

Classification of Reactions to Nonsteroidal Antiinflammatory Drugs

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KEYWORDS

- Nonsteroidal antiinflammatory drugs • Aspirin • Hypersensitivity • Adverse effects
- Aspirin exacerbated respiratory disease (AERD)

KEY POINTS

- Adverse reactions to aspirin or other NSAIDs may occur in up to 30% of drug taking patients.
- Hypersensitivity reactions occurring in small number of patients taking NSAIDs may be either non-immunological (cross-reactive) or allergic (IgE or T-cell mediated).
- Assignment of a patient reaction to one of the specific categories allows for the application of the most effective diagnostic procedures.
- Proper classifications of the reaction may allow for type-specific patient management.

HISTORY OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin, are among the most commonly used drugs in the world, with billions of tablets taken over the counter or sold as prescriptions every year.¹ The history of their development is fascinating and dates back to the nineteenth century. Antipyrine was synthesized by German chemist Ludwig Knorr in 1883 and sold as an oral antipyretic and analgesic. Although not known at the time, antipyrine inhibits cyclooxygenase (COX). Antipyrine was sold as an oral drug under the name of Phenazone, until cases of agranulocytosis led to its discontinuation by the manufacturer in the 1930s. However, it is currently in use as one component of an ear drop, along with a local anesthetic benzocaine.

Acetylsalicylic acid, the second NSAID, was synthesized in 1897 by Felix Hoffman, who bound salicylic acid, extracted from willow bark, with acetic acid. Hoffman's father treated his own rheumatism with salicylic acid, which induced an adverse effect of abdominal pain. Hoffman's unrealized hope was to relieve his father of

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abdominal pain by changing the molecule and thus decreasing gastrototoxicity, previously assumed to be a direct toxic effect of salicylic acid. Two years later, the molecule was commercialized by the Bayer Company under the name “aspirin,” but Felix Hoffman, an employee of the company, received no royalties or compensation for his efforts. At the same time, aspirin started an amazing world career as a painkiller, antiinflammatory compound, and antithrombosis drug.

In 1922, Widal and colleagues² conducted oral challenges with aspirin and antipyrine in a patient with all the characteristics of aspirin exacerbated respiratory disease (AERD). Both aspirin and antipyrine initiated asthma attacks and profuse rhinorrhea during oral drug challenges, whereas chloral hydrate of quinine, urotropin, and pyramidon did not initiate any reactions. The second nonaspirin NSAID is phenylbutazone, which was introduced in 1952. It was followed in the 1960s by indomethacin and ibuprofen.³ Since then, numerous COX-1 inhibiting compounds, with similar antiinflammatory activity and wide therapeutic applications for pain and inflammatory disorders, were synthesized and commercialized. However, with success comes problems, and the clinical efficacy of aspirin and other NSAIDs has been accompanied by a variety of common side effects during both short- and long-term therapies. Thus, designing less toxic compounds has continued to be an insurmountable challenge for pharmacologists of the twentieth and the twenty-first centuries as it was for Ludwig Knorr and Felix Hoffman at the end of the nineteenth century.

In 1971, Sir John Vane published his breakthrough discovery of the mechanism of antiinflammatory activity of aspirin and other NSAIDs.⁴ In his Nobel Prize-winning experiments, he used a bioassay to demonstrate that NSAIDs share common pharmacologic effects, namely, inhibition of prostaglandin synthesis. His discoveries led to an understanding of the molecular mechanism of the activity of NSAIDs, which derives from their ability to specifically inhibit COX, originally called prostaglandin G/H-synthase, which is responsible for the biosynthesis of all downstream prostanoids (prostaglandins, prostacyclin (PGI₂), and thromboxane) (Fig. 1).⁵ It is imperative that

