

Natural History and Clinical Features of Aspirin-Exacerbated Respiratory Disease

John M. Fahrenholz

*Allergy and Asthma Specialists, Nashville, TN 37205;
Formerly Scripps Clinic and Green Hospital, La Jolla, CA*

Abstract

Aspirin-exacerbated respiratory disease (AERD) is a clinical syndrome characterized by chronic rhinosinusitis, nasal polyposis, asthma and precipitation of asthma, and rhinitis attacks after ingestion of aspirin (ASA) and most other nonsteroidal antiinflammatory drugs (NSAIDs). Although precipitation of asthma attacks by ingestion of ASA and other NSAIDs is considered a hallmark of the syndrome, the respiratory mucosal inflammatory disease process begins and continues in the absence of ongoing or even intermittent exposure to ASA or NSAIDs. The typical patient with AERD is an adult who develops refractory chronic rhinitis in the third or fourth decade of life. The chronic rhinitis evolves into chronic eosinophilic rhinosinusitis with associated nasal polyposis. Anosmia appears in most patients. CT of the sinuses most often demonstrates pansinusitis and patients often undergo multiple sinus operations resulting in only limited temporary benefit. During the evolution of the sinus disease persistent asthma develops. Finally, if patients are exposed to ASA or NSAIDs acute respiratory reactions begin to occur. Despite subsequent avoidance of ASA and other NSAIDs, the respiratory mucosal inflammatory disease persists, often requiring systemic corticosteroids for control of both upper- and lower-respiratory tract symptoms. Adequate control of asthma can often only be accomplished with the simultaneous control of the associated rhinosinusitis. With few exceptions, once AERD develops it remains for the remainder of the patient's life.

Index Entries:

Aspirin-sensitive asthma; aspirin triad; nonsteroidal antiinflammatory drugs; adverse reactions.

Introduction

The association of aspirin sensitivity (ASA), asthma, and nasal polyposis was first described in 1922 by Widal, Abrami, and Lermoyez (1). The work of Samter and Beers in the late 1960s led to widespread recognition of the clinical syndrome, now known as “aspirin triad” or “Samter’s triad” (2,3). The syndrome has been referred to by a variety of names over the years, including aspirin-induced asthma (AIA), aspirin-sensitive asthma, aspirin idiosyncrasy, aspirin disease, and most recently, aspirin-exacerbated respiratory disease (AERD). The AERD nomenclature is currently preferred because it implies that the disease process is not limited to asthmatic lower respiratory disease and reactions, but rather is a more generalized respiratory mucosal disease with major disease activity in the nasal and sinus tissues.

Furthermore, in contrast to the term “ASA-induced asthma,” AERD does not imply that the underlying disease is caused by ASA. AERD is a clinical syndrome characterized by chronic rhinosinusitis, nasal polyposis, asthma and precipitation of asthma, and rhinitis attacks after ingestion of ASA and most non-steroidal antiinflammatory drugs (NSAIDs). Although precipitation of asthma attacks by ingestion of ASA or other NSAIDs is considered a hallmark of the syndrome, the respiratory mucosal inflammatory disease process begins and continues in the absence of ongoing or even intermittent exposure to ASA or NSAIDs (4). The clinical features of patients with AERD are listed in Table 1.

Using oral ASA challenges to identify AERD in adult asthmatic patients, the prevalence appears to be between 9% and 20% (5,6). The prevalence in the subpopulation of adult asthmatics with associated nasal polyposis and sinusitis approaches 33% (7). Based on history alone, Falliers reported that less than 2% of approx 1300 asthmatic children were ASA-sensitive (8). Other studies in children, utilizing single-blind oral challenges, have

demonstrated rates of ASA sensitivity between 0% and 28% (9–12). The study by Rachelefsky et al. (13) that reported a 28% prevalence of positive oral ASA challenges included children over 10 yr of age with more severe asthma and a high prevalence of chronic sinusitis. Overall, the prevalence of AERD in prepubescent children appears to be quite low (14). However, the Rachelefsky study suggests that among older children, particularly those with chronic sinusitis and more severe asthma, the prevalence of AERD may approach that of adults.

Ingestion of ASA and most other NSAIDs induces a spectrum of respiratory reactions in AERD patients that range from life-threatening asthma to isolated rhinitis attacks. Generally speaking, the reactions are observed within 3 h of ingestion of ASA or any other NSAID, which inhibits cyclooxygenase-1 (COX-1) (15). Cross-reactivity among compounds, which inhibit COX-1, is 100%. Adverse reactions to ASA and NSAIDs in the setting of AERD appear to be dose-dependent and related to COX-1 inhibition (4). The newer, highly selective cyclo-oxygenase-2 inhibitors do not appear to cross-react (16). A detailed discussion of reaction mechanisms and the issue of crossreactivity can be found in another section of this review.

