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Delabeling delayed drug hypersensitivity: how far can you safely go?

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Abstract

Delayed immune mediated adverse drug reactions (IM-ADRs) are defined as reactions occurring more than 6 hours after dosing. They include heterogeneous clinical phenotypes that are typically T-cell mediated reactions with distinct mechanisms across a wide spectrum of severity from benign exanthems through to life-threatening cutaneous or organ-specific diseases. For mild reactions such as benign exanthem, considerations for delabeling are similar to immediate reactions, and may include graded or single dose drug challenge with or without preceding skin or patch testing. Evaluation of challenging cases such as the patient who is on multiple drugs at the

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time a severe delayed IM-ADR occurs should prioritize clinical ascertainment of the most likely phenotype and implicated drug(s). Although not widely available and validated, procedures such as patch testing, delayed intradermal skin testing and laboratory-based functional drug assays or genetic (HLA) testing may provide valuable information to further help risk stratify patients and identify the likely implicated and/or cross-reactive drug(s). The decision to use drug challenge as a diagnostic or delabeling tool in a patient with a severe delayed IM-ADR should weigh the risk-benefit ratio, balancing the severity and priority for the treatment of the underlying, and the availability of alternative efficacious and safe treatments.

Keywords

delabel; delayed hypersensitivity; in vivo; ex vivo; ELISpot; lymphocyte transformation; HLA; phenotype; drug timeline; drug challenge

Case

A 48-year-old female with known with systemic lupus erythematosus (SLE) presents to your clinic with a ten-day history of a blistering eruption (Figure 1). She had been diagnosed with drug-susceptible pulmonary tuberculosis (TB) five weeks earlier and a fixed dose combination anti-tuberculous (anti-TB) treatment comprising rifampicin, isoniazid, pyrazinamide and ethambutol was initiated the same day. She had been on SLE treatment for at least 10 years and the disease was stable on chloroquine and low dose oral prednisone. She reported that the diagnosis of SLE followed the first episode of TB, for which she had uneventfully completed treatment.

Two weeks after initiating anti-TB treatment she had developed a malar rash, joint pains and marked hepatitis. She was diagnosed as a flare-up of SLE at a secondary hospital and anti-TB treatment was stopped. The laboratory and clinical parameters returned to baseline and rifampin, isoniazid and ethambutol were re-initiated at 20 days. Pyrazinamide was omitted on the assumption it was the cause of hepatitis. However, nine days after re-initiating anti-TB treatment with rifampin, isoniazid and ethambutol she developed a photo-distributed eruption with epidermal necrosis that progressed to affect photo-protected skin and one mucosal surface. Liver function tests were normal. A differential diagnosis of SJS/TEN or SJS/TEN-like acute cutaneous lupus erythematosus was made. A skin biopsy was compatible with SJS/TEN (Figure 1). She is referred to you for identification of the offending drug to facilitate optimization of her anti-TB treatment because there are few other alternatives.

Introduction and classification of delayed drug hypersensitivity reactions

Delayed immune-mediated adverse drug reactions (IM-ADRs) are simply defined by the time from drug intake to onset of ADR. Currently accepted criteria for designation as a delayed reaction include any reaction that occurs more than 6 hours after dosing(1). Thus, delayed IM-ADRs comprise a very large and heterogenous group of clinical phenotypes and underlying immune mechanisms. The most benign delayed exanthems may be maculopapular or urticarial in quality and occur in ~5% of all treatment courses with

common drugs such as antibiotics(1). The acute management of a delayed IM-ADR is guided by identification of the clinical phenotype which is based on historical features such as the time from initiation of the drug to clinical presentation, quality of rash or systemic features (e.g. fever), hematological abnormalities (e.g. eosinophilia or atypical lymphocytosis), organ involvement and ancillary diagnostic tests such as biopsy of the skin or affected organ (Table 1, Figure 1) (2). The diagnosis and management of delayed hypersensitivity reactions has been met with challenges and controversies based on a narrow evidence base, absence of multicenter controlled studies and lack of availability of validated diagnostics and therapeutics. For mild to moderate rashes where definitive treatment is required with the implicated drug a decision may be made to “treat through” (3–5). In more complex cases such as the case under discussion the clinician is faced with the most difficult task of attempting to provide a drug causality for a specific severe clinical drug hypersensitivity reaction in the face of urgent need for treatment of a life-threatening infection or other disease. The most common and the most severe delayed hypersensitivity reactions encountered in clinical practice are T-cell mediated which are associated with heterogeneous mechanisms and both ecological and genetic risk factors(6). Unquestionably, as our mechanistic understanding of specific drug and immune phenotypes continues to expand, the management of delayed drug hypersensitivity reactions will become precise and personalized, matching specific drug and clinical phenotype to a host with specific genetic risk factors. Currently small molecules or drugs are thought to activate T cells through three models that are non-mutually exclusive(6). In the hapten/prohapten model the drug covalently binds to a peptide, either intracellularly in the endoplasmic reticulum before peptide processing and presentation or at the cell surface. In the other two models – the pharmacological-interaction and altered peptide repertoire model drugs non-covalently interact with immune receptors in a dose dependent fashion simulating what we see when drugs are dosed in clinical practice and result in delayed and presumed T-cell mediated reactions(6–8). Examples include the higher risk of allopurinol hypersensitivity reactions in patients with chronic renal failure where oxypurinol, the active metabolite that has been shown to activate T cells *in vitro*, accumulates; and the higher risk of severe cutaneous T-cell mediated reactions associated with phenytoin and nevirapine conferred through the poor metabolism states of CYP2C9 (CY2C9*3) and CYP2B6 respectively(9–12).

