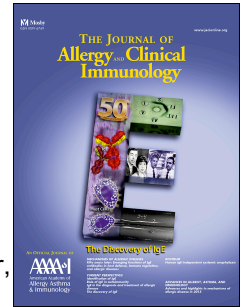


Accepted Manuscript

Safety and outcomes of aspirin desensitization for aspirin-exacerbated respiratory disease: a single center study

Jeremy Waldram, MD, Kristen Walters, MD, Ronald Simon, MD, Katherine Woessner, MD, Jill Waalen, MD, MPH, Andrew White, MD



PII: S0091-6749(17)30841-2

DOI: [10.1016/j.jaci.2017.05.006](https://doi.org/10.1016/j.jaci.2017.05.006)

Reference: YMAI 12823

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 24 June 2016

Revised Date: 14 April 2017

Accepted Date: 3 May 2017

Please cite this article as: Waldram J, Walters K, Simon R, Woessner K, Waalen J, White A, Safety and outcomes of aspirin desensitization for aspirin-exacerbated respiratory disease: a single center study, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2017.05.006.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Safety and outcomes of aspirin desensitization for aspirin-exacerbated respiratory disease: a single center study

Jeremy Waldram, MD,^a Kristen Walters, MD,^a Ronald Simon, MD,^a Katherine Woessner, MD,^a Jill Waalen, MD, MPH,^b Andrew White, MD.^a

From ^athe Department of Allergy and Immunology at Scripps Clinic, San Diego, CA; ^bthe Scripps Translational Science Institute, La Jolla, CA.

Dr. Waalen's work is supported by the Scripps Translational Science Institute's Clinical Translational Science Award UL54 AI108353 from the National Institutes of Health.

Corresponding author: Jeremy Waldram, MD. 3811 Valley Centre Dr, San Diego, CA 92130. Telephone number 323-376-8492. Fax number 858-764-9011. Email address jdwaldram@gmail.com

Abstract

Background: Aspirin desensitization is an effective treatment option for aspirin-exacerbated respiratory disease (AERD). Aspirin desensitization protocol modifications have improved the safety and efficiency of this procedure, yet some providers remain reluctant to perform it.

Objective: The primary objective of this study was to evaluate the safety and outcomes of outpatient aspirin desensitization procedures. A secondary objective was to assess for clinical characteristics that might predict reaction severity during aspirin desensitization.

Methods: Two hundred seventy-five patients underwent aspirin desensitization at Scripps Clinic between January 2009 and August 2015. Baseline patient characteristics and reaction results were analyzed in the 167 patients who reacted during desensitization.

Results: All of the 167 reactors, including 23 who were classified as severe reactors, were successfully desensitized in the outpatient setting. The average desensitization duration among reactors was 1.67 days, and the average duration for GI reactors was 2.29 days. Mean baseline SNOT-22 score was higher in severe reactors compared to non-severe reactors ($p=.05$). Overall, patients on omalizumab had a similar reaction profile to those not on omalizumab.

Conclusions: Most patients undergoing aspirin desensitization will develop symptoms. It remains difficult to predict the severity of these symptoms. However, desensitization can be done safely and efficiently in an appropriately equipped outpatient setting. This treatment option should be made available to all patients with AERD. The SNOT-22 score may be able to predict more severe reactions and merits further study. Eight of the 9 patients on omalizumab reacted during desensitization, suggesting that it does not block reactions during aspirin desensitization.

Clinical implications: Aspirin desensitization is a relatively safe procedure that may be performed in a properly equipped outpatient setting and it is a treatment option that should be made available to all patients with AERD.

Capsule Summary: This study demonstrates that despite the variation in reaction severity among AERD patients undergoing aspirin desensitization, it may be accomplished safely and efficiently in an outpatient setting.

Key Words: AERD, aspirin-exacerbated respiratory disease, asthma, chronic rhinosinusitis, aspirin desensitization

Abbreviations used: AERD (aspirin-exacerbated respiratory disease), CRS (chronic rhinosinusitis), COX-1 (cyclooxygenase-1), NSAIDs (nonsteroidal anti-inflammatory drugs), ASA (aspirin), PGE₂ (prostaglandin E₂), cysLTs (cysteinyl leukotrienes), FEV₁ (forced expiratory volume in 1 second), LTMD (leukotriene

modifying drug), GI (gastrointestinal), PNIF (peak nasal inspiratory flow), ACT (asthma control test),
SNOT-22 (sino-nasal outcome test), IM (intramuscular)

Introduction:

Aspirin-exacerbated respiratory disease (AERD) is characterized by chronic rhinosinusitis (CRS), nasal polyposis, asthma, and intolerance to cyclooxygenase-1 (COX-1) inhibiting medications [1-3]. The estimated prevalence among asthmatics is 7%, and the prevalence is even higher in severe asthmatics and in those with CRS and nasal polyps [4]. Patients with AERD experience various naso-ocular and/or lower airway symptoms following ingestion of COX-1 inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs). Less commonly, patients experience nausea, vomiting, abdominal pain, urticaria/angioedema, and rarely, hypotension.

