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Old dog begging for new tricks – Current practices and future directions in the diagnosis of delayed antimicrobial hypersensitivity

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Abstract

Purpose of review—Antimicrobials are a leading cause of severe T-cell-mediated adverse drug reactions (ADRs). The purpose of this review is to address the current understanding of antimicrobial cross-reactivity and the ready availability of and evidence for *in vitro*, *in vivo* and *ex vivo* diagnostics for T-cell-mediated ADRs.

Recent findings—Recent literature has evaluated the efficacy of traditional antibiotic allergy management including patch testing, skin prick testing, intradermal testing and oral challenge. While patch and intradermal testing are specific for the diagnosis of immune-mediated (IM) ADRs, they suffer from drug-specific limitations in sensitivity. The use of *ex vivo* diagnostics, especially ELISpot has been highlighted as a promising new approach to assigning causality. Knowledge of true rates of antimicrobial cross-reactivity aids empirical antibiotic choice in the setting of previous IM-ADRs.

Summary—In an era of increasing antimicrobial resistance and use of broad-spectrum antimicrobial therapy, ensuring patients are assigned the correct “allergy label” is essential. Re-exposure to implicated antimicrobials, especially in the setting of severe adverse cutaneous

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reaction is associated with significant morbidity and mortality. The process through which an antibiotic label gets assigned, acted on and maintained is still imprecise. Predicting T-cell-mediated ADRs via personalised approaches, including HLA-typing may pave future pathways to safer antimicrobial prescribing guidelines.

Keywords

ELISpot; antibiotic allergy; severe cutaneous adverse reactions; patch testing; hypersensitivity; lymphocyte transformation test

Introduction

T-cell-mediated drug hypersensitivities are a group of immune-mediated (IM) adverse drug reactions (ADRs) of varying phenotype and severity. Descriptions of antimicrobial associated T-cell-mediated ADRs date back to the use of the first sulfa antimicrobials [1] and then almost a decade later to early preparations of penicillins [2,3]. These IM-ADRs result in antimicrobial allergy “labels” that impact patient outcomes and antimicrobial usage [4–6]. For the diagnosis of antimicrobial allergy, the use of skin prick and intradermal testing (SPT/IDT) remain the mainstay of first-stage diagnosis for immediate reactions suspected to be IgE-mediated. This should be followed by an ingestion challenge which, in combination with SPT/IDT, is still considered to be the gold standard [7]. However, in the setting of serious T-cell-mediated ADRs, both patch testing, a more established test for the diagnosis of delayed reactions, and SPT/IDT lack the 100% negative predictive value necessary to re-challenge patients to drugs either orally or systemically following negative testing [8]. In this review, we will address the current understanding of antimicrobial cross-reactivity and the ready availability of and evidence for IM-ADR *in vitro*, *in vivo* and *ex vivo* diagnostics.

The epidemiology of serious T-cell-mediated reactions varies according to the region studied and is driven by genetic predisposition to these reactions. In general, given the high prevalence of antibiotic use, 50% or more of severe cutaneous adverse reactions (SCAR) globally are associated with antimicrobials, commonly penicillins, glycopeptides and sulphonamide antibiotics and antiretrovirals [5,9,10]. The most serious of these reactions include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustolosis (AGEP). Additionally, abacavir, a guanosine analogue nucleoside reverse transcriptase inhibitor (NRTI), is associated with a severe HLA-B*57:01-restricted, CD8+ T-cell-mediated hypersensitivity reaction (AHS) which is characterized clinically by fever, malaise, gastrointestinal symptoms and late onset of rash (70%) a median of 8 days after initiation of dosing. In the setting of multiple implicated antimicrobials, the cause of SCAR and other IM-ADRs is often unclear despite application of published causality assessments [11,12].

Effector immunology of T-cell-mediated ADRs

IM-ADRs can be classified by the revised Gell and Coombs classification (Table 1)[13]. This review focuses on Type IV, T-cell-dependent IM-ADRs. The pathogenesis of T-cell-

mediated immune responses has been long debated, yet the presence of allergen-specific T lymphocytes is an observation in most drug-allergy reactions. White *et al.* reviewed the current mechanistic hypotheses of T-cell-dependent IM-ADRs namely (i) pharmacological interaction of drugs with immune receptors (the p-i concept), (ii) the hapten/pro-hapten model and (iii) the altered peptide repertoire model (Figure 1)[4]. The cellular and cytokine response within IM-ADRs vary (Table 1).

Many of the SCAR reactions are known to rely on drug specific T-cell responses that can persist in the circulation for >20 years after drug exposure [60]. Blistering and severe IM-ADRs (SJS/TEN or AHS) are thought to correlate with CD8+ T-cell infiltration, while simple exanthema and DRESS are largely associated with CD4+ T cells or mixtures of CD4+ and CD8+ T cells [61,62]. In general, cytokines upregulated in IM-ADRs are IL-2, IL-5, IL-13 and IFN-y [63]. The key immune mediators differ slightly for each IM-ADR phenotype, summarised in Table 1. An understanding of immune mediators is vital for future works measuring cytokines in *ex vivo* T-cell diagnostics.

