

Aspirin and Nonsteroidal Antiinflammatory Drugs Hypersensitivity and Management



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KEYWORDS

- Aspirin • Nonsteroidal antiinflammatory drugs • Chronic spontaneous urticaria
- Aspirin-exacerbated respiratory disease • Desensitization • Oral challenge

KEY POINTS

- Hypersensitivity reactions to aspirin and nonsteroidal antiinflammatory drugs (NSAIDs) are common, and the allergist must carefully elicit the history when these drugs could be the cause.
- Desensitization protocols are an option for most causes of hypersensitivity reactions. Oral challenges can be equally useful to identify safe alternatives.
- Cyclooxygenase-2-specific medications are often well-tolerated in the NSAID- or aspirin-allergic patient.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) are a group of pharmaceuticals primarily used for analgesic purposes with the exception of acetylsalicylic acid (aspirin [ASA]) whose primary use is for its antiplatelet effect. The availability of these medications over the counter, combined with their often first-line use in most types of pain and fever, make them one of the most popular classes of medications used worldwide. The use of ASA for primary and secondary prevention of cardiovascular disease significantly increases the global use of this medication class. In 2005, 19.3% of adult Americans took ASA daily or every other day.¹ Although the prevalence of hypersensitivity to NSAIDs may be low, the sheer volume of use and exposure makes

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consultation to the allergist for a reaction to one of these medications a relatively common occurrence.

The existence of several types of hypersensitivity reactions can make the approach to these patients somewhat challenging. Yet, hypersensitivity reactions can be most effectively compartmentalized into pharmacologic (secondary to cyclooxygenase-1 [COX-1] inhibition) or a specific (likely IgE) mediated effect. The presence of reactions to more than one structurally dissimilar NSAID will greatly inform the clinician to the presence of a COX-1 based hypersensitivity reaction.

Several specific reaction phenotypes have been described² and will be outlined below, and discussed throughout the article in finer detail.

1. *NSAID-exacerbated cutaneous disease (NECD)*: Sensitivity to all COX-1-inhibiting NSAIDs in the setting of active chronic spontaneous urticaria (pharmacologic effect of COX-1 inhibition).
2. *NSAID-induced urticaria/angioedema (NIUA)*: These patients have no underlying chronic urticaria, but experience cutaneous symptoms with all COX-1-inhibiting NSAIDs.
3. *Single NIUA, anaphylaxis, or both*: Patients experience cutaneous or systemic anaphylactic reactions isolated to a single NSAID.
4. *ASA-exacerbated respiratory disease (AERD)*: A complex pharmacologic effect of COX-1 inhibition leading to primary respiratory hypersensitivity reactions. This occurs with all COX-1-inhibiting NSAIDs.
5. *Non-mast cell-related* (drug rash with eosinophilia and systemic symptoms, aseptic meningitis etc): These involve immune reactions do not depend on mast cell involvement and will not be specifically addressed further.

As would be true for any consultation for a drug allergy, the differentiation of immunologic hypersensitivity from adverse drug effect becomes paramount. NSAIDs are well-known for effects on the gastrointestinal tract. These reactions can vary from annoying to severe, with severe gastritis potentially being inaccurately labeled as an “allergy” in the electronic health record.³

NONSTEROIDAL ANTIINFLAMMATORY DRUG HYPERSENSITIVITY ENDOTYPES AND MECHANISMS

ASA had been in clinical use since 1899 when Bayer began marketing it. Yet, it was not until John Vane published the first study of prostaglandin inhibition by ASA in 1971⁴ that the pharmacology of NSAIDs became defined. The ensuing decades saw significant progress to the point we are today with numerous COX-1 and COX-2 selective agents on the market. Nonspecific NSAIDs can have action at both COX-1 and COX-2. COX-1 has a constitutive “housekeeping” function in endothelium, kidney, and stomach as well as other locations.⁵ Yet, it is most likely that the benefits of the NSAID class are related to the effect on COX-2, which is an inducible enzyme at the site of inflammation. COX-2 inhibition can decrease localized prostaglandin formation therefore improving pain and swelling. It is now felt likely the most common side effects of NSAIDs (gastritis, increased thrombosis potential, etc) are related to the NSAID effects on COX-1.

One potential pitfall for the clinician might be to dichotomize this class of drugs into COX-1 versus COX-2 inhibitors. Although this fits into the general paradigm of hypersensitivity reaction phenotypes that can be seen, it also may be overly simplified. A better understanding of NSAID function in and around COX-1 and COX-2 might help to inform reaction phenotypes that do not also fit into a classic pattern. In that

regard, 4 broad groups have been described within the NSAID family (**Box 1**). First, there are compounds that produce full inhibition of both COX-1 and COX-2 with poor selectivity. Second are compounds that fully inhibit COX-1 and COX-2 with preferential COX-2 activity. A third group strongly inhibits COX-2 with minimal activity at COX-1, and finally, there are compounds that only weakly act at both COX 1 and COX-2.⁵

PREVALENCE

It is somewhat difficult to pinpoint a precise NSAID hypersensitivity prevalence estimate because the various subtypes of hypersensitivity discussed make it challenging to identify in the general population. Furthermore, some reactions only occur within a specific defined disease population (AERD in nasal polypsis and NECD in chronic urticaria), making it less relevant to describe global prevalence. Yet, with millions of Americans using an NSAID on a regular basis, it is important to understand the scope of the problem that allergists encounter. In nearly all subtypes of drug allergy, NSAIDs are a common cause.

In a Latin American study, of confirmed cases of drug-induced anaphylaxis, 57.8% were secondary to an NSAID.⁶ In 806 patients with adverse drug reactions, anaphylaxis was identified in 14.5%. NSAIDs represented the most frequent cause.⁷ In

Box 1

List of NSAIDs classified by effects on COX-1 and COX-2

NSAIDs that fully inhibit COX-1 and COX-2

- Aspirin
- Piroxicam
- Sulindac
- Ibuprofen
- Ketorolac
- Naproxen
- Ketoprofen
- Indomethacin
- Diclofenac

Preferential COX-2 inhibitors with partial COX-1 inhibition

- Etodolac
- Meloxicam
- Nimesulide^a
- Nabumetone

Primary COX-2 inhibitors with little action at COX-1

- Rofecoxib^a
- Etoricoxib^a
- Valdecoxib^a
- Lumiracoxib^a
- Celecoxib

Weak inhibitors of both COX-1 and COX-2

- 5-ASA
- Acetaminophen
- Diffunisal
- Sulfasalazine

Abbreviations: COX, cyclooxygenase; NSAIDs, nonsteroidal antiinflammatory drugs.

^a Not available in the United States.

cutaneous drug reactions in the outpatient clinic, NSAIDs were the second most common cause behind antimicrobials.⁸ NSAID induced adverse cutaneous drug reactions in Chinese inpatients caused 18.5% of all drug induced reactions and were the third most common behind antimicrobials and radiocontrast media.⁹

Ortiz-Sanjuán and colleagues¹⁰ evaluated 239 patients with drug-induced cutaneous vasculitis and identified the cause as NSAIDs in 10% (second only to beta-lactams). In Brazil, 10.5% of severe cutaneous adverse reactions were secondary to analgesic or antiinflammatory drugs.¹¹

It would seem that, globally, in any case of a suspected hypersensitivity reaction, a specific and focused history on NSAID exposure is imperative. The fact that many of these medications are available over the counter and will not necessarily show up on pharmacy or medical records adds to the importance of inquiring specifically about these medications.

NONSTEROIDAL ANTIINFLAMMATORY DRUG-EXACERBATED CUTANEOUS DISEASE

Patients with chronic spontaneous urticaria who experience an exacerbation of their underlying urticaria and/or angioedema with COX-1 inhibitors are defined as having NECD.¹²

Clinical Presentation of Nonsteroidal Antiinflammatory Drug-exacerbated Cutaneous Disease

In patients with chronic spontaneous urticaria, approximately 12% to 30% will experience an exacerbation of their urticaria and/or angioedema with minutes to hours of exposure to COX-1-inhibiting NSAIDs.^{13,14} As seen in AERD, individuals with NECD react to all COX-1-inhibiting NSAIDs and, despite avoidance of NSAIDs, the underlying disease process continues (ie, avoidance of COX-1-inhibiting NSAIDs will not ameliorate their chronic urticaria).¹⁵ In general, the highly selective COX-2 inhibitors are well-tolerated.^{16,17} The sensitivity to NSAIDs can fluctuate over time and, in general, during periods of remission of their chronic urticaria, all NSAIDs are well-tolerated.¹⁸

Diagnosis of Nonsteroidal Antiinflammatory Drug-exacerbated Cutaneous Disease

The single criterion for diagnosing NECD is flare of their underlying chronic urticaria with NSAID exposure.

