# Rash diagnostics: an update on the diagnosis of allergic rashes

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**Purpose of review**
The purpose of this review is to summarize recent research regarding the diagnosis of allergic rashes and to suggest future directions for the promotion of accurate diagnosis and endotype specification.

**Recent findings**
Multiple cohort studies demonstrate that with appropriate clinical evaluation, drug allergy labels can be removed in up to 90% of cases. Genetic tests can predict severe adverse cutaneous drug reactions in some cases and in vitro tests are being sought to identify causative drugs in others. Biomarkers to define endotypes of atopic dermatitis are needed to predict which patients will benefit from evolving targeted therapies. Hyperspectral imaging is a rapidly evolving technology in medical diagnostics; additional research is needed to demonstrate whether this promising technology can be used to distinguish allergic rashes and/or endotypes in atopic dermatitis.

**Summary**
Diagnostic tools for the assessment of allergic rashes are primitive in that they frequently rely on challenges to ascertain whether suspected allergens were causative. Validated in vitro tests with high sensitivity and specificity for drug allergies would benefit the field, particularly in delayed type reactions, as would identification of any hyperspectral signatures that could identify endotypes in atopic dermatitis.

**Keywords**
adverse cutaneous drug reaction, allergic rash, atopic dermatitis, hyperspectral imaging, physical diagnosis

## INTRODUCTION

In September 2015, the National Academy of Medicine released the report 'Improving Diagnosis in Healthcare' with a major goal being to 'expose a critical type of error in healthcare – diagnostic error' [1] (page xiii). In keeping with a theme in this report: 'the data on diagnostic error are sparse', and while preparing this review, the author could find no data regarding clinician accuracy in allergic rash diagnosis. The closest, perhaps, are numerous studies describing that patients with mild rashes attributed to antibiotic allergy can tolerate those antibiotics without reaction in up to 90% of cases. We certainly strive for greater than 10% accuracy in diagnosis.

The purpose of this review is to summarize recent research regarding the diagnosis of allergic rashes and to suggest future directions for the promotion of accurate diagnosis. The term allergic rash as used in this review encompasses a variety of cutaneous disorders and is not limited to rashes with immediate immunoglobulin E-mediated causes. With the precision medicine initiative comes the push not only to accurately diagnose individual patients who may have differing presentations of the same diseases but also to tailor therapies specifically to each individual's needs. Following this trend, this review will also address the increasingly recognized need to break down the heterogeneous diagnosis of atopic dermatitis into distinguishable endotypes to guide appropriate use of rapidly emerging medications targeting specific molecules.

### Adverse cutaneous drug reactions

In Naranjo *et al.*'s [2] validated adverse drug reaction probability scale, which is often used to determine

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## KEY POINTS

- Diagnostic tools for the assessment of allergic rashes are primitive.
- The majority of patients who are labeled with amoxicillin or other β-lactam allergy are able to tolerate these medications in medically supervised drug challenges.
- Novel therapeutics targeting specific molecules integral in allergic inflammation have demonstrated benefit in some patients with atopic dermatitis in phase 3 trials.
- Biomarkers to define endotypes of atopic dermatitis are needed to identify which patients will benefit most from new targeted therapies.
- Hyperspectral imaging is an emerging technology in the field of medical diagnostics and has potential use in the field of allergy particularly in the evaluation of skin; research is needed to clarify its applications.

the likelihood that the suspect drug was indeed causative, labeling a drug reaction 'definite' requires not only improvement of the reaction when the drug is withdrawn but also 'reappear(ance) on reexposure' (page 241). To date, the most reliable diagnosis of drug allergy is based on a double-blind placebo controlled challenge. In cases of severe reactions, such reexposure is usually imprudent and surrogate markers of likely susceptibility are highly sought.

The majority of reported adverse cutaneous drug reactions are not severe. Severe cutaneous adverse drug reactions (SCAR) are typically defined as being of one of the following types: Stevens Johnson syndrome, acute generalized pustolosis, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, and toxic epidermal necrolysis (Fig. 1). In cases of mild cutaneous reactions, several recent studies have demonstrated the feasibility and safety of medically supervised drug challenges.

