

The system classifies cases as no case, possible case, probable case, and definite case based on the number of criteria met, with a score of greater than 5 considered definite. Criteria include (1) temperature higher than 38°C, (2) lymphadenopathy, (3) skin involvement, (4) involvement of at least one organ system, (5) atypical lymphocytes, (6) eosinophilia, (7) time of resolution of 15 days or longer, and (8) exclusion of other causes, with hepatitis serologic findings, antinuclear antibody, and blood cultures.<sup>1</sup> The Japanese consensus group describes a scoring system that includes similar criteria but also expands to include leukocytosis and HHV 6 reactivation.<sup>6</sup> Our patient met the criteria for definite DRESS syndrome with a RegiSCAR score of 6 and a Japanese consensus group score of 6 after appropriate evaluation for other etiologies.<sup>6</sup>

DRESS syndrome has been well documented in the literature in adults with HIV on various antiretroviral regimens; however, it is rarely described in children. Integrase inhibitors, such as raltegravir, are a newer class of oral HIV-1 medications that have a long safety record with relatively few adverse effects.<sup>7</sup> A MEDLINE search using the Medical Subject Headings of *DRESS syndrome* and *raltegravir* yielded 4 reported cases of raltegravir-induced DRESS syndrome, all in adult patients with an age range of 18 to 64 years (Table 1).<sup>2–5</sup> All patients were female, 3 were of African descent, and all presented with fever, morbilliform rash, elevated transaminases, and lymphadenopathy. Three had probable and 1 had definite DRESS syndrome based on the RegiSCAR scoring. The patients did well, and only 1 patient relapsed with DRESS syndrome.<sup>4</sup>

Although abacavir hypersensitivity is a common cause of drug rash and eosinophilia in HIV, this was not the case in our patient because she had 2 negative test results that correlate with cutaneous reactions to abacavir, patch testing at multiple concentrations, and HLA B-5701 testing.<sup>8–10</sup> Patch testing to abacavir is an accurate way to diagnose abacavir sensitivity. This correlates with HLA B-5701 testing in patients with HIV and suspected hypersensitivity reactions to abacavir with positive and negative predictive values of 82% and 85%, respectively. The HLA B-5701 test specificity is 90% to 100%, regardless of presentation.<sup>8–11</sup> There are no published cases of DRESS syndrome associated with emtricitabine, and our patient had history of long-term lamivudine use (a similar nucleoside analogue) before starting emtricitabine therapy. This evidence strongly suggests that the culprit drug in our case was raltegravir.

DRESS syndrome is an uncommon hypersensitivity reaction that, when seen in children, is typically associated with anticonvulsant or antibiotic therapy. Raltegravir has been infrequently associated with DRESS syndrome. As with other antiretroviral medications, practitioners should closely monitor patients when switching to this class of therapeutic agents for serious drug reactions.

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## Contact urticaria caused by alcohol Clinical characteristics and cross-reactions

Contact urticaria (CU) from alcohol is often underdiagnosed and undertreated because it is much less frequent than allergic eczema and is transient in nature.<sup>1</sup> Its mechanism can be mediated by immunologic and nonimmunologic processes.<sup>2</sup> Few data on CU caused by alcohol have been published. This study investigated

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Felicia A. Scaggs, MD\*  
Mariam S. Aziz, MD\*†‡  
Erica L. Palmisano, MD§  
Mahboobeh Mahdavinia, MD, PhD\*§  
Sheela S. Raikar, MD\*||  
Latania K. Logan, MD\*†

\*Department of Pediatrics  
Rush University Medical Center  
Chicago, Illinois

†Section of Pediatric Infectious Diseases  
Rush University Medical Center  
Chicago, Illinois

‡Department of Internal Medicine  
Division of Infectious Diseases  
Rush University Medical Center  
Rush Medical College  
Chicago, Illinois

§Section of Allergy and Immunology  
Department of Immunology and Microbiology  
Rush University Medical Center  
Chicago, Illinois

||Section of Pediatric Gastroenterology  
Rush University Medical Center  
Chicago, Illinois

