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Special Article

Update on hypersensitivity reactions to nonsteroidal anti-inflammatory drugs – Part 2: clinical features, phenotypes, diagnosis, and management

Atualização em reações de hipersensibilidade aos anti-inflamatórios não esteroidais – Parte 2: manifestações clínicas, fenótipos, diagnóstico e manejo

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ABSTRACT

Nonsteroidal anti-inflammatory drugs are a major cause of drug hypersensitivity reactions in clinical practice. In this "Update Part 2", we discuss the clinical picture, including the main signs and symptoms, how to distinguish clinical phenotypes, how to manage affected patients, and when to indicate additional procedures, such as skin testing, challenge, and desensitization.

Keywords: Nonsteroidal anti-inflammatory drugs, drug hypersensitivity, phenotype.

RESUMO

Os anti-inflamatórios não esteroidais (AINE) são os fármacos mais frequentemente associados a reações de hipersensibilidade (RH) na prática clínica. Na parte 2 dessa atualização sobre as RH aos AINE, discutiremos os aspectos clínicos dessas reações, com foco nos sinais e sintomas, como diferenciar os fenótipos clínicos, fazer a orientação desses pacientes e quando indicar procedimentos complementares, como testes cutâneos, de provocação e dessensibilização.

Descritores: Anti-inflamatórios não esteroidais, hipersensibilidade a drogas, fenótipo.

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Introduction

In Part 1 of this review, we discuss the pharmacology of nonsteroidal anti-inflammatory drugs (NSAIDs), including the pathophysiological role of the inhibition of cyclooxygenase (COX) 1 and 2 in the genesis of most hypersensitivity reactions (HR), the genetic and epidemiological aspects of these reactions, and the mechanisms involved in their occurrence, whether they are allergic (Gell and Coombs' type I and IV) or non-allergic.[1] In Part 2, we will approach the clinical picture of each of the classical phenotypes of NSAID HRs, other possible and less frequent phenotypes, particularities in the pediatric population, and mainly the management of these patients, which includes all steps between diagnosis and treatment. Their treatment can involve adequate guidance on restricting or substituting the drugs in question or indicating desensitization.

Clinical features and phenotypes

Clinically, HRs to NSAIDs can be classified according to the timing of symptom onset into *acute* – when occurring less than 24 hours after exposure to the medication (usually immediately, less than 60 minutes after drug administration) – and *delayed*, when they occur after these 24 hours.[2] However, more than just the time between exposure and reaction, the pattern of clinical manifestations has fundamental importance when defining the phenotype.

NSAID-exacerbated respiratory disease (NERD)

In 1922, Widal and colleagues published the first study describing the association between aspirin hypersensitivity, asthma, and nasal polyps; the researchers also conducted the first aspirin challenge followed by desensitization. However, this syndrome was only recognized in the 1960s, when Samter published two studies with a condition that he named Samter's triad; it included asthma, nasal polyps, and aspirin reactions. Many other names were used for this respiratory disease, such as aspirin-induced asthma, aspirin hypersensitivity, and aspirin intolerance.[3] In 2001, Stevenson and colleagues coined the term "aspirin-exacerbated respiratory disease" (AERD), including not only asthma but also the upper airways, in addition to valuing the frequent association with an underlying respiratory disease.[4]

All these terms refer to the same untreatable inflammatory condition of the upper and lower airways; many further studies demonstrated the importance of eosinophilic inflammation of the respiratory tract in this triad. Exposure to aspirin does not initiate or even perpetuate an underlying inflammatory disease; however, after disease onset, aspirin and NSAIDs induce the liberation or synthesis of critical mediators that lead to the clinical manifestations of the characteristic respiratory reactions.[3]

Clinically, AERD is characterized by the triad: chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), asthma, and hypersensitivity to aspirin or other NSAIDs.[5,6] Therefore, the currently used acronym is "NERD," referring to "NSAID-exacerbated respiratory disease" and not just aspirin.

Other clinical features have been shown to be frequent in NERD, such as marked anosmia, atopy, alcohol intolerance, and a shorter interval between polypectomies.[6,7]

The clinical features of NERD are not usually present at disease onset; most times, they progress according to a pattern. The first clinical manifestation to appear in patients with NERD is rhinitis, considered as nasal obstruction, nasal discharge, anosmia/hyposmia, and sneezing. Anosmia/hyposmia is frequent (89%) and intense. Chronic rhinitis progresses to chronic hyperplastic eosinophilic sinusitis, which can be seen in up to 99% of patients as hyperdensity on computed tomography scans of the sinuses. The first manifestation of asthma appears on average two years after rhinitis, and hypersensitivity to aspirin or other COX-1-inhibiting NSAIDs tends to appear four years later. However, other studies demonstrated that hypersensitivity to aspirin/NSAIDs can appear at any moment during the course of the disease.[8]

The frequency of respiratory symptoms induced by alcohol consumption in patients with NERD is high; upper airway symptoms (rhinorrhea, nasal obstruction) are reported in up to 75% of the patients, and lower airway symptoms (wheezing and dyspnea) are reported by 51% of the patients.[9]

Although NERD has a characteristic presentation, including the presence of respiratory symptoms a few minutes to hours after the use of any COX-1-inhibiting NSAID (acute reaction), patients with NERD are heterogeneous[3]. Bochenek and colleagues classified patients with NERD into four subtypes. Class 1: moderate asthma, severe CRS, and peripheral blood

eosinophilia; Class 2: mild CRS, mild and relatively well-controlled asthma; Class 3: severe, poorly controlled asthma, severe exacerbations, and severe bronchial obstruction; and Class 4: poorly controlled asthma with frequent and severe exacerbations in women, normal lung function, and obesity.[10]

Another study classified NERD through an analytical strategy named latent class analysis into three subphenotypes, considering the inflammatory pathways and clinical manifestations of asthma. The subphenotypes included 16 variables: clinical characteristics such as gender, body mass index, age of asthma onset, history of asthma exacerbation, control and severity of asthma, use of inhaled and/or systemic corticosteroid, forced expiratory volume in 1 second (FEV_1), serum eosinophil count, total serum IgE, atopy (status determined by skin prick tests), and inflammatory characteristics on induced sputum (IS), such as prostaglandin (PG)D2, PGE2, and LTE4.[11]

– *Class 1:* mild to moderate asthma, with no pulmonary dysfunction, IS with low levels of eosinophils and other mediators.
– *Class 2:* severe, poorly controlled asthma with bronchial obstruction, frequent exacerbations, marked eosinophilic inflammation, and increased inflammatory markers on IS.
– *Class 3:* mild to moderate and relatively well-controlled asthma, eosinophilic inflammation and increased pro- and anti-inflammatory mediators on IS.