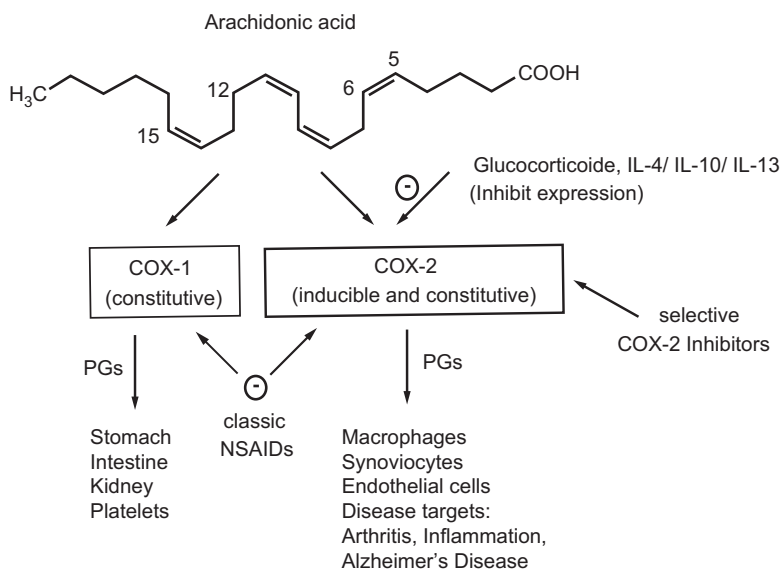


Fig. 1. Arachidonic acid metabolism and the mechanism of NSAID activity.

the allergy consultant understand this pharmacologic effect of NSAIDs because most of the positive and adverse effects of NSAIDs are through this pathway. COX, which is the first enzyme in the generation of prostanoids from arachidonic acid, exists in 2 distinct isoforms, referred to as COX-1 and COX-2.^{6,7} COX-1 is expressed constitutively in most mammalian cells and is a major source of prostanoids that have important positive housekeeping functions, such as gastric epithelial cytoprotection by PGI₂. COX-2 is expressed either constitutively or after induction by inflammatory stimuli, hormones, and growth factors and generates prostanoids important for inflammation and is also involved in reproduction, renal physiology, bone resorption, and neurotransmission.⁸ Discovery of COX isoforms prompted the development of molecules with selective inhibitory activity for COX-2, resulting in the introduction of a new class of NSAIDs, namely, COX-2 inhibitors (coxibs). These new compounds, although expressing strong antiinflammatory activity, have less gastrointestinal (GI) toxicity due to their preferential inhibition of COX-2 and inability to prevent the synthesis of COX-1 products, such as PGI₂, which is cytoprotective for gastric mucosa.⁹ Both COX-1 and COX-2 inhibitors temporarily block COX enzyme channels and are therefore competitive inhibitors. Aspirin, on the other hand, acetylates COX enzymes, causing irreversible destruction. However, several reports have suggested that NSAIDs may also exert their therapeutic benefits by other mechanisms that are parallel to COX-1 inhibition (eg, direct inhibition of “inflammatory” transcription factors (nuclear factor-kappaB [NFkB]) or induction of resolvins generation). Thus, the understanding of their activities is still evolving.^{10,11}

Differences in the molecular structures of NSAIDs may have important implications, not only for their shared ability to inhibit COX but also from an immunologic perspective. Their diverse molecular structures determine the differences in the capacity of specific NSAIDs to induce immune responses and the development of IgE-mediated or T-cell-mediated allergic reactions in susceptible individuals, which is the most confusing feature of reactions to NSAIDs. There is a group of molecules, with different structures, all of which block COX, with its confusing consequences. At the same time, each NSAID is uniquely antigenic, capable of sensitization in unlucky patients, followed by reexposure and a whole spectrum of immune reactions that are specific to that sensitizing NSAID. To make things even more complicated, some NSAIDs share epitopes and can therefore be recognized by antibodies or T cells, even though they are different NSAIDs (Figs. 2 and 3). Based on their similar molecular structures, NSAIDs have been categorized into several classes (Table 1), with some classes (eg, pyrazolones or oxicams) showing higher immunogenicity, leading to more frequent sensitization and anaphylactic reactions in sensitized patients.¹² Furthermore, structural similarities between NSAIDs tend to determine immunologic cross-reactivity, resulting in allergic reactions to drugs belonging to specific chemical classes.¹³

