

Aspirin and Nonsteroidal Anti-Inflammatory Drug Hypersensitivity

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Abstract

Acetylsalicylic acid (ASA) or aspirin and nonsteroidal anti-inflammatory drug (NSAID) sensitivities encompass a diverse group of both pharmacological and hypersensitivity reactions. Conventionally, hypersensitivities include aspirin-exacerbated respiratory disease (AERD), ASA-induced urticaria, and anaphylaxis. With an increasing prevalence of coronary artery disease in an aging population, aspirin continues to play a significant role in cardiac prophylaxis in a large patient population. Invariably, the clinician will encounter patients with clear indications for aspirin therapy but a history of aspirin sensitivity. Although protocols have been established for aspirin challenge and desensitization, it is not always an efficacious or safe procedure. This article reviews the different classifications of ASA/NSAIDs hypersensitivities to better guide the clinician in dealing with this patient population. History of crossreactivities between multiple NSAIDs implies a non-IgE-mediated process. Similarly, a history of monosensitivity to one NSAID implies an IgE-mediated process, although specific antibodies are often elusive. Despite the name, AERD can potentially be exacerbated by all cyclooxygenase (COX) inhibitors based on dose-dependent inhibition of COX-1. Aspirin desensitization can be achieved to improve both upper and lower respiratory symptoms for most patient with AERD. Aspirin desensitization can usually be achieved for those in need of the antiplatelet effects of aspirin, with the exception of those with aspirin-induced urticaria and baseline chronic urticaria.

However, desensitization should only be attempted in those with stable coronary artery disease because the process of desensitization carries the inherent risk of anaphylaxis/anaphylactoid reaction, which may further increase cardiac demand and bring about ischemic injury. Therefore, desensitization is reserved until coronary artery disease is stabilized.

Index Entries

Aspirin; nonsteroidal anti-inflammatory drugs; adverse events; sensitivity; hypersensitivity; leukotrienes; cyclooxygenases; arachadonic acid; aspirin exacerbated respiratory disease; urticaria; angioedema; anaphylaxis; anaphylactoid.

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Introduction

Arachidonic Acid Metabolites

It is important to understand the metabolism of arachidonic acid to dissect the pharmacologically adverse events associated with aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Acetylsalicylic acid (ASA or aspirin) was the first NSAID and differs from all NSAIDs because it irreversibly acetylates cyclooxygenase (COX-1) (1). This mechanism is partly responsible for the antiplatelet effect of aspirin utilized in cardiovascular disease via the reduction of thromboxane A₂ (TXA₂). However, as a secondary effect, prostaglandin E₂ (PGE₂) is also reduced. PGE₂ normally provides negative feedback via inhibition of 5-lipoxygenase (5-LO). 5-lipoxygenase converts arachidonic acid into 5-hydroperoxyeicosatetraenoic acid (5HPETE), which is the precursor for cysteinyl leukotriene metabolites (LTA₄, LTB₄, LTC₄, LTD₄, LTE₄). These metabolites are partly responsible for the vasodilation and smooth muscle constriction that leads to prototypical asthma phenotype in the form of wheezing, cough, and shortness of breath. This shunting of the arachidonic acid into cysteinyl leukotriene metabolites is the putative mechanism behind the ability of aspirin and other COX-1 inhibitors to cause respiratory exacerbation in sensitive individuals (Fig. 1).

ASA as the First NSAID

Since 1896, ASA, or aspirin, has been given to humans to treat headaches, lower fever, and reduce pain (2). Although it is effective in treating these ailments, ASA does have a significant side effect profile. It is important to understand that most sensitivities to ASA are nonimmunological in nature. In fact, drug-specific IgE has not been reliably demonstrated, even in situations when the history has been consistent with an immunological mechanism. However, multiple syndromes of sensitivities have been described. In simplistic terms, adverse reactions to ASA can be causally linked to its inherent pharmacological effects or hypersensitivity.

Adverse Pharmacological Effects of Aspirin and NSAIDs

Adverse pharmacological effects of aspirin and NSAIDs include gastritis and peptic ulcers resulting from inhibition of COX and a decrease in mucosal-protective prostaglandins; nephritis caused by a decrease in PGE₂ to counter the vasoconstrictive effects of angiotensin; hepatitis resulting from uncoupling of oxidative phosphorylation in hepatic mitochondria and thus decreased hepatic adenosine triphosphate production (3) and microsomal lipid peroxidation (4); and various blood dyscrasias resulting from ASA's irreversible inhibition of COX and subsequent reduction in TXA₂ responsible for aspirin's antiplatelet effect (5,6). Other NSAIDs are capable of antiplatelet effects, but these occur in a reversible manner because they are reversible inhibitors of COX.

