

Clinical Communications

A 5-year retrospective review of outpatient graded drug challenges

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Clinical Implications

- Graded drug challenges can be safely performed in the outpatient setting and are an effective strategy for delabeling drug allergies.

TO THE EDITOR:

Drug allergies are commonly over-reported. These inaccurate drug allergy labels adversely impact patient care because first-line medications are unnecessarily avoided. For penicillin allergy, use of second-line antibiotics is associated with increased adverse reactions, cost, hospital length of stay, and bacterial resistance in both children and adults.¹⁻³ Despite the harm of unnecessarily avoiding first-line medications, there is limited validated diagnostic testing for drug allergy. Graded drug challenges (GDCs) are the gold standard for the diagnosis or exclusion of IgE-mediated drug allergy in the office, and delayed reactions outside of the office. GDCs consist of administering 1 to 3 doses of the medication in question over time.⁴ Although GDCs have an excellent safety record with no reported deaths, more data are required to better characterize GDCs.⁴

All GDCs performed in an outpatient allergy/immunology practice from 2013 to 2018 were identified retrospectively through an electronic medical record (EMR) report (Epic, Verona, Wis). This retrospective cohort included any GDC not preceded by skin testing. Drug allergy histories included self-report and/or information in the allergy field of the EMR. Although there were no specific criteria to undergo GDC, patients were selected if a trained allergy/immunology physician felt GDC to be clinically indicated. GDCs were performed with 2 oral doses (one-tenth and full dose) or 3 oral doses (one-hundredth, one-tenth, then a full dose) separated by 30 minutes. There were no intravenous or intramuscular challenges. GDCs to penicillin-related antibiotics that were preceded by the penicillin skin test were excluded. Patient demographics, historical reactions, indication, and outcome of the GDC were recorded. All dichotomous comparisons were done using Fisher's exact test. Parametric age analysis was done with Student's *t*-test, and nonparametric age analysis was done with the Mann-Whitney *U* test.

There were 172 GDCs performed over the 5-year period. The mean age ($\pm$ standard deviation [SD]) of patients undergoing GDCs was 38.1 ± 28.3 years. The ages of the patients ranged from 1 to 88 years. The majority of patients were female ($n = 106$, 61%), whereas 67 (39%) were male. The mean time ($\pm$ SD) since the historical reaction to the medication in question was 8.0 ± 13.0 years.

Indications for GDCs performed are shown in Figure 1. Although the majority of GDCs were performed electively ($n = 88$, 51.2%), other common indications included management of

recurrent infections ($n = 30$, 17.4%), such as recurrent otitis media or recurrent urinary tract infection, and analgesia ($n = 20$, 11.6%). Other indications included management of chronic conditions, such as chronic obstructive pulmonary disease ($n = 4$, 2.3%), and treatment of active infection ($n = 2$, 1.2%).

Both historical reactions and failed reactions of patients who underwent GDCs are shown in Figure 2. For historical reactions, 68 (35.2%) cases reported urticaria, 50 (25.9%) reported a rash, 40 (20.7%) reported angioedema, 10 (5.2%) reported dyspnea, 9 (4.7%) reported pruritus, 3 (1.6%) reported flushing, and 6 (3.1%) did not recall their historical reaction. Other less common reactions included hypotension in 3 patients (1.6%), nausea/vomiting in 3 (1.6%), and 1 reported diarrhea (0.4%).

GDCs were performed for 113 (65.7%) antibiotics, 37 (21.5%) nonsteroidal anti-inflammatory drugs (NSAIDs), 7 (4%) oral steroids, and 15 (8.7%) other medications. The most commonly challenged antibiotics were amoxicillin ($n = 35$, 31.0%), macrolides ($n = 21$, 18.6%), cephalosporins ($n = 19$, 16.8%), and sulfamethoxazole ($n = 18$, 15.9%). Of the 172 GDCs that were performed, 13 (7.6%) resulted in a positive reaction in the office or immediately after.

Of the 13 positive GDCs, 5 (38.4%) patients experienced pruritus, 4 (30.8%) experienced urticaria, 2 (15.4%) experienced a nonspecific rash, 4 (30.8%) experienced angioedema, 1 (7.7%) experienced flushing, and 2 (15.4%) experienced dyspnea. Two (15.4%) reactions occurred after the first dose, 4 (30.8%) reactions occurred after the second dose, and 7 (53.8%) reactions occurred after the final dose. There were 3 positive reactions to NSAIDs and 10 positive reactions to antibiotics. Of the 13 failed reactions, 4 (30.8%) required no treatment and self-resolved within 60 minutes. Seven (53.8%) reactions were treated with antihistamines only, and another (7.7%) required the addition of ipratropium/albuterol. One patient (7.7%) who underwent a GDC to azithromycin required treatment with epinephrine and ipratropium/albuterol.