In this study, LTE4 levels were correlated with peripheral eosinophil counts.[11]

NSAIDs-exacerbated cutaneous disease (NECD)

NECD is characterized by patients presenting chronic spontaneous urticaria (CSU) with or without angioedema as an underlying disease, who have an acute worsening (minutes to a few hours) of cutaneous symptoms after ingesting NSAIDs, usually strong COX-1 inhibitors.[12]

Studies indicate the presence of this phenotype in 12%-30% of patients with CSU. Since CSU is a self-limited disease lasting for months to years, NECD can disappear when CSU is resolved. However, phenotypical differences arise when they are compared to patients with CSU who tolerate NSAIDs. NSAID tolerance in the presence of CSU was demonstrated to be a good prognostic factor, as these patients present shorter CSU and a lower frequency of associated angioedema.[13] Other studies demonstrated that NSAIDs that selectively inhibit COX-2 can be used in these patients as a therapeutic alternative.[14,15]

NSAIDs-induced urticaria/angioedema (NIUA)

This is the most frequent phenotype of NSAID HR. Patients present acute NSAIDs-induced urticaria or angioedema (minutes to a few hours) and do not have CSU as the underlying disease. These symptoms are manifested only after NSAID ingestion, usually with a strong COX-1 inhibitor. Patients may report urticaria only, angioedema, or a combination of both. Around 60% of all patients with NIUA have a concomitant atopic disease.[16] In a study performed in Spain, these patients were followed-up for 12 years and 62% of them developed NSAID tolerance five years after disease onset.[17] On the other hand, another study demonstrated that 33% of these patients developed CSU during follow-up[18], and this finding was not confirmed years later in a Spanish cohort[17]. This way, the theory that NIUA may be a risk factor for the development of CSU remains controversial.

Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)

SNIUAA is biologically and phenotypically different from other NSAID hypersensitivity syndromes because patients react acutely to only one NSAID class, most frequently pyrazolones (including metamizole), and tolerate strong COX-1 inhibitors of different classes (aspirin, diclofenac, or ibuprofen, for example)[2,19].

Symptoms are triggered by the Gell and Coombs' type I hypersensitivity mechanism (IgE-mediated) and reactions are usually more severe than those in the previous syndromes[20]. Similarly to classical IgE-mediated reactions, they occur immediately, usually within an hour of exposure. There are reports of cases of SNIUAA associated with NSAID classes other than pyrazolones, such as propionic acid derivatives (ibuprofen or ketoprofen), but the occurrence of specific IgE has not yet been demonstrated for other NSAID classes apart from that including metamizole as the main example available.

Single NSAID-induced delayed hypersensitivity reaction (SNIDHR)

SNIDHR has symptoms triggered by a type IV mechanism (T cell-mediated). Symptoms usually appear within 24-48 hours of NSAID ingestion.

Reactions may vary from mild symptoms such as maculopapular exanthem and localized fixed drug eruption (FDE) to severe symptoms, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and generalized bullous FDE.[2,21]

Morphologically differentiating skin lesions is fundamental for excluding other phenotypes. Dermatological findings such as lesions lasting more than 24 hours, appearance of residual lesions, multiple vesicles vesicles, skin peeling, or exudates help exclude urticaria as the diagnosis of cutaneous manifestations. Once this is performed, in case the reaction was NSAID-induced, SNIDHR can be confirmed. The next step would be to define which other delayed dermatoses can define the case. The European position paper on cutaneous manifestations of drug HR brings a simple and objective algorithm for diagnosing cutaneous drug hypersensitivity reactions and can also be used for NSAID HRs.[22]

Other phenotypes

The classification of NSAID HRs into these five clinical phenotypes (NERD, NECD, NIUA, SNIUAA, and SNIDHR) proposed 10 years ago by the European Academy of Allergy and Clinical Immunology (EAACI) was extremely helpful to the management of these cases in clinical practice.[2,23,24] Among these, non-allergic HRs with cross-intolerance between classes of COX-1 inhibitors (NERD, NECD, and NIUA) are the most frequent in all age groups. On the other hand, our incomplete knowledge of the basic mechanisms of NSAID HRs makes the definition of phenotypes and endotypes difficult and highlights the need to identify new biomarkers for improving the diagnosis and classification of these reactions.[25]

Not all patients with HRs to NSAIDs can be classified into one of these five phenotypes suggested by the EAACI. Some other phenotypes have been described: mixed or combined reactions, food-dependent NSAID-induced anaphylaxis, and selective immediate reactions to multiple NSAIDs.

Mixed or blended reactions

Non-allergic cutaneous reactions (NIUA and NECD) and respiratory reactions (NERD) can be combined and simultaneously involve cutaneous and respiratory symptoms, or even affect other organs.[26] Some studies indicate that mixed reactions are responsible for more than 25% of cross-intolerance in adults and are the second most frequent among all phenotypes.[27] The most common symptoms of combined reactions are urticaria and angioedema associated with rhinitis or bronchospasms, although other symptoms such as laryngeal edema, hypotension, and gastrointestinal symptoms have also been described. Since they simultaneously affect two organs or systems in a short period of time, these reactions end up constituting anaphylaxis, but according to the European classification, anaphylaxis would only involve the IgE-mediated phenotype (SNIUAA). The largest Brazilian case series of drug-induced anaphylaxis showed that NSAIDs were the drug class most frequently involved in this type of reaction and almost all of these patients were cross-reactive, presenting blended reactions[28].

