GUIDELINES

Practical Guidelines for Diagnosing Hypersensitivity Reactions to Nonsteroidal Anti-inflammatory Drugs

N Ortega,[1] I Doña,[2] E Moreno,[3] MT Audicana,[4] MJ Barasona,[5] MP Berges-Gimeno,[6] N Blanca-Lopez,[7] T Lobera,[8] A Padial,[9] A Rosado,[10] MJ Torres[2]

[1]Allergy Service, Hospital Doctor Negrín, Las Palmas de Gran Canaria, Spain
[2]Allergy Unit, Hospital Regional Universitario de Málaga, Málaga, Spain
[3]Allergy Service, Hospital Universitario de Salamanca, Salamanca, Spain
[4]Allergy Service, Santiago Apóstol Hospital, Vitoria-Gasteiz, Spain
[5]Allergy Service, Reina Sofía University Hospital, Córdoba, Spain
[6]Allergy Division, Ramon y Cajal University Hospital, Madrid, Spain
[7]Allergy Service, Infanta Leonor Hospital, Madrid, Spain
[8]Allergy Service, Centro de Alta Resolución San Millán, Logroño, Spain
[9]Allergy Service, La Paz Hospital, Madrid, Spain
[10]Allergy Service, Alcorcón Hospital, Madrid, Spain

Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs most frequently involved in hypersensitivity reactions. These reactions include various clinical entities with different mechanisms leading to the release of inflammatory mediators. Characterization of patients based on clinical manifestations and suspected underlying mechanisms is critical for implementation of adequate diagnostic procedures and patient management. Our objectives were to prepare a systematic review of available scientific evidence and to provide general guidelines for the diagnosis and management of patients with hypersensitivity reactions to NSAIDs. We also propose a practical algorithm for the diagnosis of specific types of hypersensitivity to NSAIDs and provide recommendations for the management of hypersensitive patients.

Key words: Nonsteroidal anti-inflammatory drugs (NSAIDs). Hypersensitivity. Intolerance. Idiosyncrasy. Acetylsalicylic acid. Algorithm. Diagnosis.

Resumen

Los antiinflamatorios no esteroideos (AINE) es el grupo farmacológico que más frecuentemente ha sido relacionado con las reacciones de hipersensibilidad. Estos cuadros incluyen entidades clínicas muy variadas, producidas por diferentes mecanismos, tanto inmunológicos como no inmunológicos. La caracterización de los pacientes que presentan estas reacciones se fundamenta, en las manifestaciones clínicas y la sospecha del mecanismo subyacente que la ha producido, lo que conduce a la puesta en práctica del procedimiento diagnóstico adecuado y la posterior orientación del paciente. El objetivo de este trabajo es elaborar una revisión sistemática, con las pruebas científicas disponibles, facilitando las directrices generales de diagnóstico y en consecuencia la actitud a tomar en este tipo de pacientes.
Se propone un algoritmo práctico de diagnóstico para cada tipo específico de hipersensibilidad a AINE, así como proporcionar las recomendaciones a seguir en el manejo de los pacientes sensibilizados.

Palabras clave: Antiinflamatorios no esteroideos (AINE). Hipersensibilidad. Intolerancia. Idiosincrasia. Algoritmo. Diagnóstico. Ácido acetilsalicílico.

Preface

These guidelines were drafted by a panel of allergy specialists with clinical and research experience from the Drug Allergy Committee of the Spanish Society of Allergy and Clinical Immunology (Sociedad Española de Alergología e Inmunología Clínica; SEAIC). The panel performed a systematic and independent review of available scientific evidence to provide general guidelines for the diagnosis and management of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). The findings presented in the document are based on the agreement reached between the participants. Applicability in daily practice in our population and the contribution of periodic updates have been taken into account. All the members have declared their conflicts of interest, and external reviewers have critically reviewed the design and preparation of the consensus guidelines. Our main objective was to achieve as accurate a diagnosis as possible in patients with hypersensitivity to NSAIDs in order to draft appropriate recommendations for patients with hypersensitivity to NSAIDs.

Methods

The participants designed a working protocol based on a number of items to define the key words and the methodology for selecting the publications included in this review.

The bibliographic search was performed using electronic databases (MEDLINE and PubMed), electronic libraries (Science Direct, OVID), and a systematic review database (Cochrane Library). Publications were selected from the period comprising January 1980 to July 2013.

The selection took into account the prevalence, pathogenesis, clinical manifestations, diagnosis, and treatment of hypersensitivity to NSAIDs. The key words used were *NSAIDs, analgesics, anti-inflammatory, nonsteroidal anti-inflammatory, aspirin, acetylsalicylic acid, urticaria, angioedema, asthma, anaphylaxis,* and the specific names of all the NSAIDs, in addition to the key word acetylsalicylic acid (ASA). These words were combined with the terms *allergy, hypersensitivity, intolerance, idiosyncrasy, fixed drug eruptions,* and *selective*. We reviewed 323 publications and finally included 195. The inclusion and exclusion criteria depended on the type of article: original research articles and systematic reviews were included; nonsystematic reviews, comments, and other types of article were excluded. We also took the study objective into account: studies examining incidence, prevalence, natural history, clinical manifestations, pathogenesis, clinical manifestations, diagnosis, and treatment were included; studies not addressing NSAID hypersensitivity and other aspects not included in the inclusion category were excluded.

Moreover, the expert panel evaluated the quality of the evidence of the literature search relevant to each type of hypersensitivity. Grades of recommendation were assigned according to the Scottish Intercollegiate Guidelines Network [1]. Wherever evidence was lacking, a consensus was reached among the experts.

Introduction

Definition and Classification

NSAIDs can be classified based on their chemical structure or mechanism of action (Table 1).

Hypersensitivity is currently the most appropriate denomination for unexpected adverse reactions to NSAIDs [2,3]. Depending on the underlying mechanisms, reactions are classified as immunological and nonimmunological [4].

Nonimmunological hypersensitivity reactions to NSAIDs, which were previously termed intolerant or idiosyncratic reactions, are the most frequently reported [5], and their pathogenesis is associated with the mechanism of action of

Table 1. Classification of Hypersensitivity Reactions Induced by Nonsteroidal Anti-inflammatory Drugs (NSAIDs) (Modified According to References [6-8])

Type of Reaction	Clinical Manifestation	Timing of Reaction	Underlying Disease	Cross-reactivity	Putative Mechanism
NSAID-exacerbated respiratory disease	Bronchial obstruction, dyspnea and/or nasal congestion/ rhinorrhea	Acute (usually immediate to several hours after exposure)	Asthma/ rhinosinusitis	Cross-reactive	COX-1 inhibition
NSAID-exacerbated cutaneous disease	Wheals and/or angioedema		Chronic urticaria		COX-1 inhibition
NSAID-induced urticaria/angioedema	Wheals and/or angioedema		No underlying chronic diseases		Unknown, probably COX-1 inhibition
Single NSAID–induced urticaria/ angioedema or anaphylaxis	Wheals/angioedema/ anaphylaxis			Non-cross-reactive	IgE-mediated
NSAID-induced delayed hypersensitivity reactions	Various symptoms and organs involved (eg, fixed drug eruption, SJS/TEN, nephritis)	Delayed (usually more than 24 hours after exposure)			T-cell–mediated

Abbreviations: COX, cyclo-oxygenase; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

the NSAIDs, namely, inhibition of the cyclooxygenase enzyme (COX-1). All NSAIDs that inhibit the COX-1 enzyme can induce symptoms, and cross-reactions can occur between them, independently of their chemical structure.

Immunological hypersensitivity reactions to NSAIDs, also known as selective reactions, are limited to 1 NSAID or to a group of NSAIDs with the same chemical structure, although patients can tolerate NSAIDs with a different structure. They are mediated by a specific humoral mechanism (specific IgE antibodies) or a specific cellular mechanism (T effector cells) [6].

In 2001, Stevenson et al [7] drafted a consensus document proposing a classification of hypersensitivity reactions to NSAIDs. The document was the basis for the new document proposed by the European Academy of Allergy and Clinical Immunology, which classified reactions as follows [8]:

I. *Non–immunologically mediated (cross-reactive) hypersensitivity reactions to NSAIDs*
   Patients have reactions to multiple NSAIDs with different chemical structures.
   1. *NSAID-exacerbated respiratory disease (NERD):* NERD is characterized by exacerbations of asthma and/or rhinitis induced by NSAIDs in patients with previous respiratory symptoms (rhinitis, nasal polyps, and/or bronchial asthma).
   2. *NSAID-exacerbated cutaneous disease (NECD):* Patients with chronic spontaneous urticaria (CSU) who develop an acute episode or have an exacerbation of urticaria after administration of NSAIDs.
   3. *NSAID-induced urticaria/angioedema (NIUA):* NIUA is characterized by the appearance of urticaria and/or angioedema after administration of NSAIDs in patients without underlying CSU. Reactions are sometimes severe, and patients can even develop systemic symptoms or anaphylaxis.

II. *Immunologically mediated (non–cross-reactive) hypersensitivity reactions to NSAIDs*
   These reactions are induced by specific NSAIDs with similar chemical structures, although patients can tolerate drugs with a different chemical structure [6].
   4. *Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA):* Reactions usually appear less than 1 hour after administration and can take the form of urticaria and/or angioedema and anaphylaxis.
   5. *NSAID-induced delayed hypersensitivity reactions (NIDHR):* In these reactions, the interval between drug intake and development of symptoms is greater than 24 hours.
   However, some patients do not fit in any of the above categories and include those with mixed reactions involving both cutaneous and respiratory symptoms [5,9].

Epidemiology

NSAIDs are the drugs most frequently involved in hypersensitivity reactions [10], which affect 0.5-1.9% of the general population [11,12]. If reactions with respiratory symptoms are taken into consideration, the prevalence of NSAID hypersensitivity in asthmatic patients is not clear, although it has been reported to range from 4% to 21% [13-15] and can increase to 25.6% in cases with asthma and nasosinusal polyposis [16].

The most frequent reactions are those involving the skin [5], which affect 0.07-0.3% of the general population [17,18]. In patients with underlying CSU, the prevalence of NSAID hypersensitivity can reach 30% [18,19]. The prevalence of NIUA, on the other hand, is unknown, although it has been reported that 36% of patients experience an adverse reaction with skin involvement after taking NSAIDs [20].

The prevalence of immunologically mediated reactions to NSAIDs ranges from 0.1% to 3.6% [21,22]. NSAIDs have been reported to be the most common pharmacological cause of anaphylaxis [23,24] or the second most common [25], since the arylacetic acid and propionic acid groups have a higher risk of inducing an anaphylactic reaction (OR, 19.7) [26]. Pyrazolones frequently induce SNIUAA [27,28]. The prevalence of nonimmediate reactions is unknown, and severe reactions are much less frequent [29].

Pathogenesis

NSAID-Exacerbated Respiratory Disease

NERD is associated with the metabolism of arachidonic acid, overproduction of cysteinyl leukotrienes (CysLT) by the eosinophils or mast cells in the target organ mucosa [30], increased expression of the CysLT receptors in the inflammatory cells of the mucosa [31], and alterations in the metabolism of prostaglandins (PG) [32-35].