Single cell approaches that integrate T-cell receptors (TCR), proteome and transcriptome, especially using site-of disease sampling e.g. tissue biopsies or blister fluid, is already transforming our knowledge of mechanisms and will continue to reclassify traditional clinical phenotypes(13, 14). For instance, gene expression profiling of peripheral blood mononuclear cells (PBMCs) during the acute and resolution phase of severe delayed IM-ADRs demonstrated that non-bullous and bullous reactions clustered separately(15). Kim *et. al.* recently described the successful use of tofacitinib in steroid and immunosuppressant recalcitrant trimethoprim-sulfamethoxazole DRESS based on single-cell RNA sequencing from peripheral blood and skin that showed upregulation of JAK and STAT signalling pathways(16). Epigenomics and exposome will likely also be important considerations in precision classification of delayed IM-ADRs. Epigenomics may influence site specific variabilities in drug disposition, toxicity and host response; helping to explain how the same drug can result in different systemic and organ IM-ADRs(17). The process of defining the

immunopathogenesis of these reactions at a single cell level and defining the HLA restriction and TCR and drug antigen specificity will lead to a heightened understanding and potential re-taxonomization of delayed hypersensitivity reactions as we currently know them(13, 14, 16). Indeed many delayed hypersensitivity reactions that are seen clinically that involve various combinations of fever with or without cutaneous and hematological manifestations, occurring within the first two weeks of treatment do not fit into any currently described severe delayed IM-ADR classification. These approaches will also lead to targeted diagnostic and therapeutic approaches. However, with our current state of knowledge a more general approach is required that needs to gather all available information for risk stratification and decision-making. Figure 2 provides our conceptual framework for this global approach to delayed IM-ADR where cumulative information from all levels, where available, contributes to the ultimate causality and phenotype assessments and allows for optimal clinical decision-making despite knowledge gaps.

The majority of delayed IM-ADR are considered to be T-cell mediated, and traditional classifications such as the modified Gell and Coombs, considering type IVa-d hypersensitivity help a broad understanding of the relative importance of particular immune effectors and cytokines.(1, 18) However, in building a comprehensive risk stratification to attribute drug causality or consider different treatment options, this classification offers little. Population-specific pharmacogenomic approaches, particularly where classification of delayed IM-ADR by HLA restriction offer clinical utility, particular where positive predictive value is high.(9) Strong associations with other risk alleles in drug metabolizing pathways also highlight the importance of considering parent drug, metabolites, and drug concentrations in pathogenesis and several of these are already in use to avoid specific drug toxicities in at risk patients (Table 2) (9, 19). Although the evidence base and availability of specific *in vivo* (e.g. patch or intradermal skin testing) and *ex vivo/in vitro* (e.g. ELISpot, lymphocyte transformation test (LTT)) testing is lacking on a global basis, and there are significant geographic differences in their use patterns, they can contribute useful adjunctive information to help with drug causality and cross-reactivity in extremely complex cases(1, 20).

The clinical history and physical exam when the patient is seen acutely is very important in formulating a diagnosis and management plan (Table 1, Figure 1). Remote and proximal drug and infection-exposures are also key considerations in phenotype and classification of delayed IM-ADRs. One of the commonest delayed IM-ADR is a delayed exanthem after antibiotic exposure in the context of an acute infection. It is still not clear the extent to which these mild to moderate rashes are parainfectious events to viral or bacterial antigens or immune stimulation with secondary cutaneous reactions to drug(6, 21, 22). In the heterologous immunity model of IM-ADR, pathogen-specific T-cell responses generate either migratory or resident memory T-cells which cross-react with drug-modified self-peptide epitopes when the drug is introduced later in life(6). This has the potential to induce pathology at the anatomic site of the resident memory T-cells but not elsewhere. The presence of a shared dominant T-cell receptor clonotype for some severe delayed IM-ADRs such as HLA-B*15:02 associated carbamazepine SJS/TEN which is absent in HLA-B*15:02 carbamazepine tolerant controls supports this model(14). Many of these remote and benign reactions result in a lifelong label of a drug allergy and many patients with such histories

have not had reproducible reactions on drug rechallenge(18, 22). The time from first treatment to presentation of the delayed IM-ADR (latency), the clinical or pathological features of the rash or organ involvement, the accompanying clinical features such as fever, lymphadenopathy, organ involvement and laboratory features all provide valuable information that contribute to the clinical phenotype (Table 1, Figure 1) (18).

Genetic testing and predictors for delayed drug hypersensitivity

Following the discovery of the association between HLA-B27 and ankylosing spondylitis there were several small studies using older serological techniques for HLA that hinted at associations between class I HLA haplotypes and allopurinol and sulfonamide antibiotic hypersensitivities(23–25). However, it was not until the advent of sequence based typing that sequential strong discoveries between HLA and specific drug hypersensitivity syndromes have been made over the last 18 years (26–32). This includes the association between HLA-B*57:01 and abacavir hypersensitivity that provided a translational roadmap from discovery through to routine clinical implementation(33). The first randomized clinical controlled trial to examine the utility of a specific genetic test to prevent a defined toxicity was performed randomizing individuals starting abacavir treatment to real-time HLA-B*57:01 testing versus non-genetic guided treatment (34). This study which enrolled almost 1956 patients of primary European ancestry over 6 months demonstrated that HLA-B*57:01 screening eliminated immunologically-mediated (patch test positive) abacavir hypersensitivity and showed 100% negative predictive value (NPV) of HLA-B*57:01 screening for abacavir hypersensitivity. The SHAPE study was a case control study that demonstrated generalizability of the 100% negative predictive value of HLA-B*57:01 for patch test positive abacavir hypersensitivity to non-White ancestry. These studies were the licensing studies and formed the basis upon which HLA-B*57:01 screening became part of routine guideline-based HIV care prior to abacavir prescription in most of the developing world (34, 35). A number of strong genetic associations between primarily HLA class I alleles and severe delayed IM-ADR have been described since 2002 with varying success in translation into clinical practice (Table 2). For abacavir the PREDICT-1 study demonstrated that 55% of those carrying HLA-B*57:01 developed abacavir hypersensitivity meaning only 13 would need to be tested to prevent one case of clinically diagnosed abacavir hypersensitivity. For other drugs the lower positive (PPV) and negative predictive values (NPV) make the cost-effectiveness of screening highly dependent on the prevalence of a given HLA risk allele in a given population (Table 2) (9). For some drugs such as flucloxacillin, an anti-Staphylococcal penicillin, the low prevalence of toxicity (hepatitis) and the low positive predictive value (0.14%) mean that even in European populations where HLA-B*57:01 is prevalent almost 14,000 would need to be screened for HLA-B*57:01 to prevent one case of flucloxacillin associated hepatitis (Table 2). Recent work suggests that genetic factors outside of the major histocompatibility complex may be important in explaining this positive predictive gap for drugs such as abacavir and nevirapine(36). The association between an HLA risk allele and an antibiotic which typically needs to be started expeditiously without delay and time to do genetic screening is a good example where HLA testing may have high utility as a pre-emptive or diagnostic test rather than a screening test. This is exemplified by the recent association between HLA-A*32:01 and vancomycin DRESS(32) With a prevalence of HLA-

A*32:01 of approximately 6.3% in most mixed ancestry populations approximately 75 patients would need to be tested to prevent one case of vancomycin DRESS. However, since vancomycin DRESS has an average latency of two or more weeks this affords a time window to do HLA testing and risk stratify patients without withholding necessary empiric antibiotic treatment. This risk stratification and the availability of single allele typing with a rapid turnaroundtime would allow for rational decisions for continued treatment to be based on need for the antibiotic and the availability of equally efficacious alternative options(37). This also facilitates informed decisions to discontinue vancomycin at the earliest sign of any potential adverse reaction. It is anticipated that as more genetic associations are discovered with delayed IM-ADR and as typing for specific HLA alleles becomes more cost-effective and available this could provide widely accessible and useful ancillary diagnostic information relevant to many delayed IM-ADR phenotypes.