### Mild cutaneous drug reactions

Amoxicillin is one of the most commonly listed drug allergies in pediatrics. Skin prick testing is a poor screening test to detect significant reactors in delayed reactions. For example, in a retrospective review of 337 pediatric cases of suspected nonimmediate amoxicillin reactions who had amoxicillin skin testing performed, specificity of skin tests for adverse cutaneous drug reactions was high at 99.7% but sensitivity was low at only 8% [3]. Because there is no standardized sensitive skin test available for amoxicillin allergy, many allergists will test patients with history of delayed reactions to amoxicillin

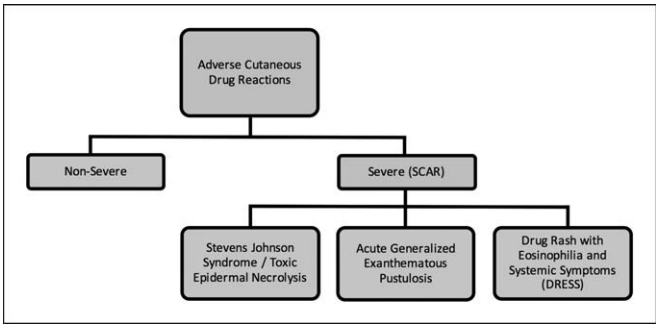


**FIGURE 1.** Adverse cutaneous drug reactions. DRESS, drug rash with eosinophilia and systemic symptoms; SCAR, severe cutaneous adverse drug reactions.

consisting of isolated mild rash with graded oral challenge doses only. In an observational cohort study of 818 children with suspected amoxicillin allergy and history of isolated mild rash, 770 (94.1%) tolerated graded oral provocation challenge consisting of one dose of amoxicillin split into two respective administrations of 10 and 90% separated by 20 minutes if initial dose were tolerated [4▪▪]. No skin prick testing was performed prior to these graded dose challenges and all reactions experienced with challenge were graded mild with rash only. The follow-up of this study was unique in that 10.9% of children who tolerated the challenge subsequently developed nonimmediate drug rashes when a full course of amoxicillin was again prescribed for suspected infectious cause, suggesting either a reaction to multiple day dosing of amoxicillin, a reaction to the infectious agent, or a reaction to the combination of the drug and the infectious agent. Using this follow-up data, a negative predictive value of 89.1% was established for patients who passed an oral challenge to a standard dose of amoxicillin. In another study of 119 pediatric patients presenting to clinic with nonimmediate mild cutaneous reactions to β-lactams, only four developed reactions on oral challenge [5]. Again, no allergy skin prick testing was performed and in the four patients reacting during the challenge, symptoms were no more severe than they had been during the initial event. Because many reactions to amoxicillin are delayed, extending amoxicillin testing to include 5 days of oral provocation if initial doses are tolerated has been advocated by some groups. In another retrospective study of children with suspected amoxicillin allergy, investigators prescribed the completion of a 5 day course of amoxicillin to be taken at home if the initial dose were tolerated in the clinic during the observed challenge [6]. Again approximately 90% of 190 children who had been labeled as amoxicillin allergic were able to tolerate the challenge. Out of the

17 children who developed rash after the challenge, six reacted on the first day (35.3%), seven on the second day (41.2%), and four (23.5%) on the fifth day, demonstrating improved challenge sensitivity with increased duration. No reactions were severe and all reactions that occurred at home after the first dose was tolerated in clinic were mild, supporting the safety of such a procedure.

Penicillin skin prick testing is a highly sensitive test when using major and minor determinants to predict immediate type I hypersensitivity reactions with risk for anaphylaxis [7]. In a study of 401 patients at least 15 years of age labeled as penicillin allergic, approximately 90% were able to subsequently tolerate penicillin after a combination of skin prick testing, intradermal testing, and oral challenge [8]. After a median of 15 months had passed, out of 182 of these patients interviewed, 132 (75.3%) were still following allergy delabeling advice. Follow-up suggested that clear communication with patients was integral to promoting the continuance of allergy delabeling over time.

