



# Angioedema associated with nonsteroidal anti-inflammatory drugs

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## Purpose of review

The review critically assesses the different phenotypes of angioedemas associated with NSAIDs. Angioedemas exacerbated or induced by NSAIDs have high morbidity and, when they affect the larynx, can lead to death by asphyxiation.

## Recent findings

Angioedema can present as a manifestation of a syndrome such as anaphylaxis or it can be a separate entity, which comprises different forms that can be diagnosed based on specific criteria. NSAIDs are the drugs most used worldwide and they are also one of the leading causes of angioedema.

## Summary

The manuscript addresses the pathophysiology and pharmacogenetics of angioedema, reviews its classification and assesses the diagnosis and management of angioedemas exacerbated and induced by NSAIDs.

## Keywords

Anaphylaxis, angioedema, hypersensitivity reactions, NSAIDs, urticaria

## INTRODUCTION

Hypersensitivity reactions (HSRs) induced by drugs are a subgroup of adverse drug reactions that are unexpected and characterized by objectively reproducible symptoms and/or signs initiated by exposure to a drug at a dose tolerated by normal individuals [1]. HSR can be classified in immediate and nonimmediate, based on the interval between drug exposure and onset of clinical manifestation. This classification intends to imply the pathophysiological mechanism involved in the reaction and it is best exemplified in the reactions to  $\beta$  lactams [2]. Immediate HSRs, those occurring within the first hour after drug exposure and involving mast-cell and basophil degranulation, are characterized by urticaria, angioedema, rhinoconjunctivitis, bronchospasm, and anaphylaxis [2,3].

NSAIDs are the drugs most used worldwide and they are also one of the leading causes of HSRs, including angioedema and anaphylaxis [4<sup>a</sup>,5,6]. Concerning NSAIDs, the classification of immediate and nonimmediate adverse drug reactions is more difficult to apply, as there are immunological and nonimmunological mechanisms involved and, in both categories, typical clinical manifestations of immediate reactions such as angioedema can appear

with intervals less than 1 h or longer. Some authors have proposed that the term 'immediate' for reactions involving mast-cell/basophil degranulation and presenting with urticaria, angioedema, bronchospasm, or anaphylaxis, should encompass manifestations occurring up to 6 h [7]. Here, we will use the term 'acute', as previously described, to name anaphylaxis type HSRs occurring immediately to several hours after drug exposure [8].

## HYPERSENSITIVITY REACTIONS ASSOCIATED WITH NSAIDs

HSRs associated with NSAIDs can be classified into two categories: the first one includes nonallergic reactions with a nonspecific immunological mechanism [cross-intolerant (CRI) responders], which

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KEY POINTS

- Angioedemas exacerbated or induced by NSAIDs are nosology entities associated with great morbidity and when they affect the larynx can lead to death by asphyxiation.
- Angioedemas exacerbated or induced by NSAIDs are frequent and underdiagnosed.
- Classification by endotype and phenotype improve angioedema diagnosis and treatment.

represent the most common type of reported reactions [9], and the second one includes allergic HSRs, in which a specific immunological mechanism is involved (selective responders), either IgE or T cell dependent [10–13]. According to clinical features, CRI patients can present acute HSRs with respiratory manifestations (asthma, rhinitis, and rhinosinusitis with nasal polyps) and/or cutaneous manifestations (urticaria and/or angioedema) [14].

Three main groups of acute HSRs associated with NSAIDs were described in the first classification systems: NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), and NSAID-induced urticaria and/or angioedema (NIUA). The NIUA was further divided in single (selective) and multiple (nonselective, CRI) NIUA [10,11]. Subsequently, some authors have suggested to call the single NSAID-induced urticaria/angioedema (single NIUA) phenotype as single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA), as patients belonging to this group have anaphylaxis more often than the ones from the multiple NSAID-induced urticaria/angioedema phenotype, which was renamed simply NIUA [15]. However, as both the single NIUA and the multiple NIUA phenotype can present anaphylaxis, we suggest for future classifications the replacement of these terms by SNIA (single NSAID-induced anaphylaxis type

reactions) and MNIA (multiple NSAID-induced anaphylaxis type reactions) (Table 1). To facilitate the incorporation of this classification in clinical practice, anaphylaxis-type reactions would include urticaria, angioedema, blended reactions, and anaphylaxis. Furthermore, even patients with NECD can present anaphylaxis triggered by NSAIDs.