A review of the same Brazilian group published a few years later proposed that anaphylaxis be included in the list of clinical manifestations of nonimmunologically mediated HRs, notably in the most frequent one, NIU.[29] With the increase in cases of mixed reactions in other parts of the world, EAACI classifications may face new changes in the future.

Food-dependent NSAID-induced hypersensitivity or anaphylaxis (FDNIH or FDNIA)

NSAID ingestion has been associated with food-depended anaphylaxis and has exacerbated food-dependent exercise-induced anaphylaxis (FDEIA). Diagnosis is difficult because no causal factor is identified, even with a negative provocation test (PT) for the drug if the food is not present. The basophil activation test (BAT) has been suggested to help in diagnosis. Its pathophysiology involves increased intestinal permeability caused by NSAIDs, which increases allergen absorption.[30] Another possibility is a direct effect of the drug, potentializing the activation and degranulation of mastocytes and basophils. The intensity of the IgE-mediated reaction is related with NSAID class, dose, and strength of COX-1 inhibition. A study evaluated 328 patients with suspected immediate reactions to NSAIDs; 199 (60%) confirmed hypersensitivity through a PT, and FDNIH was confirmed in 52 cases (16%); of these, 44 individuals (84%) presented sensitivity to the lipid transfer protein (LTP) Pru p 3 through skin tests and/or specific IgE measurements. World Allergy Organization (WAO) and EAACI suggest that FDNIH should be considered and food allergy tests should be included in the diagnostic evaluation of patients with HRs to NSAIDs.[31]

Selective immediate hypersensitivity reactions to NSAIDs (SIHRN)

Some studies showed that individuals may develop SIHRN while tolerating acetylsalicylic acid (ASA).[32,33] Children with paracetamol-induced urticaria and angioedema who tolerate ASA have also been described.[34]

A Spanish research group has described this phenotype and suggested that patients should not be defined as having NIUA, that is, cross-reactive patients with cross-intolerance to NSAIDs of different classes, until reactivity to ASA is confirmed (or not).[35] However, since these studies have not been replicated in other populations and the mechanisms involved in this phenomenon are not known, the possibility of patients reacting to more than one class of NSAIDs and tolerating others, including ASA, should be considered. Other aspects could influence this picture, such as cofactors, overlapping infection, drug dose or interval between doses, etc.

Advances in the knowledge of the pathophysiological mechanisms of NSAID HRs have led to the recommendation of revising the current classification, as it does not contemplate these "new phenotypes." Other important and still unknown factors are the development of tolerance over time, the role of atopy, the progression of different phenotypes, and the potential for phenotype conversion or switching.[36]

Table 1 shows a new classification proposed for NSAID HRs, including phenotypes not previously considered by the EAACI.[24]

Cross-intolerance

Most NSAIDs perform nonselective COX-1 inhibition. They interfere with arachidonic acid synthesis, leading to a blockage of PG synthesis and overproduction of the leukotriene (LT) pathway, contributing to various presentations of NSAID HRs, notably NIUA, NERD, NECD, and blended reactions.[24,37] In these phenotypes, the patient may probably present cross-intolerance between different classes of strong COX-1 inhibitors, such as virtually all carboxylic acid derivatives (ASA, diclofenac, ibuprofen, ketorolac, etc.), in addition to pyrazolones, mefenamic acid, and some oxicam drugs.[1] However, some preferential COX-2 inhibitors such as nimesulide, paracetamol, and meloxicam are tolerated by most cross-reactive patients with the aforementioned phenotypes.

Although many patients arrive at evaluation having already used these medications after their first reactions, particularly urticaria and angioedema, others do not know their tolerance to these options. Clearly, in patients who have used one of these drugs after a first reaction to another COX-1 inhibitor, their personal history of tolerance should be the main factor when evaluating whether to indicate future use of these medications. On the other hand, few studies evaluated tolerance to nimesulide and meloxicam in patients with cross-reactive NSAID intolerance. Tolerance to meloxicam (92% to 96%) appears to be slightly superior to that to nimesulide (86% to 90%) in patients with NIUA or NECD.[38-40] In an Italian study[40] evaluating patients with cross-reactive intolerance to ASA and/or other NSAIDs, when they were subjected to a PT with celecoxib, rofecoxib, or meloxicam, reactivity was only observed in individuals with cutaneous symptoms. Among those with respiratory symptoms only (NERD), all patients tolerated the three drugs.[40]

Paracetamol, on the other hand, seems to be well tolerated in a 500 mg dose in adults or an equivalent dose in children (10 to 15 mg/kg/dose) In a Turkish study, the rate of reactivity to 500 mg paracetamol was only 5.8%.[38] In children, a study could not find patients presenting reactivity to paracetamol[41]. However, this intolerance increases proportionally with the dose and can reach 25% when the paracetamol dose reaches 900 mg.[42] In a Brazilian study, 116 patients with NIUA or NECD who also reported paracetamol intolerance were challenged in a single-blind, placebo-controlled design with 500 mg of the drug. Reactivity was confirmed in only 6.9% of the patients, all of which were not severe cases; 3.4% of the individuals reacted to placebo.[42]

Considering selective COX-2 inhibitors (coxibs), tolerance seems to be even higher. In a thorough literature review published in 2019, Lilly Li and Tanya Laidlaw compiled cases published thus far and found a rate of reactivity of 3.3% to coxibs in patients with any HR to NSAIDs and highlighted that only one report of laryngeal edema was found among more than 3,000 challenges with coxibs. Moreover, no severe reaction required emergency care or adrenaline use. When specifically evaluating patients with NERD, researchers found only 0.13% of positive tests (1 positive result among 753 PTs).[44]