Inaccurate attribution of rash to drug allergy is also prevalent in other antibiotic classes. In a prospective study of 95 patients with suspected non-β-lactam antibiotic allergy, only four (4.7%) out of 85 tested had positive intradermal or oral provocation testing [9]. When the remaining 11 individuals were included who had clinically concerning allergic presentations that prevented testing, only 15 patients (15.6%) had evidence of reactions. In summary, increasing numbers of studies are affirming that up to 90% of patients labeled with antibiotic allergies have inaccurate drug allergy diagnoses. Patients labeled as drug allergic may benefit from further allergy work-up to rule out these drug allergies, particularly in cases where mild cutaneous rash was the only associated symptom.

## Severe cutaneous adverse drug reactions

Genetic screening is increasingly used to identify patients at high risk to develop SCAR to particular drugs. The human leukocyte antigen (HLA) complex can drive DRESS reactions involving certain medications including allopurinol [10]. Screening for associated HLA allele prior to use and selecting alternative medications for those with positive screening has been an effective strategy in decreasing incidence of SCAR [11]. HLA screening is recommended by the US Food and Drug Administration (FDA) prior to initiation of abacavir in all patients and carbamazepine in patients with high risk ancestry; these two medications have been associated with SCAR in predisposed individuals. Ongoing efforts attempt to implicate other genetic loci in drug allergy with limited success to date. A recent genome-wide association study did not identify implicated genes in sulfonamide antibiotic reactions [12].

In cases where SCAR cannot be predicted with HLA testing and subsequently avoided, there is significant debate regarding which forms of testing to use to diagnose reactions and how to identify the causative drugs. Although many physicians assume biopsy is helpful in rash diagnosis, 'There are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and a skin biopsy may not definitively exclude alternate causes' (7) (page 273.e36). In an articulate review of eosinophilic drug allergy, Kuruvilla and Khan [13] highlight that neither peripheral nor tissue eosinophilia is pathognomonic for an adverse cutaneous drug reaction and eosinophilia in biopsy specimens do not make drug allergy more likely than viral-mediated exanthema. The differential diagnosis for eosinophilia is wide and is not limited to drug allergy. Recent descriptive studies, including biopsy analyses from multiple patients with DRESS, did not find any new definitive diagnostic properties on histopathology [14,15] and biopsies from patients presenting with adverse cutaneous drug reactions did not predict who would go on to develop SCAR [16].

Additional tools in the diagnosis of SCAR are experimental. Patch testing for SCAR is generally not performed in the United States because of safety concerns although it is common practice in Europe [17] and increasing consensus promotes patch testing as a well tolerated and effective diagnostic tool specifically for DRESS secondary to antiepileptic drugs [13]. In a recent case series, 10 out of 11 patients with HIV with history of adverse cutaneous drug reactions developed systemic reactions within 48 h of patch testing to antituberculosis drugs, suggesting particular safety concerns for patch testing in this population [18]. In vitro tests showing some promise include lymphocyte transformation tests [19–21], although specificity of results are in general much better than sensitivity, making them possible confirmatory tests but poor screening tests. Amali *et al.* [22] developed a B-cell culture and stimulation method to detect B-cell responses specific to piperacillin using blood from patients with piperacillin allergy, a common hypersensitivity in patients with cystic fibrosis. Patients with history of piperacillin allergy and positive lymphocyte transformation test were more likely to generate piperacillin-specific immunoglobulin G than tolerant patient controls. Most promisingly, Klaewsongkram *et al.* [23▪▪] developed an in vitro interferon-γ enzyme-linked immunospot assay that predicted diagnosis of allopurinol-induced SCAR

with a sensitivity of 79.2% and specificity of 95.2% in a small cohort of 24 patients and 21 controls. The high specificity if validated in additional studies suggests this tool could be used to confirm SCAR due to allopurinol.

