Original Article

Alcohol-induced Respiratory Symptoms Are Common in Patients With Aspirin Exacerbated Respiratory Disease

Juan Carlos Cardet, MD[a], Andrew A. White, MD[b], Nora A. Barrett, MD[a,c], Anna M. Feldweg, MD[a,c], Paige G. Wickner, MD[a,c], Jessica Savage, MD, MHS[a,c], Neil Bhattacharyya, MD[d,e], and Tanya M. Laidlaw, MD[a,c]
Boston, Mass; and San Diego, Calif

What is already known about this topic? Alcohol-induced respiratory reactions are common in patients with asthma and are associated with aspirin sensitivity, but their prevalence and characteristics in patients with aspirin exacerbated respiratory disease are unknown.

What does this article add to our knowledge? The majority of patients with aspirin exacerbated respiratory disease experience alcohol-induced reactions, and these are more severe than in patients with aspirin tolerance. The severity of reaction to aspirin correlates to the severity of the reaction to alcohol.

How does this study impact current management guidelines? A history of respiratory reactions on alcohol ingestion may aid in the suspicion of aspirin exacerbated respiratory disease; clinicians should warn their patients about this possibility.

BACKGROUND: A large percentage of patients with aspirin exacerbated respiratory disease (AERD) report the development of alcohol-induced respiratory reactions, but the true prevalence of respiratory reactions caused by alcoholic beverages in these patients was not known.
OBJECTIVE: We sought to evaluate the incidence and characteristics of alcohol-induced respiratory reactions in patients with AERD.
METHODS: A questionnaire designed to assess alcohol-induced respiratory symptoms was administered to patients at Brigham and Women's Hospital and Scripps Clinic. At least 50 patients were recruited into each of 4 clinical groups: (1) patients with aspirin challenge−confirmed AERD, (2) patients with aspirin-tolerant asthma (ATA), (3) patients with aspirin tolerance and with chronic rhinosinusitis, and (4) healthy controls. Two-tailed Fisher exact tests with Bonferroni corrections were used to compare the prevalence of respiratory symptoms among AERD and other groups, with $P \leq .017$ considered significant.
RESULTS: The prevalence of alcohol-induced upper (rhinorrhea and/or nasal congestion) respiratory reactions in patients with AERD was 75% compared with 33% with aspirin-tolerant asthma, 30% with chronic rhinosinusitis, and 14% with healthy controls ($P < .001$ for all comparisons). The prevalence of alcohol-induced lower (wheezing and/or dyspnea) respiratory reactions in AERD was 51% compared with 20% in aspirin-tolerant asthma and with 0% in both chronic rhinosinusitis and healthy controls ($P < .001$ for all comparisons). These reactions were generally not specific to one type of alcohol and often occurred after ingestion of only a few sips of alcohol.
CONCLUSION: Alcohol ingestion causes respiratory reactions in the majority of patients with AERD, and clinicians should be aware that these alcohol-induced reactions are significantly more common in AERD than in controls who are aspirin tolerant. **© 2014 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2014;2:208-13)**

Key words: *Samter Triad; Aspirin exacerbated respiratory disease; AERD; Aspirin intolerant asthma; Aspirin triad; Nonsteroidal anti-inflammatory drug; Asthma; Alcohol; Wine; Leukotriene*

Aspirin exacerbated respiratory disease (AERD) is characterized clinically by the triad of asthma, recurrent nasal polyposis, and hypersensitivity to COX-1 inhibitors.[1] This asthma subtype accounts for 5% to 10% of adults with asthma,[2] yet represents a disproportionately high proportion of severe asthma cases[3] and can be difficult to diagnose and treat. Formal aspirin challenges are required for a definitive diagnosis of AERD,[4] in part, because self-reported aspirin sensitivity is not reliably predictive[5-8] and

[a]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, Mass
[b]Division of Allergy, Asthma and Immunology, Scripps Clinic, San Diego, Calif
[c]Department of Medicine, Harvard Medical School, Boston, Mass
[d]Department of Surgery, Harvard Medical School, Boston, Mass
[e]Division of Otolaryngology, Brigham and Women's Hospital, Boston, Mass
This work was supported by National Institutes of Health grants K23 HL111113-01 and T32AI07306-24, and by generous contributions from the Vinik Family.
Conflicts of interest: J. C. Cardet has received research support from the National Institutes of Health; is employed by Partners Healthcare and Brigham and Women's Hospital. N. Bhattacharyya has received consultancy fees from IntersectENT Inc/Entellus Inc. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication October 10, 2013; revised November 22, 2013; accepted for publication December 1, 2013.
Corresponding author: Tanya M. Laidlaw, MD, Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, 1 Jimmy Fund Way, Smith Building, Room 626B, Boston, MA 02115. E-mail: tlaidlaw@partners.org.
2213-2198/$36.00
© 2014 American Academy of Allergy, Asthma & Immunology
http://dx.doi.org/10.1016/j.jaip.2013.12.003

