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POSITION PAPER

Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs

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Abstract

Hypersensitivity reactions to aspirin (acetylsalicylic acid) and other nonsteroidal anti-inflammatory drugs (NSAIDs) constitute only a subset of all adverse reactions to these drugs, but due to their severity pose a significant burden to patients and are a challenge to the allergist. In susceptible individuals, NSAIDs induce a wide spectrum of hypersensitivity reactions with various timing, organ manifestations, and severity, involving either immunological (allergic) or nonimmunological mechanisms. Proper classification of reactions based on clinical manifestations and suspected mechanism is a prerequisite for the implementation of rational diagnostic procedures and adequate patient management. This document, prepared by a panel of experts from the European Academy of Allergy and Clinical Immunology Task Force on NSAIDs Hypersensitivity, aims at reviewing the current knowledge in the field and proposes uniform definitions and clinically useful classification of hypersensitivity reactions to NSAIDs. The document proposes also practical algorithms for the diagnosis of specific types of NSAIDs hypersensitivity (which include drug provocations, skin testing and *in vitro* testing) and provides, when data are available, evidence-based recommendations for the management of hypersensitive patients, including drug avoidance and drug desensitization.

Nonsteroidal anti-inflammatory drugs (NSAIDs) induce a whole range of adverse reactions related to their pharmacological properties. In susceptible individuals, NSAIDs may induce hypersensitivity reactions varying in timing (immediate/delayed), organ involvement (skin, airways, or other organs), and severity (from mild dyspnea, rhinorrhea, exanthema, or urticaria, to anaphylaxis and death). Since aspirin (acetylsalicylic acid; ASA), the first synthetic compound with antipyretic, analgesic, and anti-inflammatory activity, was synthesized in 1893, dozens of compounds with similar activity have been developed and commercialized and almost all of them were reported to induce hypersensitivity reactions in susceptible subjects. The large variety of NSAIDs inducing hypersensitivity reactions, the wide spectrum of symptoms observed, and different pathomechanisms involved create a challenge to an allergist especially if an unified and practical

classification of hypersensitivity reactions to NSAIDs is lacking.

The purpose of this paper is to review the field and to propose uniform definitions and a clinically useful classification of hypersensitivity reactions to NSAIDs. In addition, practical algorithms for diagnosis and general rules for management are proposed. Due to a paucity of published data and the lack of evidence-based studies, several parts of the document are based on the analysis of available series or case reports and represent consensus reached by the group of experts from the Task Force. Although this document refers to the previous review published by the EAACI/GA2LEN experts (1), it proposes further unification of classification and a new nomenclature and offers, for the first time, graded recommendations based on the literature review. The recommendations were evidence-graded by the members of the Task Force following literature search relevant to each type of hypersensitivity. Grades of recommendations are defined according to the SIGN statement (2). Where evidence was lacking, a consensus was reached among the experts of the Task Force.

We are aware that some proposals of this consensus may be a matter of debate and will be modified in the future, whenever more data will become available. We also point at gaps in our knowledge, which will require further studies. In addition, as a result of the Task Force activity, a series of papers addressing more specific types of reactions and various aspects of hypersensitivity to NSAIDs have been prepared.

Definitions and classification

Hypersensitivity reactions to NSAIDs fulfill the criteria of type B adverse drug reaction (unpredictable and occurring in susceptible individuals) as defined by the WHO (3), and should be clearly differentiated from type A reactions (predictable, based on pharmacological mechanisms and occurring in all individuals if a sufficient dose is applied) (4).

Based on the EAACI/WAO nomenclature, hypersensitivity reactions to NSAIDs are further divided into allergic (immunologically mediated) and nonallergic, depending on identified or suspected nonimmunological mechanisms (5). Accordingly, it is strongly advised that terms previously used to describe nonimmunologically mediated (nonallergic) hypersensitivity reactions to NSAIDs (e.g., intolerance, pseudoallergy, or idiosyncrasy) should be abandoned. Aspirin and other NSAIDs share similar anti-inflammatory mechanisms related to the inhibition of cyclooxygenases, enzymes which are responsible for the generation of prostaglandins and thromboxanes. Since for decades aspirin was the only and at present is still the most commonly used NSAID, hypersensitivity reactions to NSAIDs were referred to as 'aspirin'-induced reactions (e.g., aspirin-induced asthma, aspirin-induced urticaria, aspirin-exacerbated respiratory disease). However, recent epidemiological data indicate that at present, the majority of NSAIDs-induced hypersensitivity reactions are evoked by nonsteroidal anti-inflammatory compounds other than aspirin, thus making 'aspirin' clinically less relevant. Accordingly, we propose that at present, it would be more appropriate to use the term 'NSAIDs' to replace 'aspirin' in descriptions and definition of particular subtypes of hypersensitivity to NSAIDs.

Hypersensitivity reactions to NSAIDs have been originally classified by Stevenson et al. (6) based on the clinical manifestation, the presence of an underlying disease, and a cross-reactivity with other cyclooxygenase (COX)-1 inhibitors. Most patients hypersensitive to NSAIDs present symptoms after intake of more than one, chemically nonrelated NSAIDs, sharing the common property of COX-1 enzyme inhibition. This is called the 'cross-reactive' type of NSAIDs hypersensitivity, and the mechanism of the reaction is not immunological. In some patients, hypersensitivity symptoms occur only after the ingestion of a single, specific NSAID (or more than one, but belonging to the same chemical group), while other chemically nonrelated drugs are generally well tolerated (Table 1 presents examples of NSAIDs grouped according to chemical structure). These types of reactions are considered immunologically mediated and thus belong to the group of allergic hypersensitivity reactions. In addition to the spectrum of drugs to which a patient reacts, the timing (immediate or delayed) may reflect the putative immunological (IgE or T-cell mediated) or nonimmunological (cross-reactive) mechanism (1) (Table 2). It should be noted that in clinical practice, reactions that are blended or not well fitting into classification reactions may occur (7).

