Alcohol-induced respiratory symptoms improve after aspirin desensitization in patients with aspirin-exacerbated respiratory disease

Jordan T. Glicksman, MD, MPH[1,2,3], Arjun K. Parasher, MD[1,4,5], Laurel Doghramji, RN, BSN[1], David Brauer, MD[6], Jeremy Waldram, MD[6], Kristen Walters, MD[6], Jeff Bulva, MD, MS[6], James N. Palmer, MD[1], Nithin D. Adappa, MD[1], Andrew A. White, MD[6] and John V. Bosso, MD[1]

Background: **Aspirin-exacerbated respiratory disease (AERD) is characterized by chronic eosinophilic rhinosinusitis, nasal polyps, asthma, and respiratory sensitivity to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). In addition to sensitivity to aspirin and NSAIDs, the majority of patients with AERD have been reported to have respiratory intolerance associated with the consumption of alcohol.**

Methods: **A multicenter prospective cohort study was performed. Patients with AERD confirmed by aspirin challenge were eligible to participate. Those who described themselves as able to tolerate alcohol consumption were excluded. Patients underwent aspirin desensitization following endoscopic sinus surgery. A questionnaire was distributed to patients before and after desensitization to determine pre-desensitization and post-desensitization symptoms associated with alcohol ingestion.**

Results: **Forty-five patients were enrolled and 37 patients completed the study. The most common pre-desensitization symptoms were nasal congestion (95.6%), rhinorrhea (46.7%), and wheezing (40%). Improvement in the ability to tolerate alcohol was noted in 86.5% of participants (95% confidence interval [CI], 75.5% to 97.5%) and 70.3% of participants (95% CI, 55.5% to 85.0%) described desensitization to be "very helpful" or "extremely helpful" for their ability to tolerate alcohol.**

Conclusion: **The majority of patients with AERD who experience respiratory symptoms with alcohol consumption describe improvement in this domain following aspirin desensitization.** © 2018 ARS-AAOA, LLC.

Key Words:
AERD; aspirin-exacerbated respiratory disease; alcohol; chronic rhinosinusitis; asthma; polyps

***How to Cite this Article*:**
Glicksman JT, Parasher AK, Doghramji L, et al. Alcohol-induced respiratory symptoms improve after aspirin desensitization in patients with aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. 2018;00:1–5.

Aspirin-exacerbated respiratory disease (AERD) is characterized by chronic eosinophilic rhinosinusitis (CRS), nasal polyps, asthma, and respiratory sensitivity to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).[1] In addition to sensitivity to aspirin and NSAIDs, the majority of patients with AERD have been reported to be intolerant of alcohol, developing upper and lower respiratory symptoms with the consumption of alcohol.[2]

Patients with AERD tend to have more severe CRS polyposis, nasal symptoms, and need for revision surgery than CRS patients without AERD.[3] Medical therapy is an important component of AERD management[1] and there is a high rate of dependence on systemic corticosteroids for symptom management in AERD patients.[4]

Aspirin desensitization after endoscopic sinus surgery (ESS) has been shown to be well tolerated and effective for controlling polyp recurrence and improving sense of smell and nasal obstruction.[5] Additionally it has been shown to improve sinonasal quality of life.[2] To date, there have only been anecdotal reports of improved alcohol tolerance after aspirin desensitization in patients with AERD.[2,6]

[1]Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania, Philadelphia, PA; [2]Department of Otolaryngology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA; [3]North Shore ENT, Danvers, MA; [4]Department of Otolaryngology–Head and Neck Surgery, University of South Florida, Tampa, FL; [5]Department of Health Policy and Management, University of South Florida, Tampa, FL; [6]Division of Allergy, Asthma, & Immunology, Scripps Clinic and Research Foundation, San Diego, CA

Correspondence to: John V. Bosso, MD, Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania, Hospital of the University of Pennsylvania, Perelman Center for Advanced Medicine, 3400 Civic Center Blvd. 3 South OTO, Philadelphia, PA 19104; e-mail: John.Bosso@uphs.upenn.edu

Potential conflict of interest: None provided.
Presented orally at the Annual ARS Meeting on September 20, 2014 in Orlando, FL.
Online version of author name was misspelled. It has been corrected now as Jeremy Waldram.