Abbreviations used
ACT- Asthma Control Test
AERD- Aspirin exacerbated respiratory disease
ATA- Aspirin-tolerant asthma
BWH- Brigham and Women's Hospital
CRS- Chronic rhinosinusitis
LT- Leukotriene
NP- Nasal polyp

because many patients with asthma do not use nonsteroidal anti-inflammatory drugs regularly and may be unaware of their hypersensitivity to these drugs.[9] Alcohol-induced respiratory reactions have been reported with rates that varied from 20% to 40% in patients with asthma[10-12] and occasionally in patients with rhinitis[13] and in the general population.[14] However, the majority of our patients with AERD described experiencing respiratory reactions after alcohol ingestion, with a seemingly greater prevalence than that known for other patient groups, and several patients with AERD reported that alcohol had induced frightening lower respiratory symptoms and acute asthma exacerbations. Although an association between aspirin sensitivity and alcohol-induced reactions in patients with asthma has been suggested,[10,11,15] these reactions have never been characterized in a well-phenotyped group of patients with aspirin challenge—confirmed AERD.

In addition, we found no published data regarding the characteristics of alcohol-induced respiratory reactions in patients with AERD. To address these issues and to explore the potential mechanisms that underlie alcohol-induced reactions, we designed a questionnaire to investigate the incidence and frequency of reactions, and to examine details, including time to onset of reactions, the amount of alcohol required to induce reactions, and the type of alcohol most likely to cause reactions. We offered participation in this multicentered questionnaire-based study to patients with AERD and confirmed aspirin challenge, and to 3 clinically defined control groups: patients with aspirin-tolerant asthma (ATA), chronic rhinosinusitis (CRS), and healthy controls. Our findings show that patients with AERD report a strikingly high prevalence of both upper and lower respiratory reactions induced by alcohol; this observation furthers the clinical characterization of AERD and may suggest its diagnosis.

METHODS

Patients and human subject characterization

Study participants between the ages of 21 and 75 years were recruited from the Brigham and Women's Hospital Allergy and Asthma and Otolaryngology Clinics, and from the Scripps Clinic's Allergy and Asthma Clinic. The subjects completed surveys in the form of printed questionnaires or through REDCap (Vanderbilt University, Nashville, Tenn), an online data-gathering and analysis tool; all the participants from the Scripps Clinic completed printed questionnaires. Due to limitations in the questionnaire protocol as approved at the Scripps Clinic, demographic information and clinical information from the medical records were only collected from subjects recruited at the Brigham and Women's Hospital. Recruitment at both centers began in April 2012 and concluded in May 2013.

The participants were allocated into 4 clinical groups: (1) patients with AERD whose diagnosis was confirmed after a respiratory reaction was documented during a supervised challenge to aspirin, (2) patients with ATA, (3) patients without asthma and with CRS, and (4) healthy controls. Patients who had never consumed alcohol and those diagnosed with cystic fibrosis were excluded from participation. All subjects with ATA had physician-diagnosed asthma and had taken a COX-1 inhibitor in the past 6 months without adverse reaction. Subjects with CRS were physician-diagnosed based on published guideline criteria,[16] had taken a COX-1 inhibitor in the past 6 months without adverse reaction, and had no history of asthma in adulthood. Subjects were excluded from the healthy control group if they had a history of asthma, rhinitis, AERD, or sensitivity to any COX-1 inhibitor. The human subjects institutional review boards of the Brigham and Women's Hospital (protocol 2012-P-000175) and the Scripps Clinic (protocol IRB-12-5856) approved the study, and all the subjects provided written consent in accordance with the Declaration of Helsinki.