Historical approaches to T-cell-mediated hypersensitivities

Testing for IM-ADRs remains problematic due to both lack of widespread availability and low sensitivity of conventional methods. Many patients with non-specific rashes or those that occur during the course of an acute infection will not demonstrate reproducible symptoms on future rechallenge. Caubet *et al.* demonstrated that only 6.8% of patients with a history of antibiotic associated “rash” had a reproducible phenotype on oral challenge. In recent studies, IDT has been suggested to be more sensitive than patch testing (PT) for T-cell-mediated ADRs [64]. However, in the setting of serious T-cell-mediated ADRs, PT is still considered “safer” than delayed-SPT/IDT [65,66]. The details of PT and IDT for T-cell-mediated ADRs are described below and a summary of T-cell-mediated ADRs is provided in Table 2.

Patch testing (PT)

The specificity of PT for SCAR has been high in settings where drug concentrations have been validated against negative controls. The sensitivity of PT varies, however, and is highest for DRESS (32–80%) [112,113] and AGEP (58–64%) [112,114], and lowest for SJS/TEN (9–24%) [112,114] and MPE (10–40%) [65,113]. Patch testing lacks an appropriate positive control and results may be difficult to interpret in patients who are on immunosuppressants that impact T-cell-mediated immunity. For antibiotics, PT to the upper back is generally recommended 6 weeks – 6 months post skin healing [115]. In a multicentre study of PT in SCAR, Barbaud *et al.* demonstrated that PTs were most frequently positive for beta-lactams (primarily amoxicillin) and pristinamycin [112]. Buonomo *et al.* demonstrated PT’s utility in IM-ADRs, predominately cephalosporin-associated MPE, in a retrospective cohort [116]. Barbaud *et al.* utilized PT in 29 cases of pristinamycin-associated IM-ADRs, with a higher that expected sensitivity noted (69%) [66]. In 27 patients with oral challenge confirmed FDE to TMP-SMX, a 93% sensitivity for PT was demonstrated [117]. However, in a recent study by Andrade *et al.* 0% (0/15) of FDE were positive on PT [118]. The utility of PT in IM-ADRs caused by quinolones and trimethoprim-sulfamethoxazole

(TMP-SMX) is notoriously poor [112,119,120]. PT has been demonstrated to be effective in a small number of antibiotic-associated SJS/TEN [114,121–123], AGEP [70,112,120,124,125], FDE [126–128], DRESS [112,129], MPE [130] and EM [131] case series. To date, success with PT in cases of suspected antiretroviral hypersensitivity has been limited to abacavir. PT for abacavir showed 100% specificity and 87% diagnostic sensitivity when used as an adjunctive test to define true AHS [8,132].

Summary & Recommendations

i. A positive PT has high specificity for a specific antibiotic-associated IM-ADRs and appears most useful for DRESS >AGEP and of lessor utility for FDE, MPE and SJS/TEN.

ii. A negative PT does not exclude a drug-specific IM-ADR and should never be used as the sole basis for rechallenge of the implicated antibiotic(s).

Delayed intradermal testing (Delayed-IDT)

The use of delayed-IDT (0.02–0.05 mLs of highest non-irritating concentration of antimicrobial applied to volar forearm skin, then read at 48–72 hours [133]) is recommended in the investigation of T-cell-mediated ADRs [134,135]. Similar to patch testing, delayed-IDT is limited by the significantly less than 100% sensitivity and lack of a suitable positive control [136]. Recommendations for IDT vary regionally and there is a lack of evidence-based volumes and reagents (beta-lactam versus non-beta-lactam) [121,133–135]. IDT has predominately been utilized for beta-lactam antimicrobials, especially penicillins > cephalosporins, in patients with a history of non-SJS/TEN T-cell-mediated ADR [122,123,137]. A positive result involves dermal induration/erythema at injection site, which will significantly exceed 5 mm from baseline, 24–72 hours post-testing. Although extension of the local dermal response at the skin testing site is uncommon, IDT is generally not recommended for the assessment of SJS/TEN [123,138], due to risk of systemic events. Adverse reactions following delayed IDT for non-SJS/TEN ADRs are rarely reported [139–141], primarily occur in the setting of immediate testing [142–144] and are often related to errors in concentrations and/or volumes used.

Alternative guidelines do not specify the same ‘contraindications’ to IDT, however suggest performing IDT only after a negative PT [145]. Whilst it appears PT is preferred over IDT for FDE [118], the sensitivity of IDT for other T-cell-mediated ADRs appears higher than that observed with PT [64,130,141,146,147]. In a study of patients with suspected reactions to beta-lactams (n = 235 MPE), 7% (18/235) had a positive delayed-IDT, while 8.5% (20/235) with negative IDT demonstrated a positive result with OC [147]. IDT has also been used less frequently for other antimicrobials associated with IM-ADRs, such as metronidazole [148]. Limitations include (i) only antimicrobials in a commercially available and sterile injectable form can be utilized, (ii) short-lived local histamine release (e.g. ciprofloxacin and vancomycin) and irritation (e.g. flucloxacillin) of some products and (iii) overall low NPV. The sensitivity of delayed-IDT from a mixture of small studies has been reported as 6.6–36.3% for MPE (higher with penicillins > cephalosporins) [149–151] and 64%–100% for DRESS [113,137].

Summary & Recommendations

i. Delayed-IDT can be employed as a first line investigation for non-SJS/TEN IM-ADRs, although the highest non-irritating concentrations for DELAYED testing have not been validated for most drugs.

ii. A positive delayed-IDT result is highly suggestive of an IM-ADR, but a negative delayed-IDT does not exclude an IM-ADR and should never be used as the sole basis for rechallenge.

