

## Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAACI/ENDA<sup>#</sup> and GA2LEN/HANNA<sup>\*</sup>

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**To cite this article:** Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, Bousquet P, Celik G, Demoly P, Gomes ER, Nizankowska-Mogilnicka E, Romano A, Sanchez-Borges M, Sanz M, Torres MJ, De Weck A, Szczeklik A, Brockow K. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAACI/ENDA and GA2LEN/HANNA. *Allergy* 2011; **66**: 818–829.

### Keywords

aspirin hypersensitivity; drug allergy; nonsteroidal anti-inflammatory drugs.

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Accepted for publication 17 January 2011

DOI:10.1111/j.1398-9995.2011.02557.x

Edited by: Hans-Uwe Simon

### Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for 21–25% of reported adverse drug events which include immunological and nonimmunological hypersensitivity reactions. This study presents up-to-date information on pathomechanisms, clinical spectrum, diagnostic tools and management of hypersensitivity reactions to NSAIDs. Clinically, NSAID hypersensitivity is particularly manifested by bronchial asthma, rhinosinusitis, anaphylaxis or urticaria and variety of late cutaneous and organ-specific reactions. Diagnosis of hypersensitivity to a NSAID includes understanding of the underlying mechanism and is necessary for prevention and management. A stepwise approach to the diagnosis of hypersensitivity to NSAIDs is proposed, including clinical history, *in vitro* testing and/or provocation test with a culprit or *alternative* drug depending on the type of the reaction. The diagnostic process should result in providing the patient with written information both on forbidden and on alternative drugs.

Following the first description of hypersensitivity reaction to aspirin (ASA) by Hirschberg in 1902, several types of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs

(NSAIDs) have been described. The NSAIDs-induced hypersensitivity reactions involve different mechanisms and present a wide range of clinical manifestations from anaphylaxis

or severe bronchospasm developing within minutes after drug ingestion to delayed-type responses appearing after days and weeks. The aim of this review prepared by a group of experts representing the EAACI/ENDA group and GA<sup>2</sup>LEN Network of Excellence is to present up-to-date information on the pathomechanisms and clinical spectrum of hypersensitivity reactions caused by NSAIDs. Additionally, practical recommendations for proper diagnosis and management of patients with NSAIDs hypersensitivity are proposed.

### Definition and classification

Several terms have been used to describe unintended and not predictable from the known pharmacology of the drug adverse reactions to NSAIDs: sensitivity, pseudoallergy, idiosyncrasy or intolerance but the term *hypersensitivity* seems to be the most appropriate and agrees with current international recommendations for nomenclature (1). Depending on the timing, symptomatology and putative mechanism of the reactions, several subtypes of hypersensitivity to NSAIDs have been distinguished (2, 3) (Table 1). In addition, some patients present mixed or blended reactions, which do not fall clearly into any of the proposed categories.

### Epidemiology

Nonsteroidal anti-inflammatory drugs have been reported to be the second most common cause of drug-induced hypersensitivity reactions (4). Aspirin (ASA) hypersensitivity affects

from 0.5% to 1.9% of the general population (5, 6). Prevalence of hypersensitivity to NSAIDs among adult asthmatic patients assessed by questionnaires or medical records is ranging from 4.3% to 11% (7) and can be as high as 21% if diagnosis includes provocation tests (8). Among patients with bronchial asthma and nasal polyps, the prevalence of ASA hypersensitivity may reach 25.6% (9). Cutaneous manifestations to NSAIDs may affect 0.3% of general population (5), and the prevalence of aspirin hypersensitivity may be as high as 27–35% in patients with chronic urticaria (10). NSAIDs have been reported to be the major (11) or the second group of drugs (12) responsible for anaphylactic reactions.

Hypersensitivity reactions to virtually all NSAIDs have been observed regardless of their chemical structure and/or an anti-inflammatory potency. The heteroaryl acetic acid group of NSAIDs (like naproxen, diclofenac, ibuprofen) seems to carry a higher risk of anaphylactic reactions than other groups (OR 19.7) (13). Pyrazolones are the most likely NSAIDs to induce immediate hypersensitivity reactions (14). Newly developed cyclooxygenase 2 selective inhibitors can also induce hypersensitivity reactions although with a very low, estimated at 0.008%, incidence (15).

The prevalence of delayed-type skin or systemic reactions to NSAIDs is not known, but severe life-threatening skin reactions as erythema multiforme, toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS) or drug reactions with eosinophilia and systemic symptoms (DRESS) are rare (16). Incidence of TEN in the general population has been estimated at 0.4–1.2 and for SJS at 1–6 cases per million person-years (15).