Definitions of types of NSAIDs hypersensitivity

Nonimmunologically mediated (cross-reactive) hypersensitivity reactions to NSAIDs

NSAIDs-exacerbated respiratory disease: Hypersensitivity reactions induced by aspirin or other NSAIDs manifesting primarily as bronchial obstruction, dyspnea, and nasal congestion/rhinorrhea, occurring in patients with an underlying chronic airway respiratory disease (asthma/rhinosinusitis/nasal polyps).

Previously used synonyms are as follows: aspirin triad, asthma triad, Samter's syndrome, Widal syndrome, aspirin-induced asthma or aspirin-sensitive rhinosinusitis/asthma syndrome, aspirin-intolerant asthma, and aspirin-exacerbated respiratory disease.

NSAIDs-exacerbated cutaneous disease: Hypersensitivity reactions induced by aspirin or other NSAIDs manifesting as wheals and/or angioedema occurring in patients with a history of chronic spontaneous urticaria.

Terms previously used to describe this type of reactions are aspirin-induced urticaria and aspirin-exacerbated cutaneous disease.

NSAIDs-induced urticaria/angioedema (NIUA): Hypersensitivity reactions induced by aspirin or other NSAIDs manifesting as wheals and/or angioedema occurring in otherwise healthy subjects (without history of chronic spontaneous urticaria). Symptoms are induced by at least two NSAIDs with different chemical structure (not belonging to the same chemical group; Fig. 2).

Table 1 NSAIDs classified according to the chemical structure

Chemical group	Drug
Salicylic acid derivates	Aspirin (acetylsalicylic acid)
	Sodium salicylate
	Salsalate
	Diflunisal
	Salsalate
	Sulfasalazine
Para-aminophenol	Acetaminophen (paracetamol)
Propionic acid derivates	Ibuprofen
	Naproxen
	Fenoprofen
	Flurbiprofen
	Ketoprofen
	Oxaprozin
Acetic acid derivatives	Diclofenac
	Etodolac
	Ketorolac
	Indomethacin
	Sulindac
	Tolmetin
	Nabumetone
Enolic acid derivatives	Pyrazolones
	Phenylbutazone
	Dipirone
	Oxicams:
	Piroxicam
	Meloxicam
	Tenoxicam
	Lornoxicam
Fenamic acid derivatives (Fenamates)	Mefenamic acid
	Meclofenamic acid
	Flufenamic acid
	Tolfenamic acid
Selective COX-2 inhibitors (Coxibs)	Celecoxib
	Rofecoxib (withdrawn from market)
	Valdecoxib (withdrawn from the market)

Terms previously used to describe this type of reactions are aspirin-induced urticaria and multiple-drug-induced urticarial angioedema.

Immunologically mediated (non-cross-reactive) hypersensitivity reactions to NSAIDs

Single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA): Immediate hypersensitivity reactions to a single NSAID or to several NSAIDs belonging to the same chemical group, manifesting as urticaria, angioedema and/or anaphylaxis. These subjects tolerate other chemically nonrelated NSAIDs and usually do not have a history of chronic urticaria or asthma.

Terms previously used to describe this type of reactions are single-drug-induced reactions and allergic reactions.

Single-NSAID-induced delayed hypersensitivity reactions (SNIRD): Hypersensitivity reactions to a single NSAID appearing usually within 24–48 h after drug administration and manifesting by either skin symptoms [exanthema, fixed

Table 2 Novel classification of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (1, 101) (modified)

Type of reaction	Clinical manifestation	Timing of reaction	Underlying disease	Cross-reactivity	Putative mechanism	
NSAIDs-exacerbated respiratory disease (NERD)	Bronchial obstruction, dyspnea and/or nasal congestion/ rhinorrhea	Acute (usually immediate to several hours after exposure)	Asthma/rhinosinusitis	Cross-reactive	Nonallergic	Cox-1 inhibition
NSAIDs-exacerbated cutaneous disease (NECD)	Wheals and/or angioedema		Chronic urticaria			Cox-1 inhibition
NSAIDs-induced urticaria/ angioedema (NIUA)	Wheals and/or angioedema		No underlying chronic diseases			Unknown, probably COX-1 inhibition
Single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)	Wheals/angioedema/anaphylaxis		No underlying chronic diseases	Non-cross-reactive	Allergic	IgE-mediated
Single-NSAID-induced delayed reactions (SNIDR)	Various symptoms and organs involved (e.g., fixed drug eruption, SJS/TEN, nephritis)	Delayed onset (usually more than 24 h after exposure)	No underlying chronic diseases			T-cell mediated

drug eruption (FDE)], other organ-specific symptoms (e.g., renal, pulmonary), or severe cutaneous adverse reactions (SCAR).

Epidemiology

The prevalence of hypersensitivity to NSAIDs has been reported to be the second highest after antibiotics, but in some centers, the reactions to NSAIDs seem to be the most prevalent. Although the overall prevalence of hypersensitivity to NSAIDs has been reported between 0.6 and 5.7% of the general population, the figures vary significantly depending on the population studied, the method of assessment, and the type of reaction (8, 9).

Cross-reactive respiratory reactions (NERD)

- The prevalence of NSAIDs-exacerbated respiratory disease (NERD) varies from 4.3 to 20% depending on the population studied and the method of the diagnosis (8, 10, 11).
- Presence of chronic rhinosinusitis with nasal polyps, severe asthma, and female gender are associated with higher prevalence rate of aspirin and other NSAIDs hypersensitivity (12).
- Presence of atopy defined by skin prick test positivity to aeroallergens is positively associated with NERD in most populations (12).

Cross-reactive cutaneous reactions (NECD and NIUA)

- Urticaria is one of the three most commonly recognized cutaneous adverse drug reactions, and NSAIDs are among the most frequent cause of drug-induced urticaria.
- NSAIDs may be an aggravating factor in approximately 10–30% of adults with chronic urticaria although older studies showed even higher numbers (up to 50%) (13). The effect is dose dependent and is greater when the disease is active and less frequent when CU is under control.
- NSAIDs typically exacerbate chronic idiopathic urticaria, but also other types of urticaria, for example cholinergic urticaria (14).
- The cross-reactive type of NSAIDs hypersensitivity may occur in 3/4 of all patients with acute cutaneous reactions to NSAIDs (15).