Questionnaire and study design

The complete questionnaire is available in Figure E1 (in this article's Online Repository at www.jaci-inpractice.org). The number of questions was limited to 18 to avoid bias from responder fatigue. The questionnaire confirmed the presence or absence of physician-diagnosed asthma, nasal polyposis, CRS, and AERD. A history of respiratory reactions to alcohol was evaluated with the question, "has drinking alcohol ever triggered any of the following symptoms? (check all that apply)," with the following possible answers: "stuffy nose and/or nasal congestion, runny nose, shortness of breath, wheezing, none of the above." Upper respiratory symptoms were defined as positive answers to either of the first 2 questions, and lower respiratory symptoms were defined as positive answers to either of the latter two. Respondents who checked any of the above respiratory symptoms were then asked several questions to detail their alcohol-induced reactions in regard to time to onset, frequency, specificity to alcohol type, and quantity of alcohol required to provoke reactions, and whether they had cut down their alcohol consumption due to the development of respiratory reactions. The subjects with AERD who had been desensitized to aspirin and continued with daily high-dose aspirin treatment were asked whether or not aspirin therapy blunted alcohol-induced reactions. Susceptibility to common environmental irritants, a self-assessment of their sense of smell, use of intranasal corticosteroids, and number of lifetime nasal polypectomies were inquired as measures of baseline respiratory disease. For participants from Brigham and Women's Hospital, asthma severity of the subjects with AERD was compared with that of the subjects with ATA by using the Asthma Control Test (ACT; GlaxoSmithKline, Brentford, UK) scores (range, 5-25; with >19 indicating well-controlled asthma) and FEV_1 values from office spirometry.

Statistical analysis

A 2-tailed Fisher exact test with Bonferroni correction was used to compare the prevalence of respiratory symptoms between AERD and other groups, with $P \leq .0125$ considered significant. This statistical tool also was used to compare sex and racial and/or ethnic compositions of the study groups, the prevalence in reaction rates in men versus women within each group, alcohol types that provoked respiratory reactions most forcefully, the quantity of alcohol required to provoke reactions, time to onset, frequency of reactions, and inter- and within-group comparisons

TABLE I. Demographics and respiratory disease characteristics

	AERD	ATA	CRS	Healthy controls	*P* value
Total no. (BWH, Scripps)	59 (23, 36)	54 (28, 26)	50 (36, 14)	50 (15, 35)	
Age (y), median (range) (BWH only)	45 (31-66)	40.5 (23-73)	44.5 (21-75)	34 (22-71)	.06
% Women (BWH only)	70	54	42	60	.29
Race and/or ethnicity (BWH only)				12/15	
White	20/23	22/28	28/36	2/15	
Hispanic	1/23	3/28	5/36	1/15	
Asian	1/23	2/28	2/36		
Declined to answer	1/23	1/28	1/36		
Mean % predicted FEV_1 (range) (BWH only)	86 (58%-114%)	85.5 (60%-123%)	N/A	N/A	.92
Mean ACT score (range) (BWH only)	17 (13-25)	21 (14-25)	N/A	N/A	.57
Presence of NPs, % BWH, % Scripps	100, 97	25, 31	50, 64	0, 0	

BWH, Brigham and Women's Hospital; *N/A*, not applicable or available.

between reactions to alcohol and reactions to other exposures. An unpaired *t* test compared the percentage predicted FEV_1 and ACT scores between subjects with AERD and those with ATA, with $P \leq .05$ considered significant.

RESULTS

Demographics and characteristics of respiratory disease

A total of 213 study participants were recruited; their demographic data are summarized in Table I. There were no statistical differences in racial and/or ethnic backgrounds or age of patients in each group. Consistent with previous reports,[3] the AERD patient group had a slight female predominance. There was no significant difference in rates of alcohol-induced reactions in female versus male patients in any clinical group. Asthma severity in Brigham and Women's Hospital's study subjects, compared by using baseline percentage predicted FEV_1 and ACT scores whenever available from the medical record, was not statistically different between patients with ATA and those with AERD. The percentage of subjects diagnosed with nasal polyps (NP) also is reported, and, as expected, nearly all the patients with AERD had NPs.