Controversy

For the patient who has chronic urticaria and needs an NSAID, determining whether or not they will tolerate one necessitates conducting a challenge. There are many variables that can lead to worsening urticaria in chronic urticaria, such as viral infections, physical factors, and hormones, thus making it difficult to rely on history for making the diagnosis of NECD. Therefore, oral ASA challenge is the gold standard for making the diagnosis. The European guidelines recommend doing a 2-day placebo controlled ASA challenge after the patient has been without any eruption for 1 to 2 weeks.¹⁹ A problem with that approach is that their chronic urticaria will be in remission and they may no longer be reactive.¹⁸ Another approach would be to withdraw the patient from antihistamines to do the challenge; however, the interpretation of the challenge is complicated by the question as to whether the ASA triggered the urticarial flare or was it the withdrawal of the antihistamines. Taking an example from a study looking at food additives in chronic urticaria, using the minimum effective dose of antihistamine to control the urticaria but still having some symptoms, an NSAID challenge can be performed while the urticaria is active.²⁰

Management of Nonsteroidal Antiinflammatory Drug-exacerbated Cutaneous Disease

Avoidance of NSAIDs is the cornerstone of management of NECD. The highly selective COX-2 inhibitors are generally well-tolerated in this patient population.^{16,17} When the chronic urticaria is quiescent, the majority of patients will be able to once again tolerate the COX-1-inhibiting NSAIDs. Often these patients and their providers believe they are hypersensitive to NSAIDs going forward and they unnecessarily avoid these medications. It is useful to rechallenge with ASA once the chronic urticaria is not active. Some patients with chronic urticaria have relapses episodically; it is likely that their sensitivity to NSAIDs will recur with subsequent flares of chronic urticaria.

Nonsteroidal Antiinflammatory Drug-exacerbated Cutaneous Disease and the Role of Aspirin Desensitization

If there is a need for ASA in chronic urticaria for cardioprotective reasons, the 81-mg dose is often below the provoking dose for exacerbating urticaria.²¹ Therefore, it is worth challenging with 40.5 mg of ASA on their maintenance dose of chronic urticaria therapy and repeat in 90 minutes. If tolerated, start ASA 81 mg/d²² (Fig. 1).

If they react to ASA, it is the authors' clinical experience that ASA desensitization is rarely successful in patients with NECD. Simon²³ reported attempts to desensitize 25 patients to ASA with a history of chronic urticaria and NECD. These patients developed marked worsening of urticaria, not responsive to antihistamines, and required

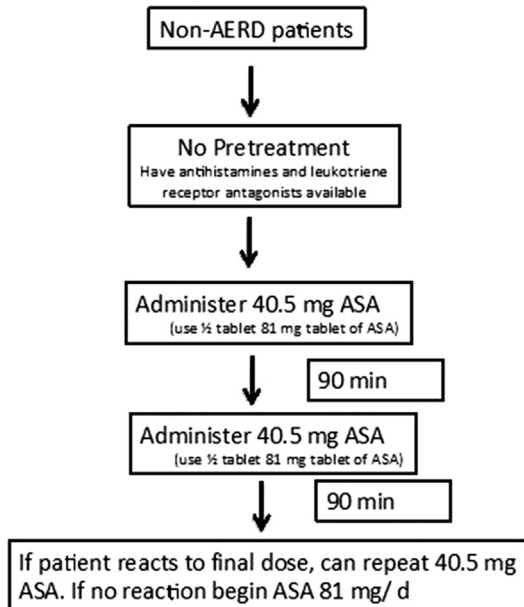


Fig. 1. Protocol for oral aspirin (ASA) challenge in patients with a history of cutaneous reactions to nonsteroidal antiinflammatory drugs. to get to 81 mg antiplatelet dose. Symptoms should be treated with antihistamines; if severe symptoms occur, treat and repeat the dose. Once tolerant can start 81 mg/d of aspirin. AERD, aspirin-exacerbated respiratory disease. (From White AA, Stevenson DD, Woessner KM, et al. Approach to patients with aspirin hypersensitivity and acute cardiovascular emergencies. *Allergy Asthma Proc* 2013;34(2):141; with permission.)

prednisone. Rechallenge with ASA met with the same reaction.²³ There are several case reports of successful desensitization to ASA in NECD, but these are isolated reports suggesting that attempts to desensitize even with high-dose antihistamines are not successful in the majority of cases.^{24,25}

NONSTEROIDAL ANTIINFLAMMATORY DRUG-INDUCED URTICARIA/ANGIOEDEMA

These patients have no underlying chronic skin disease but develop urticaria and/or angioedema within minutes to hours after ingesting COX-1 inhibiting NSAIDs. NSAID-induced angioedema (often periorbital) without urticaria can be seen sometimes developing up to 24 hours after exposure.^{26–28} It was originally suggested that NIUA was a precursor to developing chronic urticaria, preceding its development by years.²⁹ However, a more recent study found that the percentage of patients with NIUA who developed chronic urticaria was not different from that among healthy control subjects.³⁰ Patients with NIUA react to chemically unrelated COX-1 inhibitors, suggesting the pathogenesis is due to COX-1 inhibition, similar to AERD.

Diagnosis of Nonsteroidal Antiinflammatory Drug-induced Urticaria/Angioedema

A history of skin reactions to at least 2 chemically unrelated NSAIDs in patients without underlying chronic cutaneous disease have a high likelihood of having NIUA.^{28,30} If the history is not clear, then an oral challenge with ASA is recommended to confirm the diagnosis of a cross-reactive type of NSAID hypersensitivity as well as to differentiate it from single NIUA.³¹

Management of Nonsteroidal Antiinflammatory Drug-induced Urticaria/Angioedema

If no NSAIDs are required, a simple management strategy is avoidance of strong COX-1 inhibitors. In general, the highly selective COX-2 inhibitors and weak COX-1 inhibitors (acetaminophen and paracetamol) are well-tolerated.^{16,17}

Aspirin Desensitization in Nonsteroidal Antiinflammatory Drug-Induced Urticaria/Angioedema

Unlike NECD, if ASA or other NSAIDs are required, these patients can undergo successful desensitization^{21,22,32} (see **Fig. 1**; **Fig. 2**). The clinical experience of the authors' is that these desensitizations can sometimes be challenging and may require multiple days to be successful. The addition of antihistamines and antileukotrienes are helpful until tolerance is established. As with AERD, when desensitized with ASA, they are cross-desensitized to all COX-1-inhibiting NSAIDs, which can be maintained with daily dosing.

A recent longitudinal study by Doña and colleagues³³ found that 63% of patients lost their sensitivity to NSAIDs and could tolerate them at 72 months after the last reaction. This stresses the importance of reassessment periodically to prevent the unnecessary avoidance of ASA or other NSAIDs.

SINGLE NONSTEROIDAL ANTIINFLAMMATORY DRUG-INDUCED URTICARIA/ANGIOEDEMA, ANAPHYLAXIS, OR BOTH

This NSAID hypersensitivity classification is characterized by wheals, angioedema and/or anaphylaxis triggered by a single NSAID or by 2 or more NSAIDs with a similar chemical structure.³⁴ Any of the following clinical manifestations may be observed after oral, topical, or injected exposure to a single NSAID: urticaria, angioedema, laryngeal edema, generalized pruritus, rhinitis, bronchospasm, anaphylaxis, and even

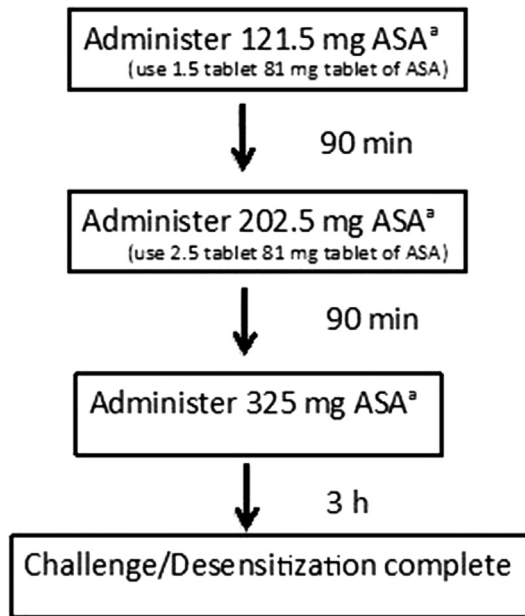


Fig. 2. Protocol for increasing the aspirin (ASA) dose from 81 mg to 325 mg. Symptoms should be treated if they occur. ^a If severe symptoms occur at any dose, that dose should be repeated before proceeding to final dose. (From White AA, Stevenson DD, Woessner KM, et al. Approach to patients with aspirin hypersensitivity and acute cardiovascular emergencies. *Allergy Asthma Proc* 2013;34(2):142; with permission.)