Hypersensitivity to Aspirin and NSAIDs

Hypersensitivity reactions to aspirin have generally been classified into three types: aspirin-exacerbated respiratory disease (AERD), aspirin-induced urticaria/angioedema, and anaphylaxis (7). Using this definition, the prevalence of aspirin hypersensitivity is estimated to be between 0.2 and 0.6% of the general population (8). However, certain patient phenotypes appear to have a higher prevalence of aspirin hypersensitivity, which is as high as 21% in asthmatic patients (9–11) and is even higher among patients with chronic idiopathic urticaria, in the range of 20 to 40% (6,12).

Aspirin and NSAID-Exacerbated Respiratory Disease

In 1922, Widel et al. first described an association of aspirin sensitivity, asthma, and nasal polyposis, and this was later coined by Samter and Beers in 1968 as the Samter's Triad (13,14). In 1985, Samter's Triad was further expanded by Stevenson and Mathison to include the quadrad of rhinitis with and without nasal

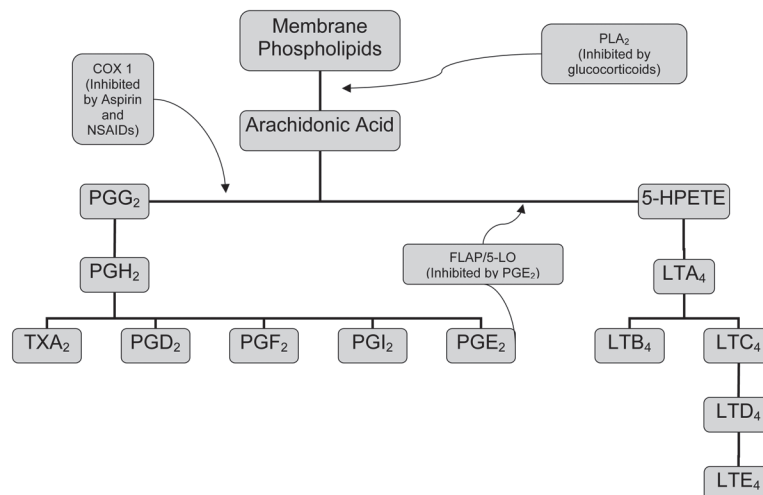


Fig. 1. Phospholipase A₂ (PLA₂) is inhibited by glucocorticoids and mediates the production of arachidonic acid from membrane phospholipids. Eicosanoids and prostanoids are synthesized from arachidonic acid via 5-lipoxygenase activating protein (FLAP)/5-lipoxygenase (5-LO) and cyclooxygenase 1 (COX1), respectively. COX1 pathway leads to prostaglandin G₂ (PGG₂) then prostaglandin H₂ (PGH₂), which then leads to terminal products: thromboxane A₂ (TXA₂), a potent stimulator of platelet activation and aggregation, and prostaglandins I₂ (PGI₂), prostaglandin F₂ (PGF₂), prostaglandin D₂ (PGD₂), and prostaglandin E₂ (PGE₂). FLAP and 5-lipoxygenase transform arachidonic acid to 5-hydroxyperoxyeicosotetraenoic acid (5-HPETE). 5-HPETE is further converted to leukotriene B₄ (LTB₄) and leukotriene C₄ (LTC₄). LTC₄ is further transformed into leukotriene D₄ (LTD₄) and leukotriene E₄ (LTE₄). PGE₂ normally inhibits 5-LO. Therefore, aspirin and NSAIDs inhibition of COX1 leads to a relative reduction of PGE₂ and, therefore, uninhibited FLAP/5-LO pathway production of leukotriene. This is at least a partial putative mechanism behind aspirin/nonsteroidal anti-inflammatory drugs exacerbated respiratory symptoms and urticaria/angio-edema.

polyposis, sinusitis, asthma, and aspirin sensitivity (15). This is now collectively termed as AERD. Realistically, AERD is not limited to aspirin. Instead, it refers to the development of bronchoconstriction following the ingestion of any NSAIDs that inhibit COX-1 and temporarily increase the formation and release of inflammatory mediators. Therefore, the term Aspirin and NSAID-exacerbated respiratory disease (ANERD) probably more accurately describes these patients with AERD.