ADVERSE REACTIONS TO NSAIDS

As with any drug, NSAIDs may be associated with the development of unwanted, adverse effects or reactions. According to the definition by the World Health Organization, an adverse drug reaction (ADR) is “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiologic function.”¹⁴ Thus, ADR is an umbrella description that covers any observed unwanted effects following the intake of the drug (regardless of the dose, timing, and host factors), providing there is a causal link between a drug and the observed undesirable effect (reaction). The most common adverse effects are in the digestive tract. Abdominal pain, occurring in 10% to 20% of subjects after a few days or weeks of ingesting daily NSAIDs, is the usual presenting

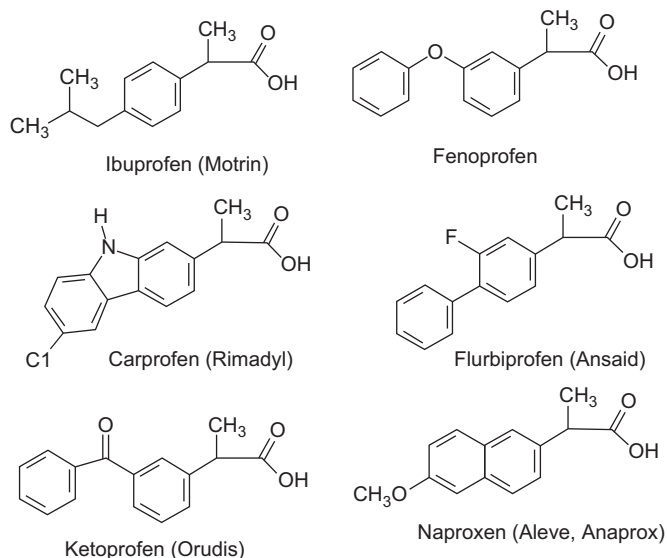


Fig. 2. Chemical structures of propionic acid NSAIDs.

symptom of NSAID-induced gastritis. It is due to the inhibition of COX-1 and the interruption of the synthesis of PGI₂. Likewise, increased bleeding, particularly in the skin, GI tract, genitourinary tract, and joints is a direct pharmacologic effect of aspirin through inhibition of thromboxane synthesis in platelets. It is rarely seen with the other NSAIDs.

However, in some patients, NSAIDs may induce acute adverse reactions in the skin (urticaria and angioedema, erythema multiforme, Stevens Johnson Syndrome [SJS], or toxic epidermal necrolysis [TEN]), respiratory tract (rhinitis, vocal cord spasm, or asthma attacks), or other organs (nephritis, hepatitis, pneumonitis, or anemia). Acute multiorgan systemic reactions such as anaphylaxis and chronic systemic reactions such as drug reactions with eosinophilia and systemic symptoms (DRESS) can also be caused by some NSAIDs.

From a practical standpoint, it is critical to distinguish between adverse effects occurring in otherwise normal patients (dose related) and NSAID reactions, which appear in small numbers of patients (non-dose related and possibly allergic). Although more recently pharmacologists proposed 6 categories of ADRs,¹⁵ for the purpose of daily clinical practice a traditional classification distinguishing type A and type B ADRs might be more useful (**Fig. 4**).¹⁶

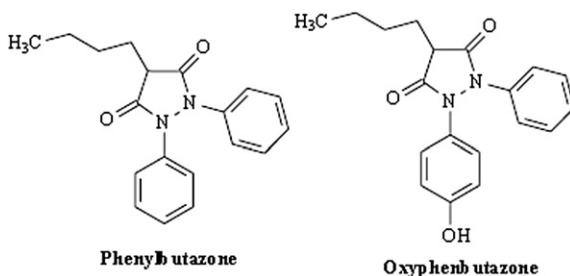


Fig. 3. Chemical structures of 2 different butazones.