Life-threatening attacks of asthma have often been reported in association with ingestion of therapeutic doses of ASA (17). In a retrospective survey of 145 asthmatic patients who required mechanical intubation for a severe exacerbation, 25% were reported to have ingested ASA (18). Based on clinical observations and oral-challenge studies, Stevenson and colleagues have described a spectrum of reactions precipitated by ASA ingestion (19). The classic reaction is that of acute bronchospasm accompanied by profuse rhinorrhea, conjunctival injection, periorbital edema, and sometimes a scarlet flushing of the head and neck (20). Furthermore, during the acute reaction following oral ASA ingestion, a significant minority of patients experience abdominal cramping, pain, and other intesti-

Table 1
Clinical Features of AERD

Category	Feature
Age of onset	After age 10, typically third or fourth decade
Rhinitis	Chronic congestion, rhinorrhea, anosmia
Sinusitis	Initially intermittent but evolving to chronic
Nasal exam	Pale and swollen turbinates, frequent polyps
Sinus radiographs	Abnormal opacifications, most frequently pansinusitis
Prior sinus surgery	Common and resulting in limited and/or transient benefit
Asthma	Persistent and usually moderate to severe, frequent exacerbations related to sinusitis flares

nal symptoms (21). In a series of 50 patients (20), 33 (66%) displayed the “classic” reaction defined by bronchospasm (forced expiratory volume in 1 second [FEV₁] decrease of 25% or more) and naso-ocular reactions within 3 h of ASA ingestion. Of note, the definition of the asthmatic response has since been modified to a decrease in FEV₁ of 20% or more within 3 h of ASA challenge. Three additional (6%) patients experienced a “partial” asthmatic response (FEV₁ decrease of 15–25%) in association with naso-ocular reactions. Three (6%) of the 50 patients experienced pure asthmatic responses with no sign of nasal or ocular symptoms and another three patients (6%) experienced isolated naso-ocular reactions. Interestingly, eight of the 50 patients (15%) with suspected AERD showed no reaction to incremental oral ASA challenge to 650 mg. In a recent report from the same center (22), 52 of 352 patients (15%) with suspected AERD displayed no clinical reaction to their incremental oral ASA challenges. The authors concluded that the historical information obtained from patients had a false-positive rate of approx 15% of all patients presenting with a history reactions to ASA and NSAIDs. The possibility of false-negative ASA challenges in a minority of these patients must also be considered, but in most cases is considered less likely than an inaccurate history of a prior ASA-induced reaction. In the few patients with false-negative challenges, the patients were taking

>10 mg of prednisone per day (23) or a leukotriene blocking drug (24). Concomitant ingestion of sodium salicylate will also block ASA-induced respiratory reactions (25). Table 2 summarizes the types of reactions observed during oral ASA challenges.

Of the group of 50 patients in the study previously discussed, 28 underwent additional ASA challenges at intervals varying from 4 mo to 6 yr from the index challenge. Seventeen (61%) of these 28 demonstrated the same type of reaction as elicited by the index challenge. However, 11 (39%) showed some variability in the type of reaction. Four of these eleven actually had one incremental ASA challenge to 650 mg that resulted in no reaction. One patient experienced a pure naso-ocular reaction, a classic reaction (bronchospasm associated with naso-ocular symptoms), and on another occasion no reaction, all within a 12-mo period. Careful evaluation of medication use at the time of ASA challenges did not support the possibility that reaction patterns varied because of differences in supportive medications such as corticosteroids. In 1983, leukotriene inhibitors were not available, and none of the patients were taking sodium salicylate. In fact, those patients whose responses changed from asthmatic to pure naso-ocular, or who appeared to lose reactivity altogether, were taking less medication—particularly corticosteroids—than when they had their more pronounced baseline

Table 2
Types of Respiratory Responses to Oral Aspirin Challenges

Classic reaction: decline of 20% or more in FEV ₁ values and a naso-ocular reaction
Pure lower: decline of 20% or more in FEV ₁ values without naso-ocular reaction
Upper airway only: naso-ocular reaction alone
Partial asthma: declines in FEV ₁ between 15% and 20% combined with naso-ocular reaction
Laryngospasm: crowing sounds in neck (flow-volume curve: inspiratory loop flat and notched)
Negative: if up to 650 mg ASA was administered without any respiratory reaction

reactions. This suggested to the authors that in this small number of AERD patients, “reduced” aspirin sensitivity is probably best associated with quiescent respiratory-tract disease (20).

Oral Aspirin Challenge

The current gold standard for the diagnosis of AERD is provocative ASA challenge. Oral challenge is the most commonly used technique, and is currently the only available method in the United States. Table 3 outlines the oral ASA challenge protocol developed at Scripps Clinic. In most patients, the threshold dose for provoking a respiratory reaction is between ASA 30 mg and ASA 150 mg (average, ASA 60 mg) (19). As discussed previously, the generally accepted criteria for a positive reaction during a single-blind ASA challenge is a decrease in FEV₁ of 20% or more and/or a prominent naso-ocular reaction. Oral challenges have proven safe and reliable for confirmation of the presence of AERD. However, this challenge should always be performed on patients with stable asthma (FEV₁ greater than 70% and less than 10% spontaneous variability) (22).

Bronchial Inhalation Challenges with ASA-Lysine

In several European centers, inhalation tests using aerosols of L-lysine acetylsalicylic acid are used as an alternative to oral ASA challenges. Nizankowska et al. (26) compared the diagnostic value of single-blind oral vs bronchial inhaled L-lysine ASA in a study that

included 35 AERD patients previously diagnosed using oral ASA challenge. Fifteen asthmatics that tolerated ASA served as the control group. Thirty-one of the 35 AERD patients (89%) reacted (decrease FEV₁ of at least 20% and/or prominent naso-ocular reactions) to incremental oral ASA challenge of 312 mg. Twenty-seven of the 35 AERD patients (77%) reacted to the ASA bronchial inhalation challenge (maximum cumulative dose=182 mg). Challenge studies in the control group revealed one positive reaction based on isolated naso-ocular symptoms during oral challenges and one similar reaction during the bronchial inhalation challenges.