Latania\_Logan@rush.edu

#### References

- [1] Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med.* 2011;124:588–597.
- [2] Loulergue P, Mir O. Raltegravir-induced DRESS syndrome. *Scand J Infect Dis.* 2012;44:802–803.
- [3] Perry ME, Almaani N, Desai N, Larbalestier N, Fox J, Chilton D. Raltegravir-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: implications for clinical practice and patient safety. *Int J STD AIDS.* 2013;24:639–642.
- [4] Yee BE, Nguyen NH, Lee D. Extensive pulmonary involvement with raltegravir-induced DRESS syndrome in a postpartum woman with HIV. *BMJ Case Rep.* 2014 May 5. <http://dx.doi.org/10.1136/bcr-2013-201545>.
- [5] Zhang KS, Modi GM, Hsu S. DRESS syndrome associated with raltegravir. *Dermatol Online J.* 2011;17:14.
- [6] Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antidrug immune responses. *Allergol Int.* 2006;55:1–8.
- [7] Markowitz M. Sustained antiretroviral effect of raltegravir after 96 weeks of combination therapy in treatment-naïve patients with HIV-1 infection. *J Acquir Immune Defic Syndr.* 2009;52:350–356.
- [8] Mallal S, Phillips E, Carosi G, et al. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358:568–579.
- [9] Phillips E, Sullivan J, Knowles S, Shear N. Utility of patch testing in patients with hypersensitivity syndromes associated with abacavir. *AIDS.* 2002;16:2223–2225.
- [10] Giorgini S, Martinelli C, Tognetti L, et al. Use of patch testing for the diagnosis of abacavir-related hypersensitivity reaction in HIV patients. *Dermatol Ther.* 2011;24:591–594.
- [11] Ma J, Lee K, Kuo G. HLA-B\*5701 testing to predict abacavir hypersensitivity. *PLoS Curr.* 2010;2:RRN1203.



clinical characteristics, cross-reactions, and association with alcohol consumption in patients who had CU caused by ethanol (ethyl alcohol).

Patients who had an urticarial reaction occurring on the skin within 30 minutes after direct contact with ethanol and who attended Siriraj Hospital during a 3-year period were enrolled. Demographic data, symptoms after application of cosmetic

