Original Article

An Hourly Dose-Escalation Desensitization Protocol for Aspirin-Exacerbated Respiratory Disease

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What is already known about this topic? Aspirin desensitization therapy using multiday protocols followed by maintenance dosing effectively treats upper and lower airway symptoms in patients with aspirin-exacerbated respiratory disease (AERD) who are inadequately controlled on inhaled glucocorticoids and leukotriene-modifying agents.

What does this article add to our knowledge? Patients reacting to aspirin or nonsteroidal anti-inflammatory drugs within 1 hour of ingestion can be safely desensitized using a protocol of hourly dose escalations that in many cases can be accomplished in a single day.

How does this study impact current management guidelines? Our findings support shortening the dosing intervals for patients without delayed reactions to aspirin, which applies to the majority of patients undergoing desensitization for AERD. This would reduce the need for prolonged observation and benefits both patients and practitioners.

BACKGROUND: Aspirin desensitization followed by maintenance therapy effectively improves symptom control in patients with aspirin exacerbated respiratory disease (AERD). The majority of current desensitization protocols use 3-hour dosing intervals and often require 2 to 3 days to complete.
OBJECTIVE: We evaluated hourly dose escalations in a subset of patients with chronic rhinosinusitis, nasal polyps, and asthma who historically reacted to aspirin within 1 hour or were avoiding aspirin with the goal of developing a safe and efficient desensitization protocol.
METHODS: Fifty-seven aspirin desensitizations were performed under the hourly protocol. All patients had refractory nasal polyposis as an indication for aspirin desensitization. The clinical characteristics of each subject were analyzed in relation to aspects of his or her reactions during the procedure.
RESULTS: Ninety-eight percent of study patients were successfully treated under the hourly protocol, including those with a history of severe reactions and intubation. None required further medication than is available in an outpatient allergy clinic. A total of 96% of reactors recorded a bronchial or naso-ocular reaction within 1 hour of the preceding dose. Of the total patients on this protocol, 40% were able to complete the procedure in a single day, and 60% within 2 days.
CONCLUSION: Patients with AERD who have a history of symptoms less than 1 hour after aspirin exposure can be safely desensitized with a 1-hour dose-escalation protocol that can often be completed in a single day. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:926-31)

Key words: *Asthma; Aspirin-exacerbated respiratory disease; Chronic rhinosinusitis; Nasal polyps; Aspirin desensitization*

Aspirin-exacerbated respiratory disease (AERD) represents one of the most significant adverse reactions to aspirin (acetylsalicylic acid [ASA]) and other nonsteroidal anti-inflammatory drugs (NSAIDs). The characteristic triad of this condition manifests as underlying asthma, chronic rhinosinusitis, and persistent sinonasal polyposis.[1] Ingestion of the offending drugs elicits any of the following reactions: bronchospasm, nasal congestion, rhinorrhea, sneezing, lacrimation, and at times gastrointestinal upset and urticaria.[2] In those patients who do not obtain adequate control with topical corticosteroids and leukotriene-modifying drugs (LMDs), or would derive benefit from chronic ASA and/or NSAID use for cardiovascular disease or inflammatory conditions, aspirin desensitization therapy is indicated.

Aspirin desensitization and maintenance therapy is a well-established and effective method of reducing upper and lower airway disease associated with AERD.[3] Over the long term, patients treated with aspirin desensitization reported significant improvements in sense of smell, rhinosinusitis, and frequency of asthma exacerbations along with reduced need for systemic corticosteroid bursts, polypectomies, and sinus operations.[4-6] This method involves the administration of oral aspirin in stepwise escalating doses over time within a controlled environment (either inpatient or in specialized allergy centers). The most well-established protocol utilizes dose escalation in 3-hour intervals and requires at least 2-3 days to complete.[7] This requires