Arachidonic acid is metabolized by 2 pathways: the COX pathway, which induces synthesis of PGs, and the lipoxygenase pathway, which induces synthesis of CysLT (Figure 1). There are at least 2 COX isoforms, COX-1 and COX-2. The former is expressed in many tissues and organs, and the latter is induced by proinflammatory stimuli [9]. Classic NSAIDs act on both enzymes, although, in susceptible patients, it is COX-1 blockade that induces a decrease in PGE_2, with an increase in CysLT synthesis being responsible for the inflammation of the respiratory tract [36]. However, it is not clear why an

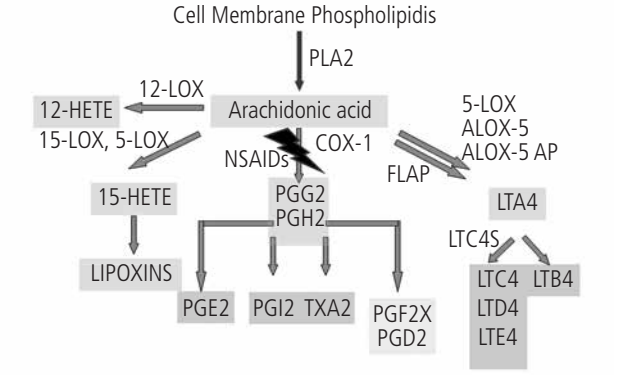

Figure 1. Metabolism of membrane phospholipids. NSAID indicates nonsteroidal anti-inflammatory drug; COX, cyclo-oxygenase; PG, prostaglandin; LT, leukotriene.

NSAID that inhibits COX-1 in all patients only induces an acute increase in CysLT in those with respiratory symptoms.

In inflammatory conditions, arachidonic acid is oxidized by 5-lipoxygenase (5-LO) to leukotriene (LT) A_4, which is metabolized into the final metabolite LTE_4. Baseline levels of CysLT in bronchoalveolar lavage, nasal secretions, blood, and urine are higher in patients with NERD than in asthmatic patients who tolerate ASA and can increase after administration of ASA [37,38]. An increase in cells expressing LTC_4-synthase has been detected in patients with NERD [39-42].

PGE_2 induces potent negative feedback in the 5-LO enzyme in many cells. Thus, suppression of PGE_2 synthesis by inhibition of COX-1 is accompanied by increased synthesis of CysLT. A parallel increase is observed in CysLT receptors (CysLT-R) in bronchial muscle and endothelial and epithelial cells, as is an increase in the proinflammatory effects of eosinophils and mast cells [31,42]. Increased levels of eosinophil cationic protein and tryptase have also been detected in nasal lavage fluid after a nasal provocation test (NPT) with lysine acetylsalicylate (LAS) in patients with NERD [38]. These observations are reinforced by the fact that previous inhalation of PGE_2 completely prevents the bronchospasm induced by ASA and the increased LTE_4 levels in urine [43].

Genetic predisposition to NERD has been observed—although a strong association has not been proven—and involves HLA alleles and single-nucleotide polymorphisms in the CysLT receptor 1 gene (*CYSLTR1*), *LTC4S*, thromboxane receptor, transcription factor T-box, PGE_2 receptor, and tumor necrosis alfa promoter [44-57]. Nevertheless, the population size and the number of gene variants were limited in most studies, the reported case populations were heterogeneous, and the association found was inconsistently replicated in independent studies [46].

NSAID-Exacerbated Cutaneous Disease

As with NERD, the mechanisms involved in NECD seem to be associated with inhibition of COX-1 and overproduction of CysLT. This hypothesis is based on the detection of increased urine LTE_4 levels after a drug provocation test (DPT) with ASA in which patients with NERD were compared with patients with CSU and good tolerance [54,55].

Asero [56] suggests a possible association between chronic urticaria, autoimmunity, and NSAID hypersensitivity.

NSAID-Induced Urticaria/Angioedema

The mechanism underlying NIUA is unknown. It has been proposed that, similar to NERD and NECD, COX-1 inhibition could be involved in pathogenesis [57]. However, patients with NIUA seem to have a distinctive phenotype: only 12% had a positive response to an NPT with LAS and they showed no significant increase in ECP or in release of tryptase in lavage fluid after an NPT with LAS [38]. Variants related to these pathways can play a role [58], as can variants other than those associated with the metabolism of arachidonic acid [59].

It has also been suggested that, in some cases, NSAID hypersensitivity could precede the onset of chronic urticaria [60], although there are not enough data to clarify this point. A recent study reported that the percentage of patients with NIUA developing CSU was similar to that found for a control group [60], thus showing NIUA to be a well-defined entity that is clearly different from NECD.

Single NSAID-Induced Urticaria/Angioedema or Anaphylaxis

The clinical pattern of this reaction, the time interval between drug administration and development of symptoms, and the selectivity of the reaction support an IgE-mediated mechanism. Specific IgE to pyrazolones has been demonstrated by skin and in vitro testing [5,61,66] and with ASA [35], although with other NSAIDs, the detection of specific IgE has only been supported by single-case studies [63].

The drugs that most frequently induce this reaction include pyrazolones [5,9,61,64,65], piroxicam [66], diclofenac [5,21,26,63,67], paracetamol (acetaminophen) [5,68,69], ibuprofen [5,9,12,26], and naproxen [26,70]. Anaphylaxis induced by celecoxib has also been described [71-73]. Finally associations with HLA-DQ and HLA-DR have been reported in hypersensitivity to pyrazolones [65,74].

NSAID-Induced Delayed Hypersensitivity Reactions

Although a T-cell–mediated mechanism seems to be involved in most cases, no studies evaluate the underlying mechanisms in a sufficient number of cases [75]. Pyrazolones, arylacetic acids, and propionic acids are the most frequently involved NSAIDs [5,8,76].

Characterization of the Clinical Entities

Hypersensitivity reactions induced by NSAIDs constitute a heterogeneous group of syndromes, in terms of both immunopathogenesis and clinical practice. Several categories can be defined.

NSAID-Exacerbated Respiratory Disease

The typical patient is an adult with recurrent episodes of asthma and rhinosinusitis. The disease progresses as persistent rhinitis—with or without polyposis—to asthma that frequently requires systemic corticosteroids to control symptoms. After administration of NSAIDs, patients develop nasal congestion or ocular itching, and nasal hydrorrhea that rapidly progress to wheezing in 30 minutes to 3-4 hours. In some cases, the NSAID only induces rhinoconjunctivitis and in others it is accompanied by cutaneous or gastrointestinal symptoms (mixed or blended reactions) [5,39,77-79].

Although these patients were traditionally thought to have nonallergic severe asthma or rhinitis, increasing evidence indicates that a large percentage (34-64%) have a history of atopy and mild symptoms [80-84]. However, in a large series of patients with nasal polyposis, more nonatopic patients had NERD than atopic patients (32.5% vs 21.1%, $P>.05$), and patients with nasal polyposis and NSAID hypersensitivity had a significantly poorer quality of life than those with nasal polyposis only [84].

NSAID-Exacerbated Cutaneous Disease

The classic picture involves a patient with CSU that worsens or reactivates after administration of an NSAID. The

condition may or may not be associated with angioedema. The intensity of the reaction may change over time, depending on the activity of the CSU, and in some patients it can even resolve [5,9,55,85].

Symptoms usually appear from 1 to 4 hours after administration of the NSAID, although lesions can appear in less than 1 hour or even 24 hours after administration [9]. Progression to systemic symptoms of anaphylaxis is quite infrequent [86].

NSAID-Induced Urticaria/Angioedema

Patients with NIUA do not have underlying CSU and present a variable combination of urticaria, angioedema, erythema, or exanthema-like reaction within minutes to 24 hours after the administration of various NSAIDs [75,77].

Atopy is a risk factor and is more frequent in NIUA than in SNIUAA (60% vs 40%) [5,9,77,81,87]. The most significant association reported was sensitization to house dust mites [5,75]. Whether NIUA also occurs with food allergens remains unknown, although preliminary studies indicate that food allergy is not an associated condition [88].

One subgroup with typical symptoms includes patients in the first and second decade of life with respiratory allergy who are sensitized to house dust mites and develop periorbital angioedema after administration of NSAIDs [77,89]. Some of these patients can develop anaphylaxis after ingestion of wheat flour contaminated with mites, although no evidence of food allergy has been reported [90].

Finally, after administration of NSAIDs, some patients develop systemic symptoms accompanied by both cutaneous and respiratory symptoms (blended reactions) [5,75-77]. Up to 30% of patients present hypotension. Pyrazolones, arylacetic acid NSAIDs, and propionic acid NSAIDs are the most frequently involved drugs [26,79,91].

Single NSAID–Induced Urticaria/Angioedema or Anaphylaxis

More than 30% of cases of NSAID hypersensitivity involve SNIUAA [5,68]. Clinical symptoms usually appear during the first hour after administration [4] and include generalized urticaria and/or angioedema, which can progress to anaphylaxis and shock [92,93]. Anaphylaxis is the initial manifestation in some cases [61,93].

Subsequent administration of NSAIDs can induce anaphylactic reactions [77,79]. In contrast with cross-reactive patients, no association has been established with atopy [5] or underlying skin diseases [86].

NSAID-Induced Delayed Hypersensitivity Reactions

NIDHRs can manifest as cutaneous systems, systemic symptoms, and fever. They can also affect other organs. Onset is from 24 hours to days or weeks after initiation of treatment. The most common manifestations [94] are the following:

Maculopapular exanthema: Maculopapular exanthema is the most common symptom and is caused mainly by ibuprofen, pyrazolones, flurbiprofen, diclofenac, and celecoxib [8,76,95-97].

Fixed drug eruption (FDE): FDE accounts for 10% of the hypersensitivity reactions induced by drugs, of which NSAIDs are the most frequently involved [98]. FDEs have been described with pyrazolones, piroxicam, paracetamol (acetaminophen), ASA, diflunisal, indomethacin, mefenamic acid, diclofenac, ibuprofen, naproxen, and nimesulide [8,99], and less frequently with COX-2 selective inhibitors [100,101].

Delayed urticaria: Delayed urticaria is similar to that which appears in acute reactions. Ibuprofen is the most frequently involved drug [102].

Severe cutaneous reactions: Stevens-Johnson syndrome and toxic epidermal necrolysis induced by NSAIDs are uncommon. The most frequently involved drugs are the oxicams, followed by the pyrazolones and COX-2 selective inhibitors [103,104]. Other severe reactions, such as drug reaction with eosinophilia and systemic symptoms [105] and acute generalized exanthematic pustulosis can be induced by NSAIDs such as ibuprofen, dipyrone, paracetamol, nimesulide, and selective COX-2 inhibitors [106-109].

Contact and photocontact dermatitis: Topical NSAIDs are frequently involved in these reactions, and some can induce severe reactions after systemic administration of the same NSAID (systemic contact dermatitis) [110]. The NSAIDs involved in reactions are ketoprofen, flurbiprofen, ibuprofen, piroxicam, pyrazolones, diclofenac, indomethacin, and etofenamate. Cross-reactivity is common between those from the same chemical family [111].

