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Frequency and severity of reactions to a 325-mg aspirin dose during desensitization

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ABSTRACT

Background: The frequency with which patients with aspirin-exacerbated respiratory disease (AERD) react to 325 mg of aspirin during aspirin desensitization, or fail to react at all, is not fully known.
Objective: To determine the rate and type of reaction at 325 mg of aspirin during desensitization.
Methods: A retrospective study of 104 patients who underwent aspirin desensitization from 2010 to 2016 was performed. A standard desensitization protocol (starting at 20–40 mg, progressing through 325 mg, and extinguishing reactions by dose repetition) was used. Reactions were defined by upper respiratory tract symptoms, lower respiratory tract symptoms, and/or forced expiratory volume in 1 second decrease of 15% or greater. Patients who did and did not react were compared by logistic regression.
Results: Eighty-four patients reacted (81%) and 20 did not (19%). Seventy-seven patients who had a provoking reaction at 162 mg of aspirin or less subsequently extinguished their reactions before they reached a dose of 325 mg and had no problems at that dose; one subsequent 325-mg reaction occurred during a protocol violation. One initial provoking reaction to 325 mg occurred. Both 325-mg reactions were mild, and neither met the forced expiratory volume in 1 second criterion for a clinically meaningful change. The remaining 5 patients could not complete the protocol because of persistent reactions or social reasons. Reactors were more likely to have had asthma for more than 10 years than nonreactors (odds ratio, 3.2; 95% confidence interval, 1.0–10.3; $P = .05$).
Conclusion: During aspirin desensitization for AERD, provoking reactions at the 325-mg dose are rare (1%) and mild. Patients who react at 162 mg or less and extinguish their reactions may be able to administer the 325-mg dose at home.

Introduction

Aspirin-exacerbated respiratory disease (AERD) as a clinical entity has been known for nearly 100 years, with the triad of aspirin sensitivity, asthma, and nasal polyposis described by Widal and Lermoyez[1] and later by Samter and Beers.[2] AERD is a heterogeneous disease with a variable course that affects 5% to 7% of all patients with asthma and 15% of patients with severe asthma.[3,4] Ingestion of aspirin or another nonsteroidal anti-inflammatory drug (NSAID) typically causes a combination of upper respiratory tract symptoms (nasal congestion, rhinorrhea, ocular tearing, periorbital swelling) and/or lower respiratory symptoms or signs (dyspnea, wheezing, and forced expiratory volume in 1 second [FEV_1] decrease); occasionally gastrointestinal symptoms or rash or urticaria are also present.[5,6] Indications for aspirin desensitization and maintenance include a lack of control of respiratory disease with topical corticosteroids and leukotriene-modifying drugs or a separate indication for aspirin or NSAID use, such as in cardiovascular disease.[7,8]

Aspirin desensitization and maintenance reduce upper and lower airway inflammation in AERD and the burden of disease.[9–11] Typical oral aspirin desensitization protocols involve stepwise administration of escalating aspirin doses in a controlled setting in 90- to 180-minute increments,[8,12] depending on the protocol. This often takes 2 to 4 days to reach the final 650-mg aspirin dose, which may be safely taken at home.[12] Recent work has focused on decreasing the waiting period between doses to 60 minutes in selected patients during the oral aspirin protocol and in using nasal applications to effect desensitization.[13–15] In our experience, few patients have reacted at the 325-mg level during the traditional oral challenge, suggesting that the protocol might be shortened, saving time and money for patients and health care systems alike. Furthermore, some patients may not react during desensitization; in patients who truly have AERD, an entity has been described called silent desensitization. Because the gold standard of diagnosing AERD is a positive aspirin challenge result, patients who do

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not react present a clinical dilemma, and characteristics that define this group are currently inadequately studied.[16,17]

We hypothesized that during aspirin desensitization, reactions to 325 mg were extremely uncommon and of mild intensity and that there may be selected patients in whom home administration of the 325-mg dose might be feasible. In addition, we aimed to identify baseline characteristics associated with those who undergo a silent desensitization.

Methods

Patient Population

A retrospective study of 104 patients who underwent oral aspirin desensitization between 2010 and 2016 at the University of Michigan allergy and immunology clinic was conducted. The study protocol was reviewed and approved by the University of Michigan Medical School Institutional Review Board on Human Subjects. Written informed consent was not required because of the retrospective nature of the work.