## Contact dermatitis

Since first described by Josef Jadassohn, a German dermatologist, in 1895, patch testing has become the gold standard for diagnosing allergic contact dermatitis. Patch testing can identify materials to which a person is sensitized, but whether the particular reagents identified are clinically relevant to the problem for which the patient presents cannot be determined by patch testing alone and is a matter of clinical judgement [24]. If dermatitis is not clearly in areas of skin exposed to relevant allergens, other diagnoses should be considered and biopsy can be performed to rule out cutaneous T-cell lymphoma.

## Atopic dermatitis

Atopic dermatitis is primarily a clinical diagnosis. Multiple clinical tools with various levels of validation have been used in research studies with Hanifin and Rajka's criteria and the UK's working party's diagnostic criteria for atopic dermatitis being among the most commonly cited. In a systematic review of validation studies of clinical tools for atopic dermatitis, the UK's working party's diagnostic criteria was determined to have the best validation studies although authors noted room for improvement [25]. Nevertheless, current definitions of atopic dermatitis are generally well accepted. The biggest diagnostic concerns raised are: can a unified severity tool be defined to meet investigators' needs around the globe so that atopic dermatitis trials can be easily compared and combined into meta-analyses? and as the heterogeneity of atopic dermatitis becomes increasingly understood at the molecular level, can atopic dermatitis be further classified into endotypes so that response to molecularly targeted medications can be predicted?

To address the first concern that comparing atopic dermatitis trials has been historically difficult because of multiple symptom measurement instruments, some of which have not been well validated, the Harmonizing Outcome Measures for eczema initiative brought together stakeholders to create a systematic review of symptom measurement instruments for atopic dermatitis [26▪]. This group classified 5 of 18 identified instruments as having potential to be including in future core symptom instruments and strives toward further defining a unifying tool. Although a unified instrument does not yet exist, pediatricians should look forward to a time when one becomes available to clarify atopic dermatitis severity assessments.

The rapid development of novel biologic pharmaceuticals to treat atopic dermatitis drives the second diagnostic concern: the need to break the diagnosis of atopic dermatitis into endotypes defined by presence or absence of particular biomarkers. Previously, atopic dermatitis medical treatments were limited to broadly acting topical corticosteroids and calcineurin inhibitors. Although the efficacy and safety of using topical low to mid-potency corticosteroids intermittently for atopic dermatitis flares has been established, safety data for long-term use of topical mid to high-potency corticosteroids is lacking [27▪▪]. With ongoing concerns regarding the long-term safety of topical corticosteroids [27▪▪,28▪,29▪] and the continued black box warning on topical calcineurin inhibitors, safer alternatives are desirable. Recently, crisaborole, a small molecule inhibitor that blocks phosphodiesterase 4, was demonstrated in topical ointment form to be well tolerated and effective in the treatment of mild-to-moderate dermatitis in two phase III clinical trials [30▪▪]. The FDA approved this medication to treat mild-to-moderate atopic dermatitis in children and adults ages 2 and older in December 2016. For adult patients with more severe or refractory atopic dermatitis, dupilumab, a mAb targeting interleukin 4 and interleukin 13 signaling, has also demonstrated safety and efficacy in two phase III clinical trials and was approved by the FDA in March 2017 for the treatment of moderate-to-severe atopic dermatitis in adults [31▪▪]. In review of these trial results in conjunction with previous phase II trials [32–34], it is notable that consistently 30–40% of patients see complete or almost complete skin clearing while on this medication. Assuming this medication will cost thousands of dollars per year as many currently approved biologics do, identifying this subset prior to treatment who best respond is important not only from a patient care perspective but also from a cost perspective. With the excitement regarding mAbs potentially being released for the treatment of atopic dermatitis, providers and patients may forget that a low-cost treatment for moderate-to-severe atopic dermatitis is wet wrap therapy for flares as recently reviewed [35▪▪]; trial of this treatment strategy has been recommended prior to initiation of systemic medications.

