

Pathogenesis, diagnosis, and treatment of aspirin intolerance

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Objectives: To provide an overview of aspirin intolerance (AI), to summarize the latest genetic and pathophysiologic findings, and to discuss the current therapeutic recommendations, including aspirin desensitization.

Data Sources: Using the PubMed database, a systematic search of articles published between 1968 and 2006 was performed to evaluate the current literature on AI. The bibliographies of selected articles served as a source of additional literature.

Study Selection: Included articles were selected for their relevance to the pathogenesis, diagnosis, and management of AI.

Results: The prevalence of AI is approximately 0.3% to 0.9%, but AI is often overlooked. It can display a wide range of clinical pictures, such as acute asthma attacks, urticaria, angioedema, chronic rhinitis, myocardial ischemia, and anaphylactic shock. Regarding the pathogenesis of AI, modifications of eicosanoid metabolism are supposed to underlie AI, including aspirin-induced asthma and aspirin-induced urticaria. However, the pathogenesis of AI has not yet been clearly elucidated. Associations of several HLA alleles with subtypes of AI, such as aspirin-induced urticaria and aspirin-induced asthma, and single nucleotide polymorphisms in genes encoding enzymes involved in arachidonic acid metabolism have been shown.

Conclusions: Because aspirin therapy should be avoided in AI patients, the use of alternative drugs is recommended. Patients intolerant of alternative drugs and those with therapy-resistant asthma or sinusitis benefit from aspirin desensitization.

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INTRODUCTION

In 1897, Felix Hoffmann, a German chemist, succeeded in formulating a stable form of acetylsalicylic acid (ASA) by mixing acetic and salicylic acids.¹ Since that time, ASA, named *aspirin*, has been one of the most widely used drugs.¹ Aspirin is commonly used for the treatment of headache, fever, pain, and musculoskeletal disorders. Its inhibitory effect on platelet aggregation often makes it the first choice for the prophylaxis of strokes, myocardial infarction, and thromboembolism. In general, aspirin is well tolerated by most patients, but despite the widespread use of the drug, a variety of potentially serious adverse effects leading to hospitalization exist. In addition to the frequent gastrointestinal adverse effects, aspirin intolerance (AI) represents a serious but often underestimated problem.

In 1911, Gilbert² described a form of asthmatic dyspnea after the ingestion of aspirin. Eleven years later, Widal and colleagues³ observed an association between nasal polyposis, bronchial asthma, and AI. These 3 symptoms were summarized by Samter and Beers in 1968 and have been designated as the classic “aspirin triad,” also known as “Samter’s triad.”⁴

As a characteristic clinical feature, affected patients develop an acute asthma attack, which is often accompanied by rhinorrhea, conjunctival irritation, and flushing of the head and neck or myocardial ischemia, within 3 hours of aspirin ingestion.⁵ In other AI individuals, involvement of the skin in the form of urticaria or angioedema can be observed.

Since the past century, scientists worldwide have focused their research on the detailed analysis of AI and its therapeutic control. Recent investigations show overproduction of cysteinyl leukotrienes (Cys-LTs) linked to an imbalance between proinflammatory and anti-inflammatory mediators derived from arachidonic acid (AA), which seems to play an important role in the pathogenesis of AI. A great amount of research has been undertaken to develop an adequate in vitro test for AI, but at present, all in vitro tests are considered additional diagnostic tools. Therefore, the aspirin provocation test represents the only method available to validate the diagnosis of AI in a solid manner. The therapeutic options range from the intake of alternative drugs instead of aspirin to aspirin desensitization. Herein we discuss recent investigations on the diagnosis and pathogenesis, genetic background, and different therapeutic options of AI to advance our under-

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standing of the mechanism and the therapeutic control of AI. Using the PubMed database, a systematic search of articles published between 1968 and 2006 was performed to evaluate the current literature on AI. The bibliographies of selected articles served as a source of additional literature. Included articles were selected for their relevance to the pathogenesis, diagnosis, and management of AI.

PREVALENCE OF AI

The prevalence of AI in the average population is 0.3% to 0.9%.⁶ To date, no racial differences have been reported. Many studies show a female predominance,^{4,7} whereas children younger than 10 years are affected less often.⁸ This finding might be explained partly by the fact that aspirin is rarely prescribed, since aspirin is contraindicated in children younger than 12 years owing to the risk of Reyes syndrome. Reyes syndrome represents a sudden, profound failure of mitochondria, which leads to acute encephalopathy and hepatic dysfunction associated with the use of aspirin.