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Abbreviations used
AERD- Aspirin-exacerbated respiratory disease
ASA- Acetylsalicylic acid
CRSwNP- Chronic rhinosinusitis with nasal polyps
ED- Emergency department
LMD- Leukotriene-modifying drug
NSAID- Nonsteroidal anti-inflammatory drug
SCIT- Subcutaneous immunotherapy

substantial investment from patients, physicians, and third-party payers. Shortening the interval between doses in a safe manner could represent substantial monetary and time savings for all involved. An Aspirin Desensitization Joint Task Force has proposed a protocol using 90-minute dosing; unfortunately no data exist on the safety or efficacy of this approach.[8] Given the lack of data on more rapid desensitization for the treatment of AERD, we evaluated a protocol of hourly dose escalation in a subset of patients who historically either reacted to aspirin within 1 hour or had not been exposed to aspirin.

METHODS

Medical records were analyzed from patients being seen for asthma and refractory nasal polyps, and/or who reported a history of hypersensitivity reactions to aspirin or another NSAID at the University of Texas Southwestern Medical Center affiliated hospitals and clinics from 2000 to 2013. Patients were desensitized to more effectively manage their AERD, most commonly due to chronic rhinosinusitis with nasal polyps (CRSwNP). Other information obtained from these records included age, sex, current medications, number of previous reactions, patient reported time from exposure to reaction, reaction type, and interventions required.

Patients who had CRSwNP with reported reaction times to NSAIDs within 1 hour and those without a documented reaction to aspirin or NSAIDs were selected for an accelerated protocol using hourly dose escalations (Table I). The length of time required for the procedure was not disclosed to patients before volunteering their clinical history and consent to proceed with therapy. For patients undergoing aspirin desensitization for CRSwNP, we felt that the optimal time to perform the procedure was generally 2-4 weeks after medical or surgical polypectomy. Although aspirin therapy can shrink formed polyps, starting therapy with a minimal polyp burden seems like the best approach to maximize benefit in patients undergoing this procedure for persistent nasal polyp disease.[9] Patients were started or continued on a premedication regimen to reduce adverse reactions during the desensitization procedure. This included LMDs, which have been shown to reduce the severity of lower respiratory reaction without concealing upper respiratory symptoms, inhaled glucocorticoids, long-acting beta agonists, and in some cases systemic glucocorticoids.[10-12] The majority of patients had a baseline FEV_1 of >60%. Rare patients with an FEV_1 of 50% to 60% were included if their asthma was extremely stable and their history of reaction to aspirin was not severe. For our procedure, we dispensed fractions of commercially available 81 or 325 mg aspirin tablets split with a pill cutter. Patients were first administered approximately 40 mg of aspirin (1/2 of an 81 mg aspirin tablet) unless they had a history of intubation in which case they were started at 20 mg. Doses of 81, 120, 162, and 325 mg were administered at 1-hour intervals under close observation with hourly spirometry. A portion of the studied patients who underwent the procedure earlier were dosed up to 650 mg; however, based on later recommendations, a final dose of 325 mg appears sufficient for successful desensitization and was used in later patients.[13] Dose escalations were continued until they experienced a positive reaction requiring therapy. For our study, the provoking dose was defined as the last dose preceding the development of symptoms. Provoking doses were repeated after symptoms resolved. Positive reactions were classified as bronchial (defined as a decrease in FEV_1 >15% from baseline, wheezing or dyspnea requiring the use of an inhaled β_2-agonist), or naso-ocular (nasal congestion, rhinorrhea, ocular injection, or lacrimation). In addition, the presence of urticaria and gastrointestinal symptoms (nausea, vomiting, and abdominal pain) was recorded though these were not used as sole determinants of a positive reaction. Depending on the reaction to aspirin, the following interventions were used: levalbuterol nebulizers every 15 minutes, oxymetazoline 2-3 sprays per nostril as needed, olopatadine to affected eyes as needed, cetirizine 10 mg, or ranitidine 20 mg orally. Those patients who did not return to their baseline lung function returned the following day to complete the protocol. The provoking dose, reaction type, and the corresponding time until reaction were recorded (Table II). On completion of the procedure, the patients were placed on 650 mg of aspirin twice daily. Desensitized patients were continued on topical nasal corticosteroids concomitantly with long-term aspirin therapy.