Nasal Inhalation Challenges with ASA-Lysine

Nasal challenges with L-lysine-ASA have also been used in the diagnosis of AERD (27–31). Milewski and colleagues (31) evaluated the value of the nasal challenge method in 51 AERD patients who were previously diagnosed with oral ASA challenges. The control groups consisted of 13 persistent asthmatics that tolerated ASA and 10 healthy non-smoking individuals. L-lysine-ASA was applied topically in solution form to the inferior turbinates bilaterally at a dose equivalent to 16 mg of acetylsalicylic acid. The criteria for a positive reaction during the single-blind challenges were a decrease in nasal flow greater than 40%, as measured by anterior rhinomanometry, along with associated clinical symptoms lasting at

Table 3
Single Blind 3-d Oral ASA Challenge Used at the Scripps Clinic*

Time	Day 1	Day 2	Day 3
7:00 AM	Placebo	ASA 30 mg	ASA 100–150 mg
10:00 AM	Placebo	ASA 45–60 mg	ASA 150–325 mg
1:00 PM	Placebo	ASA 60–100 mg	ASA 325–650 mg

*Schedule and dose may be altered by MD, depending upon patient profile, lung function, and history of prior reaction.

least 30 min during the 3-h observation period. In 10 of the 51 AERD patients (10%), the test could not be performed because of either total nasal obstruction or marked spontaneous fluctuations of nasal flows (more than 40%). In 35 of the 41 AERD patients (89%) who were able to perform the test, nasal challenge with L-lysine-ASA elicited a positive response. Nasal challenges were negative in 9 of 10 healthy individuals (90%), and in all 13 ASA-tolerant asthmatics. Notably, pulmonary function tests showed no significant changes in any of the participants. This included five AERD patients with unstable airways (FEV_1 48% to 69%). Thus, a major advantage of the nasal ASA-challenge method is the ability to perform the test in patients with severe asthma. The key limitation is the inability to perform the test in a significant percentage of patients (10–20%) with total nasal blockage or with large fluctuations in nasal flow. Table 4 contains a comparison of the reported sensitivities and specificities of the various ASA-challenge tests based on the data reviewed here. In conclusion, a positive ASA challenge test in a patient with a compatible history confirms the diagnosis of AERD with almost complete certainty. A negative ASA challenge, however, does not completely rule out the presence of AERD. Unfortunately, adequate biochemical markers that would provide a definitive laboratory diagnosis of AERD have not yet been identified.

Medications That Block ASA Challenges

Several medications have been reported to block or attenuate the ASA/NSAID-induced respiratory reactions observed in AERD patients. Antihistamines are capable of blocking the upper respiratory reaction (32), and inhaled beta-agonists may inhibit the acute asthmatic lower-respiratory reaction (33). Salmeterol, a long-acting beta-agonist, may be particularly likely to block the lower-respiratory reaction, as it has been shown to modulate the inflammatory response associated with ASA ingestion in AERD patients (34). However, salmeterol has no blocking effect on the upper airway. Inhaled cromolyn has been reported to prevent (35,36) or at least delay (37) the onset of ASA-induced respiratory reactions. The leukotriene inhibitors zileuton, zafirlukast, and montelukast have also been evaluated in terms of their ability to block ASA reactions (24,38,39). In most instances, these medications do not protect against reactions precipitated by full therapeutic doses of ASA. However, during oral ASA challenges, a higher provoking dose of ASA may be required to elicit the reaction, and occasionally the reaction may be masked completely (24). A study of 10 AERD patients by Nizankowska and Szczeklik (23) found no evidence that reactions to oral ASA challenge could be blocked with the use of prednisone 75 mg daily for 2 d prior to ASA challenge. In the second part of this study, patients received 10 d of pretreatment with

Table 4
Comparison of the Three Types of Challenges with Aspirin in AERD Patients

	Oral ASA challenge	Inhaled bronchial ASA challenge	Nasal ASA challenge
Sensitivity %	89%	77%	89%
Specificity %	93–100%	93–100%	96%
Positive predictive value %	97–100%	96–100%	97%
Negative predictive value %	77%	64%	79%

*See text for details on reaction criteria and study methods

prednisone (15 mg daily) combined with inhaled corticosteroids. Following this pretreatment they underwent oral ASA challenges at doses up to double their previously established threshold levels. In three of eight patients with prior documented asthmatic reactions (FEV₁ decrease of 20% or more), no reaction was observed at twice the threshold dose of ASA. Steroid pretreatment prevented naso-ocular reactions to ASA challenge in six of nine patients. Nevertheless, ASA reactions routinely occur in AERD patients who are using topical and systemic corticosteroids (20,22). Clinical experience indicates that use of inhaled and intranasal corticosteroids, even in combination with systemic corticosteroids, is highly unlikely to completely block reactions to therapeutic doses of ASA or other NSAIDs. Yet, given the limited data, further study is warranted to more carefully define the role of corticosteroids in attenuating ASA-induced reactions in AERD patients.