**Table 1** Classification of hypersensitivity reactions to ASA and other nonsteroidal anti-inflammatory drugs (NSAIDs) (Modified from [3])

Timing of reaction	Clinical manifestation	Type of reaction	Underlying disease	Putative mechanism
Acute (immediate to several hours after exposure)	Rhinitis/asthma	Cross-reactive	Asthma/rhinosinusitis/ nasal polyps	Inhibition of COX-1
	Urticaria/angioedema	Cross-reactive	Chronic urticaria	Inhibition of COX-1
	Urticaria/angioedema	Multiple NSAIDs-induced	No underlying chronic disease (in some patients, the reaction to NSAIDs may precede development of chronic urticaria)	Unknown Presumably related to COX-1 inhibition
	Urticaria/angioedema/ anaphylaxis	Single drug-induced	Atopy Food allergy Drug allergy	IgE-mediated
Delayed (more than 24 h after exposure)	Fixed drug eruptions. Severe bullous skin reaction Maculopapular drug eruptions Pneumonitis Aseptic meningitis Nephritis Contact and photocontact dermatitis	Single drug or multiple drug-induced	Usually no	T-cell-mediated (Type IV) Cytotoxic T cells NK cells Other

## Cross-reactive types of hypersensitivity to NSAIDs

### NSAID-induced rhinitis/asthma (Aspirin-Exacerbated Respiratory Disease: AERD)

#### Definition

The coexistence of hypersensitivity to aspirin (and to other NSAIDs) with upper airway (rhinosinusitis/nasal polyps) and lower airway (asthma) disease was referred to as aspirin triad, asthma triad, Widal's syndrome, Samter's syndrome, aspirin-induced asthma, aspirin intolerant asthma or aspirin-sensitive rhinosinusitis/asthma syndrome (17). More recently, the term *aspirin-exacerbated respiratory disease* (AERD) was proposed stressing the fact that the core issue in these patients is not drug hypersensitivity, but the underlying chronic inflammatory respiratory disease only occasionally exacerbated by aspirin or other NSAIDs (18).

#### Pathomechanisms

The mechanism of hypersensitivity to ASA and other NSAIDs in asthmatic patients is not immunological, but has been attributed by Szczeklik et al. (19) to pharmacological properties of the drugs, namely to inhibition of cyclooxygenase (COX), an enzyme that metabolizes arachidonic acid to prostaglandins, thromboxanes and prostacyclin. According to the 'cyclooxygenase' hypothesis, inhibition of COX-1 (but not COX-2) by ASA or other NSAIDs triggers mechanisms leading to asthmatic attack and/or nasal symptoms (20). It has been proposed that in AERD patients, deprivation of PGE<sub>2</sub> may lead to activation of inflammatory pathways, including increased local and systemic generation of cysteinyl leucotrienes. However, abnormalities in the lipoxygenase pathway of arachidonic acid (AA) metabolism (increased levels of urinary leucotrienes and upregulation of LTC<sub>4</sub> synthase or cysteinyl LT receptors in the airway tissue) are present at baseline as well (2). Several genetic polymorphisms (most related to AA metabolism pathway enzymes) have been associated with AERD.

#### Clinical manifestations

In patients with AERD, ingestion of aspirin or other NSAID induces within 30- to 120-min nasal congestion and watery rhinorrhea followed by shortening of breath and rapidly progressing bronchial obstruction (21). Respiratory symptoms are usually accompanied by other extrabronchial symptoms including ocular, cutaneous (flushing, urticaria and/or angioedema) or gastric symptoms. The threshold dose of aspirin during oral challenge defined as the smallest dose evoking a significant fall in FEV<sub>1</sub> seems to be an individual feature of a patient and varies from 10 mg (or even lower dose) up to 600 mg (21–23).

#### Underlying diseases

A typical patient with AERD is a 30- to 40-year-old woman with a history of asthma and/or chronic rhinosinusitis complicated by recurrent nasal polyps (2, 18, 21). Patients hypersensitive to aspirin suffer from persistent asthma of greater than average severity and of higher than ordinary medication requirements, including dependence on corticosteroids. Spi-

rin hypersensitivity is not only a significant risk factor for development of severe chronic asthma, but is also strongly associated with near-fatal asthma (24).

Most AERD patients suffer from chronic, usually severe form of rhinosinusitis and nasal polyps which have a high tendency to recur after surgery. The degree of polypoid hypertrophy of the sinus mucosa and severity of inflammation is more extensive in ASA hypersensitive when compared to ASA-tolerant patients (25).

#### Diagnosis

The diagnosis of ASA hypersensitivity is based on a reported history of adverse reactions precipitated with ASA and/or other NSAID. In patients without clear history, provocation tests are necessary to confirm or exclude hypersensitivity (26). In recent years, new *in vitro* testing methods have been proposed, but their usefulness for the diagnosis of NSAIDs hypersensitivity is still being debated (27).

*Provocation test with NSAIDs.* The most reliable method to confirm the diagnosis of hypersensitivity to NSAIDs in AERD patients is aspirin challenge (28). European (28) and American (29) guidelines on aspirin provocation tests have been recently published. Although sensitivity of oral, inhalation and nasal aspirin challenges (89%, 77–90% and 80–86.7%, respectively) do not differ significantly, oral challenge is considered to be the gold standard in confirming NSAID hypersensitivity (28–30). Oral and inhalation challenges should be performed under the supervision of physician skilled in performing provocation tests, and the emergency equipment should be available. It is contraindicated to perform oral and inhalation challenge in patients with unstable asthma or FEV<sub>1</sub> lower than 70% of the predicted value (28) or lower than 1.5 L according to American experience (recommendations) (31). Nasal aspirin challenge is recommended particularly for patients with severe asthma and may be performed in an outpatient clinic (27).