The pathophysiology of angioedemas associated with NSAIDs is complex. Recently, groups in Spain reported selective multiple immediate responders to NSAIDs tolerating acetylsalicylic acid (ASA) [16,17]. These findings suggest that within SNIUA there would be selective reactors to a single drug or multiple selective reactors.

ANGIOEDEMA

Angioedema is a localized, self-limiting, asymmetric noninflammatory edema of the deep dermis, subcutaneous or submucosal tissues, as a result of vasodilation and increased vascular permeability. It can present as a manifestation of a syndrome such as anaphylaxis or it can be a separate entity, which comprises different forms that can be diagnosed based on specific criteria [18].

Two major pathophysiological mechanisms of angioedema have been described: one of them is induced by the activation of mast cells and/or basophils, resulting in release of histamine and other mediators (histaminergic angioedema), and the other because of excess of bradykinin (bradykinin-mediated or nonhistaminergic angioedema), as seen in hereditary angioedema, acquired angioedema with C1-inhibitor deficiency (acquired angioedema; associated with lymphoproliferative and autoimmune disorders), and in angioedema induced by angiotensin converting enzyme inhibitors or other drugs involved in bradykinin metabolism. Recently, a classification of angioedema by endotypes was proposed, providing insights into the cause and/or pathophysiological mechanism of the different types

Table 1. Classification of hypersensitivity reactions associated with nonsteroidal anti-inflammatory drugs

| Classification | Kowalski <i>et al.</i> [15]                                                     | Proposed in this review                                                |
|----------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Phenotypes     | NERD (NSAID-exacerbated respiratory disease)                                    | NERD (NSAID-exacerbated respiratory disease)                           |
|                | NECD (NSAID-exacerbated cutaneous disease)                                      | NECD (NSAID-exacerbated cutaneous disease)                             |
|                | NIUA (NSAID-induced urticaria/angioedema)                                       | MNIA (multiple NSAID-induced anaphylaxis type reactions <sup>a</sup> ) |
|                | SNIUAA (single NSAID-induced urticaria/angioedema or anaphylaxis <sup>b</sup> ) | SNIA (single NSAID-induced anaphylaxis type reactions)                 |
|                | SNIDR (single NSAID-induced delayed hypersensitivity reactions)                 | SNIDR (single NSAID-induced delayed hypersensitivity reactions)        |

<sup>a</sup>Anaphylaxis type reactions include anaphylaxis, urticaria, angioedema, and blended reactions.  
<sup>b</sup>New findings suggest that within SNIUA there would be selective reactors to a single drug or multiple selective reactors [16,17].  
Pink: cutaneous acute hypersensitivity reactions.