The population of our hourly group was further divided into 4 classes (A-D) based on the frequency and severity of their described

TABLE I. Hourly dose-escalation aspirin desensitization protocol

Time	Dose
08:00	40 mg (20 mg if history of serious reaction)
09:00	81 mg
10:00	120 mg
11:00	162 mg
12:00	325 mg
13:30	Observation period

Doses are based on fractions of 81 and 325 mg tablets split with a pill cutter. Start with a dose of 40 mg (or 20 mg if history of serious reaction), followed by 81, 120, 162, and 325 mg in hourly intervals.

Patient selection

1. Suspected AERD with rhinosinusitis, asthma, and nasal polyposis refractory to inhaled corticosteroids, long-acting beta agonists, and LMDs.
2. Historical aspirin or NSAID reaction occurring within 1 hour of ingestion.

Determine asthma stability and premedication

1. FEV1 >60% of the predicted value, rare exceptions for values 50%-60% based on clinical judgment. Polyps—debulking nasal polyposis 2-4 weeks before desensitization is ideal because desensitization is most effective in preventing new polyp formation, and the procedure may be safer because there is less polyp tissue to produce inflammatory mediators.
2. Start or continue LMD.
3. Start or continue inhaled corticosteroid and/or long-acting β-agonist.
4. Start oral steroids for FEV_1 <80% of personal best or any bronchial instability.

Monitoring and therapy during desensitization protocol

1. Maintain close observation with hourly measurement of FEV_1.
2. On reaching the provoking dose, treat the reaction as follows:
   Bronchial: nebulized β-agonist every 10 minutes three times as needed until the patient is comfortable. Epinephrine should be available for refractory reactions.
   Nasal: topical oxymetazoline, oral and/or intranasal antihistamine.
   Ocular: topical antihistamine and/or mast cell stabilizer or oral antihistamine.
   Gastrointestinal: H2-agonist.
   Urticaria: oral antihistamine.
3. After stabilization, repeat the provoking dose, and if tolerated, continue escalations at hourly intervals until 325 mg is reached. If further reactions are encountered, treat as above and repeat.
4. If unable to reach the 325 mg dose by 2-3 hours before clinic closure, have the patient return the following day to complete the protocol.

TABLE II. Demographics and outcomes of patients undergoing hourly dose-escalation protocol for aspirin desensitization therapy

Historical class	A [%] (n = 7)	B [%] (n = 11)	C [%] (n = 22)	D [%] (n = 17)	All [%] (n = 57)
Sex					
Male	2 [29]	6 [54]	10 [45]	5 [29]	23 [40]
Female	5 [71]	5 [45]	12 [54]	12 [71]	34 [60]
Age, mean (SD), y	42 (16.5)	49.4 (11.4)	49.3 (9.5)	51.2 (11.1)	48.8 (11.9)
LMD use	6 [86]	10 [91]	22 [100]	17 [100]	55 [96]
Observed reaction					
No reaction	2 [29]	2 [36]	3 [14]	2 [12]	9 [16]
Bronchial only	2 [29]	3 [45]	6 [27]	8 [47]	19 [33]
Naso-ocular only	2 [29]	0 [0]	6 [27]	5 [29]	13 [23]
Naso-ocular and bronchial	1 [14]	6 [54]	7 [32]	3 [18]	17 [30]
Total reactions	5 [71]	9 [82]	19 [86]	16 [94]	49 [86]
Ancillary reaction					
Gastrointestinal	0 [0]	3 [27]	1 [5]	2 [12]	6 [10]
Urticaria	0 [0]	1 [9]	2 [9]	1 [6]	4 [7]
Measured data					
ΔFEV_1, mean % (95% CI)	−15.8 (−3.6-30.4)	−19.9 (−8.2-31.7%)	−12.0 (−6.9-16.9)	−17.0 (−8.9-25.1)	−15.5 (−12.0-18.9)
Time to reaction, min (SD)	41 (21.9)	52.8 (26.1)	44.8 (17)	59 (20.5)	50.3 (21)
Provoking dose, mg (SD)	113 (52.9)	157.4 (71.8)	140.3 (133.6)	194 (155)	157.5 (126)
Single day	3 [43]	3 [45]	11 [50]	6 [35]	23 [40]
Completed procedure	7 [100]	11 [100]	22 [100]	16 [94]	56 [98]