death can occur.^{35,36} Reactions to a single NSAID are seen most commonly with the pyrazolone class followed by acetaminophen, paracetamol, diclofenac, and ibuprofen.^{37–41}

Diagnosis of Single Nonsteroidal Antiinflammatory Drug-Induced Urticaria/Angioedema

Diagnosing single NSAID reactors can be challenging. With the exception of pyrazolones, there are no standardized skin tests or in vitro assays. Relying on the patient's history is unreliable, as was shown in a study by Viola and colleagues,⁴² in which they assessed NSAID hypersensitivity in 275 patients with a history of an NSAID reaction with provocation tests. Despite a history of reacting to an NSAID, 77.8% of their subjects tolerated that NSAID in an oral challenge (patients with AERD were excluded).⁴²

In the absence of a reliable in vitro test, an accurate diagnosis depends on a careful history and oral drug challenge and provocation testing. In patients with a history of anaphylaxis or a very severe reaction, an oral provocation test with the suspect drug should almost never be performed because alternative NSAIDs are readily available.³⁴

Management of Single Nonsteroidal Antiinflammatory Drug-Induced Urticaria/Angioedema

Once the culprit NSAID is identified in single NSAID reactors, management involves avoidance of that drug and others that are chemically related (**Box 2**). Desensitization is not recommended because the multiple other NSAID alternatives on the market

Box 2 List of NSAIDs classified by physical structure
<i>Enolic acids</i>
Oxicams
Piroxicam (Feldene)
Pyrazoles
Phenylbutazone (Butazolidin)
Oxyphenbutazone (Tandearil)
<i>Carboxylic acids</i>
Salicylates
Acetylsalicylic acid (aspirin)
Salsalate (Disalcid)
Difunisal (Dolobid)
Choline salicylate (Trilisate)
Acetic acids
Indomethacin (Indocin)
Etodolac (Lodine)
Sulindac (Clinoril)
Tometin (Tolectin)
Zomepirac (Zomax)
Diflofenac (Voltaren)
Fenamates
Meclofenamate (Meclomen)
Mefenamic acid (Ponstel)
Pyrrolo-pyrrole
Ketorolac tromethamine (Toradol)
Propionic acids
Ibuprofen (Motrin, Rufen)
Naproxen (Naprosyn)
Naproxen sodium (Anaprox)
Benoxaprofen (Oraflex)
Fenoprofen (Nalfon)
Ketoprofen (Orodis)
<i>Abbreviation:</i> NSAIDs, nonsteroidal antiinflammatory drugs.

make substitution of a COX-2 or structurally dissimilar NSAID a better option in almost all cases.

ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Clinical Characteristics

AERD, a specific subtype of chronic rhinosinusitis and asthma, is characterized by chronic eosinophilic sinonasal and lower airway inflammation with severe and recurrent nasal polyposis, asthma, and acute exacerbations of upper and lower respiratory symptoms when exposed to ASA or other COX-1-inhibiting NSAIDs. AERD occurs in roughly 7% of asthmatics, although the prevalence is 1 in 8 of those with severe asthma. It occurs in roughly 9% of patients with chronic rhinosinusitis, and one-third of those with asthma and nasal polyposis.⁴³

A recent survey of 190 participants with AERD showed that the impact of AERD on quality of life is substantial.⁴⁴ Using a scale of 1 (mild) to 9 (severe), the mean score

was 6, with roughly 28% of patients reporting either an 8 or 9. When asked to identify the one aspect that most reduced their quality of life, chronic nasal symptoms and anosmia were most common, reported in 43% and 39% of respondents, respectively. Further, 87% and 89% of patients reported that chronic nasal symptoms and a decreased sense of smell decreased their quality of life, which compared with only 65% reported chronic asthma symptoms.

It is increasingly recognized that alcohol ingestion also induces respiratory symptoms in patients with AERD. A survey of 59 patients with AERD (confirmed by a positive reaction to a supervised ASA challenge) found that 75% reported upper respiratory reactions (rhinorrhea or nasal congestion) and 51% reported lower respiratory reactions (wheezing or dyspnea) with ingestion of only a few sips of alcohol.⁴⁵ Overall, 83% of patients with AERD reported alcohol-induced respiratory symptoms, compared with 43% of patients with ASA-tolerant asthma and 43% of patients with nasal polyps (with ASA tolerance). The etiology of this phenomenon is yet to be elucidated, but the authors theorize that alcohol-induced reactions occur by altered production or metabolism of cysteinyl leukotrienes, the putative mediators of ASA-induced reactions.

Not only are daily symptoms contributing to the morbidity of AERD, but the aggressive nature of the inflammation tends toward more severe outcomes in both the upper and lower airways. Patients with AERD are at a 10-fold greater risk for sinus surgery and have much higher rates of recurrence 6 months after surgery.⁴⁶ In terms of lower airway involvement, patients with AERD are much more likely to have persistent airflow limitation, to have been intubated for asthma, to have had an asthma exacerbation in the past year, and to require systemic corticosteroids when compared with ASA-tolerant asthmatics.^{47–49}

Pathogenesis of Aspirin-Exacerbated Respiratory Disease

The etiology of AERD is incompletely understood. AERD occurs typically in adulthood. Nasal and sinus symptoms typically precede lower airway disease, and the development of pulmonary symptoms is believed to indicate disease progression. Thus, the development of AERD is possibly the result of a combination of environmental insults and airway changes, likely in individuals with a yet-to-identified genetic susceptibility.

The molecular pathophysiology is characterized by an imbalance in proinflammatory and antiinflammatory mediators of the arachidonic acid signaling pathway. Particularly, the overproduction of inflammatory cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄, which are potent inducers of mucous production, bronchospasm, and airway edema,⁵⁰ and a reduction in the antiinflammatory prostaglandin E₂ (PGE₂) are believed to have central roles.

Mast Cells

Mast cell activation and marked tissue eosinophilia characterize airway inflammation in AERD. Degranulated mast cells are readily found in nasal polyps,^{51,52} and their presence does not depend on allergic sensitization.⁵³ Administration of ASA has shown to acutely increase mast cell granule contents (ie, tryptase and histamine) and eicosanoid mediators (ie, PGD₂) in the nasal passage.^{54–56} As a result, mast cell degranulation is believed to contribute to the acute symptoms of an ASA reaction. Supportively, mast cell-stabilizing medications, such as cromolyn sodium, have shown to prevent ASA-induced bronchoconstriction.^{57,58}

The mechanisms by which COX-1 inhibiting medications trigger mast cell degranulation are unknown, but likely involve reduction in PGE₂, an inhibitor of mast cell degranulation. AERD airway mast cells produce diminished levels of PGE₂ at

baseline.^{59,60} A further reduction of PGE₂ by COX-1 inhibition is likely central to the pronounced mast cell degranulation.^{59,61}

Additionally, activated mast cells are responsible for the production of prostaglandin D₂ (PGD₂), a proinflammatory arachidonic acid metabolite overrepresented in AERD airways at baseline and further increased during an ASA challenge reaction.^{55,62–64} PGD₂ causes airway bronchoconstriction and nasal congestion by dilatation of sinusoid vessels, which occurs mechanistically by increases in cyclic adenosine monophosphate tissue levels.^{63,65} PGD₂ mediates chemotaxis of eosinophils and newly described ILC2b.^{66,67} PGD₂ activates T2-delineated T cells, basophils, and monocytes via the CRTH2 receptor.⁶⁸ Finally, a failure of ASA desensitization has been recently associated with markedly higher levels of basal urine PGD₂ metabolite, termed PGD-M.⁶⁴