Table 1 NSAIDs grouped in classes determined by similar chemical structures	
Group	Drugs
Salicylic acid derivatives	Aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfalazine, olsalazine
Para-aminophenol derivatives	Acetaminophen
Indol and indene acetic acids	Indomethacin, sulindac, etodolac
Heteroaryl acetic acid	Tolmetin, diclofenac, ketorolac
Arylpropionic acid	Ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin
Anthranilic acid (fenamates)	Mefenamic acid, meclofenamic acid
Enolic acid	Oxicams (piroxicam, tenoxicam), pyrazolidinediones (phenylbutazone, oxyfentathrazone)
Alkalones	Nabumetone
Pyrazolic derivatives	Antipyrine, aminopyrine, dipyrone

Data from Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A, et al. Hypersensitivity reactions to non-steroidal anti-inflammatory drugs: an update. *Pharmaceuticals* 2010;3:10–8.

Type A reactions, also called dose-related or augmented reactions, are common and predictable, because they are related to the pharmacologic action of the drugs. They may occur in any healthy subject who takes a drug in sufficiently high doses. These reactions tend to have low morbidity and mortality and in some cases can be managed by dose reduction.

In contrast, type B reactions (called non-dose related or “bizarre”) are less common, unpredictable, and associated with high mortality. Type B NSAID-induced reactions, which occur in a small fraction of susceptible patients and are of interest because they include various types of hypersensitivity reactions, are traditionally designated as allergic, pseudoallergic, or idiosyncratic. In agreement with the nomenclature recommended by the European Academy of Allergy and Clinical Immunology (EAACI)/World Allergy Organization, drug hypersensitivity reactions are defined as “objectively reproducible signs or symptoms initiated by a drug at a dose tolerated by

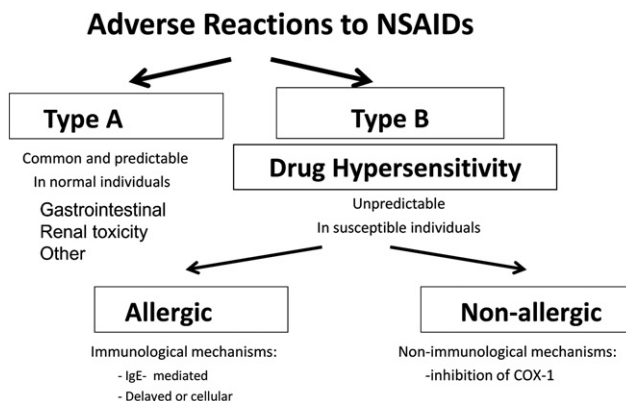


Fig. 4. Classification of NSAID-induced adverse reactions.

normal subjects” and are divided into immunologic (allergic) and nonimmunologic (nonallergic) reactions.^{17,18} Thus, the term “drug allergy” should be used only for drug hypersensitivity reactions with a clearly defined immunologic (IgE- or non-IgE-mediated) mechanism, whereas “nonallergic” drug hypersensitivity should refer to other reactions with other pathogenic mechanisms. Accordingly, poorly defined terms traditionally used to describe drug reactions, such as idiosyncrasy, pseudoallergy, or intolerance should be abandoned. This modern classification of drug hypersensitivity reactions has practical implications for diagnosis and management and can be directly applied to the classification of NSAID hypersensitivity reactions.¹⁹