Direct oral challenge

Since first-stage tests such as PT and IDT do not have 100% negative predictive values, oral challenge is contraindicated in certain SCAR (e.g. SJS/TEN/DRESS) [8,152] and AHS. Oral challenge is required to confirm IM-ADRs following negative delayed-IDT or PT in the remaining phenotypes [150,153]. For the investigation of delayed reactions, a prolonged oral challenge (5–7 versus 3 days) increases sensitivity [150,154]. Due to the low rate of positives obtained from isolated delayed-IDT or PT [153,155–157], and high rate of Type A ADRs clouding “labels” [6], a move toward direct oral challenge has been proposed, especially for ‘low-risk’ phenotypes [6,158]. This is particularly true in children where viral infections or drug-infection interactions are prevalent. Direct oral rechallenge in a cohort of patients with a history of MPE demonstrated only a 6.9% adverse event rate (compared with 3.5% prior) [159]. A direct 5-day oral rechallenge in 119 pediatric patients with mild antibiotic-associated MPE elicited a 5.4% positive response rate, none of which were serious [80]. The safety of oral rechallenge for antiretroviral IM-ADRs has not been established, but guidelines advise that patients with mild to moderate rash without constitutional symptoms can continue antiretrovirals with close clinical monitoring. In these cases, symptoms should be managed with anti-histamines and topical corticosteroids. Physicians commonly “treat through” mild ADRs to non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine or efavirenz, hepatitis C drugs such as telaprevir and antibiotics such as beta-lactams and sulfa antimicrobials [160,161]. Desensitization protocols exist for hypersensitivity reactions to the antiretrovirals tipranavir [162], amprenavir [163], darunavir [164], efavirenz [165] and have been tried with nevirapine [166].

Recommendations

i. Direct oral challenge for 5–7 days should be employed after a negative PT or delayed-IDT in the setting of mild to moderate antibiotic skin rashes without evidence of fever, mucosal involvement, malaise or internal organ involvement.

ii. Oral challenge with a suspected drug should never be employed in the setting of SJS/TEN or DRESS.

iii. Ideally, an observed oral or ingestion challenge in the setting of required antibiotic therapy should be employed following negative IDT/PT and knowledge of antibiotic cross-reactivity (Box 1).

iv. In acute settings, of mild to moderate rash without fever, mucosal or internal organ involvement, antimicrobials can be continued with close monitoring.

Box 1

Heading: Empirical antimicrobial therapy recommendations in the setting of T-cell-mediated ADR (non-SCAR) where in vivo and ex vivo testing is not available

Antimicrobial allergy "label"	Antimicrobials to avoid in the setting of known T-cell-mediated ADR history
Penicillin V/G	Cephalothin Cefoxitin
Aminopenicillins	Ampicillin/amoxicillin Cefaclor[a] Cephalexin[a]
Anti-staphylococcal penicillin	Penicillin V/G Flucloxacillin/dicloxacillin/oxacillin Piperacillin-tazobactam Ticarcillin-clavulanate
1st Generation cephalosporins[b]	Amoxicillin[c] Cefaclor[d]
2nd Generation cephalosporins	Ceftriaxone[e] Cefotaxime[e] Cefepime[e] Cephalexin[f]
3rd Generation cephalosporins	Cefepime[g] Cephalothin[h] Cefuroxime[g] Cefotaxime[g]
4th Generation cephalosporins	Aztreonam[i] Cefitraxone[j] Cefuroxime[j] Cefotaxime[j]
Carbapenems	Carbapenems
Monobactams	Ceftazadime[k]
Antibiotic sulphonamides	Nil

References:[79,152,167–174]

Abbreviations:

SCAR, severe cutaneous adverse reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis; drug reaction with eosinophilia and systemic symptoms; acute generalised exanthematous pustolosis.

ADR, adverse drug reaction.

[a] Avoid if amoxicillin/ampicillin delayed IM-ADR due to shared/similar R1 side chain

[b] If cefazolin is the implicated antimicrobial, this is generally an isolated reaction due to the absence of shared side chains and therefore other beta-lactams could be employed for non-SCAR phenotypes.

[c] If cephalexin allergy then avoid amoxicillin/ampicillin due to shared/similar R1 side chain

[d] Avoid if cephalexin allergy due to shared/similar R1 side chain

[e] Avoid if cefuroxime allergy due to shared/similar R1 side chain

[f] Avoid if cefaclor allergy, due to shared/similar R1 side chain

[g] Avoid if ceftriaxone allergy due to shared/similar R1 side chain.

[h] Avoid if cefoxitin allergy due to shared/similar R1 side chain.

[i] Avoid if ceftazadime allergy due to shared/similar R1 side chain

[j] Avoid if cefepime allergy due to shared/similar R1 side chain

[k] Avoid if aztreonam allergy due to shared/similar R1 side chain

T-Cell Diagnostics

Lymphocyte transformation test

Ex vivo investigations have been explored for T-cell-mediated ADRs, including the lymphocyte transformation test (LTT). LTT has a reported sensitivity of 27–70% and specificity of 72.7–100%, however remains hindered by testing time, requirement for radioactive materials and potential dependence on B-cell proliferation [8,175–177]. LTT has been used for causality assessments in ceftriaxone, ampicillin/sulbactam and metronidazole-associated linear IgA disease, ceftriaxone-associated MPE, penicillin/amoxicillin-induced MPE and ceftazidine-induced DRESS [178–181]. In a small study of amoxicillin-induced IM-ADR, correlation between positive *in vivo* IDT and LTT was not demonstrated [182]. LTT has also been used in a small number of other case reports/series for IM-ADRs secondary to anti-tuberculosis therapies [129], aminopenicillins [122,123,177], cephalosporins [183] and anti-staphylococcal penicillins [137].