According to the protocol of the EAACI/GA<sup>2</sup>LEN, oral aspirin challenge takes 2 days: on the first day, 4 placebo capsules are administered, and on the second day, 4 increasing doses of ASA until a maximum single dose of 500 mg is reached or a clinical reaction has taken place (28). Other protocols recommend 325 mg as the maximal dose excluding hypersensitivity to aspirin (31). Both placebo and aspirin are administered at 1.5- to 2-h intervals, and FEV<sub>1</sub> is measured at the baseline and every 30 min. A decrease in FEV<sub>1</sub> ≥ 20% of baseline and/or appearance of clinical symptoms following aspirin administration (or ingestion) are considered as a positive reaction. Inhalation challenge involves administration of increasing doses of lysine-aspirin (L-ASA) with dosimeter-controlled jet-nebulizer every 30 min with FEV<sub>1</sub> measurement every 10 min after each ASA administration. Criteria of a positive response are the same as for oral aspirin challenge, and a dose–response curve is constructed to calculate the PC<sub>20</sub>. In nasal challenges, performed with increasing doses of lysine-aspirin, the response is evaluated by recording nasal symptoms quantified with a 10-cm visual analogue scale and in addition by one of objective

techniques: acoustic rhinometry, active anterior rhinomanometry or peak nasal inspiratory flow (PNIF) (28).

*In vitro diagnosis.* Several *in vitro* tests have been proposed to confirm aspirin hypersensitivity in patients with AERD, but none can be recommended for routine diagnosis (27). More recently, three *in vitro* tests measuring aspirin/NSAIDs-specific peripheral blood leucocyte activation have been proposed.

*Sulfidoleucotrienes release assay.* Aspirin can induce LTC<sub>4</sub> release from peripheral blood leucocytes (PBL) of sensitive patients, and measurement of sulfidoleucotriene release has been used for the diagnosis of AERD. However, the results of the studies are inconsistent (32, 33). The sensitivity of sulfidoleucotriene test could be further improved, if in addition to aspirin other NSAIDs were tested and the combined results analysed (34).

*Basophil activation test (BAT).* Measurement of cell surface molecule CD63 expression upon *in vitro* challenge has been proposed for *in vitro* diagnosis of AERD (35). However, reported specificity and sensitivity were variable, and no firm conclusion could be proposed for the reliability of this test in the routine setting (36).

*15-HETE generation assay (ASPITest).* Aspirin can specifically trigger *in vitro* generation of 15-hydroxyeicosatetraenoic acid (15-HETE), an arachidonic acid metabolite, from nasal polyp epithelial cells, and peripheral blood leucocytes from ASA-sensitive patients but not ASA-tolerant asthmatics or healthy subjects (37). Based on this observation, measurement of 15-HETE release from PBL has been proposed as Aspirin Sensitive Patient Identification Test (ASPITest<sup>®</sup>) (38). Clinical usefulness of this test has not yet been confirmed by larger studies.

#### Management of a patient with AERD

*Avoidance and alternative drugs.* Nonsteroidal anti-inflammatory drugs like indomethacin, naproxen, diclofenac or ibuprofen, which are strong cyclooxygenase inhibitors with dominant preferential activity towards COX-1, precipitate adverse symptoms in a significant (ranging from 30% to 80%) proportion of ASA-hypersensitive patients (19) (Table 2). Thus, a history of hypersensitivity reactions to one NSAID should prompt a strict avoidance of other NSAIDs with known moderate to strong cyclooxygenase inhibitory activity. On the other hand, NSAIDs with weaker inhibitory potency towards prostaglandin synthase (e.g. acetaminophen) and selective COX-2 inhibitors seem to be tolerated by patients with AERD (39) (Table 2).

Low doses of paracetamol (below 500 mg) are relatively safe, with a prevalence of adverse reactions ranging from 0% to 8.4% in NSAID-sensitive patients (19, 40). However, increasing the dose of paracetamol in challenge procedure was associated with an increased prevalence of bronchial

reactions to up to 30% after use of 1000 mg of paracetamol (41). In clinical practice, oral tolerance test should be performed with 500 mg of paracetamol before the drug is recommended for regular use.

The preferential COX-2 inhibitors meloxicam and nimesulide are quite well tolerated by most (86–96%) patients with AERD (42). However, high doses of COX-2 inhibitors with lower selectivity can lead to a loss of tolerance and induce hypersensitivity reactions (43). The use of nimesulide and meloxicam should be preceded by tolerance test. Selective COX-2 inhibitors are usually well tolerated (39, 42).

*Desensitization.* Repeated administration of aspirin may induce tolerance to aspirin. To maintain desensitization, a patient has to ingest aspirin on a regular, usually daily basis because the tolerance state disappears within 2–5 days after aspirin treatment has been interrupted (44). Aspirin desensitization may be indicated for patients who need daily treatment with aspirin and NSAIDs because of other diseases (e.g. coronary ischaemic disease or rheumatologic disorders). Moreover, chronic treatment with aspirin following desensitization alleviates the symptoms of rhinosinusitis and to less extent of asthma, reducing the requirement for systemic corticosteroids and decreases the number of polypectomies (45,