The prevalence of ANERD in an asthmatic adult population is 9 to 20%, but the prevalence in adult asthmatics with nasal polyps is closer to 34% (9,16,17). Patients afflicted with ANERD are usually older than age 10 yr and frequently manifest during the third to fourth decade of life, with a prevalence in females of 57% (16). Interestingly, in a European study of ANERD,

the diagnosis of rhinitis usually predated the diagnosis of asthma. Aspirin/NSAID-induced respiratory symptoms subsequently developed, and nasal polyposis typically developed last. In this data set, the female-to-male ratio was 2.3:1, and females had both earlier onset and increased severity of disease. Surprisingly, atopy was only present in one-third of the study population, and only 6% had a family history of ANERD (17).

The spectrum of clinical manifestations includes intense rhinorrhea, nasal congestion, conjunctival injection, peri-orbital edema, laryngospasm, bronchospasm, wheezing, SOB, and chest tightness. These reactions can be slow in onset and occur 30 to 120 min after ingestion of aspirin or NSAID. Although most patients experience symptoms in both the lower and upper respiratory tracts, patients

may experience either one alone or both. The dose of ASAs or NSAIDs that provokes symptoms is the most important indicator of severity. Unfortunately, no in vitro test or specific historical cues can be reliably used to differentiate patients with true ANERD vs those without it. When challenged, adult asthmatics with a history of respiratory symptoms to ASA/NSAIDs have a positive oral challenge to ASA/NSAIDs only two-thirds of the time (18). Therefore, aspirin challenge is often required in most cases to identify patients with ANERD. As stated earlier, although the history of ANERD may suggest a type I IgE-mediated reaction, IgE-mediated mechanisms have never been clearly demonstrated for ANERD. Skin test responses with ASA are typically negative, and the search of serum antibodies against ASA or its derivatives are usually nonrevealing.

The putative pathogenesis of ANERD is based on observations that COX-1 is expressed in all mammalian cells, whereas COX-2 is inducible by inflammatory mediators. ASAs and NSAIDs inhibit COX-1 and -2 to some degree. With inhibition of COX-1 and -2, excess arachidonic acid is shunted via the 5-lipoxygenase pathway to produce leukotrienes. Specifically, LTC₄, LTD₄, and LTE₄ lead to bronchoconstriction, vasodilation, mucous secretion, and eosinophil chemotaxis. In support of this hypothesis, bronchial alveolar (BAL) fluids of patients with ANERD have shown an increase in LTC₄ compared to non-ANERD asthmatics. Furthermore, inhibition of cysteinyl leukotriene has been shown to inhibit ANERD bronchoconstriction. Recently, in patients with aspirin-sensitive rhinoconjunctivitis, an elevated number of inflammatory cells displayed cysteinyl leukotriene receptor (CysLT1), which can be downregulated with aspirin desensitization (19). Measurements of breath-condensate cysteinyl leukotrienes are generally not elevated in patients with ANERD, perhaps because of concurrent use of inhaled steroids (20). However, LTE₄ is typically elevated in urine. This is true even before ingestion of ASA/NSAID, com-

pared to asthmatics without ANERD (21). Measurement of LTE₄ may perhaps provide a good diagnostic tool for the diagnosis of aspirin-induced asthma without the use of aspirin challenge if it is routinely available. Additionally, patients with ANERD have decreased levels of anti-inflammatory lipoxins, which is also generated via the 5-LO pathway and may someday prove another method for diagnosis of ANERD (20).

The shunting of arachidonic metabolites may explain the crossreactivity of all NSAIDs in ANERD (even on first exposure), because all NSAIDs are nonspecific COX inhibitors and most preferentially inhibit COX-1 more potently than COX-2. Indeed, the degree of crossreactivity between NSAIDs is often proportional to the degree of COX-1 inhibition of the NSAID. Similarly, selective COX-2 inhibitors (rofecoxib and celecoxib) typically do not crossreact in ANERD. Partially selective COX-2 inhibitors (nimesulide, meloxicam) do not crossreact until higher doses are given, presumably because of a dose-dependent selection of COX-1 at high doses and COX-2 at lower doses. On exposure to ASA/NSAIDs, COX-1 is inhibited and causes a decrease in production of PGE₂, which normally inhibits 5-LO. In its absence, arachidonic acid is preferentially shunted via the 5-LO pathway, leading to excessive leukotriene production.

