

Accepted Manuscript

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Author: Charles F. Schuler IV, James L. Baldwin, Alan P. Baptist

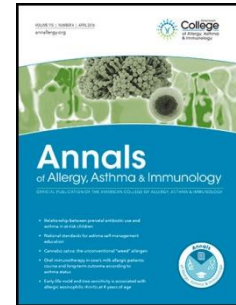
PII: S1081-1206(18)30256-4
DOI: <https://doi.org/10.1016/j.anai.2018.04.005>
Reference: ANAI 2522

To appear in: *Annals of Allergy, Asthma & Immunology*

Received date: 4-1-2018
Revised date: 16-3-2018
Accepted date: 3-4-2018

Please cite this article as: Charles F. Schuler IV, James L. Baldwin, Alan P. Baptist, Factors correlated with repeated aspirin dosing during aspirin desensitization, *Annals of Allergy, Asthma & Immunology* (2018), <https://doi.org/10.1016/j.anai.2018.04.005>.

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Title: Factors correlated with repeated aspirin dosing during aspirin desensitization

Authors: Charles F. Schuler IV, M.D.¹, James L. Baldwin, M.D.¹, Alan P. Baptist, M.D., M.P.H.¹

Affiliations: ¹Division of Allergy and Clinical Immunology, Michigan Medicine, University of Michigan, Ann Arbor, Michigan, USA

Corresponding Author information:

Charles F. Schuler IV, Fellow, Division of Allergy and Clinical Immunology

Address: Domino's Farms, 24 Frank Lloyd Wright Drive, PO Box 442, Suite H-2100, Ann Arbor, MI, 48106-0442

Telephone: 734-936-5634

Fax: 734-647-6263

Email: schulerc@med.umich.edu

Conflict of Interest: None

Funding Source: No direct funding source was used for this research. Charles Schuler's salary is partially supported by federal NRSA grant 5 T32 HL7517-35.

Clinical Trial Registration: Not applicable

Keywords: Aspirin-exacerbated respiratory disease; triad asthma; aspirin desensitization; aspirin challenge; aspirin reactions; asthma; sinusitis; nasal polyps; oral challenge; drug allergy; drug desensitization

Abbreviations/Acronyms: aspirin-exacerbated respiratory disease (AERD), forced expiratory volume in 1 second (FEV1), non-steroidal anti-inflammatory drug (NSAID), leukotriene-modifying drugs (LMDs), Institutional Review Board on Human Subjects (IRB), aspirin (ASA), body mass index (BMI), national health and nutrition examination

survey (NHANES), inhaled corticosteroid (ICS), long-acting beta agonists (LABA), short-acting beta agonists (SABA), leukotriene receptor antagonists (LTRA), national heart, lung, and blood institute (NHLBI), gastro-intestinal (GI), standard deviation (SD).

Word Count: 3037

Figures: 1

Tables: 4

Acknowledgements

The center for consulting for statistics, computing, and analytics research (CSCAR) at the University of Michigan provided initial consultation for our statistical needs.

Abstract: Background: Aspirin desensitization is an appropriate procedure for many patients with aspirin-exacerbated respiratory disease (AERD). Patients can require aspirin re-dosing, which prolongs the desensitization process. The frequency of this is not widely reported, nor is it known which patients will require multiple re-dosing.

Objective: To determine the frequency of and factors associated with repeat aspirin re-dosing during desensitization.

Methods: Charts of aspirin desensitization procedures from 2011-2016 at the University of Michigan

Allergy/Immunology Clinic were reviewed. Reactions with provoking doses and number of dose

repetitions were characterized. Prior AERD history, medical history, medications, and baseline

spirometry were also recorded. Bivariate correlation and multivariate logistic regression were used to

analyze associations between patient characteristics and need for repeated dosing of aspirin.

Results: A total of 84 positive reacting patients during desensitization were found. 33% of these patients required two or more aspirin dose repetitions during desensitization. Requiring two or more repeat doses during desensitization was associated with male gender (odds ratio = 6.194, $p = 0.008$), FEV1 decrease during desensitization (odds ratio = 1.075 per percent point drop, $p = 0.021$), and initial aspirin provoking dose during desensitization of 81 mg or lower (odds ratio = 11.111, $p = 0.003$). No association was found with pre-desensitization medications, asthma severity, AERD duration, or number/character of reported prior aspirin reactions.