Single-NSAID-induced urticaria/angioedema or anaphylaxis

- Up to 30% of all NSAIDs-induced skin reactions can represent a non-cross-reactive (a single-drug-induced) hypersensitivity reaction (13).
- The most frequently described causes of this type of reaction are pyrazolones, ibuprofen, diclofenac, aspirin, and paracetamol (16–18).

Delayed NSAIDs hypersensitivity

- The prevalence of NSAIDs-induced delayed reactions is not known.
- The most common delayed reactions due to NSAIDs are maculopapular eruptions (MPE), FDE, contact dermatitis, and photosensitivity reactions.
- Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) drug reaction with eosinophilia, and systemic symptoms (DRESS), drug-induced hypersensitivity syndrome (DIHS), and other organ-specific reactions can be also induced by NSAIDs.

Clinical subsets of hypersensitivity reactions to NSAIDs

NSAIDs-exacerbated respiratory disease

Clinical presentation

- Bronchial obstruction induced by aspirin/NSAIDs develops within 30–180 min after ingestion of the drug and may be accompanied by extrabronchial symptoms including nasal (rhinorrhea, nasal congestion), ocular, cutaneous (flushing of the upper thorax, urticaria and/or angioedema), or gastric symptoms (19).
- Symptoms of chronic rhinosinusitis and/or asthma usually precede the development of hypersensitivity to aspirin although in some patients ASA/NSAIDs intake may precipitate the first asthma attack (12).
- Most patients with NERD suffer from chronic rhinosinusitis complicated by mucosal hypertrophy and polyp formation.
- History of aspirin hypersensitivity is a risk factor for severe chronic asthma (20) and is strongly associated with near-fatal asthma, and fatal outcome of asthma occurs more often than in asthmatics without NERD (21).
- A subgroup of NSAID-sensitive patients exhibits a reaction exclusively in the upper respiratory tract. These patients may develop asthmatic symptoms in the future.

Pathomechanisms of NERD

- Respiratory reactions induced by aspirin or other NSAIDs are not immunologically mediated, but represent a cross-reactive type of nonallergic drug hypersensitivity (22–24).
- The mechanism of the reaction has been associated with inhibition of COX-1 (and subsequent activation of mast cells and eosinophils with release of inflammatory mediators) as mostly NSAIDs that are strong COX-1 inhibitors induce reactions in these patients. Weak COX-1 inhibitors in low doses or selective COX-2 inhibitors are generally well tolerated.
- Cysteinyl leukotrienes (LTs) are major (but not exclusive) mediators generated during NSAIDs-induced reactions and pharmacological inhibition of LTR1 receptors alleviates NSAIDs-induced symptoms (25).
- Chronic eosinophilic inflammation of higher than usual severity is a typical feature in both lower and upper airway mucosa.
- Crucial arachidonic acid metabolism abnormalities detected in patients with NERD include (26):

(a) Elevated levels of leukotriene E4 (LTE4) in the urine and less consistently in exhaled breath condensates, bronchoalveolar fluid, induced sputum, and in saliva. Overproduction of LTs is associated with overexpression of 5-lipoxygenase and related enzymes.
(b) Deficient generation of prostaglandin E2 in the upper and lower airway epithelial cells/fibroblasts, accompanied by a downregulation of COX-2 and lower baseline production of lipoxin A4 (LXA4) in peripheral blood leukocytes (23, 24).
(c) Increased expression of leukotriene LT1 receptors in the nasal mucosa

- Chronic viral infections might be involved in the development and persistence of airway inflammation in patients with NERD (27).
- Several genetic polymorphisms have been associated with NERD, but only few have been replicated and the relative contribution of particular variants is rather small (28).

Diagnosis

- A well-documented history of repeated previous reactions to aspirin and other NSAIDs predicts future response to NSAIDs (29) (grade of recommendation C).
- An oral provocation test (OPT) with aspirin is the most sensitive method (sensitivity ranges from 89 to 90%) to confirm the presence of hypersensitivity to aspirin and other cross-reactive NSAIDs in patients with NERD (30, 31) (grade of recommendation C).
- A negative result of the oral tests in a patient with a positive history does not exclude NSAIDs hypersensitivity if the patient is on long-term corticosteroid therapy and/or has been well controlled for a longer period of time (30, 31) (grade of recommendation C).
- An inhalation provocation test with lysine aspirin (L-ASA) is safer and faster to perform than the oral, but it is less sensitive (77–90%) for the diagnosis of NERD (32) (grade of recommendation C).
- A negative result of an inhalation test does not exclude NSAIDs hypersensitivity, so, subsequently, an oral aspirin challenge should be performed (if necessary). Inhalation challenges may be associated with systemic reactions; thus, precautions during the procedure are necessary (30, 31) (grade of recommendation C).
- Diagnostic nasal challenges with L-ASA can be performed if oral/inhalation provocation is not feasible. The sensitivity of a nasal provocation test (80–86.7%) does not differ significantly from inhalation provocation tests, and its negative result cannot rule out NSAIDs hypersensitivity (32, 33) (grade of recommendation C).
- Although several *in vitro* cell activation tests have been proposed and tested, none has been proven to be sensitive, specific, and reproducible enough to be recommended for routine practice (34–36) (grade of recommendation C).