The usual guidelines for asthma therapy also apply to ASA/NSAID-intolerant asthmatics. However, all routes of ASA/NSAID administration should be avoided. Acetaminophen is generally a safe substitute as an analgesic, but a few case reports have described exacerbation of ANERD with acetaminophen because it has a very low but detectable COX inhibition activity. Similarly, magnesium salicylate and salicylic acid also have very low COX activity and are alternatives. All patients with ANERD can be desensitized by increasing exposure to oral ASA. This usually requires a 2 to 3 d hospitalization, and desensitization may be lost if ASA

Table 1
Oral Challenge Protocol to Detect AERD

Time	Day 1	Day 2	Day3
7 AM	Placebo	30 mg	100–150 mg
10 AM	Placebo	45–60 mg	150–325 mg
1 PM	Placebo	60–100 mg	650 mg

Forced expiratory volume in 1 s (FEV₁) should be >1.5 liters and preferably >70% of predicted with <10% variability on placebo day; FEV₁ should be measured hourly; dose should be advanced by 30 to 45 mg with each 3-h dosing, depending on severity of historical reaction. Potential reactions include naso-ocular symptoms, naso-ocular symptoms with ≥15% decline in FEV₁, isolated lower respiratory reaction >20% decline in FEV₁, laryngospasm with or without above reaction as assessed by flat or notch inspiratory flow volume loop, systemic reactions in the form of hives, flushing, gastric pain, hypotension. (Adapted from ref. 1.)

is stopped after more than 2 to 5 d. This may be especially important for patients who require continuous ASA in the setting of cerebral vascular accident or coronary artery disease prophylaxis. With desensitization, improvements have also been demonstrated for both upper and lower airway disease in patients with ANERD (Table 1; ref. 22). This is especially true in asthmatics who are not well-controlled on steroids and leukotriene who have had repeated nasal polypectomies and sinus operations.

The diagnosis of ANERD is primarily based on a history of respiratory symptoms in an asthmatic after ingestion of ASA/NSAIDs, because in vitro testing has not been commercially available or validated. Aspirin challenge can be performed if the diagnosis is unclear, especially because one-third of patients have a negative challenge. Additionally, challenge protocols are effectively desensitization protocols as well. For patient safety, this must be performed in a hospital setting, preferably when asthma is under control. All asthmatic medications may be continued, with the exception of leukotriene antagonists because they may decrease the lower respiratory response and decrease the diagnostic yield for the aspirin challenge (23,24). Under the right patient selection, up to one-third of patients with

convincing histories may have a negative oral challenge. Lysine-ASA, a soluble form of aspirin, has been used for nebulized broncho-provocation challenge in an outpatient setting, but it is not available in the United States

Subdividing Aspirin and NSAID-Induced Urticaria: Those With and Those Without Underlying Chronic Urticaria

In patients with chronic idiopathic urticaria, ASA-induced urticaria has been reported in 20 to 40% (6, 12). This usually occurs 2 to 4 h after ingestion in a dose-dependent fashion. Antihistamines and leukotriene receptor antagonists appear to prevent or modify these reactions. Unlike ANERD, the mechanism of ASA-induced urticaria is less well-defined, and various mechanisms have been suggested (25). Those patients with underlying chronic urticaria/angioedema are believed to be sensitive to inhibition of COX-1 because these individuals tend to react to multiple NSAIDs. Those who develop urticaria/angioedema to only one NSAID suggests an IgE-mediated type I event, despite the fact that detection of antibodies to specific NSAIDs is usually nonrevealing (2). In fact only 1 of 17 patients with aspirin sensitivity demonstrated IgE binding to ASA-human serum albumin (26). However, remember that there is a 3-log or greater difference between the relative inhibition of COX-1 among the different NSAIDs (27).

In the 1980s, successful oral challenge desensitization to ASA in patients with ASA/NSAIDs-induced urticaria/angioedema was described using a treatment protocol with interval dosing between 2 and 24 h (28,29). Conversely, Stevenson (30), who has published extensively on ASA, had difficulty maintaining desensitization in this group. In 2000, this discrepancy was resolved by Wong (25), who further characterized aspirin desensitization in ASA/NSAIDs-induced urticaria/angioedema by subdividing them into two groups: those with a history of chronic urticaria/angioedema independent of ASA/NSAIDs and those who only

Table 2
Aspirin Challenge/Desensitization Protocol
for Patients With Aspirin-Induced Cutaneous Disease

Time	Aspirin dose
0	0.1 mg
15 min	0.3 mg
30 min	10 mg
45 min	30 mg
60 min	40 mg
85 min	81 mg
110 min	162 mg
135 min	325 mg

Range of reaction is 30 to 60 mg. This protocol is particularly useful if desensitization needs to be accomplished within a few hours. (Adapted from ref. 26.)

get urticaria/angioedema with ASA/NSAIDs. Wong (25) found that ASA desensitization was not achieved in the subgroup of ASA/NSAIDs-induced urticaria/angioedema with a history of chronic urticaria/angioedema independent of ASA/NSAIDs, whereas those without this history could be successfully desensitized using the protocol outlined in Table 2 (25).

