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Drug Allergy (MJ Torres Jaén, Section Editor)

NSAIDs Hypersensitivity: When and How to Desensitize?

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Opinion statement

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs and are among the major causes of hypersensitivity reactions. NSAIDs can evoke different types of both immunological and non-immunologically mediated hypersensitivity reactions, and management of these reactions depends on type of hypersensitivity reaction. As NSAIDs are comprised of several drugs with different chemical structures which can inhibit both cyclooxygenases or selectively cyclooxygenase type 2 (COX-2), in most of the cases, it is possible to find a safe non-cross-reactive drug for a patient. However, in certain situations, especially when patients require anti-platelet treatment, patients can be desensitized to aspirin.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are among the most commonly prescribed and used drugs in the world and, along with antibiotics, are the top two (depending on the population studied) causes of adverse drug reactions [1]. It is estimated that hypersensitivity to NSAIDs affects from 0.5 to 1.9 % of general population [2], but in certain populations like patients with bronchial asthma or with chronic rhinosinusitis, the prevalence of NSAIDs hypersensitivity is much higher [3, 4••].

The management of drug hypersensitivity reactions always starts with advice on avoidance of the culprit drug and any cross-reactive compounds [5••], but in some patients, induction of tolerance to the drug can be also considered. In case of NSAIDs hypersensitivity, despite large number of compounds belonging to this group, only desensitization to aspirin has been sufficiently documented.

When to desensitize a patient with NSAIDs hypersensitivity?

While considering aspirin desensitization in a patient with a history of hypersensitivity to NSAIDs, the following aspects have to be taken into consideration:

1. Determination of a subtype of NSAIDs hypersensitivity, since desensitization is possible only for some subtypes, while in other subtypes desensitization may be contraindicated.
2. Analysis of clinical benefit from treatment with aspirin (NSAID) after desensitization.
3. General safety of desensitization procedure.
4. Selection of desensitization protocol—different protocols are used depending on the indication for desensitization.

Subtypes of NSAIDs hypersensitivity and possibility of desensitization

NSAIDs can evoke a wide spectrum of adverse drug reactions (respiratory, cutaneous, anaphylactic, or other organ-specific) involving different pathomechanisms. Induction of tolerance to aspirin is possible and indicated only in two subtypes of NSAIDs hypersensitivity: (1) NSAIDs-exacerbated respiratory disease (NERD) and (2) NSAIDs-induced urticaria/angioedema (NIUA), thus determination of the type of hypersensitivity is prerequisite to successful desensitization.

According to novel classification of NSAIDs hypersensitivity, either immunologically and non-immunologically mediated reactions can be distinguished [4••] (Table 1). Most of the hypersensitivity reactions to NSAIDs are non-immunologically mediated but are cross-reactive hypersensitivity reactions as the patients usually do not tolerate all NSAIDs with COX-1 inhibitory activity. Among these cross-reactive reactions, three clinical subtypes can be distinguished:

NSAIDs-exacerbated respiratory disease (NERD)

This hypersensitivity reaction is manifested mainly by respiratory symptoms and occurs in patients with underlying chronic airway disease like asthma and/or rhinosinusitis with nasal polyps. NSAIDs-induced bronchial symptoms (dyspnea, cough) usually appear within 1–2 h and are preceded by nasal symptoms (rhinorrhea, nasal congestion) [4••]. Other extrabronchial symptoms: ocular, cutaneous (flushing of the upper thorax, urticaria, and/or angioedema) or gastric are less frequent [6]. Typical natural history of the diseases starts with development of chronic rhinosinusitis with polyps, followed by asthma, which usually precede the first of hypersensitivity reaction [3]. Patients with NERD usually have more severe asthma as compared to aspirin-tolerant asthmatics [7]. Furthermore, chronic rhinosinusitis in NERD patients is usually more severe, very often