Conclusion: During aspirin desensitization for AERD, approximately 1/3 of our patients require multiple repeat doses. Risk factors for multiple repeated doses include male gender, drop in FEV1, and lower aspirin provoking doses during desensitization. This information can help inform which patients might require multiple re-dosing for desensitization.

Introduction

Aspirin exacerbated respiratory disease (AERD), defined as the triad of aspirin (ASA) sensitivity, asthma, and nasal polyposis, has been recognized for almost 100 years^{1, 2}. AERD is a heterogeneous disease process affecting 5-7% of all asthma patients and 14% of severe asthmatics³. Exposure to a COX-1 inhibiting medicine, such as aspirin or another non-steroidal anti-inflammatory drug (NSAID), leads to upper or lower airway symptoms; occasionally, cutaneous or gastro-intestinal symptoms may also be present^{4, 5}. Aspirin desensitization and maintenance is indicated when there is a lack of respiratory disease control with inhaled corticosteroids and leukotriene-modifying drugs (LMDs), poorly controlled chronic rhinosinusitis with nasal polyposis (CRSwNP), or another separate indication for aspirin or NSAID use^{6, 7}.

Aspirin desensitization and maintenance reduces airway inflammation and reduces AERD disease burden⁸⁻¹⁰. There are multiple protocols available for aspirin

desensitization, including oral aspirin protocols and nasal/oral hybrid applications^{4, 6, 11}. Typical oral aspirin desensitization protocols involve administration of escalating aspirin doses in 90 to 180 minute intervals in a controlled setting^{6, 12}. Recent work has focused on reducing the time needed for aspirin desensitization, such as by decreasing the waiting period between doses, decreasing the number of doses given in clinic, or by using nasal applications to shorten the protocol^{4, 13-16}. Some patients react only once, allowing for shorter procedure times given the lack of need for repeated dosing; other patients require dose repetitions to induce tolerance¹⁵. Patient-specific factors associated with the need for repeated aspirin dosing, and thus longer protocols due to repeat aspirin dosing for individual patients, are not clear – if these could be identified clinics may be able to more efficiently allocate space and time for desensitizations.

We hypothesized that during aspirin desensitization, demographic features, provoking dose of aspirin, medications prior to desensitization, and/or severity of aspirin reaction might correlate with the number of repeated doses needed to induce tolerance during aspirin desensitization and thus help identify patients that might require more time to desensitize.

Methods

Patient Population

We conducted a retrospective study of 104 patients who underwent oral aspirin challenge and desensitization between 2010 and 2016 at the University of Michigan Allergy and Immunology clinic. 84 patients had positive reactions and were included in this study; the 20 patients who did not react were not included. The University of Michigan Medical School Institutional Review Board on Human Subjects (IRB) reviewed and approved the protocol. Written informed consent was not required because of the retrospective nature of the study.

Desensitization Protocol

The patients had a history suggestive of AERD (including asthma, aspirin or NSAID sensitivity, and chronic rhinosinusitis with nasal polyposis). The diagnosis of AERD was determined by the treating physician on an individual basis, and subsequent formal aspirin challenge prior to desensitization was at the physician's discretion. Patients were required to record peak flow values at home; stable asthma, denoted by consistent peak flows with no evidence of a current exacerbation, was required prior to desensitization. The oral aspirin challenge followed published protocols and is standardized across the clinic^{6, 12, 16}. All seven allergists who perform aspirin desensitizations in our clinic follow the same standardized protocol. 20 or 40 mg was the initial dose, and this proceeded every three hours through 40, 81, 162, and 325 mg over two to four days (depending on the presence of a reaction at each dose). The 650 mg dose was given at home^{16, 17}. Doses other than these mentioned constituted a

protocol violation. Any positive reaction at a particular dose led to dose repetition after a three-hour waiting period and resolution of the reaction until the reaction would no longer occur in response to the same dose prior to advancing to the next dose. Positive reactions were defined by naso-ocular symptoms (rhinorrhea, congestion, tearing, or periorbital swelling), and/or lower respiratory symptoms consistent with bronchoconstriction (dyspnea or wheezing), and/or an FEV1 drop of at least 15% below baseline⁶. Gastro-intestinal upset and rash/ urticaria were recorded as well but did not alone constitute a positive reaction. Positive reactions as defined above prompted symptomatic treatment according to published protocols^{6, 17}. No pre-treatment was given routinely, and all home medications were continued; all patients were on at least one home medication that included a nasal corticosteroid, oral corticosteroids after surgery, LTRA/zileuton, and/or ICS/LABA. The supervising physician had discretion in treating reactions; albuterol via nebulizer, intranasal/oral antihistamines, decongestants, corticosteroids, anti-emetics, and/or acid-suppressing medications were used as appropriate, and montelukast was uniformly included in treatment of reactions^{6, 11, 17}.