Management

- Avoidance of aspirin and other cross-reacting NSAIDs is strictly recommended in patients with NERD to avoid acute hypersensitivity reactions (grade of recommendation C).
- Patients with NERD should be supplied with written information on potentially cross-reactive NSAIDs as well as alternatively well-tolerated NSAIDs (37) (grade of recommendation D).
- Avoidance of aspirin and other NSAIDs does not improve the clinical course of underlying asthma/rhinosinusitis in patients with NERD (grade of recommendation D).
- Salicylate free diet does not improve the clinical course of underlying asthma/rhinosinusitis in patients with NERD (grade of recommendation D).
- Nonacetylated salicylates (e.g., trisalicylate or salsalate) and paracetamol in low (< 1000 mg) doses are well tolerated by most patients with NERD. Selective COX-2 inhibitors are generally well tolerated by these patients, but some of them (1–2%) with unstable asthma may also react to selective COX-2 inhibitors (38) (grade of recommendation B).
- Management of asthma and rhinosinusitis in patients with NERD should follow international guidelines (grade of recommendation D).
- Antileukotriene drugs may improve the clinical course of asthma and rhinosinusitis in patients with NERD, but they are not more effective in NSAIDs-hypersensitive as compared to NSAIDs-tolerant asthmatics (39, 40) (grade of recommendation B).
- Sinus surgery (functional endoscopic sinus surgery; FESS) improves chronic rhinosinusitis symptoms, but is less effective in NERD in terms of recurrence rate of nasal polyps as compared to NSAIDs-tolerant patients (41, 42) (grade of recommendation C).
- Chronic treatment with aspirin after desensitization may be considered as therapeutic option in NERD patients. Treatment with aspirin (600–1200 mg daily) may alleviate upper airways symptom, reduce the use of intranasal corticosteroids, and improve asthma symptoms (43) (grade of recommendation B).
- In a certain proportion of patients, a decrease in recurrence of nasal polyps and need for sinus surgery was observed after chronic aspirin desensitization (44, 45) (grade of recommendation C).
- Along with asthma symptoms improvement, aspirin may decrease the need for oral corticosteroids and reduce exacerbation rates (44, 45) (grade of recommendation C).

NSAIDs-exacerbated cutaneous disease

Clinical presentation

- Symptoms of urticaria and/or angioedema appear usually 0.5–6 h after drug ingestion, although both immediate (within 15 min of ingestion) and late (several hours) reactions have been described. Skin eruptions usually subside

within few hours, but may persist for several days (15, 46).
- The magnitude of drug-induced symptoms is dose dependent and is greater when the chronic urticaria is active. NSAIDs-induced reactions are less frequent and less intense when chronic urticaria is in remission or under control.
- NSAIDs hypersensitivity may precede the onset of chronic spontaneous urticaria by years (47).
- Patients with NSAIDs-exacerbated cutaneous disease (NECD) suffer from chronic spontaneous urticaria that can be also exacerbated by triggers other than NSAIDs (infections, antibiotics, physical factors, stress) (48).

Pathomechanisms
- Cutaneous reactions induced by aspirin or other NSAIDs in patients with chronic urticaria are not immunologically mediated, but represent a cross-reactive type of nonallergic drug hypersensitivity.
- It has been postulated that the mechanism of the reaction in NECD patients similarly to NERD patients is related to inhibition of cyclooxygenase(s)and increased generation of cysteinyl leukotrienes (49).
- Patients with NECD cross-react to COX-1 inhibitors while selective COX-2 inhibitors are tolerated by the majority of them (50).

Diagnosis
- A history of NSAIDs-induced symptoms in patients with chronic urticaria is usually not reliable for predicting future reactions (51, 52).
- Skin tests with NSAIDs in patients with NECD have no diagnostic value and are not recommended for diagnosis (grade of recommendation D).
- *In vitro* basophil activation tests have limited diagnostic value with low negative predictive values (53) (grade of recommendation D).
- An oral provocation with the culprit drug should be done to confirm the hypersensitivity, if the history is unclear or when a definite diagnosis is required. The necessity for doing a provocation test has to be judged in each patient individually balancing the benefit of confirming the diagnosis versus the risk and effort involved (grade of recommendation D).
- Provocation tests with the culprit as well as with alternative NSAIDs should be performed if underlying skin disease is controlled, preferentially in inpatient settings by physicians experienced with this procedure and with emergency treatment available (grade of recommendation D).
- There is no formal consensus on the oral provocation protocol. However, it would be possible to start with 1/10 of the single dose and increase doses in two to three steps every 2 h till inducing symptoms or reaching the single therapeutic dose of the culprit drug (grade of recommendation D).
- Patients should be tested during a symptom-free phase (at least 1–2 weeks without any skin eruptions and free of antihistamines), if possible (grade of recommendation D).
- Low doses of NSAIDs have a lower sensitivity to detect NSAID hypersensitivity in patients with NECD (grade of recommendation D).
- If aspirin is not the culprit drug, an oral challenge test with aspirin should be performed to confirm/exclude a cross-reactive type of hypersensitivity (54) (grade of recommendation C).

Management
- Avoidance of all NSAIDs is recommended to prevent exacerbations of urticaria/angioedema. Strict avoidance of NSAIDs does not improve the clinical course of an underlying spontaneous urticaria/angioedema (grade of recommendation D).
- Oral tolerance tests (preferably placebo-controlled) should be carried out before prescribing alternative NSAIDs including COX-2 inhibitors (grade of recommendation D).
- Selective COX2 inhibitors (coxibs) are tolerated by the majority (75–90%) of NECD patients (50, 55).
- Preferential COX-2 inhibitors, such as nimesulide, or meloxicam or paracetamol (weak inhibitor of COX-1), may be used as alternative analgesic drug if tolerated on the provocation tests (56, 57) (grade of recommendation D).
- Similarly, the risk for patients with chronic urticaria to react to opioids is low. However, exceptional cases have been described and if justified a provocation test is advisable (58) (grade of recommendation D).
- In mild reactions to paracetamol and urgent need for medication, pretreatment of an antihistamine may be an option (59) (grade of recommendation D).
- Treatment of underlying chronic symptoms of urticaria/angioedema does not differ between patients with NECD or NSAIDs-tolerant patients (grade of recommendation D).