CLASSIFICATION OF NSAID-INDUCED HYPERSENSITIVITY REACTIONS

In 1902, only a few years after aspirin was commercially available, Dr Hirschberg from Poznań in western Poland reported the first case of a hypersensitivity reaction to aspirin manifesting as angioedema and dyspnea.²⁰ The first hypersensitivity reaction in an asthmatic patient was reported in 1910 by Dr Gilbert from Colorado,²¹ and since then many different hypersensitivity reactions to aspirin affecting the skin, the respiratory tract, and other organs have been reported. The association of aspirin hypersensitivity, nasal polyposis, and asthma was described by Widal and colleagues² in 1922, and the syndrome defined as “aspirin triad” was characterized in a larger group of patients by Samter and Beers²² in 1968. With the subsequent introduction of new NSAIDs, a variety of hypersensitivity reactions have been continuously reported.^{23–26} The prevalence of NSAID hypersensitivity in the general population is high (varying from 0.5% to 5.7 %), and in some studies it is higher than allergy to antibiotics.^{27,28} However, in high-risk populations, NSAIDs may induce hypersensitivity reactions in up to 20% in asthmatics with nasal polyps and pansinusitis (particularly in severe asthmatics) or 30% in patients with chronic idiopathic urticaria.¹⁹

Hypersensitivity reactions to NSAIDs vary in symptom (skin, respiratory tract, and solid organs), severity (from mild skin or respiratory reactions to severe generalized SJS/TEN or DRESS), and timing (may occur immediately after drug intake or weeks later). Over the years, the nomenclature of these reactions has become complicated and confusing because several poor descriptive terms have been used to describe various reactions (eg, aspirin allergy, idiosyncrasy, pseudoallergy, or intolerance), with little attention to the progress in understanding the mechanisms of these reactions. Samter and Beers²² coined the term “aspirin triad” (nasal polyps, asthma, and aspirin-induced respiratory reactions). Triad has been replaced with the descriptor “aspirin exacerbated respiratory disease” (AERD).

Further progress in the classification of NSAID-induced reactions emerged with the understanding of the pathologic mechanism of reactions to NSAIDs. Before Max Samter’s keen observations,²² these reactions were suspected to be allergic. Over time, it became apparent that no NSAID-specific IgE or T cells could be identified. For decades, physicians were puzzled by the observations that patients sensitive to aspirin also cross-reacted to other NSAIDs, whose molecular structures were completely different and could never be recognized by antibodies or T cells. New light on that dilemma was shed in 1975 by Szczeklik and colleagues,²⁹ who demonstrated that the capacity of NSAIDs to induce respiratory and/or skin reactions was closely related to the drug’s ability to prevent prostaglandin synthesis. Combining results of clinical experiments (involving provocation tests with NSAIDs) and laboratory tests (using bioassay developed by John Vane to assess the potency of NSAIDs), Szczeklik and his group documented that only NSAIDs that were strong prostaglandin inhibitors *in vitro* were capable of eliciting adverse respiratory reactions during clinical

challenges in a subpopulation of asthmatics who are now known to have had AERD.³⁰ These experiments gave rise to the “prostaglandin hypothesis,” which, for the first time, explained the phenomenon of cross-reactivity to NSAIDs observed in patients with asthma or urticaria. It was discovered later that NSAIDs block COX-1 and COX-2 but that only NSAIDs that are strong COX-1 inhibitors are capable of inducing adverse respiratory or skin reactions. On the other hand, selective COX-2 inhibitors are generally well tolerated, because COX-1 continues to function. This finding led to the follow-up “cyclooxygenase hypothesis.”³¹ According to this theory, in susceptible individuals, inhibition of COX-1, but not COX-2, by any NSAID, leads to an acute deficiency of protective prostaglandins, which in turn results in the activation of inflammatory cells, with subsequent generation of potent mediators responsible for the development of symptoms of hypersensitivity. Originally, such a nonimmunologic mechanism was documented only for respiratory reactions occurring in patients with asthma/rhinosinusitis/nasal polyps, but it is now known that this also occurs in patients with chronic urticaria. To further complicate the picture, in some patients hypersensitivity reactions can be evoked only by a single NSAID or only a group of closely chemically related compounds (see **Figs. 2** and **3**), whereas other NSAIDs, with different chemical structures, are well tolerated.³² In these patients developing either acute or delayed reactions, immunologic mechanisms of hypersensitivity are highly likely to be mediated by specific IgE antibodies or T cells.³³

