

# An Overview of Nonsteroidal Antiinflammatory Drug Reactions



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## KEYWORDS

- Nonsteroidal antiinflammatory drugs (NSAIDs) • NSAID-induced asthma
- NSAID-induced urticaria • NSAID reactions • NSAID hypersensitivity
- Aspirin intolerance • Drug allergy

## KEY POINTS

- Adverse reactions owing to ingestion of nonsteroidal antiinflammatory drugs (NSAIDs) can manifest as an array of symptoms, from mild gastrointestinal upset up to life-threatening anaphylaxis.
- NSAID-induced hypersensitivity may be divided into immunologic and nonimmunologic reactions and should be differentiated from the predictable side effects of the drug.
- The pathophysiology underlying hypersensitivity reactions is related to cyclooxygenase-1 inhibition (nonimmunologic type) or typical IgE-mediated reactions (immunologic type).
- Although difficult, it is imperative to appropriately diagnosis and categorize the type of NSAID-induced reaction so that the affected patient may be managed effectively.

## INTRODUCTION

Since the introduction of the first nonsteroidal antiinflammatory drug (NSAID) to medical practice in the late 1800s, NSAIDs, including aspirin (ASA), have become one of the most commonly used class of drugs in the world. It is estimated that more than 20 million people in the United States use an NSAID on a consistent basis,<sup>1</sup> and this number is steadily increasing owing to our aging population and subsequent treatment of various inflammatory and cardiovascular conditions. Consequently, the number of adverse reactions owing to NSAID ingestion have paralleled the increase in NSAID use and may account for up to 10% of preventable drug-related hospital admissions.<sup>2</sup> These reactions vary in severity, from mild gastrointestinal (GI) or cutaneous symptoms, to severe life-threatening anaphylaxis.

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The ability to distinguish between a suspected, but unwanted, side effect of a medication and a true hypersensitivity reaction is paramount but frequently met with challenge. In addition to the wide range of symptoms that characterize these reactions, they are often accompanied by abnormal immunologic and/or nonimmunologic processes, which can further complicate the clinician's ability to diagnose and manage NSAID-induced reactions.

Over the years, several classification schemes have been proposed to assist the clinician in identifying and understanding the different forms of NSAID hypersensitivity reactions. In this review, these classification strategies will be used to provide the reader with an in-depth overview of the clinical presentation and management of both immunologic and nonimmunologic NSAID reactions.

## MECHANISM AND CLASSIFICATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

It is well-understood that NSAIDs, including ASA, share a common pharmacologic method of action via the inhibition of cyclooxygenase (COX) enzymes. The inhibition of COX leads to altered arachidonic acid metabolism and decreased formation of prostaglandins, prostacyclin, and thromboxanes (**Fig. 1**).<sup>3</sup> Two isoforms of COX have been described, COX-1 and COX-2:

- **COX-1:** Often referred to as the “housekeeping” enzyme owing to its role in maintaining various protective cellular functions, such as the integrity of gastric mucosa, platelet aggregation, and renal function, via production of prostanoids.<sup>4</sup> It is constitutively expressed by most human cell types.
- **COX-2:** Expression is primarily induced in response to inflammatory or mitogenic stimuli (eg, interleukin-1, endotoxin), and inhibited by glucocorticoids. It is constitutively expressed in specific cell types with physiologic roles in reproduction, bone reabsorption, renal function, and neurotransmission.<sup>5</sup> There exists a potential association between COX-2 and adverse cardiovascular outcomes, but this remains to be fully elucidated.<sup>6,7</sup>

The strength of enzyme inhibition is known to vary among the different NSAIDs and explains their ability to generate different levels of clinical effectiveness, side effects, and hypersensitivity reactions.

In general, NSAIDs that inhibit COX-1 are considered to be “cross-reactive” with ASA (eg, ibuprofen, naproxen, ketorolac). NSAIDs that inhibit both COX isoforms are considered “nonselective.” Highly selective COX-2 inhibitors have a 200- to 300-fold selectivity for COX-2 at approved therapeutic doses. The 4 broad categories of COX inhibition are listed as follows (**Box 1**):

- Highly selective COX-1 inhibitors
- Weakly selective COX-1 inhibitors
- Preferentially selective COX-2 inhibitors
- Highly selective COX-2 inhibitors

Despite all NSAIDs sharing a similar mechanism of action, it is important to note that they demonstrate differences in their chemical structure (**Table 1**). This enables certain NSAIDs to have antigenic activity and elicit a drug-specific immunologic response. It is vital that the clinician has a sound understanding of the pharmacologic properties of NSAIDs, including their mechanisms of action and degree of COX-1/COX-2 selectivity and chemical structure, to appropriately diagnose and efficiently manage any NSAID-induced reaction.

