



Editorial

Drug patch testing for severe cutaneous adverse reactions: Not in the United States?



Patch testing patients with Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) on multiple medications has precedent elsewhere in the world but is not used this way in the Western hemisphere. Are we missing an opportunity to improve care for these patients? The systematic review in this month's issue delves into that question.¹

Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for their literature search, 58 articles describing 82 patients with SJS/TEN with positive patch tests are reviewed by the authors. Four of these articles were prospective trials, whereas most were cases or case series.

The overall rates of positivity were modest when testing for entire classes of drugs, ranging from 13% to 33%. However, when a medication was suspected to be causative, the rates of positivity for patch testing substantially increased, ranging from 54% to 77%. This is best exemplified when testing for antibiotics as a class (13.1%, 30/229) vs testing an antibiotic specifically thought to be the cause (77.8%, 28/36). If there is an obvious suspect, patch testing can be useful to confirm this. One might ask, "If there is an obvious suspect, why do patch testing?" For a truly single-suspect situation, this is a valid question. In a complex medical situation in which one medication is favored but others are possible and needed for sustaining life or fighting infection, being able to positively identify the causative agent prevents restrictions on drugs for which substitutes are not equal. The most frequent cases of SJS/TEN are often in diseases for which proper treatment is imperative—epilepsy, tuberculosis, and resistant infections.

Of the 58 articles identified, none was from the United States! Is it fear of reactivation, lack of standardized antigens, payment concerns, reliance on in vitro assays, number of visits, or lack of training? If half of the patch tests to suspected medications have positive results, what is the risk of causing SJS/TEN in that individual by doing the patch test? Only 3 of 82 patients had a systemic reaction to the patch testing. None of these reactions was life threatening, and 1 of the 3 was reported as mild. Notably, 2 of the 3 patients who reacted systemically had HIV with active TB, for whom testing was done to first-line antituberculosis medications.¹ A study from 8 French centers found 22 positive patch-test results in 113 similar patients. No patient had an adverse reaction.² Thus, safety was found to be high in the reported cases.

The practice parameters approved and published by the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology do refer to the use of patch testing for patients with delayed hypersensitivity drug reactions.^{3,4} A consensus document from the 2018 American Academy of Allergy, Asthma and Immunology/World Allergy Organization international drug allergy

symposium states, "Given the rarity of severe cutaneous adverse reactions (SCAR), large collaborative networks are needed to study the sensitivity, specificity, and safety of intradermal and patch testing as well as potential cross-reactive drugs and future drug choices."⁵

In vitro tests can assess lymphocyte transformation and mediator release such as granzyme and granulysin but are still considered experimental and are not commercially available.⁶ Genetic tests can only identify a few susceptible individuals: HLA-B*15:02 for carbamazepine, HLA-B*13:01 for dapsone, and HLA-B*58:01 for allopurinol. Allopurinol is conspicuously absent among the drugs with reported positive tests because it is a well-known trigger of SJS/TEN. This is speculated to be because a metabolite of allopurinol, oxypurinol, is the immunogenic trigger rather than the parent drug. It is somewhat surprising that none of the other frequently causative medications displayed this false negativity. Perhaps some of the less recognized agents do it outside our awareness? Given the possibility that a metabolite could be responsible and the lack of standardized data on how to test these medications as a patch, negative readings do not preclude the drug from causation. When the patch test is positive, the data suggest this is reliable. False positivity, defined as a positive patch-test result to a drug not suspected to cause the SJS/TEN, was only reported in 1 case among all the literature included in this analysis. Thus, a negative test is not helpful, but a positive test can help the clinician make a life-saving decision.

Is patch testing worth the effort in SJS/TEN? Some investigators feel that it is not sensitive enough in SJS/TEN, and that it might be better used in evaluating drug rash with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis.⁷ Clinicians in the United States and elsewhere have not embraced this use of patch testing, but the data presented in this month's issue challenge us to consider whether our patients are suffering because of it.

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