CI, Confidence interval; *LMD*, leukotriene-modifying drug; *SD*, standard deviation.
Class Definitions
A: No history of aspirin and/or nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity.
B: Single reaction to aspirin and/or NSAIDs not requiring acute care visit.
C: Two or more reactions to aspirin and/or NSAIDs not requiring acute care visit.
D: One or more reactions requiring acute care visit.
All patients were seen for chronic rhinosinusitis with nasal polyposis and asthma. Those in classes B-D reported a history of reactions within 1 hour of acetylsalicylic acid or NSAID ingestion. Percentages based on historical class.

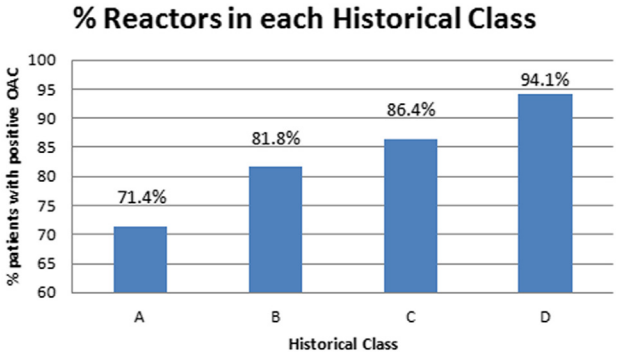

FIGURE 1. Proportion of patients with either naso-ocular or bronchial reactions during aspirin desensitization therapy, according to historical classification. Class A: no prior reaction, class B: one reaction not requiring ED visit or hospitalization, class C: two or more reactions not requiring ED visit or hospitalization, class D: one or more reactions requiring ED visit and hospitalization.

reactions, to assign a pretest probability of having a positive aspirin challenge based on the study by Durson et al.[14] Class A did not exhibit prior ASA or NSAID hypersensitivity and were being seen in our facility on the basis of nasal polyps, sinusitis, and asthma. These individuals avoided aspirin and NSAIDs as a precaution or because they had no indication for them. Individuals in class B reported a single bronchospastic or naso-ocular reaction associated with aspirin and/or NSAIDs without emergency department (ED) visit or hospitalization. Class C reported 2 or more historical reactions that also did not require ED treatment. Class D reported 1 or more reactions severe enough to require acute medical interventions up to and including intubation.

Statistical analysis was performed with Microsoft Excel 2007 for Windows. The mean and standard deviation were calculated for patient characteristics. The 95% confidence interval (CI) was calculated for all results. Logistic regression was used to determine the presence of significant predictors of provoking dose or time to reaction.

RESULTS

Fifty-seven hourly desensitizations were reviewed (Table II). For reference, we encountered only 9 additional cases within the study time frame that did not qualify for the rapid protocol by history, so this approach was applicable to the bulk of our patient group. The average age of our study population was 49 years, with a mean baseline predicted FEV_1 of 84%. Within the group, 23 cases involved male patients and 34 female. More than 96% (55 of 57) of our cases were premedicated using an LMD before the procedure.