It is important to highlight that coxibs have been associated with increased cardiovascular risk, which took some of them off the market.[45] In

Table 1
Classification proposed for NSAID hypersensitivity reactions including phenotypes not previously considered by the EAACI*

Type of hypersensitivity	Phenotypes	Time between exposure and reaction	Underlying chronic disease	Underlying mechanism
Cross-intolerance	NIUA	< 24 hours (mostly < 1 hour)	No	COX-1 inhibition
	NECD		CSU	
	NERD		CRSwNP and/or asthma	
	Blended or mixed reactions		Yes/No	Probable COX-1 inhibition
	FDNIA		Food allergy	Unknown
Non-cross-reactive	SNIUAA		No	IgE-mediated
	SIHRN			Unknown, probably IgE-mediated
	SNIDHR	> 24 hours		T cell-mediated

* Adapted from Doña I, et al.[24] NSAID = nonsteroidal anti-inflammatory drug, NIUA = NSAIDs-induced urticaria/angioedema, NECD = NSAIDs-exacerbated cutaneous disease, NERD = NSAID-exacerbated respiratory disease, FDNIA = food-dependent NSAID-induced anaphylaxis, SNIUAA = single NSAID-induced urticaria/angioedema or anaphylaxis, SIHRN = selective immediate hypersensitivity reaction to NSAIDs, SNIDHR = single NSAID-induced delayed hypersensitivity reaction, CSU = chronic spontaneous urticaria, CRSwNP = chronic rhinosinusitis with nasal polyps, COX-1 = cyclooxygenase 1.

Brazil, etoricoxib and celecoxib remain available for oral administration and parecoxib is available for parenteral administration. We highlight that etoricoxib and celecoxib are still in the national market but at lower doses than those used when they were first launched. Etoricoxib is available at a maximum dose of 90 mg once a day, and celecoxib is available at 200 mg, twice a day. Therefore, these drugs should be avoided in older adults and individuals with cardiovascular or cerebrovascular disease.

Peculiarities in children

NSAIDs and beta-lactams are the main causes of drug HR in the pediatric age group.[46,47] Cutaneous reactions induced by infectious agents, such as viruses, constitute an important confounding factor in the context of adverse reactions to medications in children and are less likely to be confirmed than in adults.[48] In a large European multicenter study including almost 700 patients from five countries with a history of NSAID HRs, the frequency of positive PTs with the suspected agent was 19%, which allowed the exclusion of an NSAID HR diagnosis in most patients.[49]

Classification and mechanisms of HRs in children

Although most pediatric patients with HRs to NSAIDs can be phenotypically classified just as the adult patients, a fraction of them would also not be

contemplated by the five classical phenotypes. A study performed by Cousin and colleagues[50] showed that 44% of 635 pediatric patients with confirmed NSAID HRs did not fit into any of the categories as stated by the European Network on Drug Allergy (ENDA).[2] Recently, ENDA proposed a consensus for the classification of NSAID HRs directed to the pediatric population through different criteria for children under 10 years old and those older than 10 and teenagers, emphasizing differences in these age groups.[47] Data in the international literature suggest that the phenotype of mixed reactions (cutaneous and respiratory) is the most frequent in smaller children. On the other hand, CSU is uncommon in this age group and NERD can be considered rare. Therefore, in children under 10 years old, ENDA recommended the unification of NIUA, NECD, and NERD in a sole phenotype, defined in this publication as "non-allergic hypersensitivity".[42] The classification proposed by ENDA for NSAID HRs in children under 10 years old is presented in Table 2.

This proposal for a new classification was based on studies that identified that most reactions in smaller children were nonimmunologically mediated (cross-intolerance), with significant influence of cofactors. In older children and adolescents, on the other hand, the clinical picture is more similar to that in adults. Changes in the classification of NSAID reactions in children should allow a better management of these reactions, but new classifications may still be necessary as the knowledge on the pathophysiological mechanisms and natural history of the disease advances.

Diagnosis of NSAID HRs in children

The diagnosis of NSAID HRs in children relies on the analysis of a detailed clinical history, with attention to the new phenotypes and the most probable mechanism involved in the reaction. In the context of current knowledge, skin tests and *in vitro* (laboratory) tests present limited levels and low applicability due to the absence of standards and a scarcity of studies on predictive values, especially in the pediatric age group. The PT is the gold standard for diagnosis and should follow doses related with the pediatric age range and the context of risk stratification in order to be used.

Skin tests, such as the skin prick test and the intradermal (ID) skin test, can be used for immediate reactions (urticaria, angioedema, and anaphylaxis) and when there is clinical suspicion of a non-cross-reactive reaction to metamizol.[47] Although a non-irritating paracetamol concentration for immediate-reading skin tests has been described, these tests should not be performed (particularly the ID test) since no parenteral formulation of this drug is available in Brazil. Regarding selective delayed HRs, there are not enough studies in the pediatric age group, in addition to the technical difficulty of performing delayed-reading skin tests in smaller children.

In vitro tests have low applicability. The alternatives, for immediate reactions, would be serum levels of specific IgE and the BAT[51,52]; however, these do not have defined validation or accuracy, particularly in children, thus should not be performed outside of research centers.

A PT may be performed to confirm NSAID hypersensitivity, to define the clinical phenotype, or to evaluate tolerance to another NSAID (eg, a selective or preferential COX-2 inhibitor). It should only be indicated after correct risk stratification, and more than one procedure may be required in each child.[53,54] The procedure is usually open or single-blind, placebo-controlled, and must be performed in an adequate setting for the care of possible severe reactions by a certified allergy specialist. Studies recommend initial doses of 10% to 25% of the therapeutic dose adjusted to the child's weight and age, but smaller doses may be initially necessary in case of a history of severe reaction. The subsequent doses may be administered at intervals of 30 to 60 minutes or more, depending on the clinical context of the suspected reaction.[55] The observation period after full administration should be of 2 to 4 hours, or until clinical stability in case of reactions.