Wong's findings were re-affirmed by two other investigators. In 2003, Simon reported his clinical experience in successful desensitization of patients with a history of single ASA/NSAIDs-induced urticaria/angioedema, beginning with 3 to 10 mg of ASA and increasing the dose every 30 min. In patients with chronic idiopathic urticaria, who reacted to ASA/NSAIDs, Simon was able to complete a desensitization protocol to 650 mg of aspirin, but hives returned within 24 h. The hives then persisted for days, despite prednisone and regardless of whether aspirin was terminated. Furthermore, future attempts at continuing aspirin after the urticaria subsided was associated with increasing urticaria (31). At Scripps Clinic in 2004, Gollapudi (32) observed that desensitization could generally be accomplished in patients with urticaria/angioedema to single and multiple NSAIDs as long as chronic idiopathic urticaria was not concomitantly present. This was not the case in patients with underly-

Table 3
Alternate Aspirin Challenge Protocol in Double-Blinded Fashion for Patients With Aspirin-Induced Cutaneous Disease

Time	Double-blinded procedure of either agent
0 min	Placebo/Placebo
60 min	150 mg Placebo/Aspirin
120 min	325 mg Placebo/Aspirin
180 min	Placebo/Placebo
240 min	325 mg Aspirin/325 mg Aspirin
300 min	Placebo/Placebo
360 min	END

This protocol is reserved for those with zero-to-minimal risk of respiratory/anaphylactoid reaction. (Adapted from refs. 6 and 7.)

ing chronic idiopathic urticaria. Although the independent observations of Wong, Simon, and Gollapudi were consistent, Gollapudi cautioned that no prospective controlled studies have been performed to confirm his observations. Table 3 provides an alternate double-blinded protocol for a patient with aspirin-induced cutaneous disease (6).

Anaphylaxis and Other Hypersensitivities to Aspirin Alone or a Single NSAID

True aspirin-induced anaphylaxis reaction is probably very rare. Because of aspirin's wide public availability in numerous over-the-counter preparations, it is interesting that no more cases of aspirin-induced anaphylactic reactions have been reported. Nonaspirin/NSAID-induced anaphylactic reactions are also rare but are probably more common compared to aspirin. A review of a Medicaid database revealed only 35 cases (0.07%) of shock of 52,000 patients on NSAID (33). Generally, crossreactivity does not occur in anaphylaxis with ASA or NSAIDs (32). Therefore, the presumed mechanism is probably IgE-mediated. Theoretically, these patients should be able to undergo desensitization. Different authors have argued the efficacy and indication of desensitization to

aspirin when the putative reaction is anaphylaxis. Certainly, an analogous argument can be made in support for aspirin desensitization for patients with a history of anaphylactic reaction, if allergists routinely desensitize patients to insect venom for anaphylactic reactions. However, the difference is that—unlike in hymenoptera desensitization—no specific data exist to support the efficacy of aspirin desensitization in patients who are experiencing anaphylaxis. Schaefer (6) argued that challenge testing in patients with clear anaphylactic reaction is not indicated because of the probability of precipitating a life-threatening reaction with challenge testing. Similarly, Simon (31) argued that the risk of inducing anaphylaxis made aspirin the only NSAID worthy of challenge/desensitization procedure because it had no substitute. Although authors have reported generally successful desensitizations to aspirin in patients with anaphylactic reactions, and protocols have been recommended (Table 4; ref. 2), these authors have conceded that indications and efficacy of desensitization in this population is limited (31,32). We cannot recommend the use of challenge/desensitization protocol in patients with a clear history of anaphylaxis outside of a research setting.

Specific NSAID-induced hypersensitivity pneumonitis and allergic alveolitis consisting of cough, fever, eosinophilia, and pulmonary infiltrates have been reported. Crossreactivities have not been reported, and aspirin has not been clearly reported as a culprit (34,35). The immunological mechanism of injury is not fully characterized but may be consistent with a delayed hypersensitivity reaction or a late-phase response. For similar reasons behind ASA/NSAID-induced anaphylaxis, challenge/desensitization cannot be recommended for patients with specific NSAID-induced pneumonitis/alveolitis.

Similarly, specific NSAID-induced aseptic meningitis has also been reported. Again, aspirin has not been clearly reported as a culprit, and crossreactivities do not appear to occur.