Of the 57 patients, 49 (86%) reacted during the desensitization. Nineteen (33.3%) developed a pure bronchial reaction. Thirteen (22.3%) experienced only naso-ocular reactions. Seventeen (29.8%) exhibited symptoms of both. Amongst those with a bronchial component, the mean maximal fall in FEV_1 was 22.3% (95% CI 15.0%-29.5%). Additionally, there were 6 instances of gastrointestinal symptoms and 4 cases of urticaria, all

occurring in patients already showing a positive challenge by the prior definition (Table II). Of 49 reactions, 47 (95.9%) were directly observed within 1 hour of the provoking dose. Of the patients who reacted, the average time of onset was 50.3 minutes after the provoking dose, with a minimum time of 10 minutes. For the entire reacting group, the mean provoking dose of aspirin was 157.4 mg (95% CI 125-189.9 mg), and the mean maximal fall in FEV_1 was −15.5% (95% CI 12.0%-18.9%). Patients with bronchial reactions generally required between 1 and 4 nebulized treatments. After treatment and observation per protocol, non-bronchial reactions rarely warranted repeat dosing. In total only 5 of the 49 reactors (10.2%) needed more than 1 dose of antihistamine or decongestant before proceeding, and none led to cessation of the procedure. One subject required epinephrine and is the only patient who did not complete the protocol.

Within each historical subgroup, class A experienced 5 of 7 reactors for a rate of 71.4%, class B had 9 of 11 (81.8%), class C 19 of 22 (86.4%), and class D 16 of 17 (94.1%) (Figure 1). Five patients within our test group specifically endorsed intubation after ASA and/or NSAID ingestion (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Of this subgroup, all patients experienced a positive reaction during desensitization, 3 with bronchospasm only, 1 with naso-ocular alone, and 1 with both. The mean maximal fall in FEV_1 was −25.2% (95% CI 9.35%-40.9%), which was not significantly greater than that for the overall population ($P = .23$). A variant classification scheme highlighting this subgroup among the others is given in Table E2, available in this article's Online Repository at www.jaci-inpractice.org. An analysis was done to determine whether a relationship existed between the patient's historical reaction time and severity to the observed time to reaction, provoking dose, and fall in FEV_1, respectively; however, no statistically significant correlation was found. We also did not find a statistically significant difference between the patients requiring only 1 day versus 2 to complete the protocol when comparing age, sex, baseline FEV_1, and historical class (data not shown).

For the 9 patients who reported a reaction time greater than 1 hour by history, a traditional approach with 3-hour intervals was utilized. This group experienced 7 of 9 reactors for a 77.8% reaction rate. There were 5 bronchial and 2 naso-ocular reactions. The average time of symptom onset was 70 minutes, with 3 cases exceeding 60 minutes. The longest delay between dosing to reaction was 120 minutes. The mean provoking dose was 123.5 mg. As mandated by the protocol, all of the patients required at least 2 days to finish. All members of this cohort finished the desensitization, and none required greater treatment than available in the office setting.

Importantly, even accounting for the 1 discontinuation, the study group had a 98.2% completion rate. Of 57 procedures, 23 (40.3%) were completed in a single day. Of the 34 patients who required a second day, nearly all were due to lower bronchial reactions (94.1%). Bronchospasm needing 2 or more nebulized treatments and waiting for return of lung function to baseline typically added a minimum of 2-3 additional hours and did not allow adequate observation for completion of the protocol in 1 day during normal clinic hours. Of the patients who completed a second day, none required treatment for further symptoms. Of the single day group, only 8 were so-called silent desensitizations with no observed reaction at any dose. No patient required ED transfer, admission, or intubation.

DISCUSSION

In recent years, there has been significant interest in mitigating one of the most common barriers to widespread use of aspirin desensitization therapy, namely the length of time and resultant expenses required for successful completion. Under the traditional method, the shortest possible time required to attain desensitization was at least 2 full days when accounting for an observation period after the final dose. Any reaction requiring treatment and repetition of the provoking dose inevitably prolongs the process into a third day. At our institution, the hourly dose-escalation protocol has shown to be a safe and effective method of ASA desensitization and has been our default approach since 2005. The vast majority of patients presenting for ASA desensitization have a history of reacting within 1 hour and qualify for this method. Therefore, this protocol could apply to a majority of patients with AERD in clinical practice. Importantly, all subjects desensitized under this system were securely managed regardless of the severity of their previous reaction, including those with a history of intubation.