Natural History of AERD

Reports by Szczeklik et al. in Europe (40) and Berges-Gimeno et al. in the United States (22) provide significant insight into the natural history of AERD. A summary of their comparative findings is shown in Table 5. The study by Szczeklik and colleagues, which is discussed first, included a total of 500 patients evaluated at 16 clinical centers in 10 European countries as part of the European Network on Aspirin-

Induced Asthma (AIANE). The diagnosis of AERD was based on a typical history, including persistent asthma, and confirmed with inhaled L-lysine-ASA challenges in 91% of the patients (FEV₁ drop of 20% or more). The other 9% were reported to have an “unequivocal” history, and confirmatory ASA challenge was not performed as a result of unstable asthma or lack of patient consent.

Rhinitis was the first manifestation of the disease, and appeared on average at 30 yr of age. Overall, 82% of the patients reported a history of rhinitis. The rhinitis was characterized as perennial, difficult to treat, and associated with anosmia in 55% of patients. In an average patient, symptoms of asthma appeared 2 yr after the onset of rhinitis. Nasal polyposis as well as sensitivity to ASA or another NSAID appeared approx 4 yr later. A total of 60% had associated nasal polyps. The authors observed a close linear association between mean age at onset of rhinitis, asthma, nasal polyps, and NSAID sensitivity. ASA was the NSAID most commonly reported to have induced a respiratory reaction (82%). Pyrazolones were a distant second at 9%. The symptoms that patients reported in association with NSAID ingestion included dyspnea (88%), nasal discharge and blockage (42%), urticaria or scarlet flush (20%), conjunctival irritation (15%), angioedema (8%), and anaphylactoid shock with hypotension and loss of consciousness (6%). In the Szczeklik study, 80% of patients were using inhaled cor-

Table 5
Comparisons of Clinical Characteristics of AERD patients based on AIANE and Scripps Clinic Cohorts

	AIANE (total patients = 500)	Scripps Clinic (total patients = 300)
Age at onset of disease	29.7	34
Occurrence of rhinitis %	82.4	100
Occurrence of nasal polyps %	60.4	99
Sinus surgeries or polypectomies number	2.6	3
Chronic oral steroid therapy %	51.4	39
Prednisone dose	7.7 mg	7.5 mg
Hospitalizations for asthma number	0.6	2.2
	(last 12 mo)	(since disease onset)
Emergency interventions for asthma number	1.3	5.1
	(last 12 mo)	(ED visits since disease onset)
Positive family history of AERD %	5.8	1.0
Atopic %	34	66
	(based on skin tests in subgroup of 103 patients)	(based on history and skin tests performed outside)

*See text for details.

ticosteroids for persistent asthma, and 51% required chronic systemic corticosteroids. Of those requiring systemic corticosteroids, a dose equivalent to prednisone 8 mg daily for an average of 7.5 yr was reported. Twenty-four percent of patients reported an asthma exacerbation requiring intravenous (iv) steroids during the 12 mo prior to their enrollment in the study.

In the Berges-Gimeno study that described a cohort of 300 patients referred for ASA desensitization to the Scripps Clinic, oral ASA challenges were used to prove AERD in all 300 patients. Eighty-percent of patients were using inhaled corticosteroids for persistent asthma, and 39% were using daily or alternate-day systemic steroids at an average daily dose of 7.5 mg prednisone or equivalent. Notably, 120 of 200 patients (60%) evaluated after the introduction of leukotriene inhibitors were taking these medications. The vast majority of patients in both of these reviews also reported refractory perennial rhinosinusitis. Many patients required surgical intervention for their disease—an average of three sinus surgeries or polypectomies were reported per patient in the

European study. The U.S. study indicated that patients experienced an average of 5–6 sinus infections in the 12 mo prior to their study evaluation, and had also undergone an average of three sinus or polyp operations during the course of their disease. Ninety-four percent of patients had undergone at least one sinus operation. Ninety-nine percent had a history of nasal polyps. Abnormal sinus opacifications by plain film or computed tomography (CT) scan were observed in 99% of the patients at some time during their disease process. These abnormal sinus opacifications had typically occurred on multiple occasions, and usually persisted despite medical and/or surgical interventions. Also, similar to the European report, anosmia was a characteristic finding. ASA was the NSAID most frequently associated with prior respiratory reactions (80%), followed by ibuprofen at (41%). Overall, 36% of the patients had experienced three or more reactions to one or more NSAIDs.

Females outnumbered males in the European review by more than 2 to 1. Symptoms of disease in the females, including rhinitis and ASA intolerance, appeared approx 3 yr earlier

than in males. Asthma tended to be less well-controlled in females compared to males, based on higher numbers of hospitalizations and emergency interventions. In the U.S. review, females were only slightly more prevalent than males (57% female, 43% male). None of the other disparate findings between males and females were observed in the U.S. review. In fact, in terms of age of onset of disease, occurrences of nasal polyps, sinus surgeries, sinus infections, anosmia scores, and emergency interventions for asthma, no significant differences were noted between men and women.

A family history of AERD was reported in 6% of the patients in the European review. Only 1% of patients in the U.S. series identified an affected family member. Data regarding ethnic background and race was obtained in 175 patients in the U.S. review. Findings were consistent with immigration patterns to the United States. The data did not support a racial or ethnic influence on the prevalence of AERD.