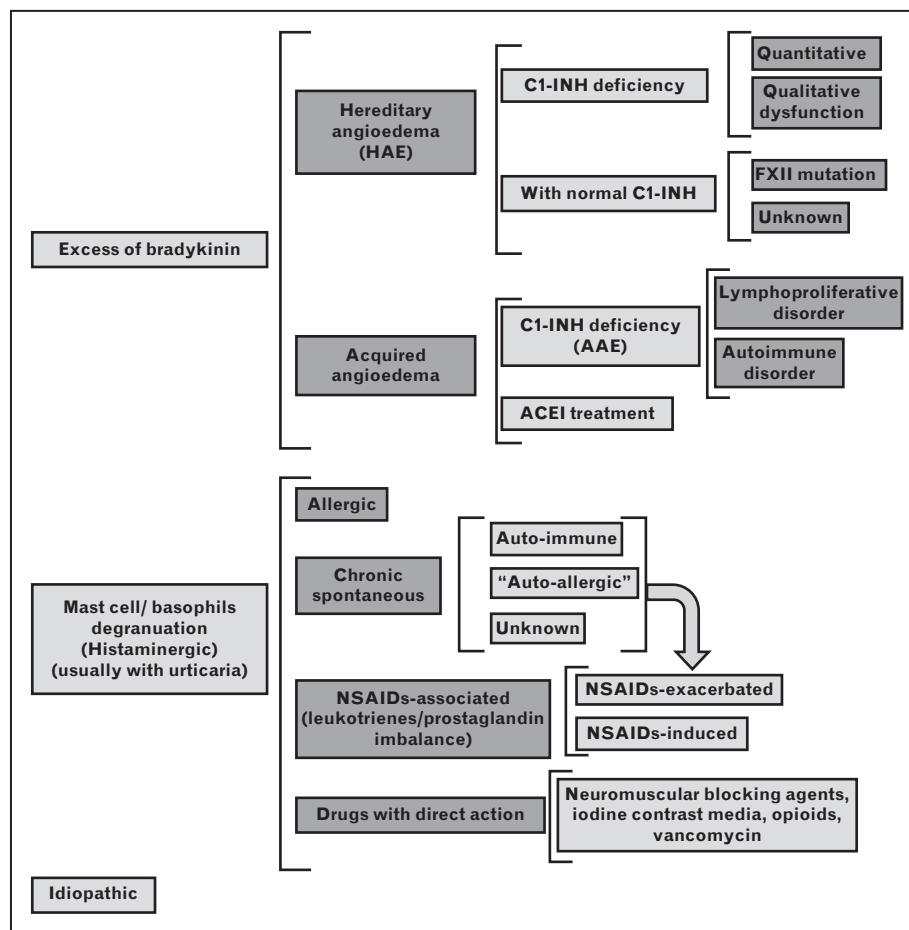


**FIGURE 1.** Classification of angioedema by endotypes. Adapted with permission [19<sup>a</sup>].

of this clinical entity (Fig. 1) [19<sup>a</sup>]. There are probably other types of angioedema, but at present the specific mechanism involved is not known.

The most frequent type of recurrent angioedema is histaminergic, which is usually associated with urticaria. It can be induced or exacerbated by the use of NSAIDs.

## **PATHOPHYSIOLOGY AND PHARMACOGENETICS**

Cutaneous manifestations (urticaria and/or angioedema) induced by NSAIDs can occur because of specific immunological mechanisms (allergy) or other mechanisms where drug is not recognized by specific immunological mechanisms. As mentioned before, patients who present with these clinical features or anaphylaxis because of a single group of NSAIDs (e.g. pyrazolones) are selective responders defined as SNIUAA [15]. These reactions would be allergic, mediated by IgE, with mast cells and basophil degranulation, in the same way as other classical type I HSRs defined by Gell and Coombs. Nevertheless, this allergic phenotype is less

frequent than NIUA, where the mechanism remains unclear. Available evidence suggests that, similarly to NERD and NECD, NIUA is induced by imbalance of the arachidonic acid pathway, but further studies are needed to confirm initial findings [15].

Although cutaneous reactions are considered the most common manifestations of HSRs associated with NSAIDs [14], respiratory involvement has long been the most well studied model. The underlying mechanism of these reactions has been associated with the inhibition of the prostaglandin endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase, PTGS-1 or COX-1) isoform in susceptible individuals (Fig. 2) [20]. This results in a deviation to the production of cysteinyl leukotrienes (CysLTs, including LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>), the byproducts of arachidonic acid metabolism, catalysed by 5-lipoxygenase (5-LO or ALOX5) and leukotriene C<sub>4</sub> synthase (LTC<sub>4</sub>S), which is over-expressed in basophils, mast cells, and eosinophils. In parallel, there is inhibition of prostaglandin E<sub>2</sub> (PTG-E<sub>2</sub>) production, a prostanoid inhibitor that can reduce the release of CysLTs and prostaglandin D<sub>2</sub> (PTG-D<sub>2</sub>) from activated mast cells [20]. This