Recommendation

i. Antibiotic LTT is an unvalidated test that has been associated with both false positive and false negative results and currently remains a research tool used in specialized centres for the investigation of T-cell-mediated ADRs.

Enzyme-Linked ImmunoSpot (ELISpot) Assay

ELISpot is an *ex vivo* technique used to analyse low-frequency antigen-specific, cytokine-producing (e.g. IFN-γ) cells in peripheral blood following exposure to pharmacological drug concentrations [8]. ELISpot can be employed for a range of cytokine responses depending on the underlying drug hypersensitivity immunopathogenesis. For example, AGEP can have high IL-13 and IFN-γ, FDE raises IL-10, while DRESS can have high IL-5 or IFN-γ [60,184]. ELISpots measuring granzyme have also been employed [175]. ELISpot studies have demonstrated that 1:150 to 1:5000 T cells remain ‘reactive’ in patients post ADR for up to 12–20 years [60,185]. ELISpot has also been shown to have better sensitivity than LTT in detecting drug-specific T-cell responses [185,186]. Nonetheless, ELISpot has only been employed in research settings for the investigation of antimicrobial allergy. Estimations of sensitivity and specificity are flawed due to the absence of a reference gold standard. However, increasing the drug concentration used to stimulate the patients’ cells and increasing incubation periods (48 hours vs. overnight) have been shown to increase assay sensitivity without decreasing specificity. An examination of ELISpot use in antimicrobial T-cell-mediated ADRs is outlined below:

ELISpot & Antiviral IM-ADRs

ELISpot is described in studies examining antiretroviral hypersensitivity reactions, notably abacavir and nevirapine. ELISpot has been used to detect abacavir hypersensitivity in patients that are HLA-B*57:01 negative [187]. IFN-γ ELISpot has also been used to demonstrate that abacavir unexposed HLA-B*57:01 positive patients have a 'resting' abacavir reactive CD8+ T-cell population [188]. In nevirapine hypersensitivity reactions, IFN-γ ELISpot has been utilised to demonstrate that specific combinations of CD4 class II-restricted and CD8 class I-restricted T cells contribute to the hypersensitivity immunopathogenesis [189].

ELISpot & Antibiotic IM-ADRs

Penicilins

Earlier studies demonstrate that ELISpot IFN-γ testing was positive in patients with a history of amoxicillin IM-ADRs [185,190]. No positive ELISpot results were identified in control patients or those with a history of IgE-mediated disease, highlighting the specificity of the test. The intensity of response was, however, proportional to time after diagnosis. The overall sensitivity and specificity was 91% and 95% respectively. Khalil *et al.* demonstrated a sensitivity and specificity of 80% and 100% respectively for ELISpot measuring IL-2, IL-5 and IFN-y in patients with amoxicillin IM-ADR. Rozieres *et al.* demonstrated *ex vivo* effectiveness for other beta-lactams, including ticarcillin [185,191]. ELISpot has also been used in models using antigen-specific T-cell clones to confirm patients with a history to piperacillin hypersensitivity [192].

Cephalosporins

Tanvarasethee *et al.* examined the use of ELISpot to diagnose cephalosporin-induced MPE and compare against SPT, delayed-IDT and PT [193]. From the 25 patients, 40% had a positive IFN-γ and IL-5 response compared with 8% who had a positive delayed-IDT or PT (p= 0.008). There was a higher probability of positive ELISpot if performed within 2 years of reaction (p=0.046) [193].

Other antimicrobials

The use of ELISpot for quinolones, glycopeptides, trimethoprim-sulfamethoxazole and other commonly used antibacterial therapy is absent. Aminoglycosides are an infrequent cause of SCAR, yet a case of amikacin-induced DRESS was confirmed on patch testing and ELISpot [194]. A case of sulfasalazine hypersensitivity syndrome was also confirmed with ELISpot [195]. The use in other antimicrobials is also ill-defined. Further research is required to evaluate this testing in a range of antimicrobial therapies.

Recommendation

i. ELISpot remains a test available only in specialized centres for the investigation of T-cell-mediated ADRs.

Predicting T-cell Responses – HLA typing

Recently, an increasing number of antimicrobial IM-ADRs have been associated with various HLA alleles (Table 3). In general, due to varying HLA allele frequencies, different ethnic populations have different genetic associations. To date, the best characterized antimicrobial-induced, HLA-associated IM-ADRs that appear to generalize across populations include AHS and nevirapine SCAR. The association between AHS and HLA-B*57:01 resulted in the implementation of a routine screening test that is widely employed in the developed world before abacavir treatment. Before widespread acceptance, the HLA-B*57:01 genetic association with abacavir was established in a large population with a diverse genetic background. This screening test has a positive predictive value (PPV) of 55% and a negative predictive value (NPV) of 100%, which is crucial for drug safety [218–220]. Less than 100% NPVs and very low PPVs of other antimicrobial drug hypersensitivity HLA associations have limited their translation into routine clinical practice as screening tests. For example, although only 13 individuals would need to be screened for HLA-B*57:01 to prevent a single case of AHS, over 14,000 individuals would have to be tested for this same allele to prevent a single case of flucloxacillin-associated hepatitis.