These adverse reactions to aspirin (ASA) and/or other NSAIDs are secondary to inhibition of COX-1 rather than an IgE-mediated phenomenon. The exact pathophysiology of AERD is not entirely understood, but involves disruption of arachidonic acid metabolism, resulting in a depletion of anti-inflammatory prostanoids, particularly prostaglandin E_2 (PGE₂), and an overproduction of pro-inflammatory cysteinyl leukotrienes (cysLTs). The ingestion of a COX-1 inhibitor exacerbates this dysregulation and causes further reduction in PGE₂, which normally functions as a “brake” mechanism on 5-lipoxygenase activity. This enhances type 2 inflammation via the actions of mast cells, eosinophils, platelets, and other mediators [5-7].

ASA challenge is considered the “gold standard” for diagnosing AERD. Once the diagnosis is confirmed with a positive challenge, management involves avoidance of all COX-1 inhibiting drugs or ASA desensitization followed by continuous ASA therapy. ASA challenge and desensitization are usually done

simultaneously in these patients and ASA desensitization will be used hereafter to refer to this combined procedure.

ASA desensitization is a provocative procedure and will likely induce symptoms in a patient with AERD. Therefore, safety is an important consideration when performing ASA desensitization in AERD. Certain risk factors have been linked to severe bronchial reactions during ASA desensitization, including no use of a leukotriene-modifying drug (LTMD) at the time of desensitization, baseline forced expiratory volume in 1 second (FEV₁) less than 80% predicted, and history of a prior emergency department visit for asthma [8]. Atopic status, gender, age at disease onset, systemic corticosteroid dependence, and the type or severity of the historical reaction to ASA/NSAIDs have not been shown to be associated with severity.

Over the years, modifications to ASA desensitization protocols have enhanced its safety. One of the best examples of this is the use of LTMDs, such as montelukast, for at least one week prior to ASA desensitization [9-11]. LTMDs reduce the intensity of the reactions to ASA, especially in the lower airways, but typically do not block the reactions completely, which is essential as one goal of desensitization is to confirm the diagnosis of AERD [9-11]. Another safety modification to the desensitization protocol was the addition of intranasal ketorolac prior to oral ASA (Figure 1). The addition of intranasal ketorolac significantly reduces the mean percent decline in FEV₁ measurement as well as decreasing the risk of extra-pulmonary reactions, such as laryngospasm and gastrointestinal (GI) symptoms [12].

Despite these modifications that have enhanced safety, a recent survey of ASA desensitization practices among allergists and fellows-in-training in the United States indicated that only 62.5% of respondents perform ASA desensitization for AERD [13]. Of those who do not, nearly 28% do not refer the patient to an allergist who does. Safety concerns, logistics of nursing care, and lack of exposure to the procedure

during fellowship training were listed as the primary deterrents to the use of desensitization in AERD.

This survey highlighted the need for more safety and outcomes data for ASA desensitization in AERD.

Over the past decade our group has successfully performed hundreds of outpatient ASA desensitization procedures without any serious complications, hospitalizations, or deaths. As a result of this familiarity with ASA desensitization, we sought to address some of the concerns highlighted in the survey and to supply readers with our outcomes and safety data by conducting a 5-year review of our ASA desensitization procedures. Additionally, we analyzed various patient characteristics to determine which factors, if any, may influence or predict reaction severity.

Methods:

This was an IRB-approved review of all ASA desensitization procedures performed at Scripps Clinic from January 2009 through August 2015. A total of 275 procedures were performed during that time period. Of those, 71 were excluded from chart review due to missing charts (n=10), patients declining participation in research (n=2), or use of an altered desensitization protocol (n=59). This latter group included 3 patients who did not receive ketorolac per patient preference, and 56 patients who participated in research projects that involved alterations of the standard desensitization protocol used at Scripps Clinic. The goal of the analysis was to gather information regarding outcomes of desensitization using the specific protocol described in Figure I. Therefore, patients who did not undergo this protocol were excluded.

The charts of the remaining 204 patients were reviewed in detail. Of the 204 patients, 167 reacted during ASA desensitization and this group became the focus of our analysis.