In some cases, additional doses may be necessary after this observation period, and these may be administered at the patient's home (extended PT). Written information on drugs that should be avoided and alternative medications with the respective doses and formulations should be provided to the child and family members. Paracetamol at low doses was shown to be well tolerated in children as an antipyretic.[56] Selective COX-1 inhibitors, despite being safe for adolescents, have not yet been approved for smaller children. In studies with children with cross-intolerance to NSAIDs, preferential COX-2 inhibitors showed to be effective and safe in more than 80% of the patients.[57] Selective COX-2 inhibitors (coxibs) are only approved for adults (over 18 years old) in Brazil, but various studies in other countries have shown the safety of these drugs, which led them to be suggested as options, even if off label, by European guidelines.[47]

The natural history of NSAID hypersensitivity is still not well understood and, in the pediatric age group, there are additional confounding factors such as the concomitant use of other medications, dose-dependency, and the coexistence of infections. The poorer knowledge on the NSAID metabolism in children, scarcity of studies on the use of skin tests in selective delayed reactions, technical difficulty, lack of standardized non-irritating NSAID concentrations, and lack of parenteral formulations for most drugs also make the management of these patients more difficult. In this context, the PT becomes fundamental for the diagnostic confirmation of NSAID HRs in children, as well as for choosing an alternative drug. Some authors report that the number of PTs required for managing children with a suspected HR is lower when they are initially treated with ASA, regardless of the reaction history.[58,59]

Recommendations for the diagnosis and management of NSAID HRs

The strategy for investigating HRs to NSAIDs initially involves a detailed clinical history of the patient, the time between exposure and symptom onset, number of reactions, and treatment. When necessary, the immediate-reading skin prick test and ID skin test are useful only for IgE-mediated HRs. The delayed-reading skin test is used for delayed HRs to NSAIDs. In non-allergic phenotypes (NIUA,

Table 2
Classification of NSAID hypersensitivity in children aged 0-10 years*

Cross-reactivity	Type of reaction	Clinical presentation	Chronology	Proposed mechanism	Influence of cofactors
Cross-intolerance reactions (non-allergic)	Non-allergic NSAID hypersensitivity (NERD, NECD, NIUA)	Urticaria, angioedema, dyspnea, rhinitis, conjunctivitis, anaphylaxis	Immediate (minutes to several hours after exposure)	COX-1 inhibition	Possible
Non-cross intolerance (allergic)	Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)	Urticaria, angioedema, anaphylaxis	Immediate (< 1 h)	IgE-mediated	Unknown
	Single NSAID-induced delayed hypersensitivity reaction (SNIDHR)	Involves various symptoms and envolvidos organs (FDE, SJS, TEN, nephritis)	Delayed onset (> 24 hours after exposure)	T cell-mediated	Unknown

* Adapted from Kidon M, et al.[47] NSAID = nonsteroidal anti-inflammatory drug, NERD = NSAID-exacerbated respiratory disease, SNIUAA = single NSAID-induced urticaria/angioedema or anaphylaxis, NIUA = NSAIDs-induced urticaria/angioedema, NECD = NSAIDs-exacerbated cutaneous disease, COX-1 = cyclooxygenase 1, FDE = fixed drug eruption, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis.

NECD, and NERD) dependent on the AA pathway, there are no available skin or *in vitro* tests for their diagnosi.[2,23]

A PT with the suspected drug is still gold standard for diagnosis, especially when the clinical history is unclear, since no other standardized tests are available in the literature for helping with this process. The PT can be used for confirming some diagnoses or for defining if there is cross-reactivity or selectivity in the reaction to the investigated drug.[2,23] In clinical practice, the most frequent doubt usually involves differentiating patients with NSAID-induced urticaria, angioedema, or anaphylaxis, especially whether their reaction is cross-reactive or not.

When the patient has not yet presented reactions to NSAIDs of different classes, anamnesis does not allow the definition of a clinical phenotype. In these cases, the international recommendation has been a PT with ASA at an anti-inflammatory dose (500 to 1,000 mg). Patients with a positive PT should thus be considered as having NIUA and should avoid all COX-1 inhibitors. Patients with negative PTs can be non-cross-reactive or even not be hypersensitive, and confirmation might require an immediate-reading skin test or even a PT with the suspected drug.[47,60]

Although NSAIDs are one of the most frequent causes of consultations with allergy specialists due to a history of drug HR in Brazil and Latin America, no robust data are found in the literature on the frequency of each clinical phenotype among patients with NSAID reactions, or on the safety and efficacy of this investigation protocol in our population.

This way, designing a diagnostic algorithm for NSAID HRs relies on an initial phenotyping based on the symptoms reported by the patient when the reactions occurred (urticaria, angioedema, other cutaneous manifestations suggesting delayed reaction, respiratory, or mixed reactions), time between exposure to NSAID and reaction onset, and underlying disease (eg, CSU or asthma and CRSwNP). Based on these data only, most patients will be classified into one of the five classical phenotypes (NIUA, NECD, NERD, SNIUAA, and SNIDHR) or into some of the other previously mentioned phenotypes (mixed or blended reactions, FDNIA, and SIHRN), and defined as a probable cross-intolerant or non-cross-reactive patient. From this moment on, adequate investigation and management should be directed according to the clinical phenotype.