Table 1. Classification of NSAIDs hypersensitivity reactions

	Reaction	Abb	Definition	Desensitization
Non-immunologically mediated reactions	NSAIDs-exacerbated respiratory disease	NERD	Hypersensitivity reactions induced by aspirin or other NSAIDs manifesting primarily as bronchial obstruction, dyspnea, and nasal congestion/rhinorrhea, occurring in patients with an underlying chronic airway respiratory disease (asthma/rhinosinusitis/nasal polyps).	Possible, everyday treatment with aspirin have additional beneficial effect on rhinosinusitis and asthma course
	NSAIDs-exacerbated cutaneous disease	NECD	Hypersensitivity reactions induced by aspirin or other NSAIDs manifesting as wheals and/or angioedema occurring in patients with a history of chronic spontaneous urticaria.	Generally not recommended
	NSAIDs-induced urticaria angioedema	NIUA	Hypersensitivity reactions induced by aspirin or other NSAIDs manifesting as wheals and/or angioedema occurring in otherwise healthy subjects (without history of chronic spontaneous urticaria). Symptoms are induced by at least two NSAIDs with different chemical structure (not belonging to the same chemical group).	Possible
Immunologically mediated reactions	Single NSAID-induced urticaria/angioedema or anaphylaxis	SNIUAA	Immediate hypersensitivity reactions to a single NSAID or to several NSAIDs belonging to the same chemical group, manifesting as urticaria, angioedema and/or anaphylaxis. These subjects tolerate other chemically non-related NSAIDs and usually do not have a history of chronic urticaria or asthma.	No data
	NSAIDs-induced delayed hypersensitivity reactions	NIDHR	Hypersensitivity reactions to a single NSAID appearing usually within 24–48 h after drug administration and manifesting by either skin symptoms (exanthema, fixed drug eruption), other organ-specific symptoms (e.g., renal, pulmonary), or severe cutaneous adverse reactions (SCAR).	No available protocols, desensitization contraindicated in SCAR, organ involvement (pneumonitis, nephritis)

complicated by recurrent nasal polyp formation which responds less to surgical treatment [3]. NERD is one of non-immunological, cross-reactive types of hypersensitivity as patients hypersensitive to one NSAIDs react to aspirin and other NSAIDs which are COX-1 inhibitors, while weak COX-1 inhibitors or preferential COX-2 inhibitors are usually well tolerated [8–10].

Aspirin desensitization

Aspirin desensitization in this subtype of hypersensitivity can be easily achieved, and treatment with aspirin after desensitization may be beneficial for improving symptoms of the underlying chronic diseases, asthma, and rhinosinusitis with nasal polyps [11••, 12].

NSAIDs-exacerbated cutaneous disease (NECD)

This type of hypersensitivity is observed in patients suffering from chronic spontaneous urticaria. Clinical symptoms (urticaria and angioedema) typically occur 0.5 to 6 h after ingestion of NSAIDs. NSAIDs-induced reactions are less frequent and less intense when chronic urticaria is in remission or under control. The mechanism of the reaction, similarly to NERD, is related to the inhibition of cyclooxygenase –1 by a culprit drug, resulting in increased generation of cysteinyl leukotrienes [13]. Thus, patients with NECD would have a cross-reaction with COX-1 inhibitors, while selective COX-2 inhibitors are generally well tolerated by the majority of them [14].

Aspirin desensitization

In this subtype of NSAIDs hypersensitivity, the tolerance of aspirin may be difficult to achieve and in some patients, cutaneous symptoms may be even exacerbated by the procedure [15]. Thus, aspirin desensitization in NECD patients is not recommended, even though there have been some reports of successful induction of tolerance to aspirin [16, 17].

NSAIDs-induced urticaria/angioedema (NIUA)

The clinical pattern of NSAID-induced symptoms is similar to NECD (wheals and/or angioedema); however, in contrast to NECD, patients with NIUA do not have history of chronic spontaneous urticaria. The mechanism is thought to be related to COX-1 inhibition, but it has not been well documented [14, 18•].

