

Investigating Nonimmediate Drug Eruptions: Diagnostic Benefit of a Structured Approach



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Nonimmediate (or delayed-type hypersensitivity) drug reactions are technically defined as occurring more than 1 hour after drug administration.¹ The most common major phenotypes of nonimmediate eruptions to drugs include allergic contact dermatitis, maculopapular exanthema, fixed drug eruption, drug reactions with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome/toxic epidermal necrolysis. The latter 3 reactions are termed severe cutaneous adverse reactions (SCARs).² The pathogenesis of nonimmediate drug reactions is commonly postulated to involve cell-mediated hypersensitivity with CD4⁺/CD8⁺ effector T cells, T_H1 and T_H2 cytokines (ie, IL-5), and eosinophilic infiltration. Genetic predisposition (ie, HLA) and viral reactivation (ie, Epstein-Barr virus [EBV], human herpesvirus 6A [HHV-6]) are also likely contributory factors in some cases (ie, DRESS).^{2,3} The triggering of T-cell activation by drugs has been hypothesized to include a hapten/prohapten model, a pharmacological interaction model, or the peptide repertoire model.² The investigative approach used for diagnosing nonimmediate drug reactions however is less well understood and standardized, with no single reliable diagnostic tool available and significant variability in sensitivity and specificity data from published studies.^{1,2,4} Currently available diagnostic tools include delayed-reading intradermal tests, patch tests, *in vitro* assays (lymphocyte proliferation and IFN- γ release), and finally provocation (challenge) tests.^{1,4-6} Desensitization in delayed-type hypersensitivity is possible for nonsevere drug eruptions (ie, maculopapular exanthema and fixed drug eruption), but it is contraindicated in SCARs.⁷

In the current issue, Kessler et al⁸ report a case of successful nitrate desensitization in a patient who experienced apparent delayed-type hypersensitivity to multiple nitrate formulations. The authors describe 2 distinctive episodes of maculopapular exanthemas, with the first occurring after topical nitroglycerin application and sublingual nitroglycerin and the latter occurring after isosorbide mononitrate (ISMN) oral therapy. Both morbilliform eruptions occurred around 12 to 24 hours after nitrate exposure. A decision to consider nitrate desensitization was later made during an inpatient admission for unstable angina.

The authors performed skin prick and intradermal testing to nitroglycerin in a step-wise approach, and skin prick test result was negative on immediate reading. However, intradermal test result was positive at the 15-minute reading with a 6-mm wheal expansion. The delayed intradermal reading at the 48-hour point was negative. Given the suggestive history of distinct maculopapular exanthemas following nitroglycerin, the authors strongly suspected delayed-type hypersensitivity and they decided to progress straight to desensitization. Drug provocation studies were not conducted. A multistep rapid desensitization protocol was used and on the second day of the process the patient was able to tolerate 60 mg of ISMN and the desensitization was deemed successful. No breakthrough reactions were observed throughout the desensitization. The patient was able to continue tolerating the recommended ISMN dose following discharge and therapeutic benefit was demonstrated (improved quality of life).

This case report by Kessler et al⁸ raises many interesting issues surrounding the investigation and management of suspected delayed-type hypersensitivity reactions. First, matching the allergy history to the correct investigative technique is of crucial importance; otherwise, interpretation can be troublesome. In this case, generalized maculopapular eruptions were described without any SCAR features and the authors chose skin prick and intradermal tests. The intradermal response was unexpectedly positive at the 15-minute reading and a delayed intradermal reaction was not demonstrated. The authors correctly conclude that this could be an irritant effect or a local vasodilatory response to the nitrate injection, because one would not expect an immediate response when the history suggests delayed-type hypersensitivity. Healthy control subjects could also have been tested here to further confirm this irritant reaction and in general this is also recommended to validate skin testing further when there is no standardized approach available.⁹ It is also important to highlight here that the patient also developed (alongside the maculopapular rash) a local cutaneous delayed reaction after nitroglycerin paste application, which is suggestive of allergic contact dermatitis. Patch testing therefore could also have been performed in this case to investigate not only the contact reaction but also the maculopapular eruptions, because it is indicated in both forms of delayed hypersensitivity.¹⁰ In a previous case study, placebo-controlled patch testing was demonstrated to be a useful tool in diagnosing nitrate-induced allergic contact dermatitis and a severe generalized maculopapular rash.¹¹

Following the negative skin test results, the authors then progressed straight to desensitization, which raises a further important question with regard to whether provocation or desensitization is the next logical step. With a negative delayed intradermal test and a history of a mild delayed hypersensitivity reaction, arguably one could progress to a provocation test over a period of 3 days followed by an observation period. This has the