Data Collection

A standardized approach was used to collect pre-specified variables from patients' charts. Demographic data collected included age, gender, race/ethnicity, and BMI. Baseline asthma and AERD variables collected included duration of asthma, duration of AERD, history of nasal polyps and sinus surgery, time from sinus surgery, and presence of atopy. A positive skin test (defined as a wheal of 3 mm greater than the

negative control) to at least one allergen defined atopy¹⁸. Allergens tested were generally trees, grasses, weeds, molds, dust mite, cat, and dog. Further, asthma control as defined by the Asthma Control Test, and baseline spirometry were recorded, with the NHANES III dataset used for normal values¹⁹. When FEV1 is reported in this study, unless otherwise indicated, it refers to the percentage of predicted. Baseline medications assessed included the following: inhaled corticosteroids (ICS), long-acting beta agonists (LABA), short-acting beta agonists (SABA), oral corticosteroids, nasal corticosteroids, leukotriene modifiers (leukotriene receptor antagonists (LTRA) and zileuton), oral antihistamines, tiotropium, and omalizumab. SABA use denotes patients who had clear documentation of an albuterol inhaler available on an as needed basis. We assessed complexity of asthma control quantitatively by characterizing each patient's step of therapy defined by medications generally according to the NHLBI asthma guidelines for patients over 12 years old²⁰. Please see supplemental table 1 for details¹⁵.

All aspirin doses that led to a reaction were recorded for each patient. Each reaction was coded by defining upper symptoms (rhinorrhea, congestion, tearing, periorbital swelling), lower symptoms or signs (dyspnea and wheezing), FEV1 decrease, and/or other (gastro-intestinal upset and rash/urticaria). A positive reaction was defined as the presence of upper respiratory symptoms, and/or lower respiratory symptoms, and/or an FEV1 drop of at least 15% from the baseline value⁶. Other symptoms such as gastro-intestinal upset or rash/urticaria were recorded but not used to define a positive reaction. Dose repetitions were defined as any dose given at the same level due to a positive reaction and after that reaction resolved. These may have

occurred repeatedly at the same dose level or at multiple dose levels (due to reactions at different doses).

Statistical Analysis

SPSS version 22 (IBM) statistical software was used to perform all statistical analysis. Potentially significant ($P < 0.2$) associations between patient characteristics and need for repeated dosing of aspirin were initially evaluated via bivariate correlation and chi-squared analysis. Logistic regression analysis was then performed on all potentially significant variables to create multivariate associations with the number of doses required to induce tolerance.

Results

Patient Characteristics

Table 1 shows the characteristics at baseline for the 84 patients in this study. The ages of the population ranged from 19 – 77 years old. 45% were female. 85% were Caucasian. The mean duration of AERD was 12.8 years, and the mean duration of asthma was 19.3 years. The mean baseline FEV1 percent predicted at the time of challenge was 89%. The mean complexity of therapy for asthma management was 4.2 out of 6, indicating a moderate level of asthma complexity.

Dose Repetition

Of a total of 84 patients who underwent desensitization, 52 (62%) patients required one dose repetition during desensitization, and then did not have another reaction throughout the desensitization protocol; these patients required an average of 3.1 days to finish the protocol. 28 (33%) patients required two or more aspirin dose repetitions for desensitization, as they had multiple reactions requiring dose repetitions to induce tolerance; these patients required an average of 3.8 days to finish the protocol. Four (5%) patients, three of whom reacted at 81 mg and one of whom reacted at 40 mg, did not have doses repeated, which was a violation of the standard protocol; all of these patients had very mild naso-ocular reactions that the treating physicians decided did not warrant re-dosing of the same aspirin dose. These patients finished the desensitization without additional reactions and were analyzed in the group requiring less than two repeated doses of aspirin.

Overall, there were three other protocol violations where patients received a dose other than the standard dosing reported in the methods. One patient received 10 mg as a starting dose, another received 60 mg as an interval dose, and another patient received 120 mg. Of the 28 patients who required two or more repeat doses, two patients reacted at doses over 81 mg. One was the patient mentioned above who was given 120 mg; this patient experienced their initial reaction at that dose. The other patient had an initial reaction at 162 mg.