In a subset of 103 German and Polish patients in the Szczeklik review, standardized skin-prick tests as well as serum-specific IgE tests were performed to common allergens. The skin-prick tests yielded positive results in 34% of patients, and the serum tests were positive in 31%. These percentages are similar to the reported prevalence of atopy in European adults. Atopic patients experienced rhinitis symptoms on an average of 6 yr earlier than non-atopics. Similarly, atopic patients reported the onset of asthma on average 7 yr earlier than the non-atopics. However, the mean age at which ASA sensitivity or nasal polyps appeared did not differ between the two groups. Sixty-six percent of patients in the U.S. review reported a history of positive skin tests to at least one common aeroallergen (skin tests not performed at Scripps Clinic). Although AERD was once believed to be nonexistent in atopic patients (2), these studies suggest otherwise. Nevertheless, the development of ASA sensitivity marks the development of an

entirely new disease. Because of the more aggressive inflammatory nature of AERD in comparison to typical allergic disease, atopic AERD patients frequently experience a limited benefit from standard medical therapy, including avoidance and immunotherapy, for allergic rhinitis and asthma. However, in atopic AERD patients who have undergone ASA desensitization, immunotherapy may play an important role in attenuating the less aggressive residual allergic inflammatory component of their disease. These observations are only theoretical, and have not been evaluated in a prospective investigation.

In the US review, patients were referred for ASA desensitization on average 13 yr after the onset of respiratory symptoms. Length of time with active disease at the time of study registration in the European group was 15 yr. Vento et al. (41) provided further evidence of the persistent and aggressive nature of AERD in their report, which described the clinical course of 41 patients with nasal polyposis over a 20-yr period. Twenty years after their initial evaluation for polypectomy or ethmoidectomy, thirty-two of the 41 (78%) reported essentially continuous nasal symptoms. Anterior rhinoscopy revealed polyps in 35 of the 41 patients (85%). Anosmia or hyposmia was reported by 25 of 41 (61%). Thirty-seven of 41 (90%) reported an additional sinus or polyp operation during the 20-yr course of follow-up. Eight patients reported 11 or more such operations per individual patient. Seven of these eight individuals with the most refractory and recurrent nasal polyposis had AERD.

In summary, the typical patient who develops AERD is an adult between 20 and 40 yr of age. Characteristically, the patient develops chronic rhinitis during the third or fourth decade of life, which proves refractory to medical management. The patient may have a history of typical allergic rhinitis, and if this is the case, positive wheal-and-flare skin tests are very common, and are linked to the prior allergic disease but not AERD. The chronic rhinitis

evolves into chronic eosinophilic rhinosinusitis with associated nasal polyposis. Anosmia appears in most patients, and its absence usually means that the patient does not have AERD. Computerized tomography of the sinuses most frequently reveals pansinusitis, and the patient often undergoes multiple sinus operations resulting in only limited temporary benefit. During the evolution of the sinus disease, asthma appears and persists. Finally, ASA- or NSAID-induced respiratory reactions begin to occur, if patients are exposed to these medications. Despite subsequent avoidance of ASA and other crossreacting NSAIDs, the patient's respiratory mucosal inflammatory disease persists, and often requires systemic corticosteroids for control of both upper- and lower-respiratory-tract symptoms. Adequate control of asthma can often only be accomplished with the simultaneous control of associated rhinosinusitis. With few exceptions, once AERD develops it remains for the remainder of the patient's life.