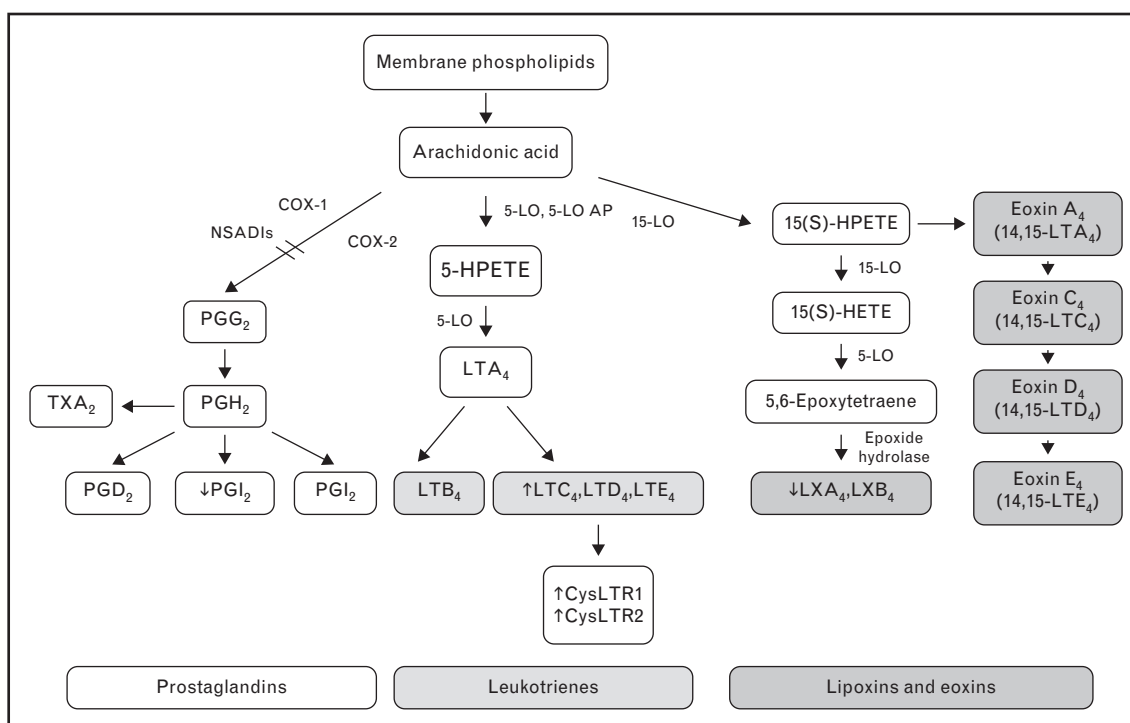


**FIGURE 2.** Arachidonic acid pathways with the generation of lipids and inflammatory mediators. Adapted with permission [20].

mechanism has also been suggested in the case of NECD [15,21]. On the other hand, mechanisms involved in NIUA are still under investigation.

Historically, most genetic association studies [20,22,23<sup>¶</sup>] have been performed in patients with NERD and NECD. However, interest in NIUA has been growing, probably because it has now been recognized as the most frequent clinical entity in NSAIDs hypersensitivity [14]. Nevertheless, most studies have been limited in scope, focusing on a limited number of genetic variants, and it is not always possible to replicate associations of independent studies [23<sup>¶</sup>]. Genetic research in HSR to NSAIDs, mainly on NERD, have started focusing on single-nucleotide polymorphisms (SNPs) in candidate genes related to the prostaglandin and leukotriene pathways, including LTC4S, ALOX5, ALOX5AP and in CysLT and PTG receptors [20]. Some studies started to evaluate patients with cutaneous reactions because of NSAIDs, but including patients with NECD and NIUA. Given the role of neutrophils in urticaria inflammation, a study [24] accessing the IL-18 gene polymorphism was published in 2011 and suggested that the high transcriptional activity haplotype *ht1* [CG] of the IL-18 gene might be associated with aspirin-induced urticaria. However, the authors included NECD and NIUA patients. It has been recently shown that these phenotypes can be different clinical entities and NIUA may not be a risk factor for chronic urticaria [25].

The first genetic work carried out exclusively in patients with NIUA was performed in Spain, with two populations from different regions (Malaga and Madrid) [20]. The authors evaluated 486 NIUA patients and 536 unrelated controls. Patients with respiratory symptoms, chronic urticaria, and selective responders were excluded. They included candidate SNPs from the arachidonic acid AA pathway based on the existence of previous evidence of associations between NSAIDs and HSR, asthma, atopy, and skin diseases. Blood testing from Malaga patients showed seven variants from six genes with nominal significance (rs1132340 at ALOX5AP, rs7220870 at ALOX15, rs8004654 at PTGDR, rs3810253 and rs3810255 at PTGER1, rs12545598 at PTGER2, and rs320995 at CYSLTR1). Then, to validate these findings, all seven nominally associated SNPs identified in the samples from Malaga were further assessed in samples from Madrid. This follow-up study confirmed three of the seven SNPs in one gene encoding an enzyme (rs7220870 at ALOX15) and in two genes encoding receptors (rs8004654 at PTGDR and rs320995 at CYSLTR1). At last, after a more conservative Bonferroni-like correction for multiple testing, only the rs320995 at CYSLTR1 remained statistically significant [20].