Under the Joint Task Force proposed 90-minute interval approach, the theoretical minimum time when combining desensitization and a 3 hour observation period comes to 9 hours, assuming no repeat doses or delays whatsoever in patient and provider logistics. This is difficult if not impossible to achieve in the clinical setting and would at best stretch the limits of normal business hours. For the preponderance of patients who are truly ASA sensitive and react as expected, a second visit is virtually assured. In addition to the former, Lee et al published a study on combined intranasal ketorolac and modified oral aspirin challenge as a method for desensitization in AERD.[15] This protocol entailed 4 escalating ketorolac doses followed by oral aspirin challenge and stepwise increases in aspirin up to 325 mg. They reported an average time to completion of 1.9 days for patients receiving ketorolac compared with 2.6 days in those receiving aspirin only under traditional regimen. Although faster than previous protocols, this approach still mandates a minimum of 2 days, and within their experimental group, 17% still needed at least a third clinical visit to finish the procedure. In comparison, patients undergoing our hourly dose-escalation technique averaged 1.6 days with none exceeding 2 days and a substantial percentage being successfully desensitized in one. Furthermore, as patients returning for a second day rarely required active treatment and could be discharged after a relatively brief dosing and observation period, the true clinical time commitment on an hourly basis is likely even lower. Preparation of an intranasal ketorolac spray also adds time and expense to the procedure. In addition, their use of 60 mg doses of aspirin is more challenging in clinical practice. In contrast, all doses used in our protocol need at most 1 division of commonly available aspirin tablets, thus minimizing mistakes in preparation. Although one of the proposed advantages of limiting exposure of the inciting drug to the nasal membranes is a lower risk of systemic reactions, the safety profiles for both the ketorolac and/or aspirin and hourly dose-escalation protocols were similar in that all reactions were treated by clinic personnel without an escalation in the level of care.

The overwhelming majority of desensitizations were performed at the University of Texas Southwestern outpatient allergy clinic. Two patients were brought in under 23-hour observation status because they were receiving care at our

affiliated county hospital and available half-day clinic hours were insufficient to conduct the procedure. These in-hospital cases were performed on the general medical floor by an allergy fellow with standard medications available at bedside. Previously, there was debate over what historical risk factors, if any, warranted in-hospital treatment. However, data published by Williams et al did not show a correlation between the severity of prior reactions and those encountered during an oral aspirin challenge.[16] Indeed, the historical severity and time to reaction in our study population were not predictive of the asthmatic response during controlled desensitization. Furthermore, no recorded reaction has required more treatment than accessible to an outpatient allergy practice. Even our most concerning patients—those with a known history of intubation for AERD—were safely treated in our clinic. For reference, a review of systemic reaction rates with subcutaneous immunotherapy (SCIT) reported in studies from 1995 to 2009 showed that the percentage of systemic reactions per injection with conventional schedules is approximately 0.2%, and 41 fatalities were reported over a 12-year period from 1990 to 2001 in an American Academy of Allergy, Asthma, and Immunology survey.[17,18] Virtually every allergy clinic is equipped to handle anaphylaxis, which is a known complication of subcutaneous immunotherapy. Comparatively, bronchospasm is a common feature of AERD reactions, but an extensive review of the existing literature did not yield any reports of anaphylactic or fatal reactions to aspirin.[19] Epinephrine certainly should be kept on hand in the rare event of overlapping NSAID-induced urticaria and angioedema or severe bronchospasm, but despite the inclusion of hypotension in some of the published literature works, in our clinical practice, we have not encountered the latter when treating AERD. If clinicians are comfortable performing SCIT in the ambulatory setting, we assert that a less hazardous procedure such as aspirin desensitization may be accomplished as well. The impact of dedicated allergy clinic staff in facilitating an organized desensitization should not be underestimated. In our experience, inpatient aspirin desensitizations conducted by hospital personnel inexperienced with the expected reactions can lead to undue stress in both patients and medical staff alike, which further leads to delays in care.