In photoallergic reactions, the symptoms are similar, but they appear in sun-exposed areas, although they may become generalized and thus affect nonexposed areas [109]. These reactions have been reported with ketoprofen, ibuprofen, piroxicam, diclofenac, and selective COX-2 inhibitors [112,113].

Organ-specific reactions: Hypersensitivity pneumonitis has been described with sulindac, ibuprofen, and naproxen [114]. Different types of kidney disease have been described with both COX-1 and selective COX-2 inhibitors [115,116]. Aseptic meningitis has been reported, particularly with ibuprofen, although cases have also been described with naproxen, diclofenac, ketoprofen, piroxicam, indomethacin, and, more recently, with rofecoxib and celecoxib [117].

Diagnosis

Currently available methods for diagnosing hypersensitivity reactions to NSAIDs include the clinical history, skin testing, in vitro testing, and DPT.

Clinical History

A detailed clinical history is essential for diagnosing hypersensitivity reactions to NSAIDs and must include a description of the symptoms, the time interval between drug administration and the onset of symptoms, the drugs involved, drugs tolerated after the reaction, route of administration, number of episodes, and the underlying diseases, including the one for which the NSAID was prescribed [118]. The clinical history is sufficient when establishing a diagnosis in cases with more than 2 episodes to NSAIDs from different chemical groups (grade of recommendation D) [6,9,118], NERD in patients with underlying asthma or rhinitis who

develop respiratory symptoms after administration (grade of recommendation C) [79,119,120], and NECD in patients with CSU who develop urticaria and angioedema after administration (grade of recommendation C) [121].

In patients with 1 or 2 episodes from 2 different NSAID groups for whom tolerance to a more potent COX-1 inhibitor is different from that to the drug involved in the reaction, the diagnosis cannot be established by the clinical history, and more studies are needed (grade of recommendation C).

Skin Tests

Skin tests are not valid for evaluating non–immunologically mediated reactions (grade of recommendation D). If the result of skin prick testing is negative in a patient with SNIUAA, then intradermal tests can be used. Most experience is with hypersensitivity to pyrazolone (grade of recommendation C) [61,70,103]. The sensitivity reported ranges widely from 41% for dipyrone [62] to 83% for propyphenazone [61], and specificity is 100% for both these pyrazolones [61,62,93]. Of note, a decrease in skin test sensitivity to pyrazolones has been described in SNIUAA (grade of recommendation C) [62,122].

As for the other NSAIDs, there are single case reports of positive skin test results, mainly with paracetamol and diclofenac (grade of recommendation D) [91,123].

In NIDHR, reading of both intradermal and patch tests at 24-48 hours or more can be useful, although sensitivity and specificity are variable [76,97,124,125] (grade of recommendation D). Patches should be applied to the upper part of the back for 48 hours with readings at 48, 72, and 96 hours, and a reading after 1 week is necessary in some patients. Patch testing on damaged skin can be useful in FDE, and a photopatch test could prove useful in photosensitivity reactions (grade of recommendation D) [126].

In Vitro Tests

Several in vitro tests can be used in the diagnosis of hypersensitivity reactions to NSAIDs. Sensitivity and specificity are variable.

Sulfidoleukotriene release test: Although this test has been proposed for the diagnosis of non–immunologically and immunologically mediated hypersensitivity reactions to NSAIDs, it does not have sufficient sensitivity and specificity to be recommended for routine diagnosis (grade of recommendation C) [127-131].

Basophil activation test: The basophil activation test is based on the determination of basophil activation markers (CD45, CD18, and CD63) using flow cytometry. Data obtained to date have only shown acceptable sensitivity in the case of SNIUAA with specific drugs such as pyrazolones (grade of recommendation C) [62,122,132-135].

Determination of specific IgE antibodies in serum: This approach has been proposed for SNIUAA, although its sensitivity is inferior to that of skin testing. The most widely used method is ELISA [61,93,136], mainly for detection of specific IgE to pyrazolones (grade of recommendation C) [61,93,136]. With other NSAIDs, specific IgE antibody detection is limited to single reports (grade of recommendation C) [67,137].

Lymphocyte transformation test: The lymphocyte transformation test is based on the capacity of T cells to proliferate after contact with an NSAID to which the patient is sensitized. Although there are few data about its sensitivity and it cannot be recommended as a routine test, the lymphocyte transformation test can prove useful for the diagnosis of NIDHR (grade of recommendation D) [138].

Drug provocation test: DPT is considered the gold standard for the diagnosis of hypersensitivity reactions to drugs and is indicated to confirm or exclude the diagnosis when no other test is available and to find an alternative NSAID once the diagnosis is confirmed. In some cases, DPT is not risk-free and is contraindicated in patients with a forced expiratory volume in 1 second (FEV_1) lower than 1.5 L or in whom exposure to placebo leads to >20% variability in FEV_1. It is also contraindicated in the following situations: pregnancy, infectious diseases, psychiatric disorders, uncontrolled asthma, severe cutaneous reactions (eg, toxic epidermal necrolysis), anaphylactic shock, and organ-specific reactions (grade of recommendation C) [139,140].

DPT must be performed by trained personnel in a clinical setting where rapid and adequate treatment can be administered if a reaction occurs. DPT should be performed in a single-blind placebo-controlled manner, although in some cases a double-blind procedure may be necessary. As a general rule, other drugs should be stopped before initiating the DPT, as follows: inhaled short-acting β_2-agonists 8 hours before; long-acting β_2-agonists, theophylline, and tiotropium bromide 24 to 48 hours before; antihistamines 3 days before; and leukotriene antagonists during the previous week.

Depending on the route of administration of the NSAID, the DPT can be nasal, bronchial, and oral.

Nasal provocation test: NPT is indicated in patients with symptoms affecting the upper or lower respiratory tract. It is usually safe, except for the occasional appearance of bronchospasm, which is easily treated (grade of recommendation C) [141,142]. NPT is contraindicated in patients with septal perforation and massive nasal polyposis [141]. Sensitivity is lower than in the oral and bronchial provocation tests (grade of recommendation C) [143]. NPT is based on the administration of 28-45 mg of LAS (1800 mg of LAS is equivalent to 1000 mg of ASA). The response is analyzed using a symptom score and active anterior rhinomanometry or acoustic rhinometry [143].

Active anterior rhinomanometry is a commonly used technique. It measures the resistance of the nasal airway, although it cannot be used if the patient has polyps or nasal obstruction. Serial dilutions of LAS are administered with an active anterior rhinomanometry measurement every 10 minutes and spirometry every 20 minutes after administration. A response is considered positive if symptoms appear, nasal resistance increases to >100%, or FEV_1 decreases by >20%. If no response appears, the next dilution is administered until the total cumulative dose is reached. The sensitivity of this method is 80%, and the specificity is 92% (grade of recommendation C) [141,142,144,145].

Acoustic rhinometry is based on acoustic reflection and can be performed in patients with nasal obstruction. A single dose of 25 mg of LAS is administered, and symptoms and nasal volumes are compared with those obtained after administration

Table 2. Doses of the Drugs Used in the Drug Provocation Tests

Drug	Dose, mg	Interval of Administration, min
Etoricoxib	60-90	60
Celecoxib	100-200	60
Paracetamol (acetaminophen)	100-250-500-1000	60
Meloxicam	7.5-15	120
Nabumetone	500-1000	120
Diclofenac	25-50	120
Metamizole (dipyrone)	First day: 50-100-250 Second day: 575	120
Ibuprofen	First day: 50-100-200-400 Second day: 600	120 180
Acetylsalicylic acid	First day: 50-100 Second day: 250-500	180 180

of saline; a response is considered positive when nasal volume decreases by >25%. The sensitivity of the test is 73%-80% and the specificity 94% (grade of recommendation C) [38,146].

Bronchial provocation test: The bronchial provocation test is indicated in patients with bronchial symptoms after intake of NSAIDs. Clinical and spirometric stability should be checked before initiating the test, and the FEV_1 must be >80% with no variations >5%. After inhalation of saline, the spirometry test should vary by <10% with respect to baseline values. Doses of LAS are then increased at 30-minute intervals, and FEV_1 is measured. If no variations or symptoms appear, the procedure is continued until the maximum dose is reached, although the number of inhalations and dose of LAS depend on the protocol [144,147,148]. The protocol is continued at home with peak-flow determinations during the following 24 hours to detect a delayed reaction [149]. The specificity of the bronchial provocation test is 100%, with a sensitivity of 62%, although it is less dangerous and time-consuming than oral DPT (grade of recommendation C).

Oral provocation test: The oral provocation test is considered the gold standard and is the only available test