**Table 1**  
Reported Symptoms After Alcohol Consumption and Open Patch Test Results<sup>a</sup>

| Case No.       | Reported Symptoms After Alcohol Consumption                       | Primary Alcohol |     |            | Benzyl Alcohol |     |            | Methanol       |     |            | Secondary Alcohol |     |            | Wine           |     |            | Beer           |     |            |
|----------------|-------------------------------------------------------------------|-----------------|-----|------------|----------------|-----|------------|----------------|-----|------------|-------------------|-----|------------|----------------|-----|------------|----------------|-----|------------|
|                |                                                                   | Ethanol         |     | Onset, min | Erythema/Edema |     | Onset, min | Erythema/Edema |     | Onset, min | Isopropyl Alcohol |     | Onset, min | Erythema/Edema |     | Onset, min | Erythema/Edema |     | Onset, min |
|                |                                                                   |                 |     |            |                |     |            |                |     |            |                   |     |            |                |     |            |                |     |            |
| 1              | Generalized urticaria                                             | 15              | 2/0 | 35         | 1/0            | 1/0 | 35         | 1/0            | 1/0 | NA         | NA                | NA  | 20         | 3/0            | 3/0 | 30         | 1/0            | 1/0 | 30         |
| 2              | Erythema                                                          | 5               | 3/0 | 15         | 2/0            | NA  | NA         | NA             | NA  | NA         | NA                | NA  | 10         | 3/0            | 3/0 | 30         | 1/0            | 1/0 | 30         |
| 3              | Generalized urticaria                                             | 5               | 4/1 | 30         | 1/0            | NA  | NA         | NA             | NA  | NA         | NA                | NA  | 15         | 3/0            | 3/0 | 20         | 2/0            | 2/0 | 20         |
| 4              | Erythema                                                          | 10              | 3/0 | 20         | 1/0            | 2/0 | 20         | 2/0            | 2/0 | 20         | 2/0               | 2/0 | 20         | 3/0            | 3/0 | NA         | NA             | NA  | NA         |
| 5              | Erythema                                                          | 8               | 3/0 | 20         | 1/0            | NA  | NA         | NA             | NA  | NA         | NA                | NA  | 10         | 3/0            | 3/0 | 15         | 2/0            | 2/0 | 15         |
| 6              | Never drunk alcohol                                               | 15              | 2/0 | NA         | NA             | NA  | NA         | NA             | NA  | NA         | NA                | NA  | 15         | 2/0            | 2/0 | NA         | NA             | NA  | NA         |
| 7 <sup>a</sup> | Generalized urticaria                                             | 15              | 4/2 | 40         | 1/0            | 1/0 | 35         | 1/0            | 1/0 | NA         | NA                | NA  | 15         | 1/0            | 1/0 | NA         | NA             | NA  | NA         |
| 8              | Erythema                                                          | 10              | 3/0 | 25         | 1/0            | 1/0 | 25         | 1/0            | 2/0 | NA         | NA                | NA  | 15         | 3/0            | 3/0 | 25         | 1/0            | 1/0 | 25         |
| 9              | Erythema                                                          | 5               | 3/0 | 15         | 4/1            | 4/1 | 10         | 2/0            | 2/0 | 30         | 2/0               | 2/0 | 10         | 3/0            | 3/0 | 15         | 2/0            | 2/0 | 15         |
| 10             | Erythema                                                          | 5               | 2/0 | NA         | NA             | NA  | NA         | NA             | NA  | NA         | NA                | NA  | 15         | 3/0            | 3/0 | 20         | 1/0            | 1/0 | 20         |
| 11             | Erythema                                                          | 15              | 2/0 | NA         | NA             | NA  | 30         | 1/0            | 1/0 | NA         | NA                | NA  | 20         | 3/0            | 3/0 | NA         | NA             | NA  | NA         |
| 12             | Itching and erythema                                              | 15              | 3/0 | 35         | 2/0            | 2/0 | 35         | 2/0            | 2/0 | NA         | NA                | NA  | 15         | 3/0            | 3/0 | NA         | NA             | NA  | NA         |
| 13             | Vodka - generalized urticaria, other alcohol beverages - erythema | 5               | 3/0 | 30         | 2/0            | 2/0 | NA         | NA             | NA  | NA         | NA                | NA  | 10         | 2/0            | 2/0 | 20         | 1/0            | 1/0 | 20         |

Abbreviation: NA, not applicable.  
The numbers 1, 2, 3, and 4 refer to slight edema, moderate (palpable wheal), intense (tense wheal), and fiery erythema (wheal extending beyond the test area), respectively.  
<sup>a</sup>Developed eczema 24 hours later.



**Figure 1.** Positive open patch test result to ethanol (edema 2+), benzyl alcohol (erythema 1+), methanol (erythema 1+), and wine (erythema 1+) in patient 7.

products, and symptoms after alcohol consumption were recorded. Primary alcohol (70% ethanol, 100% benzyl alcohol, and 100% methanol), secondary alcohol (100% isopropyl alcohol), wine, and beer were used to perform open patch testing (OPT) and skin prick testing (SPT). Wheat (1:10) and yeast (1:10) weight by volume (ALK Abello Inc, Round Rock, Texas) were also used to perform the tests. In OPT, the primary test for the diagnosis of CU, 0.1 mL of the test substances (as is) is spread over a 3 × 3-cm area on the volar aspect of the normal skin of the left forearm. The results were interpreted within 1 hour to see the maximal response.<sup>3</sup> SPT is the preferred method if the OPT result is negative. One drop of each test allergen, buffer saline solution (negative control), and histamine (positive control) were applied on the normal skin of the volar aspect of the right forearm. Procedure and interpretation were performed according to the standard technique of SPT.<sup>3</sup> Every patient was carefully monitored after the test. The OPT and SPT with wine, beer, and primary and secondary alcohols had been tested in 10 controls, which revealed negative reactions. Data were analyzed using PAWS Statistics, version 18.0 (SPSS Inc, Chicago, Illinois). This study was approved by the ethics committee of the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand.