Adjunctive approaches to aid in the diagnosis of delayed hypersensitivity reactions

Delayed hypersensitivities, a group of presumed T-cell mediated disorders (18, 38), have become an increasing focus of drug allergy delabeling programs internationally and are of interest to allergists and immunologists as well as infectious diseases experts as tools to integrate into stewardship programs. Although drug allergy programs, in particular antibiotic allergy testing, have historically focused on specific testing for immediate (IgE mediated) hypersensitivities (18), the evidence base to support delabeling in T-cell mediated reactions has been slower to evolve. This has primarily been due to an absence of high sensitivity diagnostics and availability of trained specialists (38–40). Compounding this are concerns of disease-relapse related to both performing skin testing and oral challenge in the setting of disease phenotypes with associated high mortality (41–44) Many patients with non-specific delayed reactions such as a mild exanthem associated with antibiotics in the face of a viral infection, have been labeled in childhood and an increasing evidence base supports ingestion challenge in this setting.(45–47) For more severe delayed and likely T-cell mediated reactions (Table 1) including DRESS, AGEP, FDE and SJS/TEN in particular, specialized testing may have an important role to provide supportive information for a causative drug and potential for cross-reactivity(1).

In vivo approaches (Patch and Intradermal Testing)

Patch testing

By applying drug allergens in a soluble vehicle under occlusion on intact skin, patch testing (PT) aims to safely reproduce in the confined area of the test the original delayed IM-ADR. Most PT in allergy practice involves the use of chamber PT that were developed to test multiple substances at the same time. Finn Chambers® are available as loose chambers which allow selection of the overlying tape or premounted on Scanpor® tape. Finn Chambers® are also now available mounted as a molded paper chamber on a polyurethane tape which has the advance of eliminating the need to add filter paper for liquid allergens. For the most part, PT in delayed IM-ADR has relied on pharmacy or in clinic preparation of the reagents without widespread standardization. However, some antibiotics, NSAIDs and

anticonvulsants, are now commercially available although mainly in Europe with very limited availability in the US (48). A negative (petrolatum or vehicle) but not positive control is utilized with PT. With the exception of FDE, which requires application of the test to previously affected skin, the upper back is the preferred site(48, 49). The readings should be at 48 hours when the PT is removed, although the reaction may occur more quickly with abacavir hypersensitivity and FDE(48). Follow-up readings should occur at 96 hours and 1 week if the original reading is negative. The results are interpreted as per standard guidelines and comparison with untested skin(50, 51). Please see the delayed hypersensitivity video for a detailed illustration of drug patch testing procedures.

The optimal PT timing has not been established for all phenotypes of delayed hypersensitivity reactions and drugs. The general consensus is that PTs, like other *in vivo* tests, should not be performed sooner than 4 to 6 weeks and preferably at least 6 months after the reaction. Although patch-testing has been shown to be safe by several groups even in DRESS and SJS/TEN this also avoids the confusion with relapse of reactions such as DRESS which is common in their natural evolution and flare-ups due to corticosteroid withdrawal all making the risk of false positive or negative results unacceptable(52). Systemic immunosuppressants like corticosteroids should have been discontinued for at least one month prior to PT(1). In certain circumstances, exemplified by anti-TB drug associated SCAR in resource-limited settings, the risks associated with early PT are outweighed by the need to continue other drugs in the multidrug regimen except the offender(53). However, this is associated with significant systemic reactions in predominantly HIV-co-infected patients which has only been rarely associated with PT otherwise (54–56). In this setting, it also has implications on whether PT in multiple drug exposures should be conducted simultaneously or sequentially.

PT in delayed hypersensitivity reactions have high specificity. On the other hand, their sensitivity varies with the clinical phenotype, offending drug, drug concentrations and the PT vehicle used amongst others(48). The sensitivity is highest for SDRIFE (52–82%), AGEP (58%), DRESS (32%–64%), FDE (up to 40%), lichenoid drug eruption (LDE) (30–50%), and MPE (10.8%–38.4%)(48, 57–60). There is general consensus that PT, with the exception of antiepileptic drugs such as carbamazepine, have minimal utility in SJS/TEN. (48, 56, 61, 62). *In vivo* testing in LDE is likely to increase with increasing incidence due to new treatments like TNF-alpha antagonists, tyrosine kinase inhibitors, programmed cell death ligand (PDL-1) antagonists, cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) blockers and other checkpoint inhibitors(63–68). PT sensitivity is also drug-specific, highest with drugs like antiepileptics, contrast media, beta lactams, tetrazepam and pristinamycin(48, 52, 69, 70). PT for allopurinol or its active metabolite oxypurinol appears to completely lack sensitivity for both allopurinol DRESS and SJS/TEN. Interestingly PT in children also seems to have lower sensitivity, although there is paucity of data(71, 72).

Persistence of PT positivity in antibiotic-associated delayed hypersensitivity reactions was investigated by Pinho and colleagues in 20 patients with MPE (n=18), DRESS (n=1) and AGEP (n=1). PT were reproducibly positive in 89% after median 6 years (range 2.0 – 14.7) and a majority had reaction intensity to PT similar to the original as found in other studies(73–75).

Overall the lack of PT sensitivity for many phenotypes as well as the clinical severity of SCAR means that the decision to attempt delabeling through a drug challenge would not be based solely on a negative PT result.