Baseline patient characteristics, such as age, sex, ethnicity, medication use, FEV₁, and symptom scores were reviewed. The reactors were then analyzed to assess the type and frequency of induced reactions, treatment provided, and changes in objective measures collected during the procedures. Basic statistical

calculations were performed to determine whether any baseline characteristic was predictive of reaction severity during desensitization and to detect differences between reactions to nasal ketorolac and those to oral aspirin.

Results:

Patient Demographics

Baseline patient characteristics for 167 reactors are presented in Table I. Mean age was 47.2 years and there were nearly twice as many females as males. Mean baseline FEV₁ was 86% of predicted (range: 37-114%). Mean peak nasal inspiratory flow (PNIF) rate was 155.7 L/min. The majority of patients (73.1%) had a history of positive skin tests to inhalant allergens. Of those, 14.4% were receiving allergy immunotherapy at the time of desensitization. The average number of sinus surgeries was 2.9 (range: 0-12). Twenty-two patients (13.2%) had previously undergone at least one ASA desensitization. The vast majority of patients (98.8%) were on a LTMD at the time of desensitization, with montelukast being the most common. Only 4.5% of patients were on omalizumab at the time of desensitization, while 26.3% were on systemic corticosteroids.

Symptom Scores

We recently began collection of the Asthma Control Test (ACT) and Sino-Nasal Outcome Test (SNOT-22) prior to ASA desensitization. Therefore, only 45 patients had these baseline symptom scores measured during the above review period. Among these patients, the average ACT score was 21.8 (range: 11-25). The average SNOT-22 score was 28.7 (range: 2-76).

Reaction Characteristics

Table II contains data on reaction characteristics. The data is separated into three columns to define ketorolac reactors, ASA reactors, and all reactors. Some patients reacted to both medications during the

procedure and were included under both columns. More patients (88%) reacted to ketorolac than to ASA (38.9%). Most ketorolac reactors (53.1%) reacted to the 7.58 mg dose, while most ASA reactors (83.1%) reacted to one of the 60 mg doses.

Reaction Types

Reactions were categorized as follows:

- Naso-ocular: Conjunctival injection, tearing, rhinorrhea, nasal congestion, sneezing, pruritus
- Classical: Naso-ocular symptoms and a $\geq 15\%$ decline in FEV_1
- Bronchial: Isolated decline in $FEV_1 \geq 15\%$
- Laryngeal: Symptoms involving the posterior oropharynx or larynx (i.e. throat tightness)
- GI: Nausea, vomiting, gastric pain or heartburn
- Cutaneous: Urticaria, angioedema, pruritus or erythema

Isolated naso-ocular reactions represented 56.5% of the reactions to nasal ketorolac, followed by classical (22.4%), mixed (17.7%), and bronchial (2.7%) reactions. A single patient had an isolated laryngeal reaction to ketorolac. No isolated GI reactions and no cutaneous reactions to ketorolac occurred. Isolated naso-ocular reactions were the most common reactions to ASA as well, comprising 26.2% of the reactions. Classical (23.1%), bronchial (20.0), and mixed (17.0%) reactions were also common. Isolated laryngeal, GI, and cutaneous reactions each occurred less than 5% of the time.

Several patients had mixed reactions, meaning they met the criteria for at least 2 of the categories described above. The most common mixed reaction among ketorolac reactors was naso-ocular combined with laryngeal. Among ASA reactors, naso-ocular with bronchial, classical with GI, and bronchial with laryngeal reactions were most common. Looking at all reactors, naso-ocular (43.1%), mixed (32.3%), or classical (18.6%) reactions occurred over 90% of the time. Isolated bronchial,

laryngeal, or cutaneous reactions were far less common. There were no isolated GI reactions when all reactors were analyzed together.

Changes in PNIF and FEV₁

The mean drop in PNIF was 32.4% and 23.0% in ketorolac and ASA reactions, respectively ($P = .02$). On average, FEV₁ declined by 11.0% (range: 0-63%) and 12.3% (range: 0-45%) in ketorolac and ASA reactions, respectively, but this difference did not reach statistical significance ($P = .51$).

Treatments Utilized During Desensitization

Table III summarizes the treatments administered for reactions during ASA desensitization. The reactors are divided into three columns to highlight treatments required for ketorolac reactors, ASA reactors, and all reactors. Patients reacting to intranasal ketorolac required 3.1 treatments, on average, compared to 2.2 for those reacting to oral ASA ($p = .01$). Considering all reactors together, the average treatment requirement per patient was 3.6.

Regarding ketorolac reactors, 74.8% received at least one antihistamine. Nasal decongestants (52.4%) and bronchodilators (40.8%) were also frequently used. GI medications were prescribed for 7.5% of all ketorolac reactors. A small percentage of ketorolac reactors required intramuscular (IM) epinephrine. Up to 15% of all ketorolac reactors did not receive any form of treatment despite having a documented reaction.