Received: 28 February 2018; Revised: 22 May 2018; Accepted: 1 June 2018
DOI: 10.1002/alr.22168
View this article online at wileyonlinelibrary.com.

Our study examines the impact of aspirin desensitization on aspirin intolerance in AERD patients at 2 academic AERD Centers.

Patients and methods

A prospective cohort study was conducted wherein AERD patients with alcohol sensitivity were assessed and compared prior to and after aspirin desensitization. Ethics approval for this study was obtained from the University of Pennsylvania Ethics Review Board and the Scripps Clinic Institutional Review Board.

Participants

Consecutive patients undergoing aspirin desensitization for AERD were offered the opportunity to enroll in this study. The 2 study sites were the Hospital of the University of Pennsylvania (Philadelphia, PA) and Scripps Clinic Carmel Valley (San Diego, CA). Enrollment took place between October 2015 and October 2017. In order to be eligible to participate the following criteria were applied: (1) challenge-proven aspirin intolerance characterized by worsening of upper and/or lower airway symptoms with ingestion of aspirin, (2) a diagnosis of asthma, (3) CRS refractory to maximal medical therapy, (4) preoperative endoscopic evidence of pansinusitis with bilateral nasal polyposis, and (5) nasal and/or lower respiratory symptoms within 24 hours of the consumption of alcohol. Exclusion criteria included age younger than 21 years, pregnancy, immunodeficiency, cystic fibrosis, and negative aspirin challenge.

Intervention

All patients underwent complete ESS, which is defined by our authors as removal of all polyp burden followed by wide bilateral maxillary antrostomies, total sphenoethmoidectomies, and frontal sinusotomies; this includes removal of all residual bony partitions, thereby skeletonizing the skull base.[1] Postoperatively, all patients were given oral prednisone taper as well as topical budesonide irrigation that was continued post-desensitization.

Three to 6 weeks after ESS, patients underwent oral aspirin challenge and desensitization. All aspirin desensitization was performed with continuous monitoring in an outpatient setting. The modified intranasal ketorolac and aspirin challenge protocol from Lee et al.[7] was followed. For maintenance therapy, patients were started on 650 mg aspirin twice per day (BID), with titration down based on patient response and tolerance to a range of 1300 mg to 325 mg total daily aspirin gradually over a period of months. By 6 months post-desensitization, patients are typically on a stable dose of aspirin for maintenance therapy.

A pre-desensitization and post-desensitization questionnaire was provided to all patients with a positive oral aspirin challenge and those with a negative challenge were excluded. The pre-desensitization questionnaire was completed on the first day of the desensitization, prior to initiation of the desensitization protocol. These questionnaires detailed their experience with symptoms related to alcohol consumption as well as demographic data. Follow-up questionnaires were distributed at a minimum of 3 months following the initiation of aspirin desensitization therapy. At the time they completed the post-desensitization questionnaire, patients included in the study were still prescribed aspirin and budesonide nasal rinses, but were not taking oral/systemic steroids.

Outcomes

The primary outcome of this study was the change in sinonasal and/or pulmonary symptoms with alcohol consumption after aspirin desensitization. We also evaluated how helpful patients perceived aspirin desensitization to be with respect to alcohol tolerance and specific symptoms before and after desensitization. The volume of alcohol required to produce symptoms as well as the latency of onset of symptoms were also examined.

Statistical analysis

Statistical analysis utilized Stata 12.0/SE, (StataCorp, LP, College Station, TX). Percentages of participant responses and 95% confidence intervals (CIs) were calculated.

Results

A total of 45 patients were eligible for inclusion in this investigation. Complete data was collected from 37 patients. Seven patients withdrew from the study as they were unable to tolerate aspirin desensitization therapy for a minimum of 3 months (due to minor adverse reactions) and 1 was lost to follow up. These patients were therefore not included in the post-desensitization analysis.

