Adverse reactions to alcohol and alcoholic beverages

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Introduction
Alcohol use is widespread and adverse reactions, although rare, do occur and warrant further evaluation. Nonimmunologic and immunologic reactions to alcohol present in different clinical situations and overlap in their presentation. Nonimmunologic reactions to ingested alcohol are due to its inherent capability to cause flushing and rhinitis through vasodilation. Immunologic reactions after alcohol ingestion show a spectrum of symptoms, ranging from dermatitis to asthma and anaphylaxis. Fatal anaphylaxis after alcohol consumption has been reported, further emphasizing the need to study this topic.1

References:
The exact prevalence of adverse reactions to alcohol is unknown because only a few studies have been completed. Adverse reactions to wine were reported in 7% of a German study population. An ongoing study recently reported prevalences of 74% for upper airway symptoms and 51% for lower respiratory symptoms after alcohol ingestion in patients with aspirin-exacerbated respiratory disease. Additional risk factors include female sex, history of allergic rhinitis, chronic obstructive pulmonary disease, and asthma. Up to one third of patients with asthma have reported worsening of asthma symptoms after alcohol ingestion. Genetic predisposition also has been reported, with the classic example being the aldehyde dehydrogenase (ALDH) polymorphism found in Asians.

**Flushing**

Alcohols are organic compounds characterized as primary, secondary, or tertiary based on their chemical structure. Ethanol, a primary alcohol, is oxidized to acetaldehyde and acetic acid. Oxidation occurs through the enzymatic action of alcohol dehydrogenase and ALDH. Altered metabolism of acetaldehyde in persons of Asian descent is due to a single nucleotide polymorphism, ALDH2*504lys (ALDH2), that results in the accumulation of acetaldehyde from decreased or absent metabolism. Accumulation of acetaldehyde results in mast cell degranulation, histamine release, and symptoms of flushing, tachycardia, and nausea after alcohol ingestion. Path testing in individuals with ALDH2 is diagnostic. The correlation between ethanol patch testing and polymerase chain reaction genotyping in this population is strong, with the mutant ALDH2 genotype having been found in 94% of patients with a positive patch test result. This polymorphism is nearly absent in whites, whereas it has been found in up to 40% of some East Asian populations. Recent studies have found additional polymorphisms, such as the alcohol dehydrogenase-1b allele, that are associated with a higher risk of adverse reactions to alcohol.

Flushing after alcohol ingestion also is potentiated by the concomitant use of drugs, such as griseofulvin, metronidazole, topical tacrolimus, chloropropamide, and disulfiram. Disulfiram is a treatment for alcohol dependence because its combination with alcohol results in symptoms of flushing, tachycardia, nausea, and vomiting. In patients with rosacea, alcohol ingestion can lead to an acute exacerbation of flushing referred to as alcohol-induced rosacea flushing. Alcoholic flushing has been described secondary to other systemic disorders, such as carcinoid tumors, mastocytosis, Hodgkin lymphoma, and hypereosinophilic syndrome.

**Urticaria**

Alcohol intake can be a causative (primary) and an aggravating (secondary) factor of urticaria. Alcohol has been identified as a trigger of urticaria in 4% to 9% of patients with chronic urticaria. Exacerbation of exercise-induced cholinergic urticaria after alcohol ingestion also has been reported.

The ethanol molecule is of low molecular weight and thus is unlikely to stimulate an immunologic response. Although a hapten effect is presumed, IgE to an ethanol–protein conjugate has yet to be reported. Ethanol also can act directly on mast cells, leading to degranulation, as has been shown in biopsies of urticarial lesions secondary to alcohol ingestion. An increase in histamine level has been noted after an oral challenge in a patient with alcohol-induced urticaria. An additional postulated mechanism includes the allergenic potential of ethanol metabolites through haptenization. Studies in mice have shown the existence of IgE antibodies against acetaldehyde–protein complexes that can be passively transferred to rats. Israel et al. demonstrated increased levels of anti-acetaldehyde–protein IgE in a non–East Asian group of patients with reported adverse reactions to ingested alcohol.

Other implicated mechanisms for alcohol-induced urticaria include the activation of prostaglandin and endogenous opioid receptors. A prostaglandin–mediated process has been proposed as a pretreatment with indomethacin, a nonselective cyclooxygenase-1 and -2 inhibitor, has been shown to prevent alcohol-induced urticaria. Alcohol also induces the endogenous opioid system by directly stimulating the release of opioids that interact with μ and δ receptors. Naloxone can inhibit this process through competitive binding of the opioid receptors and can prevent the development of alcohol-induced urticaria and cutaneous flushing in alcohol-induced rosacea flushing.