Aspirin desensitization

Aspirin desensitization is possible in most patients. Tolerance state can be easily maintained with continuous intake of aspirin [19••, 20, 21].The two remaining subtypes of NSAIDs hypersensitivity are immunologically mediated and are distinguished by intolerance of a single drug (chemical molecule) and good tolerance of other chemically unrelated NSAIDs.

Single NSAIDs-induced urticaria/angioedema/anaphylaxis (SNIUAA)

A subpopulation of patients reports immediate hypersensitivity reaction to a single NSAID (or to several NSAIDs but belonging to the same chemical group). Patients usually present with a history of good tolerance to other chemically unrelated NSAIDs, including aspirin [18•]. The symptoms range from mild urticaria and localized angioedema to laryngeal edema and anaphylaxis and usually develop within first hour after the drug intake [18•]. However, in some instances, symptoms may develop within minutes or even seconds (e.g., after intravenous injection of metamizole) [22]. These subjects are usually otherwise healthy individuals without any specific underlying chronic disease. The reactions are most often induced by pyrazolones, ibuprofen, or diclofenac; however, other NSAIDs as paracetamol have been implicated as well. Aspirin incidentally evokes hypersensitivity reactions in this mechanism.

Aspirin desensitization

There is no data on desensitization in this type of reactions. As symptoms of hypersensitivity are usually evoked by a single drug, the chemical compound with different chemical structure can be prescribed and will be well tolerated.

NSAIDs-induced delayed hypersensitivity reactions (NIDHR)

Reactions developing usually after more than 24 h after the drug intake are considered to represent delayed type of immunological hypersensitivity. Delayed cutaneous manifestation are the most common and involve maculopapular eruptions (MPE), fixed drug eruptions (FDE), photosensitivity reactions, delayed urticaria [23–25], and contact dermatitis [26]. In addition, severe drug hypersensitivity reactions (drug induced hypersensitivity syndrome (DIHS), acute generalized exanthematous pustulosis (AGEP), and severe cutaneous adverse reactions (SCAR) [27–29] as well as organ-specific injury (pneumonitis and nephritis) may occur [30].

The presumed immunological mechanism involves the stimulation of drug-specific CD4+ and CD8+ T cells through their T cell receptors (TCR) and represents a delayed type hypersensitivity (type IV according to Gell Coombs) T cell-dependent mechanisms have been documented in delayed urticaria, MPE induced by aceclophenac [31] and metamizol and in SCAR induced by ibuprofen [32, 33].

Aspirin desensitization

There is no data on desensitization to aspirin. In most patients with delayed type hypersensitivity reactions (SCAR, DRESS, AGEP, and pneumonitis and nephritis), a challenge with culprit drug is generally contraindicated [5••, 34]. In case of less severe delayed drug reactions, e.g., maculopapular eruptions, there is no attempts of desensitization have been reported.

Furthermore, since the reactions are evoked by a single NSAID, the culprit drug can be usually replaced.

Clinical indications to NSAIDs desensitization

Avoidance of culprit drug as well as other cross-reactive compounds is the first recommendation in the management of NSAIDs hypersensitivity [4••]. If the treatment with analgesic/anti-inflammatory drug is needed, a non-cross-reactive drug should be given, selected depending on the known mechanism. Most patients with cross-reactive, non-immunologically mediated types of NSAIDs hypersensitivity will tolerate preferential COX-2 inhibitors like meloxicam or nimesulide or selective COX-2 inhibitors (celecoxib) with relevant anti-inflammatory effect. Aspirin, however, have additional important pharmacological effects going beyond anti-inflammatory or analgesic activity. As a key anti-platelet drug, aspirin is recommended for primary and secondary prevention in patients with a high risk of major cardiovascular events (death, myocardial infarction, or stroke) [35, 36]. Recent data show that low doses of aspirin can decrease the risk of certain malignant tumors development: e.g., colorectal cancer [37] or ovarian cancer [38].