ASA reactors were most commonly treated with a bronchodilator (56.9%), followed by antihistamines (52.3%), nasal decongestants (18.5%), and GI medications (10.8%). No ASA reactor required IM epinephrine and 10.8% of aspirin reactors did not receive any treatment.

The final column in table III looks at treatment frequency among all reactors. Overall, antihistamines were used in 76% of patients. Other commonly used medications were bronchodilators, nasal

decongestants, and GI medications. Overall, 21 (12.6%) patients did not require any form of treatment despite objective reactions.

Length of Desensitization

The average length of desensitization among all reactors was 1.67 days (range: 1-4 days). Among those who had a GI reaction, the average length of desensitization was 2.29 days (range: 1.5-4 days) ($P = 0.006$).

Severe Reactions

Twenty-three patients (13.8%) had severe reactions during desensitization. We defined a severe reactor as follows:

- Required IM epinephrine and/or
- Required ≥ 3 doses of a β_2 -agonist and/or had an FEV₁ drop of $\geq 30\%$

Four patients required IM epinephrine and 21 required ≥ 3 doses of a β_2 -agonist and/or had an FEV₁ drop of $\geq 30\%$. Two of the patients requiring IM epinephrine also met the other criterion. Table IV provides data for each patient requiring epinephrine administration during the desensitization. All 4 patients received epinephrine as treatment for ketorolac reactions.

GI Reactors

Of the 17 patients who had a GI reaction, 10 had the reaction to nasal ketorolac, 6 to oral ASA, and a single patient had a GI reaction to both ketorolac and ASA. Eight of the 17 (47%) reported having had a historical GI reaction upon ASA or NSAID ingestion in the past.

Predictive Risk Factors

The final analysis performed attempted to identify whether any baseline characteristics were predictive of a severe reaction (Table V). Severe reactors, as defined above, were compared to those who did not have a severe reaction. Severe reactors had a higher mean baseline SNOT-22 score compared to non-severe reactors ($p=.05$), and may be able to predict severe reactions, but only 45 of 167 participants had a baseline SNOT-22 score. Patients on systemic corticosteroids at the time of desensitization were more likely to have a severe reaction. The time interval between the most recent sinus surgery and ASA desensitization was not found to be predictive of a severe reaction, and that time interval did not correlate with the patient's baseline SNOT-22 score.

Omalizumab Use During Desensitization

Eight of the 167 (4.8%) reactors were receiving omalizumab during ASA desensitization. Of the 37 non-reactors, only 1 was on omalizumab therapy. Average baseline FEV₁ and PNIF among these patients was 2.79 L, 85.4% of predicted and 166.9 L/min, respectively. These measurements were comparable to the patients in this study who were not receiving omalizumab. However, the average number of sinus surgeries (5.1) prior to desensitization was higher in patients on omalizumab compared to all reactors (2.9). Fifty percent of the patients on omalizumab experienced a decline in FEV₁ $\geq 15\%$. There was no difference in the number of treatments received for patients on omalizumab versus those not on anti-IgE therapy. Average length of desensitization was slightly higher in this subset of patients at 1.8 days compared to 1.67 days for all reactors. None of the patients receiving omalizumab were severe reactors.

Discussion:

ASA desensitization followed by daily ASA treatment has long been regarded as an effective treatment modality in AERD. Various safety measures have been implemented into ASA desensitization protocols to mitigate the risks inherent in a provocative challenge. However, despite the efficacy and improved safety and efficiency of ASA desensitization, a recent survey found that safety and logistical concerns

deter many providers from using ASA desensitization in the management of AERD [13]. Our current study helps to address these issues and also highlights other features relevant to ASA desensitization in AERD.

Using criteria consistent with higher severity of reactions, we found that nearly 14% of patients undergoing ASA desensitization were classified as severe reactors. We also described 4 patients who received IM epinephrine during desensitization. These patients were not hypotensive nor demonstrated other findings suggestive of an anaphylactic reaction. Rather, it was the combination of symptoms (usually laryngospasm and/or GI symptoms) in light of the entire clinical course that prompted the supervising allergist to use epinephrine to more rapidly resolve the reaction. The percentage of severe reactions is a reminder that these procedures are not without risk and should be performed with proper precautions in place. Yet, desensitization was successfully performed in an outpatient setting in 100% of the patients, including severe reactors.