In our study, there were 2 cases in which a bronchial or naso-ocular reaction was not documented within 1 hour of the provoking dose. In one case, a patient developed abdominal pain and nausea within 30 minutes of the 120 mg dose followed by a decrease in FEV_1 minutes at 115 minutes. Although we did not include gastrointestinal manifestations as a sole indicator of a positive reaction, they represent a known component of aspirin hypersensitivity, and this patient very well could have started the reaction 30 minutes after ingestion. The second case involved a mild naso-ocular reaction approximately 2 hours after the 325 mg dose. Our protocol would have repeated the dose before the onset of these symptoms; however, her procedure started later than expected and went past clinic operating hours. Had her first dose started at 08:00, she would have been quickly desensitized on the second day.

As discussed previously, during our 10-year study period, we encountered 1 patient who terminated the protocol. This was a 50-year-old woman with a strong AERD history including 2 intubations. She had severe asthma and reacted on day 1 after the 40 mg dose with bronchospasm responsive to multiple nebulized albuterol treatments. On day 2, she returned with a lower than normal baseline FEV_1, but desensitization proceeded thinking she was in a refractory period. She reacted this time after the 81 mg dose with refractory bronchospasm despite aggressive nebulizer treatments, and a single dose of intramuscular epinephrine was administered with improvement. Repeat desensitization was not attempted. To date, this has been the only patient at our institution not to complete the desensitization procedure regardless of the dosing interval. Although there were not any measured parameters that distinguished her from the rest of the cohort, a recent article by Cahill et al hypothesizes that overproduction of prostaglandin D2, a potent bronchoconstrictor and chemoattractant for eosinophils and basophils, may be associated with a higher likelihood of treatment failure in AERD.[20]

One potential limitation is the retrospective nature of the study, in which patients were identified as having AERD through history alone and not with blinded placebo-controlled challenges. Therefore, it is possible that some of the subjects did not truly have AERD. Reports exist of false-negative aspirin challenges in certain individuals despite a convincing clinical history of aspirin or NSAID sensitivity, though the actual prevalence of these "silent desensitizations" is not known.[21] However, published data provide a pretest probability of positive reaction to aspirin challenge based on the historical reaction to aspirin including whether the patient had a single or multiple reactions to aspirin and/or NSAIDs, and if his or her historical response was severe enough to warrant hospitalization.[14] A single reactor has a pretest probability of 80%. Two or more reactions increase this to 89.4%. Patients with severe enough symptoms that required significant medical intervention up to hospitalization and intubation have a nearly 100% pretest probability. By this method, we were able to group each patient by his or her likelihood of reaction. In our study, 50 of 57 patients had an at least 80% pretest probability. Indeed, there were a higher percentage of bronchial and naso-ocular symptoms with increasing risk groups. As 49 of 57 desensitizations elicited an objective reaction, this would suggest that the vast majority of our patients veritably had AERD. The reasons for a lack of reaction despite clinical history include much smaller starting doses than what they encountered in real-life situations and aggressive use of premedications such as LMDs. From a pragmatic standpoint, placebo-controlled challenges are rarely used to identify patients with AERD in clinical practice.

Another limitation of the data is the inability to determine whether the observed symptoms were in response to the most recent dose, or if they were simply reacting to an earlier one. It is possible that with longer dosing intervals, the mean elapsed time to reaction would be greater, which would reduce the apparent provoking dose. Compared with other data waiting 3 hours between doses, the mean provoking dose of our study is higher (153 mg vs 68 mg), which means that participants could have reacted to the lower dose.[13] However, nearly all of our patients were premedicated with drugs known to attenuate reactions and modify the threshold for reactions to aspirin. Notably, a recent double-blind placebo-controlled study utilizing 4 increasing doses of aspirin every 1.5 hours reported a provoking dose of 287 $\pm$ 161 mg while achieving desensitization in challenge-positive patients with AERD.[22] Our sample size is smaller compared with previously published multiday aspirin desensitization protocols, but nevertheless, there appears to be little difference in regard to the rate of successful desensitization and adverse outcome between these protocols.