The story of nevirapine-induced IM-ADRs is quite complex. Nevirapine-induced IM-ADRs have been associated with different HLA alleles across different ethnic populations. These HLA associations appear to be phenotype specific and involve both Class I and Class II HLA alleles. An association between nevirapine-induced hepatitis and HLA-DRB1*01:01 was first reported in a Western Australian population [217] and has since been reported in other Caucasian populations [216]. The closely related allele HLA-DRB1*01:02 was associated with nevirapine-induced hepatitis in a South African cohort [196]. Nevirapine DRESS has been associated with the HLA-Cw*8 or Cw*8-B*14 haplotype in Japanese and Italian populations and also with HLA-Cw*4 and HLA–DRB1*15 in Han Chinese, HLA-B*35:05 in Asians and HLA-B*35:01 and HLA-B*15/DRB1*15 in an Australian cohort [189,212–215]. Many of these alleles including HLA-DRB*01, HLA-Cw*04 and HLA-B*35:05 are also associated with nevirapine-induced rash [209–211,215,216].

Other HLA associations have been described for IM-ADRs to efavirenz, dapsone, flucloxacillin, amoxicillin-clavulanante, sulfamethoxazole, aminopenicillins, sulphonamides, isoniazid and levamisole (Table 3).

Many of these antimicrobials such as flucoxacillin and amoxicillin-clavulanate are specifically associated with drug-induced liver injury (DILI), which can be associated with fulminant hepatic failure [220]. Although few HLA screening tests have advanced to the level of routine clinical practice, HLA associations have significantly advanced our understanding of the immunopathogenesis of IM-ADRs.

Recommendation

i. Level IA evidence exists to support screening for HLA-B*57:01 prior to initiation of abacavir therapy. This screening test has a 100% negative

predictive value and is widely recommended as part of guideline-based practice.

Cross Reactivity in T-Cell-Mediated Reactions

In settings where *in vivo* and *ex vivo* diagnostics are unavailable, understanding cross-reactivity based on shared chemical structure amongst antimicrobials is essential (Box 1). Most of the rates of cross-reactivity for delayed IM-ADRs are extrapolated from data that exists for cross-reactivity in the setting of immediate hypersensitivities. Earlier reports of high rates of penicillin/cephalosporin cross-reactivity were confounded by penicillin contamination of cephalosporin manufacturing [2,3,222]. Current literature supports that most cross-reactivity that occurs in the beta-lactam class occurs on the basis of shared R1 and/or R2 side-chains [85,149,150). Recent reports suggest patients with a history of delayed hypersensitivity to aminopenicillins most commonly cross react with aminocephalosporins sharing an R1 group such as cephalexin, cefaclor and cephadroxil and generally tolerate all other cephalosporins [223,224]. Challenging patients with a penicillin/amoxicillin allergy history with a cephalosporin not sharing the same side chain (e.g. cefuroxime or ceftriaxone) proved successful in a study of 41 patients by Novalbas *et al.* [225]. The rate of cross-reactivity between penicillin and 3rd generation cephalosporins now approaches 1%, a far cry from the 10–25% initially quoted in very early studies [226] Romano *et al.* demonstrated that patients with cephalosporin immediate hypersensitivity can still be safely treated with compounds that have side-chain determinants different from those of the responsible cephalosporin [169].

Cross-reactivity between carbapenems has been infrequently reported [227]; a shared T-cell epitope remains unknown [227]. Cross-reactivity between macrolides also appears rare, with infrequent reports of immediate cross-reactivity noted particularly between those with 14-membered ring such as erythromycin, clarithromycin and roxithromycin and the 15-membered azalide, azithromycin [228]. T-cell-mediated cross-reactivity between tetracyclines [229], in particular doxycycline and minocycline has been reported [229]. Cross-reactivity [230] and tolerance [231] have been reported for aminoglycoside antibiotics in which ADRs are more common for topical than systemic agents due to contact sensitization [194,232]. For nitroimidazoles (e.g. metronidazole, tindazole) T-cell-mediated ADRs have been reported, with cross-reactivity noted [94–96,233].

Delayed IM-ADRs are less frequent than immediate ADRs in regards to quinolones [234], with cross-reactivity more commonly occurring between 1st and 2nd generation quinolones than 3rd and 4th generation [234–237]. Glycopeptide (vancomycin and teicoplanin) cross-reactivity is also reported [238–240], however remains controversial, with many reports extrapolated from reoccurrence of haematological disturbances. Patients with isolated vancomycin hypersensitivity have also been known to tolerate teicoplanin [97,238,241–243].

An estimated 3–6% of the population are considered “allergic” to sulphonamides, with trimethoprim-sulfamethoxazole (TMP/SMX) the most commonly implicated example [244]. Whilst belief in overall sulphonamide cross-reactivity persists [245], recent reviews do not support cross-reactivity between antibacterial and non-antibacterial sulphonamides

[244,246–249]. There is cross-reactivity between antibiotic sulfonamides, especially sulfasalazine and sulfamethoxazole [250]. The non-antibacterial sulphonamides (e.g. azetazolamide, forusemide, celecoxib, thiazide diuretics, sumatriptan, sotalol, probenacid) do not contain the structural region known to cause the allergic response (i.e., N1 heterocyclic ring; an N-containing ring attached to the N1 nitrogen of the sulfonamide group and arylamine group at the N4 position). Although early reports questioned the potential for cross-reactivity between TMP-SMX and darunavir [249,251,252], authors have noted an absence of TMP-SMX allergy history in those with darunavir hypersensitivity [253–255]. Notably patients with a history of sulfa antimicrobial allergy were not excluded from darunavir clinical trials.