Table 4
Aspirin Challenge/Desensitization for Patients
With History of Anaphylaxis

Time	Aspirin dose
0 min	10 mg
30 min	20 mg
60 min	40 mg
90 min	81 mg
120 min	162 mg
150 min	325 mg

Range of reaction is 20 to 30 mg. Challenge should be performed in an intensive care setting and reserved for individuals with history suggestive of anaphylaxis to aspirin. (Adapted from ref. 2.)

Patients have typically been on NSAIDs for numerous months. The immunological mechanism of injury is also not fully characterized, but in vitro studies have demonstrated the presence of immune complexes and specific IgG in the spinal fluid of patients, and it has appeared to be a lymphocyte-mediated process (36,37). The nature of delayed presentation in NSAID-induced meningitis makes challenge/desensitization an unrealistic expectation for patients with specific NSAID-induced meningitis.

Aspirin Sensitivity in Patients With Coronary Artery Disease

The allergist/immunologist is often consulted by cardiologists for the desensitization of patients to ASA (aspirin) for use as an antiplatelet agent for both primary and secondary prevention of coronary artery disease. Aspirin has repeatedly been shown to reduce cardiovascular event rate by 44% in primary prevention and 30 to 40% in secondary prevention (38–40). Although guidelines from the American College of Cardiology and the American Heart Association both allow for the use of thienopyridine (clopidogrel bisulfate, ticlopidine hydrochloride) for coronary artery disease when a true sensitivity to ASA or NSAIDs exists, monotherapy with thienopyridine is not only less cost-effective but also carries its inherent

risks in terms of neutropenia and thrombotic thrombocytopenia purpura (41–43). Additionally, recent trial data have demonstrated additive protection from the use of both aspirin and clopidogrel against future coronary events in patients with unstable angina/non-Q-wave myocardial infarction (44,45). Furthermore, the increased use of drug-eluting stents for percutaneous coronary intervention often requires the combination of aspirin and thienopyridine to reduce acute and subacute stent thrombosis (46–48). Therefore, aspirin is likely to continue to have a significant role in the management of patients with coronary artery disease.

Because cutaneous tests for aspirin sensitivity have failed to reproducibly elicit wheal-and-flare responses and no in vitro testing for aspirin sensitivity exists, oral challenge/desensitization remains the only way to definitively make the diagnosis (bronchial and nasal challenges have been described, but only oral aspirin challenges are available in the United States) (7,49). Challenge/desensitization can serve the dual purpose of diagnosis and therapy. For patients with a single non-aspirin NSAIDs sensitivity that is not anaphylactic in nature and is consistent with an IgE-mediated process, aspirin can be started safely without the need for challenge/desensitization because it would be unlikely for a separate antibody against aspirin to be present (32).

Patients with coronary artery disease and concomitant ANERD, isolated aspirin-induced urticaria/angioedema, or aspirin/NSAIDs-induced urticaria/angioedema without underlying chronic urticaria/angioedema may undergo challenge/desensitization protocols if they are stable. If they are unstable, then coronary intervention and medical management of the coronary artery disease should be addressed first with a future evaluation and treatment for their aspirin/NSAIDs sensitivity. Perhaps bare metal stents, such as heparin-coated stents, can be used instead of drug-eluting stents for percutaneous coronary intervention, thereby negating the need for combination antiplatelet therapy

of aspirin and thienopyridine in the periprocedure period. Certainly, it has been demonstrated that ticlopidine is at least equivalent to aspirin as monotherapy regarding in-hospital death, cardiac events, or vascular access-site complication after bare metal stenting. Furthermore, stent thrombosis was not observed in patients treated with ticlopidine in this study (50).

In 2005, Silberman reported a small series of 16 patients with imperative indications for percutaneous coronary intervention who underwent rapid aspirin challenge/desensitization in the coronary care unit. Of the patients who underwent coronary stenting, four patients had unstable angina pectoris, five had recent ST-segment elevation myocardial infarction, and two had non-ST-segment elevation myocardial infarction with imperative need for aspirin therapy. Desensitization protocols require stopping the β -blockade for 24 h before the procedure; the dosing schedule is presented in Table 5a and 5b. No premedication with antihistamines or corticosteroids was used. Fourteen of the 16 patients had uneventful challenge/desensitization. One patient developed angioedema 3 h after the procedure and was successfully rechallenged 2 d later, whereas a second patient developed shortness of breath and nasal swelling 1 h after the procedure (51). Although the outcome of this study is encouraging, we note that neither of the two patients with reactions received epinephrine for treatment of their skin and respiratory symptoms. Therefore, the risk of treatment with sympathomimetics for severe adverse reactions during aspirin challenge/desensitization is still unknown in patient populations with unstable coronary disease. The authors concede that patients with acute ST-segment elevation myocardial or history of anaphylaxis should not undergo challenge/desensitization protocol because their inherent risk, albeit unknown, is presumably high.