Demographic data is outlined in Table 1. The mean ± standard deviation (SD) age of patients was 43.3 ± 28.0 years and the majority of patients (60%) were female and white (86.7%). Among patients included in the study 77.8% of patients described being able to tolerate alcohol about one-half the time or less that they consume it and 42.2% of patients described never or almost never being able to tolerate alcohol consumption. Two-thirds of patients reported having cut down on alcohol consumption due to their symptoms. The most common symptoms described following alcohol consumption were nasal congestion (95.6%), rhinorrhea (46.7%), and wheezing (40.0%). The majority of patients (60%) described that symptoms were elicited by the equivalent of 1 to 3 glasses of wine and over one-half (53.3%) experienced described a latency of onset of symptoms of 15 minutes to 1 hour.

Following aspirin desensitization an improvement in the ability to tolerate alcohol without sinonasal and/or pulmonary symptoms was noted in 86.5% of participants

TABLE 1. Baseline demographic data

Demographic characteristic	Value
Total patients, n (%)	45 (100)
Gender, n (%)	
Male	18 (40)
Female	27 (60)
Age (years), mean ± standard deviation	43.3 ± 28
Race/ethnicity, n (%)	
White	39 (86.7)
African American/Black	4 (8.9)
Hispanic	1 (2.2)
Asian	1 (2.2)
Self-reported ability to tolerate alcohol, n (%)	
Almost always	10 (22.2)
About half of the time	16 (35.6)
Almost never	10 (22.2)
Never	9 (20)
Symptoms from alcohol consumption, n (%)	
Nasal congestion	43 (95.6)
Rhinorrhea	21 (46.7)
SOB	8 (17.8)
Wheezing	12 (40.0)
Patient reduced alcohol consumption due to symptoms, n (%)	
Yes	30 (66.7)
No	15 (33.3)
Volume of alcohol required to produce symptoms, n (%)	
A few sips	14 (31.1)
1–3 glasses (or equivalent)	27 (60.0)
More than 3 glasses (or equivalent)	4 (8.9)
Latency from consumption to onset of symptoms, n (%)	
Less than 15 minutes	12 (26.7)
15 minutes to 1 hour	24 (53.3)
1–24 hours	9 (20)

SOB = shortness of breath.

(95% confidence interval, CI 75.5% to 97.5%) (Table 2); 70.3% of participants (95% CI, 55.5% to 85.0%) described aspirin desensitization to be "very helpful" or "extremely helpful" for their ability to tolerate alcohol.

Improvement was noted across all common symptoms associated with alcohol consumption. Among the 37 patients who completed desensitization and completed post-desensitization questionnaires, 35 reported nasal

TABLE 2. Post-desensitization results

Outcome	n	%	95% CI (% range)
Total patients	37	100	
Self-reported ability to tolerate alcohol	32	86.5	75.5–97.5
Always	14	37.8	22.2–53.5
Almost always	17	45.9	29.8–62.0
About half of the time	4	10.8	0.8–20.1
Almost never	2	5.4	0–12.7
Never	0	0	0
Patients with improved alcohol tolerance			
Symptoms improved following desensitization[a]			
Nasal congestion (n = 35)	30	85.7	74.1–97.3
Rhinorrhea (n = 18)	13	72.2	47.8–96.6
SOB (n = 8)	6	75	45.0–100
Wheezing (n = 17)	13	76.5	56.3–96.6
None (n = 37)	4	10.8	0.8–20.1
Patient increased alcohol intake following desensitization			
Yes	8	21.6	8.3–34.9
No	29	78.4	65.1–91.7
Volume of alcohol required to produce symptoms			
A few sips	1	2.7	0–8.0
1–3 glasses (or equivalent)	10	27.0	12.7–41.3
More than 3 glasses (or equivalent)	5	13.5	2.5–24.5
N/A (no symptoms)	21	56.8	40.1–72.8
Latency from consumption to onset of symptoms			
Less than 15 minutes	1	2.7	0–8.0
15 minutes to 1 hour	8	21.6	8.3–34.9
1 to 24 hours	7	18.9	6.3–31.5
N/A (no symptoms)	21	56.8	40.1–72.8
Helpfulness for alcohol-induced symptoms			
Extremely helpful	11	29.7	15.0–44.4
Very helpful	15	40.5	24.7–56.3
Somewhat helpful	6	16.2	4.3–28.1
Slightly helpful	4	10.8	0.8–20.1
Not helpful at all	1	2.7	0–8.0