In 2001, Stevenson and colleagues³⁴ proposed a new classification of hypersensitivity reactions to NSAIDs, which was based on the spectrum of observed symptoms and included the presence or absence, in the affected patient, of the underlying chronic diseases (**Table 2**). Furthermore, for the first time, subtypes of hypersensitivity were defined while taking into account not only clinical descriptions but also putative pathologic mechanisms. This classification has been widely accepted and with minor modifications recommended for the diagnosis and management of patients with NSAID hypersensitivity.¹⁹

Description of Reactions	Underlying Disease	Cross-reactions	Current Terminology
NSAID-induced rhinitis and asthma	Asthma/nasal polyps/sinusitis	Yes	Intolerance, ASA-induced, sensitivity
NSAID-induced urticaria/angioedema	Chronic idiopathic urticaria	Yes	Acute/chronic urticaria angioedema
Single drug-induced urticaria/angioedema	None	No	Acute urticaria/angioedema
Multiple drug-induced urticaria/angioedema	None	Yes	Acute urticaria
Single drug-induced anaphylaxis	None	No	Anaphylactoid
Single drug- or NSAID-induced blended reactions	Asthma, rhinitis, urticaria or none	No or yes	Asthma and urticaria

Abbreviation: ASA, acetylsalicylic acid.

Data from Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. *Ann Allergy Asthma Immunol* 2001;87:177–80.

DEFINITIONS OF NSAID-INDUCED HYPERSENSITIVITY REACTIONS

Based on the original classification of Stevenson and colleagues,³⁴ further work has progressed and a new unified definitions of NSAID-induced hypersensitivity reactions have been proposed.¹⁹ Five major distinct types of reactions have been identified, 4 acute, occurring within minutes to several hours after exposure and 1 delayed, developing more than 24 hours after exposure. It should be emphasized that other blended reactions that cannot be assigned into any classification are encountered in clinical practice.

Aspirin Exacerbated Respiratory Disease

Hypersensitivity reactions, manifested primarily as bronchial obstruction, dyspnea, vocal cord spasm, ocular injection, and nasal congestion/rhinorrhea, occur in patients with underlying chronic airway respiratory disease (asthma/rhinosinusitis/nasal polyps). These patients have been said to have Widal syndrome, aspirin triad, asthma triad, Samter syndrome, aspirin-induced asthma or aspirin-sensitive rhinosinusitis/asthma syndrome, and aspirin-intolerant asthma. They are now called AERD.

Aspirin Exacerbated Cutaneous Disease

Reactions manifested by urticaria and/or angioedema occur in patients with histories of chronic idiopathic spontaneous urticaria. This type of reaction was previously referred to as aspirin-induced urticaria or chronic idiopathic urticaria with aspirin exacerbation.

Multiple NSAID-Induced Urticaria/Angioedema

Cutaneous reactions of urticaria and/or angioedema occur in otherwise healthy subjects who do not have a history of chronic spontaneous urticaria. At least 2 NSAIDs must induce urticaria, and these NSAIDs must have different chemical structures (do not belong to the same chemical group; see [Table 1](#)). This condition was previously called aspirin-induced urticaria.

Single NSAID-Induced Acute Reactions

In this condition, wheals, angioedema, and/or anaphylaxis is evoked by a single NSAID or by 2 or more NSAIDs (belonging to the same chemical group). Other chemically non-related NSAIDs are well tolerated, and if these patients have a history of chronic urticaria it is coincidental. Previously used names are single drug-induced reactions and NSAID allergic reactions.

NSAID-Induced Delayed Reactions

This condition is characterized by reactions to a single NSAID, developing within 24 to 48 hours to weeks after drug administration, manifested by skin reactions (eg, exanthema, fixed drug eruption), other organ-specific symptoms (eg, renal, pulmonary), or severe bullous cutaneous reactions.