Generally, patients who have anaphylaxis with aspirin and underlying coronary artery disease should not undergo desensitization.

Table 5A,B
Rapid Aspirin Challenge/Desensitization Protocol
for Patients With Imperative Indications
for Coronary Intervention

A	
Time	Aspirin dose
0 min	5 mg
30 min	10 mg
60 min	20 mg
90 min	40 mg
120 min	75 mg
150 min	325 mg
B	
Time	Aspirin dose
0 min	1 mg
30 min	2 mg
60 min	4 mg
90 min	8 mg
120 min	16 mg
150 min	32 mg
180 min	64 mg
210 min	100 mg

Adapted from ref. 52.

Although challenges are frequently negative, this subgroup had never been evaluated in trials (7,52). If anaphylaxis occurs during aspirin desensitization, then significant strain may be placed on the myocardium of an already diseased heart. Additionally, the treatment of anaphylaxis is epinephrine, which is a sympathomimetic that may further increase cardiac demand. Therefore, desensitization in patients with anaphylaxis caused by aspirin should not be routinely conducted outside of the context of a clinical research trial (7).

Aspirin Desensitization

Although the use of aspirin desensitization in ANERD- and aspirin-exacerbated urticaria/angioedema has been considered accepted practice since Stevenson first reported efficacy in 1984 (53), a thorough review of the literature has revealed a relative paucity of data evidence to support its use for situations not involving

ANERD (Table 6). The 1984 study remains the only randomized, placebo-controlled trial; only 25 patients were enrolled in the randomized portion of this trial, and only 60% of the patients had a positive oral aspirin challenge. The remaining studies were often not placebo-controlled and usually involved less than 100 subjects. Studies on the efficacy of aspirin desensitization have primarily addressed whether aspirin desensitization along with its continued use will improve overall asthma/rhinitis symptoms. Nearly all controlled prospective trials were performed by the outstanding group at Scripps Medical Center. Similar caliber studies have not been repeatedly performed elsewhere. None of the studies on aspirin desensitization for ASA/NSAIDs-induced urticaria/angioedema were controlled for true positive sensitivities with aspirin challenges, and no published data exist that specifically assess the efficacy of aspirin desensitization for aspirin-induced anaphylaxis. In fairness, Stevenson and his group (54) have since argued that double-blind placebo trials are not possible because nasal congestion, at least in the case of ANERD, occurs in most patients at the time of challenge/desensitization, and nasal congestion returns after discontinuing aspirin for 48 to 72 h, thus effectively unblinding the subjects. Furthermore, it has been proposed that aspirin challenge/desensitization should only be performed in patients with an impending need for aspirin and, therefore, it would be unethical to use a placebo as a desensitizing control agent. As stated earlier, despite a good history of aspirin sensitivity, patients can have negative challenges one-third of the time or more. The devil's advocate could argue that patients with putatively successful aspirin desensitizations may simply be those who do not have aspirin sensitivity at the start.

An ideal scenario for testing the efficacy of aspirin desensitization may be: (a) enroll patient with a history of aspirin sensitivity; (b) enroll them in a run-in period of aspirin challenge with objective measures for a positive chal-