In most patients, the classic aspirin triad develops between the ages of 30 and 35 years.⁹ The coincidence of AI in patients with asthma, nasal polyps, or nasal chronic rhinitis has been analyzed in several studies. Accessory AI occurs in approximately 2% to 23% of asthmatic patients, depending on the populations studied and the diagnostic methods used to evaluate AI.^{5,10} Approximately 14% to 22% of patients with nasal polyps show an intolerance reaction against aspirin (Table 1),⁶ whereas in patients with nonallergic rhinitis only, the incidence of AI is relatively low (0.7%–1.4%).⁶

Atopy has been supposed to be a possible risk factor for the development of AI in some studies because of the higher prevalence of atopy in patients with intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) compared with individuals who tolerate NSAIDs.¹¹ The question of whether atopy really represents a risk factor for AI has not been sufficiently answered yet, and the associations shown so far might also simply be related to the high prevalence of atopic disorders.^{7,11,12} Even if there are reports that atopy might affect the transition from AI to aspirin-induced asthma (AIA), note that most AIA patients have the intrinsic, nonatopic form of asthma, which might indicate that atopy represents an unimportant co-factor in most cases.

CLINICAL MANIFESTATIONS OF AI

Several NSAIDs can cross-react with aspirin in aspirin-sensitive patients,⁶ but the clinical symptoms differ in severity

and frequency depending on the dosage, the anti-cyclooxygenase (anti-COX) activity of the NSAIDs used, and the sensitivity of each individual patient. Clinical manifestations of AI may affect the skin or the respiratory tract, and they occur only rarely in combination. Concerning skin disorders, urticaria with or without angioedema is the most common drug eruption induced by aspirin.¹³ Approximately 10% of patients with AI develop urticaria or angioedema, alone or, rarely, combined with respiratory inflammation.¹⁴ Approximately 21% to 30% of patients with chronic urticaria (urticaria persisting ≥ 6 weeks) are affected by intolerance to aspirin or other NSAIDs.¹⁵ Because of this high contingent of patients with both urticaria and AI, AI should be considered as a possible cause of urticaria. Another clinical manifestation of AI, which occurs rarely, is the development of life-threatening anaphylactic shock with airway obstruction and the risk of cardiac and respiratory arrest in severe cases.

The bronchospastic type of aspirin sensitivity is frequently associated with intrinsic asthma and nasal polyps, leading to the classic triad. The triad follows a specific clinical pattern.⁶ Sometimes the triad is described as a “quadrate” and includes rhinosinusitis.¹⁰ The disease often starts with rhinitis combined with a viral infection. The rhinitis persists for a long time, might be refractory to treatment, and might lead to recurrent sinusitis and nasal polyps. Asthma and AI typically develop a few months to several years later.⁵ Some patients are affected by acute asthma within a few hours of ingestion of aspirin, but most of them have chronic asthma, which aggravates after intake of aspirin.¹⁴ Twenty percent of patients with AIA have a mild form of asthma, whereas 30% are moderate asthmatic patients who can control their disease with inhaled corticosteroid therapy. Fifty percent of AIA patients have chronic corticosteroid-dependent asthma.¹⁶ Seventy percent of AI patients have nasal polyps,¹⁷ which generally involve not only the nasal cavity but also all paranasal sinuses bilaterally.¹⁸ Because AI remains underdiagnosed worldwide despite its relatively high incidence, the diagnosis of AI should be considered in suspected individuals showing any chronic respiratory disease or recurrent skin diseases, such as urticaria and angioedema.

PATHOGENESIS OF AI

The pathogenetic mechanism of AI is complex and is not fully understood. One common hypothesis proposes that AI results directly from an unspecific, non-IgE-dependent degranulation of mast cells and eosinophils as a pseudoallergic reaction in which, in contrast to allergic reactions, symptoms already appear after the first intake of the drug. Drugs known to be cross-reactive are ASA and other NSAIDs, which preferentially inhibit COX-1,⁶ whereas some studies showed that cross-reactivity between aspirin and highly specific COX-2 inhibitors (eg, celecoxib), known as “coxibs,” does not occur in individuals with previous pseudoallergic respiratory reactions. For example, meloxicam inhibits COX-2 at low therapeutic concentrations but also inhibits COX-1 at

Table 1. Incidence of AI in Different Subgroups of Patients

Patient group	Incidence of AI, %
Mild asthma	2–10 ^{14,63}
Severe asthma	20 ^{14,63}
Nasal polyps	14–22 ⁶⁴
Nasal polyps and severe asthma	78 ⁶⁵
Chronic rhinitis	0.7–1.4 ⁶⁶
Chronic urticaria	23–28 ⁶