Eosinophils

Eosinophils comprise more than 60% of nasal polyp cell population, and can be found in mostly between the thickened basement membrane and epithelial cells.⁵¹ Patients with AERD have higher sinonasal and lower airway eosinophilia than patients with chronic rhinosinusitis with nasal polyps alone.⁵¹ Mast cells contribute to eosinophil chemotaxis into the airways by secretion of eosinophil chemoattractant factors eotaxin and IL-5,⁶⁹ providing a link between mast cell degranulation/activation and eosinophil infiltration, and perhaps the first step in polyp formation. Eosinophils alternatively act on mast cells, and the 2 cell types act reciprocally to guide and enhance each other's function, something that has recently been termed the "allergic effector unit."⁷⁰

Notwithstanding the paradigm that mast cells and eosinophils conspire to produce AERD airway inflammation, several studies have shown that it is the intensity of eosinophil infiltration of the sinuses and lungs, and not the presence of mast cells, that distinguishes AERD from ASA-tolerant asthma.^{71,72} Like mast cells, PGE₂ acts through receptor EP2 to inhibit eosinophil activation.⁷² PGE₂ production is suppressed, and expression of its receptor EP2 is diminished in AERD. COX-1-inhibiting enzymes further suppress PGE₂ production, overcoming inhibition thresholds of eosinophils.⁷² The breakthrough release of the PGE₂ 'brake' leads to a surge in cysteinyl leukotriene secretion by airway eosinophils, which mechanistically occurs by a dramatic upregulation in leukotriene C₄ synthase.⁷³ Platelets that are adherent to eosinophils in the inflammatory milieu and other leukocytes also express LTC₄ synthase and contribute to the surge in leukotriene production.⁷⁴ Further, there is recent evidence that impaired granulocyte protein kinase A synergizes with adherent platelets to dysregulate PGE₂-dependent suppression of 5-lipoxygenase activity.⁷⁵

As an alternative explanation to mast cell degranulation, this surge in cysteinyl leukotrienes produced by platelets and eosinophils is theorized to be the primary driver of bronchospasm. Supportively, drugs that inhibit leukotrienes are shown to increase FEV₁ after 6 weeks of therapy,⁷⁶ and blunt the decrease in FEV₁ in response to ASA ingestion.⁷⁷ Of note, mast cells in AERD have shown to modestly express LTC₄ synthase,⁷³ and are thought to be unlikely contributors to the "leukotriene surge."⁷² Yet, in 30 patients with ASA-tolerant asthma, it was mucosal mast cells, and not eosinophils, that were the dominate cells containing LTC₄ synthase.⁷⁸

Tissue Remodeling

Nasal polyps are edematous and fibromatous structures surrounded by a thick basement membrane, and demonstrate high rates of extracellular matrix breakdown and tissue remodeling. Nasal polyp tissues express high levels of matrix

metalloproteinases (MMPs).^{79,80} Matrix metalloproteinase-9 is secreted by activated mast cells with levels paralleling eosinophil cationic protein, an eosinophil matrix protein, and its activity upregulated by the presence of mast cell enzymes tryptase and chymase.⁸¹

The growth factor transforming growth factor-beta, which is secreted by mast cells, eosinophils, macrophages, and epithelial cells, causes fibroblastic proliferation, collagen production, and nasal polyp fibroblast expression of vascular endothelial growth factor.⁸² Transforming growth factor-beta enhances eosinophilic inflammation by augmentation of eotaxin production.^{83,84}

PGE₂, which has demonstrated an antiproliferative effect on nasal fibroblasts via the E prostanoid (EP2) receptor, may play a second important role in the prevention of nasal polyp growth. AERD nasal fibroblasts have demonstrated decreased expression of EP2 receptors and the ability to resist the antiproliferative effect of PGE₂.⁸⁵ Providing evidence that environmental insults and influences are responsible for development of AERD by way of epigenetic modification of DNA, histone acetylation at the EP2 promotor site has been shown to correlate with EP2 messenger RNA levels.

Aspirin Challenges and Diagnosis of Aspirin-Exacerbated Respiratory Disease

AERD reactions are prototypically described as acute worsening of upper and lower airway symptoms, most often an increase in nasal congestion with accompanying shortness of breath, wheezing and/or chest tightness within 2 to 3 hours of ingesting ASA or other NSAIDs. NSAID reactions are not mediated by IgE, and are believed to result from a chemical imbalance in arachidonic acid metabolites. Individual responses to NSAIDs can vary from mild pruritus and nasal congestion to life-threatening acute asthma exacerbation, with reaction characteristics and severity are dependent on intrinsic and extrinsic factors not yet fully understood.

A positive provocation challenge to ASA or NSAIDs in an individual with nasal polypoidosis and asthma makes the diagnosis of AERD. To date, there are no validated biomarkers to make the diagnosis.⁸⁶ Only 43% of ASA challenges result in bronchial reactions in those suspected to have AERD,⁸⁷ and the sensitivity is only 45% to 69% when a positive response is defined as decrease in the FEV₁ of 20% or greater.^{88–92} Further, with the increased use inhaled corticosteroids and leukotriene-modifying drugs before drug challenges and the transition to intranasal ketorolac with modified oral ASA challenge as a safe alternative to an oral ASA challenges, the number and severity of bronchial reactions and extrapulmonary reactions has decreased significantly.^{92–94}

Several recent studies have proposed a decrease in the FEV₁ of 15% or greater as a new diagnostic criterion for ASA positive response. The lowered criterion seems to improve sensitivity while maintaining a satisfactory specificity. Yet, if this criterion were used alone to make the diagnosis, it would miss many “reactors”; an estimated 65% of individuals reportedly experience eye and/or nasal symptoms alone.

Peak nasal inspiratory flow is another measure that has been used to quantify nasal reactions, where a decrease of greater than 25% is highly specific for a positive reactions.⁹⁰ Like the use of spirometry, peak nasal inspiratory flow is not sensitive and neglects other symptoms that indicate a positive allergic response, such as tearing, rhinorrhea, or pruritus. As a result, the determination of a positive challenge still depends on the clinical judgment of the supervising physician.

Recently, a composite score termed the 10-Symptom AERD Composite Score, based on patient yes or no responses to the presence of 10 clinical symptoms, has been developed to aid physicians in quantifying subjective complaints during an ASA challenge. Specifically, 1 point is awarded for each yes response to nasal

congestion, runny nose, itchy nose, sneezing, itchy or watery eyes, itchy tongue or mouth, throat tightness, and wheezing or chest tightness. Although not validated on an external cohort, an additive score of 5 or greater was moderately sensitive and highly specific in an internal cohort of 115 suspected patients with AERD.⁹⁵

Aspirin Desensitization for Aspirin-exacerbated Respiratory Disease

There are several methods described for ASA desensitization. The general recommendations for any patient undergoing ASA desensitization for AERD include ensuring that the underlying asthma is well-controlled before commencing the desensitization and using a leukotriene modifier drug during the desensitization unless there is a contraindication. It would seem obvious that an unstable asthmatic patient should not undergo a desensitization, which could worsen asthma further. This caution sometimes means that a patient requires a step up in asthma management or even a systemic corticosteroid burst before the desensitization. The use of leukotriene modifier drugs during the desensitization have been shown to have a significant effect on blunting the asthmatic reaction while preserving the upper airway reaction in most patients, allowing for the desensitization to serve a diagnostic purpose in those patients where the diagnosis of AERD is in doubt.^{94,96}

Initial desensitization protocols were often spread out over an entire week. When done exclusively under a research protocol, the first day generally included placebo challenges only to ensure stable airways. In the past decade, the desensitization setting has migrated to the outpatient and nonresearch setting. This change has generated interest in accelerating the desensitization, while preserving the excellent safety record of ASA desensitization. Lee and colleagues⁹² described the use of nasal ketorolac in an effort to diminish lower respiratory reactions and increase the speed of the desensitization (**Table 1**). Many institutions use an oral ASA protocol with approximately 90-minute dosing intervals. Both the nasal ketorolac and the oral ASA protocols involved more than 1 clinic day to accomplish; with most patients finishing on day 2 and some on the third day. Chen and colleagues⁹¹ describe an hourly dose escalation protocol that allows those patients with a completely negative challenge to be completed on the first day. Even in this protocol, many patients needed to return on the second day to complete the protocol. Overall, there are several published protocols describing successful ASA desensitization in patients with AERD.