**Table 2** NSAIDs tolerance in patients with acute, cross-reactive type of aspirin hypersensitivity

Group A: NSAIDs cross-reacting in majority of hypersensitive patients (60–100%)	
Ibuprofen	Etololac
Indomethacin	Diclofenac
Sulindac	Ketoprofen
Naproxen	Flurbiprofen
Fenoprofen	Piroxicam
Meclofenamate	Nabumetone
Ketorolac	Mefenamic acid
Group B: NSAIDs cross-reacting in minority of hypersensitive patients (2–10%)	
Rhinitis/asthma type	
acetaminophen (doses below 1000 mg)	
meloxicam	
nimesulide	
Urticaria/angioedema type	
acetaminophen	
meloxicam	
nimesulide	
selective COX-2 inhibitors (celecoxib, rofecoxib)	
Group C: NSAIDs well tolerated by all hypersensitive patients*	
Rhinitis/asthma type	
selective cyclooxygenase inhibitors (celecoxib, parvocoxib)	
trisalicylate, salsalate	
Urticaria/angioedema type	
new selective COX-2 inhibitors (etoricoxib, pavocoxib)	

\*Single cases of hypersensitivity have been reported

46). Thus, for selected patients, chronic treatment with aspirin after desensitization can be considered as an additional option for pharmacological management of AERD.

*Management of underlying chronic disease.* Although avoidance of causative NSAIDs is critical to prevent drug-induced exacerbations, it does not alleviate the clinical course of the underlying lower and upper airway diseases. Asthma and rhinosinusitis should be treated according to current guidelines. Treatment of asthma in most patients requires combined therapy with the highest recommended inhaled corticosteroid dose and long acting beta-2 agonists (2). Many patients require long-term oral glucocorticosteroids to achieve asthma control. Leucotriene receptor antagonists and synthesis inhibitors may also be of clinical benefit, although the magnitude of improvement after leucotriene antagonists did not seem to exceed that observed in ASA-tolerant patients (47).

Management of chronic rhinosinusitis and nasal polyps (both medical and surgical if necessary) is essential, may be a prerequisite for the improvement of bronchial symptoms and should be conducted in close collaboration with the ENT specialist (22, 48).

#### NSAIDs-exacerbated urticaria/angioedema

##### *Definition*

In some patients with chronic urticaria, ingestion of aspirin or other NSAIDs, which inhibit the cyclooxygenase, may exacerbate the underlying disease and induce hives with or without angioedema.

##### *Pathomechanisms*

Because patients with NSAIDs-induced urticaria/angioedema cross-react only with COX-1 inhibitors, it has been postulated that the mechanism of reaction is similar to that of AERD (19). According to this hypothesis, inhibition of cyclooxygenase by NSAIDs may lead to a decrease in protective prostaglandins production, leading to activation of mediator release from inflammatory cells in the skin. This hypothesis was further supported by observations that skin eruptions after oral aspirin challenge were accompanied by the release of eicosanoids similarly to patients with AERD (49, 50).

##### *Clinical manifestations*

Symptoms of urticaria and/or angioedema appear usually 1–4 h after ingestion of the drug, although both immediate (within 15 min of ingestion) and late (up to 24 h) reactions have been described. Skin eruptions usually subside within few hours but may persist for several days. The degree of sensitivity to NSAIDs may show temporary fluctuations related to activity of underlying chronic disease and may even disappear in some patients (50). A certain proportion of patients with cutaneous adverse reactions may also develop respiratory symptoms. Based on recent studies, the incidence rates of asthma and nasal polyps are increased in patients with chronic urticaria with NSAIDs hypersensitivity compared to those with chronic urticaria only (51).

##### *Underlying chronic disease*

Cutaneous cross-reactive type of hypersensitivity to NSAIDs occurs in patients with chronic urticaria. Because up to 90% of these patients have either a positive reaction in the autologous serum skin test (ASST) (10) or the autologous plasma skin test (APST), an autoimmune type of underlying chronic urticaria has been suggested (52).

##### *Diagnosis*

Skin tests with NSAIDs are not indicated.

*Challenge tests.* Oral provocation is the 'gold standard' for the diagnosis, but should not be performed during an urticaria exacerbation (28). The EAACI/GA<sup>2</sup>LEN guideline proposes (28) subjects should be challenged under single-blind, placebo-controlled conditions, after at least 1–2 weeks without any skin eruptions. In patients with persistent cutaneous symptoms, therapy, including oral corticosteroids at doses  $\leq 0$  mg per day of prednisone, should be continued. In this consensus study, 2-day ASA challenges are recommended, administering on the first day 4 capsules of placebo and on the second day exponentially increasing doses of ASA (71, 117, 312, and 500 mg) at 1.5- to 2-h intervals, up to a cumulative dose of 1000 mg of ASA. However, it has to be noted that different protocols are used by the vast majority of ENDA members in their clinical practice and that further standardization is required. The challenge procedure is interrupted if cutaneous reactions appear or when other symptoms of NSAID hypersensitivity develop. Challenge protocols for NSAIDs other than ASA are available in the literature (53).

Most patients react to a single dose of ASA between 325 and 650 mg, and the time interval between ASA intake and onset of hives is generally longer than one hour.

The sensitivity of challenge is not 100%, negative results of challenges with the suspected NSAIDs being reported, even in cross-reactive patients (54).

*In vitro testing.* Although measurements of sulfidoleucotrienes from leucocytes and basophile activation tests have been proposed, there is no *in vitro* test approved for routine diagnosis of cutaneous type of NSAID hypersensitivity (49, 55).