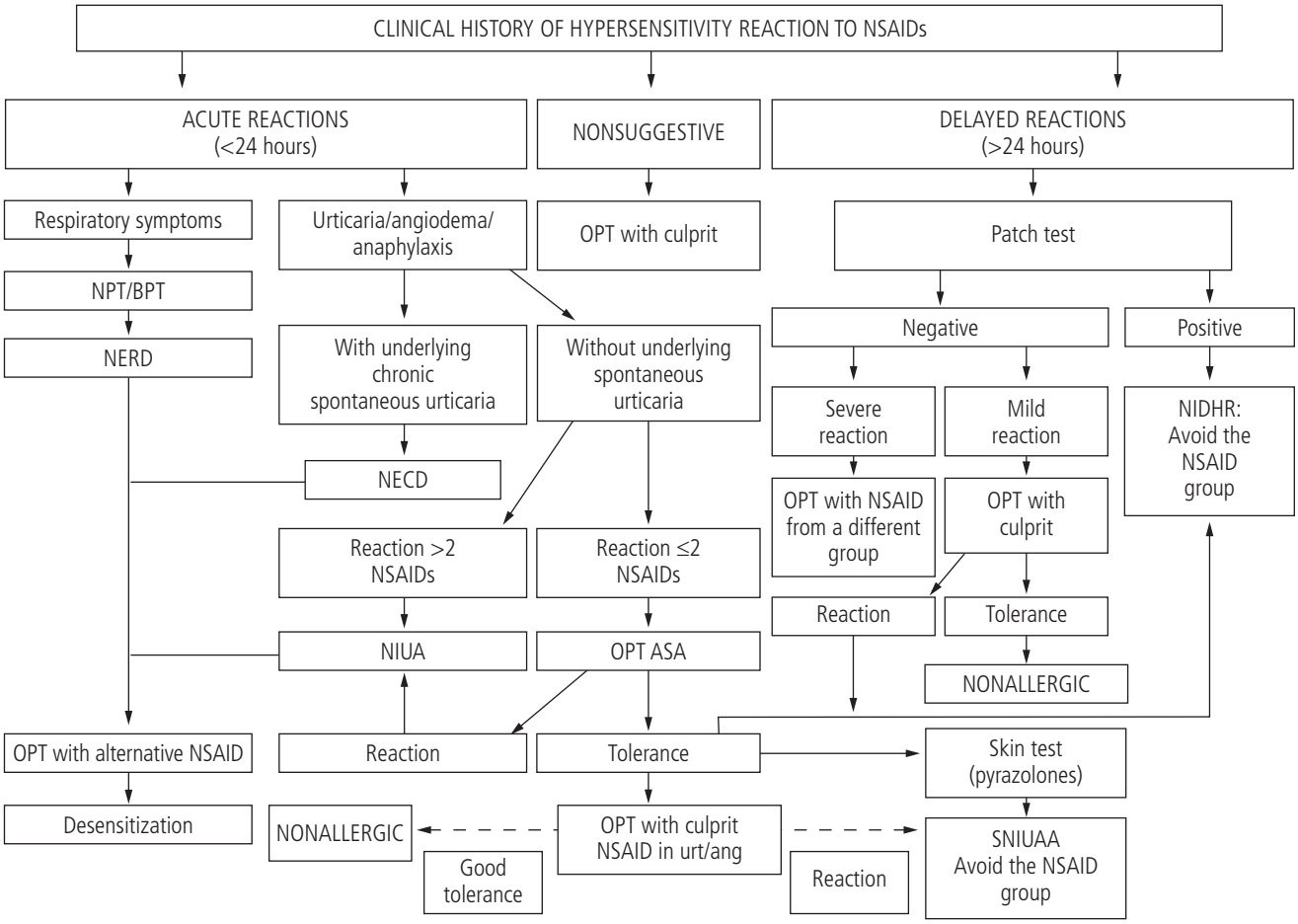

Figure 2. Proposed diagnostic algorithm for patients with hypersensitivity reactions to NSAIDs. NSAID, nonsteroidal anti-inflammatory drug; OPT indicates oral provocation test; NPT, nasal provocation test; BPT, bronchial provocation test; NERD, NSAID-exacerbated respiratory disease; NIDHR, NSAID-induced delayed hypersensitivity reactions; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; ASA, acetylsalicylic acid; SNIUAA, single NSAID–induced urticaria/angioedema/anaphylaxis.

Table 3. Methods Recommended for Diagnosis of Hypersensitivity Reactions to NSAIDs

	Skin Test	In Vitro Test	OPT	NPT/BPT
NERD	No	No	Optional	Yes
NECD	No	No	Optional	No
NIUA	No	No	>2 NSAIDs: Optional ≤2 NSAIDs: ASA/indomethacin	No
SNIUAA	Prick/ID	IgE serum BAT	ASA Mild: Culprit Severe: Alternative	No
NIDHR	ID delayed Patch test	LTT	Mild: Culprit Severe: Alternative	No

Abbreviations: BAT, basophil activation test; BPT, bronchial provocation test; ID, intradermal; LTT, lymphocyte transformation test; NECD, NSAID-exacerbated cutaneous disease; NERD, NSAID-exacerbated respiratory disease; NIDHR, NSAID-induced delayed hypersensitivity reactions; NIUA, NSAID-induced urticaria/angioedema; NPT, nasal provocation test; NSAID, nonsteroidal anti-inflammatory drug; OPT, oral provocation test; SNIUAA, single NSAID–induced urticaria/angioedema/anaphylaxis.

for diagnosing patients with NECD and NIUA (grade of recommendation D) [143,150]. It is not usually performed in patients with respiratory symptoms owing to the possibility of severe bronchospasm (grade of recommendation C). Different protocols are available, with different time intervals to the total cumulative dose. The most widely recommended are those shown in Table 2 (grade of recommendation D) [6]. If the oral provocation test is to be performed with different NSAIDs, an interval of at least 1 week should be left between studies.

Diagnostic Algorithm

The diagnosis of hypersensitivity reaction to NSAIDS is based on symptoms reported in the clinical history and timing. A diagnostic algorithm is proposed in Figure 2, and the methods most often used in each clinical category are shown in Table 3.

Clinical History Indicative of Acute Reactions

Respiratory symptoms

The first approach, if available, is a nasal or bronchial provocation test with LAS, depending on the symptoms reported. If the result is positive, the patient will be diagnosed with NERD. If the result is negative, the diagnosis is based on the consistency of the clinical history. Oral provocation testing with ASA is not recommended in a patient whose history is compatible with NERD, as a severe respiratory reaction can be induced. Consequently, the risk-benefit ratio always needs to be taken into account. Oral provocation testing with ASA is only recommended if desensitization with ASA is to be performed.

Regardless of whether the diagnosis was by clinical history, tolerance of an alternative analgesic (paracetamol) or COX-2 inhibitors should be evaluated using nasal or bronchial provocation testing.

Cutaneous symptoms

In cases with underlying CSU or exacerbation of wheals and angioedema after administration of NSAIDs, NECD can be diagnosed by means of the clinical history. As with NERD, tolerance to alternative analgesics (paracetamol) or COX-2 inhibitors should be assessed.

In patients with urticaria and/or angioedema and underlying CSU, 2 options are available. First, if the patient reports reactions with more than 2 NSAIDs from unrelated chemical groups, a diagnosis of NIUA can be established [121]. Tolerance of an alternative analgesic (paracetamol) or COX-2 inhibitors should be assessed if it is not known. Second, if the patient reacted to ≤2 NSAIDs from unrelated chemical groups, oral provocation testing with ASA or indomethacin should be performed (if ASA is involved). If the result is positive, the diagnosis will be NIUA, and tolerance to an alternative analgesic (paracetamol) or COX-2 inhibitor should be assessed if it is not known. If the patient tolerates ASA, then oral provocation testing should be performed with the culprit drug. If the result is positive, the diagnosis is SNIUAA. If a pyrazolone is the NSAID involved, skin tests and in vitro tests should be performed beforehand. If tolerance to the culprit NSAID is good, the patient should be considered nonallergic. The decision of whether to administer the culprit drug in this group depends on the type of reaction; testing with the culprit drug is not recommended in patients with anaphylaxis.

Nonsuggestive Reaction

In cases of a nonsuggestive reaction, oral provocation testing with the culprit NSAID is the best approach; if the result is negative, the patient will be considered nonallergic. If a reaction appears, oral provocation testing should be performed with either ASA or indomethacin (if ASA is the NSAID involved). If the response is positive, the diagnosis is NIUA; if negative, it is SNIUAA or NIDHR, depending on the time interval between administration and onset of symptoms.

Clinical History Indicative of Delayed Reactions

Patch testing should be performed with readings at 48, 72, and 96 hours. A positive response indicates NIDHR; therefore, the culprit NSAID and those belonging to the same chemical family should be avoided.

In patients with negative patch test results, the approach will depend on the severity of the reaction. In severe reactions, oral provocation testing should be performed with an alternative NSAID from a different group; if tolerance is

good, the diagnosis is NIDHR, and the recommendation is to avoid the culprit NSAID and those from a chemically related family. In mild reactions, oral provocation testing should be performed with the culprit NSAID; if the result is negative, the patient is considered nonallergic, and, if positive, oral provocation testing should be performed with ASA or with indomethacin (if ASA is the culprit). In the case of a positive reaction, the diagnosis is NIUA; if negative, it is NIDHR, and the recommendation is to avoid the culprit NSAID and drugs from a chemically related group.

Hypersensitivity Reactions in Children

The drugs that most often induce hypersensitivity reactions in children are ß-lactam antibiotics, followed by NSAIDs [151,152]. In many cases, reactions appear in children who received both types of drug during a viral infection, thus complicating diagnosis, as viral infections can also induce cutaneous symptoms. In general, only a low percentage of children with a history of hypersensitivity reactions to drugs (<10%) are finally confirmed as allergic [153].

The clinical picture is similar to that of adults, although facial angioedema is the most frequent manifestation, especially in cases mediated by a nonimmunological mechanism; the frequency of this symptom increases progressively until the age of 21 years [154-168]. The clinical history has low negative and positive predictive values for diagnosis, the gold standard being DPT, with skin testing proving useful in some cases [159]. Hypersensitivity reactions are confirmed in only 1% to 50% of children with a clinical history of allergy to NSAIDs [156,158], and most are non–immunologically mediated hypersensitivity reactions [155,158,160], with ibuprofen as the most frequently involved drug. Typical symptoms include angioedema, and the reactions are often associated with atopy; DPT is a safe diagnostic method in this population [161]. Once a cross-reactive hypersensitivity reaction is confirmed, the approach is to recommend alternative treatment; reactivity to paracetamol has been shown to range from 0% to 25% [161,163]. In a recent study, all patients tolerated etoricoxib with fewer than 5% reacting to meloxicam. It remains to be determined whether this response can vary over time in this population [164].

Management: Avoidance and Desensitization

Management of patients with hypersensitivity reactions induced by NSAIDs varies according to the underlying mechanism. Patients with immunologically mediated hypersensitivity reactions must avoid the culprit drug and chemically related drugs (grade of recommendation D). In contrast, patients with non–immunologically mediated hypersensitivity reactions must avoid strong COX-1 inhibitors because of the high possibility of cross-reactivity (grade of recommendation C). However, weak COX-1 inhibitors (eg, paracetamol) and preferential COX-2 inhibitors (eg, meloxicam and nimesulide) are safe and can be tolerated by more than 80% of patients (grade of recommendation C) [9,57,165-168]. Selective COX-2 inhibitors are also well tolerated in patients with NERD, and only anecdotal cases have been reported (grade of recommendation B) [169-171]. In contrast, in patients with NECD and NIUA, the percentages of positive responses to COX-2 inhibitors range from 7% to 33% (grade of recommendation D) [169,170,172,173]. It has been reported that the 25% of patients with NIUA have a positive response to selective COX-2 inhibitors if they also have symptoms induced by paracetamol (acetaminophen). Therefore, in patients with non–immunologically mediated hypersensitivity reactions to NSAIDs, tolerance to weak COX-1 and preferential and selective COX-2 inhibitors should be previously assessed in an allergy department (grade of recommendation D).

Desensitization involves daily controlled administration of increasing doses of the NSAID (mainly ASA) in order to reduce and avoid hypersensitivity reactions while the drug is administered. Since desensitization can be lost within 2 to 5 days after interruption, the procedure should be reinitiated if it has been stopped for more than 48 hours. The minimal dose capable of maintaining desensitization is 81 mg of ASA (grade of recommendation C) [174,175]. The procedure is indicated in patients with NERD that can only be controlled with high doses of corticosteroids or who have undergone several nasal polypectomies, as well as in patients requiring ASA or other NSAIDs for treatment of cardiovascular, hematological, or rheumatologic diseases (grade of recommendation C) [176-179]. Less information exists about desensitization in patients with skin symptoms. The procedure is contraindicated in patients with gastroduodenal ulcer, coagulation disorders, and kidney or liver disease. It is also contraindicated during an asthma exacerbation and in patients with severe cutaneous reactions such as Steven-Johnson syndrome or toxic epidermal necrolysis.

Desensitization is a risky procedure that has to be carried out by qualified personnel in an appropriate setting where treatment can be administered if a reaction occurs (grade of recommendation D) [168]. Airway stability is especially important in patients with NERD, who should continue to take asthma medication and initiate antileukotriene treatment 2 to 4 weeks before initiating desensitization [180]. In some patients with skin symptoms, antihistamines and corticosteroids have been used as premedication.