COX-2 INHIBITORS

COX-2 inhibitors have been available throughout the world primarily for use as analgesic and antiinflammatory agents. Initially, the lack of safety data in COX-1–hypersensitive patients and warning labels from the US Food and Drug Administration (which are still present) raised the specter of possible cross-reactivity in NSAID-hypersensitive patients. Yet, mechanistically, the COX-2 inhibitors would not be expected to cause a problem in COX-1 reactors. Because, by definition, the COX-2 inhibitors have little to no activity at COX-1 and are structurally dissimilar, it became a logical conclusion that COX-2 agents would provide an alternative to narcotics in COX-1–sensitive patients. Numerous studies have now shown this to be the case in both AERD and NECD.^{17,97,98} In a metaanalysis of blinded, placebo-controlled clinical trials, there was no respiratory reactivity seen in AERD upon selective COX-2 challenge.⁹⁹ With selective NSAIDs (weak COX-1 activity at higher doses), approximately 1 in 13 patients with AERD reacted⁹⁹ (curiously, a small number of COX-2 induced reactions are reported in COX-1 reactors). Bobolea and colleagues¹⁰⁰ report a case of

Table 1
Nasal ketorolac and oral aspirin challenge protocol

Time	Dose ^a
Day 1	
8:00 AM	1 spray ketorolac (1 spray in 1 nostril)
8:30 AM	2 sprays ketorolac (1 each nostril)
9:00 AM	4 sprays ketorolac (2 each nostril)
9:30 AM	6 sprays ketorolac (3 each nostril)
10:30 AM	60 mg aspirin
12:00 PM	60 mg aspirin
3:00 PM	Discharge patient
Day 2	
8:00 AM	150 mg aspirin
11:00 AM	325 mg aspirin ^b
2:00 PM	Discharge patient

^a (1) Spirometry (FEV₁) and objective clinical evaluation should be performed before each dose. (2) Treat reactions appropriately and wait until symptoms resolve. (a) Reactions are classified as follows: (i) Nasoocular. (ii) Nasoocular with $\geq 15\%$ decline in FEV₁ ("Classic reaction"). (iii) Lower respiratory reaction [$\geq 20\%$ decline in FEV₁]. (iv) Laryngospasm with or without (i), (ii), or (iii). (v) Systemic reaction (urticaria, gastrointestinal symptoms, hypotension). (3) Aspirin desensitization: (a) After reactions are treated and resolve, continue next scheduled ketorolac dose OR repeat oral provoking aspirin dose. (b) Desensitization is complete after 325 mg of aspirin. (c) Patient should take 650 mg of aspirin that evening then continue 650 mg twice daily as their continuous aspirin dose until further instructed. *Preparing nasal ketorolac*: (1) Take ketorolac (60 mg/2 mL) and mix with preservative-free normal saline (2.75 mL). (2) Place combined solution in a nasal spray bottle (one that delivers 100 μ L/actuation). (3) Prime with 5 sprays before use. Each spray will now actuate 1.26 mg of ketorolac solution. (4) Patient should tilt head down during sprays and sniff gently to avoid swallowing solution.

^b If no reaction occurs within 3 hours after 325 mg dose, consider it a negative challenge.

Adapted from Lee RU, White AA, Ding D, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2010;105(2):132; with permission.

an individual with respiratory reactions to high-dose NSAIDs and 2 different COX-2 inhibitors, despite being on low-dose ASA (100 mg) for antiplatelet effect. The authors hypothesize that COX-2 inhibitors, which might have a gradual effect on total body PGE₂ levels,¹⁰¹ might be more likely to cause acute symptoms in patients with a chronically low PGE₂ from low-dose ASA. Indeed, recent studies demonstrate the central involvement of COX-2 in the pathophysiology of AERD.¹⁰² Although there is no clear mechanism to explain this phenomenon, the presence of these rare dual reactors suggests that most COX-1 reactive patients should receive the first dose of a COX-2 inhibitor under observation in the office.

SALICYLATES

There is no known cross-reactivity between salicylates and NSAIDs. The potential concern for reactivity likely comes from the common salicylate component of acetyl salicylic acid (ASA) and other nonacetylated salicylates. This issue tends to emerge in the clinical setting when a patient has a history of NSAID hypersensitivity and is a candidate for a salicylate compound for an autoimmune indication. Direct challenges with salicylates in AERD subjects were tolerated in all.^{103–105}

CHILDREN

Clearly, far less is known regarding hypersensitivity reactions to NSAIDs in pediatric patients. The general approach to categorizing reactions would be similar to that of adults, with the main exception being that AERD does not occur in young children. Although there are rare case reports of AERD in the pediatric age group, even those are primarily in the teenage years.^{106,107} In challenge studies of children with a history of NSAID hypersensitivity, the reaction could be confirmed in only one-third to two-thirds (31% to 68%).^{108–110} As in adults, it seems that clinical history is insufficient to make the diagnosis, and drug provocation studies are likely necessary to truly confirm the diagnosis. In children with a negative provocative challenge, 12% reported subsequent NSAID reactivity, including several cases that were subsequently proven upon reevaluation.¹¹¹ It is important to note that several studies point out that there are a group of children with NSAID reaction patterns that cannot be explained by our current mechanistic understanding of these reactions.^{109,112}

Chronic Urticaria

In pediatric patients with chronic urticaria, single-blinded, placebo-controlled challenges identified 24% reacting to ASA in the daily or near daily hive group, and in only 1 in 10 of the recurrent urticaria group (urticaria 2–4 days per week).¹¹³

Respiratory Reactions

Interestingly, a small group of pediatric patients have been described with respiratory reactions to NSAIDs. This number is 2% of all asthmatics,¹¹⁴ although a much earlier study suggested that as many as 28% might be ASA intolerant with respiratory reactions.¹¹⁵ It seems unlikely that these subjects had the clinical phenotype of AERD, making reactivity at this level hard to explain. Perhaps differences in asthma control over the decades could explain either true or perceived reactivity to NSAIDs in these patients. Larger challenge studies include cutaneous, respiratory, and anaphylaxis reactions; therefore, it seems that some children are prone to respiratory reactions (whether or not they have asthma).¹¹⁶ In general, the limited literature on this subject would suggest that drug provocation challenges are necessary and safe in children. Most pediatric reactors react to more than 1 drug.¹¹⁷ Cross-reactions to paracetamol are not unusual (10%).¹¹⁶

COMMON CLINICAL SCENARIOS

There are a few common situations that merit specific discussion. These are situations that emerge in the literature repeatedly and are also the most common clinical questions posed to the authors by referring providers.

Emergent Need for Aspirin in Acute Coronary Syndrome

First is the acute need for ASA in the cardiac care unit in a patient with a history of an ASA or NSAID reaction. This is a logistical challenge for the allergist, frequently involving a vague and remote history of NSAID reactivity. Fortunately, there now are several studies addressing this issue. The main limitation of all of these studies is the inability to prove the patient truly has hypersensitivity. Thus, desensitization protocols proceed under the assumption that the patient has ongoing hypersensitivity. The tremendous success of these protocols should not be used as a diagnosis of NSAID reactivity unless the patient clearly has a reaction during the procedure. Many times, in the acute setting in the coronary care unit, the medical need for ASA outweighs the desire to make an accurate diagnosis.

The literature clearly supports the safety of performing one of the various desensitization protocols that have been published.^{21,118–120} Although previous studies were generally just small case series, a large multicenter prospective trial involving 330 patients provides convincing evidence that it is safe to perform ASA desensitization in the acute setting.¹²¹ When reactions occur, they are mild and easy to treat. The authors' experience is that most of these cases can be approached with a graded ASA challenge in the cardiac care unit (see **Figs. 1** and **2**; **Fig. 3**). This allows a more accurate determination of ongoing hypersensitivity, while also allowing the timely administration of ASA.

It is critical to point out that a patient with a high suspicion of AERD who requires ASA presents a different challenge. This patient should not undergo a rapid desensitization, because these protocols are not studied in the acute setting. A rapid desensitization would likely lead to more severe asthma and a potentially more dangerous situation in a patient recovering from a cardiac event. The initial consultation in the coronary care unit should identify anosmia, history of asthma, and types of NSAID reactions, which would help to raise the suspicion for AERD.