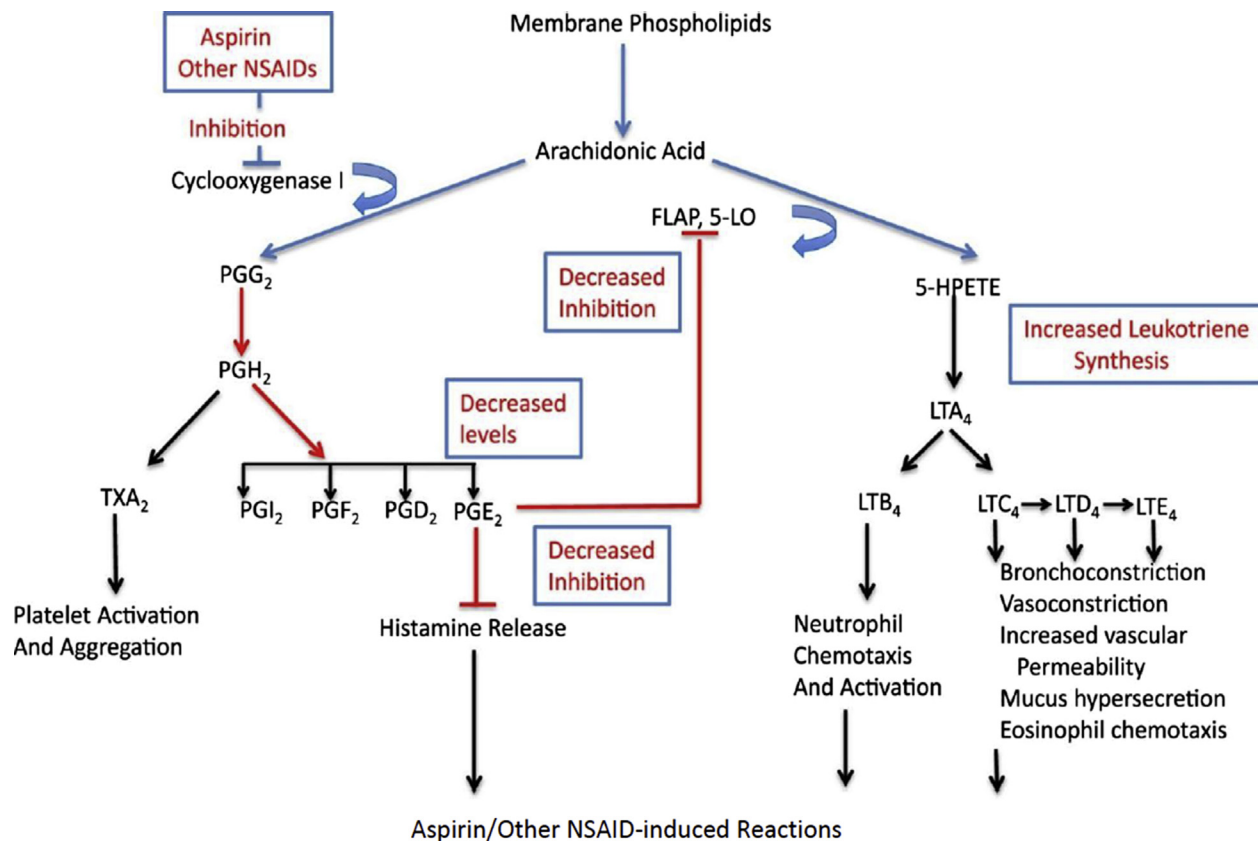


**Fig. 1.** Alteration of arachidonic acid metabolism in nonsteroidal antiinflammatory drugs (NSAID)-induced reactions after inhibition of cyclooxygenase I (COX-I). 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; 5-LO, 5-lipoxygenase; FLAP, 5-lipoxygenase-activating protein; LT, leukotriene; PG, prostaglandin; TX, thromboxane. (Adapted from Woessner KM, Simon RA. Cardiovascular prophylaxis and aspirin "allergy". Immunol Allergy Clin North Am 2013;33(2):264; with permission.)

**Box 1****Cross-reactivity of nonsteroidal antiinflammatory drugs (NSAIDs) based on potency of COX-1 and COX-2 inhibition***Highly selective COX-1 inhibitors*

Acetylsalicylic acid  
Diclofenac  
Etodolac  
Fenoprofen  
Ibuprofen  
Indomethacin  
Ketoprofen  
Ketorolac  
Naproxen  
Naproxen sodium  
Mefenamic acid  
Oxaprozin  
Piroxicam  
Sulindac  
Tolmetin

*Highly selective COX-2 inhibitors*

Celecoxib  
Etoricoxib  
Lumiracoxib  
Parecoxib

*Weakly selective COX-1 inhibitors; cross-reactive only at high concentrations*

Acetaminophen  
Choline magnesium trisalicylate  
Diflunisal  
Salsalate

*Preferentially selective COX-2 inhibitors; cross-reactive at high concentrations*

Meloxicam  
Nabumetone  
Nimesulide

*Abbreviation:* COX, cyclooxygenase.