Desensitization Protocol

Patients selected for desensitization had a history suggestive of AERD, including asthma, aspirin or NSAID sensitivity, and chronic rhinosinusitis with nasal polyposis. A diagnosis of AERD was individually determined by the treating physician, and formal aspirin challenge before desensitization was at the physician's discretion. Before desensitization, all patients were required to record peak flow values at home and to have stable asthma control denoted by consistent peak flows with no evidence of a current exacerbation. The oral aspirin desensitization followed published protocols[5,8,12] but varied slightly among individual physicians. The protocol generally started at 20 or 40 mg as an initial dose and proceeded every 3 hours through 40, 81, 162, and 325 mg for 2 to 4 days, with the 650-mg dose given at home.[12,18] A positive reaction at any dose prompted dose repetition until the reaction extinguished before advancement. A positive reaction included naso-ocular symptoms (rhinorrhea, nasal congestion, ocular tearing, or periorbital swelling), lower respiratory tract symptoms suggestive of bronchoconstriction (dyspnea or wheezing), and/or an FEV_1 decrease of 15% or greater from baseline.[8] Gastrointestinal upset and/or urticaria or rash was also recorded in addition to the more classic respiratory reactions outlined above. Patients with a reaction were treated symptomatically according to published protocols and had the reactive dose repeated before advancing to the next dose.[8,18] Home medications were continued, and no additional pretreatment was given routinely. Reactions were treated at the discretion of the supervising physician with albuterol via nebulizer, intranasal and oral antihistamines, montelukast, decongestants, corticosteroids, antiemetics, and/or acid-suppressing medications as needed.[8,13,18]

Data Collection

Data were collected from patients' medical records using a standardized approach involving prespecified variables. Demographic data were collected, including age, sex, race/ethnicity, and body mass index. Baseline asthma and AERD characteristics were evaluated, which included duration of AERD, history of nasal polyps and polypectomy, time from polypectomy, asthma duration, and the presence of atopy. A positive allergy skin test result was defined as a wheal size of 3 mm greater than the negative control.[19] Atopy was defined as a positive skin test result to at least one allergen. Typical allergens tested included trees, grasses, weeds, molds, dust mite, dog, and cat. Additional data included perception of asthma control, evaluated via the Asthma Control Test, and baseline spirometry. The National Health and Nutrition Examination Survey III data set was used for normal values.[20] FEV_1 is reported as percentage of predicted value unless otherwise stated. Baseline medications assessed included nasal corticosteroids, inhaled corticosteroids, oral corticosteroids, leukotriene modulators (including leukotriene receptor antagonists [LTRAs] and zileuton), long-acting β-agonists, short-acting β-agonists, oral antihistamines, and omalizumab. Complexity of asthma control was quantified by assessing the patient's step of therapy by characterizing the medications of each patient generally following the National Heart, Lung, and Blood Institute asthma guidelines for patients older than 12 years (eTable 1).[21]

For the desensitization protocols, all provoking, interval, and final reactive doses were recorded. Desensitization reaction response was coded according to upper respiratory tract symptoms (rhinorrhea, nasal congestion, ocular tearing, periorbital swelling), lower respiratory tract symptoms and signs (dyspnea and wheezing), FEV_1 decrease, and/or other (gastrointestinal upset or urticaria or rash). The reaction threshold for FEV_1 decrease was a decrease of at least 15% from the predesensitization value.[8]

Patients who did not have a reaction during desensitization were identified as nonreactors. For these patients, the presence or absence of a prior, in-office observed aspirin challenge with subsequent naso-ocular and/or bronchial reaction was assessed. Medication changes to the above medications between challenge and desensitization were also recorded for all nonreactors. Patients were considered to have potentially undergone silent desensitization if they had a prior positive in-office aspirin challenge result and had at least 7 days between challenge and desensitization.

Statistical Analysis

SPSS statistical software, version 22 (IBM Inc, Armonk, New York) was used to perform all statistical analyses. The t test, χ^2 analysis, and Mann-Whitney analysis were performed to evaluate the differences between reactors and nonreactors. Bivariate correlation was used to identify significant variables ($P < .05$), with logistic regression performed as appropriate to create multivariate models to evaluate associations with the presence or absence of a reaction.