**Dermatitis**

Systemic dermatitis after the ingestion of alcohol has been associated with previous sensitization to alcohol found in hormone or analgesic transdermal patches. Alcohol-induced dermatitis has been associated with a sparse perivascular and interstitial infiltrate with increased mast cells, polymorphonuclear cells, and rare eosinophils suggestive of a delayed type IV reaction on biopsy examination.

**Respiratory Reactions**

Asthmatic exacerbations after alcohol ingestion have been reported in up to 47% of Japanese patients. Acetaldehyde accumulation with direct mast cell stimulation is responsible for bronchoconstriction. A significant increase in acetaldehyde and histamine levels after alcohol ingestion occurs in patients with ALDH2. Myou et al. determined that inhaled acetaldehyde produced a greater than 20% decrease in one-second forced expiratory volume in patients with asthma that could be inhibited by terfenadine. Interestingly, studies also have shown a bronchodilator effect of alcohol. After ingestion, alcohol diffuses from the bronchial circulation through the ciliated epithelium, where it vaporizes in the airway. In a 2007 review on the impact of alcohol on the airways, it was noted that oral and intravenous alcohol were associated with alleviated asthma symptoms.

**Anaphylaxis**

Anaphylaxis from alcohol has been described and reactions involve multiple organ systems. Reactions have been reported after the ingestion of different alcoholic beverages, over-ripe fruit, and after ingestion and subsequent exercise. One fatal case was attributed to alcohol in a 28-year-old Filipino woman with a recurrent purpuric urticarial rash related to beer and whiskey ingestion. Proposed mechanisms for alcohol-induced anaphylactic reactions include the hapten effect of ethanol or one of its metabolites. An elevation in tryptase has been documented in patients with alcohol-induced anaphylaxis. There is greater evidence that...
acetic acid, a metabolite of ethanol and an additive in alcoholic beverages, might function as a mediator of anaphylactic reactions, whereas acetaldehyde seems to be the primary mediator in cutaneous reactions. Although tolerance to vinegar has been used to assess for reactivity to acetic acid, there appears to be an inconsistent relationship between skin test reactivity to acetic acid and clinical reactivity to vinegar or alcohol.26,27 A history of tolerance to vinegar in patients with reactions to alcoholic beverages should not automatically exclude the potential role of acetic acid in causing adverse reactions. Similarly, a negative skin test result should be followed by an oral challenge if the history is concerning for an adverse reaction.

The need for oral challenge testing is further highlighted in a study by Ehlers et al.28 In their prospective study of 12 patients with alcohol-induced anaphylaxis, double-blinded placebo-controlled oral challenges to increasing concentrations of ethanol were positive in 6 of 11 patients tested. A nonimmunologic etiology was suspected because the reactions occurred only after a cumulative dose of ethanol was ingested.28 However, it is possible that reactions can only be elicited in a dose-dependent fashion.

Reactions to Beer

Beer is formed by saccharification, or the breakdown of complex carbohydrates to monosaccharides, and fermentation of the resulting sugar. Malted cereals are used as the starches and can be germinated to modify their protein content. Malted cereals are used as the starches and can be germinated to modify their protein content. Malted cereals are used as the starches and can be germinated to modify their protein content.

Reactions to beer range from isolated urticaria to anaphylaxis. Reactions after isolated contact to beer are rare, with only a few cases reported in atopic individuals.29 Reactions after beer ingestion are more common and can be due to grains or the modified grain proteins that are formed by fermentation. For instance, it has been postulated that the germination process to make malted grains leads to new epitopes that enhance the allergenic potential of the grains. In a case series of 3 atopic patients with generalized urticaria and angioedema after beer ingestion, Curioni et al.30 determined that the reactions were due to an IgE-mediated hypersensitivity to a 10-kDa protein. Immunoblotting showed weak binding with ungerminated barley that significantly increased with malt extract, suggesting modification during germination.30 The 10-kDa protein has been identified as the nonspecific lipid transfer protein (LTP) also found in different fruits and vegetables. Cross-reactivity with LTP from Rosaceae fruits also has been shown.31 LTP can withstand the germination and fermentation process, thereby making it a relevant allergen in patients sensitized to LTP.31 Further studies have identified different beer proteins as potential allergens. Barley proteins of 16, 18, 40, and 45 kDa have been identified.30,32–34

Although hops have been suspected as the allergen in beer reactions, there are no cases showing a causative relationship. Rare cases of urticaria, rhinitis, and respiratory symptoms occurring in hop pickers have been identified as an occupational hazard.35 Of the studies reviewed, none demonstrated evidence of IgE to hops or did not include testing to hops as part of the evaluation.