**Table 1**  
Examples of NSAIDs based on chemical structure

| Salicylic Acid Derivatives                         |                                                                                                        | Para-Aminophenol Derivative        | Phenyl-Propionic Acids                                                         | Pyrano-Indoleacetic Acids (Acetic Acids)                       | Enolic Acid Derivatives (Oxicams)   | Anthranilic Acids (Fenamates)                       |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------|-----------------------------------------------------|
| Acetylated<br>Acetylsalicylic acid (aspirin [ASA]) | Nonacetylated<br>Choline<br>Magnesium<br>Trisalicylate<br>Diflunisal<br>Salsalate<br>Sodium salicylate | Acetaminophen (paracetamol [APAP]) | Fenoprofen<br>Flurbiprofen<br>Ibuprofen<br>Ketoprofen<br>Naproxen<br>Oxaprozin | Diclofenac<br>Etodolac<br>Indomethacin<br>Sulindac<br>Tolmetin | Meloxicam<br>Piroxicam<br>Tenoxicam | Meclofenamic acid (meclofenamate)<br>Mefenamic acid |

*Abbreviation:* NSAIDs, nonsteroidal antiinflammatory drugs.

## CLASSIFICATION OF ADVERSE DRUG REACTIONS

An ADR describes any unpleasant and/or unwanted reaction that results from ingestion of a particular medication. ADRs are divided into 2 categories, types A and B:

- *Type A:* Make up the majority of ADRs (85%–90%). Distinguished by their predictable nature (ie, symptoms can arise in any individual and risk is increased with higher doses and/or repeated exposure to the drug). The reaction results from the known pharmacologic properties of the medication.

*Examples:* Gastritis owing to chronic NSAID use; tinnitus from high-dose ASA use.

- *Type B:* Represents 10% to 15% of all ADRs. Reactions are not predictable, not dose dependent, and only occur in susceptible patients.

*Examples:* NSAID-exacerbated cutaneous disease (NECD); anaphylaxis to ibuprofen.

Type B reactions can be further subclassified as follows:

- Exaggerated sensitivity to known drug toxicities;
- Idiosyncratic drug reactions; and
- Hypersensitivity drug reactions:
  - Nonimmunologic; and
  - Immunologic.

### ***Exaggerated Sensitivity to Known Drug Toxicities***

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This is similar to a type A reaction because it results from a known and predictable pharmacologic property of the drug. However, the toxicity occurs after exposure to a low and/or subtherapeutic concentration of medication, likely owing to altered drug metabolism or increased end-organ sensitivity to the particular drug.

*Example:* Onset of tinnitus after a single dose of ASA.

### ***Idiosyncratic Drug Reactions***

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These reactions are often specific to a single drug, but separate from its known pharmacologic properties. The exact mechanism remains unknown but is thought to involve various metabolic, immune and/or genetic factors.

*Examples:* Fixed drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema nodosum, hypersensitivity pneumonitis, aseptic meningitis, interstitial nephritis, and bullous leukocytoclastic vasculitis.

### ***Hypersensitivity Drug Reactions***

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This subcategory is divided into nonimmune and immune-mediated drug reactions. The classification of NSAID hypersensitivity reactions was originally proposed by Stevenson and colleagues<sup>8</sup> to assist the clinician in identifying and understanding the specific pathophysiologic mechanisms behind each type of hypersensitivity reaction. In recent years, a task force created by the European Academy of Allergy and Clinical Immunology presented a modified classification scheme with evidence-based recommendations for the diagnosis and management of these reactions.<sup>9,10</sup> In this review, we provide a blended classification and in-depth overview of each NSAID-induced reaction subtype.

### ***Nonimmunologic hypersensitivity drug reactions***

These reactions represent the majority of NSAID-induced hypersensitivity reactions. They have been previously referred to as “pseudoallergic” reactions because they

often present with similar signs and symptoms of a typical immunologic drug reaction; however, no exact immune mechanism has been validated for these particular reactions. As such, nonimmunologic reactions are often difficult to distinguish clinically from a true allergic reaction and may create a diagnostic dilemma for the clinician.

The pathophysiology of NSAID-induced nonimmunologic reactions is not entirely known, but it is strongly tied to the inhibition of the COX-1 enzyme (see [Fig. 1](#)). COX-1 inhibition by either ASA or any cross-reactive NSAID results in decreased synthesis of antiinflammatory prostanoids, particularly prostaglandin E<sub>2</sub>. This depletion in prostaglandin E<sub>2</sub> removes the “brake” on 5-lipoxygenase activity, thus allowing a shift toward the production of cysteinyl leukotrienes and the start of the inflammatory cascade. Decreased prostaglandin E<sub>2</sub> levels also enhance mast cell activation resulting in release of tryptase and histamine.