Table 4. Desensitization Protocol

	Day 1	Day 2	Day 3
9 AM	Placebo	ASA: 20-40 mg	ASA: 100-160 mg
12 AM	Placebo	ASA: 40-60 mg	ASA: 160-325 mg
3 PM	Placebo	ASA: 60-100 mg	ASA: 325 mg

Abbreviation: ASA, acetylsalicylic acid.

Procedure in patients with NERD

Different protocols have been described for the oral, intranasal, and bronchial inhaled routes, although the oral route is the most widely used; the procedure is shown in Table 4 [181-184]. The patient should have an intravenous line inserted during the desensitization procedure. Blood pressure and heart rate should be monitored and lung function measured

before and 30 minutes after each dose. FEV_1 has to be >70% or >1.5 L. Patients with FEV_1 <80% or an exacerbation of their asthma are considered high-risk; consequently, the starting dose must be <20 mg of ASA [179].

If a reaction appears, it should be treated immediately. The next dose can be administered once the patient is stabilized and 3 hours after the last dose. If the reaction persists, the procedure should be stopped and reinitiated the following day beginning with the last tolerated dose. If doses are tolerated, the procedure is continued until a dose of 325 mg of ASA is tolerated.

In patients requiring ASA as antiplatelet therapy, the total cumulative dose is lower (100 mg), and doses can be administered at 20-minute intervals with the following schedule: 0.1, 0.2, 1, 3, 10, 25, 50, and 100 mg [185]. If desensitization is performed to treat asthma and nasal polyposis, a dose of 650 mg should be administered twice a day for 1 month; if the patient's condition improves, the dose will be progressively reduced to 325 mg twice a day [186]. Administration of ASA can change the course of the disease in 25% of cases [187-190], with a marked improvement in symptoms and quality of life [191-193].

Procedure in Patients With NECD and NIUA

Data on desensitization in patients with NECD or NIUA are limited. In one study, 11 patients with NIUA tolerated the desensitization procedure [194]. However, in patients with NECD, desensitization seems to be less effective; in some cases, it is impossible [195].

Procedure in Patients With Immunologically Mediated Hypersensitivity Reactions to NSAIDs

Since these patients develop symptoms with one group of NSAIDs and tolerate others, desensitization is not usually necessary. Desensitization is only indicated in patients with SNIUAA to ASA, and the procedure is the same as that described above. There is less evidence about desensitization in NIDHR.

Acknowledgments

We thank Professors Miguel Blanca and Ignacio Dávila for their in-depth review of our manuscript. We also thank Ian Johnstone for his help with the English language version of the manuscript.

Funding

The authors declare that they received no funding for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ. 2001;323:334-6.
2. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P, van Hage-Hamsten M, Wüthrich B; EAACI (the European Academy of Allergology and Clinical Immunology) nomenclature task force. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy. 2001;56:813-24.
3. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113:832-6.
4. Anderson JA, Adkinson NF Jr. Allergic reactions to drugs and biologic agents. JAMA. 1987;258:2891-9.
5. Doña I, Blanca-Lopez N, Cornejo-García JA, Torres MJ, Laguna JJ, Fernández J, Rosado A, Rondón C, Campo P, Agúdez JA, Blanca M, Canto G. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. Clin Exp Allergy. 2011;41:86-95.
6. Szczeklik A, Nizankowska-Mogilnicka E, Sanak M. Hypersensitivity to Aspirin and Nonsteroidal Anti-Inflammatory Drugs. In: Adkinson, Busse, Bochner, Holgate, Simons&Lemanske, editors. Middleton's Allergy 7th Edition. Mosby Elsevier; 2009: p. 1227-43.
7. Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. Ann Allergy Asthma Immunol. 2001;87:177-80.
8. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, Brockow K, Campo P, Celik G, Cernadas J, Cortellini G, Gomes E, Nizankowska-Mogilnicka E, Romano A, Szczeklik A, Testi S, Torres MJ, Wöhrl S, Makowska J. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013;68:1219-32.
9. Ortega N. Quiralte J, Fraj J, Palacios L. Reacciones adversas a los AINE: alergia, intolerancia. In: Pelàez, Dávila, editor. Tratado Alergología. Ergón; 2007: p. 1461-81.
10. Doña I, Blanca-Lopez N, Torres MJ, Garcia-Campos J, Garcia-Nuñez I, Gómez F, Salas M, Rondon C, Canto MG, Blanca M. Drug hypersensitivity reactions: patterns of responses, drug involved and temporal variation in a large series of patients evaluated. J Investig Allergy Clin Immunol. 2012;22:363-71.
11. Settipane RA, Constantine HP, Settipane GA. Aspirin intolerance and recurrent urticaria in normal adults and children. Epidemiology and review. Allergy. 1980;35:149-54.
12. Gomes E, Cardoso MF, Praca F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy. 2004;34:1597-601.
13. Vally H, Taylor ML, Thompson PJ. The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. Thorax. 2002;57:569-74.
14. Kasper L, Sladek K, Duplaga M, Bochenek G, Liebhart J, Gladysz U, Malolepszy J, Szczeklik A. Prevalence of asthma

with aspirin hypersensitivity in the adult population of Poland. Allergy. 2003;58:1064-6.
15. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. BMJ. 2004;328:434.
16. Kim JE, Kountakis SE. The prevalence of Samter's triad in patients undergoing functional endoscopic sinus surgery. Ear Nose Throat J. 2007;86:396-9.
17. Sánchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. NSAID-induced urticaria and angioedema: a reappraisal of its clinical management. Am J Clin Dermatol. 2002;3:599-607.
18. Erbagci Z. Multiple NSAID intolerance in chronic idiopathic urticaria is correlated with delayed, pronounced and prolonged autoreactivity. J Dermatol. 2004;31:376-82.
19. Stevenson DD. Aspirin and NSAID sensitivity. Immunol Allergy Clin North Am. 2004;24:491-505.
20. Asero R. Multiple sensitivity to NSAID. Allergy. 2000;55(9):893-4.
21. Van der Klauw MM, Stricker BH, Herings RM, Cost WS, Valkenburg HA, Wilson JH. A population based case-cohort study of drug-induced anaphylaxis. Br J Clin Pharmacol. 1993;35:400-8.
22. Berkes EA. Anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs. Clin Rev Allergy Immunol. 2003;24:137-48.
23. Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis. A review of 266 cases. Arch Intern Med. 1995;155:1749-54.
24. Mullins RJ. Anaphylaxis: risk factors for recurrence. Clin Exp Allergy. 2003;33:1033-40.
25. Cianferoni A, Novembre E, Mugnaini L, Lombardi E, Bernardini R, Pucci N, Vierucci A. Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985-1996). Ann Allergy Asthma Immunol. 2001;87:27-32.
26. Van Puijenbroek EP, Egberts AC, Meyboom RH, Leufkens HG. Different risks for NSAID-induced anaphylaxis. Ann Pharmacother. 2002;36:24-9.
27. Van der Klauw MM, Wilson JH, Stricker BH. Drug-associated anaphylaxis: 20 years of reporting in The Netherlands (1974-1994) and review of the literature. Clin Exp Allergy. 1996;26:1355-63.
28. Asero R. Oral aspirin challenges in patients with a history of intolerance to single non-steroidal anti-inflammatory drugs. Clin Exp Allergy. 2005;35:713-6.
29. Mockenhaupt M, Kelly JP, Kaufman D, Stern RS. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with nonsteroidal antiinflammatory drugs: a multinational perspective. J Rheumatol. 2003;30:2234-40.
30. Farooque SP, Lee TH. Aspirin-sensitive respiratory disease. Annu Rev Physiol. 2009;71:465-87.
31. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. N Engl J Med. 2002;347:1493-9.
32. Celik G, Bavbek S, Misirligil Z, Melli M. Release of cysteinyl leukotrienes with aspirin stimulation and the effect of prostaglandin E(2) on this release from peripheral blood leucocytes in aspirin-induced asthmatic patients. Clin Exp Allergy. 2001;31:1615-22.
33. Sestini P, Armetti L, Gambaro G, Pieroni MG, Refini RM, Sala A, Folco GC, Bianco S, Robuschi M. Inhaled PGE_2 prevents aspirin-induced bronchoconstriction and urinary LTE4 excretion in aspirin-sensitive asthma. Am J Respir Crit Care Med. 1996;153:572-5.
34. Corrigan CJ, Napoli RL, Meng Q, Fang C, Wu H, Tochiki K, Reay V, Lee TH, Ying S. Reduced expression of the prostaglandin E2 receptor E-prostanoid 2 on bronchial mucosal leukocytes in patients with aspirin-sensitive asthma. J Allergy Clin Immunol. 2012;129:1636-46.
35. Wang XS, Wu AY, Leung PS, Lau HY. PGE suppresses excessive anti-IgE induced cysteinyl leucotrienes production in mast cells of patients with aspirin exacerbated respiratory disease. Allergy. 2007;62:620-7.
36. Szczeklik A. The cyclooxygenase theory of aspirin-induced asthma. Eur Respir J. 1990;3:588-93.
37. Christie PE, Tagari P, Ford-Hutchinson AW, Charlesson S, Chee P, Arm JP, Lee TH. Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. Am J Respir Crit Care Med. 1991;143:1025-9.
38. Campo P, Ayuso P, Salas M, Plaza MC, Cornejo-García JA, Doña I, Torres MJ, Blanca-López N, Canto G, Guéant JL, Sanak M, Blanca M. Mediator release after nasal aspirin provocation supports different phenotypes in subjects with hypersensitivity reactions to NSAIDs. Allergy. 2013 doi: 10.1111/all.12187. [Epub ahead of print]
39. Cowburn AS, Sladek K, Soja J, Adamek L, Nizankowska E, Szczeklik A, Lam BK, Penrose JF, Austen FK, Holgate ST, Sampson AP. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. J Allergy Clin Immunol. 1998;101:834-46.
40. Adamjee J, Suh YJ, Park HS, Choi JH, Penrose JF, Lam BK, Austen KF, Cazaly AM, Wilson SJ, Sampson AP. Expression of 5-lipoxygenase and cyclooxygenase pathway enzymes in nasal polyps of patients with aspirin-intolerant asthma. J Pathol. 2006;209:392-9.
41. Szczeklik A, Nizankowska E, Dworski R. Choline magnesium trisalicylate in patients with aspirin-induced asthma. Eur Respir J. 1990;3:535-9.
42. Sanak M, Pierzchalska M, Bazan-Socha S, Szczeklik A. Enhanced expression of the leukotriene C(4) synthase due to overactive transcription of an allelic variant associated with aspirin-intolerant asthma. Am J Respir Cell Mol Biol. 2000;23:290-6.
43. Szczeklik A, Mastalerz L, Nizankowska E, Cmiel A. Protective and bronchodilator effects of prostaglandin E and salbutamol in aspirin-induced asthma. Am J Respir Crit Care Med. 1996;153:567-71.
44. Kim SH, Park HS. Genetic markers for differentiating aspirin-hypersensitivity. Yonsei Med J. 2006;47:15-21.
45. Kim SH, Ye YM, Palikhe NS, Kim JE, Park HS. Genetic and ethnic risk factors associated with drug hypersensitivity. Curr Opin Allergy Clin Immunol. 2010;10:280-90.
46. Duroudier NP, Tulah AS, Sayers I. Leukotriene pathway genetics and pharmacogenetics in allergy. Allergy. 2009;64:823-39.
47. Torres-Galván MJ, Ortega N, Sánchez-García F, Blanco C, Carrillo T, Quiralte J. LTC4-synthase A-444C polymorphism: lack of association with NSAID-induced isolated periorbital angioedema in a Spanish population. Ann Allergy Asthma Immunol. 2001;87:506-10.