Results

Patient Characteristics

Table 1 gives the baseline characteristics for all 104 patients in this study. The population age ranged from 19 to 77 years old, 43% were female, and 85% were white. The mean AERD duration was 10.9 years, whereas the mean duration of asthma was 17.4 years. A total of 98.1% had previously undergone nasal polypectomies. The mean step of asthma therapy was 4.2, indicating a moderate severity of asthma typically treated by medium-dose inhaled corticosteroids plus LTRAs or long-acting β-agonists (eTable 1). The mean FEV_1 at the time of challenge was 89%, with 11 patients starting with an FEV_1 less than 70%.

Aspirin Desensitization and Aspirin Provoking Doses

Eighty-four patients (81%) had a reaction of any type during the desensitization protocol, and 20 patients (19%) did not have a reaction. Figures 1 and 2 depict the number of patients who reacted at each provoking dose. The most common provoking dose was 81 mg (34 patients). The mean time from aspirin ingestion during challenge to reaction onset was 99 minutes, and a mean of 1.4 doses were repeated per patient. In addition to the typical respiratory symptoms shown in Figures 1 and 2, 14 patients also experienced gastrointestinal symptoms, hives, and/or rash. Additional detailed tabulations of the different types of reactions at various doses are listed in eTables 2 and 3.

Table 1
Baseline Patient Characteristics for All Patients[a]

Characteristic	All patients (N = 104)
Age, mean (range), y	49.2 (19–77)
Female sex	43.3
BMI, mean (SD)	29.4 (5.6)
Race	
White	84.6
Black/African American	6.7
Unknown	7.7
Duration of AERD, mean (SD), y	10.9 (10.9)
Polypectomy	98.1
Time from polypectomy, median (interquartile range), y	9.0 (3.0–38.0)
Nasal corticosteroid use	83.7
Inhaled corticosteroids	
Inhaled corticosteroid use	82.7
Fluticasone dose, mean, μg	399.6
Leukotriene inhibitor use	
LTRA	69.2
Zileuton	10.6
Oral corticosteroids	
Oral corticosteroid use	29.8
Oral corticosteroid dose, mean, mg/d	12.4
LABA use	76.0
SABA use	84.6
Oral antihistamine use	47.1
Omalizumab use	3.8
Asthma duration, mean, y	17.4
Atopy presence	77.9
Baseline FEV_1, mean (SD), % predicted	88.7 (16.1)
Patients with FEV_1 <70%	10.6
Asthma complexity by step therapy	4.2

Abbreviations: AERD, aspirin-exacerbated respiratory disease; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); FEV_1, forced expiratory volume in 1 second; LABA, long-acting β-agonist; LTR, leukotriene receptor; SABA, short-acting β-agonist.

[a]Data are presented as percentage of patients unless otherwise indicated. eTable 1 provides the definition of asthma complexity above. The Methods section provides the definition of atopy and a discussion of normal values used for FEV_1.

Seventy-seven patients had a provoking reactive dose at or below 162 mg and extinguished their reactions; none of these patients had a reaction to 325 mg. Twenty-one (27%) of these 77 patients were taking oral prednisone, with 5 patients taking more than 10 mg of prednisone daily; 4 patients were taking 20 mg and 1 was taking 30 mg. Two other patients had reactions to 325 mg and are described below. Neither of these was taking oral prednisone.

Five patients did not complete the desensitization process. Three of these therapy withdrawals were attributable to persistent

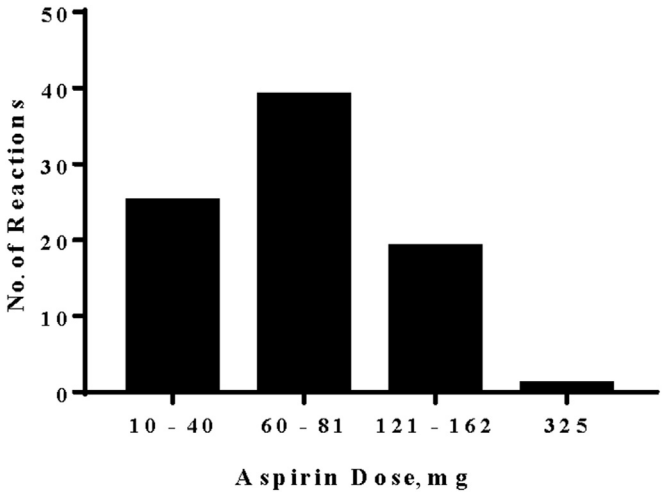

Figure 1. Number of provoking reactions seen at each aspirin dose. Provoking doses are grouped by range for simplicity.