In general, the chance that a particular NSAID will cause a nonimmunologic reaction is highly linked to the selectivity of that NSAID for COX-1 inhibition. Given this mechanism, affected patients will almost always present with a history of reactions to several different NSAIDs, including those with dissimilar chemical structures. This is in contrast to immunologic drug reactions, in which the affected patient should only react to a single NSAID (with the exception of those that are strongly similar in chemical structure).

Nonimmunologic/nonallergic reactions can be divided into 4 subtypes ([Table 2](#)):

- NSAID-exacerbated asthma and rhinosinusitis;
- NSAID-exacerbated urticaria/angioedema in patients with chronic urticaria;
- NSAID-induced urticaria/angioedema (NIUA) in healthy individuals; and
- Mixed NSAID-induced reactions.

### ***Asthma and rhinosinusitis exacerbated by nonsteroidal antiinflammatory drugs***

This subtype of nonimmunologic hypersensitivity reactions is characterized by onset of upper and/or lower airway symptoms upon ingestion of an NSAID in the setting of chronic rhinosinusitis, nasal polyposis, and/or asthma. This constellation of symptoms is more commonly described as “ASA-exacerbated respiratory disease” (AERD). Chronic rhinosinusitis and/or asthma often precede the onset of ASA or NSAID hypersensitivity; however, NSAID/ASA ingestion will occasionally be the precipitator of the first asthma exacerbation.

Patients typically report the onset of rhinorrhea, nasal congestion, conjunctival injection, bronchospasm, and/or laryngospasm within 30 to 180 minutes of NSAID exposure. These reactions may also be accompanied by nonrespiratory symptoms including facial flushing, urticaria, angioedema, nausea, vomiting, or diarrhea.

Clinically, these patients typically experience a more severe course of their asthma and chronic rhinosinusitis. The latter is complicated by marked eosinophilic inflammation and frequently results in recurrent nasal polyp formation requiring surgical management. NSAID-induced asthma exacerbations are a significant risk factor for fatal outcomes, and are responsible for a higher incidence of emergency room visits and hospital admissions compared with ASA-tolerant asthmatics.<sup>11</sup> A detailed discussion of AERD is available in later articles of this review issue.

NSAID-induced respiratory reactions are dose-dependent and related to the potency of COX-1 inhibition of the particular NSAID. As described, NSAIDs that are said to be cross-reactive with ASA are considered strong COX-1 inhibitors and subsequently have a greater risk of inducing respiratory reactions in susceptible patients. On the other hand, weak COX-1 inhibitors or selective COX-2 inhibitors are generally well-tolerated.<sup>12</sup>

| <b>Table 2</b><br><b>Subtypes of nonimmunologic hypersensitivity reactions to NSAIDs</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                 |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| <b>Reaction Subtype</b>                                                                  | <b>Signs and Symptoms</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>Risk Factors</b>                                                             |
| NSAID-induced/exacerbated asthma and rhinosinusitis                                      | Nasoocular <ul style="list-style-type: none"> <li>• Rhinorrhea<sup>a</sup></li> <li>• Nasal obstruction<sup>a</sup></li> <li>• Periorbital edema</li> <li>• Conjunctival injection<sup>a</sup></li> </ul> Respiratory <ul style="list-style-type: none"> <li>• Throat tightness</li> <li>• Laryngospasm</li> <li>• Bronchospasm<sup>a</sup></li> </ul> Cutaneous <ul style="list-style-type: none"> <li>• Skin flushing<sup>a</sup></li> <li>• Urticaria</li> </ul> Gastrointestinal <ul style="list-style-type: none"> <li>• Abdominal pain</li> <li>• Nausea/vomiting</li> </ul> | Asthma<br>Chronic rhinosinusitis<br>Nasal polyposis<br>AERD                     |
| NECD                                                                                     | Urticaria<br>Angioedema<br>Frequent involvement of the face and upper respiratory tract<br>Severity is linked to overall control of their chronic hives                                                                                                                                                                                                                                                                                                                                                                                                                            | Chronic urticaria (presence of hives $\geq 6$ wk in duration)<br>Dose-dependent |
| NSAID-induced urticaria/angioedema                                                       | Urticaria<br>Angioedema<br>Isolated angioedema of the face may be seen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | None, patients are generally healthy<br>Often with a history of atopic disease  |
| Mixed reactions                                                                          | Combination of symptoms involving the skin and respiratory tract.<br>Example: AERD patient with historical reaction to ASA (bronchospasm, nasal obstruction) who now develops cutaneous symptoms upon ASA/NSAID ingestion.                                                                                                                                                                                                                                                                                                                                                         | None, may be seen in healthy individuals or those with chronic disease          |

*Abbreviations:* AERD, aspirin exacerbated-respiratory disease; ASA, aspirin; NECD, NSAID-exacerbated cutaneous disease; NSAIDs, nonsteroidal antiinflammatory drugs.