NSAIDs-induced urticaria/angioedema

Clinical presentation
- Symptoms of urticaria and/or angioedema appear usually within the first hour after the drug ingestion, although both immediate (within 15 min of ingestion) and late (several hours) reactions have been described (15, 50).
- As opposed to NECD patients, individuals suffering from NIUA do not suffer from any chronic cutaneous symptoms when unexposed to NSAIDs (urticaria and/or angioedema).
- Aspirin and other strong COX-1 inhibitors almost invariably induce symptoms in patients with NIUA. Weak COX-1 inhibitors may induce symptoms in up to 25% of patients, especially when high doses are used (e.g., 1000 mg or more of paracetamol) (15, 50).
- Selective COX-2 inhibitors (coxibs) are usually well tolerated.

Diagnosis
- Diagnosis is based on a history of repeated episodes of cutaneous symptoms occurring after administration of

NSAID in otherwise healthy individuals (grade of recommendation D).
- A history of reactions to at least two chemically unrelated NSAIDs allows for distinguishing NIUA from single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) (grade of recommendation D).
- Consistent repeated episodes with more than two different NSAIDs are indicative of NIUA, however, the value of clinical history (without oral challenge) for the diagnosis of NSAIDs hypersensitivity remains controversial (15, 60, 61) (grade of recommendation D).
- The diagnosis may be confirmed by an OPT with the culprit drug in a case of equivocal history (grade of recommendation D).
- If aspirin is the culprit drug, an alternative strong COX-1 inhibitor (e.g., indomethacin) must be administered to confirm/exclude cross-reactivity (15, 50) (grade of recommendation C).
- Challenge protocols similar to NECD can be used in patients with NIUA.
- Skin tests and *in vitro* tests have no diagnostic value (grade of recommendation D).

Management
- Avoidance of culprit NSAIDs as well as other NSAIDs with strong COX-1 inhibitory activity is recommended (grade of recommendation C).
- If analgesic or anti-inflammatory treatment is necessary, COX-2 or weak COX-1 inhibitors can be given (grade of recommendation C).
- Before prescription of an alternative drug, oral tolerance tests are recommended (grade of recommendation D).

Single-NSAID-induced urticaria/angioedema or anaphylaxis

Clinical presentation

A range of symptoms from mild urticaria and localized angioedema to laryngeal edema and anaphylaxis develop usually within minutes after a single-NSAID intake (15).
- Reaction to a single NSAID usually appears at shorter intervals than NIUA and may develop within seconds (e.g., after intravenous injection of metamizol) or minutes (after oral exposure). In most patients, symptoms appear in up to 1 h (62).
- Patients usually present with a history of good tolerance to other chemically unrelated NSAIDs, including aspirin (15).
- Patients do not have a history of underlying chronic urticaria, but may have a history of hypersensitivity to food or other drugs (e.g., antibiotics) (15).

Pathomechanisms
- The clinical spectrum of symptoms and timing of reactions suggest an allergic type I mechanism.
- Reactions to very closely chemically related compounds within the same chemical group (e.g., to different pyrazolones) can occur suggesting epitope-specific immunological mechanism of reactions (18).
- In a small proportion of patients, specific IgE can be detected in the skin test, in the serum or on peripheral blood basophils, which further supports an IgE-mediated mechanism of drug hypersensitivity (18, 63).

Diagnosis
- Diagnosis is based on a history of immediate symptoms induced by a single NSAID in a patient without an underlying chronic cutaneous disease (grade of recommendation D).
- The diagnosis is further strengthened if a patient has a history of tolerance to other chemically unrelated drugs taken after the episode (grade of recommendation D).
- To exclude a cross-reactive type of hypersensitivity, an oral challenge with a chemically unrelated strong COX-1 inhibitor (preferable aspirin) may be considered (grade of recommendation D).
- Skin tests with the culprit drug may be performed to confirm a selective, IgE-mediated type of hypersensitivity. The usefulness of skin testing has been documented for pyrazolones, although sensitivity is not optimal and the risk of systemic responses after intradermal testing exists (18, 62) (grade of recommendation C).
- Skin tests with the other-than-pyrazolones NSAIDs may be performed, but the usefulness has not been proven in large series (63) (grade of recommendation D).
- The presence of positive skin tests decreases with the time elapsed from the reaction; thus, skin testing should be performed as soon as possible after the allergic episode (62) (grade of recommendation C).
- Although in patients with SNIUAA, drug-specific IgE to some NSAIDs (e.g., aspirin, ibuprofen, propyphenazone or diclofenac) have been detected in the serum, measurement of drug-specific IgE in serum is not recommended for diagnosis (16) (grade of recommendation C).
- Basophil activation test (CD63/CD203) with a culprit drug has been reported to be of diagnostic value for metamizol, but not for other NSAIDs (64) (grade of recommendation C).

Management
- If a SNIUAA is diagnosed, a patient can safely take other chemically unrelated NSAIDs (grade of recommendation D).
- If the tolerance to a possible alternative NSAIDs is not known, the first approach is to verify the possible existence of cross-intolerance by challenge with alternative NSAIDs (usually aspirin) (grade of recommendation D).
- Desensitization in this type of reaction has not been documented.

Single-NSAID-induced delayed hypersensitivity reactions

Clinical presentation
- Delayed reactions to NSAIDs are developing more than 24 h after exposure and may be manifested by a variety of symptoms (65–67).

- The skin is the organ most frequently involved, usually with mild symptoms such as MPE, FDEs, photosensitivity reactions, and delayed urticaria (67–69).
- NSAIDs can induce contact dermatitis (70).
- More severe reactions such as drug-induced hypersensitivity syndrome (DIHS/DRESS), acute generalized exanthematous pustulosis (AGEP) and TEN/SJS occur less frequently (71–73).
- Other organ-specific reactions involving lung (pneumonitis) or kidneys (nephritis) have been observed rarely (74).
- The clinical presentation varies upon the drugs involved. Metamizol, paracetamol, and mefenamic acid are the most frequent elicitors of FDE; ibuprofen and naproxen of MPE; bufesamab, ketoprofen, and diclofenac of contact dermatitis (69, 70, 75).
- The topical and oral use of NSAIDs (e.g., ketoprofen) can induce allergic photocontact dermatitis (76).
- NSAIDs, especially oxicams, followed by COX-2 inhibitors (valdecoxib and celecoxib), diclofenac, and paracetamol have been associated with Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (71, 77).
- Single case of DIHS associated with ibuprofen and AGEP after ibuprofen, nimesulide, celecoxib, etoricoxib, valdecoxib, metamizol, and paracetamol have been reported (78, 79).

