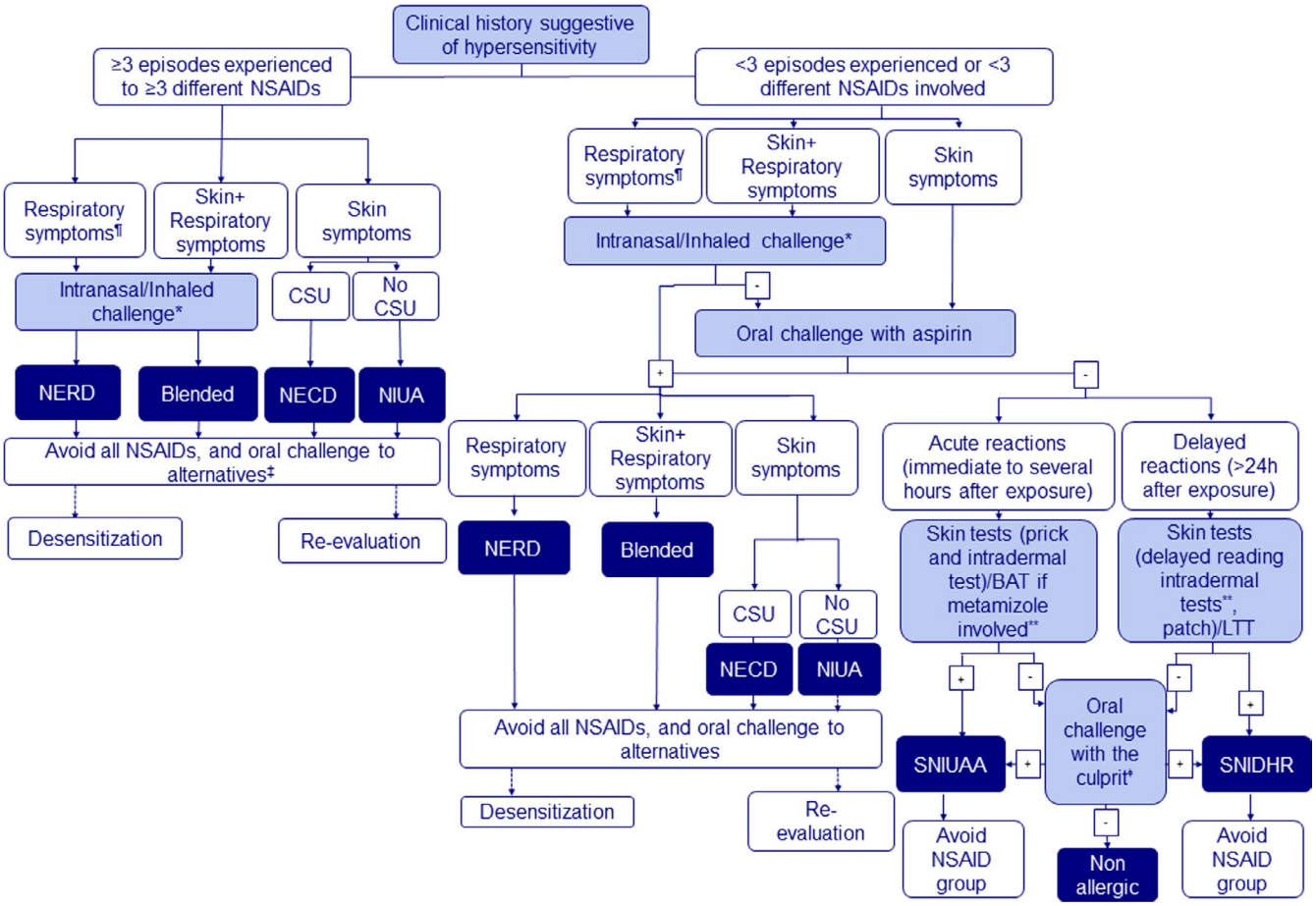

FIGURE 1 Algorithm for diagnosing and managing patients with suspected hypersensitivity reactions to NSAIDs. ¶NERD can be diagnosed with high probability if >1 reaction occurred, reactions to ≥2 different NSAIDs have been reported, the latest reaction occurred within the last 5 y, and the underlying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

in life-threatening reactions (ie, 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 and nimesulide), and selective COX-2 inhibitors (etoricoxib and 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 nonatopics, 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).

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CONFLICT OF INTEREST

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

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REFERENCES

1. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy*. 2013;68(10):1219-1232.
2. Doña I, Jurado-Escobar R, Perkins JR, et al. Eicosanoid mediator profiles in different phenotypes of nonsteroidal anti-inflammatory drug-induced urticaria. *Allergy*. 2019;74(6):1135-1144.
3. Pichler WJ. Immune pathomechanism and classification of drug hypersensitivity. *Allergy*. 2019;74:1457-1471.
4. Blanca-Lopez N, Torres MJ, Doña I, et al. Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance. *Clin Exp Allergy*. 2013;43(1):85-91.
5. Doña I, Barrionuevo E, Salas M, et al. NSAIDs-hypersensitivity often induces a blended reaction pattern involving multiple organs. *Sci Rep*. 2018;8(1):16710.
6. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-exacerbated respiratory disease (N-ERD)-a EAACI position paper. *Allergy*. 2019;74(1):28-39.
7. Mayorga C, Celik G, Rouzaire P, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI drug allergy interest group position paper. *Allergy*. 2016;71(8):1103-1134.
8. Doña I, Blanca-López N, Jagemann LR, et al. Response to a selective COX-2 inhibitor in patients with urticaria/angioedema induced by nonsteroidal anti-inflammatory drugs. *Allergy*. 2011;66(11):1428-1433.
9. Doña I, Barrionuevo E, Salas M, et al. Natural evolution in patients with nonsteroidal anti-inflammatory drug-induced urticaria/angioedema. *Allergy*. 2017;72(9):1346-1355.