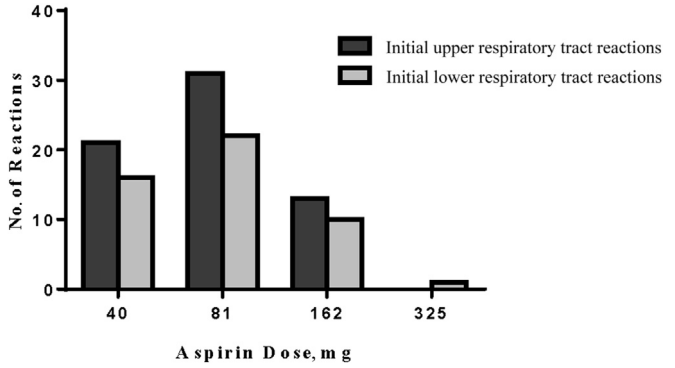

Figure 2. Number of patients with provoking doses at each level of aspirin according to naso-ocular and bronchial symptoms. Some patients appear in both categories. Not shown, for simplicity, are 1 patient with naso-ocular reaction at 10 mg, 1 patient with a bronchial reaction at 60 mg, and 1 patient with a naso-ocular reaction at 120 mg.

reactions with rash or abdominal symptoms that did not extinguish; the maximum aspirin doses achieved for these 3 were 40, 40, and 81 mg. Another patient did not complete the protocol because of late development of anaphylaxis followed by a myocardial infarction after a maximal aspirin dose achieved of 81 mg (previously reported by our institution).[22] The final patient failed to complete the protocol for social reasons; this patient left the clinic with a maximum aspirin dose achieved of 162 mg.

Aspirin Reactions at 325 mg

Two of the 99 patients who completed the protocol reacted to 325 mg of aspirin. The first patient had no prior documented in-office aspirin challenge. He was taking an LTRA and antihistamine the day of the reaction and had recently finished a course of oral corticosteroids. He completed 40, 81, and 162 mg without symptoms. With 325 mg, the patient was asymptomatic for 3 hours and then stated that he felt “a little tight in the chest.” He had no upper respiratory tract symptoms or wheezing on examination. His FEV_1 had decreased 10%, which did not meet the threshold cutoff for a positive reaction. He declined a nebulized albuterol treatment and left the clinic to go to an otolaryngology appointment, where he reported no respiratory symptoms of any kind. The next day he had no symptoms or physical examination changes, and he tolerated 325 mg without symptoms or qualifying FEV_1 decrease.

The second patient who reacted to 325 mg did not follow the protocol of repeating a dose after a reaction. This patient had a positive aspirin challenge result with 162 mg 4 months earlier with both upper and lower respiratory tract symptoms but without a qualifying FEV_1 decrease. At desensitization, she was taking an LTRA, and the patient tolerated 40 and 81 mg without symptoms. With 162 mg (the prior reactive dose), she experienced watery eyes but otherwise reported no lower respiratory tract symptoms and had no FEV_1 decrease. Per protocol, the upper respiratory tract symptom should have prompted a repetition of the 162-mg dose, but this was not done. With 325 mg, the patient experienced itchy tongue and persistent watery eyes. She had subjective chest tightness, and her FEV_1 decreased 9% (not meeting the cutoff threshold). She was given 50 mg of diphenhydramine and albuterol with resolution of symptoms. She tolerated 325 mg without incident the next day.