References

1. Stevenson, D. and Simon, R. A. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs, in *Allergy: Principles and Practice*, Middleton, Jr., E., Ellis, E. F. Yunginger, J. W., Reed, C. E., Adkinson, N. F., Jr., and Busse, W. W., eds., vol 2, 5th ed. Mosby, St. Louis, 1998, pp. 1225–1234.
2. Stevenson, D. D. (2001), Anaphylactic and anaphylactoid reactions to aspirin and nonsteroidal anti-inflammatory drugs. *Immunology and Allergy Clinics of North America* **21**, 745–768.
3. Czerniawska-Mysik, G. and Szczeklik, A. (1981), Idiosyncrasy to pyrazolone drugs. *Allergy* **36**, 381–384.
4. Stevenson, D. D. (1995), Aspirin and nonsteroidal antiinflammatory drugs. *Immunology and Allergy Clinics of North America* **15**, 529–549.
5. Quiralte, J., Blanco, C., Castillo, R., Ortega, N., and Carrillo, T. (1997), Anaphylactoid reactions due to nonsteroidal antiinflammatory drugs: clinical and cross-reactivity studies. *Ann. Allergy Asthma Immunol.* **78**, 293–296.
6. Stevenson, D. (1998), Adverse reactions to nonsteroidal antiinflammatory drugs. *N. American Clinics Allergy and Immunology* **18**:4, 773–798.
7. Settupane, R. A. and Stevenson, D. D. (1989), Cross sensitivity with acetaminophen in aspirin sensitive asthmatics. *J. Allergy and Clin. Immunol.* **84**, 26–33.
8. Stevenson, D. D., Hougham, A., Schrank, P., Goldlust, B., and Wilson, R. (1990), Disalcid cross-sensitivity in aspirin sensitive asthmatics. *J. Allergy Clin. Immunol.* **86**, 749–758.
9. Stevenson, D. D. Simon, R. A., Lumry, W. R., and Mathison, D. A. (1986), Adverse reactions to tartrazine. *J. Allergy Clin. Immunol.* **78**, 182–191.
10. Stevenson, D. D. and Simon, R. A. Sulfite induced asthma, in *Current Therapy in Internal Medicine*, Bayless, Brain, and Cherniack, eds., B.C., 1987, pp. 14–10.
11. Feigenbaum, B. A., Stevenson, D. D., and Simon, R. A. (1995), Lack of cross-sensitivity to IV hydrocortisone in aspirin-sensitive subjects with asthma. *J. Allergy Clin. Immunol.* **96**, 545–548.
12. Woessner, K., Simon, R. A., and Stevenson, D. D. (1999), Monosodium glutamate sensitivity in asthma. *J. Allergy Clin. Immunol.* **104**, 305–310.
13. Stevenson, D. and Simon, R. A. (2001), Lack of cross-reactivity between rofecoxib and aspirin in aspirin sensitive asthmatic patients. *J. Allergy Clin. Immunol.* **108**, 47–51.
14. Woessner, K., Simon, R. A., and Stevenson, D. D. (2002), The safety of celecoxib in aspirin exacerbated respiratory disease. *Arthritis Rheum.* **46**, 2201–2206.
15. Sanchez-Borges, M., Capriles-Hulett, A., Caballero-Fonseca, F., and Ramon-Perez, C. (2001), Tolerability to new Cox-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann. Allergy Asthma Immunol.* **87**, 201–204.
16. Pacor, M., Di Lorenzo, G., Biasi, D., Barbagallo, M., and Corrocher, R. (2002), Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and/or non-steroidal antiinflammatory drugs. *Clin. Exp. Allergy* **32**, 397–400.
17. Quiralte, J. S. ds. P., B., and Florido, J. J. (2002), Safety of selective cyclooxygenase-2 inhibitor rofecoxib in patients with NSAID-induced cutaneous reactions. *Ann. Allergy Asthma Immunol.* **89**, 63–66.
18. Berges-Gimeno, M., Camacho-Garrido, E., Garcia-Rodriguez, R. M., Martin-Garcia, C., Alfaya, T., and Hinojosa, M. (2001), Rofecoxib: safe in NSAID intolerant patients. *Euro. J. Allergy Clin. Immunol.* **56**, 1017–1018.
19. Berges-Gimeno, M., Simon, R. A., and Stevenson, D. D. (2002), The effect of leukotriene modifier drugs on asa-induced asthma and rhinitis reactions. *Clin. Exp. Allergy* (Accepted for publication.)
20. Zeiss, C. R. and Lockey, R. F. (1976), Refractory period to aspirin in a patient with aspirin-induced asthma. *J. Allergy Clin. Immunol.* **57**, 440–448.
21. Pleskow, W. W., Stevenson, D. D., Mathison, D. A., Simon, R. A., Schatz, M., and Zieger, R. S. (1982), Aspirin desensitization in aspirin sensitive asthmatic patients: clinical manifestations and charac-