Isolated respiratory reactions after beer ingestion can be due to prior sensitization to grains, yeasts, or molds. Heaney et al.36 reported the case of a brewer who developed respiratory symptoms attributed to sensitization to ground malt contaminated with Aspergillus niger. Similarly, Vidal and Gonzalez-Quintela37 described a case of occupational asthma in an individual sensitized to barley with reproducible symptoms after exposure to barley beer and barley flour. Patients with yeast sensitivity, such as those with baker’s asthma, may be at increased risk for respiratory exacerbations with exposure to products that also use yeast, such as beer and wine. Prospective studies have failed to show the presence of yeast antigen in bakery and brewery products with immunoblotting.38 A higher prevalence of chronic respiratory symptoms and skin test reactivity to molds, hops, and barley has been reported in brewery workers. However, compared with controls, it was noted that skin test reactivity was not predictive of the presence of chronic respiratory symptoms in this population.39

Anaphylactic reactions after beer ingestion include a range of symptoms, such as urticaria, angioedema, rhinocconjunctivitis, chest tightness, dyspnea, and even loss of consciousness.40 Exercise-dependent reactions are related to the ingestion of wheat beer. Gamma gliadin, previously identified as the causative allergen in patients with wheat-dependent exercise-induced anaphylaxis, also has been identified in these cases through IgE immunoblotting.41

Reactions to Wine

Wine production, or vinification, starts with the harvest of grapes. White wine is produced by fermenting the juice alone, whereas red wine production occurs when the must, or pulp, of red and black grapes is fermented with the juice. Yeast is added to catalyze the fermentation of sugar into alcohol. Secondary fermentation is mediated by bacteria. Tannins are biomolecules found in grape skins and stems that are involved in the aging process and lend some of the bitterness and astrignent taste to wine. Wines undergo a clarification step, during which fining agents, such as gelatin, casein, or isinglass (sturgeon bladder), are used to remove tannins. Preservatives such as sulfur dioxide and potassium metabisulfite are added as part of the vinification process.

Reactions after wine ingestion range from systemic urticaria to anaphylaxis. Mechanisms underlying wine reactions seem to be more diverse than those described for beer. In addition to the possible ethanol- and metabolite-induced reactions described earlier, wine-specific considerations include the role of contaminants, clarifying agents, biogenic amines, sulfites, and grapes in the development of adverse reactions to wine.

Contaminants

Contaminants may play a role in adverse reactions to wine. Armentia et al.42 described 5 patients with reactions to newly pressed wines that ranged from localized oral symptoms to asthma and anaphylaxis. Hymenoptera species contamination was presumed to occur during grape harvesting. Oral sensitization to Hymenoptera species was suspected because patients lacked a history of previous Hymenoptera stings and had positive skin prick test (SPT) reactions to Apis mellifera, Vespula species, and Polistes species. Although immunoblotting showed protein binding to grape and newly pressed wines with subsequent inhibition using Polistes venom, a causative relationship between Hymenoptera sensitization and adverse reactions to wine was not established in this small cohort of patients.43 To date, there are no additional studies that have confirmed this phenomenon.

Fining Agents

Wine clarification can be performed with a wide range of fining materials that could lead to potential adverse reactions. However, studies have failed to show the persistence of fining agents in finished wines using enzyme-linked immunosorbent assay and polymerase chain reaction techniques.44 Kirschner et al.45 were able to show skin test reactivity to fining agents in patients with reported reactions to the relevant food allergens. Double-blinded placebo-controlled food challenges to fined and un fined wines, however, were negative in all patients, indicating that despite skin test reactivity to fining products, clinical reactivity is absent in these individuals.45
Biogenic Amines

Biogenic amines, such as histamine and tyramine, are found naturally in food and can be produced by bacterial fermentation during storage or decay. Although intolerance to biogenic amines has frequently been quoted as a cause of adverse reactions to wine, a study failed to demonstrate increased symptoms after ingestion of high histamine wine in patients with self-reported amine intolerance. Moreover, it has been postulated that poorly controlled asthma is a precursor of wine-induced asthma. A possible mechanism for increased susceptibility to histamine is a deficiency in diamine oxidase (DAO), which is one of the enzymes responsible for histamine breakdown. Alcohol can produce a secondary deficiency through the inhibition of DAO. Testing for DAO deficiency is performed with tissue biopsy or by serum testing. Treatment includes antihistamines, DAO supplementation, or a histamine-free diet. Of note, concomitant reactions to beer also may be related to histamine because it can be present in beer in varying amounts.