In 2013, another genetic study [26] in NIUA patients was carried out in two different populations. Performing a genome-wide association study, an alternative to the candidate-gene

approach, in collaboration with Asian investigators, the authors evaluated 232 ethnically distinct NIUA individuals (Spanish and Han Chinese). This was the first study in which genome-wide association study was carried out in cutaneous NSAIDs hypersensitivity. Although no polymorphism reached genome-wide significance, they found suggestive associations for three clusters in the Spanish group (*RIMS1*, *BICC1*, and *RAD51L1*) and one region in the Han Chinese population (*ABI3BP*). Furthermore, they performed a meta-analysis, which showed suggestive associations in five regions: *HLF*, *RAD51L1*, *COL24A1*, *GalNAc-T13*, and *FBXL7*. Most of these genes are related to  $\text{Ca}^{2+}$ , cAMP, and/or P53 signaling pathways. These data suggested the potential participation of other pathways in NIUA different from the arachidonic acid pathway, especially the possibility of a role for the second-messenger signaling [26].

CRI responders to NSAIDs and polymorphisms of the gene encoding the centrosomal protein of 68 KDa (CEP68) were assessed. The authors included patients with NIUA, NERD, and blended reactions (acute urticaria/angioedema and respiratory symptoms) [27]. They observed 17 variants associated with NIUA, including the nonsynonymous Gly74Ser variant (rs7572857), previously associated with aspirin hypersensitivity in asthmatics [28].

It has recently been shown that patients with NIUA can present with copy deletions of some genes considered to be involved in the arachidonic acid pathway [29]. Using TaqMan copy number assays, the existence of copy number variations of *ALOX5*, *LTC4S*, *PTGS1*, *PTGS2*, *PTGER1*, *PTGER2*, *PTGER3*, and *PTGER4* genes was assessed in 299 NIUA patients and 279 controls. Deletions in exonic regions of *ALOX5* and *PTGER1* (3.5 and 6.8%, respectively) were observed in patients, whereas no deletions were found in controls. Moreover, the presence of one copy loss in one of these genes can be accompanied by a copy loss in the other. These data also suggest some role of lipid metabolism in the development of NIUA [29].

Polymorphism of histamine receptor genes in NSAIDs hypersensitivity was also studied. Although histamine and its receptors are essential in the pathogenesis of CRI to NSAIDs and in the mast-cell activation because of specific IgE cross-linking, no major association of common genetic variations in histamine receptor genes (*HRH1*, *HRH2*, and *HRH4*) was found in CRI responders to NSAIDs [30].

These genetic studies suggested that pathogenesis of NIUA is not only related to the arachidonic acid pathway, but more complex mechanisms are probably involved. All manuscripts cited above assessed patients with CRI to NSAIDs, including

NERD, NECD, and NIUA individuals (Table 2). However, there are some researchers who believe that NIUA is not a unique phenotype [19<sup>o</sup>,32]. We have recently proposed a new classification of angioedema based on the mechanisms and mediators involved (Fig. 1). We also showed that in a Brazilian cohort of NIUA patients, isolated angioedema induced by NSAIDs was more common than urticaria, alone, or combined with angioedema [19<sup>o</sup>]. Professor Miguel Blanca's group evaluated NIUA patients according to clinical presentation: patients who only developed urticaria, patients who only developed angioedema, and those who developed both [31]. They analyzed the association between NIUA and SNPs in five genes related to mast-cell activation. Although several SNPs were more common in NIUA patients, the differences were not statistically significant. On the other hand, when patients were classified according to their clinical manifestation in those three groups, they observed several associations: *PLA2G4A* rs12746200 G allele (more common in urticaria patients than in controls), *PLCG1* rs2228246 A/G-G/G genotypes (less frequent in angioedema individuals than in controls), and *TNFRS11A* rs1805034 T/C-C/C genotypes (more frequent in urticaria and angioedema patients than in controls) [31]. These data are compatible with the hypothesis that NIUA is not a unique clinical entity, but it includes three different groups of individuals, who are distinct in phenotype and genotype. This hypothesis still needs further verification.