Continued

TABLE 2. Continued

Outcome	n	%	95% CI (% range)
Helpfulness for overall AERD symptoms			
Extremely helpful	17	45.9	29.8–62.0
Very helpful	10	27.0	12.7–41.3
Somewhat helpful	6	16.2	4.3–28.1
Slightly helpful	3	8.1	68.4–93.6
Not helpful at all	1	2.7	0–8.0

[a]The sample size for individual symptoms is less than 37 as not all patients experienced all symptoms prior to desensitization.
AERD = aspirin-exacerbated respiratory disease; CI = confidence interval; N/A = not applicable; SOB = shortness of breath.

congestion, 18 reported rhinorrhea, 17 reported wheezing, and 8 reported shortness of breath with alcohol consumption prior to desensitization. Improvement was noted in each of nasal congestion (n = 30), rhinorrhea (n = 13), wheezing (n = 13), and shortness of breath (n = 6). Four patients noted no improvement in nasal or pulmonary symptoms.

Following desensitization there was an increase in the volume of alcohol required to produce symptoms among 78.4% of patients (95% CI, 65.1% to 91.7%). The latency of onset of symptoms increased among 81.1% of patients (95% CI, 68.4% to 93.7%). Among those completing the study 8 (21.6%; 95% CI, 8.3% to 34.9%) reported increasing their alcohol consumption after desensitization.

Discussion

In this prospective cohort study, the vast majority of patients with AERD and alcohol intolerance described improvement in their ability to tolerate alcohol consumption following treatment with aspirin desensitization. Improvements were seen in the volume of alcohol required to develop a variety of nasal and respiratory symptoms. The majority of patients reported no nasal or pulmonary symptoms from alcohol following aspirin desensitization.

Steinke et al.[8] demonstrated that in AERD, aspirin directly activated eosinophils and mast cells by inducing calcium fluxes and resulting in the release of eosinophil derived neurotoxin (EDN) from eosinophils and prostaglandin 2 (PGD2) from mast cells. Sodium salicylate was unable to elicit either of these effects.

The mechanism of alcohol intolerance in AERD has not been specifically delineated. Payne et al.[9] studied the activation of basophils and eosinophils by alcohol in CRS and asthma patients with alcohol sensitivity. They did not segregate the subset of CRS/asthma patients with AERD in this study. However, they provide in vitro evidence for the activation of basophils but not eosinophils by ethyl alcohol and the red wine polyphenolic compound catechin in this cohort. No cellular activation occurred in the presence of resveratrol, another polyphenol compound found in red wine.

Patients with AERD have elevated circulating cysteinyl leukotrienes levels, which are thought to mediate the nasal and pulmonary responses to aspirin.[10] Cardet et al.[2] proposed that cysteinyl leukotrienes mediate the respiratory reactions of AERD patients to alcohol as well. Aspirin desensitization has been shown to downregulate mediator release from mast cells and eosinophils.[9] Given the recent finding of alcohol and catechin induced basophil mediator release in CRS with nasal polyps and asthma patients, one can speculate that aspirin desensitization could also downregulate basophil mediator release, which may allow for improved alcohol tolerance.[9] Further study would be required to confirm this hypothesis.

AERD is a condition that has a significant impact on patient quality of life and can be challenging to manage, particularly with respect to the CRS component of the disease. Historically, these patients have had a high rate of revision surgery and systemic steroid use.[4,11,12] Aspirin desensitization has been shown to improve sinonasal quality of life in AERD patients and decrease the need for revision surgery compared to historical revision rates.[5,13,14]

Aspirin desensitization, however, is not without risk and treatment failure. Within our cohort 16% of patients withdrew from therapy due to minor treatment side effects, which is similar to other cohorts.[15] While adverse reactions leading to cessation of aspirin desensitization therapy are typically minor (eg, gastrointestinal upset), rare severe adverse events such as gastrointestinal bleeding are possible.[15] Therefore, it is important for patients to be fully informed prior to pursuing aspirin desensitization. The results of this study—that aspirin desensitization improves the ability of most patients to tolerate alcohol consumption—add to the information available to patients with AERD considering aspirin desensitization as a part of their disease management strategy.