The potential for cross-reactivity between dapsone and TMP-SMX is now somewhat controversial with most reports occurring in HIV-infected individuals without evidence of positive rechallenge. The current estimated rate of cross-reactivity is less than previously reported (9–11% vs. 20–45%) [256,257]. In those requiring TMP-SMX therapy with a history of non-SCAR adverse drug reaction to antibacterial sulfonamide, we recommend a supervised oral rechallenge, rather than drug avoidance [258,259].

Antiretroviral

Cross-reactivity between most antiretroviral classes is likely very low due to the lack of structural similarities. However, patients with prior severe hypersensitivity to an NNRTI should be monitored if new NNRTI therapy is initiated. Mehta and Maartens reported recurrent reactions in 12.6% of patients with reported rash who were switched from nevirapine to efavirenz, compared with 50% of patients switched from efavirenz to nevirapine [260]. Cross-reactivity is reported to be higher between nevirapine and delavirdine which have a similar structure, but delavirdine is not currently used because of its difficult dosing, pill burden, drug interactions and lower efficacy compared to contemporary NNRTIs [261].

Recommendations for antimicrobial use, in relation to likely cross-reactivity, in patients with delayed hypersensitivities to isolate antimicrobials are given in Box 1.

Conclusions

In an era of increasing antimicrobial resistance and use of broad-spectrum antimicrobial therapy, ensuring patients are correctly “labelled” in respect to antimicrobial-associated IM-ADRs is essential. Re-exposure to the implicated antimicrobial, especially in the setting of SCAR and AHS is associated with significant morbidity and mortality. The key messages from this review are:

1. Antimicrobials are a leading cause of T-cell-mediated ADRs.
2. The antimicrobials primarily associated with T-cell-mediated ADRs include glycopeptides, sulphonamides, beta-lactams, antiretrovirals and hepatitis C antivirals.

3. An understanding of drug latency and allergy ‘phenotypes’ can aid drug causality assessment.

4. Whilst PT and IDT are specific in the diagnosis of T-cell-mediated ADRs, they suffer from drug-specific limitations in sensitivity and when negative they can never be used as the sole basis for rechallenge.

5. A knowledge of side chain cross-reactivity aids empirical antibiotic choice in the setting of IM-ADRs.

6. The use of *ex vivo* diagnostics, especially ELISpot are promising new approaches to assigning causality in antimicrobial associated T-cell-mediated ADRs.

    a. An understanding of cytokine outputs specific to each phenotype will aid the development of these tools in the future.

7. Predicting T-cell-mediated ADRs via personalised approaches, including HLA-typing may pave future pathways to safer antimicrobial prescribing.

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Papers of particular interest, published within the annual period of review, (2015–2016) have been highlighted as:

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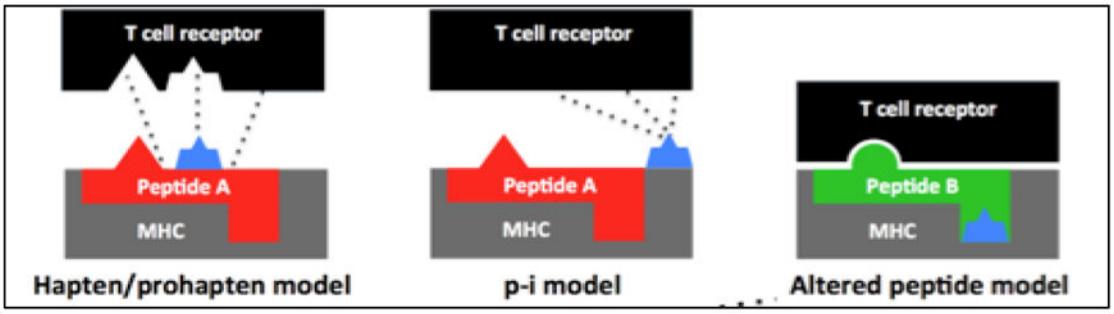

Figure 1. Heading: Schematic of proposed T-cell-mediated ADR pathogenesis theories

(i) The hapten/prohapten model is where an antigen (e.g. antibiotic) covalently binds to a self-peptide, is intracellularly processed and then presented with MHC to T cells as a 'foreign antigen' [51,52]. An example of the hapten/prohapten model is when penicillin G derivatives bind lysine residues on serum albumin [53–55].

(ii) The p-i concept (the pharmacological interaction with immune receptor) is based upon non-covalent binding of antigens to HLA or TCR without immune processing, explaining how reactions can occur upon first presentation [51,56].

(iii) The 'altered self-repertoire model' is based upon drug models (e.g. abacavir) that demonstrated that drugs can occupy positions in the peptide binding groove of the MHC, altering the binding cleft and subsequently the specificity of MHC binding [57–59]. Source: [51,52], [53–55], [51,56], [57–59].