Nonresponders

Twenty patients (19%) did not have any reaction during the desensitization protocol. Table 2 compares baseline characteristics for all patients who reacted (n = 84) against all nonreactors

Table 2
Baseline Characteristics for Reactors vs All Nonreactors[a]

Characteristic	All reactors (n = 84)	Nonreactors (n = 20)	*P* value
Age, mean (range), y	49.5 (19–77)	48.1 (21–71)	.64
Female sex	45.2	35.0	.41
BMI, mean (SD)	29.0 (5.5)	31.1 (5.4)	.13
Race			.21
White	84.5	85.0	
Black/African American	7.1	5.0	
Unknown	8.3	5.0	
Duration of AERD, mean (SD), y	12.8 (15.6)	8.5 (9.0)	.39
Polypectomy	98.8	95.0	.26
Time from polypectomy, median (interquartile range), y	8.0 (3.0–30.0)	20.0 (6.0–165.0)	.30
Nasal corticosteroid use	84.5	80.0	.62
Inhaled corticosteroids			.62
Inhaled corticosteroid use	83.3	85.0	
Fluticasone dose, mean, μg	438.4	496.5	
Leukotriene inhibitor use			.57
LTRA	72.6	65.0	
Zileuton	10.7	10.0	
Oral corticosteroids			.499
Oral corticosteroid use	19.0	45.0	
Oral corticosteroid dose, mean, mg	13.4	10.6	
LABA use	76.2	75.0	.91
SABA use	84.5	85.0	.96
Antihistamine use	48.8	40.0	.48
Omalizumab use	4.8	0.0	.32
Duration of asthma, mean, y	19.3	9.8	.03
Atopy presence	78.6	75.0	.85
Baseline FEV_1, mean (SD), % predicted	88.7 (17.1)	88.6 (11.4)	.98
Patients with FEV_1 <70%	13.1	0.0	
Asthma complexity by step therapy	2.3	3.1	.27

Abbreviations: AERD, aspirin-exacerbated respiratory disease; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); FEV_1, forced expiratory volume in 1 second; LABA, long-acting β-agonist; LTR, leukotriene receptor; SABA, short-acting β-agonist.
[a]Data are presented as percentage of patients unless otherwise indicated. eTable 1 provides the definition of asthma complexity above. The Methods section provides the definition of atopy and a discussion of normal values used for FEV_1.

(n = 20). There was one statistically significant difference on bivariate analysis between these 2 groups, which was mean asthma duration ($P = .03$) (the nonreactor group had 6.5 years of asthma vs 20.3 years in the reactor group). On logistic regression, those who had a reaction were significantly more likely to have had asthma for greater than 10 years compared with those who did not have a reaction (odds ratio, 3.2; 95% confidence interval, 1.0–10.3; $P = .05$).

Six of these nonreactors (5.8% of total patients) met the definition for a possible silent desensitization; they had a prior positive in-office aspirin challenge result and were at least 7 days past the challenge. Some patients had been prescribed new medications between aspirin challenge and desensitization: one started had taking intranasal corticosteroids, and another had started taking a long-acting β-agonist. No patients were prescribed an LTRA or antihistamine in the interim. Three of the 6 had undergone nasal polypectomy within 2 weeks of desensitization, and for this reason these patients were taking new, tapering oral corticosteroids after polypectomy; daily prednisone doses at the time of desensitization were 0, 0, 5, 10, 10, and 20 mg.

Discussion

The current treatment for AERD includes aspirin desensitization, yet this procedure can be time consuming and costly. In the current study, we have determined that patients who had a provoking dose of less than 162 mg and extinguished their aspirin reaction did not subsequently react to 325 mg. In patients with this profile, it is likely that home administration of the 325-mg dose is safe. We propose a decision tree as shown in Figure 3. If a patient has a provoking reaction at or below the 162-mg aspirin dose (such as at 40, 81, or 162 mg in the typical protocol) and then extinguishes the reaction, this patient is a candidate to have the 325-mg dose given at home. In patients who do not react, the current approach of observed in-office administration of the 325-mg dose remains warranted.

The goal dose of aspirin desensitization is 650 mg twice daily, which was historically given in an observed setting. Because of work showing a reaction rate of 0% at 650 mg,[12] this dose can be safely given at home, which is now the standard.[18] In prior work, the rate of patients with provoking doses of 325 mg was approximately 1%.[12] Our study confirms this provoking rate of 1.0% (n = 1/99), and the reaction was mild. The other reaction at 325 mg was a protocol violation, as described; we suspect that this patient would have extinguished her reaction with a repeated 162-mg dose. This study is limited by the 5 patients who did not complete desensitization. The possibility exists that these patients may have had a subsequent reaction to 325 mg if they had been able to progress through the protocol. However, a subgroup of patients seem to overproduce prostaglandin D_2, which seems to be associated with failure to complete desensitization; these patients might fall in this group.[23] With larger numbers of patients, it may be possible to conclude that more patients than those described above might be able to have the 325-mg dose given at home as well; further work is needed to investigate this group of patients.