It would certainly be helpful to accurately predict reaction severity based on baseline patient characteristics, but this proves to be difficult. A high SNOT-22 score may be predictive of reaction severity, but this finding requires further study given the smaller numbers of SNOT-22 scores that were collected during the review period. However, it is reasonable to conclude that patients with more active inflammation, particularly of the upper airway, are more likely to experience a significant reaction with COX-1 inhibition.

Despite previous findings by other authors [8], we did not see a correlation between FEV₁ and reaction severity. This potential association may have been missed in our study due to the widespread use of LTMD drugs in our patients. The average baseline FEV₁ measurement among our patients was relatively high at 86% of predicted and nearly all were treated with a LTMD prior to and throughout desensitization, which has been shown to decrease bronchial reaction severity [9-11]. We also did not see a correlation between age and reaction severity as seen in prior studies [8, 14] However, it is

important to point out that the definition of a “severe reaction” is arbitrary, and is not necessarily consistent across different studies.

This study addresses an important safety issue, which is the development of GI symptoms during desensitization. In our experience, GI reactions during desensitization can be severe and frequently prolong desensitization. Half of the GI reactors in our study had no reported historical GI reaction to ASA or other NSAID. Thus, in this group of GI reactors, a history of previous GI reaction may predict a similar reaction during desensitization, but many patients will experience a GI reaction for the first time during their desensitization. In our series, 5.3% (9/167) had a GI reaction in the absence of a history. This requires some degree of caution in terms of protocol choice. A rapid protocol may lead to the administration of an additional dose of medication while a reaction is already progressing, which could lead to a more significant GI reaction.

As mentioned previously, one of the other common deterrents to performing ASA desensitization is logistics, including the time commitment required from both patients and providers. Balancing efficiency with safety is certainly an important consideration in ASA desensitization. A recent publication by Chen et al. proposed an hourly dose-escalation protocol with an average desensitization length of 1.60 days in their 57 patients [15]. This average included 9 patients who had a silent desensitization, which requires less time to perform. In our study, patients required an average of 1.67 days to complete desensitization, and this number did not include any non-reactors. Furthermore, this number was reduced to an average of 1.60 days when excluding GI reactors.

A faster protocol may be useful in some patients, but selecting which patients are appropriate candidates remains problematic. We did have a small percentage of patients (12.6%) with only mild reactions during desensitization and no need for treatment, which may make them suitable candidates for more rapid desensitization protocols. However, given the difficulty in predicting reaction severity,

and the possibility of dose stacking, the hourly dose-escalation protocol will need to be approached with caution.

Our study addresses another important topic in ASA desensitization in AERD, which is the role of omalizumab. A few case reports suggest a potential benefit of omalizumab use during ASA desensitization. In a small total number of AERD patients who received omalizumab treatment during ASA desensitization, respiratory symptoms were significantly reduced or even absent following provocation with oral ASA [16-18]. Omalizumab was discontinued in some of these patients and subsequent ASA challenges were able to elicit typical ASA-provoked symptoms. A recent double-blind randomized trial of AERD patients undergoing ASA desensitization while on omalizumab also showed attenuation of ASA-induced respiratory reactions as compared to placebo [19]. These authors suggest that omalizumab may be able to restore ASA tolerance without the need for ASA desensitization. Yet, if omalizumab can truly diminish the response to ASA, it may introduce diagnostic uncertainty in those who do not react.

However, in our study, we did not find any clear difference in reaction type or severity among those on omalizumab compared to those not on it during the time of ASA desensitization. Furthermore, all 8 patients in our study had objective upper and/or lower airways reactions that did not appear to be blunted by the medication. Our data does not support the findings suggested by recent case reports. It is the authors' opinion that omalizumab remains an option for AERD patients who are unable to complete ASA desensitization or continue to have poorly controlled symptoms following desensitization. However, given the small number of patients on omalizumab in our study, more studies will need to be conducted to determine whether any true benefit may be obtained from using omalizumab during, or in place of, ASA desensitization.

In summary, the safety and efficiency of in-office oral ASA desensitization have improved and will likely continue to improve, thus making it a viable option for patients with AERD. The consistent theme of this, and other studies of ASA desensitization is that the reactions, even when more severe, are able to be managed in an outpatient setting. There may be circumstances that make it difficult for individual offices to perform ASA desensitization, but the opportunity to discuss this treatment option should be made available to each patient with AERD. Unfortunately, it is still difficult to predict who will have minimal symptoms and thus could be eligible for a faster dosing protocol, or who will have more severe symptoms and require a multi-day desensitization. Developing biomarkers or clinical scores to predict desensitization reactions are ideal targets for future study.