Two patients required four dose repetitions of aspirin, and one patient required five repetitions before achieving tolerance and finishing the desensitization. The patient who required five dose repetitions had repeated reactions including upper and lower respiratory symptoms, an FEV1 drop of over 15%, and hives. One patient who required four dose repetitions had both upper and lower respiratory symptoms and a non-significant FEV1 drop of 14%. The other patient who required four dose repetitions experienced repeated naso-ocular symptoms. All three patients did finish the desensitization successfully.

Five patients did not finish the desensitization. One patient suffered an episode of late anaphylaxis followed by a myocardial infarction at the 81 mg dose of aspirin (previously reported)²¹. Three patients had persistent rash or abdominal symptoms that did not cease with dose repetitions. These patients achieved maximal doses of 40, 40, and 81 mg. One patient failed to finish the protocol due to social reasons after reacting to 40, 81, and 162 mg. These patients all required at least two repeated doses of aspirin and were included in the analysis as such.

Factors associated with requiring multiple repeat doses of aspirin

Table 2 details baseline characteristics between those patients who required fewer than two doses versus those who required at least two repeated doses during desensitization. Table 3 details desensitization-related characteristics between these same groups. Requiring two or more repeat doses during desensitization was significantly associated on univariate analysis with an aspirin provoking dose less than or equal to 81 mg ($p = 0.011$), higher eosinophil count ($p = 0.021$), and FEV1 percent decrease during desensitization ($p = 0.005$). Requiring two or more repeat doses was also possibly associated with male gender ($p = 0.088$), a reported historical aspirin reaction ($p = 0.08$), and dyspnea during desensitization ($p = 0.054$).

To control for confounding, a multivariate logistic regression model was constructed (see Table 4). Requiring two or more repeat doses during desensitization was significantly associated with male gender (odds ratio = 6.194, $p = 0.008$), FEV1 decrease during desensitization (odds ratio = 1.075 per percent point drop, $p = 0.021$), and initial aspirin provoking dose during desensitization of 81 mg or lower (odds ratio = 11.111, $p = 0.003$). Eosinophilia and duration of AERD were not included in the final model due to a substantial number of cases without those data points. No association was found with pre-desensitization medications, asthma duration, history of nasal polyps, atopic sensitization, wheeze or dyspnea during desensitization, or prior aspirin reactions. In particular, LTRA medication and zileuton use were not significantly different between the two groups when analyzed as separate variables and when analyzed in aggregate (data not shown).

Discussion

Current AERD treatment guidelines recommend aspirin desensitization to impede polyp regrowth and reduce respiratory disease burden. This procedure can be costly and time consuming. During aspirin desensitization for AERD, approximately 1/3 of our patients required multiple repeated doses and, consequently, required more time to finish a protocol. Risk factors that were positively correlated with need for multiple repeated doses include male gender, a large decrease in FEV1 during the challenge, and a lower aspirin provoking doses during desensitization.

The need for re-dosing of aspirin during desensitization may reflect greater aspirin sensitivity as evidenced by the associated lower aspirin provoking dose and greater FEV1 decrease. Uncontrolled asthma was not likely to be a contributor given that all patients were required to have stable peak flows prior to desensitization along with no albuterol use the day prior to desensitization. Furthermore, the complexity of asthma was similar between the two groups, suggesting the FEV1 drop likely does not represent patients with more severe or complex asthma at baseline. In prior work, a lower baseline FEV1 has been correlated with more severe reactions, but this was not directly correlated to the need for repeated dosing¹⁶. Rather, in our cohort, a larger drop in FEV1 and lower aspirin provoking dose likely correlates with a greater aspirin sensitivity given the need for repeated re-dosing of aspirin in these patients in the context of otherwise controlled asthma of similar complexity and similar baseline FEV1.

It is not clear why male gender should correlate with need for multiple dose repetitions of aspirin. While this might also correlate with more severe disease or more sensitivity to aspirin, some prior work has suggested that it is actually women who tend

to have more severe chronic rhinosinusitis with nasal polyps and are more likely to have AERD²². Thus, while women may overall have more difficulty with aspects of AERD, it may be that men are more sensitive at a specific dose level to aspirin, given the need for multiple aspirin re-dosing in men shown here. This cohort of AERD patients had fewer females than other cohorts; prior reports have suggested the rate is approximately 60% women versus 45% here²³. The association of male gender with the need for repeat aspirin dosing may not persist if this analysis were extended to a larger cohort with a sex distribution more representative of the AERD population.