Moreover, in patients with NSAIDs-exacerbated respiratory disease daily treatment with aspirin can bring additional beneficial effects like alleviation of nasal symptoms, decreased formation of nasal polyps, and reduced need for oral corticosteroids and sinus surgeries. Clinical indications for aspirin desensitization are listed in Table 2.

Aspirin desensitization in patients with need for anti-platelet treatment

Cardiovascular events are the major cause of mortality in developed countries [39]. Aspirin is the most studied anti-platelet agent in this context of prevention

Table 2. Clinical indications for aspirin desensitization

1. Patients with need of anti-platelet treatment	Treatment of acute coronary disease, stroke Secondary prevention of cardiovascular events (patients after acute coronary syndrome, stroke, patients after stent implantation, patients after coronary artery bypass surgery, patients with peripheral artery disease, patients with antiphospholipid syndrome Primary prevention (patients with high risk of cardiovascular events, patients with antiphospholipid syndrome)
2. Chemoprotection of certain types of cancer (colon cancer, ovarian cancer)	Colon cancer Ovarian cancer
3. Patients with NERD and severe course of rhinosinusitis and asthma	Severe osteoarthritis Seronegative spondyloarthropathies
4. Need for chronic anti-inflammatory treatment—patients with severe osteoarthritis, seronegative spondyloarthropathies	

and treatment of cardiovascular disease (coronary artery disease, stroke, peripheral artery disease). Aspirin decreases mortality and reinfarction when given as short-term therapy for acute myocardial infarction [40], when given to patients with unstable angina [41], and when given as long-term secondary preventive therapy in wide range of patients with cardiovascular disease [42].

Although, in recent years, novel anti-platelet drugs become available like adenosine diphosphate receptor inhibitors (clopidogrel, prasugrel, ticlopidine, ticagrelor), glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide), or adenosine reuptake inhibitors (dypirimidamole). Given its relative safety and low cost, aspirin will continue to be an important agent in the treatment and prevention of cardiovascular diseases.

Moreover, in certain clinical situations, dual anti-platelet therapy is mandatory, e.g., after myocardial infarction and/or after stent implantation [43, 44]. A great majority of patients after cardiovascular events will require treatment with aspirin till the end of life [43].

For patient with aspirin hypersensitivity and acute coronary syndrome, either use of clopidogrel or aspirin desensitization is recommended by cardiologists (ACC/AHA guidelines from 2007 [45] and ESC guidelines [46]).

Although there is plenty of data on safety of aspirin desensitization in patients with stable coronary heart disease, much more challenging is taking decision on aspirin desensitization in patient with acute coronary syndrome as patient very often received drugs that are contraindicated during desensitization (beta blockers and ACE inhibitors) and there is fear that hypersensitivity reaction which may occur can further destabilize the patient. Moreover, desensitization can be avoided by using more aggressive anti-platelet treatment with intravenous drugs such as abciximab, integrilin, or tirofiban.

There is limited data on aspirin desensitization in acute phase of acute coronary syndrome [47]. De Luca et al. presented in prospective way group of patient undergoing coronary angioplasty (53 % due to acute coronary syndrome) who were desensitized with aspirin. Procedure of intravenous desensitization was effective in 97.6 % of patients [47]. Thus, it seems that at least some of the proposed protocols can be implemented safely even in patients with acute coronary syndrome. However, as the hypersensitivity reaction was not proven by challenge test, it is not clear how many of those patients were really hypersensitive. The aspirin desensitization in patients with ACS should be performed after stabilization of acute phase, and it should be performed in monitored conditions and by experienced staff.