Prevalence of alcohol-induced respiratory symptoms

The prevalence of upper and lower alcohol-induced respiratory reactions reported by each patient group is summarized in Figure 1. To address the concern that nasal polyposis may confound differences of reaction rates among groups, an additional clinical subgroup was defined to include all respondents who were aspirin tolerant and with NPs, derived from the ATA and CRS groups; no healthy controls had NPs. Upper respiratory reactions to alcoholic beverages were reported by 75% of respondents with AERD, in contrast to 33% of respondents with ATA, 30% of respondents with CRS, 40% of respondents who were aspirin tolerant and with NPs, and 14% of healthy controls ($P < .001$ for the above 4 comparisons, Figure 1, *A*). Lower respiratory reactions also were significantly more common in patients with AERD (51%) versus patients with ATA (20%) and patients with aspirin tolerance and with NPs (10%); no subject without asthma (CRS and healthy controls) reported lower respiratory reactions to alcohol ($P < .001$ for the above 4 comparisons, Figure 1, *B*). Respiratory reactions of either type, upper and/or lower, were more frequently reported by patients with AERD (83%) than by those with ATA (43%), CRS (30%), patients who were aspirin tolerant and with NPs (43%), or healthy controls (14%) ($P < .001$) (Figure 1, *C*). These reported reaction rates were not statistically different within any patient group between those subjects surveyed at the Scripps Clinic and those surveyed at the Brigham and Women's Hospital. Of respondents who reported alcohol-induced respiratory reactions, 73% of those with AERD reduced alcohol consumption or quit after developing these reactions, and 57% of patients with asthma and with aspirin tolerance did so. This difference was not statistically significant ($P = .18$).

Characterization of respiratory reactions to alcoholic beverages

Participants who reported alcohol-induced respiratory reactions were asked to identify which type of alcohol elicited reactions most forcefully. Responses were similar across patient groups (Figure 2). Although many patients identified red wine as the most forceful trigger, no single alcohol type was determined to be the main culprit, and more than one-third of the subjects with AERD and ATA reported that all alcohol types were equivalent triggers for respiratory reactions. The quantity of alcohol needed to elicit respiratory reactions was similar between AERD and ATA, and was $\leq$3 glasses for almost all participants; the majority of patients with AERD (51%) reported that "a few sips" would elicit their reactions (Table II). The majority of respondents with both AERD and ATA developed their reactions $\leq$1 hour of alcohol intake (84% and 78%, respectively) (Table III) and reported doing so "more than half the time" or "all the time" they drank alcohol in 65% and 61% of cases, respectively (data not shown). In addition, of the respondents with AERD who had begun high-dose daily aspirin therapy and had re-tried drinking alcohol after starting aspirin, 63% reported an improvement in alcohol-induced respiratory reactions since starting this therapy (data not shown). To assess whether reactivity to alcohol was associated with reactivity to other types of exposures and, therefore, associated with general respiratory sensitivity, the participants were asked about respiratory reactions to cold or hot air, use of toothpaste, beef consumption, cold or hot beverages, or "any." The prevalence of reactions to these exposures was similar across all 4 patient groups and also similar for all study groups when patients were subcategorized into alcohol responders and nonresponders, without statistically significant differences noted (data not shown).