Limitations

Our investigation is not without limitations. There was no control group as aspirin desensitization is offered to all patients with AERD unless a contraindication is present. While this could raise the question that the improvement in alcohol tolerance relates to surgery or systemic steroid use, all patients in this investigation had prior surgery and courses of steroids without abatement of symptoms and patients were not using systemic steroids at the time of the post-desensitization questionnaires. Further, it would be difficult to justify a mechanism by which surgery was the factor that mediated the improvement in symptoms with alcohol consumption following desensitization. This makes it more likely that the improvement seen is actually due to aspirin desensitization. Additionally, this study is restricted by the inherent limitations of self-report. Further investigations with objective measures of symptoms could help overcome this limitation.

Conclusion

Alcohol consumption induces a variety of nasal and pulmonary symptoms in patients with AERD. In this prospective cohort study of AERD patients, alcohol tolerance improved following aspirin desensitization. These findings may help inform patients' decisions about whether or not to undergo aspirin desensitization.

References

1. Tajudeen BA, Schwartz JS, Bosso JV. The role of aspirin desensitization in the management of aspirin-exacerbated respiratory disease. *Curr Opin Otolaryngol Head Neck Surg*. 2017;25:30–34.
2. Cardet JC, White AA, Barrett NA, et al. Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2014;2:208–213.e2.
3. Kim JE, Kountakis SE. The prevalence of Samter's triad in patients undergoing functional endoscopic sinus surgery. *Ear Nose Throat J*. 2007;86:396–399.
4. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J*. 2000;16:432–436.
5. Cho KS, Soudry E, Psaltis AJ, et al. Long-term sinonasal outcomes of aspirin desensitization in aspirin exacerbated respiratory disease. *Otolaryngol Head Neck Surg*. 2014;151:575–581. https://doi.org/10.1177/0194599814545750.
6. Calais CJ, Banks TA. Resolution of alcohol-induced respiratory symptoms following aspirin desensitization in aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2015;114:429–430.
7. Lee RU, White AA, Ding D, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2010;105:130–135. https://doi.org/10.1016/j.anai.2010.05.020.
8. Steinke JW, Negri J, Liu L, Payne SC, Borish L. Aspirin activation of eosinophils and mast cells: implications in the pathogenesis of aspirin-exacerbated respiratory disease. *J Immunol*. 2014;193:41–47. https://doi.org/10.4049/jimmunol.1301753.
9. Payne SC, Peters RD, Negri JA, Steinke JW, Borish L. Activation of basophils and eosinophils by EtOH in alcohol sensitive patients with CRS and asthma. *J Allergy Clin Immunol*. 2017;139(2 Suppl):AB90.
10. Christie PE, Tagari P, Ford-Hutchinson AW, et al. Urinary leukotriene E_4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis*. 1991;143:1025–1029. https://doi.org/10.1164/ajrccm/143.5_Pt_1.1025.
11. Mendelsohn D, Jeremic G, Wright ED, Rotenberg BW. Revision rates after endoscopic sinus surgery: a recurrence analysis. *Ann Otol Rhinol Laryngol*. 2011;120:162–166. https://doi.org/10.1177/000348941112000304.
12. White A, Stevenson D. Aspirin-exacerbated respiratory disease: update on pathogenesis and desensitization. *Semin Respir Crit Care Med*. 2012;33:588–594. https://doi.org/10.1055/s-0032-1325618.
13. Adappa ND, Ranasinghe VJ, Trope M, et al. Outcomes after complete endoscopic sinus surgery and aspirin desensitization in aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. 2018;8:49–53. https://doi.org/10.1002/alr.22036.
14. Fruth K, Pogorzelski B, Schmidtmann I, et al. Low-dose aspirin desensitization in individuals with aspirin-exacerbated respiratory disease. *Allergy*. 2013;68:659–665. https://doi.org/10.1111/all.12131.
15. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2003;111:180–186. https://doi.org/10.1067/mai.2003.7.