Management of SNIDHR

Patients with cutaneous manifestations other than urticaria and angioedema, such as exanthem, eczematous dermatitis, fixed eruption, etc., whose onset is characteristically delayed, should be diagnosed as having SNIDHR; in case of doubt, these patients would benefit from a classical patch test with 48h and 96h readings using the suspected medication diluted at 10% in petroleum vaseline. In case of doubt, a final reading after 7 days may be necessary. If the doubt persists, a PT may be performed with an NSAID from a different class just to confirm tolerance, or with the suspected NSAID for confirming or excluding a prior HR. This PT will be clearly contraindicated with the suspected agent or another from the same class in case of a severe delayed reaction (organ-specific, DRESS, SJS, TEN, PEGA).

Patients subjected to a PT with the suspected NSAID whose results are negative should be considered tolerant to all NSAIDs, and these drugs are considered unrelated with the previous clinical picture. However, patients with SNIDHR confirmed by a positive patch test or PT can be allowed to use NSAIDs of other classes with no need for additional investigation.

Management of NERD and mixed reactions

In case of respiratory symptoms only (bronchospasms, laryngeal edema, acute sinonasal symptoms), especially in patients with asthma or CRSwNP or in patients with a clinical picture suggesting anaphylaxis (mixed reaction), we do not recommend a PT for diagnosis (with ASA at an anti-inflammatory dose) outside of reference and research centers due to the high risk of severe reactions of difficult treatment[61].

In these cases, patient management should follow the steps of CSU and NIUA cases, focusing on allowing alternative NSAIDs such as preferential COX-2 inhibitors (paracetamol, nimesulide, meloxicam) or selective COX-2 inhibitors (etoricoxib, celecoxib), as shown in Figure 1. For AERD, coxibs can be allowed without a PT as long as the patient's underlying disease is controlled, preferably with a pulmonary function above 70% of the predicted value or the patient's highest value.

Management of NECD

In patients with CSU and possible exacerbations with the use of NSAIDs, the confirmation of NECD –

and thus of NSAID intolerance via an immunological mechanism – can only be done after a positive PT with 500 mg ASA or more. If this PT is negative, the patient can be considered tolerant to NSAIDs and no additional exclusion or restriction recommendations are necessary. In those with a positive PT or unequivocal history of exacerbation with NSAIDs, the use of 500 mg paracetamol (or an age-adjusted dose) can be allowed as an analgesic and antipyretic drug, and we recommend that other preferential or selective COX-2 inhibitors be allowed if tolerance is confirmed with a negative PT (Figure 1). Logically, in patients who report also being reactive to paracetamol at a 500 mg dose or at an unknown dose, we suggest a PT for confirming (or not) the reported reactivity.

Management of NIUA and SNIUAA

In patients who clearly, due to their clinical history, react (urticaria, angioedema, or even anaphylaxis) to more than one COX-1 inhibitor of different classes, even though the international literature recommends confirming NSAID intolerance with an ASA PT, we do not recommend this procedure as routine in the clinical practice outside of large reference centers. The doctor is authorized to recommend excluding all strong COX-1 inhibitors and allow the use of 500 mg paracetamol (or an age-adjusted dose) as an alternative analgesic and antipyretic drug. Just as in NECD, we suggest that other preferential or selective COX-2 inhibitors be allowed if tolerance is confirmed with a negative PT (Figure 1). Similarly, for patients who report also being reactive to paracetamol at a 500 mg dose or at an unknown dose, we suggest a PT for confirming (or not) the reported reactivity. Moreover, in high-risk patients with a history of severe initial reaction (anaphylaxis), even paracetamol should only be allowed after a negative PT.

However, patients with a first reaction to an NSAID or more than one reaction to the same NSAID (for example, metamizole) or to more than one NSAID from the same class (eg, ibuprofen and ketoprofen) may be non-cross-reactive cases (SNIUAA). In these cases, immediate-reading skin tests (prick and ID tests) may be used in case the drug is metamizole, but the phenotype will only be defined after a challenge with ≥ 500 mg ASA. If the patient tolerates ASA at these doses, he or she may be considered a non-cross-reactive patient (SNIUAA) and will be allowed NSAIDs of different classes from that which caused the initial reaction. In these cases, when metamizole is involved and the skin test is positive, the IgE-mediated mechanism is confirmed. Conversely, in case the PT is positive for ASA, cross-intolerance is confirmed and the previously mentioned recommendation of prioritizing alternative NSAIDs (preferential or selective COX-2 inhibitors) prevails. The same flow should be used in patients with an unclear history, where the involvement of an NSAID or even one or more different classes of NSAIDs is not certain. On the other hand, in patients whose initial reaction was induced exactly by ASA, we follow the recommendation by the Spanish group of performing an ibuprofen PT. However, other strong COX-1-inhibiting NSAIDs (eg, diclofenac, ketorolac, ketoprofen, indomethacin) might serve the same objective.

In all these groups, analgesic and/or anti-inflammatory drugs with different mechanisms of action – not acting as COX inhibitors – such as antispasmodics (scopolamine, hyoscine), opioids (tramadol, codeine, morphine), and corticosteroids should be allowed at the initial assessment, with no need to confirm their tolerance.

The algorithm suggested for managing patients with NSAID-induced immediate skin reactions (urticaria, angioedema) or anaphylaxis (NIUA and SNIUAA) is summarized in Figure 1.