More mAbs are being developed and trialed to target newly recognized molecular mechanisms in atopic dermatitis [36,37]. Case series and a phase II double-blind, placebo-controlled trial for

ustekinumab, an antibody blocking the p40 subunit common to interleukin 12 and interleukin 23 note varying levels of improvement in moderate-to-severe atopic dermatitis [38–41]. In a phase I study of a mAb targeting interleukin 31, medication was well tolerated and patients with atopic dermatitis had decreased itch, improved sleep, and decreased need for topical corticosteroids [42]. Additional targets being studied in various clinical trials include interleukin 13, thymic stromal lymphopoietin, prostaglandin D2 receptor 2, interleukin 22, histamine 4 receptor, and interleukin 1 receptor type 1 among others [37]. Another noteworthy study implicates the aryl hydrocarbon receptor in air pollution's promotion of atopic dermatitis through artemin, and these may serve as targets for the development of other mAbs [43].

Despite successes in developing targeted therapies in atopic dermatitis, predictive biomarkers in atopic dermatitis that split patients into endotypes to guide treatment strategies have not been identified [44]. The American Academy of Allergy, Asthma, and Immunology and the European Academy of Allergy, Asthma, and Clinical Immunology put forth a practical allergy consensus that included three proposed endotypes for atopic dermatitis: type 2 immune response, nontype 2 immune response, and epithelial dysfunction [45] with the need to further explore what appropriate biomarkers may correspond to each type. Two subsets of noncirculating resident memory T cells in the skin have been described with evidence that they secrete more cytokines than their circulating peers, suggesting that the search for atopic dermatitis biomarkers may benefit from skin-centered approaches [46▪▪]. Because the majority of atopic dermatitis occurs in children during critical developmental periods, noninvasive biomarker capture would be ideal.

In summary, new therapies are emerging to treat atopic dermatitis. As more studies demonstrate that not all patients with atopic dermatitis respond equally to targeted systemic therapies, atopic dermatitis is increasingly understood as a heterogenous disorder. No available test exists to predict who will respond to which medication. As new therapies emerge, patients who remain uncontrolled on current therapies may benefit from newly available medications. Hopes are that biomarkers will be found to methodically determine which drug to try first in which patient.

## Rashes secondary to food allergy

Food allergy may cause rashes and severe allergy is often accompanied by other signs and symptoms that can include anaphylaxis. Owing to space limitations, the author refers readers to a recent review on the cutaneous manifestations of food allergy; this review describes diagnostic challenges in food allergy, another diagnosis where double-blind, placebo-controlled challenge is the gold standard for diagnosis and should only be performed in appropriate medical settings [47]. As highlighted there, chronic urticaria is not a typical manifestation of food allergy and patients with this history should be worked up for chronic spontaneous urticaria (previously known as chronic idiopathic urticaria), treated appropriately, and offered medically supervised food challenges to avoid unnecessary dietary restrictions.

## Differential diagnosis for allergic rashes

Complex, multisystem disorders may present with allergic rashes as outlined in two excellent reviews [48,49]. Patients with severe disease, unusual presentations, or comorbid conditions should be evaluated for other diagnoses and skin biopsies considered.

## Looking to the future

With the charge from our nation's leaders to increase diagnostic accuracy, how can we respond to the problem of inaccurate drug allergy labeling for so many of our patients who have history of rashes? Ongoing efforts by several national medical organizations promote allergy evaluation for those patients labeled drug allergic prior to introduction of second-line antibiotic alternatives. Medically supervised food and drug challenges in appropriately monitored venues can decrease false allergy labeling, particularly when nonsevere rash was the only correlated manifestation.