## DIAGNOSIS

In NSAIDs-induced angioedema, there are both patients who react to two or more therapeutic chemical groups of NSAIDs (nonallergic pathogenesis) or those that react to only one NSAID group, known as selective reactors (allergic pathogenesis presumably mediated by IgE). On the other hand, chronic spontaneous angioedema may be exacerbated by NSAIDs. The frequency appears to be greater the more active is the basic framework. These patients have angioedema even in the absence of NSAIDs, but when they take the drug the disease worsens. Therefore, three questions to be asked to the patient are crucial (Fig. 3): Has the patient presented with angioedema in the past after taking NSAIDs? Has the patient presented with angioedema in the past on one or several occasions even when not taking NSAIDs? Has the patient presented with angioedema in the past after taking different chemical groups of NSAIDs?

Skin prick and intradermal tests are indicated when there is a suspicion of an allergic immediate

**Table 2.** Genetic variants described in patients with nonallergic hypersensitivity reactions to nonsteroidal anti-inflammatory drugs

| SNP        | Gene                   | Allele/<br>Genotype | Biological action/<br>Pathway             | NIUA risk | Population              | Reference                |
|------------|------------------------|---------------------|-------------------------------------------|-----------|-------------------------|--------------------------|
| rs1132340  | ALOX5AP                | G                   | Arachidonic acid pathway                  | Decreased | Spanish                 | Cornejo-García 2012 [20] |
| rs7220870  | ALOX15                 | C                   | Arachidonic acid pathway                  | Decreased |                         |                          |
| rs8004654  | PTGDR                  | T                   | Arachidonic acid pathway                  | Increased |                         |                          |
| rs3810253  | PTGER1                 | G                   | Arachidonic acid pathway                  | Increased |                         |                          |
| rs3810255  | PTGER1                 | A                   | Arachidonic acid pathway                  | Increased |                         |                          |
| rs1254598  | PTGER2                 | A                   | Arachidonic acid pathway                  | Increased |                         |                          |
| rs320995   | Cys-LTR1               | C                   | Arachidonic acid pathway                  | Increased |                         |                          |
| rs2249625  | RIMS1                  | C                   | Ca <sup>2+</sup> channels                 | Increased | Spanish                 | Cornejo-García 2013 [26] |
| rs2496515  | RIMS1                  | Not cited           | Ca <sup>2+</sup> channels                 | Increased |                         |                          |
| rs282674   | BICC1                  | G                   | cAMP synthesis                            | Increased |                         |                          |
| rs282673   | BICC1                  | T                   | cAMP synthesis                            | Increased |                         |                          |
| rs3125447  | BICC1                  | C                   | cAMP synthesis                            | Increased |                         |                          |
| rs8008961  | RAD51L1                | A                   | DNA repair                                | Increased |                         |                          |
| rs3784099  | RAD51L1                | A                   | DNA repair                                | Increased |                         |                          |
| rs4928089  | ABI3BP                 | A                   | p53                                       | Increased | Han Chinese             |                          |
| rs12330531 | ABI3BP                 | T                   | p53                                       | Increased |                         |                          |
| rs1116931  | ABI3BP                 | A                   | p53                                       | Increased |                         |                          |
| rs9833094  | ABI3BP                 | T                   | p53                                       | Increased |                         |                          |
| rs4617927  | HLF                    | Not cited           | NSAID metabolism and lipids synthesis     | Increased | Spanish and Han Chinese |                          |
| rs1477141  | HLF                    | Not cited           | NSAID metabolism and lipids synthesis     | Increased |                         |                          |
| rs7148416  | RAD51L1                | Not cited           | DNA repair                                | Increased |                         |                          |
| rs3784099  | RAD51L1                | Not cited           | DNA repair                                | Increased |                         |                          |
| rs10873740 | COL24A1                | Not cited           | Inflammation                              | Increased |                         |                          |
| rs11161717 | COL24A1                | Not cited           | Inflammation                              | Increased |                         |                          |
| rs1324713  | Unknown (chromosome 1) | Not cited           | Unknown                                   | Increased |                         |                          |
| rs6702266  | Unknown (chromosome 1) | Not cited           | Unknown                                   | Increased |                         |                          |
| rs7565078  | GALNT13                | Not cited           | Mucins glycosylation                      | Increased |                         |                          |
| rs12693918 | GALNT13                | Not cited           | Mucins glycosylation                      | Increased |                         |                          |
| rs11748700 | FBXL7                  | Not cited           | Inflammation                              | Increased |                         |                          |
| rs4289558  | FBXL7                  | Not cited           | Inflammation                              | Increased |                         |                          |
| rs6728523  | CEP68                  | Not cited           | Epidermal growth factor signaling pathway | Decreased | Spanish                 | Cornejo-García 2014 [27] |
| rs2302647  | CEP68                  | Not cited           | Epidermal growth factor signaling pathway | Decreased |                         |                          |
| rs2901749  | CEP68                  | Not cited           | Epidermal growth factor signaling pathway | Decreased |                         |                          |