Intradermal Testing

Consensus on performance of intradermal testing (IDT) involves injection of 0.02–0.05 ml of the highest non-irritating drug concentration in a tuberculin syringe (0.5–1 ml) and needle gauge 25, 27 or 30 with reagent applied bevel-up, to the volar forearm of skin.(1) Using saline control and amoxicillin 20 mg/ml as their standard, the European Network for Drug Allergy (ENDA) recently performed a multicenter study of 11 sites in attempts to produce reproducible approaches that would reduce variability and standardize IDT to allow more reliable comparison between centers performing either immediate or delayed IDT(76). The definition of a positive delayed IDT has varied but in general is defined as an erythematous induration or swelling at the IDT injection site at 24 hours, 48 hours and out to 72 hours if negative at 48 hours(77, 78). Current guidelines recommend the use of IDT only with drugs available in sterile parenteral commercially manufactured preparations(76). In a recent consensus guideline there was agreement amongst international experts that delayed IDT using sterile preparations of drugs can aid drug allergy assessment and that similar to PT should not be performed sooner than 4–6 weeks following an acute reaction (1). The use of IDT in SCAR has predominately been in the setting of hypersensitivity associated with anti-infective drugs which are commonly available as sterile preparations and for which the greatest delabeling need exists (79). Prior studies have indicated that IDT has increased sensitivity over patch testing and this appears particularly true for antibiotic associated DRESS and MPE (80, 81). Torres *et al.* performed patch and IDT in a cohort 21 patients and 30 controls with delayed hypersensitivities to penicillins and no allergy history, respectively. They demonstrated no false positives in the controls and 20/21 were positive to penicillins by IDT compared with 18 by PT (81). A number of other earlier reports of IDT being performed safely has been extensively demonstrated in Europe, although the specifics of phenotypic severity for which testing was undertaken is often limited (81–86). On review of the literature, we believe that IDT can be safely employed by specialists in the outpatient setting, predominantly for beta-lactam antibiotics and syndromes such as MPE, DRESS and AGEP. The utility in FDE (intralesional) and SJS/TEN (concern for low sensitivity and safety), still remains ill-defined. Reactions to IDT are rare in general drug allergy testing (87). There have been only infrequent reported systemic reactions following IDT even in severe delayed-type hypersensitivity (81, 88–91). Konvinse *et al.* reviewed the sensitivity of delayed IDT for antimicrobials - ranging from 6.6–36.3% for MPE and 64–100% for DRESS (38). What remains uncertain is both the specificity and false positive rate in this context. In ambiguous settings concordance of PT and delayed IDT adds more certainty however the higher sensitivity of delayed IDT for many reactions including MPE and DRESS means that negative PT will legitimately occur in the setting of positive IDT(52). Due to the life-threatening nature of these SCAR reactions, and without an appropriate reference standard to accurately determine specificity and sensitivity of IDT, drug challenges of patients with positive tests cannot be justified, however identification of a likely implicated drug through a combination of clinical causality assessment and positive testing

opens a pathway for potential challenge to drugs that test negative and are less likely to be implicated.

Although the specific antigens that activate T cells remain elusive for most delayed IM-ADRs, recent data demonstrate the importance of the parent drug for delayed reactions to penicillins. In these cases the implicated drug can be identified through IDT without use of minor determinant mixture (MDM) and penicilloyl-polylysine (PPL) (81, 92, 93). Outside of antibiotics, recent work from Trautman and colleagues also demonstrate the utility of IDT in delayed IM-ADR (n = 13) to iodinated radiocontrast media (RCM) (94), similar to other authors (95, 96) yet not supported by earlier studies (97). Utility has also been demonstrated in delayed IM-ADR to chemotherapeutics, proton pump inhibitors, NSAID-induced reactions and analgesics (98–100). In regard to NSAIDs, IDT should be used when sterile intravenous preparations are available (100). PT still remains the preferred methodology for corticosteroid reactions over IDT as it allows a broader range of drugs and cross-reactivity patterns to be studied (101). Use of IDT for corticosteroids however has the advantage of testing for delayed reactions to excipients such as polyethylene glycol (PEG) 3350, polysorbate 80, carboxymethylcellulose and benzalkonium chloride that are present in the injectable forms of methylprednisone acetate, triamcinolone and betamethasone respectively. (102) Further, the utility of testing for some drugs remains limited, including macrolides, sulfonamides and allopurinol (103). The apparent lack of sensitivity of IDT for some drugs may be due to use of non-irritating concentrations established for immediate drug reactions which may be insufficient for IDT. Recent work for drugs associated with non-IgE-mediated mast cell activation demonstrated that concentrations elucidating immediate histamine release in the skin (e.g. above the non-irritating concentration for immediate reactions) appear to be necessary for improved sensitivity for delayed reactions. Examples include drugs such as vancomycin and fluoroquinolones that are common causes of non-IgE mediated mast cell activation through their interaction with MRGPRX2(32, 104–106) The difficulty in interpreting skin testing for antibiotics such as fluoroquinolones and sulfonamide antibiotics (107) means that drug challenge maybe preferable in individuals with remote or low risk histories (108).

The use of delayed IDT in pediatrics, and particularly in children less than 3, is further limited due to logistical difficulties and higher rates of negative testing in children with mild delayed hypersensitivities which are presumed to be due to viral infection or drug-viral interactions in the majority of cases (109–111). However, Atanaskovic *et al.* demonstrated that from a cohort of 76 patients with non-immediate hypersensitivity, 57 (75%) had a positive delayed IDT highlighting potential utility in carefully selected populations (71). Unlike immediate reactions where several studies have demonstrated that a positive IDT to penicillins and cephalosporins will wane over time, the persistence of delayed IDT remains ill-defined, with few studies that have followed patients longitudinally. Rodriguez-Alvarez *et al.* reported on 23 patients reporting mild delayed hypersensitivities demonstrated reproducibility in only 1 patient 4 years post initial testing (82). The barriers that still remain for widespread implementation of IDT for delayed hypersensitivities include: (i) absence of commercially available sterile preparations for all drugs; (ii) overall low or unknown NPV; iii) absence of knowledge as to whether the highest non-irritating concentration relevant to performance and interpretation of immediate IDT is relevant to delayed IDT and (iv) limited

data in specific phenotypes such as FDE and SJS/TEN. Of great interest is recent evidence noting strong IDT responses in patients with severe delayed reactions with the absence of T-cell responses in peripheral blood (112).