References:

1. Samter M, Beers RF Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med.* 1968; 68:975-983.
2. Szczeklik A, Nizankowska-Mogilnicka E, Sanak M. Hypersensitivity to aspirin and non-steroidal antiinflammatory drugs. In: Adkinson N Jr, Bochner B, Busse W, Holgate S, Lemanske R Jr, Simons F, editors. *Middleton's Allergy: Principles and Practice.* 7th ed. Philadelphia: Elsevier; 2014. p. 1227-43.
3. Stevenson DD. Aspirin and NSAID sensitivity. *Immunol Allergy Clin North Am* 2004; 24:491-505.
4. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature. *J Allergy Clin Immunol.* 2015; 135(3):676-81.
5. Fischer AR, Rosenberg MA, Lilly CM, Callery JC, Rubin P, Cohn J, et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. *J Allergy Clin Immunol* 1994; 94:1046-56.
6. Liu T, Laidlaw TM, Katz HR, Boyce JA. Prostaglandin E2 deficiency causes a phenotype of aspirin sensitivity that depends on platelets and cysteinyl leukotrienes. *Proc Natl Acad Sci* 2013; 110:16987-16992.
7. Choi JH, Kim JH, Park HS. Upper airways in aspirin-exacerbated respiratory disease. *Curr Opin Allergy Clin Immunol* 2015; 15:21-26.
8. Hope AP, Woessner KA, Simon RA, Stevenson DD. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2009; 123:406-10.
9. Dahlen B. Treatment of aspirin-intolerant asthma with antileukotrienes. *Am J Respir Crit Care Med* 2000; 161(Suppl):S137-41.
10. Berges-Gimeno MP, Simon RA, Stevenson DD. The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions. *Clin Exp Allergy* 2002; 32:1491-6.
11. White AA, Ludington E, Mehra P, Stevenson DD, Simon RA. Effect of leukotriene modifier drugs on the safety of oral aspirin challenges. *Ann Allergy Asthma Immunol* 2006; 97:688-93.
12. Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon RA, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2010; 105:130.

13. Waldram JD, White AA. A survey of aspirin desensitization practices among allergists and fellows in training in the United States. *J Allergy Clin Immunol Pract* 2016; 4:1253-1255.
14. Dursun AB, Woessner KA, Simon RA, Durdu K, Stevenson DD. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol* 2008; 100:420-425.
15. Chen JR, Buchmiller BL, Khan DA. An hourly dose-escalation desensitization protocol for aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2015; 3:926.
16. Aksu K, Kurt E. Aspirin tolerance following omalizumab therapy in a patient with aspirin-exacerbated respiratory disease. *Allergol Immunopathol (Madr)* 2013; 41(3):208-10.
17. Bobolea L, Barranco P, Fiandor A, Cabañas R, Quirce S. Omalizumab: a potential new therapeutic approach for aspirin-exacerbated respiratory disease. *J Investig Allerg Clin Immunol* 2010; 20(5):448-9.
18. Bergmann KC, Zuberbier T, Church MK. Omalizumab in the treatment of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2015; 3(3):459-60.
19. Lang DM, Aronica MA, Maierson E, Wang XF, Vasas DC, Hazen S. Omalizumab Inhibits Aspirin-Provoked Respiratory Reaction in Patients with Aspirin Exacerbated Respiratory Disease. *J Allergy Clin Immunol*. 2016; 137(2, Suppl.): AB91.

Figure Legends:**Figure I. Nasal Ketorolac and Oral Aspirin Challenge Protocol.**

[†]If no reaction occurs within 3 hours after 325 mg dose, consider it a negative challenge.

- a. After reactions are treated and resolve, continue next scheduled ketorolac dose OR repeat oral provoking aspirin dose.
- b. Desensitization is complete after 325 mg of aspirin.
- c. Patient should take 650 mg of aspirin that evening then continue 650 mg twice daily as their continuous aspirin dose until further instructed.

Table Legends:**Table I. Baseline Patient Characteristics.**

Abbreviations: SD (standard deviation); N (number); FEV₁ (forced expiratory volume in 1 second); PNIF (peak nasal inspiratory flow); ACT (Asthma Control Test); SNOT-22 (Sino-Nasal Outcome Test); LTMD (leukotriene modifying drug); LTRA (leukotriene receptor antagonist)

*45 patients had baseline SNOT-22 and ACT scores

Table II: Reaction characteristics for positive intranasal ketorolac and oral aspirin challenges.

Abbreviations: N (number of patients); PNIF (peak nasal inspiratory flow); SD (standard deviation); FEV₁ (forced expiratory volume in 1 second); NO (naso-ocular); GI (gastrointestinal); LTMD (leukotriene modifying drug); IV (intravenous)

^a Nausea, vomiting, gastric pain or heartburn

^b Urticaria, angioedema, pruritus or erythema

^c Mixed reaction means the patient experienced a combination of reaction types

*p-value .02

**p-value .51

Table III. Treatments utilized during reactions to intranasal ketorolac and aspirin challenges.