48. Kim SH, Choi JH, Holloway JW, Suh CH, Nahm DH, Ha EH, Park CS, Park HS. Leukotriene-related gene polymorphisms in patients with aspirin-intolerant urticaria and aspirin-intolerant asthma: differing contributions of ALOX5 polymorphism in Korean population. J Korean Med Sci. 2005:20:926-31.
49. Kim SH, Oh JM, Kim YS, Palmer LJ, Suh CH, Nahm DH, Park HS. Cysteinyl leukotriene receptor 1 promoter polymorphism is associated with aspirin-intolerant asthma in males. Clin Exp Allergy. 2006;36:433-9.
50. Choi JH, Park HS, Oh HB, Lee JH, Suh YJ, Park CS, Shin HD. Leukotriene-related gene polymorphisms in ASA-intolerant asthma: an association with a haplotype of 5-lipoxygenase. Hum Genet. 2004;114:337-44.
51. Kim SH, Yang EM, Park HJ, Ye YM, Lee HY, Park HS. Differential contribution of the CysltR1 in patients with aspirin hypersensitivity. J Clin Immunol. 2007;27:613-9.
52. Park JS, Chang HS, Park CS, Lee JH, Lee YM, Choi JH, Park HS, Kim LH, Park BL, Choi YH, Shin HD. Association analysis of cysteinyl-leukotriene receptor 2 (CYSLTR2) polymorphisms with aspirin intolerance in asthmatics. Pharmacogenet Genomics. 2005;15:483-92.
53. Jinnai N, Sakagami T, Sekigawa T, Kakihara M, Nakajima T, Yoshida K, Goto S, Hasegawa T, Koshino T, Hasegawa Y, Inoue H, Suzuki N, Sano Y, Inoue I. Polymorphisms in the prostaglandin E2 receptor subtype 2 gene confer susceptibility to aspirin-intolerant asthma: a candidate gene approach. Hum Mol Genet. 2004;13:3203-17.
54. Mastalerz L, Setkowicz M, Sanak M, Szczeklik A. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. J Allergy Clin Immunol. 2004;113:771-5.
55. Setkowicz M, Mastalerz L, Podolec-Rubis M, Sanak M, Szczeklik A. Clinical course and urinary eicosanoids in patients with aspirin-induced urticaria followed up for 4 years. J Allergy Clin Immunol. 2009;123:174-8.
56. Asero R. Predictive value of autologous plasma skin test for multiple nonsteroidal anti-inflammatory drug intolerance. Int Arch Allergy Immunol. 2007;144:226-30.
57. Asero R. Risk factors for acetaminophen and nimesulide intolerance in patients with NSAID-induced skin disorders. Ann Allergy Asthma Immunol. 1999;82:554-8.
58. Cornejo-García JA, Jagemann LR, Blanca-López N, Doña I, Flores C, Guéant-Rodríguez RM, Torres MJ, Fernández J, Laguna JJ, Rosado A, Agúndez JA, García-Martín E, Canto G, Guéant JL, Blanca M. Genetic variants of the arachidonic acid pathway in non-steroidal anti-inflammatory drug-induced acute urticaria. Clin Exp Allergy. 2012;42:1772-81.
59. Ayuso P, Cornejo-García JA, Blanca M, Torres MJ, Doña I, Salas M, Blanca-López N, Canto G, Rondon C, Campo P, Laguna JJ, Fernández J, Martínez C, García-Martín E. The diamine oxidase gene is associated with hypersensitivity response to non-steroidal anti-inflammatory drugs. PLoS One. 2012;7(11):e47571.
60. Doña I, Blanca-Lopez N, Torres MJ, Gomez F, Fernandez J, Zambonino MA, Monteseirin FJ, Canto G, Blanca M, Cornejo-Garcıa JA. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. Allergy. 2014;69:438-44.
61. Himly M, Jahn-Schmid B, Pittertschatscher K, Bohle B, Grubmayr K, Ferreira F, Ebner H, Ebner C. IgE-mediated immediate-type hypersensitivity to the pyrazolone drug propyphenazone. J Allergy Clin Immunol. 2003;111:882-8.
62. Gómez E, Blanca-López N, Torres MJ, Requena G, Rondon C, Canto G, Blanca M, Mayorga C. Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. Clin Exp Allergy. 2009;39:1217-24.
63. Canto MG, Andreu I, Fernandez J, Blanca M. Selective immediate hypersensitivity reactions to NSAIDs. Curr Opin Allergy Clin Immunol. 2009;9:293-7.
64. Quiralte J, Blanco C, Delgado J, Ortega N, Alcantara M, Carrillo R. Challenge-based clinical patterns of 223 Spanish patients with non-steroidal anti-inflammatory drug-induced reactions. J Investig Allergol Clin Immunol. 2007;17:182-8.
65. Kowalski ML, Woszczek G, Bienkiewicz B, Mis M. Association of pyrazolone drug hypersensitivity with HLA-DQ and DR antigens. Clin Exp Allergy. 1998;28:1153-8.
66. Carmona MJ, Blanca M, Garcia A, Fernandez S, Burgos F, Miranda A, Vega JM, Garcia J. Intolerance to piroxicam in patients with adverse reactions to nonsteroidal antiinflammatory drugs. J Allergy Clin Immunol. 1992;90:873-9.
67. Harrer A, Lang R, Grims R, Braitsch M, Hawranek T, Aberer W, Vogel L, Schmid W, Ferreira F, Himly M. Diclofenac hypersensitivity: antibody responses to the parent drug and relevant metabolites. PLoS One. 2010;5:e13707.
68. Kvedariene V, Bencherioua AM, Messaad D, Godard P, Bousquet J, Demoly P. The accuracy of the diagnosis of suspected paracetamol (acetaminophen) hypersensitivity: results of a single-blinded trial. Clin Exp Allergy. 2002;32:1366-9.
69. Vidal C, Pérez-Carral C, González-Quintela A. Paracetamol (acetaminophen) hypersensitivity. Ann Allergy Asthma Immunol. 1997;79:320-1.
70. Klote MM, Smith LJ. A case of anaphylaxis to naproxen. Allergy. 2005;60:260-1.
71. Schuster C, Wüthrich B. Anaphylactic drug reaction to celecoxib and sulfamethoxazole: cross reactivity or coincidence? Allergy. 2003;58:1072.
72. Fontaine C, Bousquet PJ, Demoly P. Anaphylactic shock caused by a selective allergy to celecoxib, with no allergy to rofecoxib or sulfamethoxazole. J Allergy Clin Immunol. 2005;115:633-4.
73. Figueroa J, Ortega N, Almeida L, Blanco C, Castillo R. Sulfonamide allergy without cross-reactivity to celecoxib. Allergy. 2007;62(1):93.
74. Vidal C, Porras-Hurtado L, Cruz R, Quiralte J, Cardona V, Colas C, Castillo LF, Marcos C, Soto T, Lopez-Abad R, Hernandez D, Audícana MT, Armisen M, Rodríguez V, Perez Carral C, Moreno E, Cabañes R, Corominas M, Parra A, Lobera T, Quiñones D, Ojeda P, Luna I, Torres M, Carracedo A. Association of thromboxane A1 synthase (TBXAS1) gene polymorphism with acute urticaria induced by nonsteroidal anti-inflammatory drugs. J Allergy Clin Immunol. 2013;132(4):989-91
75. Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions - new concepts. Clin Exp Allergy. 2007;37:989-9.
76. Bernedo N, Audicana MT, Uriel O, Velasco M, Gaztaminza G, Fernandez E, Muñoz D. Metamizol as a cause of postoperative erythroderma. Contact Dermatitis. 2004;50:317-8.
77. Quiralte J, Blanco C, Castillo R, Delgado J, Carrillo T. Intolerance to non-steroidal anti-inflammatory drugs: results of controlled