In vitro and ex vivo diagnostics

Currently, laboratory-based *in vitro* and *ex vivo* diagnostics, such as LTT, enzyme linked ImmunoSpot (ELISpot) assay and flow cytometry are not available for use as routine diagnostics in most centers, and are still primarily employed in a research only setting (Table E1, online repository). The reported sensitivity of LTT in delayed hypersensitivity reactions ranges from 27% (113) to 74% (114) and specificity quoted as 85% (114, 115) to 100% (113, 116–126). False positives exist for some drugs such as NSAIDs and glycopeptides preclude against the use of the LTT in these settings. Putting aside the demanding and time consuming laboratory manipulations, the LTT can provide useful adjunctive information towards drug causality and drug hypersensitivity diagnosis (127). The largest study describes LTT in 923 patients with suspected hypersensitivity among which only 100 patients were positive (58/78 penicillin allergy labeled patients presented a positive)(114). In the last 10 years, aside from case reports or small cases series (128–131), very few studies have focused solely on the LTT method for diagnosis (Table E1, online repository).

The ELISpot technique was initially developed to quantify secretion and activation of T-cell responses to specific viral peptides(132). For T-cell mediated drug hypersensitivity the assay has been adapted to quantify secretion and activation of responses to T cells stimulated by varying concentrations of suspected implicated drugs or metabolites. The number of spot-forming units (SFU) or spot-forming cells (SFC) that release cytokine markers or cytolytic molecules, such as IFN- γ and granzyme B (GrB) are quantified after the patient's peripheral blood mononuclear cells (PBMC), are stimulated with pharmacologically relevant concentrations of the suspected drug(s). As the incubation time is shorter and T-cell activation occurs after 24–48 hours, this has clinical appeal. In a recent study of IFN- γ ELISpot in SCAR the sensitivity was reported as 52% (10/19) and with a specificity of 100% (133). In a study of amoxicillin MPE and piperacillin delayed hypersensitivity the sensitivity was reported as 91% (15/22) and 87.5% (7/8), respectively(115, 134–136). The GrB ELISpot has a lower reported sensitivity (33%–55%) from smaller cases series (113, 116), with similar specificity. Although a commonly defined threshold for ELISpot assays performed in triplicate has been 50 spots per million, there remains variability in the definition of a positive ELISpot assay, as outlined in Table E1, online repository (116, 137–147), likely impacting reported sensitivities.

The flow cytometry technique is used to determine various phenotypic parameters such as T cell-surface activation markers that could indicate drug-specific T-cell populations and T-cell proliferative responses(148–150). Different cell surface receptors and markers have been described in the delayed hypersensitivity setting such as decrease of Tim3 and Gal9 in patients with MPE (151) and increase in CD137 (152) and granulysin in SJS/TEN patients (113), α -defensin 1–3 peptides (153) as well as CD69 (154) in MPE and SCAR patients. There at present remains no large cohort of clinical studies using flow cytometry as a clinical diagnostic.

Although there is emerging data for use of *ex vivo* and *in vitro* diagnostics to aid in the delabeling of delayed hypersensitivities they have to-date been the province of specific research environments making scalable approaches difficult. Similar to *in vivo* testing the lack of a 100% negative predictive value means that their utility relies on the presence of other clinical and laboratory information to help make decisions in an individual patient about the risk and benefit of future drug therapy. Moreover, implementation is still hampered by an absence of routinely used cut-offs and variable diagnostic sensitivity. Used in combination with clinical information and delayed IDT and PT, these novel diagnostics provide a pathway for utilization of class-related drugs in severe delayed IM-ADR.

Cross-reactivity in delayed hypersensitivity and role of Adjunctive Testing

For some drug classes cross-reactivity is a myth and patients can be delabeled based on history alone. The absence of cross-reactivity between sulfonamide antibiotics (e.g. sulfamethoxazole) and non-antibiotic sulfonamides (e.g. furosemide) for both immediate and delayed hypersensitivity reactions is an evidence-based example of this (155, 156). Reports of PT or IDT being utilized to demonstrate the presence or absence of cross-reactivity in delayed hypersensitivities have largely related to antibiotics, radiocontrast dye(95), chemotherapeutics, anti-epileptic drugs and corticosteroids. The vast majority of data exists for beta-lactams (18). Cross-reactivity has been demonstrated in delayed hypersensitivity between aminopenicillins and aminocephalosporins that share the same R1 group – noted in 18.7% – 31.2% of those tested (157–160). Beta-lactam delayed IDT has been useful in demonstrating tolerance of cephalosporins (92, 161), carbapenems(161, 162) and monobactams (163) in those reporting a primary penicillin delayed phenotype, with infrequent reports demonstrating cross-reactivity rates greater than 2% (164). Further data demonstrating absence of cross-reactivity in beta-lactam cross-reactivity between beta-lactams with non-shared R1 or R2 side chains in delayed IM-ADR is demonstrated in Table 3.

Data evaluating cross-reactivity for other drugs includes absence of cross-reactivity in a cohort of vancomycin DRESS between vancomycin and other available glycopeptides (13%; 2/15). Cross-reactivity was predicted by interferon (IFN)- γ ELISpot, IDT and a shared class II HLA haplotype(105). This lack of consistent cross-reactivity is supported by earlier clinical data reporting an absence of cross-reactivity between vancomycin and teicoplanin(105). An absence of cross-reactivity has also been reported between drugs within the rifamycin class (e.g. rifampin, rifabutin). Lehloeny *et al.* demonstrated tolerance of rifabutin in 6 cases of rifampicin DRESS (165). Cross-reactivity can also be predicted for IM-ADR to anti-epileptic drugs, especially among aromatic antiepileptic drugs where cross-reactivity has been extensively reported (phenobarbital, phenytoin, oxcarbazepine and carbamazepine) (166, 167). In this setting nonaromatic antiepileptic drugs and benzodiazepines were well tolerated (168). Cross-reactivity for common delayed reactions associated with corticosteroids such as contact hypersensitivity has been predicted by the Coopman classification which groups corticosteroids according to their side chain substitutions and patch test cross-reactivity patterns(169).

Drug challenges and delabeling of delayed immune-mediated adverse drug reactions

In situations where the patient has experienced a mild to moderate delayed exanthem and the drug is needed, consideration should be given to “treat through” the reaction which is presumed to induce tolerance although the mechanism is unknown(3, 4). Similarly, where the drug is urgently needed without time to consider diagnostic drug challenge(s), graded introduction of one of multiple drugs can be considered(170).