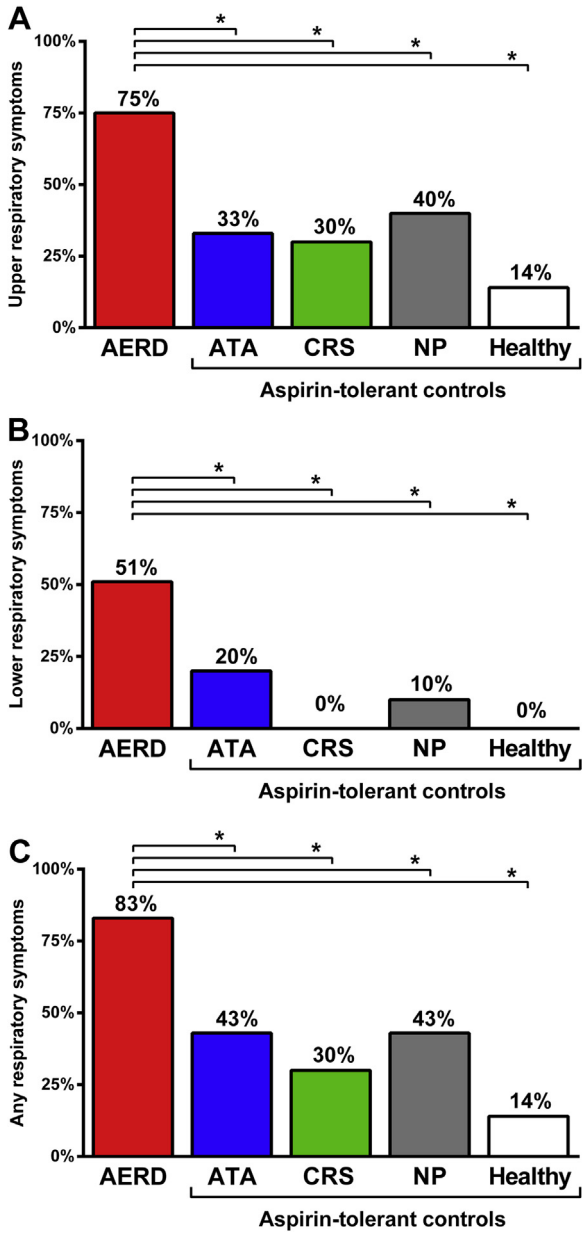

FIGURE 1. Prevalence of alcohol-induced respiratory symptoms. Rates of alcohol-induced (**A**) upper, (**B**) lower, and (**C**) upper and/or lower respiratory reactions among survey respondents with AERD, ATA, CRS, aspirin-tolerant subjects with NPs, and healthy controls. $^{*}P < .001$ for all 4 rates compared with the AERD group in **A**-**C**.

Relationship between the severity of aspirin-induced reactions and alcohol-induced reactions in patients with AERD

We sought to determine whether a relationship existed between the severity of aspirin-induced reactions and the severity of alcohol-induced reactions in patients with AERD. Nasal symptoms that involved only the upper respiratory tract are generally considered to be mild and less intense than potentially life-threatening lower respiratory symptoms of wheezing and shortness of breath, and, therefore, patients who developed lower respiratory symptoms were defined as having "severe" reactions. The 23 patients with AERD and for whom clinical data from their aspirin challenge were available were subdivided into those who developed only upper respiratory reactions (n = 10) and those who developed lower respiratory reactions (including a fall of $\geq$15% in FEV_1 during aspirin challenge [n = 13]); their likelihood of reacting to alcohol was compared. The patients who developed only upper respiratory reactions or no reactions to alcohol were statistically significantly more likely to have developed only upper respiratory reactions to aspirin, and patients who developed lower respiratory reactions to alcohol were statistically significantly more likely to have developed lower respiratory reactions during aspirin challenge (Table IV). The odds of developing a lower respiratory reaction to aspirin was 8.2-fold greater (95% CI, 1.2-59.0) for subjects with AERD who had developed lower respiratory reactions to alcohol compared with those who had developed upper respiratory only or no reactions to alcohol.

DISCUSSION

Previous studies have shown that respiratory reactions may result from alcohol consumption, especially in persons with asthma. In a cross-sectional study in 2008 with 4066 participants, Linneberg et al[14] found the rates of alcohol-induced upper and lower respiratory reactions to be 7.6% and 3.2%, respectively. These reactions were more prevalent in persons with asthma, with 17.5% reporting upper and 12.9% reporting lower respiratory reactions. Other studies reported similar rates of alcohol-induced respiratory reactions in persons with asthma, which ranged from 21% to 40%.[10-13] However, less was known about alcohol-induced respiratory reactions in patients with AERD. The only previous study that investigated both alcohol-induced reactions and AERD was a survey by Vally et al[10] of 366 subjects with asthma, of whom 11% self-reported aspirin-induced asthma. This study found that 33% of the subjects with asthma reported alcohol-induced respiratory exacerbations and noted increased rates in patients with self-reported aspirin-induced asthma because the odds ratio for alcohol-induced respiratory reactions was 2.98 for this subgroup of subjects with asthma. To more specifically examine this phenomenon, we sought to investigate the rates and characteristics of alcohol-induced reactions in patients who were well-phenotyped and with AERD and in controls who were aspirin tolerant.

A large portion of the subjects with asthma who completed our survey reported the onset of respiratory reactions upon alcohol ingestion. Our finding, that 43% of patients with ATA developed upper and/or lower alcohol-induced respiratory reactions was similar to rates described for subjects with asthma in other studies.[10,12] However, we found that 83% of patients with AERD developed alcohol-induced respiratory reactions, which is strikingly higher than the rates found in any other clinical group and is in keeping with the anecdotal evidence from our clinic patients. Analysis of our data did not suggest that this high reaction rate was due to differences in severity of baseline pulmonary disease because there was no difference in asthma severity or control between patients with AERD and ATA as measured by the ACT score and FEV_1. These high reaction rates also were not explained by the presence of NPs because the reaction rates in patients with aspirin tolerance and with NPs was approximately half that of patients with AERD and with NPs. There was a slight female predominance in our AERD