An interesting approach to ASA-desensitization in patients with coronary artery disease has been proposed by Cortellini et al. A patient with stable coronary artery disease and history of mild symptoms after NSAIDs intake at first should be challenged with aspirin to confirm hypersensitivity [19]. If a patient presented history of severe symptoms after NSAID intake, desensitization procedure was done without attempts to confirm hypersensitivity. Interestingly, 29 from 30 patients with history of mild symptoms of urticaria and/or angioedema fully tolerated the cumulative dose of 160 mg of acetylsalicylic acid during the challenge. There are at least 2 explanation of this observation, either patients were not hypersensitive or the threshold dose of aspirin to evoke clinical symptoms was not reached during the tolerance test.

Aspirin desensitization and aspirin treatment in patients with NERD

It has been documented that in a subgroup of patients with NSAIDs-exacerbated respiratory disease (NERD), ingestion of aspirin after desensitization results in alleviation of both upper and lower airway symptoms [11••, 12, 48–53]. The long-term effects of aspirin treatment include improvement in nasal symptoms, decrease in the maintenance dose of intranasal glucocorticosteroids, and a decrease in the number of polypectomies [12, 50, 52, 54]. Aspirin desensitization can slow down regrowth of nasal polyps and prevent further nasal surgeries [55]. Usually, it is recommended that aspirin desensitization should follow sinus surgery [55].

Aspirin treatment after desensitization may also have an impact on asthma control. When the patients were treated with aspirin for 6 months to 6 years, a significant reduction in hospitalization, emergency room visits, outpatient visits was observed and in some patients, a reduction in daily oral prednisone doses was achieved [12, 49, 50]

There are two placebo-controlled studies that support these benefits. Swierczynska-Kempa et al. [11••] randomly selected both aspirin hypersensitive and aspirin-tolerant asthmatics to aspirin or placebo treatment group. The improvement in nasal symptoms score and reduction in sneezing and nasal blockade was observed only in patients with aspirin hypersensitivity treated with aspirin. The nasal symptoms improved within the first month of treatment, and improvement was seen throughout the entire observation period. However, it has to be noted that computed tomography (CT) sinus scan scores did not change in parallel to clinical improvement. Asthma control was improved, and the dose of inhaled corticosteroids was decreased; however, asthma symptoms score and spirometric values did not change significantly [11••].

Efficacy of treatment with various doses of aspirin from 100 to 1300 mg have been reported. While some studies report that aspirin dose as low as 100 mg daily for 1–3 years may provide benefit with respect to the recurrence rate of nasal polyps, severity of bronchial asthma and sense of smell in desensitized patients with NERD [51], another studies suggest that clinical efficacy starts from 300 mg/day [52]. However, it seems that the dose should be tailored to the patient and both clinical efficacy and side effects should be taken into consideration while determining the maintenance dose. A study comparing 325 with 650 mg twice a day showed that in almost half of patients, half of the dose was enough while the rest of the patients required higher doses [56]. The reports from Scripps Clinic suggest starting with 650 mg twice a day and titrate the dose down by 325 mg each month, as tolerated [57]. In our clinic, we desensitize patient to 650 mg of aspirin and give a maintenance dose of 325 mg twice a day.

In order to maintain tolerance state, aspirin has to be given on a regular basis—if not, the tolerance state disappears after 2–5 days. In most of the studies, aspirin was given once or twice a day.

How and where to desensitize?

Aspirin desensitization is a high-risk procedure, which has to be done after assessment of risk-benefit ratio following discussion with a patient. Before desensitization, the patient should be provided with information about procedure risk and benefits and sign the consent.

Desensitization is contraindicated in patients with previous severe, life-threatening cutaneous reactions like Stevens-Johnson syndrome/toxic epidermal necrolysis, DIHS/DRESS, AGEP, erythema multiforme and serum sickness disease, and organ involvement [5••, 34]. Risk factors for severe bronchial reaction in patients with NERD during desensitization include severe reaction with fall of FEV1>20 %, uncontrolled asthma, baseline FEV1 less than 80 %, lack of leukotriene modifier premedication, previous emergency department visits due to asthma exacerbation [58].