##### *Management of patients with cutaneous NSAID hypersensitivity*

*Avoidance and alternative drugs.* Avoidance measures and recommendations for alternative drugs in these patients are similar to those for patients with cross-reactive AERD (3, 42). COX-1 selective NSAIDs should be avoided. Paracetamol has been shown to be tolerated by 89.8% of patients (56). On the other hand, the tolerability of selective COX-2 inhibitors among patients with cross-reactive cutaneous hypersensitivity to NSAIDs varies widely. In most studies, rofecoxib, celecoxib and etoricoxib are well tolerated by all patients (55). However, in some studies, celecoxib and rofecoxib induced skin reactions in 7–33% of patients submitted to controlled challenges (57). These data strongly suggest that, before prescription of alternative treatment for pain and

inflammation, a placebo-controlled provocation test should be performed.

**Desensitization.** The possibility of desensitization to aspirin in individuals with cross-reactive type of aspirin-induced urticaria angioedema is controversial and because of limited number of patients studied any recommendation is not feasible (58, 59).

**Management of chronic urticaria.** Careful avoidance of aspirin and NSAIDs does not improve clinical course of underlying chronic skin symptoms. Thus, chronic urticaria/angioedema in NSAID-sensitive patients should be treated according to general rules and guidelines (60). Leucotriene receptor antagonists taken alone or in conjunction with antihistamines may have some benefit for treatment of chronic symptoms in patients with ASA-sensitive urticaria (61).

## Multiple NSAIDs-induced urticaria/angioedema

### Definition

Urticaria and angioedema are induced by various NSAIDs in otherwise healthy subjects without history of underlying chronic skin and/or respiratory disorders.

### Pathomechanisms

The mechanism of multiple drug-induced reactions is not clear. IgE-mediated mechanism seems to be unlikely because patients may react to NSAIDs with completely different chemical structures. Mechanisms related to inhibition of COX-1, as in case of cross-reactive types of NSAIDs hypersensitivity, have been suggested (56).

### Clinical manifestations

The most frequent reactions are urticaria and facial angioedema occurring within minutes or up to 24 h after ingestion of different NSAIDs (62).

### Underlying disease

In a recent study involving controlled oral challenges in patients with history of cutaneous reactions to NSAIDs, 86 of 110 (79%) had no underlying chronic skin disease, suggesting that this form of hypersensitivity may be more common than reported before (13). Although at the time of the reaction patients do not have any underlying chronic skin disorder, it has been reported that up to 37% of these patients may develop chronic urticaria in the future (63).

### Diagnosis

Diagnosis is based on history of reactions to more than one NSAID in otherwise healthy persons.

Because these reactions do not result from allergic hypersensitivity, skin tests with NSAIDs are not relevant and

should not be performed if a history of cross-reactivity is convincing. However, skin testing may be useful for differential diagnosis if single-drug reaction cannot be excluded by history. Although diagnosis may be confirmed by oral challenge, indications for provocation and diagnostic value of provocation tests in these patients have not been established.

The diagnostic value of *in vitro* tests is not known.

### Management

Up to 80% of patients with hypersensitivity to multiple NSAIDs (including aspirin) tolerate paracetamol and nimesulide. Thus, weak COX inhibitors can be recommended as alternative drugs, if their tolerance is confirmed by a negative challenge (57).

A successful desensitization to aspirin in patients with NSAIDs hypersensitivity without underlying chronic skin disorder has not been reported (59).

## Single NSAID-induced reactions

### Definition

Urticaria, angioedema and/or anaphylaxis are induced by a single NSAID or a group of closely chemically related compounds.

Except for hypersensitivity to pyrazolones, most studies reporting single-drug reactions are case reports. Studies performing challenges with other potent COX-1 inhibitors showed that as much as 30% of patients with history of NSAID hypersensitivity appeared to be single-drug reactors (13). From a practical standpoint, distinguishing single-drug reaction from cross-reactive NSAIDs hypersensitivity is important because in the former case a culprit drug may be safely substituted with another NSAID with different chemical structure but similar anti-inflammatory potency.

### Pathomechanisms

Patients with this type of hypersensitivity tolerate other chemically unrelated NSAIDs with strong anti-inflammatory activity, arguing against involvement of COX-1 inhibition-related mechanisms. The clinical pattern of symptoms as well as the timing of the reaction strongly suggests immunological IgE-mediated type of reaction. Positive skin tests to a culprit drug or drug-specific serum IgE may be found in a significant proportion of patients with noncross-reactive type of hypersensitivity to pyrazolones (64). However, only anecdotal reports were able to detect presence of specific IgE in other single NSAIDs reactors (65). In patients with pyrazolone drug hypersensitivity, strong association with HLA-DQ and HLA DR loci was found (66).

### Clinical manifestations

Generalized urticaria and/or angioedema appear within minutes after oral or intravenous administration of the culprit drug. Both skin swelling and mucosal (laryngeal) angioe-

dema may be present, and progression of these reactions to anaphylactic shock and death has been described (67, 68). Anaphylactic shock was observed in 18–30% of patients hypersensitive to pyrazolones (e.g. metamizole) (67, 68). Other symptoms, such as generalized pruritus, rhinitis, and bronchospasm, may also be present in some patients. In single-drug reactors to acetaminophen, generalized urticaria and angioedema are most prevalent, although anaphylactic shock has also been described (69).