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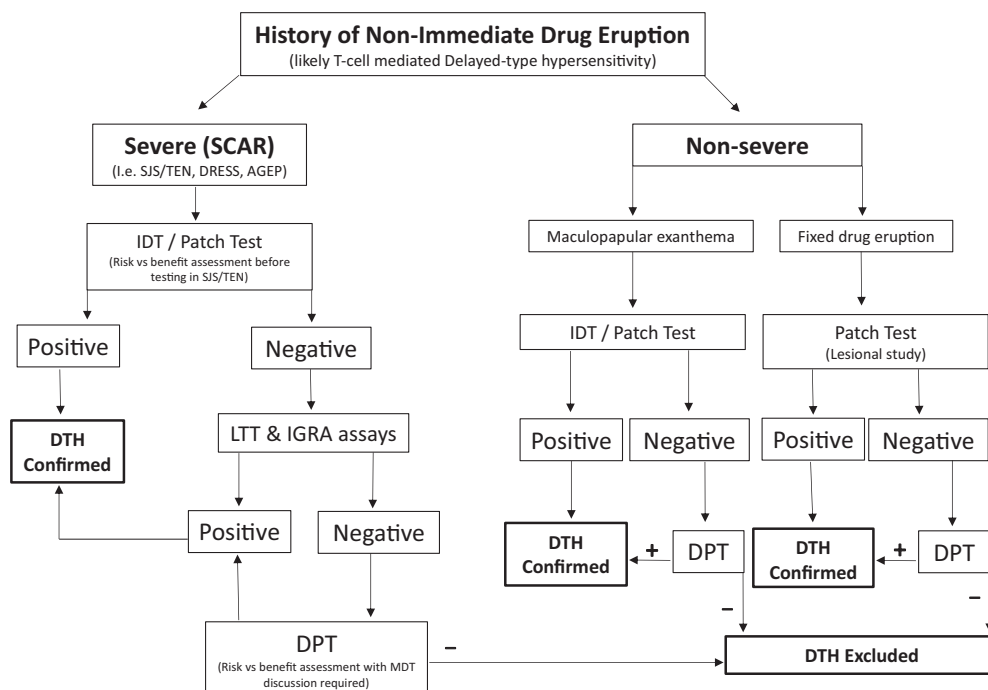


FIGURE 1. Algorithm for the investigation of nonimmediate drug eruptions used at the Department of Adult Allergy, Guy's & St Thomas' Hospitals, London. *AGEP*, Acute generalized exanthematous pustulosis; *DPT*, drug provocation test; *DTH*, delayed-type hypersensitivity; *IDT*, intradermal test (with delayed reading); *IGRA*, IFN- γ cytokine release assay; *LTT*, lymphocyte transformation/proliferation test; *MDT*, multidisciplinary team; *SJS/TEN*, Stevens-Johnson syndrome/toxic epidermal necrolysis.

benefits of (hopefully) confirming or excluding delayed hypersensitivity; however, in the context of an acutely unwell patient, it would ultimately delay starting therapeutic doses of the medication and could significantly reactivate the exanthema, which would not be desirable. The authors' desensitization protocol was initiated on the basis of a suggestive history of delayed hypersensitivity and was certainly successful in safely initiating the oral ISMN regimen without adverse events. However, there was no evidence of a breakthrough reaction in this short rapid desensitization protocol, which could suggest the absence of true drug allergy. Desensitization has the distinct disadvantage of potentially propagating false allergy labels unless adequate objective evidence of allergy exists and therefore a provocation test could be considered later on, to formally confirm or refute drug allergy. Desensitization initiated primarily from a suggestive history is not uncommon in allergy practices¹²; however, it is increasingly advised to first conduct diagnostic challenge studies when skin test results are negative, equivocal, or unavailable.¹³ Even in severe drug eruptions (ie, DRESS) there is growing evidence that oral provocation studies can be safe and feasible if performed in supervised conditions.²

An algorithm used by our Adult Allergy Department at Guy's & St Thomas' Hospitals for investigating nonimmediate (delayed-type hypersensitivity) drug reactions is detailed in Figure 1. It is important to stress that in particularly severe drug reactions (ie, Stevens-Johnson syndrome/toxic epidermal necrolysis), a thorough risk versus benefit analysis should be implemented before conducting formal allergy testing due to the risk of reactivation.² Both patch tests and intradermal tests are

useful diagnostic tools in investigating various severe and non-severe delayed-type hypersensitivity reactions,^{4,14} with patch testing having reportedly higher specificity than intradermal testing and conversely intradermal testing higher sensitivity than patch testing.^{3,10} In SCARs it is advised to perform patch testing first due to its greater safety profile and if test results are negative, intradermal testing can then be performed.³ Patch testing has added benefits in diagnosing fixed drug eruptions (via lesional testing)¹⁰ and a distinct advantage when only oral drug preparations are available for testing.^{1,5} *In vitro* assays (ie, lymphocyte proliferation and IFN- γ release) can also be useful, especially for SCAR cases, although they are typically confined to research laboratories with limited wider availability.¹⁵ Sensitivity and specificity of these *in vitro* assays also vary with phenotype of the drug eruption and causative drug.² The decision to progress to drug provocation studies in SCAR cases requires careful consideration, ideally with multidisciplinary team discussion and often a modified challenge protocol taking place over several weeks.²

In summary, the case report by Kessler et al⁸ certainly demonstrates the safety and efficacy of desensitization for nitrate-induced delayed-type hypersensitivity; however, it is important to highlight the complexities and challenges in investigating nonimmediate drug eruptions in the wider clinical context.

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