Abbreviation: AI, aspirin intolerance.

increasing concentrations, whereas at higher doses it cross-reacts poorly or not at all.¹⁹

These reactions were associated with an increase in Cys-LTs and eosinophilic cationic protein, reflecting activation of eosinophils and an increase in prostaglandin D₂ (PGD₂), which mirrors mast cell activation. Studies reporting an increase in histamine and tryptase levels after intake of aspirin in AI individuals²⁰ without detection of aspirin specific IgE support the theory of a pseudoallergic reaction as a cause of AI in most cases.

However, some patients develop an anaphylactic reaction with acute urticaria and angioedema or even anaphylactic shock after the second exposition to NSAIDs or aspirin, although it has been well tolerated during previous applications. In these cases, the reactions are based on the development of drug specific IgE antibodies against aspirin²¹ or NSAIDs, which explains the relatively low rate of cross-reactions to other NSAIDs observable in these patients.²²

Focusing on the pathogenesis of respiratory disease in AI, it is more than likely that AI is linked to abnormalities in AA metabolism. There are at least 2 ways in which AA can be metabolized: the lipoxygenase pathway and the COX pathway (Fig 1A). Under physiologic conditions the metabolites produced via the COX pathway are prostaglandin E₂ (PGE₂), prostacyclin I₂, and thromboxanes, whereas under inflammatory conditions the metabolites also include PGD₂ and PGF₂. It is known that COX exists in 2 different isoforms: COX-1 is constitutively expressed, and COX-2 is induced under inflammatory conditions. Arachidonic acid is metabolized via the lipoxygenase pathway to LTA₄ and further hydroxylated to LTB₄ or converted into Cys-LTs such as LTC₄, LTD₄, and LTE₄ in the presence of LTC₄ synthase (LTC₄S) (Fig 1A). Other important products of the lipoxygenase pathway are hydroperoxyeicosatetraenoic acid and hydroxyeicosatetraenoic acid (HETE), a more stable form of hydroperoxyeicosatetraenoic acid, which play a role in the biosynthesis of lipoxins, act as anti-inflammatory mediators, and behave as functional antagonists of the leukotrienes.²³

Several hypotheses concerning the pathogenetic mechanism of AA metabolism exist (Fig 1B), but all of them fail to explain why aspirin does not cause an intolerance reaction in every individual. It has been proposed as early as 1975 that the inhibition of COX by drugs such as aspirin leads to asthma attacks after the intake of NSAIDs.²⁴ One of the hypotheses describes inhibition of COX-1, which shunts the metabolism away from the production of protective prostanooids toward the lipoxygenase pathway and the production of Cys-LTs.²⁵ Another hypothesis claims that the structure of COX-2 is changed by aspirin. This change might result in the generation of products of the lipoxygenase pathway.²⁵ There are also hypotheses proposing abnormal regulation of the lipoxygenase pathway as a reason for the development of asthma attacks in patients with AI. It has been assumed that an aspirin-induced accumulation of 15-HETE in patients with AIA results in a diminished biosynthesis of lipoxins, which act as anti-inflammatory derivatives of AA and might play a

protective role against the Cys-LT-generated inflammation. This could be another reason for the increased activity of Cys-LTs observable in patients with AIA.