<sup>a</sup> Most commonly identified in clinical history.

***Urticaria/angioedema exacerbated by nonsteroidal antiinflammatory drugs in patients with chronic urticaria***

In those patients with a history of chronic urticaria (defined by the presence of urticaria for  $\geq 6$  weeks), ingestion of COX-1 inhibiting NSAIDs can result in an acute flare of urticaria with or without concomitant angioedema. This nonimmunologic hypersensitivity reaction is known as “NSAID-exacerbated cutaneous disease.” In a 2015 study, NECD was reported to affect nearly 12% of patients with underlying chronic urticaria,<sup>13</sup> but has been shown to be as high as 30% in other studies.<sup>14</sup>

Cutaneous reactions typically develop between 0.5 and 6 hours after NSAID ingestion and may last for up to 24 to 48 hours. In comparison with chronic urticaria patients without NSAID sensitivity, patients with NECD have been shown to have longer duration of their disease, a higher frequency of angioedema and atopic disease, and greater involvement of the face and upper respiratory tract.<sup>13</sup>

These NSAID-induced reactions are generally dose dependent and greatly influenced by the overall control of their urticaria. For example, those with active urticaria will show a greater sensitivity to cross-reactive COX-1 inhibiting NSAIDs compared with those individuals whose hives are quiescent. Thus, avoidance of these NSAIDs are helpful in reducing acute exacerbations of hives. However, it has not been shown to alter or reduce the overall disease course. For NECD patients who require anti-inflammatory treatment, selective COX-2 inhibitors are generally well tolerated.<sup>15</sup>

### ***Nonsteroidal antiinflammatory drug-induced urticaria/angioedema in healthy individuals***

This reaction subtype is similar to NECD; however, it is characterized by the occurrence of urticaria and/or angioedema after NSAID ingestion in asymptomatic or otherwise healthy individuals (ie, no history of chronic urticaria). These reactions typically develop within 1 to 6 hours of exposure to a COX-1 inhibiting NSAID. Isolated angioedema may be seen and is often localized to the face with particular involvement of the periorbital skin, lips, and mouth.<sup>16</sup>

Although affected individuals, by definition, are considered “healthy,” it has been reported that up to 60% have underlying atopic disease (ie, allergic rhinitis, asthma). Sensitization to various inhalant aeroallergens and increased serum levels of total IgE are frequently identified.<sup>17</sup> As with other nonimmunologic reactions, the pathogenesis is thought to be tied to COX-1 inhibition. However, given the increased incidence of atopy in these patients, the involvement of IgE-related mechanisms should also be considered (but remains to be established).

Avoidance of ASA and other cross-reactive NSAIDs generally results in symptom resolution. Like patients with NECD, those affected by NIUA generally do well with selective COX-2 inhibitors. It is unknown whether individuals with NIUA are more likely to go on to develop chronic urticaria compared with the general population. However, a recent long-term study suggested no difference in overall risk between NIUA patients and healthy control subjects.<sup>18</sup>

### ***Mixed nonsteroidal antiinflammatory drug-induced reactions***

Occasionally, NSAID-induced symptomatology does not fit into any of the 3 categories described and manifests as a mixed reaction of subtypes. For example, some healthy individuals (ie, without underlying AERD) can develop a combination of respiratory and cutaneous symptoms after ingestion of COX-1 inhibiting NSAIDs. Additionally, it has been reported that nearly 18% of NIUA and 10% of NECD patients develop concomitant respiratory symptoms (eg, bronchospasm) after NSAID ingestion.<sup>19,20</sup> The time course of symptom onset is variable, but generally similar to the other nonimmunologic hypersensitivity subtypes.

### ***Immunologic hypersensitivity reactions***

In contrast with the nonimmunologic/pseudoallergic hypersensitivity reactions described, these reactions are thought to be allergen-induced (drug metabolite bound to a carrier protein), IgE-mediated hypersensitivity reactions. These reactions are different from the nonimmunologic subtypes in that they are provoked by a single NSAID, or occasionally by another with similar chemical structure (see [Table 1](#)). After exposure to the culprit NSAID, patients may experience a wide range of symptoms, from mild urticaria to life-threatening anaphylaxis, but are able to tolerate chemically dissimilar NSAIDs, including ASA.<sup>21</sup>

The NSAIDs most often linked with these immune responses are ibuprofen (most common in the United States), diclofenac, members of the pyrazolone class, and paracetamol.<sup>22–24</sup> Patients who experience these types of reactions need to have

had at least one prior exposure to the particular NSAID to become sensitized to the drug. Thus, this serves as an important diagnostic clue when evaluating an individual with an NSAID-induced reaction.

Allergic hypersensitivity reactions can be divided as follows:

- Single NIUA and
- Single NSAID-induced anaphylaxis.