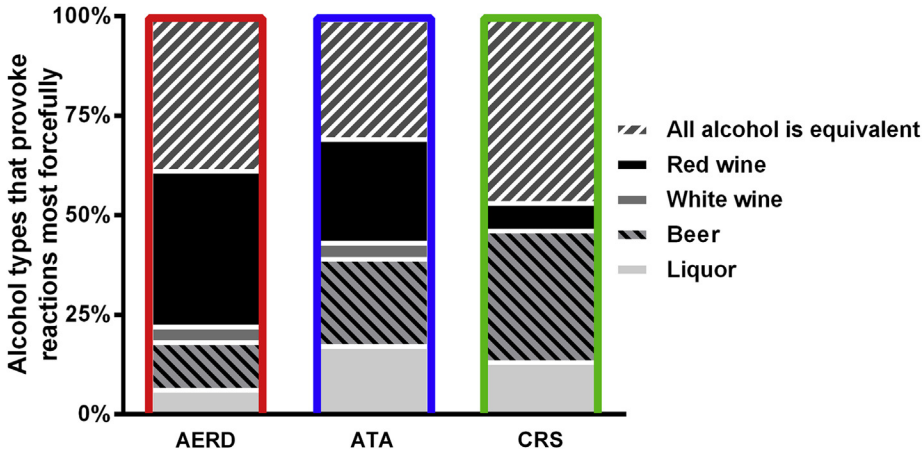

FIGURE 2. Alcohol types that provoke reactions most forcefully. Among participants who reported alcohol-induced respiratory reactions, the types of alcohol they identified as eliciting reactions most forcefully are shown. Significantly more patients with AERD (39%) identified red wine as the most forceful trigger than did patients with CRS (7%) ($P = .02$). No other comparisons were significantly different across patient groups.

TABLE II. Quantity of alcoholic beverage required to provoke reactions*

Dose	AERD	ATA	*P* value
A few sips	25/49 (51)	9/23 (39)	.45
1-3 glasses	21/49 (43)	11/23 (48)	.8
>3 glasses	3/49 (6)	3/23 (13)	.38

*Data are the number of those who reported the dose of alcohol needed to trigger respiratory reactions over the number of those who experienced respiratory reactions with alcoholic beverages; percentages are given in parentheses.

TABLE III. Time to onset of respiratory reactions after ingestion of alcohol*

Time	AERD	ATA	*P* value
<15 min	16/49 (33)	6/23 (26)	.78
15 min to 1 h	25/49 (51)	12/23 (52)	> .99
≤1 h	41/49 (84)	18/23 (78)	.74
1-24 h	8/49 (16)	5/23 (22)	.74

*Data are the number of those who reported time of onset of respiratory reactions after alcohol ingestion over the number of those who experienced respiratory reactions with alcoholic beverages; percentages are given in parentheses.

population, which paralleled the findings of previous groups,[3] although there was no sex-specific difference in alcohol-induced reaction rates in either patients with aspirin tolerance or those with AERD. Because respiratory reactions began for most respondents within minutes of drinking even very small amounts of alcohol, alcohol intoxication is also unlikely to be the causative mechanism of these reactions. However, the <30-minute time-to-onset of reaction may correlate with peak blood alcohol levels because peak alcohol levels are often achieved within 30 minutes of ingestion.[17] Sulfite hypersensitivity also exists in some patients with asthma[18,19] and, although one-third of our respondents with AERD reported that red wine was the alcohol type that caused the most forceful respiratory reactions, most patients found that all alcohols incited reactions, even those with little to no sulfites. In addition, studies that compared bronchoconstriction induced by wine with high versus low sulfite content have not found any difference between the two,[20-22] which suggests that alcohol itself, and not an additive, is the culprit for these reactions. Sensitivity to alcohol is common in Asian populations due to a polymorphism in acetaldehyde dehydrogenase, and patients classically present with facial flushing and occasionally respiratory symptoms.[23] In Western populations; however, this polymorphism is infrequent and thus unlikely to be the mechanism that underlies the reactions described by our patients with AERD.

One consistent finding in AERD is that patients have elevated cysteinyl leukotrienes (LT) levels at baseline, reflected by the detection of the end metabolite LTE_4 in urine, which increases further during reactions to aspirin.[24] Cysteinyl LTs are powerful bronchoconstrictors and the main effectors of aspirin-induced reactions, but neither the cellular source of cysteinyl LTs nor the mechanisms of aspirin-induced increase are known. The mechanisms that underlie the alcohol-induced respiratory reactions in patients with AERD also are unknown, but, when considering the dominant role that cysteinyl LTs play in AERD pathogenesis, we suspect that a similar LT-dependent mechanism may underlie their alcohol-induced respiratory reactions. Moreover, the baseline level of urinary LTE_4 is currently the only biomarker available to clinicians for predicting the severity of aspirin-induced reactions in patients with AERD.[25] However, in this study, we found that the severity of aspirin-induced reactions (observed in the clinic during aspirin challenges) positively correlated with the severity of alcohol-induced reactions (self-reported by the survey respondents). Given that urinary LTE_4 measurements are mostly limited to research centers, this new finding may aid clinicians in predicting the severity of reactions during aspirin challenges and in counseling patients about consequences of alcohol consumption.