Drug challenges are still considered the diagnostic gold standard for proving tolerance to a drug, and in allergy practice are considered to be the ideal final testing step prior to therapeutic dosing. Lower dose single dose oral challenges that will adequately exclude IgE-mediated reactions (e.g. amoxicillin 250 mg) may not adequately exclude delayed T-cell mediated reactions. In addition, several studies, particularly in the context of antibiotics have suggested that single dose challenges with the treatment dose of a drug will not exclude a delayed reaction and that multiple (3–10) day challenges will pick-up an additional 5–15% of reactions(171–176). Other reports largely from the US have suggested that <2% will have delayed reactions after negative penicillin skin testing and graded or single dose challenge even after prolonged therapeutic dosing(177–182). Particularly for remote delayed reactions or where the history suggests a mild to moderate delayed rash, current consensus suggests that given the low probability of recurrence and the mild nature of rash if there is recurrence, a graded or single observed drug challenge may be adequate to delabel a patient. A common office procedure for drug challenges includes a full dose drug challenge followed by 1–2 hours of observation or a graded challenge including one-tenth to one-quarter of a dose followed either 30–60 minutes later or 3–7 days later by the full dose (84). For diagnostic purposes for delayed reactions, rechallenges involving greater than two steps have been avoided because of the concern that multistep multidose challenges may lead to desensitization.

Drug challenges should always be considered in the context of a risk benefit ratio (Figure 2) and should generally be contraindicated in severe delayed IM-ADR particularly where the treatment is not necessary or where there are efficacious and safe treatment alternatives. For serum-sickness like reaction which is more prevalent in children accumulating evidence suggests that many patients will tolerate future drug challenge with the originally implicated drug, particularly for more remote reactions(45). For severe well documented T-cell mediated reactions such as DRESS, SJS/TEN and drug-induced organ involvement this generally means avoidance of all possible implicated drugs and all likely cross-reactive drugs. Where treatment is necessary, ancillary information such as skin or patch testing, *ex vivo* or *in vitro* testing or genetic testing may be helpful to narrow down the most likely implicated drug and risk stratify patients for selective drug challenges (Figure 2)(1, 86, 92, 133). In South Africa, rechallenges have been studied with anti-TB drugs and one study showed that 50% of patients with history of SCAR on anti-TB drugs developed reactions on observed drug challenges(183). Furthermore, in this study the majority of rechallenge reactions were mild to moderate (71%) although 26% were severe. Rifampin was the most commonly offending drug overall (57%), followed by isoniazid, pyrazinamide and ethambutol. Both rifampin rechallenge and lack of previous anti-TB treatment were independently associated with the likelihood of a rechallenge reaction(183). This provided a

useful strategy to resume efficacious therapy in most patients. Although reactions were usually mild to moderate in most patients, the occurrence of severe rechallenge reactions has now led to further study and implementation of immediate intervention with high dose steroids to successfully abort severe reactions. This South African experience illustrates that when treatment is necessary and sequential rechallenges are considered because of lack of alternative drugs working with a collaborative specialist team to determine the optimal need for therapy and the optimal therapy is essential. A detailed construct of how to approach multiple drug challenges in this setting is shown (Figure E1,

Delabeling of the patient with a delayed hypersensitivity reaction requires special care as test results are generally not available at the in-clinic appointment and may only be definitively determined after sequential therapeutic drug rechallenge. Care should be taken to ensure documentation in the electronic health record (EHR) is accurate and widely disseminated to all members of the healthcare team. Furthermore, results should be documented even when testing is still in process to give interim recommendations (see delayed hypersensitivity video for demonstration).

Management of the Case

In resource poor settings, where comorbidities such as tuberculosis ideally require effective combination therapy with first-line drugs for 6 months or longer particularly in the context of the high prevalence of HIV coinfection, management decisions for IM-ADRs can be extremely complicated. In this situation the risk of morbidity, mortality and the significant negative public health consequences of inadequately treated or recurrent infection outweigh the risk of rechallenge morbidity and mortality. In the case of our 48-year old woman with pulmonary tuberculosis that we previously described, a decision of sequential rechallenge for the purpose of completing life-saving therapy had to be made in the setting of an SJS/TEN-like illness (Figure 1). Had it been possible to conduct patch testing and/or ex vivo testing such as IFN- γ ELISpot these may have provided useful adjunctive information, particularly for risk assessment and the specific order of the drug challenges, however, their lack of 100% negative predictive value would have still necessitated oral challenge as the gold standard. Her situation was unusual in that it seems likely that she may have developed drug-induced lupus related to isoniazid with her original course of anti-TB therapy and upon rechallenge with isoniazid, rifampin, ethambutol and pyrazinamide she developed an SJS/TEN like illness. In this setting once her clinical status had stabilized and laboratory parameters had returned to baseline, she underwent sequential drug challenges with all of the four possible implicated drugs from least likely to most likely based on initial clinical presentation and literature probability. The drugs were initiated sequentially and additively four days apart in the order rifampin, ethambutol, pyrazinamide and isoniazid. Within 20 minutes of exposure to isoniazid, she developed photophobia, rigors, tachycardia, fever, pruritus, painful skin including palms and soles, indurated erythema of the skin and injected conjunctiva. She was given 120 mg infusion of methylprednisolone within 3 hours. Her symptoms resolved within 45 minutes and the skin healed over the following days. Isoniazid was stopped and she completed nine months of rifampin, ethambutol and pyrazinamide uneventfully.

Conclusions and Future Considerations

Considerations for delabeling delayed IM-ADRs must take into account the severity of the original reaction, and the evidence for the likely implicated drug as provided by clinical history, phenotype ascertainment, drug causality assessment and adjunctive diagnostic information (Figure 2). For mild reactions the considerations for delabeling are similar to immediate reactions and drug challenge preceded by IDT or PT where available is a reasonable approach to guide future drug therapy. For severe delayed IM-ADRs, the recommended approach is to avoid future use of all potentially implicated drugs and cross-reactive drugs without attempts at delabeling unless safe and efficacious alternative treatment options are limited and the benefit of treatment outweighs any risk of a rechallenge reaction. Advancement in our understanding of clinical phenotypes, mechanisms, genetic risk and development of highly sensitive and specific drug-specific functional assays will drive precision medicine approaches that help progress delabeling strategies for delayed IM-ADRs, and this ultimately will improve both individual and public health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. A case of an SJS/TEN-like illness in a 48-year-old woman on anti-tuberculous therapy

A. Photo showing skin necrosis and separation over nonsun-exposed areas. The reaction initially was photo-distributed but then progressed to affect photo-protected skin and genital mucosa 9 days after reinitiating rifampin (R), isoniazid (H) and ethambutol (E). **B. H&E stain of punch biopsy of affected skin** showing interface dermatitis with basal vacuolar degeneration, scattered Civatte bodies in the superficial dermis with melanin incontinence, mild lymphocyte infiltrate and perivascular lymphocyte inflammation in keeping with SJS/TEN. **C. Drug timeline** showing course of patient from the initial lupus like reaction through recommencement of treatment with RHE, development of SJS/TEN type illness, termination of all treatment, recovery and sequential drug challenges (DC) with rifampin (R), ethambutol (E), pyrazinamide (Z) and subsequently isoniazid (H). **D. Drug challenge reaction to isoniazid** consisting of tender palmoplantar erythema with blisters two hours after drug challenge with isoniazid. This reaction was successfully aborted with administration of methylprednisolone 120 mg intravenously.