**Table 2** (Continued)

| SNP         | Gene     | Allele/<br>Genotype | Biological action/<br>Pathway             | NIUA risk           | Population | Reference             |
|-------------|----------|---------------------|-------------------------------------------|---------------------|------------|-----------------------|
| rs2080385   | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs75678687  | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs79157909  | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs7572857   | CEP68    | A                   | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs17849707  | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs12621608  | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs76221156  | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs1894874   | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs113359765 | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs6546125   | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs78945874  | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs1050675   | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs1229      | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs61758846  | CEP68    | Not cited           | Epidermal growth factor signaling pathway | Decreased           |            |                       |
| rs12746200  | PLA2G4A  | G                   | Mast-cell activation                      | Increased (UT)      | Spanish    | Ayuso 2015 [31]       |
| rs2228246   | PLCG1    | A/G, G/G            | Mast-cell activation                      | Decreased (AE)      |            |                       |
| rs1805034   | TNFRS11A | T/C, C/C            | Mast-cell activation                      | Increased (UT + AE) |            |                       |
| None        | ALOX5    | Deletion            | Arachidonic acid pathway                  | Increased           | Spanish    | Plaza-Serón 2016 [29] |
| None        | PTGER1   | Deletion            | Arachidonic acid pathway                  | Increased           |            |                       |

AE, Angioedema; NIUA, NSAID-induced urticaria and/or angioedema; UT, Urticaria.

HSR in patients with SNIUAA, although there are only preliminary studies supporting these tests and their predictive values are unknown [12]. Case reports in the literature describe the concentrations

of dipyrone, diclofenac, and paracetamol, among others, to be applied in the skin tests [33–35]. Drug provocation test (DPT) is the gold standard for the diagnosis of HSR to drugs when the clinical history is

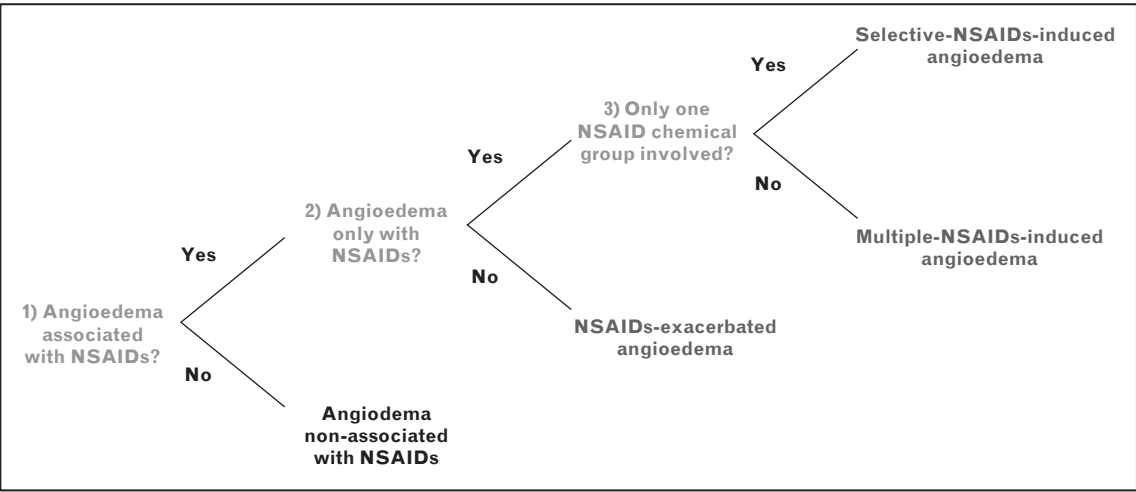


**FIGURE 3.** Crucial questions to be asked to the patient with angioedema induced by NSAIDs.

not definitive, and it is the only available test to [36]: confirm the diagnosis of NECD and NIUA; differentiate single NIUA and multiple NIUA. DPT usually should be done in a single blind placebo controlled manner with ASA. If ASA is involved in the HSR according to the clinical history, another potent COX-1 inhibitor such as ibuprofen or diclofenac should be used in the DPT.