Indeed, excessive ethanol consumption by healthy individuals has been shown to increase urinary LTE_4 excretion, which presumably reflects elevated systemic cysteinyl LT levels due to ethanol-induced inhibition of LT catabolism.[26] Although these alcohol-induced urinary LTE_4 elevations did not cause reactions in healthy individuals, patients with asthma are known to be

TABLE IV. Correlation of aspirin-induced respiratory reactions with alcohol-induced respiratory reactions in subjects with AERD

	Reactions during aspirin challenge		
	Only upper respiratory reactions	Lower respiratory reactions	*P* value
Reactions to alcoholic beverages			
Upper respiratory or no reactions	6/10 (60%)	2/13 (15%)	.04
Lower respiratory reactions	4/10 (40%)	11/13 (85%)	

200-fold more sensitive to LTE_4-induced bronchoconstriction than are persons without asthma,[27] and patients with AERD are 16-fold more sensitive to bronchoconstriction by LTE_4 than patients with asthma who are aspirin tolerant.[28] It is suspected that this hyperresponsiveness to LTE_4 in AERD is due to overexpression of a yet undiscovered LTE_4-specific receptor, but, to date, no such receptor has been reported. Interestingly, 63% of respondents with AERD on high-dose daily aspirin therapy who had retried drinking alcohol after starting aspirin reported an improvement in alcohol-induced respiratory reactions, which suggests that high-dose aspirin therapy may attenuate alcohol hyperresponsiveness in patients with AERD.

This study has several limitations, principally those inherent in survey research and its liability to patient recall and response bias. In addition, due to the relatively small population of subjects with AERD available for study, our questionnaire was not able to be formally validated. Therefore, it was subjected to screening by our multiple authors for re-test reliability and linguistic validity before institutional review board submission and administration to study participants, and was based in part on previously published questionnaires.[10-14] In addition, our survey queried susceptibility to environmental exposures as a measure of interpretability and specificity, and we found similar reaction rates to environmental exposures among study participants (excluding healthy controls), which suggests that our survey questions on respiratory reactions to alcohol were correctly interpreted by respondents and that respiratory reactions to alcohol are specific. For future studies, a double-blind, placebo-controlled alcohol challenge study would be optimal to circumvent our study's limitations and clarify the mechanisms that underlie our findings.

In this study, we thoroughly examined the effects of alcoholic drinks on the development of respiratory reactions in patients with AERD and found that alcoholic beverages are common and occasionally dangerous triggers for respiratory reactions in these patients. This finding may aid clinicians in the suspicion of AERD and suggests that clinicians should warn their patients with AERD about the potential for alcohol-induced respiratory reactions.

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Effect of Alcohol Consumption on Patients with Aspirin Exacerbated Respiratory Disease (AERD)

This survey should take 5-10 minutes to complete.

By completing this questionnaire, it is understood that you are giving your permission and consent to participate in this research survey. Participation is voluntary, and you may decide against completing or submitting this survey at any time. Your decision will not change the medical care you receive now or in the future. The purpose of this study is to determine which triggers worsen nasal or breathing symptoms in patients with asthma and hay fever, and to learn if drinking alcohol causes these symptoms. We obtained your name and contact information at the time you were booked for an appointment at our clinic, or at the time you agreed to participate in another ongoing research study about aspirin exacerbated respiratory disease. We are asking you to participate in this study because you may have asthma, hay fever, or aspirin exacerbated respiratory disease, and we hope to enroll 80 patients per clinical group from the Brigham and Women's Hospital. The information we obtain from this study will be useful for better understanding diseases associated with aspirin allergy, asthma, and hay fever symptoms.

The principal investigator of this study is Dr. Tanya M. Laidlaw, who may be contacted at 617-732-9850 to answer any questions. If you would like to speak to someone not involved in this research about your rights as a research subject, or any concerns or complaints you may have about the research, contact the Partners Human Research Committee at 617-424-4100.

There is no outside funding or sponsors for this survey study. You will not be paid for completing this survey.