A STEPWISE APPROACH TO THE DIAGNOSIS OF A PATIENT WITH HYPERSENSITIVITY TO NSAIDS

Taking into account the diversity of mechanisms, proper assignment of a patient with symptoms of NSAIDs hypersensitivity to one of the aforementioned types of reaction is important because it includes the application of the most effective diagnostic procedures (provocation, skin testing, and/or in vitro testing) and may result in type-specific patient management. Patients want to know which NSAIDs to avoid and which can be used in the future. In addition to avoidance, recommending alternative NSAIDs or

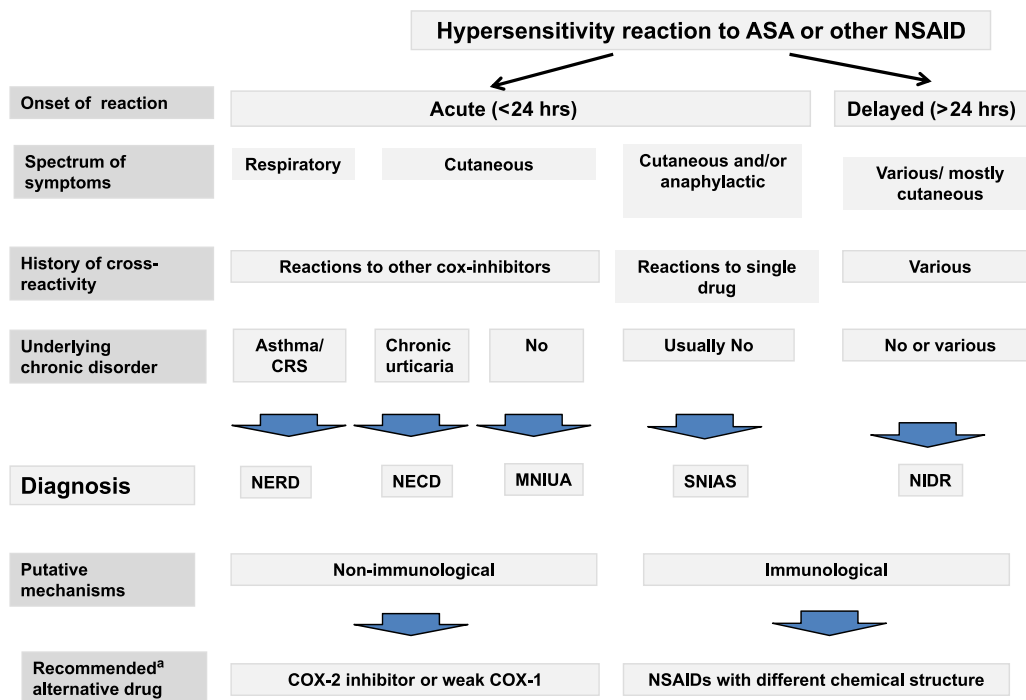


Fig. 5. Diagnosis and management of hypersensitivity to NSAIDs—a stepwise approach. AECD, aspirin exacerbated cutaneous disease; AERD, aspirin exacerbated respiratory disease; MNIUA, multiple NSAID-induced urticaria/angioedema; NIDR, NSAID-induced delayed reactions; SNIAR, single NSAID-induced acute reactions. ^a A tolerance test should be performed before the drug is recommended for regular use. (Data from 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;66:818–29.)

other drug solutions is an important part of such allergy consultations. Furthermore, some drugs are innocent bystanders, and avoidance of drugs that have not caused reactions and have present or potential therapeutic benefits is not helpful and may even deprive the patient of a life-saving medication. EAACI Task Force on NSAID hypersensitivity proposed a diagnostic algorithm, which uses a stepwise approach, facilitates classification of reaction to a specific type, and applies adequate diagnostic methods and avoidance.¹⁹ A modified algorithm is proposed for the classification of patients with hypersensitivity to aspirin or other NSAIDs (**Fig. 5**).

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