Where

Desensitization procedure can be performed both in hospital and outpatient setting after risk stratification. The severity and time course of initial hypersensitivity reaction have to be assessed, and the concomitant use of medication such as beta blockers and ACE inhibitors and the severity of underlying disease need to be taken into consideration [59].

Patients with severe asthma, acute coronary syndrome, patients using beta blockers, angiotensin converting enzyme (ACE) inhibitors, severe life-threatening aspirin hypersensitivity reaction, underlying medical condition that make management of hypersensitivity reaction more difficult (e.g., cardiac insufficiency) should be exceptionally desensitized (after careful assessment of risk-benefit ration), only in hospital settings.

If aspirin desensitization is to be performed in the outpatient setting, the following conditions should be fulfilled [59]:

- A physician experienced in assessing and treating acute, severe hypersensitivity reactions is immediately available for patient evaluation and treatment.
- Medically qualified personnel experienced with assessing and treating of severe asthma exacerbation is available to monitor patient.
- At least one experience medical staff member is solely dedicated to evaluation of patient being desensitized until desensitization is completed.
- The equipment for continuous respiratory and cardiovascular monitoring, spirometry, cardiopulmonary resuscitation, pulsoximetry, is readily available.

In summary, desensitization procedure should be performed by well-trained, experienced allergists and nurses who are familiar with treatment of acute hypersensitivity reactions and anaphylaxis. Emergency equipment for continuous pulmonary and cardiovascular monitoring and treatment like epinephrine,

oxygen, beta-2 mimetics, intravenous glucocorticosteroids, antihistamines, glucagon should be available at bedside.

Preparation to desensitization and pretreatment

Patient planned for desensitization should have stable underlying disease, e.g., asthma. Treatment of chronic diseases should be continued, but drug which can interfere treatment of hypersensitivity reaction like beta blockers or ACE inhibitors should be discontinued/replaced by drugs from other pharmacological groups whenever possible. The Macy's recommendation is to stop antihistamines 48 h before desensitization not to mask naso-ocular symptoms which usually precedes onset of bronchial symptoms and decreasing of FEV1. The use of asthma controller medication prior to desensitization is recommended as they prevent severe decreases of FEV1 [60]. Duration of the supervision depends on initial hypersensitivity reaction.

Pretreatment with leukotriene blockers may alleviate symptoms of breakthrough reaction in patients with NERD by shifting reaction from bronchial to naso-ocular symptoms [60].

Desensitization procedures

In most protocols for aspirin desensitization, the procedure begins with provoking the reaction with a standard, as low as possible aspirin dose (threshold dose) followed by administration of increasing doses which usually are well tolerated. However, it has been documented that the tolerance state to full dose of aspirin (e.g., 600 mg) can be also induced, without evoking the initial reaction, by timely and gradual administration of small, subthreshold doses of aspirin [61]. Such procedure has been recently referred to as "silent desensitization" [62].

There are two major types of protocol used in clinical practice for aspirin desensitization depending on the indications for the procedure: "slow desensitization" protocols used to desensitize patients with NSAIDs-exacerbated respiratory disease and "rapid desensitization" protocols used to desensitize patients with cardiologic indications to use low doses of aspirin (Table 3)

Protocols for patients with NERD

Several protocols for desensitization of patients with NERD have been proposed and used [58, 59, 63–67]. The recommended starting dose is between 10 and 30 mg [58, 59, 63, 65], but the time interval between consecutive increasing doses varies from 30 min to 24 h in different protocols [68]. The most widely used protocols have been proposed by the Scripps Clinic [63]. One of the proposed schedules advices giving following doses of aspirin: 30, 45, 60, 100, 150, 325, and 650 mg. The recommended time interval between doses is 3 h, but FEV1 and clinical assessment should be performed every hour or upon presentation of any symptoms. Reaction will likely occur with doses between 20 and 101 mg, and reaction should be treated immediately.