Thirteen patients (11 women and 2 men) with a mean (SD) age of 38.2 (11.9) years were enrolled. Eleven patients (84.6%) had atopic diseases. Allergic rhinitis (53.8%) was the most common, followed by allergic conjunctivitis (23.1%) and atopic dermatitis (15.4%). Nine patients (69.2%) had a history of CU from cosmetic products, all of whom were female. All patients, except the one who had never drunk alcoholic beverages, reported cutaneous reactions without systemic symptoms after drinking alcohol (Table 1). Ethanol was commonly found to cross-react with benzyl alcohol (76.9%), followed by methanol (53.8%) and

isopropyl alcohol (15.4%). One patient (patient 7) developed eczematous dermatitis 24 hours later. Negative reactions to wheat and yeast but positive reactions to ethanol, benzyl alcohol, methanol, and wine were found in patient 7 (Fig 1). SPT with wheat, yeast, and primary and secondary alcohols revealed negative findings in all patients.

Cosmetic products and skin care may contain different types of alcohols, such as ethanol, benzyl alcohol, methanol, isopropyl alcohol, and 2-phenoxyethanol. Several cases of CU induced by 2-phenoxyethanol in sunscreens, moisturizers, skin-cleansing solutions, and pharmaceutical products have been reported in the literature.<sup>4</sup> Our study found that cross-reactions among substances in primary alcohols were commonly found, whereas cross-reactions between primary and secondary alcohols were infrequent as previously described.<sup>1</sup> Benzyl alcohol, which can induce nonimmunologic CU,<sup>5</sup> was the most common substance that had a cross-reaction to ethanol in our study. Generally, the term *alcohol-free products* in cosmetic labeling indicate products that do not contain ethanol but may contain other forms of alcohols. Thus, patients who had CU from ethanol should carefully check the ingredient of product even it is labeled as alcohol free to make sure that the product is truly free from any alcohol, especially benzyl alcohol. A previous study reported that cinnamic aldehyde can induce eczematous reaction after CU.<sup>6,7</sup> Fregert et al<sup>7</sup> suggested that ethanol converted to acetaldehyde and subsequent binding to protein in the skin to form a complete allergen. It is possible that the eczematous reaction in patient 7 may be attributable to either ethanol itself or metabolites of the ethanol (acetaldehyde and acetic acid) in the skin.

Ethanol, which is derived from sugars during the fermentation attributable to the metabolic activities of yeast, is the principle ingredient in alcoholic beverages. It was proposed that ethanol and metabolites of ethanol (acetaldehyde and acetic acid) were common causative agents in hypersensitivity reaction to alcoholic beverages.<sup>8</sup> Reactions to wheat and yeast of all patients who reported symptoms after drinking alcoholic beverages were excluded by negative OPT and SPT results. Cutaneous reactions to alcohol could not imply that systemic contact dermatitis would develop after drinking alcohol whether caused by delayed or immediate-type sensitivities.<sup>1</sup> The dose-response reactions and individual susceptibility are the responsible factors that enable prediction of symptoms. The concentrations of ethanol by volume in wines, beer, and strong spirits (vodka and whisky) are approximately 7% to 24%, 3% to 5%, and 50%, respectively.<sup>9</sup> The dose-response reaction may be the reason why patient 13 in our study (Table 1) had more reaction with vodka than wines and beer.