Overall, the change in protocol described in Figure 3 would be helpful to patients because it would save the time devoted to in-office monitoring after aspirin dose administration. Furthermore, it would help address increasing health care costs by reducing the staff time associated with desensitizations. Indeed, novel changes to the standard protocol have been suggested, and the search for an optimal approach remains ongoing. Alternative protocols designed to address this issue have been proposed and include nasal lysine-aspirin administration, intranasal ketorolac, and an hourly administration of oral aspirin desensitization.[13–15,24] A safe and effective means to shorten the oral desensitization protocol would be a valuable addition to this discussion because not all clinics have the resources, access to appropriate medications, or experience to provide these more advanced protocols. In addition, the reaction rate at 325 mg in alternative protocols deserves further investigation because it is possible that reactions remain extremely low in such instances as well.

The low rate of reaction to 325 mg led us to consider factors associated with a nonreactive or possible silent desensitization. In prior work,[25–27] leukotriene modifiers, inhaled corticosteroids, and long-acting β_2-agonists affect responses to aspirin challenge. In this study, duration of asthma was positively correlated with producing a reaction when comparing reactors and nonreactors. Asthma as a separate entity is known to lead to progressive inflammation and airway remodeling,[28] and this process may increase the reactivity of patients with AERD toward aspirin, making a positive aspirin reaction more likely as time passes with the disease.

As discussed by other authors,[16,18] silent desensitization presents a clinical dilemma. We are aware of only 7 formally described cases previously.[16] The group of 6 patients in our study who met a definition of silent desensitization add to this number. This small group limits a statistical analysis, making factors associated with silent desensitization difficult to ascertain. Four of these 6 patients were taking an oral corticosteroid, which was a change between challenge and desensitization; it may be that the medication change explains the change in the patients' aspirin reactivity. Three of these patients newly taking an oral corticosteroid had also recently undergone sinus surgery; it may be that the intervening polyp removal played a role. Four of these 6 were also taking an LTRA or zileuton, although none had been added