Pathomechanisms

- The pathomechanism of SNIDHRs involves the stimulation of drug-specific CD4+ and CD8+ T cells through their T-cell receptors (TCR) and represents a delayed type hypersensitivity.
- T-cell-dependent mechanisms have been documented in delayed urticaria, MPE induced by aceclofenac and metamizol and in SCAR induced by ibuprofen (80, 81).

Diagnosis

- The diagnosis is mainly based on clinical history.
- Although patch tests with specific NSAIDs have not been sufficiently standardized, these tests can be useful for the identification of the culprit NSAID inducing the delayed reaction particularly in cases of contact dermatitis and FDE (82, 83) (grade of recommendation D).
- If a FDE is being suspected, lesional skin should also be used for patch testing, what is called 'in loco patch testing' (grade of recommendation D).
- Photopatch tests are indicated for NSAID-induced photoallergic reactions (84) (grade of recommendation D).
- Patch testing and delayed reading of intradermal skin testing have a low sensitivity, but a high specificity (83) (grade of recommendation D).
- Intradermal skin test with delayed reading with NSAIDs, particularly metamizol, is more sensitive than patch tests (85) (grade of recommendation D).
- There is no standardized protocol for drug provocation tests in delayed reactions to NSAIDs (86).
- The provocation test with culprit NSAIDs can be considered in the following types of delayed reactions: MPE, urticarial, and FDEs (grade of recommendation C).
- Drug provocation tests with the culprit NSAIDs are contraindicated in the following reaction types: bullous drug eruptions such as TEN, Stevens–Johnson syndrome, AGEP, or organ-specific reactions (e.g., nephritis) (grade of recommendation C).
- The provocation test with alternative NSAIDs can be performed in all other situations (grade of recommendation D).
- There are limited data on the diagnostic value of a lymphocyte transformation test (LTT) in patients with delayed reactions to NSAIDs, and the test cannot be recommended for routine diagnosis (87) (grade of recommendation D).

Diagnostic algorithms

Definitions of diagnostic procedures

History

A detailed history should include all information usually collected in all cases of drug hypersensitivity: description of spectrum and timing of symptoms (beginning and full development of symptoms after drug intake), indications for what the NSAID was administered, brand of the culprit drug, dose and route of administration and list of concomitant medications (1, 24, 30, 46). Already available drug allergy questionnaires (e.g., European Academy of Allergy and Clinical Immunology – EAACI) may be helpful at the early stage of the diagnostic process.

In case of NSAIDs hypersensitivity, several additional specific information should be obtained:

- History and timing of previous hypersensitivity reactions to other NSAIDs.
- History of previously tolerated NSAIDs (names, doses).
- History of NSAIDs tolerated after the adverse reaction under investigation occurred.
- History of underlying chronic disorders and specifically bronchial asthma, chronic rhinosinusitis, nasal polyps, and chronic spontaneous urticaria/angioedema.

Predictive value of history for diagnosis of NSAIDs hypersensitivity: Generally, a history of hypersensitivity is not considered to be a reliable predictor of a future reaction to the same drug. The predictive value of the history may depend on the type of the reaction with probable higher predictive value for bronchial/nasal symptoms or anaphylaxis as compared to cutaneous reactions.

Drug provocation test

Oral challenge with NSAID can be performed for three reasons: (i) with a culprit drug to confirm hypersensitivity; (ii) with other than causative NSAIDs (usually challenge test with aspirin) in order to confirm/exclude cross-reactivity, and (iii) with the most likely tolerated alternative drug.

Ad 1. The oral challenge test with the culprit drug remains the gold standard to confirm the diagnosis of NSAIDs hypersensitivity, and all patients with equivocal history should be tested.

However, oral challenge with a culprit NSAIDs is not recommended in the following situations:

- Severe delayed type reactions (only patients with MPE or, FDE can be tested).
- A history of severe anaphylaxis.
- Noncontrolled underlying chronic disease (asthma, urticaria).
- Low pulmonary function test in an asthma patient.
- Concomitant disorders that could be aggravated by challenge or treatment.

Ad 2. If aspirin is not the suspected culprit drug, the patient should be challenged with aspirin to confirm/exclude cross-sensitivity. Positive reaction would confirm a cross-reactive type of hypersensitivity, and negative reaction would speak for a single-drug-type reaction. If the causative drug was aspirin, patient can be provoked with other strong COX-1 inhibitor to confirm the cross-reactive type of hypersensitivity.

Ad 3. A carefully performed diagnostic procedure (tolerance test) usually allows for the identification of a potentially safe alternative drug for the patient with NSAID hypersensitivity (e.g., selective COX-2 inhibitor or paracetamol if NERD has been diagnosed). However, it is recommended that in every case, tolerance test should be performed in the office before the drug is prescribed to the patient.

Predictive value of drug provocation test. A positive OPT is confirmatory for suspected NSAIDs hypersensitivity. The test has been documented to have a very high (97.8%) negative predictive value allowing for safe use of NSAIDs in most patients with equivocal history of hypersensitivity to NSAIDs (88). The positive predictive value of OPT is close to 100%.

Other routes of provocations

The inhaled route of provocation with lysine aspirin is recommended for the diagnosis of NSAIDs hypersensitivity in patients with a history of bronchial symptoms (bronchospasm) after drug ingestion and underlying history of bronchial asthma. In patients with a history of lower and/or upper airways symptoms, intranasal challenge with soluble aspirin or ketorolac can be employed. The usefulness of other routes of provocation (e.g., intravenous, conjunctival) has not been sufficiently documented.

Skin testing

Skin testing with a culprit drug may be useful only if a history suggests a SNIUAA. In patients with a history of delayed type of reaction, intradermal tests with the drug and delayed reading of the skin response or patch test can be considered, although these tests have not be validated. If a nonimmunological (cross-reactive) type of hypersensitivity is suspected skin testing is of no value.