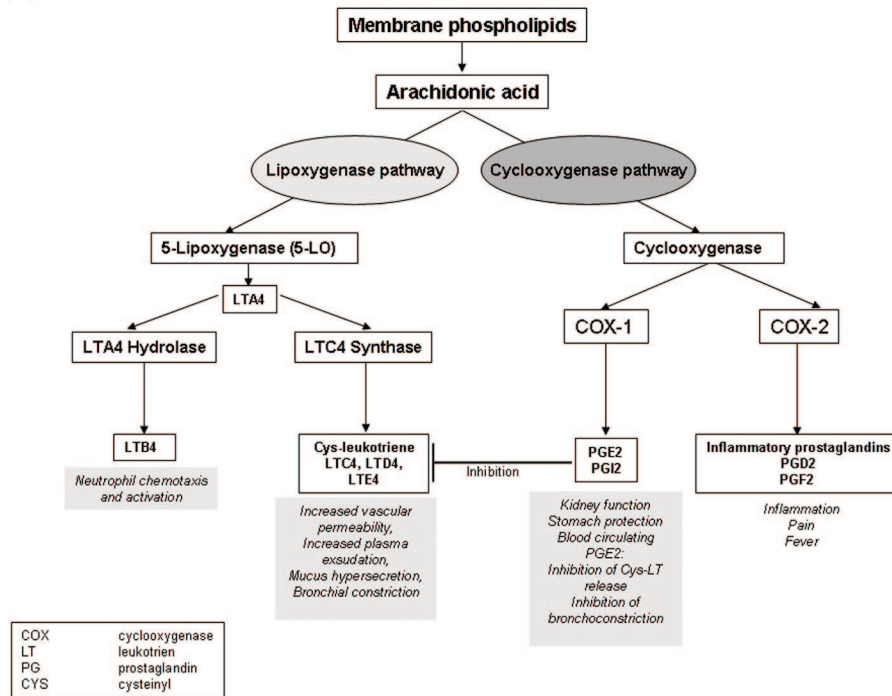
An elevated level of Cys-LT already during baseline represents a common feature of all pathways; it is further elevated after aspirin challenge and can be measured in urine, sputum, and peripheral blood²⁵ and in the exhaled breath of individuals with AIA. An association of the increment in Cys-LT with a decrease in prostaglandin E₂ (PGE₂) has been supposed that can inhibit aspirin-induced phenomena such as bronchoconstriction, elevated urinary LTE₄ concentrations, and the release of Cys-LT from peripheral blood leukocytes.²⁶ However, the validity and sensitivity of urinary LTE₄ as a readout variable are believed to be pure because of low quantity. After aspirin challenge, the aspirin-induced COX inhibition leads secondarily to decreased release of PGE₂ and in this way to an increase in Cys-LT release. Overexpression of the terminal enzyme for Cys-LT synthesis, LTC₄S, has been observed in bronchial biopsy samples from patients with AIA. In this context, overexpression of LTC₄S has also been observed in the nasal airways of AI patients.²⁷

The Cys-LTs become operative only by binding 2 known G protein-coupled receptors: Cys-LT type I receptor (Cys-LTR1) and Cys-LT type II receptor (Cys-LTR2). The Cys-LTR1 can be blocked with Cys-LTR antagonists such as montelukast, zafirlukast, and pranlukast, whereas Cys-LTR2 is resistant to most Cys-LTR antagonists. Both receptor types are expressed by cells involved in allergic inflammation, such as eosinophils, basophils, mast cells, monocytes, and macrophages. In this context, it has been shown that patients affected by aspirin-induced rhinosinusitis display increased expression of the Cys-LTR1 on inflammatory leukocytes in nasal biopsies. Other features, such as alterations in eicosanoids, do not predominate only in AIA but have been shown also in patients with aspirin-induced urticaria (AIU).²⁸

GENETIC BACKGROUND OF AI

Research focused on the genetic background of AI. Recently the results of the latest genetic research have been summarized to identify genetic markers for asthma and urticaria induced by aspirin.²⁹ In these studies, the AIU and the AIA genotype in a Korean cohort differed in the frequency of specific HLA alleles. HLA-DPB1 0301 has been shown to be associated with the AIA phenotype (this association was previously reported in a Polish population³⁰), whereas HLA-DRB1 1302 or HLA-DQB1 0609 has been shown to be associated with AIU.²⁹ In addition, an association of single nucleotide polymorphisms (SNPs) in genes encoding key enzymes involved in AA metabolism with AIA and AIU has been described. As an example, an SNP in the gene region encoding LTC₄S has been shown to be associated with AIA in a Polish population.³¹ However, the association could not be replicated in other populations, including Japanese, American, and Korean cohorts.^{32–34} Recently this polymorphism in the *LTCS4* gene has been shown to be associated with AIU.³⁵