Need Assessment of Nonsteroidal Antiinflammatory Drug Hypersensitivity for Pain Management Options

The other common clinical situation is a patient with a history of an NSAID reaction in the past who wants to know what they can take for pain. Generally, these patients

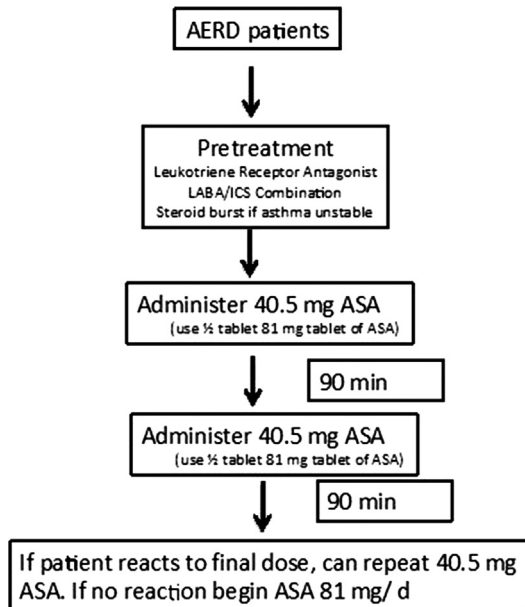


Fig. 3. Protocol that could be used in the acute hospital setting for a patient with aspirin-exacerbated respiratory disease (AERD) needing desensitization emergently owing to acute coronary syndrome. Be prepared to treat respiratory reactions: bronchodilators, antihistamines, and so on. Typical provoking dose between 60 and 100 mg in AERD. ASA, aspirin. (From White AA, Stevenson DD, Woessner KM, et al. Approach to patients with aspirin hypersensitivity and acute cardiovascular emergencies. *Allergy Asthma Proc* 2013;34(2):141; with permission.)

present with a history of a cutaneous reaction or systemic anaphylaxis symptoms. Many times, the patient and referring provider are unaware that a COX-2 inhibitor could be an option. Office challenge with a COX-2 is recommended because there are rare cases of reactivity, but in general COX-2 inhibitors are well-tolerated and provide an adequate solution for intermittent pain relief. The next step would be to address whether the reaction is cross-reactive or not. Cross-reactivity reactions can present a challenge, because there become few options for the patient to take. There are reports that premedication with antihistamines could allow tolerance in some patients.¹²² Desensitization could be attempted, but would require daily administration to maintain desensitization, a circumstance that might not be necessary or valuable in a patient who only needs intermittent use.

SUMMARY

The successful approach to NSAID hypersensitivity can be distilled down to 2 critical elements: the ability to obtain a history that points toward a specific NSAID reactivity pattern and the willingness to perform targeted graded dose challenges. The literature supports these as safe and extremely useful in guiding the use of pain medications, antiplatelet ASA, or therapeutic ASA in AERD.

REFERENCES

1. Soni A. Aspirin use among the adult U.S. noninstitutionalized population with and without indicators of heart disease. Brief #179-Medical Expenditure Panel Survey. Rockville (MD): Agency for Healthcare Research and Quality; 2005.
2. Gollapudi RR, Teirstein PS, Stevenson DD, et al. Aspirin sensitivity - Implications for patients with coronary artery disease. *JAMA* 2004;292(24):3017-23.
3. Feng CH, White AA, Stevenson DD. Characterization of aspirin allergies in patients with coronary artery disease. *Ann Allergy Asthma Immunol* 2013;110(2):92-5.
4. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* 1971;231(25):232-5.
5. Warner TD, Giuliano F, Vojnovic I, et al. Nonsteroid drug selectivities for cyclooxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A* 1999;96(13):7563-8.
6. Jares EJ, Baena-Cagnani CE, Sánchez-Borges M, et al. Drug-induced anaphylaxis in Latin American Countries. *J Allergy Clin Immunol Pract* 2015;3(5):780-8.
7. Aun MV, Blanca M, Garro LS, et al. Nonsteroidal anti-inflammatory drugs are major causes of drug-induced anaphylaxis. *J Allergy Clin Immunol Pract* 2014;2(4):414-20.
8. Drago F, Cogorno L, Agnoletti AF, et al. A retrospective study of cutaneous drug reactions in an outpatient population. *Int J Clin Pharm* 2015;37(5):739-43.
9. Tian XY, Liu B, Shi H, et al. Incidence of adverse cutaneous drug reactions in 22,866 Chinese inpatients: a prospective study. *Arch Dermatol Res* 2015;307(9):829-34.
10. Ortiz-Sanjuán F, Blanco R, Hernández JL, et al. Drug-associated cutaneous vasculitis: study of 239 patients from a single referral center. *J Rheumatol* 2014;41(11):2201-7.
11. Grando LR, Schmitt TA, Bakos RM. Severe cutaneous reactions to drugs in the setting of a general hospital. *An Bras Dermatol* 2014;89(5):758-62.

12. Kowalski ML, Makowska JS, Blanca M, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA and GA2LEN/HANNA. *Allergy* 2011;66(7):818–29.
13. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. *J Allergy Clin Immunol* 1977;60(5):276–84.
14. Mathison DA, Stevenson DD. Hypersensitivity to nonsteroidal antiinflammatory drugs: indications and methods for oral challenges. *J Allergy Clin Immunol* 1979;64(6 pt 2):669–74.
15. Mastalerz L, Setkowicz M, Szczeklik A. Mechanism of chronic urticaria exacerbation by aspirin. *Curr Allergy Asthma Rep* 2005;5(4):277–83.
16. Zembowicz A, Mastalerz L, Setkowicz M, et al. Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopathic urticaria with sensitivity to nonsteroidal anti-inflammatory drugs. *Arch Dermatol* 2003;139(12):1577–82.
17. Asero R. Etoricoxib challenge in patients with chronic urticaria with NSAID intolerance. *Clin Exp Dermatol* 2007;32(6):661–3.
18. Setkowicz M, Mastalerz L, Podolec-Rubis M, et al. Clinical course and urinary eicosanoids in patients with aspirin-induced urticaria followed up for 4 years. *J Allergy Clin Immunol* 2009;123(1):174–8.
19. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62(10):1111–8.
20. Rajan JP, Simon RA, Bosso JV. Prevalence of sensitivity to food and drug additives in patients with chronic idiopathic urticaria. *J Allergy Clin Immunol Pract* 2014;2(2):168–71.
21. McMullan KL, Wedner HJ. Safety of aspirin desensitization in patients with reported aspirin allergy and cardiovascular disease. *Clin Cardiol* 2013;36(1):25–30.
22. White AA, Stevenson DD, Woessner KM, et al. Approach to patients with aspirin hypersensitivity and acute cardiovascular emergencies. *Allergy Asthma Proc* 2013;34(2):138–42.
23. Simon RA. Prevention and treatment of reactions to NSAIDs. *Clin Rev Allergy Immunol* 2003;24(2):189–98.
24. Slowik SM, Slavin RG. Aspirin desensitization in a patient with aspirin sensitivity and chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2009;102(2):171–2.
25. Lee J. Aspirin desensitization as a treatment for aspirin-sensitive chronic spontaneous urticaria. *Dermatol Ther* 2015;28(1):4–6.
26. Leeyaphan C, Kulthanan K, Jongjarearnprasert K, et al. Drug-induced angioedema without urticaria: prevalence and clinical features. *J Eur Acad Dermatol Venereol* 2010;24(6):685–91.
27. Katz Y, Goldberg N, Kivity S. Localized periorbital edema induced by aspirin. *Allergy* 1993;48(5):366–9.
28. Quiralte J, Blanco C, Delgado J, et al. Challenge-based clinical patterns of 223 Spanish patients with nonsteroidal anti-inflammatory-drug-induced-reactions. *J Investig Allergol Clin Immunol* 2007;17(3):182–8.
29. Asero R. Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. *J Allergy Clin Immunol* 2003;111(5):1095–8.