Figure 2. A conceptual approach to the patient with a delayed IM-ADR history:

This figure outlines strategies to prioritize and obtain as feasible all levels of information required to diagnosis delayed immune-mediated adverse drug reactions (IM-ADRs), correctly identify offending drugs, and make decisions around future drug(s) avoidance or re-challenge. Genetic testing e.g. HLA-typing, should be considered as a screening test where testing is available, where the number needed to treat to prevent a given IM-ADR is favorable and when time allows for testing to be done prior to initiation of therapy. Recognition of the clinical phenotype is the usual starting point in delayed hypersensitivity with stratification of mild to severe IM-ADRs; for severe IM-ADRs this often requires in-patient monitoring and adjunctive laboratory testing. A detailed history including drug exposure timelines allows consideration of all possible offending drugs, and causality assessments e.g. Naranjo should be performed for all possible offenders. The **drug timeline** shown for a patient who develops toxic epidermal necrolysis (TEN) in Figure 2 is key to identifying the most likely drug. For instance in the timeline above, drug D and E can be ruled out as implicated as both are started after the onset of TEN symptoms. The latency period for drug A (35 days) is longer than average for SJS/TEN (4–28 weeks) making Drug C the most likely implicated drug associated with TEN. The particular offending drug; known diagnostic accuracy data in specific phenotype or population; and local availability and experience determines which adjunctive diagnostic testing should be applied. All

preceding cumulative information is then weighed against the need for treatment and availability of effective alternative drugs, and depending on this risk benefit stratification, an informed decision can be made about the need for lifelong avoidance (implicated and cross-reactive drugs) or one of several strategies of drug re-exposure and a repeated attempt at treatment.

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Table 1:

Delayed Hypersensitivity Reactions: Presentation and In Vivo Testing*

Type of Delayed Reaction	Average Latency	Clinical Presentation	Patch testing Utility	Delayed Intradermal Utility	Drug Challenge Recommendation
Maculopapular eruption (MPE)/benign delayed exanthem	4–12 days	Morbilloform rash may have mild eosinophilia	moderate	moderate	Consider if need for treatment
Contact reaction (generalized eczema)	Days to weeks	Erythema and edema with vesicles and bullae	high	high	Consider after negative skin/patch test
Serum sickness-like reaction	4–10 days	Fever, rash (urticarial or MPE) with arthralgia	-	unknown	Consider if need for treatment
Photosensitivity (photoallergic drug eruption)	Hours to days	Eczematous, edema or blistering rash in photodistribution	moderate (photopatch)	-	Consider with Avoidance of UVA
Fixed Drug Eruption (FDE)	Days to weeks (within hours of second exposure)	Erythematous and/or indurated plaque recurring at same location. Commonly lip, tongue, face or genitalia. Can be multifocal, bullous and severe	low to moderate (previously affected skin)	Unknown	Consider (not recommended for generalized bullous FDE)
Acute generalized exanthematous pustulosis (AGEP)	Hours to 2 days (aminopenicillins) Up to 2 weeks or longer (hydroxychloroquine and other drugs)	Pustular eruption widespread but more prominent on flexures	moderate (reaction mimics acute pustular reaction)	moderate	Not recommended unless benefit>>> risk
Systemic-drug-related intertriginous and flexural exanthema (SDRIFE)	Hours to days	Sharply demarcated gluteal or perianal erythema, involvement of at least one other flexure. Systemic symptoms absent	high	high	+ Consider after negative skin/patch test
Abacavir hypersensitivity	8 days	Fever, malaise, gastrointestinal symptoms. Rash late, occurs in 70%	high	No	In select cases with non-suggestive history where HLA-B*57:01 and patch test negative
Drug eosinophilia and systemic symptoms (DRESS)	2–8 weeks	Fever, extensive rash, facial swelling, eosinophilia, atypical lymphocytosis, organ involvement	moderate	moderate	Not recommended unless benefit>>> risk
Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)	4–28 days	Rash with skin detachment, 2 mucosae involved. Body surface area detached SJS 10%; SJS/TEN overlap 10–30%; TEN 30%. Positive Nikolsky sign	low	-	Not recommended unless benefit>>> risk
Drug-induced liver disease (DIL)	5–90 days (average > 4 week)	Hepatocellular, cholestatic or mixed. Some may have mild rash, fever or eosinophilia	-	-	Not recommended unless benefit>>> risk
Drug-induced interstitial nephritis	2–3 weeks or later	Acute kidney injury, eosinophilia, eosinophiluria, white cell casts, may have mild rash	-	-	Not recommended unless benefit>>> risk
Drug-induced vasculitis	Months	Fever, myalgia, arthralgia, rash Evidence of positive serology (e.g. ANCA)	-	-	+ If low pretest probability for drug only
Drug-induced lupus erythematosus	Months	Systemic, subacute cutaneous and discoid lupus-like picture, arthralgia, fever. Can have serositis	-	-	Not recommended unless benefit>>> risk

Type of Delayed Reaction	Average Latency	Clinical Presentation	Patch testing Utility	Delayed Intradermal Utility	Drug Challenge Recommendation
		hematological findings uncommon. ANA and anti-histone+ > 90%; anti-RNP > 20%; anti-ENA < 5%			
Drug-induced autoimmune bullous eruptions	Days	Wide-spectrum from linear IgA bullous disease (most commonly to vancomycin), pemphigus and bullous pemphigoid	-	-	Not recommended unless benefit >> risk
Lichenoid drug eruption	Weeks to months	Violaceous or erythematous patches or flat-topped papules. May itch, be photodistributed and affect scalp and mucosae	moderate	unknown	Consider after negative skin/patch test

* see Figure for conceptual timeline in Delayed Hypersensitivity Video

HLA and Delayed Immune Mediated Adverse Drug Reactions: Role in Screening and Diagnosis

Table 2:

Drug Phenotype	HLA Allele	HLA Risk Allele Prevalence	NPV	PPV	NNT	Screening Test	Diagnosis
Abacavir Hypersensitivity Syndrome (33,34) [#]	B*57:01	5–8% Caucasian <1% African/Asia 2.5% African American	100% for patch test confirmed	55%	13	Routine	Not recommended
Allopurinol SJS/TEN and DRESS(28)	B*58:01	9–11% Han Chinese 1–6% European ancestry	100% (Han Chinese) [*]	3%	250	Selectively (incomplete NPV in Africans and European ancestry)	Potentially useful [*]
Carbamazepine SJS/TEN (27) [#]	B*15:02	10–15% Han Chinese <1% Koreans, Japanese <0.1% European Ancestry	100% (Han Chinese)	3%	1000	Consider (low allele prevalence in non-SE Asian ancestry)	Potentially useful [*]
Dapsone DRESS(30)	B*13:01	2–20% Chinese 28% Papuans/Australia n Aboriginals 0% European/African 1.5% Japanese <2% African and African American	99.8%	7.8%	84	Screening programs implemented in China and Southeast Asia where leprosy prevalent	Potentially useful [*]
Flucloxacillin(31)	B*57:01	5–8% European ancestry <1% African/Asia 2.5% African American	99.99	0.14%	13819	No	Potentially useful [*]
Vancomycin(32)	A*32:01	6–8% European 3–4% African <2% Asian	Unknown in Africans and Asian ancestry	20%	75	Unlikely in nonelective situations	Potentially useful for pre-emptive management and diagnosis [*]

NPV: negative predictive value; PPV: positive predictive value; NNT: number needed to test to prevent 1 case;

^{*} particularly in settings where multiple drugs used concurrently could be implicated in an IM-ADR

[#]Part of FDA drug label (19).

Table 3 –
Use of intradermal testing and cross-reactivity in antibiotic severe cutaneous adverse reactions†

Author (year) Country	N	Phenotypes	Implicated drugs	Testing	Test positive N (%)	Adverse events ‡	Cross-Reactivity	Proposed cross reactivity pattern	Post testing tolerance *
Trubiano (2020) Australia (92)	32	DRESS, AGEP, severe MPE	Penicillins	IDT	18 (56)	Nil	37% (penicillins)	Penicillin ring - thiazolidine	Cephalosporins§
Nakkam (2020) (105)	15	DRESS	Vancomycin	IDT	NP	Nil	2 (13%)	Unknown	NP
Konvinse (2019) US (32)	23	DRESS	Vancomycin	IDT	1 (33%)	Nil	NP	NP	NP
Trubiano (2019) Australia (79)	31	SJS/TEN, DRESS, AGEP, FDE	Antibiotics	IDT +PT	13 (42)	Nil	NP	NP	NP
Watts (2018) UK (160)	1	DRESS	Penicillin G	IDT PT	1 (100) 1 (100)	Nil	Penicillin G, amoxicillin	Penicillin ring - thiazolidine	Oral cephalosporin
Romano (2016) Italy (158)	11	TEN, AGEP, Bullous exanthema	Penicillins	IDT PT	NA	Nil	NP	NP	NP***
Buonomo (2014) Italy (157)	97	Delayed unspecified (MPE, urticaria)	Aminopenicillins	IDT PT	97 (100)- inclusion criteria 92 (95)	MPE (N=4)	17% (amino- cephalosporins) 10.9% 1 st gen cephalosporins 1.1% 3 rd -gen cephalosporins	Amino-penicillins/ amino- cephalosporin	Unknown
Cabanas (2014) Spain(131)	8	DRESS	Antibiotics; Piperacillin tazobactam	IDT PT	IDT:3 (40%) PT: 1 (25)	Nil	NP	NP	Meropenem**
Barbaud (2013) France (52)	134	SJS/TEN, DRESS, AGEP	Beta-lactams Pristinamycin PPI ¶	IDT PT (4)	76 (56.7) 3 (7.5)	1 case of AGEP relapse	Ciprofloxacin Norfloxacin and Pefloxacin (N=1)	NP	Unknown
Romano (2010) Italy (93)	214	Delayed unspecified TEN (5), AGEP (3)	Aminopenicillin	IDT PT	40 (18.7)	Nil	37.5% (amino- cephalosporins)	Amino-penicillins/ amino- cephalosporin	NP
Torres (2004) Spain(81)	8	TEN/SJS (4), EM (1), MPE (3)¶	Penicillin/ Aminopenicillins	PT	4 (50%)	1 (16)	NP	NP	NP
Phillips (2001) Canada (159)	16	Delayed unspecified	Aminopenicillin	PT	14 (87.5)	Nil	32% (amino- cephalosporins)	Amino-penicillins/ amino- cephalosporin	68% tolerated cephalexin
Romano (1993) Italy (62)	2	TEN	Penicillins	IDT PT	2 (100)	Nil	NP	Amoxicillin/ Ampicillin	NP
Osawa (1990) Japan (80)	197	MPE, EM, erythroidemic reactions	All drugs	IDT PT	105 (89.7) 62 (31.5)	Nil	NP	NP	NP

Abbreviations – AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; EM, erythema multiforme; FDE, fixed drug eruption; IDT, intradermal testing; RCM, iodinated radiocontrast media; No, number of patients that underwent intradermal testing; MPE, severe maculopapular exanthema; NA, not applicable (all known test positive); NP, not provided; PPI, pump proton inhibitors; PT, patch testing; SJS, Stevens Johnson syndrome; TEN, toxic epidermal necrolysis; UK, United Kingdom; US, United States.

[‡]SJS, TEN, DRESS, AGEP in studies where 1 test was positive and details regarding testing results of these patients was available

[‡]Reaction following intradermal testing requiring systemic therapies (i.e. steroids or other immunosuppression) or admission to hospital for management

[§]All patients positive to penicillin (n = 12) tolerated an oral cephalosporin (i.e. cephalexin or cefuroxime)

[‡]Desquamating exanthema

[¶]This study included multiple drugs: allopurinol, salazopyrin, glycopeptides, quinolones, amikacin, minocycline, pyrimethamine, Celecoxib, acyclovir, ramipril, olanzapine, citalopram, lamotrigine, etc.

^{*}In those that were intradermal test positive

^{**}Meropenem given in 1 of 8 patients

^{***}3 TEN patients not challenged to cephalosporin, intradermal testing not performed in the TEN/AGEP patient