A



B

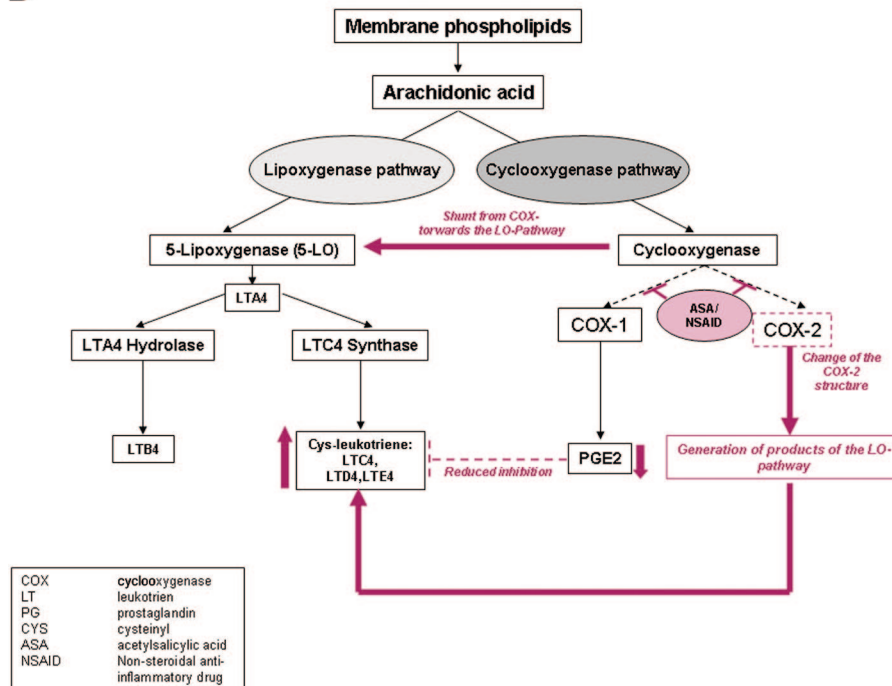


Figure 1. A, Overview of the arachidonic acid metabolic pathway. Via the cyclooxygenase (COX) pathway, prostanoids (prostaglandins, prostacyclins, and thromboxanes) result, whereas the lipoxygenase pathway produces leukotrienes. B, Summary of the pathogenetic mechanisms of arachidonic acid metabolism. Aspirin inhibits the COX pathway and diverts arachidonic acid metabolites to the lipoxygenase pathway (shunt from production of protective prostanoids toward the lipoxygenase pathway) and the production of inflammatory cysteinyl leukotrienes [Cys-LTs]. By inhibition of COX-1, the production of the anti-inflammatory prostaglandin E₂ (PGE₂) decreases. Low levels of PGE₂ lead to increased synthesis of inflammatory Cys-LTs. The inhibition of COX-2 might lead to a structural change in the enzyme, which results in the generation of products of the lipoxygenase pathway. ASA indicates acetylsalicylic acid; NSAIDs, nonsteroidal anti-inflammatory drugs.

Furthermore, several SNPs in leukotriene-related genes (5-lipoxygenase gene, 5-lipoxygenase-activating protein gene, and COX 2 gene) differ significantly in their genotypic frequency in AIU and AIA patients in the Korean population.²⁹ In 2005, genetic associations between SNPs in genes encoding Cys-LTRs and the development of AIA have been observed. Four SNPs in the gene encoding Cys-LTR2 on chromosome 13q14.2 to 21.1 and 3 in the gene region encoding Cys-LTR1 have been considered as a genetic marker for AIA,³⁶ whereas an FCER1A promoter polymorphism has been shown to be associated with the development of AIU.²⁹ Further studies are required to create new diagnostic markers and therapeutic options for AI based on genetic information.

DIAGNOSIS OF AI

Although a lot of research has been performed on the improvement of the diagnostic methods applicable to the diagnosis of AI, no specific *in vitro* test that can be used exclusively for the diagnosis of AI or replace the provocation tests exists at present.³⁷ There are 3 types of provocation tests differing in the method of administration of aspirin.

Aspirin may be applied orally, inhalative, and nasally.⁵ The most frequent method for confirming AI is oral aspirin challenge. It is considered the gold standard for respiratory and cutaneous reactions suspected to be caused by aspirin. Comparison of oral and bronchial provocation tests, which are accomplished with lysine ASA (Lys-ASA), showed similar specificity of both tests and higher sensitivity of the oral provocation test.³⁷ However, note that Lys-ASA is not available in the United States at present.

Another way to diagnose AIA with lower risk than using oral or bronchial provocation is nasal provocation, also conducted with Lys-ASA or, as reported recently, with ketorolac tromethamine (Toradol; Roche Laboratories, Nutley, NJ), which is, in contrast to Lys-ASA, available in the United States. Because of the poor absorption of Lys-ASA administered directly into the nasal mucosa, the risk of serious adverse reactions is much lower than with oral or bronchial provocations.³⁸ As a general feature, aspirin provocation tests should be placebo controlled owing to the variability of bronchial responsiveness. As a putative readout criterion for the reactivity during provocation tests, urinary LTE₄ excretion has been shown to correlate with the severity of respiratory responses.³⁹ In addition, the mean baseline excretion of LTE₄ is 3- to 5-fold elevated in patients with AIA compared with controls.⁵ The limitation of this additional diagnostic tool is a high rate of false-positive test results in asthmatic patients.⁵ An alternative diagnostic *in vitro* test that might be helpful for the diagnosis of AI is the basophil activation test (BAT) or a combined test evaluating basophil activation and determining the release of sulfidoleukotrienes by basophils after challenge with aspirin or NSAIDs.⁴⁰ The BAT has been clinically validated for several IgE-mediated reactions, whereas the diagnostic value of the flow cytometric analysis of *in vitro* activated basophils for the diagnosis of ASA and NSAID intolerance is not completely clarified.⁴¹ A study