Table 1

T-cell-mediated ADR classification, pathogenesis and phenotype guide

Type IV ADR	Cellular mediators	Cytokine mediators	Phenotype	Specific immunological parameters for phenotype
Type IVa	*Primary:* Th1 *Secondary:* Macrophages	IFN-y TNF-a IL-18	Contact dermatitis Tuberculin reactions	**Contact dermatitis** – Primarily CD8+ T cell infiltrate. ↑ IFN-y, TNF-a, IL-18. Also noted ↑lL-31, IL-6 in serum and IL-33 IL-9, IL-4 in skin [14–18].
Type IVb	*Primary:* Th2 *Secondary:* B-cells, IgE, IgG4, mast cells, Eosinophils	IL-4 IL-5 IL-13	MPE[a] HSS DRESS	**MPE** – CD4 > CD8+ T cells. Acute episodes Th1 predominate, ↑ IL-12, IFN-y/TNF-b in blood, CXCL9/CXCL10 skin. ↓ IL-17 compared with SJS/TEN. ↑ Th2/IL-5 later explains pruritis [19–24]. **DRESS** - ↑ TNF-a, IFN-y and IL-2 production, production correlates with disease severity. Activation-regulated chemokine (TARC/CCL17) drive Th2 responses, higher than observed in SJS/TEN. Skin biopsies noted eosinophils in 20%; whilst CD8+ T cells and granzyme B(+)lymphocytes ↑ in severe disease [25–27].
Type IVc	*Primary:* Cytotoxic T cells	Granzyme B Perforin Fas ligand Granulysin	SJS TEN Linear IgA disease DILI[b] *FDE *EM	**SJS/TEN** – CD8+ T-cells and NK cells lead to keratinocyte apoptosis. Granulysin specific to SJS/TEN. ↑ IL-10 and T_{reg} associated with resolution of TEN/SJS. T_{reg} function often impaired. ↑ IL-2, IL5, IL6, IL-17 and CCL27 in plasma/blister fluid. Th17 cells also have a role [23,28–35]. **Linear IgA disease** – Often mistaken for TEN, however characteristic linear IgA deposits are evident on direct immunofluorescence studies. ↑ CD4+ T-cell, neutrophils and eosinophilis. Mixed Th1/Th2 cytokine response. ↑ IL-2, IL-4, IL-5 and IL-8 noted [36–41]. **FDE** – ↑Intraepidermal CD8+ T-cells, ↑IFN-y, cytotoxic granules, granzyme B and perforin. ↑CD8+ T-cells, CD4+ T-cells and neutrophils cause tissue damage. Late - ↑IL-10 & T_{reg}(CD4+CD25+Foxp3+) control immune reaction, however IL-15 secreted by keratinocytes continue to propagate CD8+ T-cell mediated injury [42,43]. **EM** – ↑IL2, IL6, IL8, IL17A, IFN-y. ↑Th1/CD4+ T-cell infiltrate with IL-17 expression. ↓ IL10, noted. At skin level, ↑ CD4+ T cell with IL-17 (Th2) expressing cells. CD8+ T cells noted within epidermis, and CD4+ T cells are noted in dermis. Variations in T-cell/cytokine expression if the stimulant is HSV or drug induced (e.g. higher CD8+ T cells and TNF-a in drug-induced EM) [44–46].
Type IVd	*Primary:* Th1/Th17 *Secondary:* Neutrophils	GM-CSF IL-8 CXCL8	AGEP	**AGEP** – ↑CD4+ T cells infiltrate, CD8+ T cells and ↑↑ CXCL8 and GM-CSF. CXCL8 is involved in the chemotaxis of neutrophils; Th17 cells involved [47–50].

References:[13]

Abbreviations: Th1, Type 1 T helper cells, Th2, Type 2 T helper cells; Th17, Type 17 T helper cells; IL, interleukin; DHR, Drug hypersensitivity reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema; DRESS, drug reaction with eosinophilia and systemic symptoms; HSS, hypersensitivity syndrome; FDE, fixed drug eruption; EM, erythema multiforme; DILI, drug induced liver injury; AGEP, acute generalised exanthematous pustolosis; GM-CSF, granulocyte monocyte colony-stimulating factor; PMN, polymorphonuclear cell.

*Not classically described by Gell and Coombs criteria of T cell-mediated hypersensitivity

[a]**MPE**, otherwise known as 'morbilliform' drug eruption, is the most commonly reported antibiotic-associated T-cell-mediated ADR.

[b]**DILI** - DILI will not be covered in detail in this review, as the mechanism can be dose dependent/predictable or unpredictable. The unpredictable reactions may in fact be IM or metabolic in origin. T lymphocytes secreting granzyme B have been noted on liver biopsy. CD4+/CD8+ T cells secreting IL-13 and IFN-y have been detected in serum from in patients with DILI.. The most commonly implicated antimicrobials are amoxicillin-clavulanate and flucloxacillin, in particular in those with HLA-B*57:01