Lack of clear biomarkers to predict response to increasingly specifically targeted therapies will limit care of patients, particularly in the area of atopic dermatitis. What novel strategies may guide us into the future? Hyperspectral imaging is a noninvasive, radiation-free imaging technology that captures the visual spectrum with superior depth than any standard camera or human eye and allows for separation of materials because of underlying physical and biological property differences [50]. Hyperspectral imagers divide light as if through a prism into hundreds or thousands of discrete colors (wavelengths), where a normal camera would group these same wavelengths into the broad bands of red, green, and blue that the human eye perceives. Like genetic sequencing, this technology generates a vast amount of data and requires knowledgeable

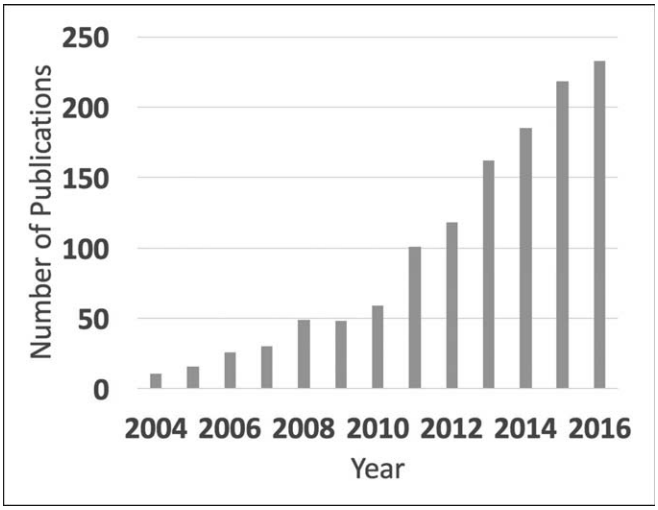


**FIGURE 2.** Number of PubMed citations per year for 'hyperspectral imaging'.

processing prior to meaningful use. Over the last 10 years, increasing research using this technology is being published as demonstrated by a histogram of citations indexed in PubMed (Fig. 2). Unique hyperspectral signatures have been used to detect various forms of cancer, including melanoma [51], prostate cancer [52], oral cancer [53], and colon cancer [54]. Hyperspectral sensors can monitor oxygenation and perfusion of transplant organ tissues [55], distinguish ablated from nonablated heart tissue [56], and identify molecular markers of age-related macular degeneration [57]. Unique hyperspectral signatures have also been seen that describe physical properties where the corresponding molecular mechanisms are not yet known, as, for example, in a study of the aging process of skin in the human hand [58]. Such studies suggest that unique hyperspectral signatures may be found to differentiate endotypes of atopic dermatitis and perhaps even better distinguish other allergic skin rashes. An exploratory study demonstrated clear hyperspectral separation between type I immediate hypersensitivity skin reactions and type IV delayed type hypersensitivity reactions [59]. If feasible, the benefits of using hyperspectral imaging as a biomarker would include its ability to identify features of human skin composition without the expense and physical disfiguration associated with serial biopsies. Sampling could recur at the same precise locations over time and cover large body surface areas. The noninvasive nature of this technology would be of particular interest for use in children in whom even serial blood draws can become anxiety-provoking procedures over time. More research is needed to explore these possibilities.

## CONCLUSION

The definition of diagnostic error in the National Academy of Medicine's report 'Improving Diagnosis in Healthcare' is 'the failure to establish an accurate and timely explanation of the patient's health problem(s) or communicate that explanation to the patient'(1) (page 4). The three areas identified in this review where diagnosis and communication of that diagnosis can be most improved are the misattribution of rashes to allergy, particularly in relation to drugs, the development or refinement of in vitro tests with good sensitivity and specificity to implicate particular drug(s) in SCAR, and the identification of atopic dermatitis biomarkers to divide patients into appropriate endotypes so that patients can be appropriately prescribed corresponding targeted therapies that are emerging. Hyperspectral imaging is a technology that has been explored with success in other areas of medicine and the field of allergy may benefit from similar exploration.

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### Conflicts of interest

*There are no conflicts of interest.*

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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