published in 2004 that evaluated the flow cytometric determination of basophil activation induced by aspirin and other NSAIDs showed a sensitivity varying for different NSAIDs from 15% for metamizol to 55% for naproxen, whereas specificity generally exceeded 90%.⁴² Therefore, the BAT is not considered a reliable standard method for the diagnosis of NSAID intolerance.⁴³

Another characteristic feature that might serve as an additional readout is an imbalance of PGE₂, other prostaglandins (such as PGD₂), and peptido-leukotrienes (pLTs) (such as LTC₄, LTD₄, and LTE₄) in AI individuals. Peripheral blood mononuclear cells of AI patients showed a significantly higher release of pLT and a significantly lower release of PGE₂ than those of controls.⁴⁴ It has been demonstrated that ASA could trigger the generation of 15-HETE from peripheral blood leukocytes in AIA patients *in vitro*.⁴⁵ Although the mechanisms underlying this phenomenon are unknown, measurement of ASA-induced 15-HETE to identify ASA-intolerant individuals has been shown to be of high diagnostic value⁴⁶ and might serve as a diagnostic test to identify ASA-intolerant asthmatic patients after sufficient validation in the future.

Only in a few single cases, *in vitro* tests currently available might be helpful as additional diagnostic tools for the detection of AI in suspected individuals so that the only method to confirm the diagnosis of AI remains the aspirin challenge test (Fig 2). Note that a great portion of patients with asthma/sinusitis and nasal polyps or urticaria do not have AI, although their symptoms resemble AI.⁴⁷ Therefore, it is a challenge to identify the subgroup of patients truly at risk for AI and related exacerbations with the help of the methods available at this time.

PREVENTION AND TREATMENT OF AI

Patients with AIA or chronic urticaria aggravated after NSAID or aspirin ingestion should be educated concerning the possibility of cross-reactions between aspirin and COX-1-inhibiting NSAIDs.²² In addition, those patients should be informed about analgetics, which are well tolerated in general because they do not or only weakly inhibit the COX-1 cascade. In AI children with mild pain or fever, acetaminophen is considered to be the alternative drug of choice.⁴⁸ Acetaminophen differs from other NSAIDs and ASA by its pharmacologic method of action. Acetaminophen inhibits the 2 prostaglandin H₂ synthase (PGHS) enzymes at the PGHS peroxidative active site, whereas most NSAIDs and ASA inhibit the PGHS at the level of the PGHS COX active site. This explains, in part, why acetaminophen, in contrast to NSAIDs, cannot prevent inflammation or platelet thrombosis.⁴⁹ However, at doses higher than 1,000 mg, acetaminophen can trigger bronchospastic reactions.⁵⁰

Furthermore, AI patients are allowed to take alternative drugs, such as choline magnesium trisalicylate, chloroquine, and propoxyphene,⁵¹ because these drugs do not inhibit COX at all or have only weak anti-COX-1 and anti-COX-2 activity. Considering the selective COX-2 inhibitors, recent stud-