This study has some limitations. First, we were unable to distinguish between allergic reactions and irritant reactions to alcohol. However, 70% of the alcohol and all alcohol reagents had been tested in 140 controls<sup>10</sup> and 10 controls (our study), respectively, which revealed no irritant reactions. Second, gene analysis of acetaldehyde dehydrogenase 2 (ALDH2) was not performed. ALDH2 is a primary catabolic enzyme of acetaldehyde that is a derivative of ethanol. It is possible that accumulation of acetaldehyde from skin-patched ethanol in patients with low ALDH2 activity resulted in vasodilatation and skin erythema.<sup>11</sup> Third, reported symptoms after drinking alcoholic beverages can

be caused by pharmacologic effects of alcohol or a reduction in ALDH2 activity in an Asian population (oriental flushing syndrome).<sup>11,12</sup>

In conclusion, we observed that patients who had CU caused by ethanol tended to have cutaneous reactions to cosmetic products and cutaneous reactions after consuming alcoholic beverages. Cross-reactions among substances in primary alcohols were commonly found. Ethanol was commonly found to cross-react with benzyl alcohol (eFig 1).

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### Supplemental Data

Supplemental data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.09.434>.

Leena Chularojanamontri, MD  
Papapit Tuchinda, MD  
Kamolwan Pongparit, MD  
Sumruay Pinkaew, MSc  
Piyavadee Nuchkull, BSc  
Kanokvalai Kulthanan, MD  
Department of Dermatology  
Faculty of Medicine  
Siriraj Hospital  
Mahidol University  
Bangkok, Thailand  
[kanokvalai.kul@mahidol.ac.th](mailto:kanokvalai.kul@mahidol.ac.th)

### References

- [1] Ophaswongse S, Maibach HI. Alcohol dermatitis: allergic contact dermatitis and contact urticaria syndrome: a review. *Contact Dermatitis*. 1994;30:1–6.
- [2] Wakelin SH. Contact urticaria. *Clin Exp Dermatol*. 2001;26:132–136.
- [3] Kim E, Maibach HI. Changing paradigms in dermatology: science and art of diagnostic patch and contact urticaria testing. *Clin Dermatol*. 2003;21:346–352.
- [4] Núñez Orjales R, Carballas Vázquez C, Carballada González F, Boquete Paris M. 2-phenoxyethanol-induced contact urticaria and anaphylaxis. *J Invest Allergol Clin Immunol*. 2010;20:354–355.
- [5] Nair B. Final report on the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate. *Int J Toxicol*. 2001;20:23–50.
- [6] Reitschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*. 6th ed. New York, NY: BC Decker; 2008.
- [7] Fregert S, Rorsman H, Tryding N, Övrum P. Dermatitis from alcohols with special reference to the possible importance of impurities and metabolites. *J Allergy*. 1963;34:404–408.
- [8] Adams KE, Rans TS. Adverse reactions to alcohol and alcoholic beverages. *Ann Allergy Asthma Immunol*. 2013;111:439–445.
- [9] Johnson MH, Gonzalez de Mejia E. Comparison of chemical composition and antioxidant capacity of commercially available blueberry and blackberry wines in Illinois. *J Food Sci*. 2012;77:141–148.
- [10] Barbaud A, Trechot P, Reichert-Penetrat S, Schmutz J. Contact dermatitis due to ethyl alcohol: how to perform patch tests? *Ann Dermatol Venerol*. 2000;127:484–487.
- [11] Matsuse H, Shimoda T, Fukushima C, et al. Screening for acetaldehyde dehydrogenase 2 genotype in alcohol-induced asthma by using the ethanol patch test. *J Allergy Clin Immunol*. 2001;108:715–719.
- [12] Linneberg A, Gonzalez-Quintela A, Vidal C, et al. Genetic determinants of both ethanol and acetaldehyde metabolism influence alcohol hypersensitivity and drinking behaviour among Scandinavians. *Clin Exp Allergy*. 2010;40:123–130.



**Figure 1.** Strong reaction (fiery erythema and wheal extending beyond the test area) to alcohol.