Prior work has focused on the role of prostaglandin D2 overproduction in patients who fail to tolerate aspirin desensitization²⁴. Such patients seemed to have more frequent gastro-intestinal or skin symptoms. Gastro-intestinal and skin-related symptoms were relatively uncommon in this study (see table 3). While there was a higher rate of such symptoms in our patients who required additional doses of aspirin to finish desensitization, the difference between groups was not statistically significant. In addition, eosinophil count was another factor that could not be fully evaluated between these groups. While eosinophil count was appeared significantly different on univariate analysis, the lack of cases where this data point was available made inclusion of this variable in the multivariate model impractical.

Medication use did not seem to be associated with multiple aspirin re-dosing in this study. Leukotriene modifying agents have been shown to decrease the number of patients with bronchospastic reactions during aspirin challenge and desensitization, but perhaps not the magnitude of the FEV1 change²⁵⁻²⁷. However, there was no significant difference between the two groups in this study regarding leukotriene modifying agents.

Not all patients were on these agents; this may limit comparisons to more recent studies where leukotriene use rates are higher^{13, 28}. Antihistamine agents have been implicated in blunting reactions as well, though this is thought to affect naso-ocular reactions more than lower respiratory reactions²⁹. The correlation found here of FEV1 percentage decrease or a lower aspirin initial provoking dose with the need for multiple aspirin dosing does not seem to be associated with leukotriene modifier or antihistamine use, as pre-desensitization medications, either individually or in aggregate, were not associated with the number of repeated aspirin doses required.

Our study has several limitations. First, this was a retrospective study, so only associations can be suggested, not causation, and confounding variables may exist not accounted for here. Another limitation of this study was the lack of routine pretreatment in some patients. All patients, however, were required to have stable asthma (see Methods) for desensitization, and all patients were on at least one controller medication. Another limitation is the fact that some patients who reacted at lower doses of aspirin (at or below 81 mg) did not have repeated reactions and did not thus have a prolonged desensitization; our study does not suggest that all patients who react at lower doses of aspirin will require additional dose repetitions, merely that the prospect may be more likely. Finally, this oral desensitization protocol generally has a longer time to desensitization than other recently published protocols^{13, 28}. Whether our findings are applicable to these protocols is unknown.

This knowledge may help inform patients about the potential length of time required for each individual desensitization by understanding which patients might require multiple re-dosing during oral aspirin desensitization. Counseling male patients

about the potential for a longer protocol requirement prior to an aspirin desensitization protocol might be of use in setting expectations. Counseling patients during desensitization with low aspirin provoking doses or large decreases in FEV1 that the protocol might extend longer than anticipated may also be of benefit in setting patient expectations. While we do not have the data to say whether the factors identified in this study would be relevant to modified nasal/oral desensitization protocols, it is possible that the factors identified here have to do with degree of aspirin sensitivity, which may or may not hold across desensitization protocols^{4, 6, 11}. How often repeated doses are needed during alternative protocols has not been detailed; more work could be done to elucidate whether there are any similar factors that might apply in other contexts.

Overall, this study identifies factors including FEV1 percent decrease, lower aspirin provoking dose, and male gender that correlate with the need for multiple aspirin re-dosing. Some of these factors may be surrogates for individual aspirin sensitivity. This information can be used in counseling patients before and during aspirin desensitization. Patients who may require repeated aspirin dosing can potentially be identified. Medications used prior to desensitization did not seem to have an effect on the need for repeated aspirin dosing. Additional research into optimal aspirin desensitization protocols for AERD patients to individualize each protocol is warranted.

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Figure 1: Graphic count of number of patients versus number of dose repetitions required. Four patients did not have repeat aspirin dosing; these patients had naso-ocular symptoms only and the treating physician decided each could be advanced without dose repetition.