30. Doña I, Blanca-López N, Torres MJ, et al. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. *Allergy* 2014; 69(4):438–44.
31. Kowalski ML, Woessner K, Sanak M. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug-related urticaria and angioedema. *J Allergy Clin Immunol* 2015;136(2):245–51.
32. Scott DR, White AA. Approach to desensitization in aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2014;112(1):13–7.
33. Doña I, Barrionuevo E, Salas M, et al. Natural evolution in patients with nonsteroidal anti-inflammatory drug-induced urticaria/angioedema. *Allergy* 2017;72(9):1346–55.
34. Woessner KM, Simon RA. Cardiovascular prophylaxis and aspirin “allergy”. *Immunol Allergy Clin North Am* 2013;33(2):263–74.
35. Dona I, Blanca-Lopez N, Cornejo-Garcia JA, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy* 2011;41(1):86–95.
36. Kowalski ML, Bienkiewicz B, Woszczek G, et al. Diagnosis of pyrazolone drug sensitivity: clinical history versus skin testing and in vitro testing. *Allergy Asthma Proc* 1999;20(6):347–52.
37. 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(12):1355–63.
38. Quiralte J, Blanco C, Castillo R, et al. Intolerance to nonsteroidal antiinflammatory drugs: results of controlled drug challenges in 98 patients. *J Allergy Clin Immunol* 1996;98(3):678–85.
39. Quiralte J, Blanco C, Castillo R, et al. Anaphylactoid reactions due to nonsteroidal antiinflammatory drugs: clinical and cross-reactivity studies. *Ann Allergy Asthma Immunol* 1997;78(3):293–6.
40. Chaudhry T, Hissaria P, Wiese M, et al. Oral drug challenges in non-steroidal anti-inflammatory drug-induced urticaria, angioedema and anaphylaxis. *Intern Med J* 2012;42(6):665–71.
41. Canto MG, Andreu I, Fernandez J, et al. Selective immediate hypersensitivity reactions to NSAIDs. *Curr Opin Allergy Clin Immunol* 2009;9(4):293–7.
42. Viola M, Rumi G, Valluzzi RL, et al. Assessing potential determinants of positive provocation tests in subjects with NSAID hypersensitivity. *Clin Exp Allergy* 2011; 41(1):96–103.
43. Rajan JP, Wineinger NE, Stevenson DD, et al. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol* 2015;135(3):676–81.e1.
44. Ta V, White AA. Survey-defined patient experiences with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2015;3(5):711–8.
45. Cardet JC, White AA, Barrett NA, et al. Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2014;2(2):208–13.
46. Kim JE, Kountakis SE. The prevalence of Samter’s triad in patients undergoing functional endoscopic sinus surgery. *Ear Nose Throat J* 2007;86(7):396–9.
47. Lee JH, Haselkorn T, Borish L, et al. Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma: insights from the TENOR study. *Chest* 2007;132(6):1882–9.

48. Mascia K, Haselkorn T, Deniz YM, et al. Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2005;116(5):970–5.
49. Koga T, Oshita Y, Kamimura T, et al. Characterisation of patients with frequent exacerbation of asthma. *Respir Med* 2006;100(2):273–8.
50. O'Byrne PM, Israel E, Drazen JM. Antileukotrienes in the treatment of asthma. *Ann Intern Med* 1997;127(6):472–80.
51. Stevenson DD, Zuraw BL. Pathogenesis of aspirin-exacerbated respiratory disease. *Clin Rev Allergy Immunol* 2003;24(2):169–88.
52. Yamashita T, Tsuji H, Maeda N, et al. Etiology of nasal polyps associated with aspirin-sensitive asthma. *Rhinol Suppl* 1989;8:15–24.
53. Ruhno J, Howie K, Anderson M, et al. The increased number of epithelial mast cells in nasal polyps and adjacent turbinates is not allergy-dependent. *Allergy* 1990;45(5):370–4.
54. Sladek K, Szczeklik A. Cysteinyl leukotrienes overproduction and mast cell activation in aspirin-provoked bronchospasm in asthma. *Eur Respir J* 1993;6(3):391–9.
55. Bochenek G, Nagraba K, Nizankowska E, et al. A controlled study of 9 alpha,11 beta-PGF₂ (a prostaglandin D-2 metabolite) in plasma and urine of patients with bronchial asthma and healthy controls after aspirin challenge. *J Allergy Clin Immunol* 2003;111(4):743–9.
56. Fischer AR, Rosenberg MA, Lilly CM, et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. *J Allergy Clin Immunol* 1994;94(6 Pt 1):1046–56.
57. Robuschi M, Gambaro G, Sestini P, et al. Attenuation of aspirin-induced bronchoconstriction by sodium cromoglycate and nedocromil sodium. *Am J Respir Crit Care Med* 1997;155(4):1461–4.
58. Yoshida S, Amayasu H, Sakamoto H, et al. Cromolyn sodium prevents bronchoconstriction and urinary LTE₄ excretion in aspirin-induced asthma. *Ann Allergy Asthma Immunol* 1998;80(2):171–6.
59. Szczeklik A, Mastalerz L, Nizankowska E, et al. Protective and bronchodilator effects of prostaglandin E and salbutamol in aspirin-induced asthma. *Am J Respir Crit Care Med* 1996;153(2):567–71. Available at: <http://onlinelibrary.wiley.com/doi/cochrane/clcentral/articles/179/CN-00123179/frame.html>.
60. Sestini P, Armetti L, Gambaro G, et al. Inhaled PGE₂ prevents aspirin-induced bronchoconstriction and urinary LTE₄ excretion in aspirin-sensitive asthma. *Am J Respir Crit Care Med* 1996;153(2):572–5.
61. Ferreri NR, Howland WC, Stevenson DD, et al. Release of leukotrienes, prostaglandins, and histamine into nasal secretions of aspirin-sensitive asthmatics during reaction to aspirin. *Am Rev Respir Dis* 1988;137(4):847–54.
62. Narayanankutty A, Resendiz-Hernandez JM, Falfan-Valencia R, et al. Biochemical pathogenesis of aspirin exacerbated respiratory disease (AERD). *Clin Biochem* 2013;46(7–8):566–78.
63. Moon TC, Campos-Alberto E, Yoshimura T, et al. Expression of DP₂ (CRTh₂), a prostaglandin D₂ receptor, in human mast cells. *PLoS One* 2014;9(9):e108595.
64. Cahill KN, Bensko JC, Boyce JA, et al. Prostaglandin D₂: a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2015;135(1):245–52.
65. Takahashi G, Tanaka H, Higuchi N, et al. The potential role of prostaglandin D₂ in nasal congestion observed in a guinea pig model of allergic rhinitis. *Int Arch Allergy Immunol* 2012;158(4):359–68.

66. Chang JE, Doherty TA, Baum R, et al. Prostaglandin D2 regulates human type 2 innate lymphoid cell chemotaxis. *J Allergy Clin Immunol* 2014;133(3): 899–901.e3.
67. Xue L, Salimi M, Panse I, et al. Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. *J Allergy Clin Immunol* 2014;133(4):1184–94.
68. Spik I, Brenuchon C, Angeli V, et al. Activation of the prostaglandin D2 receptor DP2/CRT2 increases allergic inflammation in mouse. *J Immunol* 2005;174(6): 3703–8.
69. Di Lorenzo G, Drago A, Esposito Pellitteri M, et al. Measurement of inflammatory mediators of mast cells and eosinophils in native nasal lavage fluid in nasal polypsis. *Int Arch Allergy Immunol* 2001;125(2):164–75.
70. Landolina N, Gangwar RS, Levi-Schaffer F. Mast cells' integrated actions with eosinophils and fibroblasts in allergic inflammation: implications for therapy. *Adv Immunol* 2015;125:41–85.
71. Payne SC, Early SB, Huyett P, et al. Evidence for distinct histologic profile of nasal polyps with and without eosinophilia. *Laryngoscope* 2011;121(10): 2262–7.
72. Steinke JW, Negri J, Liu L, et al. Aspirin activation of eosinophils and mast cells: implications in the pathogenesis of aspirin-exacerbated respiratory disease. *J Immunol* 2014;193(1):41–7.
73. Cowburn AS, Sladek K, Soja J, et al. Overexpression of leukotriene C-4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998;101(4):834–46.
74. Laidlaw TM, Kidder MS, Bhattacharyya N, et al. Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. *Blood* 2012;119(16):3790–8.
75. Laidlaw TM, Cutler AJ, Kidder MS, et al. Prostaglandin E2 resistance in granulocytes from patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2014;133(6):1692–701.e3.
76. Dahlen B, Nizankowska E, Szczeklik A, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1187–94.
77. Israel E, Fischer AR, Rosenberg MA, et al. The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. *Am Rev Respir Dis* 1993;148(6 Pt 1):1447–51.
78. Cai Y, Bjerrmer L, Halstensen TS. Bronchial mast cells are the dominating LTC4S-expressing cells in aspirin-tolerant asthma. *Am J Respir Cell Mol Biol* 2003; 29(6):683–93.
79. Chen YS, Langhammer T, Westhofen M, et al. Relationship between matrix metalloproteinases MMP-2, MMP-9, tissue inhibitor of matrix metalloproteinases-1 and IL-5, IL-8 in nasal polyps. *Allergy* 2007;62(1):66–72.
80. Yeo NK, Eom DW, Oh MY, et al. Expression of matrix metalloproteinase 2 and 9 and tissue inhibitor of metalloproteinase 1 in nonrecurrent vs recurrent nasal polyps. *Ann Allergy Asthma Immunol* 2013;111(3):205–10.
81. Lee YM, Kim SS, Kim HA, et al. Eosinophil inflammation of nasal polyp tissue: relationships with matrix metalloproteinases, tissue inhibitor of metalloproteinase-1, and transforming growth factor-beta1. *J Korean Med Sci* 2003;18(1):97–102.