drug challenges in 98 patients. J Allergy Clin Immunol. 1996;98:678-85.
78. Quiralte J, Torres MJ. Aspectos genéticos de la intolerancia a AINES y su correlación clínica. Allergol Immunol Clin. 2000;15:50-5.
79. Quiralte J, Blanco C, Castillo R, Ortega N, Carrillo T. Anaphylactoid reaction due to nonsteroidal anti-inflammatory drugs: clinical and cross-reactivity studies. Ann Allergy Asthma Immunol. 1997;78:293-6.
80. Bochenek G, Nizankowska E, Szczeklik A. The atopy trait in hypersensitivity to nonsteroidal antiinflammatory drugs. Allergy. 1996;51:16-23.
81. Sanchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. Ann Allergy Asthma Immunol. 2000;84:101-6.
82. Berges-Gimeno MP, Simon RA, Stevenson DD. The effect of leukotriene-modifier drugs on aspirin on aspirin-induced asthma and asthma and rhinitis reactions. Clin Exp Allergy. 2002;32:1491-6.
83. Kupczyk M, Kuprys I, Gorski P, Kuna P. Aspirin intolerance and allergy to house dust mites: important factors associated with development of severe asthma. Ann Allergy Asthma Immunol. 2004;92:453-8.
84. Dávila I, Rondón C, Navarro A, Antón E, Colás C, Dordal MT, Ibáñez MD, Fernández-Parra B, Lluch-Bernal M, Matheu V, Montoro J, Sánchez MC, Valero A. Aeroallergen sensitization influences quality of life and comorbidities in patients with nasal polyposis. Am J Rhinol Allergy. 2012;26(5):e126-31.
85. Grattan CE. Aspirin sensitivity and urticaria. Clin Exp Dermatol. 2003;28:123-7.
86. Quiralte J, López-Pascual E, Palacios L, Saenz de San Pedro B, Navarrete MA, Florido F. Una propuesta de clasificación de las reacciones idiosincrásicas a fármacos antiinflamatorios no esteroideos. Alergol Inmunol Clin. 2004;19:185-94.
87. Capriles-Behrens E, Caplin J, Sanchez-Borges M. NSAID facial angioedema in select pediatric atopic population. J Investig Allergol Clin Immunol. 2000;10:277-9.
88. Gómez F, Doña I, Blanca-López N, Torres MJ, Salas M, Rondon C, Campo P, Posadas T, Guerrero MA, Canto G, Blanca M. Food Allergy Is Not A Risk Factor in Cross-Intolerance to NSAIDs for Induction of Symptoms. J Allergy Clin Immunol. 2013;131(2):AB167
89. Quiralte J. Aspirin-induced isolated periorbital angioedema. Ann Allergy Asthma Immunol. 1998;81:459.
90. Blanco C, Quiralte J, Castillo R, Delgado J, Arteaga C, Barber D, Carrillo T. Anaphylaxis after ingestion of wheat flour contaminated with mites. J Allergy Clin Immunol. 1997;99:308-13.
91. Del Pozo MD, Lobera T, Blasco A. Selective hypersensitivity to diclofenac. Allergy. 2000;55:412-3.
92. Patriarca G, Venuti A, Bonini W. Allergy to pyramidon (aminopyrine). Ann Allergy. 1973;31:84-6.
93. Kowalski ML, Bienkiewicz B, Woszczek G, Iwaszkiewics J, Poniatowska M. Diagnosis of pyrazolone drug sensitivity: clinical history versus skin testing and in vitro testing. Allergy Asthma Proc. 1999;20:347-52.
94. Sanchez-Borges M, Capriles-Hulett A. Risk of skin reactions when using ibuprofen-based medicines. Expert Opin Drug Saf. 2005;4:837-48.
95. Patel RM, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol. 2008;74:430.
96. Titchen T, Cranswick N, Beggs S. Adverse drug reactions to non-steroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. Br J Clin Pharmacol. 2005;59:718-23.
97. Macias E, Ruiz A, Moreno E, Laffond E, Davila I, Lorente F. Usefulness of intradermal test and patch test in the diagnosis of nonimmediate reactions to metamizol. Allergy. 2007;62(12):462-4.
98. Savin JA. Current causes of fixed drug eruption in the UK. Br J Dermatol. 2001;145:667-8.
99. Brahimi N, Routier E, Raison-Peyron N, Tronquoy AF, Pouget-Jasson C, Amarger S, Machet L, Amsler E, Claeys A, Sassolas B, Leroy D, Grange A, Dupuy A, Cordel N, Bonnetblanc JM, Milpied B, Doutre MS, Guinnepain MT, Barbaud A, Chosidow O, Roujeau JC, Lebrun-Vignes B, Descamps V. A three-year-analysis of fixed drug eruptions in hospital settings in France. Eur J Dermatol. 2010;20:461-4.
100. Bellini V, Stingeni L, Lisi P. Multifocal fixed drug eruption due to celecoxib. Dermatitis. 2009;20:174-6.
101. Niesvaara D, Ortega Rodríguez N, Hernandez HR, Suarez R, Castillo Sainz C, Carrillo Diaz T, Suarez Lorenzo I. Exantema fijo medicamentoso multiple en paciente con intolerancia a los AINEs. J Investig Allergol Clin Immunol. 2011;21(4):201.
102. Nettis E, Giordano D, Colanardi MC, Paradiso MT, Ferrannini A, Tursi A. Delayed-type hypersensitivity rash from ibuprofen. Allergy. 2003;58:539-40.
103. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A. Stevens-Johnson syndrome and toxic epidermal necrolysis: assement of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008;128:35-44.
104. Sanchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. Cutaneous hypersensitivity reactions to inhibitors of cyclooxygenase-2. Results of 307 oral provocation tests and review of the literature. Allergy Clin Immunol Int. 2007;19:44-9.
105. Ward KE, Archambault R, Mersfelder TL. Severe adverse skin reactions to non-steroidal anti-inflammatory drugs: A review of the literature. Am J Health Syst Pharm. 2010;67:206-13.
106. Yesudian PD, Penny M, Azurdia RM, King CM. Ibuprofen-induced acute generalized exanthematous pustulosis. Int J Dermatol. 2004;43:208-10.
107. Gonzalo-Garijo MA, Pérez-Calderón R, De Argila D, Rodríguez-Nevado I. Metamizole-induced acute generalized exanthematous pustulosis. Contact Derm. 2003;49:47-8.
108. De Coninck AL, Van Strubarq AS, Pipeleers-Marichal MA, Huyghens LP, Suys ET, Roseeuw DI. Acute generalized exanthematous pustulosis induced by paracetamol. A case with severe hemodynamic disturbances. Dermatology. 1996;193:338-41.
109. Mäkelä L, Lammintausta K. Etoricoxib-induced acute generalized exanthematous pustulosis. Acta Derm Venereol. 2008;88:200-1.
110. Brandao FM, Goossens A, Tosti A. Topical drugs. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin, eds. Textbook of Contact Dermatitis. 3rd ed. Berlin: Springer-Verlag; 2001. p. 689-723.

111. Barbaud A. Contact dermatitis due to topical drugs. G Ital Dermatol Venereol. 2009;144:527-36.
112. White IR. Phototoxic and Photoallergic Reactions. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin, eds. Textbook of Contact Dermatitis. 3rd ed. Berlin: Springer-Verlag; 2001.p. 367-79.
113. Ophaswongse S, Maibach H. Topical nonsteroidal antiinflammatory drugs: allergic and Photoallergic contact dermatitis and phototoxicity. Contact Dermatitis. 1993;29:57-64.
114. Weber JC, Essigman WK. Pulmonary alveolitis and NSAIDs-factor or fiction? Br J Rheumatol. 1986;25:5-6.
115. Esteve JB, Launay-Vacher V, Brocheriou I, Grimaldi A, Izzedine H. COX-2 inhibitors and acute interstitial nephritis: case report and review of the literature. Clin Nephrol. 2005;63;385-9.
116. Ravnskov U. Glomerular, tubular and interstitial nephritis associated with non-steroidal anti-inflammatory drugs. Evidence of a common mechanism. Br J Clin Pharmacol. 1999;47:203-10.
117. Ashwath ML, Katner HP. Recurrent aseptic meningitis due to different non-steroidal anti-inflammatory drugs including rofecoxib. Postgrad Med J. 2003;79:295-6.
118. Blanca-López N, Doña I, Torres M, Campo P, Rondón C, Seoane ME, Salas M, Canto G, Blanca M. Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance. Clin Exp Allergy. 2013;43:85-91.
119. Yoshimine F, Hasegawa T, Suzuki E, Terada M, Koya T, Kondoh A, Arakawa M, Yoshizawa H, Gejyo F. Contribution of aspirin-intolerant asthma to near fatal asthma based on a questionnaire survey in Niigata Prefecture, Japan. Respirology. 2005;10:477-84.
120. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. Eur Respir J. 2000;16:432-6.
121. Lumry WR, Mathison DA, Stevenson DD. Aspirin in chronic urticaria and/or angioedema: studies of sensitivity and desensitization. J Allergy Clin Immunol. 1982;69:135-43.
122. Gamboa PM, Sanz ML, Caballero MR, Antepara I, Urrutia I, Jauregui I, González G, Diéguez I, De Weck AL. Use of CD63 expression as a marker of in vitro basophil activation and leukotriene determination in metamizol allergic patients. Allergy. 2003;58:312-7.
123. De Paramo BG, Gancedo SQ, Cuevas M, Camo IP, Martin JA, Cosmes EL. Paracetamol (acetaminophen) hypersensitivity. Ann Allergy Asthma Immunol. 2000;85:508-11.
124. Whittam LR, Wakelin SH, Barker JN. Generalized pustular psoriasis or drug-induced toxic pustuloderma? The use of patch testing. Clin Exp Dermatol. 2000;25:122-4.
125. Zedlitz S, Linzbach L, Kauffmann R, Boehncke WH. Reproducible identification of the causative drug of a fixed drug eruption by oral provocation and lesional patch testing. Contact Dermatitis. 2002;46:352-3.
126. Hassan T, Jansen CT. Photopatch test reactivity: effect of photoallergen concentration and UVA dosaging. Contact Dermatitis. 1996;34:383-6.
127. Mewes T, Riechelmann H, Klimek L. Increased in vitro cysteinyl leukotriene release from blood leukocytes in patients with asthma, nasal polyps, and aspirin intolerance. Allergy 1996;51:506-10.
128. Kubota Y, Imayama S, Toshitani T, Uemura Y, Koga T, Sugawara N, Kurimoto F, Hata K. Sulfidoleukotriene release test (CAST) in hypersensitivity to nonsteroidal anti-inflammatory drugs. Int Arch Allergy Immunol. 1997;114:361-6.
129. Pierzchalska M, Mastalerz L, Sanak M, Zazula M, Szczeklik A. A moderate and unspecific release of cysteinyl leukotrienes by aspirin from peripheral blood leucocytes precludes its value for aspirin sensitivity testing in asthma. Clin Exp Allergy. 2000;30:1785-91.
130. De Weck AL, Sanz ML, Gamboa PM, Aberer W, Blanca M, Correia S, Erdman S, Jermann JM, Kanny G, Kowalski M, Mayorga L, Medrala W, Merk A, Sturm GJ, Sainte-Laudy J, Schneider MS, Szczeklik A, Weber JM, Wedi A. Nonsteroidal anti-inflammatory drug hypersensitivity syndrome. A multicenter study. Clinical findings and in vitro diagnosis. J Investig Allergol Clin Immunol. 2009;19:355-69.
131. De Weck AL. Cellular Allergen Stimulation Test (CAST) 2003: a review. J Invest Allergol Clin Immunol. 2004;14:253-73.
132. Gamboa P, Sanz ML, Caballero MR, Urrutia I, Antepara I, Esparza R, de Weck AL. The flow-cytometric determination of basophil activation induced by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is useful for in vitro diagnosis of the NSAID hypersensitivity syndrome. Clin Exp Allergy. 2004;34:1448-57.
133. Celik GE, Schroeder JT, Hamilton RG, Saini SS, Adkinson NF. Effect of in vitro aspirin stimulation on basophils in patients with aspirin exacerbated respiratory disease. Clin Exp Allergy. 2009;39:1522-31.
134. Sanz ML, Gamboa P, De Weck AL. A new combined test with flowcytometric basophil activation and determination of sulfidoleukotrienes is useful for in vitro diagnosis of hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs. Int Arch Allergy Immunol. 2005;136:58-72.
135. Sanz ML, Gamboa PM. Effect of in vitro aspirin stimulation on basophils in patients with aspirin-exacerbated respiratory disease. Clin Exp Allergy. 2010;40:520-1.
136. Rubio M, Herrero T, De Barrio M. Alergia a pirazolonas. Allergol Immunopathol.1994;22:104-6.
137. Blanca M, Perez E, Garcia JJ, Miranda A, Terrados S, Vega JM, Suau R. Angioedema and IgE antibodies to aspirin: a case report. Ann Allergy. 1989;62:295-8.
138. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy. 2004;59:809-20.
139. Stevenson DD. Diagnosis, prevention and treatment of adverse reactions to aspirin and non-steroidal anti-inflammatory drugs. J Allergy Clin Immunol. 1984;74:617-22.
140. Stevenson DD, Mathison DA. Aspirin sensitivity in asthmatics: when may this drug be safe? Posgrad Med. 1985;78:111-3.
141. Milewski M, Mastalerz L, Nizankowska E, Szczeklik A. Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. J Allergy Clin Immunol. 1998;101:581-6.
142. Alonso-Llamazares A, Martinez-Cócera C, Domínguez-Ortega J, Robledo-Echarren T, Cimarra-Alvarez M, Mesa del Castillo M. Nasal provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA). Allergy. 2002;57:632-5.
143. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczynska M, Picado C, Scadding G, Kowalski ML, Setkowicz M, Ring J, Brockow K, Bachert C, Wöhrl S, Dahlén B, Szczeklik

A. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. Allergy. 2007;62:1111-8.
144. Phillips GD, Foord BM, Holgate ST. Inhaled lysine-aspirin as a bronchoprovocation procedure in aspirin-sensitive asthma: its repeatability, absence of a late phase reaction, and the role of histamine. J Allergy Clin Immunol. 1989;84:232-41.
145. Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A. Oral and bronchial provocation test with aspirin for diagnosis of aspirin-induced asthma. Eur Resp J. 2000;15:863-9.
146. Casadevall J, Ventura PJ, Mullol J, Picado C. Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. Thorax. 2000;55:921-4.
147. Alonso-Llamazares A, Rosado A, Vives R. Test de provocación bronquial y nasal con acetilsalicilato de lisina en el diagnóstico de Intolerancia a AINE. Alergol Inmunol Clin. 2002;17:168-74.
148. Melillo G, Padovano A, Cocco G, Masi C. Dosimeter inhalation with lysine acetyl-salicylate for the detection of aspirin-induced asthma. Ann Asthma Allergy Immunol. 1993;71:61-5.
149. Park HS. Early and late onset asthmatic responses following lysine-aspirin inhalation in aspirin-sensitive asthmatic patients. Clin Exp Allergy. 1993;25:38-40.
150. Macy E, Bernstein JA, Castells MC, Gawchik SM, Lee TH, Settipane RA, Simon RA, Wald J, Woessner KM; Aspirin Desensitization Joint Task Force. Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: a practice paper. Ann Allergy Asthma Immunol. 2007;98:172-4.
151. Gamboa PM. Alergia a los medicamentos. In: Alergológica 2005. Factores epidemiológicos, clínicos y socioeconómicos de las enfermedades alérgicas en España en Primera edición. Madrid: Luzán. 2005. p. 255-82.
152. Torres MJ, Blanca M, Fernández J, Romano A, Weck A, Aberer W, Brockow K, Pichler WJ, Demoly P; ENDA; EAACI Interest Group on Drug Hypersensitivity. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy. 2003;58:961-72.
153. Ponvert C, Le Clainche L, Blic J, Le Bourgeois M, Scheinmann P, Paupe J. Allergy to beta-lactam antibiotics in children. Pediatrics. 1999;104:1-9.
154. Botey J, Ibero M, Malet A, Marin A, Eseverri JL. Aspirin-induced recurrent urticaria and recurrent angioedema in non-atopic children. Ann Allergy. 1984:53:265-7.
155. Capriles-Behrens E, Caplin J, Sanchez-Borges M. NSAID facial angioedema in a selected pediatric atopic population. J Invest Allergol Clin Immunol. 2000:10:277-9.
156. Botey J, Navarro C, Aulesa C, Marin A, Eseverri JL. Acetyl salicylic acid-induced urticaria and/or angioedema in atopic children. Allergol Immunopathol. 1988:16:43-7.
157. Diaz-Jara M, Perez-Montero A, Gracia-Bara MT, Cabrerizo S, Zapatero L, Martinez-Molero MI. Allergic reactions due to ibuprofen in children. Pediatr Dermatol. 2001;18:66-7.
158. Hassani A, Ponvert C, Karila C, Le Bourgeois M, De Blic J, Scheinmann P. Hypersensitivity to cyclooxygenase inhibitory drugs in children: a study of 164 cases. Eur J Dermatol. 2008;18:561-5.
159. Benahmed S, Picot MC, Dumas F, Demoly P. Accuracy of a pharmacovigilance algorithm in diagnosing drug hypersensitivity reactions. Arch Intern Med. 2005;165:1500-5.
160. Kidon MI, Kang LW, Chin CW, Hoon LS, Hugo VB. Nonsteroidal anti inflammatory drug hypersensitivity in preschool children. Allergy Asthma Clin Immunol. 2007;3:114-22.
161. Zambonino MA, Torres MJ, Muñoz C, Requena G, Mayorga C, Posadas T, Urda A, Blanca M, Corzo JL. Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children. Pediatr Allergy Immunol. 2013;2:151-9.
162. Kidon MI, Kang LW, Chin CW, Hoon LS, See Y, Goh A, Lin JT, Chay OM. Early presentation with angioedema and urticaria in cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs among young, Asian, atopic children. Pediatrics. 2005;116:675-80.
163. Pastorello EA, Zara C, Riario-Sforza GG, Pravettoni V, Incorvaia C. Atopy and intolerance of antimicrobial drugs increase the risk of reactions to acetaminophen and nimesulide in patients allergic to nonsteroidal anti-inflammatory drugs. Allergy. 1998;53:880-4.
164. Corzo JL, Zambonino MA, Muñoz C, Mayorga C, Requena G, Urda A, Gallego C, Blanca M, Torres MJ. Tolerance to COX-2 inhibitors in children with hypersensitivity to non-steroidal anti-inflammatory drugs. Br J Dermatol. 2014;170(3):275-9.
165. Ortega N, Castillo R, Blanco C, Carrillo T. Nimesulide and rofecoxib tolerance in patients with allergy to nonsteroidal anti-inflammatory drugs. Recent Res Del Allergy, Asthma & Immunol 1, Transworld Research Network. India. 2001. p.121-8.
166. Ortega N, Torres MJ, Almeida L, Navarro L, Carrillo T. Tolerancia a los nuevos inhibidores de la COX-2 en el asma y urticaria angioedema con intolerancia a los AINES. Alergol Inmunol Clin. 2002;17(2):30-34.
167. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. J Allergy Clin Immunol. 2006;118(4):773-86.
168. Kowalski ML, Makowska J. Use of nonsteroidal anti-inflammatory drugs in patients with aspirin hypersensitivity: safety of cyclo-oxygenase-2 inhibitors. Treat Respir Med. 2006;5(6):399-406.
169. Levy MB, Fink JN. Anaphylaxis to celecoxib. Ann Allergy Asthma Immunol. 2001;87:72-3.
170. Mastalerz L, Sanak M, Gawlewicz A, Gielicz A, Faber J, Szczeklik A. Different eicosanoid profile of the hypersensitivity reactions triggered by aspirin and celecoxib in a patient with sinusitis, asthma, and urticaria. J Allergy Clin Immunol. 2006;118(4):957-8.
171. Muñoz-Cano R, Bartra J, Vennera MC, Valero A, Picado C. Asthmatic reaction induced by celecoxib in a patient with aspirin-induced asthma. J Investig Allergol Clin Immunol. 2009;19:75-6.
172. Passero M, Chowdhry S. Cyclooxygenase-2 inhibitors in aspirin-sensitive asthma. Chest. 2003;123(6):2155-6.
173. Woessner KM, Simon RA, Stevenson DD. Safety of high-dose rofecoxib in patients with aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2004;93(4):339-44.
174. Stevenson DD, Simon RA. Selection of patients for aspirin desensitization treatment. J Allergy Clin Immunol. 2006;118:801-4.
175. Berges-Gimeno MP, Simon RA, Stevenson DD. Long term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2003;11:180-6.
176. White AA, Hope AP, Stevenson DD. Failure to maintain an aspirin-desensitized state in a patient with aspirin-

exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2006;97:446-8.
177. Rothe T, Acherman R, Hug J, Karrer W. Incomplete aspirin desensitization in an aspirin-sensitive asthmatic. Int Arch Allergy Immunol. 1996;109:298-300.
178. Dankner RE, Wedner HJ. Aspirin desensitization in aspirin-sensitive asthma: failure to maintain a desensitized state during prolonged therapy. Am Rev Respir Dis. 1983;128;953-5.
179. Stevenson DD, Simon RA. Sensitivity to aspirin and nonsteroidal anti-inflammatory drugs. In: Middleton E Jr, Ellis EF, Yunginger JW, Reed CE, Adkinson NF Jr, Busse WW, editor. Allergy: principles and practice. 5th ed. Vol 2. St Louis: Mosby; 1998. p.1225-34.
180. White AA, Stevenson DD, Simon RA. The blocking effect of essential controller medications during aspirin challenges in patients with aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2005;95:330-5.
181. Patriarca G, Bellioni P, Nucera E, Schiavino D, Papa G, Schinco G, Fais G, Pirotta LR. Intranasal treatment with lysine acetylsalicylate in patients with nasal polyposis. Ann Allergy. 1991;67:588-92.
182. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: a controlled trial. Laryngoscope. 2005;115:1385-90.
183. Ogata N, Darby Y, Scadding G. Intranasal lysine-aspirin administration decreases polyp volume in patients with aspirin-intolerant asthma. J Laryngol Otol. 2007;121:1556-60.
184. Stevenson DD. Aspirin Sensitivity and Desensitization for asthma and sinusitis. Curr Allergy Asthma Rep. 2009;9:155-63.
185. Dalmau G, Gaig P, Gázquez V, Mercé J. Rapid desensitization to acetylsalicylic acid in acute coronary syndrome patients with NSAIDs intolerance. Rev Esp Cardiol. 2009;62:224-30.
186. Lee JY, Simon RA, Stevenson DD. Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2007;119:157-64.
187. White AA, Stevenson DD. Side effects from daily treatment in patients with AERD: Identification and management. Allergy Asthma Proc. 2011;32:333-4.
188. Lee RU, Stevenson DD. Aspirin-exacerbated respiratory disease: evaluation and management. J Allergy Clin Immunol. 2011;3:3-10.
189. Berges-Gimeno MP, Simon RA, Stevenson DD. Long term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2003;11:180-6.
190. Klimek L, Pfaar O. Aspirin intolerance: does desensitization alter the course of the disease? Immunol Allergy Clin North Am. 2009;29:669-75.
191. Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. J Allergy Clin Immunol. 1996;98:751-8.
192. Sweet JM, Stevenson DD, Simon RA, Mathison DA. Long-term effects of aspirin desensitization treatment for aspirin sensitive rhinosinusitis/asthma. J Allergy Clin Immunol. 1990;85:59-65.
193. Forer B, Kivity S, Sade J, Landsberg R. Aspirin desensitization for ASA triad patients – a prospective study of the rhinologist's perspective. Rhinology. 2011;49;95-100.
194. Wong JT, Nagy CS, Krinzman SJ, Mac Lean JA, Blosch KJ. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. J Allergy Clin Immunol. 2000;105:997-1001.
195. Mathison DA, Lumry WR, Stevenson DD, Curd JG. Aspirin in chronic urticaria and/or angioedema: Studies of sensitivity and desensitization. J Allergy Clin Immunol. 1982;69:135.

Manuscript received February 26, 2014; accepted for publication April 22, 2014.

Nancy Ortega

Allergy Service
HU de Gran Canaria Dr Negrín
Bco de la Ballena, s/n
35010 Las Palmas de Gran Canaria, Spain
E-mail: nortrod@gobiernodecanarias.org