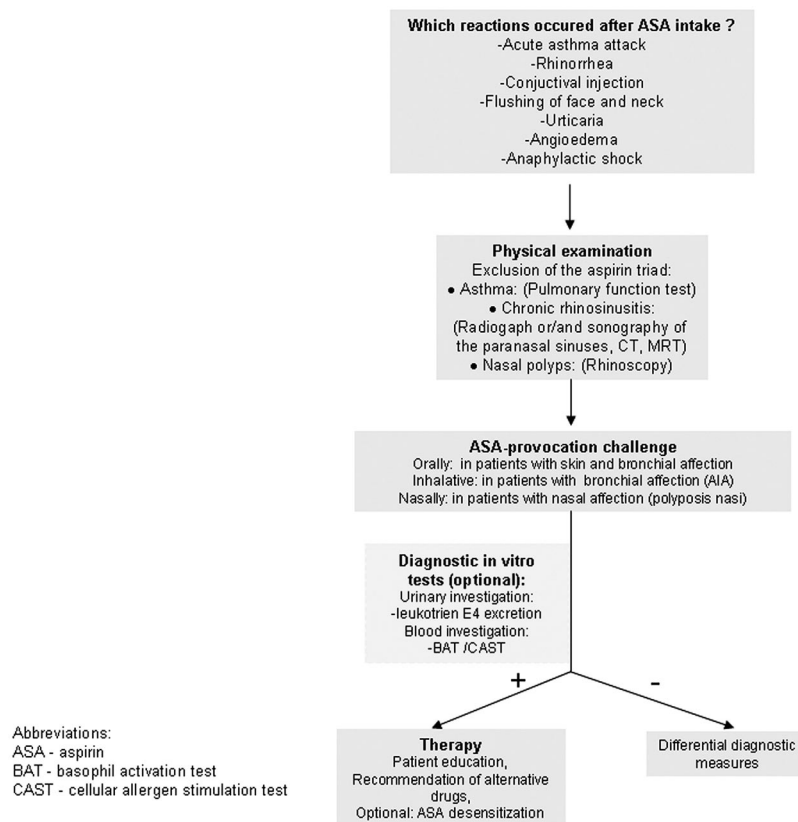


Figure 2. Flowchart of the diagnostic pathway. After detailed anamnesis (Was aspirin ingested by the patient? Was it the first ingestion or was the drug tolerated during previous applications? How long did it take between the ingestion of aspirin and the occurrence of symptoms? Which symptoms did the patient report about? What was the duration and what was the severity of the symptoms?), a physical examination focusing on the aspirin triad with nasal polyposis and bronchial asthma should be performed. In patients with clinical aspects, aspirin intolerance (AI) should be confirmed by means of aspirin provocation challenge (oral, nasal, or inhalative). Individuals with positive test results should be educated concerning drug intolerance. Aspirin desensitization represents a therapeutic option in a subgroup of AI patients. In individuals with negative test results, further diagnostic measures should be administered. AIA indicates aspirin-induced asthma; ASA, acetylsalicylic acid; BAT, basophil activation test; CAST, cellular allergen stimulation test; CT, computed tomography; and MRI, magnetic resonance imaging.

ies showed that celecoxib, the only COX-2 inhibitor available in the United States, and rofecoxib show the highest tolerability,⁵³ whereas nimesulide and meloxicam could induce mild bronchial obstruction. Although the COX-2 inhibitors seem to be safe alternative drugs, the reported increased risk of serious cardiovascular events has to be considered. Therefore, warnings for several COX-2 inhibitors have been released in many countries during the past 2 years so that in every individual case the risk-benefit ratio has to be weighed up.

In patients with anaphylaxis induced by NSAIDs or aspirin, the primary mechanisms are most likely related to drug specific IgE-mediated mechanisms. In such patients challenges with alternative NSAIDs under the survey of a physician are accomplished even if cross-reactions to other NSAIDs are extremely unlikely.²²

Nasal polypectomy and sinus surgery are useful invasive methods to treat AI aggravated by chronic sinusitis. Improve-

ment of asthmatic symptoms after endoscopic sinus surgery in the first years has also been shown,⁵⁴ and it is a generally accepted method to perform aspirin desensitization after surgical treatment of AI.

THE VALUE OF ASPIRIN DESENSITIZATION

It is possible to desensitize AI patients by means of repeated application of aspirin. The first desensitization was reported in 1922.³ Desensitization is a valuable therapeutic option in patients with chronic pain disorders or in patients taking aspirin to prevent vascular diseases. Nowadays alternative drugs are available for pain and for cardiovascular and thromboembolic diseases. However, the alternative drugs are not always well tolerated, and in some cases the effectiveness of aspirin monotherapy or combination therapy with aspirin and other platelet inhibitors is superior to therapy with an alternative platelet inhibitor alone. Therefore, in patients with NSAID intolerance and concomitant coronary artery disease