The NSAIDs most frequently reported to induce this type of reaction are pyrazolones (67, 68), paracetamol, ibuprofen, diclofenac and naproxen. The data from Netherlands (years 1974–1994) showed that NSAIDs which most frequently caused anaphylaxis were glafenine (withdrawn from the market for this reason), pyrazolones, diclofenac and ibuprofen (70).

### Underlying diseases

Most patients with noncross-reactive type of NSAIDs hypersensitivity have no underlying chronic skin disorder. However, according to Asero (63), the eventual prevalence of chronic urticaria may be as high as 30% and is similar to prevalence in subjects with multiple NSAIDs hypersensitivity (37%). Also in some patients, single NSAID hypersensitivity might precede the onset of chronic urticaria by years (63). Higher prevalence of atopic background was reported among patients with hypersensitivity to pyrazolones (78%) and other NSAIDs (86%) (71).

### Diagnosis

#### *Skin testing*

Standards for skin testing have not been universally accepted, and a significant variability in specificity and sensitivity has been reported for different NSAIDs.

Skin prick and intradermal tests with different dilutions of noraminophenazone, propyphenazone or aminophenazone were used in patients with suspected pyrazolone hypersensitivity (67, 68). The diagnosis of propyphenazone allergy could be confirmed with the combination of skin prick tests and intradermal skin test in the majority of the patients (68). This study demonstrated a lack of complete cross-reactivity between different pyrazolone derivatives, suggesting that the culprit pyrazolone derivative should be used for skin testing.

A progressive loss of sensitivity to skin testing with time elapsed from the drug-induced reaction has been reported (67). These observations suggest that reliable diagnosis skin testing should be performed as soon as possible after clearance of the reaction and interruption of the antiallergic treatment. A few studies only, including small number of patients, assessed the diagnostic value of skin tests in patients with suspected immediate-type allergy to paracetamol or other NSAIDs (69, 72).

#### *Provocation tests*

Oral provocation with a culprit drug is controversial. Some centres recommend oral challenge with a culprit drug, but

other stress the risk of severe anaphylactic reaction (particularly to pyrazolones). In patients with a history of severe reactions (anaphylactic shock and/or angioedema), the benefit of an oral provocation test with the culprit drug should be seriously weighed against the risk involved.

Oral challenge with aspirin and other NSAIDs should be performed to exclude cross-reactive type of hypersensitivity and to confirm the safety of alternative drugs. Using this approach, the unnecessary exclusion of potentially useful NSAIDs can be avoided.

#### *Measurement of specific IgE in serum*

Assessment of specific IgE with commercially available immunoassays seems to be less useful than skin testing. For most NSAIDs, no data assessing sensitivity and specificity are available. In one study using a commercially available immunoassay, no specific IgE for noraminophenazone was detected in a group of 28 patients (67). Specific IgE to propyphenazone detected by a self-made radioimmunoassay has been reported in 58% of patients (68) and specific IgE to noraminophenazone and propyphenazone in 41.5% of patients (73).

#### *Cell activation tests*

Assessment of noraminophenazone-induced CD63 expression on basophils has been shown sensitive to detect hypersensitivity to pyrazolones, but testing early after the reaction seems to be critical for the test positivity (74, 75).

### Management

Strict avoidance of the culprit and potentially cross-reactive chemically similar compounds should be recommended. Alternative NSAIDs can be proposed, but should be preceded by oral challenge to confirm tolerance.

Possibility of desensitization to a culprit drug in patients with IgE-mediated noncross-reactive type of NSAIDs hypersensitivity has not been documented.

### Delayed reactions to NSAIDs

#### Definition

Cutaneous and/or systemic reactions involving other organs and developing after more than 24 h following drug exposure occur. Symptoms usually occur several days (or even weeks) after initiation of a new drug, while symptoms induced by reintroduction of a drug may develop earlier.

#### Pathomechanisms

Delayed-type hypersensitivity reactions to NSAIDs seem to involve immunological mechanisms classified as type IV reactions with dominant role of effector drug-specific, cytotoxic T cells. Various subtypes of type IV reactions have been described and associated with particular clinical manifestations in a small group of patients and for some NSAIDs (76, 77).

However, no systematic studies of NSAID-induced delayed-type reaction have been published so far.

### Clinical manifestations

Cutaneous symptoms are the most frequent manifestations of delayed hypersensitivity to NSAIDs. Much less frequently, reactions specific to other organs and/or systemic forms of reactions have been reported (78).

#### *Fixed drug eruptions*

Fixed drug eruptions (FDE) constitute about 10% of all drug reactions, and NSAIDs are among the most common causes of FDE (79). Pyrazolones, piroxicam, phenylbutazone, paracetamol, aspirin, mefenamic acid, diclofenac, indomethacin, ibuprofen, diflunisal, naproxen and nimesulide have been associated with FDE.

Cross-sensitivities among piroxicam, tenoxicam and droxicam have been reported (80), whereas no cross-reactivity between naproxen and other propionic acid derivatives was demonstrated in another study (81).

#### *Severe bullous cutaneous reactions*

Stevens–Johnson syndrome and TEN are rare but severe skin reactions associated with a high mortality rate. Symptoms can occur 1–8 weeks after administration of incriminated drugs (16). Oxicams seem to be the most common NSAIDs inducing this type of reaction, but phenylbutazone and oxyphenbutazone have also been incriminated (16, 82). Recently, the association of SJS/TEN with the use of selective COX-2 inhibitors has been reported (15, 83).