In vitro *testing*

Due to diverse immunological and nonimmunological mechanisms involved in the NSAIDs hypersensitivity reactions, no universal *in vitro* test, which would be applicable to the diagnosis of all types of NSAIDs hypersensitivity, can be recommended.

Measurement of drug-specific IgE in serum in patients with a history of reaction to a single NSAID (SNIUAA) has been proposed, but has not been validated.

In patients with acute form of reactions to NSAIDs, cell activation tests (Basophil Activation Test Cellular Allergy Stimulation Test *CAST-ELISA) or Aspirin Sensitive Patient Identification Test, ASPITest) have been employed, and in delayed reaction to NSAIDs, the LTT was used. None of these *in vitro* test has been validated sufficiently to justify recommendation for routine diagnosis of NSAIDs hypersensitivity.

Description of the algorithm

The diagnostic approach, particularly based on anamnesis, can be initiated by nonspecialists, but the completion of the diagnostic procedure requires the expertise of an allergy specialists or qualified physicians with sufficient experience.

The timing and the others characteristics of the episode/episodes of the reaction, based on initial anamnesis, as outlined above, should determine further diagnostic procedures, and accordingly, separate algorithms are proposed for acute and delayed types of hypersensitivity (Figs 1 and 2, Table 3).

If the reaction started to develop within hours (up to 24 h) after the drug intake the acute type of the reaction can be suspected and the information on clinical pattern of symptoms, history of underlying diseases and list of drugs that evoked reaction should be analyzed.

If a patient manifested respiratory symptoms (dyspnea, wheezing, cough, nasal discharge, nasal congestion) and has a history of asthma and/or rhinosinusitis with nasal polyps, the NERD subtype of NSAID hypersensitivity can be suspected. A history of similar symptoms evoked in the past by other strong COX-1 inhibitors and/or history of good tolerance of selective COX-2 inhibitors suggests the cross-reactive type of hypersensitivity and further confirms the diagnosis NERD.

Patients with acute cutaneous symptoms (urticaria/angioedema) and/or anaphylactic symptoms after intake of NSAIDs can represent one of three subtypes of hypersensitivity: NECD, NIUA, or SNIUAA. The first step should be to establish, based on detailed history of previous reactions, whether the patient represents the cross-reactive type of NSAIDs hypersensitivity or whether he/she is sensitized to a single drug. If a patient has a history of reactions to more than one chemically unrelated COX-1 inhibitor, the cross-reactive (nonallergic) type can be suspected. Concomitant history of episodes of spontaneous chronic urticaria/angioedema, unrelated to NSAIDs intake, allows for the diagnosis of NECD. Patients with a negative history of spontaneous urticaria/angioedema but presenting reliable history of hypersensitivity cutaneous reactions to several chemically unrelated NSAIDs should be referred as NIUA. In patients who have a history of cutaneous (urticaria and or angioedema) and/or anaphylactic reactions to a single NSAID, an allergic type I reaction (SNIUAA) may be suspected.

Skin testing or *in vitro* testing with a culprit drug has limited usefulness in the diagnosis of NSAIDs hypersensitivity,

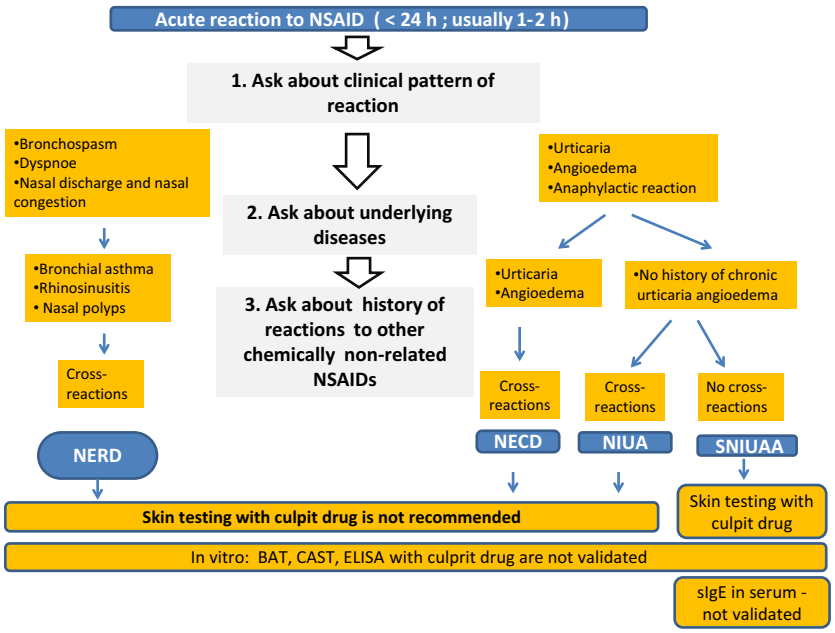

Figure 1 Algorithm for the diagnosis of acute forms of nonsteroidal anti-inflammatory drugs (NSAIDs) hypersensitivity.

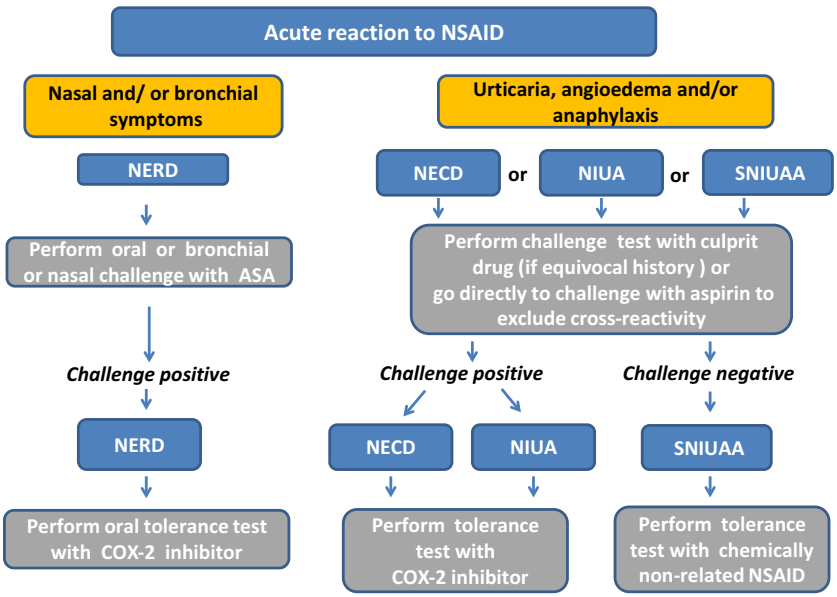

Figure 2 Provocation challenges in patients with a history of acute reactions to nonsteroidal anti-inflammatory drugs (NSAIDs).

and the selection of testing method depends on the type of hypersensitivity suspected (described in specific sections above).