Table 1**Baseline characteristics for all patients**

Patient Characteristic	All Patients (n=84)
Demographic	
Age (mean years [range])	49.5 (19 – 77)
Gender (% female)	45.2
BMI (mean [SD])	29.0 (5.5)
Race (%)	
Caucasian	84.5
Black/African American	7.1
Unknown	8.3
AERD	
Duration of AERD (mean years [SD])	12.8 (15.6)
Nasal sinus surgery (%)	98.8
Time from sinus surgery (median days [interquartile range])	8.0 (3.0 - 30.0)
Presence of historical aspirin reaction (%)	64.3
Medications	
Nasal corticosteroid use (%)	84.5
Inhaled corticosteroid use (% [mean fluticasone µg])	83.3 (438.4)
Leukotriene inhibitor (% LTRA [% zileuton])	72.6 (10.7)
Oral corticosteroid use (% mean mg daily)	19.0 (13.4)
LABA use (%)	76.2
SABA use (%)	84.5
Anti-histamine use (%)	48.8
Omalizumab use (%)	4.8
Tiotropium use (%)	6.0
Asthma/Atopy	
Mean duration asthma (years)	19.3
Atopy presence (%)	78.6
Mean baseline FEV1 (% predicted [SD])	88.7 (17.1)
Asthma Complexity by Step Therapy	4.2
Eosinophil count (10 ³ cells/µL)	0.489

Note: Please [etable](#) 1 for definition of asthma complexity above. Please see methods section for discussion of definition of atopy and normal values used for FEV1. [SABA use denotes patients with clear documentation of an albuterol inhaler prescription.](#)

Table 2

Baseline characteristics for patients requiring < 2 repeat doses versus ≥ 2 repeat doses

Patient Characteristic	< 2 Repeat Doses (n=56)	≥ 2 Repeat Doses (n=28)	P values
Demographic			
Age (mean years [range])	49.5 (19 - 77)	49.6 (31 - 69)	0.943
Gender (% female)	51.8	32.1	0.088
BMI (mean [SD])	29.3 (5.8)	28.5 (5.0)	0.499
Race (%)			
Caucasian	85.7	82.1	0.855
Black/African American	7.1	7.1	
Unknown	7.1	10.7	
AERD			
Duration of AERD (mean years [SD])	12.1 (12.0)	9.6 (9.8)	0.405
Nasal sinus surgery (%)	100.0	96.4	0.155
Time from sinus surgery (median days [interquartile range])	8 (6.5 - 22.5)	8.5 (4.0 - 21.0)	0.583
Presence of historical aspirin reaction (%)	57.1	78.6	0.080
Medications			
Nasal corticosteroid use (%)	82.1	89.3	0.394
Inhaled corticosteroid use (% [mean fluticasone μ g])	85.7 (464.9)	78.6 (421.1)	0.605
Leukotriene inhibitor (% LTRA [% zileuton])	75.0 (7.1)	67.9 (17.9)	0.324
Oral corticosteroid use (% [mean mg daily])	19.6 (12.8)	39.3 (9.1)	0.253
LABA use (%)	76.8	75.0	0.856
SABA use (%)	85.7	82.1	0.670
Anti-histamine use (%)	46.4	53.6	0.537
Omalizumab use (%)	7.1	0.0	0.147
Tiotropium use (%)	8.9	0.0	0.103
Asthma/Atopy			
Mean duration asthma (years)	20.8	15.2	0.181
Atopy presence (%)	77.4	89.3	0.189
Mean baseline FEV1 (% predicted [SD])	88.3 (17.3)	88.2 (16.5)	0.994
Asthma Complexity by Step Therapy (Mean)	4.3	4.1	0.862
Eosinophil count (10^3 cells/ μ L)	0.396	0.680	0.021

425 Note: Please etable 1 for definition of asthma complexity above. Please see methods
426 section for discussion of definition of atopy and normal values used for FEV1. SABA
427 use denotes patients with clear documentation of an albuterol inhaler prescription. P
428 values are bolded for significant ($p < 0.05$) associations.

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Table 3

Desensitization-related characteristics for patients requiring < 2 repeat doses or ≥ 2 repeat doses