Additives

Wine additives are commonly used to preserve wine and serve to give wines more complex tastes. Acetaldehyde and acetic acid are common additives and can be present as byproducts of yeast fermentation. As discussed earlier, these 2 compounds have been implicated in reactions to alcohol and need to be considered when evaluating reactions to wines.

Sulfur dioxide is an additive that functions as an antioxidant and prevents bacterial overgrowth. It has been cited as a cause for wine-induced asthma. Although some studies have noted more severe reactions with high sulfite wine, others have failed to show similar and reproducible findings. Other markers of asthma, such as bronchial hyper-responsiveness, also have failed to show consistent results. Additional studies have investigated the role of prostaglandins and leukotrienes as mediators of bronchoconstriction associated with sulfur dioxide. Although evidence of mast cell involvement exists, it is independent of the sulfite content of wine. A limiting factor in these studies is the inclusion of patients with stable asthma because there is anecdotal evidence suggesting that poorly controlled asthma is a precursor of wine-induced asthmatic reactions. Moreover, it has been postulated that reactions occur in a dose-dependent fashion, with a sulfite content of at least 300 ppm needed to induce symptoms and produce an objective decrease in one-second forced expiratory volume.

Food Associations

Reactions to grape (Vitis vinifera), although rare, also have been implicated in cases of adverse reactions to wine. In a case series of 4 patients with reactions to wine, 2 patients endorsed oral allergy symptoms to grape, peach, and cherry. All 4 had positive SPT reactions to grapes and experienced anaphylaxis with wine challenges. The investigators identified the major grape allergens as endochitinase 4A (30 kDa) and grape LTP (9 kDa), which was homologous to peach LTP. A minor allergen identified was homologous to cherry and apple thamautin-like allergens (Pru av 2 and Mal d 2, respectively). Grape chitinases, thamautin proteins, and LTP are thought to persist through vinification.

Distilled Spirits

Spirits are produced by distillation, which results in concentrated ethanol content. Different spirits can be produced by fermenting different grains, fruits, or vegetables. Reactions to distilled spirits have ranged from generalized urticaria after whiskey and vodka to frank anaphylaxis secondary to whiskey. Alcohol-induced rhinitis has been attributed to spirits in 13% to 24% of patients. Lichen planus has been associated with the ingestion of gold-containing spirits in patients with and without gold hypersensitivity. Like reactions to wine, there is a theoretical risk of reactions to additives, contaminants, or preservatives in distilled spirits. For instance, it is not uncommon for spirits to undergo an aging process in wood barrels similar to wines. In a patient with reactions to gold tequila, sensitization to oak was the presumed underlying etiology because gold tequila obtains its characteristic golden hue by aging in oak barrels.

Approach to the Patient with Adverse Reactions to Alcohol

The evaluation of adverse reactions to alcohol must be guided by the history. Figure 2 provides an overview of the reactions described earlier and categorizes them as nonimmunologic or immunologic. Because alcohol intolerance may present secondary to systemic conditions, new-onset symptoms to alcoholic beverages should prompt an evaluation for disorders such as lymphoma or hypersensitivity syndrome. After these conditions have been ruled out, the initial step in evaluating alcohol-induced reactions includes a complete history of previous reactions and inciting factors. In addition, a history of the use of other alcohol-based products should be sought (Table 1). Screening for the ALDH2 polymorphism can be performed by patch testing to ethanol and acetaldehyde.
Differences in the production of alcoholic beverages can help differentiate among the many possible underlying mechanisms. For instance, tolerance to spirits with a history of reactions to wine and beer effectively rules out ethanol- or metabolite-mediated reactions because these reactions would be expected to occur with any alcoholic beverage. Reactions to all types of alcoholic beverages can be due to an ethnic predisposition or to a hapten-mediated process. Individuals with ALDH2 commonly present with flushing or respiratory symptoms, whereas a hapten-mediated process tends to produce systemic symptoms. Table 2 presents a frame of reference for evaluation based on the types of alcoholic beverages that led to the reaction.

In general, the workup for alcohol-induced reactions should include skin testing, laboratory evaluation, and oral challenges. If immediate cutaneous symptoms are prominent, further evaluation with SPT can be performed. Although patch testing can be performed for delayed cutaneous reactions, it has not proved helpful in cases of anaphylaxis to alcoholic beverages. Laboratory evaluation is typically limited unless there is concern for a food association.