- terization of the refractory period. *J. Allergy Clin. Immunol.* **69**, 11–19.
22. Widal, M. F., Abrami, P., and Lermeyez, J. (1922), Ana-phylaxie et idiosyncrasie. *Presse Med.* **30**, 189–192.
 23. Mathison, D. A., Lumry, W. R., and Stevenson, D. D. (1982), Aspirin in chronic urticaria and/or angioedema: studies of sensitivity and desensitization. *J. Allergy Clin. Immunol.* **69**, 135.
 24. Slavin, R. G. (1992), Asthma and sinusitis. *J. Allergy Clin. Immunol.* **90**, 534–537.
 25. Mastalerz, L., Milewski, M., Duplaga, M., Nizankowska, E., and Szczeklik, A. (1997), Intranasal fluti-casone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. *Allergy* **52**, 895–900.
 26. Berges-Gimeno, M., Simon, R. A., and Stevenson, D. D. (2002), The natural history and clinical characteristics of aspirin exacerbated respiratory disease. *Ann. Allergy Asthma Immunol.* (Accepted for publication.)
 27. Mathison, D. A. and Stevenson, D. D. Aspirin sensitivity in rhinosinusitis-asthma, in *Current Therapy in Allergy, Immunology and Rheumatology*, Lichtenstein, L. M. and Fauci, A. S., eds., vol. 1, 1st ed. Mosby, St. Louis, 1985, pp. 27–30.
 28. McFadden, E. A., Woodson, B. T., Fink, J. N., and Toohill, R. J. (1997), Surgical treatment of aspirin triad sinusitis. *Am. J. Rhinol.* **11**, 263–270.
 29. Nakamura, H., Kawasaki, M., Higuchi, Y., and Takahashi, S. (1999), Effects of sinus surgery on asthma in aspirin triad patients. *Acta Otolaryngol.* **119**, 592–598.
 30. Schaitkin, B., May, M., Shapiro, A., Fucci, M., and Mester, S. J. (1993), Endoscopic sinus surgery: 4-year follow-up on the first 100 patients. *Laryngoscope* **103**, 1117–1120.
 31. Kennedy, D. W. (1992), Prognostic factors, outcomes and staging in ethmoid sinus surgery. *Laryngoscope* **102**, 1–18.
 32. Stevenson, D. D., Hankammer, M. A., Mathison, D. A., Christensen, S. C., and Simon, R. A. (1996), Long term ASA desensitization-treatment of aspirin sensitive asthmatic patients: clinical outcome studies. *J. Allergy Clin. Immunol.* **98**, 751–758.
 33. Dahlen, B. N., Szczeklik, A., Zetterstrom, O., Bochenek, G., Kumlin, M., Mastalerz, L., et al. (1998), Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am. J. Respir. Crit. Care Med.* **157**, 1187–1194.
 34. Dahlen, S., Malstrom, K., Nizankowska, E., Dahlen, B., Kuna, P., Kowalski, M., et al. (2002), Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist. A randomised, double blind, placebo controlled trial. *Am. J. Respir. Crit. Care Med.* **165**, 9–14.
 35. Dahlen, B. (2000), Treatment of aspirin-intolerant asthma with antileukotrienes. *Am. J. Respir. Crit. Care Med.* **161**, S137–S141.
 36. Stevenson, D. D., Simon, R. A., and Mathison, D. A. (1980), Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. *J. Allergy Clin. Immunol.* **66**, 82–88.
 37. Stevenson, D. D., Pleskow, W. W., Simon, R. A., Mathison, D. A., Lumry, W. R., Schatz, M., et al. (1983), Treatment of aspirin sensitive asthma rhinosinusitis with aspirin. *J. Allergy Clin. Immunol.* **71**(2), 272–270.
 38. Sweet, J. A., Stevenson, D. D., Simon, R. A., and Mathison, D. A. (1990), Long term effects of aspirin desensitization treatment for aspirin sensitive rhinosinusitis asthma. *J. Allergy Clin. Immunol.* **86**, 59–65.
 39. Patriarca, G., Bellioni, P., Nucera, E., Schiavino, D., Papa, G., Schinco, G., et al. (1991), Intranasal treatment with lysine acetylsalicylate in patients with nasal polyposis. *Ann. Allergy* **67**, 588–593.
 40. Widal, M. F., Abrami, P., Lermeyez, J. (1922), Anaphylaxie et idiosyncrasie. *Presse Med.* **30**, 189–192.
 41. Samter, M. and Beers, R., Jr. (1968), Intolerance to aspirin: clinical studies and consideration of its pathogenesis. *Ann. Intern. Med.* **68**, 975–983.
 42. Samter, M. and Beers, R. F. (1967), Concerning the nature of the intolerance to aspirin. *J. Allergy* **40**, 281–293.
 43. Szczeklik, A. and Stevenson, D. D. (1999), Aspirin-induced asthma: advances in pathogenesis and management. *J. Allergy Clin. Immunol.* **104**, 5–13.
 44. Spector, S. L., Wangaard, C. H., and Farr, R. S. (1979), Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J. Allergy Clin. Immunol.* **64**(6 Pt 1), 500–506.
 45. McDonald, J., Mathison, D. A., and Stevenson, D. D. (1972), Aspirin intolerance in asthma—detection by challenge. *J. Allergy Clin. Immunol.* **50**, 198–207.
 46. Weber, R. W., Hoffman, M., Raine, D. A., and Nelson, H. S. (1979), Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. *J. Allergy Clin. Immunol.* **64**, 32–37.
 47. Falliers, C. J. (1973), Aspirin and subtypes of asthma: risk factor analysis. *J. Allergy Clin. Immunol.* **52**, 141–147.
 48. Raika, G. and Skog, E. (1965), On the relationship between drug allergy and atopy. *Acta Allergol.* **20**, 387.
 49. Schuh, J. F. and Pereyra, J. G. (1979), Oral acetylsalicylic acid (aspirin) challenge in asthmatic children. *Clin. Allergy* **9**, 83–88.
 50. Towns, S. J., and Mellis, C. M. (1984), Role of acetyl salicylic acid and sodium metabisulfite in chronic childhood asthma. *Pediatrics* **73**, 631–637.
 51. Vedanthan, P. K., Menon, M. M., Bell, T. D., and Bergin, D. (1977), Aspirin and tartrazine oral chal-