(CAD), ASA desensitization should be considered as an additional therapeutic option with good clinical efficacy, a low risk profile, and high cost-effectiveness.¹⁹ However, data about the safety and efficacy of desensitization therapy in patients with ASA intolerance and concomitant CAD are limited to small studies in which ASA desensitization was accomplished without impairment of coronary disease. In patients with unstable CAD, coronary intervention and special medical management should be conducted before the onset of desensitization. In patients with stable CAD, desensitization can be started without former medical or operative therapy in most cases unless the patients have chronic urticaria/angioedema or anaphylaxis.¹⁹ To date, there are no data about the value of desensitization in patients with CAD and anaphylactic reactions induced by NSAIDs,⁵⁵ whereas in patients with CAD and chronic urticaria/angioedema induced by NSAIDs, a lack of efficacy has been observed.²² In addition, desensitization is performed in AI patients with therapy-resistant rhinosinusitis and recurrent nasal polyps, which cannot be controlled with polypectomy or sinus surgery,²² patients affected by AIA requiring long-term high-dose systemic corticosteroids to control their disease, and patients whose asthma or rhinosinusitis is not optimally treated with inhaled glucocorticosteroids or drugs interfering with the leukotriene pathway. To date, different investigators^{4,5,9} reported successful aspirin desensitization by oral application of aspirin, whereas endonasal desensitization with Lys-ASA, which is not available in the United States, has been demonstrated to represent a valid alternative, especially in patients with therapy-resistant nasal polyposis.⁵⁶

In most cases oral administration is used for desensitization. Within 2 or 3 days the administered dose of aspirin is increased until 650 mg of aspirin is tolerated without any adverse effects.^{51,52} With an intake of 650 mg 2 times daily, the highest clinical efficacy has been achieved. A few studies suggest that lower doses, such as 100 mg/d orally, as maintenance might also be effective. In these studies, high effectiveness regarding the recurrence rate of nasal polyps has been observed and has been significantly reduced with daily administration of only 100 mg of aspirin after successful build up performed under controlled conditions in a hospital.⁵⁷ However, desensitization protocols with lower doses than 650 mg of aspirin are not yet used as standard therapy because sufficient data are still missing.

Concerning the risks of desensitization, cutaneous reactions⁵¹ and gastrointestinal symptoms, observable in approximately 20% of patients treated with aspirin,⁵⁸ have to be mentioned. Furthermore, after successful desensitization, aspirin therapy must be continued for an indefinite time to prevent possible resensitization. By discontinuing aspirin use for some days, patients can develop acute pseudoallergic reactions, such as life-threatening asthma attacks, after reexposure.⁵¹

The pathophysiologic mechanisms of desensitization remain obscure. Different studies observed a change in the balance of inflammatory mediators after desensitization.

Most likely, desensitization in patients with non-IgE-mediated AI reactions (that means reactions related to COX-1 inhibition) and IgE-mediated AI reactions differ. In patients with IgE-mediated AI reactions mechanisms similar to desensitization with penicillin are assumed, in which repeated exposure to NSAIDs leads to saturation of anti-NSAID IgE antibody binding sites on mast cells and basophils. In patients with reactions related to COX-1 inhibition, ASA desensitization leads to decreased leukotriene production, down-regulation of Cyst-LT receptors, and decreased histamine and tryptase release acutely within 3 hours of exposition.⁵⁹

The relevance of diagnostic tools to monitor and verify the effect of desensitization has been evaluated, and a balance between PGE₂ and pLTs and the correlation of these variables with clinical symptoms or changes in thromboxane levels has been observed.^{56,60} A reduction in urinary LTE₄ excretion after 2 weeks and LTB₄ synthesis in peripheral monocytes after desensitization has been shown in another study.⁶¹ Elevated numbers of nasal inflammatory leukocytes expressing the Cys-LTR1 parallel to the increase in Cys-LT production in aspirin-sensitive patients and down-regulation of Cys-LTR1 expression after desensitization to aspirin indicate Cys-LTR1 expression as another putative readout variable.⁶²

CONCLUSIONS

Aspirin is an effective drug used for the treatment of a wide spectrum of diseases. A range of 0.3% to 0.9% of the population has hypersensitivity to aspirin and other inhibitors of COX-1, such as NSAIDs.⁶ Up to 20% of all asthma patients have AI mirrored by exacerbation of their respiratory disease after aspirin ingestion. In individuals with suspected AI, diagnosis can be confirmed exclusively by means of provocation tests.³⁷ Concerning the underlying pathogenetic mechanisms of AI, different hypotheses exist, but most of them focus on abnormal AA metabolism. Analysis of the genetic background of this heterogeneous disease might open new diagnostic and therapeutic options. Patients with AI have to avoid aspirin and other cross-reacting COX-1 inhibitors and should change to alternative drugs available. To prevent recurring sinusitis episodes and recurrent nasal polyps and to reduce concomitant asthma attacks, aspirin desensitization might be an alternative therapeutic option in a subgroup of AI patients.

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