Abbreviations: N (number of patients); GI (gastrointestinal); H2 (histamine 2 receptor); LTMD (leukotriene modifying drug); IV (intravenous)

*Each patient may have received more than one type of medication within a medication class (i.e. nasal and ocular antihistamines, for example), so the number of specific medications within each medication class will not necessarily add up to the number of patients treated with that medication class.

Table IV. Characteristics of those treated with intramuscular epinephrine during desensitization.

Abbreviations: LTMD (leukotriene-modifying drug); FEV₁ (forced expiratory volume in 1 second); PNIF (peak nasal inspiratory flow); GI (gastrointestinal)

Table V. Reaction severity and baseline patient characteristics.

Abbreviations: SNOT-22 (Sino-Nasal Outcome Test); SD (standard deviation); FEV₁ (forced expiratory volume in 1 second); PNIF (peak nasal inspiratory flow); ACT (Asthma Control Test); ASA (aspirin)
*by Fisher's exact test (for proportions) or Wilcoxon rank sum test for (continuous variables).

1 Table I. Baseline Patient Characteristics.

Age, mean (SD) [range], y	47.2 (11.7) [19-81]
Sex	
Male, N (%)	63 (37.7)
Female, N (%)	104 (62.3)
Ethnicity	
Caucasian, N (%)	107 (64.1)
African-American, N (%)	3 (1.8)
Hispanic, N (%)	6 (3.6)
Asian, N (%)	1 (0.6)
Unknown, N (%)	50 (29.9)
Number of sinus operations, mean (SD) [range]	2.9 (2.2) [0-12]
Baseline FEV ₁ , mean (SD) [range], L	2.89 (0.76) [1.25-5.27]
Baseline FEV ₁ , mean (SD) [range], % predicted	86.0 (14.6) [37-114]
Baseline PNIF, mean (SD) [range], L/min	155.7 (49.9) [50-350]
Baseline ACT score*	21.8 (3.9) [11-25]
Baseline SNOT-22 score*	28.7 (21.0) [2-76]
Positive skin test to aeroallergens, N (%)	122 (73.1)
Active allergen immunotherapy, N (%)	24 (14.4)
LTMD use, N (%)	165 (98.8)
LTRA	
Montelukast	152 (91.0)
Zafirlukast	7 (4.2)
Zileuton	1 (0.6)
Zileuton and montelukast	5 (3.0)
Omalizumab use, N (%)	8 (4.5)
Systemic corticosteroid use, N (%)	44 (26.3)
Previous aspirin desensitization, N (%)	22 (13.2)

1 Table II: Reaction characteristics for positive intranasal ketorolac and oral aspirin challenges.

Characteristic	Ketorolac reactor N = 147 (88.0%)	Aspirin reactor N = 65 (38.9%)	All Reactors N = 167
Most common provoking dose (mg)	7.58	60	n/a
PNIF mean % decrease, (SD) [range]	32.4 (26.1) [0-100]*	23.0 (28.2) [0-100]*	29.5 (27.0) [0-100]
FEV1 mean % decrease, (SD) [range]	11.0 (14.0) [0-63]**	12.3 (10.4) [0-45]**	11.4 (13.0) [0-63]
Type of reaction, N (%)			
NO	83 (56.5)	17 (26.2)	72 (43.1)
Classical	33 (22.4)	15 (23.1)	31 (18.6)
Bronchial	4 (2.7)	13 (20.0)	6 (3.6)
Laryngeal	1 (0.7)	2 (3.1)	2 (1.2)
GI ^a	0 (0.0)	3 (4.6)	0 (0.0)
Cutaneous ^b	0 (0.0)	3 (4.6)	2 (1.2)
Mixed ^c	26 (17.7)	11 (17.0)	54 (32.3)