Table 3. Protocols (studies reporting rapid desensitization in patients with coronary heart disease) for aspirin desensitization

Author	No of patients desensitized	No of protocol steps	Time interval between subsequent doses	Success rate	Journal
Wong TJ	11	10 steps	10–30 min	81 %	JACI 2000;105:997-1001
Silberman S	16	8 steps 5 steps		88 %	Am J Cardiol 2005;95:509-510
Ortega-Loayza AG	3	10 steps	10–30 min		Am J Sci 2010, 340 (5):418-20
Rossini R	26	6 steps	30 min	88.50 %	Am J Cardiol 2008;101:786-89
Dalmau G	5	8 steps	15–20 min	100 %	Rev Esp Cardiol 2009;62:224-30
Alijotas-Reig J	4	9 (10) steps	15 min	100 %	Am J Reprod Immunol 2006;55:45-50
DeLuca G*	43	9 steps	30 min	97.60 %	Int J Cardiol 2013:167:561-63
Fajt ML	9	10–12 steps		89 %	Crit Path Cardiol 2011, 10:17-21
McMullan KL	26	7 steps	15–20 min	87.00 %	Clin Cardiol 2013, 36:1, 25-30
Cortellini G	35	12 steps	20 min	90 %	Eur Ann Allergy Clin Immunol 2012; 44:160-162

Following the dose that evoked symptoms (called the provoking/threshold dose) and before the next dose of aspirin is given, the patient should completely stabilize, and the respiratory function should return to baseline values. The provoking/threshold dose is usually repeated on the same day, although some recommend the next morning. If the dose is tolerated, the dose is increased every 3 h (101.25, 162, 325, and 650 mg). The chance of a reaction to the repeated threshold dose is small, but if it occurs, the dose should be repeated again until reactions cease and then the next highest dose of aspirin may be given.

Safety of long-term treatment with NSAIDs

The incidence of side effects of aspirin treatment in patients with NERD followed by aspirin desensitization varies from 6–32 %. The most common adverse reactions in patients on maintenance therapy are the following:

1) Dyspepsia
2) Bleeding from gastrointestinal system
3) Urticaria/angioedema
4) Loss of tolerance and asthma/rhinosinusitis exacerbation

The concomitant use of proton pump inhibitors can prevent symptoms of dyspepsia, gastric ulceration, and bleeding, but it won't prevent bleeding from lower parts of gastrointestinal system. Recently published data indicates that proton pump inhibitors (PPIs) can even exacerbate NSAID-induced intestinal

damage at least in part because of significant shifts in enteric microbial populations [69, 70]. Helicobacter pylori, an independent risk factor for ulcers, should be sought out and eradicated in patients at increased gastrointestinal risk, typically those with an ulcer history prior to aspirin desensitization [71].

Protocols for patients with need of anti-platelet treatment

Desensitization protocols for patients who need treatment with anti-platelet doses of aspirin differs from protocols used in NERD desensitization because: (a) patients need to be desensitized to lower dose of aspirin—75–150 mg, (b) patients represent different subtypes of hypersensitivity (NERD or NIUA), (c) very often, patients require rapid desensitization (patient with acute coronary syndrome).

Several protocols of rapid aspirin desensitization have been published [19••, 20, 21, 47, 72–77]. These protocols differ in starting dose, time interval between subsequent doses, and number of steps. Rapid protocols usually start with lower aspirin dose (from 0.1 to 5 mg of ASA) [20, 21, 72, 73], and increasing doses of aspirin are given every 10–30 min. Protocols consist of 5–12 steps. (Table 3)

Interesting, alternative approach to aspirin desensitization was proposed by DeLuca et al. [47] who employed intravenous protocol in patients with myocardial infarction. The desensitization procedure involved intravenous administration of nine sequential doses of aspirin (1, 2, 4, 8, 16, 32, 64, 128, 250 mg) over 4.5 h [47]. The protocol appeared to be safe and effective (the success rate reached 97.6 %).