- lence: incidence of adverse response in chronic childhood asthma. *J. Allergy Clin. Immunol.* **60**, 8–13.
52. Rachelefsky, G. S., Coulson, A., Siegel, S. C., and Stiehm, E. R. (1975), Aspirin intolerance in chronic childhood asthma: detection by oral challenge. *Pediatrics* **56**, 443–448.
 53. Szczeklik, A. and Sanak, M. (2000), Genetic mechanisms in aspirin-induced asthma. *Am. J. Respir. Crit. Care Med.* **161**, S142–S146.
 54. Stevenson, D. (1998), Adverse reactions to nonsteroidal anti-inflammatory drugs. *N. American Clinics Allergy and Immunology* **18**:4, 773–798.
 55. Stevenson, D. and Simon, R. A. (2001), Lack of cross-reactivity between rofecoxib and aspirin in aspirin sensitive asthmatic patients. *J. Allergy Clin. Immunol.* **108**, 47–51.
 56. Picado, C., Castillo, J. A., Montserrat, J. M., and Agusti-Vidal, A. (1989), Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. *Eur. Respir. J.* **2**, 127–129.
 57. Marquette, C., Saulnier, F., Leroy, O., Wallaert, B., Chopin, C., Demarcq, J. M., et al. (1992), Long-term prognosis for near-fatal asthma: a 6-year follow up study of 145 asthmatic patients who underwent mechanical ventilation for near fatal asthma. *Am. Rev. Resp. Dis.* **146**, 76–81.
 58. Stevenson, D. and Simon, R. A. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs, in *Allergy: Principles and Practice*, Middleton, Jr., E., Ellis, E. F., Yunginger, J. W., Reed, C. E., Adkinson, Jr., N. F., and Busse, W. W., eds., vol. 2, 5th ed., Mosby, St. Louis, 1998, pp. 1225–1234.
 59. Pleskow, W. W., Stevenson, D. D., Mathison, D. A., Simon, R. A., Schatz, M., and Zieger, R. S. (1983), Aspirin-sensitive rhinosinusitis/asthma: spectrum of adverse reactions to aspirin. *J. Allergy Clin. Immunol.* **71**, 574–579.
 60. Bosso, J. V., Schwartz, L. B., and Stevenson, D. D. (1991), Tryptase and histamine release during aspirin-induced respiratory reactions. *J. Allergy Clin. Immunol.* **88**, 830–837.
 61. Berges-Gimeno, M., Simon, R. A., and Stevenson, D. D. (2002), The natural history and clinical characteristics of aspirin exacerbated respiratory disease. *Ann. Allergy Asthma Immunol.* (Accepted for publication.)
 62. Nizankowska, E. and Szczeklik, A. (1989), Glucocorticosteroids attenuate aspirin-precipitated adverse reactions in aspirin-intolerant patients with asthma. *Ann. Allergy* **63**, 159–162.
 63. Stevenson, D., Simon, R. A., Mathison, D. A., and Christiansen, S. C. (2000), Montelukast is only partially effective in inhibiting aspirin responses in aspirin sensitive asthmatics. *Ann. Allergy Asthma Immunol.* **85**, 477–482.
 64. Nizankowska, E., Dworski, R., Soja, J., and Szczeklik, A. (1990), Salicylate pre-treatment attenuates intensity of bronchial and nasal symptoms precipitated by aspirin in aspirin-intolerant patients. *Clin. Exp. Allergy* **20**, 647–652.
 65. Nizankowska, E., Bestynska-Krypel, A., Cmiel, A., and Szczeklik, A. (2000), Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. *Eur. Respir. J.* **15**, 863–869.
 66. Patriarca, G., Nucera, E., and Di Rienzo, V. (1991), Nasal provocation test with lysine acetylsalicylate (LAS) in aspirin-sensitive patients. *Ann. Allergy* **67**, 60–62.
 67. Pawlowicz, A., Williams, W. R., and Davies, B. H. (1991), Inhalation and nasal challenge in the diagnosis of aspirin induced asthma. *Allergy* **46**, 405–409.
 68. Schapowal, A., S.-S. M., Szczeklik, A., Bruijnzeel, P., Hansel, T., and Virchovsen, Chr. (1990), Lysine-aspirin nasal provocation and anterior rhinomanometry for the diagnosis of aspirin-sensitive asthma. *Atemwegs. Lungenkrankh* **16**, S1–S5.
 69. Wellbrock, M. M. J., Cornelius, M., and Brasch, J. (1993), Intranasal provocation with lysine acetylsalicylic acid. *HNO* **41**, 577–581.
 70. Milewski, M., Mastalerz, L., Nizankowska, E., and Szczeklik, A. (1998), Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. *J. Allergy Clin. Immunol.* **101**, 581–586.
 71. Szczeklik, A. and Serwonska, M. (1979), Inhibition of idiosyncratic reactions to aspirin in asthmatic patients by clematine. *Thorax* **34**, 654–658.
 72. Szczeklik, A., Mastalerz, L., Nizankowska, E., and Cmiel, A. (1996), Protective and bronchodilator effects of prostaglandin E and salbutamol in aspirin-induced asthma. *Am. J. Respir. Crit. Care Med.* **153**, 567–571.
 73. Szczeklik, A., Dworski, R., Mastalerz, L., Prokop, A., Sheller, J., Nizankowska, E., et al. (1998), Salmeterol prevents aspirin-induced attacks of asthma and interferes with eicosanoid metabolism. *Am. J. Respir. Crit. Care Med.* **158**, 1168–1172.
 74. Martelli, N. A. U. G. (1977), Inhibition of aspirin-induced bronchoconstriction by sodium cromoglycate inhalation. *Thorax* **32**, 684.
 75. Basomba, A. R. A., Pelaez, A., Villalmanzo, I. G., and Campos, A. (1976), The effect of sodium cromoglycate in preventing aspirin induced bronchospasm. *Clin. Allergy* **6**, 269.
 76. Stevenson, D. D., Simon, R. A., and Mathison, D. A. (1984), Cromolyn pretreatment delays onset of aspirin (ASA) induced asthmatic reactions. *J. Allergy Clin. Immunol.* **73**, 162.
 77. Pauls, J. D., Simon, R. A., Daffern, P. J., Stevenson, D. D. (2000), Lack of effect of the 5-lipoxygenase inhibitor zileuton in blocking oral aspirin challenges in aspirin-sensitive asthmatics. *Ann. Allergy Asthma Immunol.* **85**, 40–45.

78. Berges-Gimeno, M., Simon, R. A., and Stevenson, D. D. (2002), The effect of leukotriene modifier drugs on ASA-induced asthma and rhinitis reactions. *Clin. Exp. Allergy* (Accepted for publication.)
79. Szczeklik, A., Nizankowska, E., and Duplaga, M. (2000), Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur. Respir. J.* **16**, 432–436.
80. Vento, S. I., Ertama, L. O., Hytonen, M. L., Wolff, C. H. J., Malmberg, C. H. J. (2000), Nasal polyps: clinical course during 20 years. *Ann. Allergy Asthma Immunol.* **85**, 209–214.