The difference between these 2 categories is solely based on the severity of the reaction. It is plausible that most patients with single NIUA would progress to anaphylaxis if they continued to repeatedly ingest that particular NSAID. Therefore, many experts consider these to be a single reaction and refer to it as “single NIUA/anaphylaxis.”

Symptoms classically present within the first 30 to 60 minutes of NSAID ingestion, although they may arise within a matter of minutes, depending on the route of administration of the drug (ie, parental vs oral).<sup>25</sup> Most affected individuals are healthy (without underlying disease) and report onset of urticaria or localized angioedema after ingestion of the single NSAID. Nonetheless, up to one-third of patients may experience true anaphylaxis with risk of death.<sup>19,23</sup> Those patients will often have a past history of urticarial reactions to the offending NSAID, but continued to expose themselves to the drug owing to not recognizing the association of the 2 actions.

The majority of the COX-1 inhibiting NSAIDs have been implicated in reports of anaphylaxis, as well as the selective COX-2 inhibitor, celecoxib.<sup>26,27</sup> It is important to note that there have been no identified cases of anaphylaxis to ASA. For this reason, ASA is frequently used in oral challenge procedures during the diagnostic work-up of NSAID-induced reactions.

### ***Nonsteroidal antiinflammatory drug-induced delayed hypersensitivity reactions***

Some experts consider this a subset of allergic hypersensitivity reactions, although the pathomechanism of these reactions are secondary to drug-specific CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte interactions rather than an IgE-mediated process. By definition, these reactions occur more than 24 hours after drug exposure and are therefore considered a delayed type of hypersensitivity reaction. Cutaneous reactions are most commonly implicated, including maculopapular eruptions, fixed drug eruptions, and photosensitivity reactions.<sup>28,29</sup> Organ injury (eg, pneumonitis, nephritis) and other severe reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis) have also been documented.<sup>30–32</sup>

## **DIAGNOSTIC APPROACH TO NONSTEROIDAL ANTIINFLAMMATORY DRUG-INDUCED REACTIONS**

The diagnostic workup for any adverse reaction to NSAIDs is heavily weighted on obtaining a detailed history of the particular drug reaction, including the timing, symptom pattern, and intolerance to other NSAIDs, as well as the presence of medical comorbidities. At present, there are no recommended or validated skin tests or in vitro tests to confirm the diagnosis of any subtype of NSAID hypersensitivity. Referral to an allergy specialist with expertise in drug allergy is encouraged, particularly for those patients who have experienced severe reactions with NSAID ingestion and/or have a medical indication for ongoing NSAID therapy.

### ***History***

When evaluating a patient with a history of an adverse NSAID-induced reaction, the following questions should be assessed.<sup>33</sup>

***Is this a predictable (type A) or unpredictable (type B/hypersensitivity) reaction?***

Type A NSAID reactions commonly manifest as GI symptoms and increased bleeding/bruising and/or nephrotoxicity, and are strongly related to the duration and dose (higher doses = higher risk) of the drug. Type A reactions can often be prevented by reintroducing the drug at a lower dose.

***How long does it take for the reaction to develop after ingestion of a nonsteroidal antiinflammatory drug?***

NSAID hypersensitivity reactions are likely if symptoms occur within the first few hours (1–6 hours) of NSAID ingestion. However, the time to symptom onset does not determine the specific type or pathophysiology of the reaction. For example, an IgE-mediated mechanism (single NIUA/anaphylaxis) may be considered if the reaction occurs within minutes of ingestion, but this pattern could also be seen in a nonimmune reaction (ie, NECD) if the patient is highly sensitive to the drug and is challenged with a drug dose exceeding their tolerance threshold. Reactions occurring more than 24 hours after NSAID ingestion are likely delayed-type hypersensitivity or idiosyncratic reactions.

***What are the symptoms that accompany the reaction?***

Assess for the presence of nasal (rhinorrhea, nasal congestion), ocular (periorbital edema, conjunctival injection), laryngeal (throat tightness, laryngospasm), bronchial (cough, wheezing, shortness of breath), cutaneous (urticaria, angioedema, flushing), GI (nausea, vomiting, abdominal pain, diarrhea), and cardiovascular (hypotension, chest pain) symptoms.

***Does the patient have any underlying chronic medical disease?***

In general, NSAID-exacerbated rhinosinusitis/asthma and NECD are associated with underlying disease, whereas NIUA and SINUA commonly affect healthy individuals.

***Is there a history of intolerance to other nonsteroidal antiinflammatory drugs?***

This question is extremely important, because it allows the clinician to determine whether the patient's hypersensitivity reaction is cross-reactive to other NSAIDs (nonimmunologic) or solely connected to a single drug. A detailed history of past NSAID exposure, including name and dose of the drug, both before and after the NSAID reaction occurred should be documented. Remember that certain patients may only report sensitivity to NSAIDs of a similar chemical structure.