1 Table III. Treatments utilized during reactions to intranasal ketorolac and aspirin challenges.

Treatments received*	Ketorolac reactor N = 147 (88.0%)	Aspirin reactor N = 65 (38.9%)	All Reactors N = 167
Antihistamine, N (%)	110 (74.8)	34 (52.3)	127 (76.0)
Oral/Parenteral	106	33	124
Nasal	63	9	71
Ocular	17	4	21
Bronchodilator, N (%)	60 (40.8)	37 (56.9)	85 (50.9)
Beta-2 agonist	56	36	82
Racemic epinephrine	19	7	23
Nasal decongestant, N (%)	77 (52.4)	12 (18.5)	84 (50.3)
GI, N (%)	11 (7.5)	7 (10.8)	18 (10.8)
Antiemetic	5	5	9
Proton pump inhibitor	0	2	2
H2 blocker	8	4	12
Antacid	6	2	7
Misoprostol	3	1	4
LTMD, N (%)	4 (2.7)	5 (7.7)	9 (5.4)
Systemic corticosteroid, N (%)	8 (5.4)	2 (3.1)	10 (6.0)
Oral	3	1	4
Parenteral	5	1	6
Systemic epinephrine, N (%)	4 (2.7)	0 (0)	4 (2.4)
Other, N (%)	9 (6.1)	3 (4.6)	12 (7.2)
IV fluids	4	2	6
Nasal saline	1	0	1
Nasal corticosteroid	2	0	2
Benzodiazepine	1	0	1
Viscous lidocaine	1	0	1
Acetaminophen	0	1	1
None, N (%)	21 (14.3)	7 (10.8)	21 (12.6)
Total, mean (SD) [range]	3.1 (2.5) [0-16]	2.2 (2.0) [0-11]	3.6 (2.4) [0-18]

Table IV. Characteristics of those treated with intramuscular epinephrine during desensitization.

Age, Sex	LTMD	Systemic steroids	Baseline FEV1 % predicted	Baseline NIF	Reaction Description	% drop in NIF	% drop in FEV1
73, M	y	y	89	100	bronchial + severe laryngospasm	0	63
55, M	y	n	82	70	bronchial + severe GI symptoms	14	7
55, M	y	y	88	230	classical + severe GI symptoms	52	51
59, F	y	y	85	110	classical + severe laryngospasm	27	27

1 **Table V. Reaction severity and baseline patient characteristics**

Characteristic	No Severe Reaction	Severe Reaction	p*
Baseline SNOT-22 Score, Mean (SD)	26.1 (20.2)	42.7 (20.7)	.05
Baseline FEV1, Mean (SD)	2.9 (0.8)	2.9 (0.7)	.97
Baseline FEV1-predicted, Mean (SD)	85.8 (14.9)	87.1 (12.1)	.70
Baseline PNIF, Mean (SD)	155.3 (49.6)	158.2 (53.9)	.81
Baseline ACT, Mean (SD)	22.2 (3.7)	20.0 (4.7)	.18
Active allergen immunotherapy, N (%)	23/144 (16.0)	1/22 (4.4)	.20
Systemic Corticosteroid Use, N (%)	33/144 (22.9)	11/23 (47.8)	.01
Number of sinus operations, Mean (SD)	3.0 (2.3)	2.1 (1.2)	.07
Atopy, N (%)	105/140 (75.0)	17/23 (73.9)	.99
Age (years), N (%)			
<30	10/144 (6.9)	1/23 (4.4)	.92
30-40	29/144 (20.1)	6/23 (26.1)	
>40	105/144 (72.9)	16/23 (69.6)	
Interval between sinus surgery and ASA desensitization, N (%)			
≤ 12 months	81/133 (60.9)	12/19 (63.2)	.99
> 12 months	52/133 (39.1)	7/19 (36.8)	
Medications			
Zileuton N (%)	6/144 (4.2)	0/23 (0)	.41
Singulair, N (%)	131/144 (91.0)	21/23 (91.3)	.99
Xolair, N (%)	8/144 (5.6)	0/23 (0)	.60
Singulair + Zileuton	5/144 (3.5)	0/23 (0)	.47
Zafirlukast	7/144 (4.9)	0/23 (0)	.35

2

3

4

Figure I. Nasal Ketorolac and Oral Aspirin Challenge Protocol.

Time	Dose	
Day 1		
8:00 AM	1 spray ketorolac (1 spray in one nostril)	<i>To prepare nasal ketorolac:</i> 1. Take ketorolac (60mg/2mL) and mix with preservative-free normal saline (2.75 mL). 2. Place combined solution in a nasal spray bottle (one that delivers 100 microliters/actuation). 3. Prime with 5 sprays before use, then each spray actuates 1.26 mg of ketorolac solution. 4. Patient should tilt head down while sprays and should sniff gently to avoid swallowing solution.
8:30 AM	2 sprays ketorolac (1 each nostril)	
9:00 AM	4 sprays ketorolac (2 each nostril)	
9:30 AM	6 sprays ketorolac (3 each nostril)	
10:30 AM	60 mg aspirin	
12:00 PM	60 mg aspirin	
3:00 PM	DISCHARGE PATIENT	
Day 2		
8:00 AM	150mg aspirin	
11:00 AM	325 mg aspirin [†]	
2:00 PM	DISCHARGE PATIENT	