Desensitization with NSAIDs

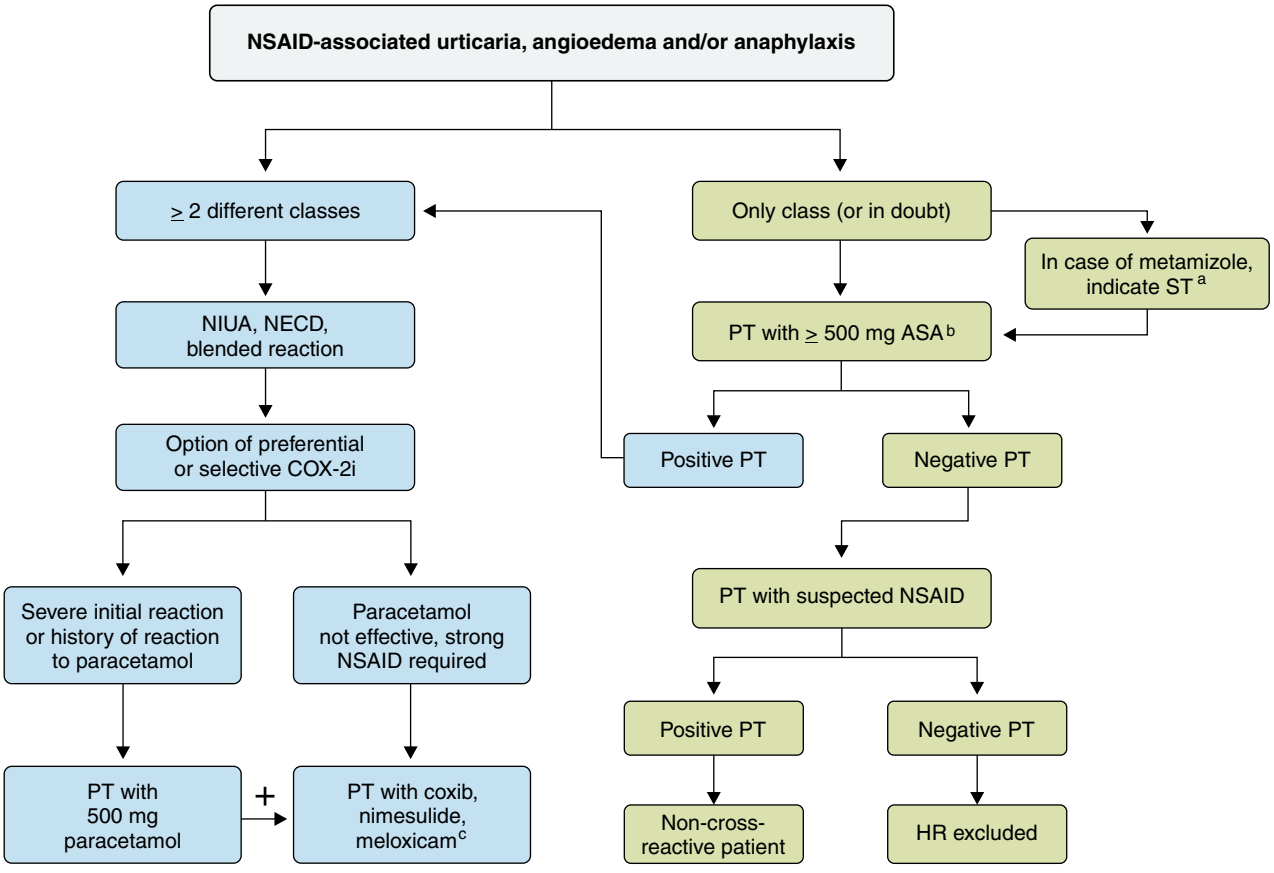
When challenging a patient with ASA, he or she is exposed to increasing doses of aspirin and the test is interrupted when the patient presents respiratory symptoms or when the maximum aspirin dose is reached. Desensitization with aspirin is the process through which aspirin tolerance is achieved, and after this period, the patient should maintain continuous and daily use of this drug. In AERD, desensitization with aspirin is achieved through the administration of high doses of aspirin after the occurrence of an initial respiratory reaction.[62]

Desensitization in cardiovascular diseases (CVD)

Patients with hypersensitivity to aspirin and CVD, with indication for this medication, are frequently not receiving adequate antiplatelet therapy. The literature presents various protocols of variable complexity for aspirin desensitization. The central role of aspirin therapy in CVD is very well established. As an irreversible COX-1 inhibitor, aspirin blocks the

biosynthesis of thromboxane A2 (TXA2), avoiding platelet aggregation. Aspirin is indicated for primary and secondary prevention in most patients with increased risk of acute myocardial infarction, stroke and cerebral ischemia, peripheral artery disease, and atrial fibrillation. Studies demonstrate that therapy with aspirin at an antiplatelet dose significantly reduced the risk of vascular events in 33%.[63]

With few exceptions, most patients with CVD and a history of aspirin hypersensitivity may be treated adequately by identifying the type of reaction to ASA and subjecting patients to challenge or desensitization



NSAID = nonsteroidal anti-inflammatory drug, NIUA = NSAIDs-induced urticaria/angioedema, NECD = NSAIDs-exacerbated cutaneous disease, COX-2i = cyclooxygenase 2 inhibitor, ST = skin test (immediate-reading prick skin test and intradermal skin test), ASA = acetylsalicylic acid, PT = provocation test, + positive, HR = hypersensitivity reaction.

[a] Non-irritating concentrations of NSAIDs other than metamizole are not known (0.1 to 4.0 mg/mL for metamizole, usually 2 mg/mL). Therefore, PTs are recommended for this drug only.

[b] When the medication involved in the initial reaction is ASA, the PT should be performed with 600 mg ibuprofen. In pediatric patients, PTs with ASA are recommended at 15-20 mg/kg/dose and, with ibuprofen, 10 mg/kg/dose[47].

[c] Maximum doses suggested for PTs with COX-2 inhibitors: 90 mg etoricoxib, 200 mg celecoxib, 100 mg nimesulide, and 15 mg meloxicam.