82. Coste A, Lefaucheur JP, Wang QP, et al. Expression of the transforming growth factor beta isoforms in inflammatory cells of nasal polyps. *Arch Otolaryngol Head Neck Surg* 1998;124(12):1361–6.
83. Pawankar R, Lee KH, Nonaka M, et al. Role of mast cells and basophils in chronic rhinosinusitis. *Clin Allergy Immunol* 2007;20:93–101.
84. Pawankar R. Mast cells in allergic airway disease and chronic rhinosinusitis. *Chem Immunol Allergy* 2005;87:111–29.
85. Cahill KN, Raby BA, Zhou X, et al. Impaired EP expression causes resistance to prostaglandin E in nasal polyp fibroblasts from subjects with AERD. *Am J Respir Cell Mol Biol* 2015;54(1):34–40.
86. Cahill KN, Laidlaw TM. Aspirin exacerbated respiratory disease: the search for a biomarker. *Ann Allergy Asthma Immunol* 2014;113(5):500–1.
87. Williams AN, Simon RA, Woessner KM, et al. The relationship between historical aspirin-induced asthma and severity of asthma induced during oral aspirin challenges. *J Allergy Clin Immunol* 2007;120(2):273–7.
88. Dahlen B, Zetterstrom O. Comparison of bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics. *Eur Respir J* 1990;3(5):527–34.
89. Nizankowska E, Bestyńska-Krypel A, Cmiel A, et al. Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. *Eur Respir J* 2000;15(5):863–9. Available at: <http://onlinelibrary.wiley.com/doi/10.1046/j.1365-0675.2000.00297.x>.
90. Celikel S, Stevenson D, Erkorkmaz U, et al. Use of nasal inspiratory flow rates in the measurement of aspirin-induced respiratory reactions. *Ann Allergy Asthma Immunol* 2013;111(4):252–5.
91. Chen JR, Buchmiller BL, Khan DA. An Hourly Dose-Escalation Desensitization Protocol for Aspirin-Exacerbated Respiratory Disease. *J Allergy Clin Immunol Pract* 2015;3(6):926–31.e1.
92. Lee RU, White AA, Ding D, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2010;105(2):130–5.
93. Berges-Gimeno MP, Simon RA, Stevenson DD. The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions. *Clin Exp Allergy* 2002;32(10):1491–6.
94. White A, Ludington E, Mehra P, et al. Effect of leukotriene modifier drugs on the safety of oral aspirin challenges. *Ann Allergy Asthma Immunol* 2006;97(5):688–93.
95. Cook K, Modena M, Wineinger N, et al. Use of a composite symptom score during challenge in patients with suspected aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2017;118(5):597–602.
96. 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(4):330–5.
97. Stevenson DD, Simon RA. Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* 2001;108(1):47–51.
98. Gyllfors P, Bochenek G, Overholt J, et al. Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgesic drug celecoxib. *J Allergy Clin Immunol* 2003;111(5):1116–21. Available at: <http://onlinelibrary.wiley.com/doi/10.1046/j.1365-0675.2003.00437.x>.

99. Morales DR, Guthrie B, Lipworth BJ, et al. NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. *Allergy* 2015;70(7):828–35.
100. Bobolea I, Cabañas R, Jurado-Palomo J, et al. Concurrent coxibs and anti-platelet therapy unmasks aspirin-exacerbated respiratory disease. *Eur Respir J* 2013;42(5):1418–20.
101. Daham K, Song WL, Lawson JA, et al. Effects of celecoxib on major prostaglandins in asthma. *Clin Exp Allergy* 2011;41(1):36–45.
102. Machado-Carvalho L, Martín M, Torres R, et al. Low E-prostanoid 2 receptor levels and deficient induction of the IL-1 β /IL-1 type I receptor/COX-2 pathway: vicious circle in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2016;137(1):99–107.e7.
103. Senna GE, Andri G, Dama AR, et al. Tolerability of imidazole salicylate in aspirin-sensitive patients. *Allergy Proc* 1995;16(5):251–4.
104. Nizankowska E, Dworski R, Soja J, et al. Salicylate pre-treatment attenuates intensity of bronchial and nasal symptoms precipitated by aspirin in aspirin-intolerant patients. *Clin Exp Allergy* 1990;20(6):647–52.
105. Szczeklik A, Nizankowska E, Dworski R. Choline magnesium trisalicylate in patients with aspirin-induced asthma. *Eur Respir J* 1990;3(5):535–9. Available at: <http://onlinelibrary.wiley.com/doi/cochrane/central/articles/194/CN-00069194/frame.html>.
106. Tuttle KL, Schneider TR, Henrickson SE, et al. Aspirin-exacerbated respiratory disease: not always “adult-onset”. *J Allergy Clin Immunol Pract* 2016;4(4):756–8.
107. Ertoý Karagöl Hİ, Yılmaz O, Topal E, et al. Nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease in adolescents. *Int Forum Allergy Rhinol* 2015; 5(5):392–8.
108. Zambonino MA, Torres MJ, Muñoz C, et al. Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children. *Pediatr Allergy Immunol* 2013;24(2):151–9.
109. Arikoglu T, Aslan G, Yildirim DD, et al. Discrepancies in the diagnosis and classification of nonsteroidal anti-inflammatory drug hypersensitivity reactions in children. *Allergol Int* 2016;66(3):418–24.
110. Topal E, Celiksoy MH, Catal F, et al. The value of the clinical history for the diagnosis of immediate nonsteroidal anti-inflammatory drug hypersensitivity and safe alternative drugs in children. *Allergy Asthma Proc* 2016;37(1):57–63.
111. Misirlioglu ED, Toyran M, Capanoglu M, et al. Negative predictive value of drug provocation tests in children. *Pediatr Allergy Immunol* 2014;25(7):685–90.
112. Cousin M, Chiriac A, Molinari N, et al. Phenotypical characterization of children with hypersensitivity reactions to NSAIDs. *Pediatr Allergy Immunol* 2016;27(7): 743–8.
113. Cavkaytar O, Arik Yılmaz E, Karaatmaca B, et al. Different phenotypes of non-steroidal anti-inflammatory drug hypersensitivity during childhood. *Int Arch Allergy Immunol* 2015;167(3):211–21.
114. Debley JS, Carter ER, Gibson RL, et al. The prevalence of ibuprofen-sensitive asthma in children: a randomized controlled bronchoprovocation challenge study. *J Pediatr* 2005;147(2):233–8.
115. Rachelefsky GS, Coulson A, Siegel SC, et al. Aspirin intolerance in chronic childhood asthma: detected by oral challenge. *Pediatrics* 1975;56(3):443–8. Available at: <http://onlinelibrary.wiley.com/doi/cochrane/central/articles/131/CN-00704131/frame.html>.

116. Hassani A, Ponvert C, Karila C, et al. Hypersensitivity to cyclooxygenase inhibitory drugs in children: a study of 164 cases. *Eur J Dermatol* 2008;18(5):561–5.
117. Sanchez-Borges M, Capriles-Behrens E, Caballero-Fonseca F. Hypersensitivity to non-steroidal anti-inflammatory drugs in childhood. *Pediatr Allergy Immunol* 2004;15(4):376–80.
118. Wong JT, Nagy CS, Krinzman SJ, et al. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. *J Allergy Clin Immunol* 2000;105(5):997–1001.
119. Rossini R, Angiolillo DJ, Musumeci G, et al. Aspirin desensitization in patients undergoing percutaneous coronary interventions with stent implantation. *Am J Cardiol* 2008;101(6):786–9.
120. Silberman S, Neukirch-Stoop C, Steg PG. Rapid desensitization procedure for patients with aspirin hypersensitivity undergoing coronary stenting. *Am J Cardiol* 2005;95(4):509–10.
121. Rossini R, Iorio A, Pozzi R, et al. Aspirin desensitization in patients with coronary artery disease: results of the multicenter ADAPTED Registry (Aspirin Desensitization in Patients With Coronary Artery Disease). *Circ Cardiovasc Interv* 2017;10(2) [pii:e004368].
122. Trautmann A, Anders D, Stoevesandt J. H1-antihistamine premedication in NSAID-associated urticaria. *J Allergy Clin Immunol Pract* 2016;4(6):1205–12.