*Acute generalized exanthematous pustulosis (AGEP)* is a rare condition but NSAID-induced AGEP has been reported. Single cases of DRESS associated with celecoxib and ibuprofen have been described (84).

#### *Maculopapular drug eruptions*

Maculopapular (exanthematous) eruptions are among the most common delayed cutaneous adverse effect of NSAIDs. Ibuprofen, pyrazolones, flurbiprofen, diclofenac and, more recently, celecoxib have been the most frequently incriminated. Exanthematic reactions to NSAIDs may result from a selective (specific) T-cell-dependent hypersensitivity (85).

#### *Pneumonitis*

Several NSAIDs including sulindac, ibuprofen and naproxen have been suspected to induce hypersensitivity pneumonitis (79, 86). Differential diagnosis should be carefully considered. Most patients will improve after drug discontinuation, although corticosteroids may be needed for severe cases.

#### *Aseptic meningitis*

Several NSAIDs such as ibuprofen (the most common, particularly in patients with connective tissue diseases), sulindac, naproxen, tolmetin, diclofenac, ketoprofen, piroxicam, indomethacin and, more recently, rofecoxib and celecoxib have been associated with aseptic meningitis (80, 87).

The pathomechanism of NSAID-induced meningitis is not known, but is not related to prostaglandin inhibition, because most patients tolerate alternative cyclooxygenase inhibitory drugs (87).

#### *Nephritis*

In elderly patients with normal kidneys function, NSAIDs may trigger a sudden impairment of renal function presumably related to immunologically mediated interstitial nephritis. Clinical symptoms of acute renal failure, proteinuria and nephrotic syndrome develop usually 2–3 weeks after starting the medication. NSAIDs may also produce glomerulopathies including minimal change nephropathy, membranous glomerulonephritis and focal sclerosis (88). Peripheral blood eosinophilia is present in almost half of patients.

Both COX-1- and new COX-2-specific NSAIDs (rofecoxib, valdecoxib) have been reported to induce nephritis (89).

#### *Contact and photocontact dermatitis*

Contact with NSAIDs can induce itchy, contact and photocontact dermatitis. Diclofenac, indomethacin, flurbiprofen, bufexamac, etofenamate, flufenamic acid, ibuprofen, ketoprofen and tiaprofenic acid are the most common inducers of these dermatoses, and cross-reactivity between some chemically related NSAIDs has been observed (90). Topical ketoprofen is frequently responsible for contact and photocontact allergy, with a prevalence of 0.008/1000–0.023/1000 applications (91). Patients sensitized to topical drug may develop severe cutaneous reactions with the systemic use of the same drug, a clinical picture designated systemic contact dermatitis.

### Underlying diseases

Unknown.

### Diagnosis

The diagnosis of delayed reactions to NSAIDs is based on the clinical picture that includes recurrent symptoms, morphology and location of the skin lesions and/or involvement of other organs. Patch (epicutaneous) tests with the culprit drug are simple and safe methods for the diagnosis of delayed-type reactions, although they are not well standardized and although sensitivity and specificity for particular reaction remain unknown (92). When photoallergy is suspected, photopatch tests are indicated (93). Skin biopsy and histopathologic assessment may be useful for the differential diagnosis of more complex reactions.

The lymphocyte transformation test (LTT) may be used for *in vitro* testing to assess proliferative response of T cells to the drug. However, validation of LTT for most drugs is lacking (94).

Rechallenge, mostly by oral drug provocation test with the drug, is considered the gold standard for the diagnosis of a drug hypersensitivity, but is contraindicated in patients with severe generalized reactions (95).



**Management of delayed-type reactions to NSAIDs**

Prompt discontinuation of incriminated medication is recommended, because early withdrawal is associated with decreased risk of fatalities. Symptomatic treatment involves systemic corticosteroids and antihistamines.

Patients with SJS/TEN should be treated in intensive care units offering typical management as for burns. There is no specific pharmacological treatment, and use of corticosteroids, plasmapheresis, intravenous immunoglobulins or immunosuppressive drugs is still controversial (96). Recently, anti-TNF- $\alpha$  therapy with infliximab has been reported as another therapeutic option for TEN (97).

**NSAIDs hypersensitivity in children**

Hypersensitivity reactions to NSAIDs in children, although reported less frequently than in adults, rank second among the self-reported and among the top three of drugs most frequently inducing adverse reactions in paediatric patients (98). The reported prevalence of NSAIDs hypersensitivity among normal children is about 0.3% (5, 8), and the prevalence of aspirin sensitivity in asthmatic children is around 5% as assessed by provocation tests (8).

All manifestations of NSAID hypersensitivity described in adulthood are also observed in children. Occurrence of isolated periorbital angioedema is particularly frequent among school children, teenagers and young adults (99). It seems to be associated with atopy in these populations (71).