In patients with a history of delayed cutaneous reactions (MPE, FDE, AGEP, SJS/TEN), the diagnosis is based on anamnesis. Skin patch tests can be useful for contact dermatitis and FDE, MPE (and some cases of SJS/TEN), and intradermal tests with delayed reading have high specificity but low sensitivity. Oral provocation with a culprit drug in NIDHR is usually not recommended (Table 3).

Role of desensitization

- Diagnosing (establishing) the type of hypersensitivity should precede decision on aspirin desensitization and treatment with aspirin (grade of recommendation D).

Table 3 Diagnostic procedures in delayed type of hypersensitivity to NSAIDs

Type of reaction	Patch test	Intradermal test with delayed readings	Oral provocation with culprit drug	Oral provocation with alternative NSAID
Fixed drug eruption	On both affected and nonaffected affected area	Yes	Yes/No	Yes
Maculopapular eruption	Yes	Yes	Yes	Yes
Allergic photosensitivity	Yes (photo-patch test)	No	Yes/No	Yes/No
Contact dermatitis	Yes	No	No	No
AGEP	Yes	Yes (perform cautiously)	No	Yes
SJS/TEN	Yes	Yes (perform cautiously)	No	Yes

- Desensitization to aspirin can be performed only in patients with NSAID-exacerbated respiratory disease (NERD) and NSAID-induced urticaria/angioedema (NIUA) (44, 45, 89) (grade of recommendation C).
- In patients with NECD, aspirin desensitization remains controversial (90–92). No data exist in patients with single-NSAID-induced urticaria and/or anaphylaxis.
- To maintain the tolerance state, patients desensitized to aspirin should take aspirin on daily basis. The refractory period lasts from 2 to 5 days in individual patients (grade of recommendation C) (93).
- Aspirin desensitization followed by treatment with aspirin can be indicated in patients with NERD to alleviate nasal symptoms (grade of recommendation B) and prevent nasal polyp recurrence (grade of recommendation C) (45, 94–96).
- Aspirin desensitization is also indicated in patients who need chronic antiplatelet treatment with aspirin and chronic anti-inflammatory treatment with NSAIDs (grade of recommendation C) (89, 97–99).
- Effective daily dose of aspirin resulting in clinical improvement in patient with NERD varies from 300 to 1300 mg daily (grade of recommendation C) (94, 96, 100)
- Aspirin desensitization should be performed in a facility able to provide appropriate intensive care and constant observation by qualified and specialized staff (grade of recommendation D).

Management of a patient with hypersensitivity to NSAIDs

- General rules of management of drug hypersensitivity apply to NSAIDs hypersensitivity and include immediate cessation of a culprit drug intake and strict avoidance of the drug in the future (grade of recommendation D).
- All patients with confirmed diagnosis of NSAIDs hypersensitivity should be supplied with information on potentially cross-reactive NSAIDs as well as with a list of safe alternative NSAIDs (grade of recommendation D).
- It is recommended that safety of alternative drugs should be confirmed by controlled tolerance test (grade of recommendation D).
- The only specific form of management is cross-reactive drug desensitization (usually aspirin) which can be considered if a specific type of NSAID hypersensitivity has been diagnosed (grade of recommendation C).
- The underlying chronic disorders (e.g., asthma or chronic urticaria) should be treated according to general guidelines (grade of recommendation C).

Conclusions and unmet needs

A significant progress in understanding of complex pathomechanisms of NSAIDs hypersensitivity has important practical implications for patients' diagnosis and management. The authors believe that these recommendations reflect the current best knowledge in this field, although we are fully aware of several limitations of our recommendations, which results mainly from the paucity of high quality data. Below are the major unmet needs in the field of NSAIDs hypersensitivity reflecting gaps in our knowledge and which according to the panel opinion should be addressed and filled in the near future:

- Determination of NSAIDs hypersensitivity prevalence in various populations (e.g., asthma, rhinosinusitis, chronic urticaria) in multicenter, epidemiological studies employing drug challenge for the diagnosis.
- Identification of susceptibility genes for development of NSAIDs hypersensitivity and genetic markers associated with severe reactions to NSAIDs.
- Further studies are needed to understand the pathomechanisms of both nonallergic (NERD, NECD,NIUA) and presumably immunologically mediated (SNlUAA, NIDHR) types of hypersensitivity to NSAIDs.
- Assessment of predictive values of both positive and negative provocation challenges for the diagnosis of various types of NSAID hypersensitivity.
- Validation of methodology (including recommended drugs concentrations) and assessment of sensitivity and specificity of skin testing with specific NSAIDs for the diagnosis of immunologically mediated types of NSAIDS hypersensitivity (SNIUAA and NIDHR).
- Evaluation and validation of *in vitro* methods (cell activation tests) to confirm various types of hypersensitivity to NSAIDs.
- Safety assessment of alternative NSAIDs for patients with NSAIDs hypersensitivity, depending of type of the reaction.
- Validation of standard protocols (including rapid protocols) for ASA desensitization in various types of NSAID hypersensitivity.

- Assessment of clinical efficacy of alternative routes of NSAIDs desensitization (intranasal, intravenous).

Conflicts of interest

The authors declare no conflicts of interest.

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