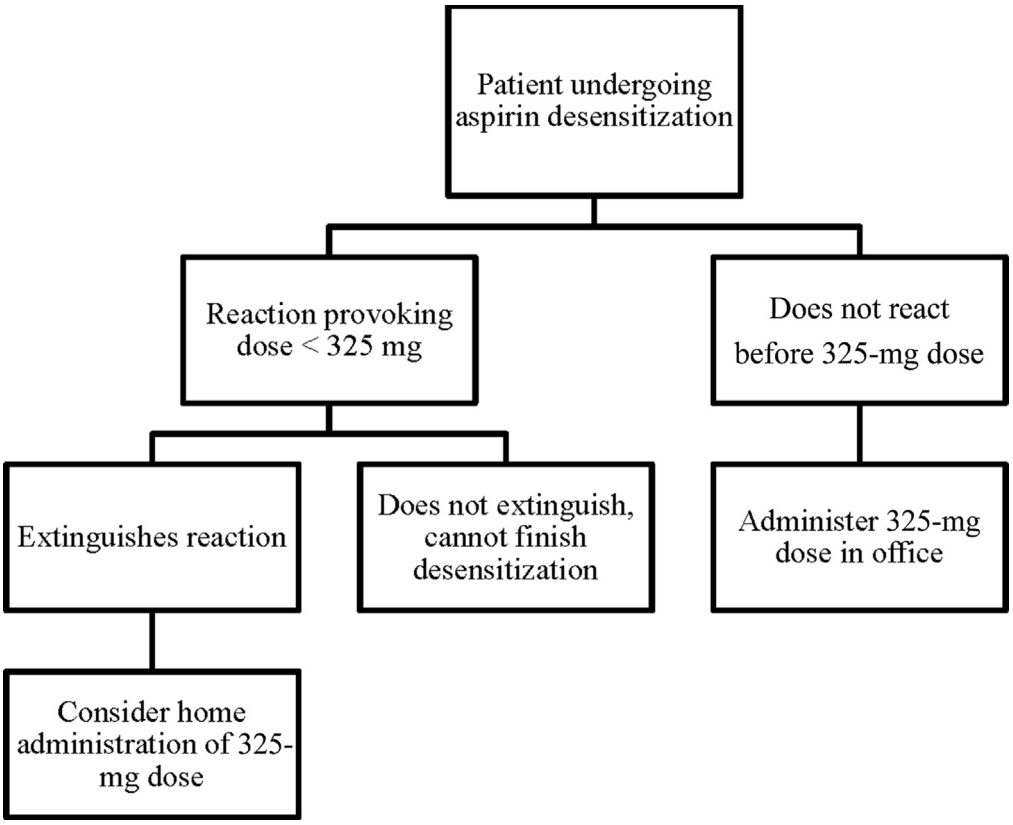

Figure 3. Suggested decision flowchart based on reaction outcomes of patients in this study.

between the initial challenge and desensitization; this may have played a role as well. Long-term aspirin therapy has been correlated with various adverse effects, including macular degeneration, although whether this implies causation remains controversial.[29,30] Given the risks associated with aspirin therapy, further study is required to understand what benefit long-term aspirin therapy would await the group of patients who undergo a silent desensitization.

In conclusion, this study identifies that those patients with AERD who react during desensitization at doses less than 162 mg and subsequently extinguish their reactions are extremely unlikely to react at the 325-mg dose. This group can be considered for home administration of the 325-mg aspirin dose. The study also suggests the overall safety of the 325-mg aspirin dose during desensitization in patients with AERD, with reactive patients experiencing mild reactions; this dose of aspirin warrants further study with larger numbers of patients to determine whether home administration might be safe for a broader group. Additional research into aspirin desensitization protocols for patients with AERD to improve protocol effectiveness, efficiency, and risks is warranted.

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2016.11.021.

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eTable 1
Asthma Step Therapy[a]

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Albuterol as needed	Low-dose ICS or LTRA	Low-dose ICS plus LABA or medium-dose ICS alone or low-dose ICS plus LTRA	Medium-dose ICS plus LABA or medium-dose ICS plus LTRA	High-dose ICS plus LABA or high-dose ICS plus LTRA	High-dose ICS plus LABA or high-dose ICS plus LTRA; either of the above with oral corticosteroids

Abbreviations: ICS, inhaled corticosteroid; LTRA, leukotriene receptor agonist.
[a]The above details the steps of asthma therapy used to grade asthma complexity according to the medications taken by the patient at the time of desensitization. These definitions are based on the National Heart, Lung, and Blood Institute asthma guidelines referenced in the Methods section.[20] Adding an LTRA or anticholinergic was used in this study to increase the step level by 1. Adding omalizumab was used as equivalent to step 6. If a patient was taking oral corticosteroids on a rapid taper from polypectomy and not for asthma control, this was discounted in the ranking.

eTable 2
Detailed Reaction Types[a]

Severity of reaction	No. (%) of total patients
Type 0 (no reaction)	20 (19.2)
Type 1 (upper respiratory tract symptoms only)	30 (28.8)
Type 2 (lower respiratory tract symptoms without FEV_1 decrease)	2 (1.9)
Type 3 (lower respiratory tract symptoms with FEV_1 decrease)	8 (7.7)
Type 4 (upper and lower respiratory tract symptoms with FEV_1 decrease)	16 (15.4)
Type 5 (upper and lower respiratory tract symptoms with no FEV_1 decrease)	11 (10.6)
Type 6 (FEV_1 decrease only)	3 (2.9)
Type 7 (upper respiratory tract symptoms with FEV_1 decrease and no lower symptoms)	11 (10.6)

Abbreviation: FEV_1, forced expiratory volume in 1 second.
[a]Detailed tabulation of how each reaction was defined accompanied by the number of patients who experienced that reaction. A qualifying FEV_1 decreased was considered to be at least 15%; see the Methods for a more detailed description.

eTable 3
Detailed Reaction Types by Dose

Dose, mg	No. of patients by reaction type						
	1	2	3	4	5	6	7
10	1	0	0	0	0	0	0
20	0	0	0	0	0	0	0
40	7	1	1	6	5	0	3
61	0	0	0	0	0	1	0
81	14	0	4	8	3	1	6
120	1	0	0	0	0	0	0
162	7	0	3	2	3	1	2
325	0	1	0	0	0	0	0