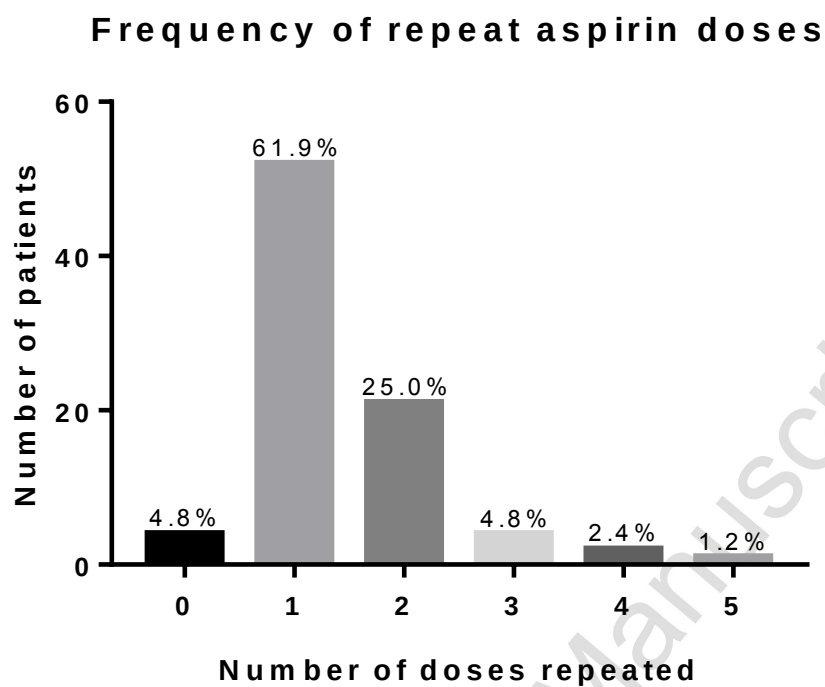
Patient Characteristic	< 2 Repeat Doses (n=56)	≥ 2 Repeat Doses (n=28)	P values
Aspirin Dosing			
Aspirin starting dose (mean mg)	42.0	35.1	0.261
Initial aspirin provoking dose (mean mg [range])	101.7 (10 – 325)	69.2 (40 – 162)	0.013
Initial aspirin provoking dose > 81 mg (%)	32.1	7.1	0.011
Reaction Characteristics			
Percent FEV1 decrease (mean % change [standard deviation, range])	9.7 (9.88, 0 – 40)	16.4 (10.38, 0 – 32)	0.005
Presence of wheezing (%)	19.6	35.7	0.109
Presence of dyspnea (%)	19.6	39.3	0.054
Presence of rhinorrhea (%)	62.5	50.0	0.273
Presence of nasal congestion (%)	67.9	64.3	0.743
Presence of ocular tearing or injection (%)	37.5	35.7	0.873
Presence of periorbital swelling (%)	5.4	3.6	0.717
<u>Presence of gastro-intestinal upset (%)</u>	<u>3.6</u>	<u>10.7</u>	<u>0.200</u>
<u>Presence of rash or urticaria (%)</u>	<u>7.1</u>	<u>10.7</u>	<u>0.582</u>

Note: P values are bolded for significant ($p < 0.05$) associations.

Table 4**Associations with requiring 2 or more repeat doses during aspirin desensitization**

Variable	Odds Ratio	P value
Male gender	6.194	0.008
FEV1 decrease per percentage point	1.075	0.021
Provoking ASA dose of ≤ 81 mg	11.111	0.003
Presence of historical aspirin reaction	3.236	0.076
Omalizumab use	NA	0.999
Tiotropium use	NA	0.999
Wheeze during desensitization	1.435	0.560
Dyspnea during desensitization	2.439	0.208

Note: Patient characteristics associated with requiring two or more dose repetitions during aspirin desensitization. Multivariate logistic regression was used. No association was found with pre-desensitization medications or presence of reported historical aspirin reaction. Eosinophilia and duration of AERD were not included in the final model due to a substantial number of cases without those data points.

447 **Figure 1: Frequency of repeat aspirin doses**

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Supplemental Information

Supplemental Table 1: Asthma step therapy

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Albuterol PRN	Low dose ICS	Low dose ICS plus LABA	Medium dose ICS plus LABA	High dose ICS plus LABA	High dose ICS plus LABA
	or	or	or	or	or
	LTRA	Medium dose ICS alone	Medium dose ICS plus LTRA	High dose ICS plus LTRA	High dose ICS plus LTRA
		or			Either of above with oral steroids
		Low dose ICS plus LTRA			

Supplemental Table 1: The above details the steps of asthma therapy used to grade asthma severity according to the medications taken by the patient at time of desensitization. Please note: Adding an LTRA or anti-cholinergic was used in this study to increase the step level by one. Adding omalizumab was used as equivalent to step six. If a patient was on oral steroids on a rapid taper from polypectomy and not for asthma control this was discounted in the ranking ¹⁵.