There is still lack of consensus, which protocol should be used for desensitization of cardiac patients, and what are the indication and contraindications to desensitization procedure. Although various authors report on excellent safety and efficacy of desensitization procedure (from 81–97 % success rate), the real effectiveness of desensitization is not clear. The assessment of reported effects is difficult since most studies included patients with various, not well

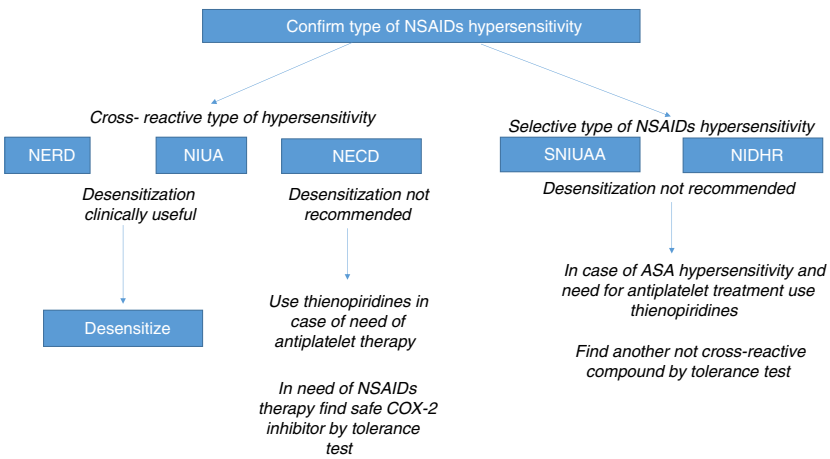

Fig. 1. Steps in management in different subtypes of NSAIDs hypersensitivity. NERD (NSAIDS-exacerbated respiratory disease), NIUA (NSAIDs-induced urticaria/angioedema), NECD (NSAIDs-exacerbated cutaneous disease), SNIUAA (single NSAIDs-induced urticaria/angioedema/anaphylaxis), NIDHR (NSAIDs-induced delayed hypersensitivity reaction).

defined types of NSAIDs hypersensitivity, diagnosis of hypersensitivity to NSAIDs was based only on clinical history and usually was not confirmed by challenge test.

There is also a debate about individual aspirin thresholds of aspirin since, as it is known from challenge studies, that some hypersensitive patients may tolerate aspirin in the dose up to 150 mg or even 325 mg. In these patients, anti-platelet treatment with low dose of aspirin after standard "desensitization" procedure can be still below the threshold dose that can evoke reaction [54, 66, 68]. These considerations support the recommendations that the first step in management of a patient with hypersensitivity reaction to NSAIDs is to confirm the presence of hypersensitivity by a challenge test. Cortellini et al. [19••] documented that more than 90 % of cardiac patients who underwent provocation procedure with increasing doses of aspirin could tolerate up to 1600 mg of the drug. If a rapid introduction of aspirin therapy is needed in a patient with cardiovascular disease and ASA-hypersensitivity, desensitization should be considered as the first choice.

In patients who have contraindications to aspirin desensitization use of alternative treatment is recommended [78] (Fig. 1).

Conclusions

Hypersensitivity to aspirin and other NSAIDs is quite common in the community. Aging population have greater needs to be treated with aspirin or other NSAIDs to prevent cardiovascular events, cancers and to improve control of rhinosinusitis and asthma, thus may be at higher risk for development of hypersensitivity reactions. Due to its exceptional pharmacological properties, aspirin is not easily replaceable in clinic and yet is a cheap drug. For some patients, desensitization to aspirin may be a cost-effective approach, although patients should be carefully selected for this procedure and the risk-benefit ratio of the procedure and chronic treatment with aspirin should be taken into consideration.

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Compliance with Ethics Guidelines

Conflict of Interest
Joanna Makowska declares that she has no conflicts of interest. Marcin Makowski declares that he has no conflicts of interest. Marek L. Kowalski declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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