### Table 1

<table>
<thead>
<tr>
<th>Product</th>
<th>Alcohol content (%)</th>
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<tbody>
<tr>
<td>Cold medicines</td>
<td>1–25</td>
</tr>
<tr>
<td>Mouthwash</td>
<td>1–25</td>
</tr>
<tr>
<td>Beer</td>
<td>6–12</td>
</tr>
<tr>
<td>Wine</td>
<td>9–16</td>
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<tr>
<td>Distilled spirits</td>
<td>20–60</td>
</tr>
</tbody>
</table>

Abbreviations: SPT, skin prick test; ETOH, ethanol; LAB, laboratory evaluation; LTP, lipid transfer protein; OAS, oral allergy syndrome; oral, challenge; patch, patch test; SPT, skin prick test.

### Table 2

<table>
<thead>
<tr>
<th>Reaction to</th>
<th>Etiology</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beer</td>
<td></td>
<td></td>
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<tr>
<td>Wine</td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: ÷÷, no reaction to product; ÷+, reaction to product; DAO, diamine oxidase; ETOH, ethanol; lab, laboratory evaluation; LTP, lipid transfer protein; OAS, oral allergy syndrome; oral, oral challenge; patch, patch test; SPT, skin prick test.

### Table 3

<table>
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<tr>
<th>Common alcoholic beverages and their starting agents</th>
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<tbody>
<tr>
<td>Starting agent</td>
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</tr>
<tr>
<td>Wheat</td>
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<tr>
<td>Barley</td>
</tr>
<tr>
<td>Rice</td>
</tr>
<tr>
<td>Corn</td>
</tr>
<tr>
<td>Rye</td>
</tr>
<tr>
<td>Grapes</td>
</tr>
<tr>
<td>Apples/peaches</td>
</tr>
<tr>
<td>Honey</td>
</tr>
<tr>
<td>Molasses/Sugarcane</td>
</tr>
<tr>
<td>Potato</td>
</tr>
<tr>
<td>Sweet potato</td>
</tr>
<tr>
<td>Juniper berries</td>
</tr>
</tbody>
</table>

Abbreviations: ÷÷, no reaction to product; ÷+, reaction to product; DAO, diamine oxidase; ETOH, ethanol; lab, laboratory evaluation; LTP, lipid transfer protein; OAS, oral allergy syndrome; oral, oral challenge; patch, patch test; SPT, skin prick test.

*Consider for dermatitis or delayed reaction.

For anaphylaxis.

*Consider an oral challenge followed by exercise for food- and exercise-dependent reactions.

The primary treatment modality for alcohol-induced reactions is avoidance. Workup to identify specific triggers becomes essential.
when one considers that alcohol is found in many products. To date, there are no studies regarding the natural history of adverse reactions to alcohol. One case of remission after a 6-month abstinence from alcoholic drinks has been reported. Successful oral induction to grape resulted in tolerance to wine in a patient with wine-induced anaphylaxis. Medicines for the prevention of alcohol-induced reactions are limited to a select few clinical phenotypes. Opioid antagonists have been successful at preventing alcohol-induced rosacea flushing and alcohol-induced urticaria. Antihistamines are effective prophylaxis for alcohol-induced urticaria and ALDH2-related bronchoconstriction. If a deficiency in DAO is suspected, supplementation with DAO or antihistamine prophylaxis can be considered. Immediate treatment of adverse reactions after alcohol ingestion is the same as that of other food allergens. Epinephrine is the treatment of choice for anaphylaxis, with the use of antihistamines, oral steroids, β agonists, and H3 blockers as adjuncts. Although there are no current recommendations for the prescription of self-injectable epinephrine in patients with reactions to alcohol, it is recommended that self-injectable epinephrine be considered given the potential for anaphylaxis after seemingly mild symptoms. Similarly, Medic Alert bracelets should be recommended. Patient education must include avoidance of aggravating factors and education about hidden sources of alcohol. A history of alcohol intolerance should be sought in patients with aspirin-exacerbated respiratory disease and in those with asthma or rhinitis.

Conclusion

Adverse reactions to alcohol present in different ways, reflecting the many etiologic mechanisms that exist. Reactions to alcoholic beverages are likely more prevalent than reported because only limited studies exist to date. Evaluation requires a systematic approach, including a careful history, targeted evaluation with skin testing, laboratory workup, and oral challenges. This review provides a framework for this evaluation based on the available literature. Further research in the form of randomized controlled trials that address the mechanisms behind adverse reactions to alcohol would provide a more robust frame of reference for evaluation and open the potential for new treatment options for affected individuals.

Acknowledgments

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References