The clinician should also assess for the presence of ASA tolerance/intolerance. If a patient is able to tolerate ASA or other strong COX-1 inhibitors (ibuprofen, ketorolac), their previous NSAID reaction is strongly suggestive of an immunologic/allergic hypersensitivity reaction.

Some experts propose the following guidelines<sup>34</sup>:

- A nonimmunologic hypersensitivity reaction should be considered if there is a history of 3 or more adverse reactions to 2 or more different NSAIDs.
- An immunologic hypersensitivity reaction should be considered if there is a history of 2 or more reactions to the same NSAID with history of tolerance to another NSAID.

***Diagnostic Testing***

The importance of obtaining a detailed history is not to be overlooked because there are no recommended in vitro or allergen skin tests to assist with confirming the diagnosis. Various testing modalities have been studied, including basophil activation testing, autologous serum skin testing, and analysis of genetic polymorphisms, but

these have shown mixed results and therefore have not been validated for use in the diagnostic workup of ASA/NSAID hypersensitivity.<sup>35</sup> There have been a few cases showing a potential benefit of intradermal skin testing in the setting of single NIUA/anaphylaxis, but it has been rejected as a diagnostic tool owing to poor sensitivity and risk of systemic reactions.<sup>10,24,36</sup>

### **Drug Challenge**

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Despite its diagnostic importance during evaluation of a suspected NSAID hypersensitivity reaction, a patient's clinical history has been shown to have an overall low specificity.<sup>37</sup> One study reported that more than 78% of patients with a past adverse reaction to an NSAID ultimately tolerated a subsequent oral challenge to that NSAID.<sup>38</sup> Thus, even with a supportive history, an oral drug challenge may be necessary to definitively rule in or out a diagnosis of NSAID hypersensitivity.

The strongest indication to perform a provocative oral challenge is for an affected individual who has a medical indication that warrants ongoing NSAID therapy, such as concomitant cardiovascular disease or a chronic inflammatory condition (ie, arthritis). An oral challenge enables the clinician to determine which type of reaction was present and what other NSAIDs the patient may safely tolerate in the future. With regard to patients with AERD, a positive ASA challenge confirms sensitivity to ASA and whether the patient may benefit from ASA desensitization and continuous ASA therapy.

Drug challenges are not without risk and should always be pursued with caution. Therefore, they are seldom recommended for patients with a history of an anaphylactic reaction to NSAIDs. In these situations, it is best to strictly avoid the culprit drug. General avoidance of NSAIDs is also a conservative and practical option for those patients who do not have a medical need for NSAID therapy.

Challenge protocols consist of a gradual administration of an increasing dose of NSAID (**Table 3**).<sup>39</sup> ASA is most often used and considered the "gold standard" of NSAID challenges because there have been no confirmed cases of anaphylaxis to the drug.

- A positive ASA challenge confirms presence of cross-reactivity and is consistent with a nonimmunologic type of reaction.
- A negative ASA challenge excludes cross-reactivity and is strongly supportive of an immunologic reaction to the single NSAID which caused the past adverse reaction.

In the case that ASA is the culprit drug, the patient can be challenged with an alternative strong COX-1 inhibitor (ie, ibuprofen) with similar conclusions based on a positive or negative challenge result.

### **MANAGEMENT OF HYPERSENSITIVITY REACTIONS TO NONSTEROIDAL ANTIINFLAMMATORY DRUGS**

Various options are available to successfully manage NSAID hypersensitivity. Nonetheless, all decisions depend on the correct identification of the type of reaction the patient experienced. If the reaction type is unclear, it is always best to have the patient strictly avoid all NSAIDs until additional evaluation can be performed by a drug allergy specialist.

Pharmacologic treatment options, listed by reaction subtype, are presented in this section. As a general rule, the best option for the affected patient is contingent upon their antiinflammatory and/or pain relief requirements.

**Table 3**  
**Oral ASA/NSAID challenge protocols based on suspected subtype of NSAID hypersensitivity reaction**

| Suspected Subtype of NSAID Hypersensitivity Reactions | NSAID-Exacerbated Asthma and Rhinosinusitis (AERD) <sup>a</sup> | NECD/NIUA <sup>b</sup> | Mixed NSAID-Induced Reactions | Single NSAID-Induced Urticaria/Angioedema <sup>c</sup> | Single NSAID-Induced anaphylaxis <sup>c</sup> |
|-------------------------------------------------------|-----------------------------------------------------------------|------------------------|-------------------------------|--------------------------------------------------------|-----------------------------------------------|
| Starting dose of ASA (mg)                             | 40.5                                                            | 40.5                   | 40.5                          | 162                                                    | 162                                           |
| Amount of ASA increased per step <sup>d</sup>         | Double prior dose                                               | Double prior dose      | Double prior dose             | Double prior dose                                      | Double prior dose                             |
| Interval time between steps                           | 3 h                                                             | 90 min                 | 90 min                        | 3 h                                                    | 3 h                                           |
| Common reaction doses (mg)                            | 60–100                                                          | 162–650                | 60–100                        | —                                                      | —                                             |

**Abbreviations:** AERD, aspirin exacerbated-respiratory disease; ASA, aspirin; NECD, NSAID-exacerbated cutaneous disease; NIUA, NSAID-induced urticaria/angioedema; NSAID, nonsteroidal antiinflammatory drug.