Table 6
Assessment of Aspirin Desensitization Studies

Studies	Design	N	Type of ASA/NSAIDs sensitivity studied	Controlled for true-positive ASA/NSAIDs sensitivity by challenge	No. placebo	No. desensitized with aspirin protocol	No. positive challenge	No. continued aspirin after desensitization protocol	Critique
Widal, 1922 (13)	Case	1	ANERD- and ASA-induced urticaria	N/A	N/A	1	1	1	1st Case study
Zeiss, 1976 (57)	Double-blind prospective trial	50	N/A unknown aspirin sensitivity status	Yes	N/A	1	3	N/A	Serendipitous observation in one patient
Stevenson, 1980 (58)	Case	2	ANERD	Yes	N/A	2	2	2	Limited case study
Pleskow, 1982 (59)	Nonrandomized prospective trial	30	ANERD	Yes	0	30	30	30	Good study; cross-desensitization demonstrated as an outcome; small N
Asad, 1983 (28)	Nonrandomized prospective trial	8	ASA induced urticaria/angioedema	Yes	N/A	5	6	5	Good study, small N
Stevenson, 1984 (53)	RDBPC crossover prospective trials	91	ANERD	Yes	25	25	54	25	Good study; small N
Kowalski, 1984 (60)	Nonrandomized prospective trial	29	ANERD	Yes	N/A	27	29	27	Good study; small N
Grzelewska-Rzymowska, 1988 (29)	Nonrandomized prospective trial	22	ASA-induced urticaria/angioedema	Yes	N/A	22	22	22	Sensitivity may be defined by patient anamnesis, small N
Sweet, 1990 (60)	Retrospective Cohort trial	107	ANERD	Yes	42	65	107	35	Small retrospective population and drop out
Stevenson, 1996 (61)	Nonrandomized prospective trial	65	ANERD	Yes	0	65	65	65	Good study with subjective improvement by phone and questionnaire
Schaefer, 1999 (6)	Case series	3	ANERD- and ASA-induced urticaria/angio-edema and anaphylaxis	No	0	3	1	3	Case series without long-term follow-up of efficacy
Wong, 2000 (25)	Nonrandomized prospective trial	11	ANERD- and ASA-induced urticaria angio-edema	No	0	11	2	9	Small number of subjects. Not controlled for true positive sensitivity
Berges, 2003 (54)	Prospective trial	38	ANERD	Yes	N/A	38	38	38	Improve nasal score
Berges, 2003 (62)	Single-blind prospective trial	172	ANERD	Yes	N/A	172	172	148	67% with clinical improvement after aspirin desensitization
Silberman, 2005 (51)	Nonrandomized prospective trial	16	ANERD- and ASA-induced urticaria angio-edema	No	0	16	2	15	Small number of subjects. Not controlled for true-positive sensitivity

lenge such as change in peak expiratory flow, presence of urticaria/angioedema, drop in blood pressure, or validated nasal symptom scores; (c) only those with positive challenges to the preset criteria are then randomized to desensitization with aspirin or placebo; (d) those who complete the desensitization protocol are then followed for outcomes of asthma/rhinosinusitis exacerbation and, most importantly, tolerance to aspirin re-challenge at a later time with objective measures such as change in forced expiratory flow after 1 s or the presence of urticaria/angioedema on re-challenge to aspirin or other NSAIDs at a prespecified time; and (e) although patients may be unblinded by the effects of aspirin use vs. placebo, the persons analyzing the data can and should be blinded. A negative study using misoprostol in aspirin-sensitive asthma was performed using a similar procedure (55).

Conclusion

ASA sensitivity encompasses a diverse group of both pharmacological and hypersensitivity reactions. Conventionally, specific hypersensitivities include AERD, ASA-induced urticaria, and anaphylaxis. Although IgE antibody has not been readily identified in the majority of patients with anaphylaxis to ASA or a single NSAID, an immunological basis for anaphylaxis remains a distinct mechanistic probability. In anaphylaxis, urticaria/angioedema limited to only ASA or a single NSAID is likely IgE-mediated as well, although identification of specific antibodies has also been elusive. The pathogenesis of ASA- and NSAID-induced urticaria/angioedema is unknown, but the fact that crossreactivity exists among different NSAIDs suggests that excessive leukotriene production may be responsible for increased vascular permeability and subsequent urticaria. ANERD is probably a more accurate description for AERD. The severity of reactions in patients with ANERD is proportional to the degree of COX-1 inhibition of the NSAIDs in question. In turn, this supports the conjecture

that this type of reaction is mediated by excessive leukotriene production, as in urticaria/angioedema to multiple NSAIDs. Simply, although reactions limited to a single ASA/NSAID is probably IgE-mediated, reactions that span multiple NSAIDs that inhibit COX are likely heightened sensitivity to an otherwise physiological/pharmacological process. Regardless of the mechanisms, these various hypersensitivities pose a clinical dilemma for patients who need aspirin for its therapeutic effects. Fortunately, at least in limited trials and case studies, aspirin desensitization has shown efficacy for most aspirin hypersensitivities, with the exception in patients with ASA/NSAID-induced urticaria with underlying chronic urticaria. It is intriguing that desensitization can be achieved in ANERD or ASA/NSAID-induced urticaria/angioedema when excess cysteinyl leukotriene metabolites is the putative mechanism, whereas desensitization has never been reported for ASA/NSAID-induced gastritis or nephritis when the putative cause has been an analogous reduction of prostaglandins. ASA/NSAIDs desensitization likely utilizes a unique and still poorly defined molecular mechanism (56).

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