Federal law requires Partners HealthCare System to protect the privacy of health information that identifies you. However, we will not be collecting sensitive or Protected Health Information (PHI) in this study. Your questionnaire data will be collected, compiled, and analyzed through REDCap (Research Electronic Data Capture), which is a password-secured database on a dedicated server, which has been built around the Health Insurance Portability and Accountability Act (HIPAA) guidelines. If your doctor has asked you to have office spirometry (breathing tests) conducted at the time this survey is presented to you, or asked you to fill out the 5-questions on the Asthma Control Test questionnaire, we will also collect the information from those tests. The reasons we might use or share this information are to do the research described and to make sure we do the research according to certain standards - standards set by ethics and law, and by quality groups. Only people or groups within Partners may use or share your data obtained from this survey, which may include researchers and the staff involved in this survey, the Partners review board that oversees the research, or staff within Partners who need the information to do their jobs (such as billing, or for overseeing quality of care or research). Your PHI will not be shared with any people or groups outside Partners.

1) Do you have asthma?
- ☐ Yes
- ☐ No

2) Has your doctor diagnosed you with aspirin exacerbated respiratory disease (AERD)? AERD is also known as aspirin sensitive asthma, aspirin intolerant asthma, or Samter's triad.
- ☐ Yes
- ☐ No

3) Has drinking alcohol ever triggered any of the following symptoms? (Check all that apply.)
- ☐ stuffy nose/nasal congestion
- ☐ runny nose
- ☐ shortness of breath
- ☐ wheezing
- ☐ none of the above

4) How quickly after drinking alcohol do you get those symptoms?
- ☐ within 15 minutes of drinking alcohol
- ☐ after 15 minutes but within 1 hour
- ☐ after 1 hour but within 24 hours
- ☐ more than 24 hours later

5) Have you cut down/stopped drinking alcohol because of those symptoms?
- ☐ Yes
- ☐ No

6) How frequently do you have any of the above symptoms after you drink alcohol (or, if you have stopped drinking alcohol, how frequently did you have them)?
- ☐ None of the time I drink alcohol
- ☐ less than half the time I drink alcohol
- ☐ half the time I drink alcohol
- ☐ more than half the time I drink alcohol
- ☐ All of the time I drink alcohol

7) Is there one kind of alcohol that triggers the symptoms more frequently than others?
- ☐ Yes
- ☐ No

8) Which alcohol triggers the symptoms most frequently?
- ☐ Red wine
- ☐ White wine
- ☐ Beer
- ☐ Hard liquor, mixed drinks, or cocktails
- ☐ All alcohol is equivalent

9) Is there one kind of alcohol that triggers the symptoms more forcefully than others?	☐ Yes ☐ No
10) Which alcohol triggers the symptoms most forcefully?	☐ Red wine ☐ White wine ☐ Beer ☐ Hard liquor, mixed drinks, or cocktails ☐ All alcohol is equivalent
11) How much alcohol do you need to drink before a reaction will start?	☐ A few sips (less than 1 glass) ☐ 1-3 glasses ☐ >3 glasses
12) If you are on a high-dose daily aspirin therapy as treatment for your AERD, has being on the aspirin therapy decreased the severity of your reactions to alcohol?	☐ Yes ☐ No ☐ Unsure/have not tried alcohol since I started aspirin therapy ☐ Not on aspirin therapy
13) Do you get nasal congestion, runny nose, shortness of breath, or wheezing with any of the following? (Check all that apply)	☐ Exposure to cold air ☐ Exposure to hot air ☐ If I use toothpaste ☐ After eating beef ☐ After drinking hot beverages ☐ After drinking cold beverages ☐ Others ☐ I do not get any of those symptoms
14) Have you been diagnosed with nasal polyps?	☐ Yes ☐ No
15) Have you been diagnosed with frequent or chronic sinus infections (2 or more sinus infections per year)?	☐ Yes ☐ No
16) How many surgeries have you had to remove nasal polyps?	☐ 0 ☐ 1-2 ☐ 3-4 ☐ 5 ☐ >5
17) How would you rate your sense of smell overall?	☐ Excellent ☐ Good ☐ Poor ☐ I have no sense of smell
18) Do you use an intranasal steroid spray to treat/control your sinusitis or nasal polyps? (Common intranasal steroid sprays include Flonase, fluticasone, Nasonex, Rhinocort, and Veramyst)	☐ Yes ☐ No

FIGURE E1. The complete questionnaire that examines the effect of alcohol consumption on patients with AERD.

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