Overall, we conclude that patients with a history of reacting to aspirin within 60 minutes from exposure can safely be

desensitized using dose escalation at 60-minute intervals. A significant number of these patients can complete the procedure in a single day, and all within 2 days. We propose a protocol that may be conducted in an outpatient setting that offers substantial time and cost savings for patients, providers, and third-party payors.

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TABLE E1. Results for subgroup with history of intubation after acetylsalicylic acid or nonsteroidal anti-inflammatory drug ingestion

Class	Intubations [%] (n = 5)
Sex	
Male	2 [40]
Female	3 [60]
Age, mean (SD), y	42 (16.5)
LMD use	5 [100]
Observed reaction	
No reaction	0 [0]
Bronchial	3 [60]
Naso-ocular	1 [20]
Bronchial and naso-ocular	1 [20]
Ancillary reaction	
Gastrointestinal	0 [0]
Urticaria	0 [0]
Measured data	
ΔFEV_1, % (95% CI)	−25.2 (−9.3-40.9)
Time to reaction, min (SD)	66 (31.9)
Provoking dose, mg (SD)	259.4 (241.8)
Single day	1 [20]
Completed procedure	4 [80]

CI, Confidence interval; *LMD*, leukotriene-modifying drug; *SD*, standard deviation.
Percentages are based on historical classification.

TABLE E2. Alternative classification system for demographics and outcomes of patients undergoing hourly dose-escalation protocol for aspirin desensitization therapy

Historical class	A [%] (n = 7)	B [%] (n = 33)	C [%] (n = 12)	D [%] (n = 5)	All [%] (n = 57)
Sex					
Male	2 [29]	16 [48]	4 [33]	1 [20]	23 [40]
Female	5 [71]	17 [52]	8 [67]	4 [80]	34 [60]
Age, mean (SD), y	40.2 (18.7)	49.3 (10.0)	51.3 (11.4)	51 (11.8)	48.8 (11.9)
LMD use	6 [86]	32 [97]	12 [100]	5 [100]	55 [96]
Observed reaction					
No reaction	2 [29]	5 [15]	1 [8]	0 [0]	8 [14]
Bronchial only	2 [29]	9 [27]	5 [42]	3 [60]	19 [33]
Naso-ocular only	2 [29]	6 [18]	4 [33]	1 [20]	13 [23]
Naso-ocular and bronchial	1 [14]	13 [39]	2 [17]	1 [20]	17 [30]
Total reactions	5 [71]	28 [85]	11 [92]	5 [100]	49 [86]
Ancillary reaction					
Gastrointestinal	0 [0]	4 [12]	2 [17]	0 [0]	6 [10]
Urticaria	0 [0]	3 [9]	1 [33]	0 [0]	4 [7]
Measured data					
ΔFEV_1, mean % (95% CI)	−15.8 (−3.6-30.4)	−15.2 (−10.9-19.5%)	−13.6 (−8.1-19.1)	−25.2 (−9.35-40.9)	−15.5 (−12.0-18.9)
Time to reaction, min (SD)	41 (21.9)	47.4 (20.2)	52.7 (16.2)	66 (31.9)	50.3 (21)
Provoking dose, mg (SD)	113 (52.9)	145.8 (116.2)	157.5 (84.7)	259.4 (241.8)	152.0 (126)
Single day	3 [43]	14 [42]	5 [42]	1 [20]	23 [40]
Completed procedure	7 [100]	33 [100]	12 [100]	4 [80]	56 [98]

CI, Confidence interval; *LMD*, leukotriene-modifying drug; *SD*, standard deviation.
Class Definitions
A: No history of aspirin and/or nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity.
B: One or more reactions to aspirin and/or NSAIDs not requiring acute care visit.
C: One or more reactions requiring acute care visit.
D: One or more reactions requiring intubation.
All patients were seen for chronic rhinosinusitis with nasal polyposis and asthma. Those in classes B-D reported a history of reactions within 1 hour of acetylsalicylic acid or NSAID ingestion.