There was no statistically significant difference between the positive and negative challenges with respect to gender, age, time since reaction, number of drug allergies, drug challenged, or historical reaction. The historical reaction was not a predictor of a passed or failed GDC. The patient requiring treatment with

Graded Drug Challenge by Indication

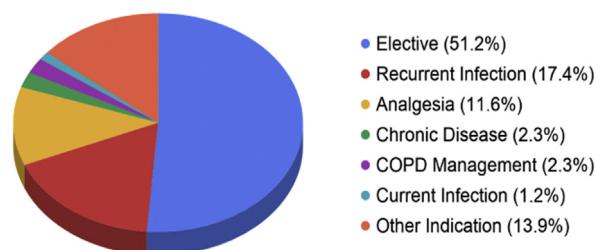


FIGURE 1. Graded drug challenge by indication. COPD, Chronic obstructive pulmonary disease.

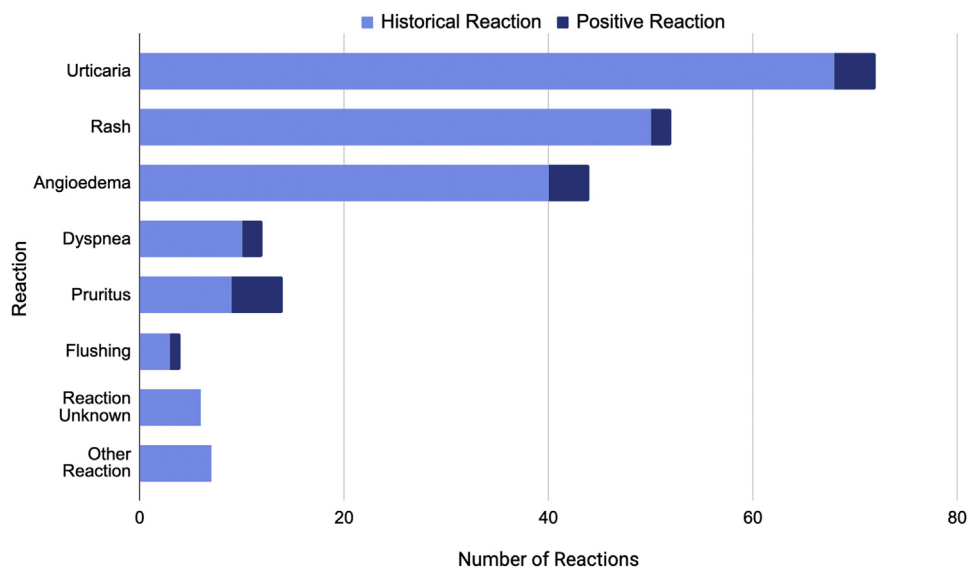


FIGURE 2. Historical and failed reactions of graded drug challenges.

epinephrine for the failed challenge reported a history of flushing and urticaria.

A limitation of our study was the small number of patients, and this may be why predictors of challenge outcomes did not reach statistical significance. The limited sample size also precluded us from drawing significant conclusions between the classes of medications that were challenged. In addition, this retrospective study has a selection bias in that GDCs are generally low risk where true drug allergy is not suspected. Continued drug avoidance would be recommended to patients with high-risk reaction histories, such as severe cutaneous reactions or anaphylaxis. This selection bias potentially accounts for our low reported reaction rate of 7.6%. Future prospective studies with larger sample sizes are warranted. Despite that limitation, our study supports that GDCs can be safely performed in the outpatient setting by an experienced allergy/immunology physician and are an effective strategy for delabeling drug allergies. Although other studies have examined the characteristics and safety of GDCs, there is still limited data on the subject.⁴⁻⁶ Our study adds to the body of knowledge regarding indications and outcomes of GDCs.

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Behring. S. Shahzad Mustafa is a speaker for CSL Behring, Genentech, Regeneron, Teva, and Astra Zeneca and has received research grants from Shire, Regeneron, and CSL Behring. The rest of the authors declare that they have no relevant conflicts of interest.

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