Table 2

Summary of antimicrobial associated T-cell-mediated ADRs

Characteristics	SJS/TEN	DRESS	AGEP	EM	FDE	Drug-induced linear IgA	MPE
Drug latency *(days)*	4–28[a]	14–42	1–18[b]	<1–10	<1 to 14[c]	1–18[d]	4–9
Prodrome	Common	Common	Uncommon – Fever with acute phase	Uncommon – Unless severe	Uncommon	Uncommon	Uncommon
Distinguishing cutaneous features	Starts face ➔ thorax. Palms, soles and scalp rarely involved. Nikolsky sign[e]	Morbilliform +/− follicular accentuation. Usually >50% BSA involvement and >2 of (i) facial oedema (50% cases) (ii) infiltrated lesions, (iii) scaling or (iv) purpura.	Starts face ➔ thorax. Dozens to hundreds non-follicular, sterile, pin-sized pustules, generally with background erythema. Flexural accentuation.	Can involve all regions. Symmetrical target lesions, spreading in centripetal fashion. Oral involvement can be isolated finding.	Can involve all regions. Commonly lips, genitalia, perianal area, hands, feet. Well demarcated +/− vesiculation or blistering.	Sub-epidermal blisters on trunk, extensor surfaces, buttocks and face (especially perioral region).	Morbilliform eruption – macules, papules or rarely pustules/ bullae. Desquamation often follows resolution.
Mucosal involvement	Yes (very common - 90%)	Yes (infrequent)	Yes (uncommon, only lips)	Yes (common, 70%)	Yes (infrequent)	Yes (common – 80%)	No
Commonly implicated antibiotics	Beta-lactams (penicillins > cephalosporins), vancomycin, sulphonamides, macrolides, quinolones, tetracycline, clindamycin	Sulphonamides, vancomycin, minocycline, dapsone ≫ beta-lactams, pristinamycin nevirapine, telaprevir, acyclovir	Vancomcyin[f], amoxycillin, ciprofloxacin, gentamicin, carbapenems[g]	Sulphonamides, penicillins, quinolones[h]	Sulphonamides, tetracyclines, penicillins, quinolones, macrolides, metronidazole,	Vancomycin ≫ amoxycillin, ADF, quinolones, sulphonamides	Beta-lactams, (especially penicillin, amoxicillin/ amoxicillin-clavulanate), sulphonamides, cephalosporins, lincosamides
Scoring Algorithms[i]	ALDEN[11]	RegiSCAR[67]	EuroSCAR[68]	Nil	Nil	Nil	Nil
Preferred diagnostics (*in vitro*)	PT	PT> Delayed-IDT	PT	PT	PT> Delayed-IDT[j]	PT	Delayed-DT
Research diagnostics (*ex vivo*)	LTT ELISpot	LTT ELISpot	LTT ELISpot	LTT ELISpot	LTT ELISpot	LTT ELISpot	LTT ELISpot

References: [5,9,39,65,69,73–111]

Abbreviations: T-cell-mediated ADRs, delayed hypersensitivity reactions; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; AGEP, acute generalised exanthematous pustolosis; EM, erythema multiforme; FDE, fixed drug eruption; Linear IgA, linear immunoglobulin IgA disease; MPE, maculopapular examthem; TMP-SMX, trimethoprim-sulfamethoxazole; ADF, amoxicillin-clavulanate; LTT, lymphocyte transformation test; ELISpot, enzyme-linked immunospot assay; BSA, body surface area.

[a]Much shorter duration for antibiotics than other drugs (1 vs. 11)

[b]Can be as early as 48 hours on drug re-exposure, median time 14 days

[c] Can be as short as 30 mins to 8 hours post drug administration [69]

[d] Latency periods are rarely up to 30 days.

[e] Nikolsky sign – The ability to extend the area of sloughing with the application of gentle lateral pressure on seemingly unaffected skin. Asboe- Hansen sign ("bullae spread") – Lateral extension of bullae with gentle pressure

[f] Vancomycin most commonly implicated antibiotic

[g] Rare reports secondary to carbapenems (meropenem, doripenem, ertapenem) [70,71]

[h] Infective causes are more common in EM than SJS (e.g. HSV1 and Mycoplasma)

[i] In cases where a specific scoring system has not been developed, 'Naranjo score' can be employed as a guide [72]

[j] At the site of previously described reaction

Table 3

Human leukocyte antigen associations for antimicrobial associated T-cell-mediated hypersensitivity syndromes

Antimicrobial	Clinical Presentation	Associated HLA allele(s)	Population	NPV	PPV	NNT
Abacavir	Hypersensitivity syndrome (fever, rash, GI distress, malaise)	HLA-B*57:01	European, African	100% for patch test confirmed	55%	13
Efavirenz	Rash	HLA-DRB1*01	French			
Nevirapine	Rash	HLA-B*35:05 HLA*Cw4	Thai African, Asian, European, Thai	97%	16%	
	DRESS	HLA-B*14/Cw8 HLA-Cw8 HLA-Cw*4 and HLA- DRB1*15 HLA-B*3505 HLA-B*3501 and HLA- B*15/DRB1*15	Italian Japanese Han Chinese Asian Australian			
	Hepatitis	HLA-DRB1*01:01 HLA-DRB1*01:02	Australian, European South African	96%	18%	
	SJS/TEN	HLA-C*04:01	Malawian			
Dapsone	Rash, hepatitis	HLA-B*13:01	Chinese	99.8%	7.8%	84
Flucloxacillin	Hepatitis (DILI)	HLA-B*57:01 HLA-DRB1*0107- DQB1*0103	European	99.99%	0.12%	13.819
Amoxicillin- clavulanate; coamoxiclav	Hepatitis (cholestatic)	HLA*02:01 HLA-DQB1*0602 and rs3135388, a tag SNP of HLA-DRB*15:01- DQB1*06:02	European			
Sulfamethoxazole	SJS/TEN	HLA-B*38	European			
	FDE	HLA-A*30-B*14-Cw*6 haplotype	Turkish			
Aminopenicillins	Rash	HLA-A*2 HLA-DR*52	Italian			
Sulphonamides	SJS/TEN	HLA-A*29 HLA-B*12 HLA-DR7	European			
Isoniazid	DILI	NAT2 slow acetylator, CYP2E1*5 and *1B	European			
	Drug-induced lupus erythematous	HLA-DR*4	Italian			
Levamisole	Agranulocytosis	HLA-B*27	South American			

Abbreviations: DILI, drug-induced liver injury; DRESS, drug reaction with eosinophilia and systemic symptoms; GI, gastrointestinal; HLA, human leukocyte antigen; NNT, number needed to treat; NPV, negative predictive value; PPV, positive predictive value; SJS/TEN, Stevens-Johnson Syndrome/Toxic epidermal necrolysis References: [196–221]