**MANAGEMENT**

The treatment of angioedema has two main objectives: to identify a possible cause and to control the disease activity. In NSAID-induced or exacerbated angioedema, patients should be educated, through written brochures, on how to avoid these medications (Table 3). In NIUA and SNIUAA, drug avoidance keeps the patient asymptomatic. In NECD, drug

|                                                                                                                                                                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Table 3.</b> Example of brochure to guide patients with angioedema exacerbated or induced by multiple nonsteroidal anti-inflammatory drugs. The brochure should be adapted to each country and can cite the trade names for each drug |
| Orientation for patients with hypersensitivity/intolerance to nonsteroidal anti-inflammatory drugs (used as anti-inflammatory, antipyretic, and analgesic drugs).                                                                        |
| Avoid nonsteroidal anti-inflammatory drugs:                                                                                                                                                                                              |
| Which belong to the following groups:                                                                                                                                                                                                    |
| Salicylic acid derivatives: acetylsalicylic acid (ASA, aspirin), diflunisal                                                                                                                                                              |
| Pyrazolones: dipyrone (metamizole), Fenylbutazone                                                                                                                                                                                        |
| Indole derivatives: indometacin, etodolac                                                                                                                                                                                                |
| Anthranilic acids: mefenamic acid                                                                                                                                                                                                        |
| Arylpropionic acids: ibuprofen, naproxen, ketoprofen                                                                                                                                                                                     |
| Enolic acids: piroxicam, tenoxicam, meloxicam                                                                                                                                                                                            |
| Heteroaryl acetic acids: diclofenac, aceclofenac                                                                                                                                                                                         |
| Pyrrole derivatives: ketorolac, etodolaco                                                                                                                                                                                                |
| Sulphonanilides: nimesulide                                                                                                                                                                                                              |
| Medicine compounds containing nonsteroidal anti-inflammatory drugs (used for cold, flu, pain, headache, cramps, and dyspepsia, between other indications)                                                                                |
| Nonsteroidal anti-inflammatory drugs that are usually tolerated and can be taken after specialist consultation:                                                                                                                          |
| Nonsteroidal anti-inflammatory drugs:                                                                                                                                                                                                    |
| Para-aminophenol derivatives: acetoaminofen or paracetamol. Take a maximum of 500 mg per dose                                                                                                                                            |
| Coxibs: celecoxib, etoricoxib                                                                                                                                                                                                            |
| Benzydamine                                                                                                                                                                                                                              |
| Medicine compounds containing paracetamol, coxibs, or benzydamine (used for cold, flu, pain, headache, cramps, and dyspepsia, between other indications)                                                                                 |
| Corticosteroids, which are steroidal anti-inflammatory drugs, are allowed                                                                                                                                                                |

avoidance decreases disease activity and improves quality of life, but patients will continue to manifest occasional episodes of angioedema.

In NECD and NIUA, patients should avoid all the NSAIDs that are COX-1 inhibitors. Most patients will tolerate paracetamol (acetaminophen) and COX-2 inhibitors (coxibs), and these drugs can be prescribed, except in patients with history of HSR to these drugs or severe HSR such as anaphylaxis to NSAIDs, when DPT should be performed. In SNIUAA, patients should only avoid the drug that induced the HSR and the NSAIDs that belong to the same chemical group. If long-term NSAIDs use is needed, patients can be desensitized [37].

## CONCLUSION

Angioedemas exacerbated or induced by NSAIDs are entities associated with great morbidity and when they affect the larynx can lead to death by asphyxiation. Although they are frequent, they are poorly recognized and mistreated by general physicians. There is still room to advance in the nomenclature and classification of NSAID-associated angioedemas. Further studies are needed to better clarify their pathophysiology and management.

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Statement of contribution

All authors meet the three conditions:

- 1) Substantial contributions to conception of the review.
- 2) Drafting the article and revising it critically for important intellectual content.
- 3) Final approval of the version to be published.

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## Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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Revision about drug desensitization.