**Diagnostic work up**

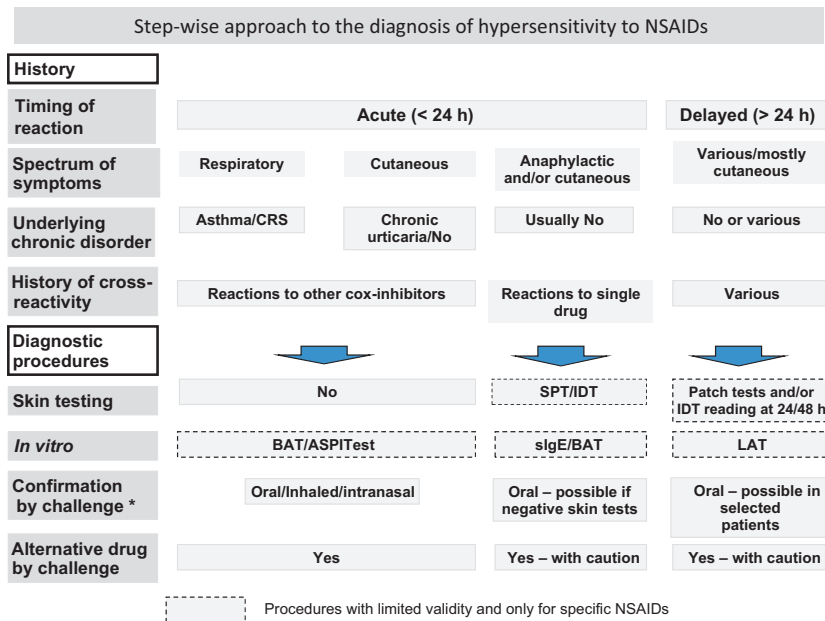
The need for a firm diagnosis of NSAID hypersensitivity in children is especially important as most of the new specific COX-2 inhibitors, commonly used as alternatives in adults with cross-reactive type of hypersensitivity to NSAIDs, are not approved for paediatric use and have no liquid formulations (99). Studies on their tolerance and safety in children are few and should be further encouraged.

**Stepwise approach to the diagnosis of hypersensitivity to NSAIDs**

Because several various mechanisms (both immunological and nonimmunological) may be responsible for hypersensitivity to NSAIDs, it is not possible at the current stage of knowledge to offer a straightforward and universal algorithm for the identification and confirmation of the culprit drug. However, a simplified stepwise approach to the diagnosis of hypersensitivity to NSAIDs includes clinical history, *in vitro* testing and/or provocation challenge with the suspected and alternative drugs (Figure 1).

In patients referred for a history of hypersensitivity to NSAIDs, a careful analysis of history should start with a review of the clinical pattern of adverse symptoms and timing of the reaction. History of cross-reactions or tolerance of other NSAIDs and presence of underlying chronic diseases should be also analysed.

Decision on the implementation of diagnostic procedures (skin testing, *in vitro* testing and/or provocation challenges



**Figure 1** Stepwise approach to the diagnosis of hypersensitivity to nonsteroidal anti-inflammatory drugs (CRS – chronic rhinosinusitis; SPT – skin prick tests; IDT – intradermal tests; LAT – lymphocyte activation tests; BAT – basophil activations tests; ASPI Test –

Aspirin-Sensitive Patient Identification Test \*In patients with a history of severe systemic reaction provocation with a culprit drug is contraindicated.

**Table 3** Recommendations of the EAACI/ENDA and GA2LEN/HANNA for the diagnosis and management of hypersensitivity to NSAIDs

1. Diagnosis and management should vary depending on the confirmed or suspected mechanism of the reaction
2. Skin tests (SPT/IDT) and *in vitro* testing should be restricted to suspected IgE-mediated reactions (noncross-reactive)
3. Diagnosis should be confirmed by a challenge with a culprit drug if appropriate
4. Safety of the alternative drug should be confirmed by oral challenge
5. Avoidance measure should always follow diagnosis
6. Management should include written information to the patient on the alternative NSAIDs

with suspected/alternative drug) should be based on the results of the above clinical assessment and will depend on the suspected type of hypersensitivity. Lack of standardization and limited availability of controlled studies does not allow for recommendation of specific skin or *in vitro* testing. The EAACI/GA2LEN group emphasizes the need for drug provocation tests to first have a firm diagnosis. Positive diagnosis of NSAIDs hypersensitivity should be followed by

offering the patient alternative drugs, and tolerance to alternative compounds should be confirmed by oral challenge. Eventually, diagnostic efforts should lead to providing the patient with written information which should include the list of forbidden and alternative drugs. Major recommendations for diagnosis and management of patients with a history of hypersensitivity reaction to NSAIDs are listed in Table 3.

### Acknowledgments

Members of GA2LEN (Global Allergy and Asthma European Network) supported by the 6th EU Framework Program for research, contract no FOOD-CT-2004-506378. *Following members of the European Network of Drug Allergy, the EAACI interest group on drug hypersensitivity, provided comments and/or endorsed the manuscript:* Werner Aberer (Austria), Andreas Bircher (Switzerland), Beatrice Bilo (Italy), Patrizia Bonadonna (Italy), Josefina Cernadas (Portugal), Martine Grosber (Germany), Violeta Kvedariene (Lithuania), Werner Pichler (Switzerland), Claude Ponvert (France), Johannes Ring (Germany), Maria Luisa Sanz (Spain), Francesca Saretta (Italy), Ingrid Terreehorst (The Netherlands), Stefan Woehrl (Austria).

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