Figure 1
Algorithm suggested for managing patients with NSAID-induced urticaria, angioedema, and/or anaphylaxis. Patients with two or more reactions to NSAIDs of different classes should be managed as cross-reactive patients, that is, considering a nonimmunologically mediated mechanism (COX-1 inhibition), as shown in the left side of the flowchart (blue). However, in case of diagnostic doubt of if the patient reacted to only one NSAID or to more than one NSAID of the same chemical class, the algorithm should be initiated through the section to the right (green)

with ASA in a well-tolerated and practical way. Challenge and desensitization with aspirin, in CVD, can be performed both at hospital and outpatient settings.[63]

In almost all environments, the urgent need for aspirin is due to its well-known antiplatelet effect. This effect can be reached with 81 mg of ASA; using this dose as an objective is reasonable for most patients. No significant difference in 30-day outcomes was observed between a low dose (75-100 mg ASA) and a high dose (300-325 mg ASA/day) in cardiovascular death, myocardial infarction, and stroke.[63,64]

A simplified approach for ASA challenge in CDV. Symptoms should be treated with antihistamines. In case of severe symptoms, these should be treated and the dose should be repeated. Considering patients with NERD, professionals should be prepared for treatment with bronchodilators and nasal antihistamines. A dose that typically triggers symptoms in NERD is between 60 and 100 mg. Once the patient is tolerant, 81 mg/day of ASA can be initiated.[63]

Desensitization in NERD

Aspirin desensitization was performed for the first time by Widal and colleagues in 1922. In 1976, Zeiss and Lockey reported a refractory period of 72 hours after a positive oral challenge with aspirin. In 1976, Bianco and colleagues induced asthma with inhaled lysine-aspirin in a patient with NERD and, in the following 72 hours, the inhalation of the same doses of lysine-aspirin did not induce any bronchospasms (refractory period). After initiating low aspirin doses and gradually increasing them, when the target dose of 325 mg is reached, any additional doses of aspirin or other COX-1-inhibiting NSAIDs do not induce HRs. Desensitization with aspirin, followed by continuous treatment at doses of 325 mg to 650 mg twice a day, is considered standard treatment for patients with NERD after polypectomy (3 to 4 weeks prior). Aspirin can be discontinued for up to 48 hours without loss of desensitization.[64,65]

Although the clinical benefits of aspirin desensitization have been clearly demonstrated, the mechanism through which this happens remains obscure. It is not a matter of simply acquiring a state of aspirin tolerance, but the dose required for improving bronchial inflammation is usually much higher than that required for initiating a respiratory reaction or maintaining desensitization. However, a series of immunological observations have been identified in the hopes of leading to a better comprehension of the pathogenesis of this disease. In the beginning of the study, in the absence of aspirin/NSAID ingestion, patients with NERD had increased LT levels, as measured by urinary LTE4, and these levels increased proportionately to reaction severity during the aspirin challenge. Studies analyzed monocytes in the peripheral blood of patients with NERD and demonstrated a decrease in LTB4 after aspirin desensitization. Other findings include the negative regulation of cysteinyl LT receptor 1 (cysLT1) in cells of the nasal submucosa and the inhibition of IL-4 production in T cells after aspirin desensitization.[64-66]

Among many observations, the downregulation of IL-4 receptors, decrease in PGD2, decreased effects of LTE4, and effects in IL-4 expression through the downregulation of STAT-6 provide opportunities for understanding the underlying mechanism of this benefit.[65]

In a large study involving patients with NERD, surgical intervention was required every three years before desensitization; after desensitization and daily maintenance with aspirin, the mean interval increased to nine years. Some patients did not present polyp recurrence, but two complications can occur and should be monitored, as expected, after long-term treatment with aspirin: the first was gastric pain or ulcer caused by decreased PGI2 and inadequate cell repopulation of the gastric mucosa (< 15% of the patients). The second complication was bleeding in the skin (ecchymosis), but occasionally the nose, bronchi, bladder, or gastrointestinal tract.[65]

Other indications of desensitization

Desensitization is indicated for patients with NSAID-induced urticaria and/or angioedema when the clinical conditions require continuous treatment with anti-inflammatory drugs and/or in primary or secondary CVD prevention (due to the antiplatelet effect of ASA), since aspirin blocks the synthesis of TXA2 and prevents platelet aggregation.[67]

Patients who react to various NSAIDs with urticaria and/or angioedema symptoms and have a history that is consistent with chronic urticaria may be subjected to an oral PT with aspirin. Pre-medications are not usually administered before this type of challenge. Antihistamines are normally interrupted before challenges with NSAIDs, because these agents can mask the detection of initial or mild symptoms. H1-antihistamines should be discontinued at least 48 hours before the challeng.[67]

An initial dose of 81 mg or 162 mg is doubled every 90 minutes until the patient reacts or the desired therapeutic dose is reached. If the patient does not develop symptoms, he or she can safely receive an NSAID that is structurally different from the one that caused the initial reaction.[67]

Another possible indication of ASA desensitization happens during pregnancy for women with a history of HRs to ASA or other NSAIDs and with clinical suspicion of cross-intolerance. ASA may be indicated during pregnancy for preventing complications such as preeclampsia, intrauterine growth restriction, prematurity, and fetal death due to maternal thrombophilias (such as antiphospholipid syndrome) or uteroplacental insufficiency.[68] For these indications, we usually administer low doses of ASA that are similar to antiplatelet doses used in CVD. Although studies defining the adequate dose of ASA for prophylaxis against these obstetric complications are scarce[69], since the dose is usually the same as that in CVD, we recommend protocols that are similar to those mentioned in the section on desensitization in CVD.

Conclusions/final considerations

NSAIDs are the most widely used medications worldwide and, at the same time, the ones most associated with HRs, particularly in Brazil and Latin America. However, these reactions have varied clinical presentations and happen due to different pathophysiological mechanisms (nonimmunological, IgE-mediated, and T-cell-mediated). Knowing these clinical phenotypes and pathophysiology is the only way of individualizing the management of clinical cases so that we do not deny non-cross-reactive patients with an allergic mechanism a whole pharmacological class unnecessarily, while also avoiding their exposure to risks of reactions that may be severe or affect their quality of life. Only this way can we adjust the treatment of the pain, inflammation, and fever of individuals who are hypersensitive to these drugs.

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