<sup>a</sup> Patients should be pretreated with leukotriene modifying drug (ie, montelukast) and inhaled corticosteroid/long-acting beta-agonist combination (ICS/LABA) before challenge. ASA challenge is to determine whether patients are sensitive to ASA and might benefit from continuous daily ASA therapy. This is not a desensitization protocol.

<sup>b</sup> If ASA is required for cardiovascular protection, challenge can stop once patient reaches 81 mg without reaction. However, consider challenging to full 325 mg dose to confirm lack of persistent sensitivity to ASA because NSAID-exacerbated cutaneous disease (NECD) patients can often tolerate 81 mg but not full-strength ASA/NSAID.

<sup>c</sup> Culprit NSAID should be avoided. ASA or other NSAID (structurally unrelated to the culprit drug) should be used during the challenge. These patients are challenged to rule out presence of a nonimmunologic reaction; therefore, symptom onset is not expected.

<sup>d</sup> The challenge is stopped when the patient has a reaction or the desired therapeutic dose is reached.

### ***Nonimmunologic Hypersensitivity Reactions***

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#### ***Acetaminophen (paracetamol)***

This is the simplest, and most likely cost-effective, option as long as the patient does not require an antiinflammatory pain reliever. Acetaminophen is generally well-tolerated at up to 650 mg per dose.<sup>25</sup> At higher doses (ie, 1000 mg), patients may experience untoward reactions owing to weak COX-1 inhibition that is induced at these doses.

#### ***Weak cyclooxygenase-1 inhibitors***

This is a valuable choice for patients who desire antiinflammatory treatment, on the condition that they get adequate pain relief from these low potency NSAIDs. As with acetaminophen, these drugs may inhibit COX-1 at higher doses. If the patient's historical reaction to an NSAID was severe, some experts suggest administering the first dose (or the highest dose the patient is expected to tolerate) in a medically supervised setting.

#### ***Weak cyclooxygenase-2 inhibitors***

There are few data on the use of these agents in patients with nonimmunologic NSAID hypersensitivity reactions. Therefore, they should be strictly avoided or given for the first time in a medically supervised setting.

#### ***Selective cyclooxygenase-2 inhibitors***

With few exceptions, these are well-tolerated by patients and an excellent option for those who require strong antiinflammatory or pain reliever treatment. Additionally, this is a favorable option for patients who have experienced GI side effects from NSAID therapy. It is generally recommended that patients start at a low dose of the medication and gradually increase the dose as tolerated, particularly in those with AERD.

### ***Immunologic Hypersensitivity Reactions***

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Given the IgE-mediated nature of these reactions and subsequent risk for anaphylaxis, all patients with these types of reactions should strictly avoid the culprit NSAID. As mentioned, if there is any uncertainty regarding the type of reaction the patient experienced, a drug challenge with ASA (under the guidance of an allergy specialist) should be considered to definitely exclude a nonimmunologic reaction. Once the diagnosis is confirmed, patients may safely take NSAIDs that are chemically dissimilar to the drug that caused the initial reaction (see [Box 1](#)). Desensitization to the culprit NSAID is not recommended given the risk of the procedure and availability of other COX-1 inhibitors for any necessary antiinflammatory treatment.

#### ***Desensitization***

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If the patient has undergone a positive oral challenge and requires chronic NSAID therapy, the clinician may elect to pursue NSAID desensitization to induce tolerance to the drug. The process of desensitization is essentially a continuation of the challenge protocol until the patient reaches the desired dose of the medication and has no further adverse reactions. Of the various nonimmunologic reaction subtypes, AERD responds most favorably to desensitization (see [Waldram JD, Simon RA: Performing Aspirin Desensitization in Aspirin Exacerbated Respiratory Disease](#), in this issue). It has shown mixed results with the other forms of nonimmunologic reactions and is generally unsuccessful for patients with NECD. It is not recommended for affected patients with immunologic reactions owing to the potential risk of inducing anaphylaxis during the procedure.

## SUMMARY

NSAIDs are among the most common causes of ADRs worldwide. Symptoms of NSAID sensitivity range from predictable side effects to life-threatening anaphylaxis. The ability to appropriately diagnose and categorize these reactions is crucial. Our understanding of both the immunologic and nonimmunologic mechanisms of these reactions, along with the pharmaceutical development of selective COX-2 inhibitors, has greatly influenced our ability to successfully manage these patients.

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