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The Three C's of Antibiotic Allergy – Classification, Cross-Reactivity and Collaboration

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Abstract

Antibiotic allergy labelling is highly prevalent and negatively impacts patient outcomes and antibiotic appropriateness. Reducing the prevalence and burden of antibiotic allergies requires the engagement of key stakeholders such as allergists, immunologists, pharmacists and infectious diseases physicians. To help address this burden of antibiotic allergy over-labelling, we review three key antibiotic allergy domains: (a) antibiotic allergy classification, (b) antibiotic cross-reactivity and (c) multidisciplinary collaboration. We review the available evidence and research gaps of currently utilized adverse drug reaction (ADR) classification systems, antibiotic allergy cross-reactivity and current and future models of antibiotic allergy care.

Keywords

Antibiotic allergy; antimicrobial allergy; cross-reactivity; prevalence; penicillin allergy; cephalosporin allergy

Introduction

Approximately 10% of populations engaged in medical care are labelled as penicillin allergic¹, so that addressing antibiotic hypersensitivity and adverse drug reactions (ADRs) has emerged as a significant public health issue.^{2–6} Reducing the prevalence and burden of antibiotic allergies requires the engagement of key stakeholders such as allergists, immunologists, pharmacists and infectious diseases physicians.^{3, 7–9}

Antibiotic allergies are often poorly documented across electronic medical platforms¹⁰ and associated with inferior microbiological outcomes (e.g. vancomycin vs. semi-synthetic penicillin for invasive methicillin sensitive *Staphylococcus aureus* infections)^{11, 12}, adverse events (e.g. ceftriaxone or clindamycin and *Clostridium difficile*)^{13, 14} and microbiological resistance.⁴ Antibiotic allergy is also associated with increased readmissions, restricted antibiotic use and excess mortality.^{3, 4, 15} A better measure of the impact of patient-reported antibiotic allergy (so-called antibiotic allergy labels [AALs]) on prescribing is an assessment of antibiotic appropriateness, recent evidence demonstrating such a negative association.^{16–18} Li *et al.* demonstrated also that a penicillin allergy was associated with a 1.82–2.58 fold increase in total antibiotic costs.¹⁹

Improving the accuracy of antibiotic allergy reporting in combination with aggressive multidisciplinary ‘de-labelling’ approaches is required to reduce the impact of AALs. We assembled a group of allergist/immunologists, infectious diseases physicians, antimicrobial stewardship physicians and pharmacists to review the three key antibiotic allergy domains that are central to effect change in antibiotic allergy over-labelling **(i) antibiotic allergy classification, (ii) antibiotic allergy cross-reactivity and (iii) multidisciplinary allergy collaboration.**

Methods

A search of PubMed and Medline was undertaken to examine the literature around antibiotic allergy classification, cross-reactivity, testing and management (1948–2017). The search utilized was: [“antibiotic allergy” OR “antibiotic hypersensitivity” OR “penicillin allergy” OR “antibiotic adverse drug reaction”] AND [“cross-reactivity” OR “side chain” OR “de-labelling” OR “pharmacists” OR “antimicrobial stewardship” OR “infectious diseases” OR “allergists” OR “classification” OR “testing”]. Only human studies in English were included. We identified 1194 articles whose content was reviewed for inclusion in this manuscript.

Classification: Antibiotic allergy and adverse drug reactions

Adverse drug reactions (ADRs) are typically described as Type A (pharmacologically predictable, dose dependent, non-immune mediated and less influenced by genetic factors) and Type B (pharmacologically unpredictable, non-dose dependent and often immune mediated) reactions.²⁰ Immunologically-mediated or drug hypersensitivity reactions were historically classified mechanistically by Gell and Coombs (Type I-IV) and later by Pichler who refined Type IV (T-cell mediated) reactions (Table 1).^{21, 22}

An improved understanding of the pathogenesis and pharmacogenomics of ADRs demands a shift in classification (Figure 1).^{23, 24} Many ADRs may be predicted as the result of “on-target” pharmacological effects of drugs (Type A),^{25–27} where “on-target” is defined as being related to the primary, intended pharmacologic mechanism of action of the drug. Individual variations in drug metabolism (i.e. genetic polymorphisms in drug metabolism and transporters) occur and may be important drivers of both the enhancement of the pharmacological effect (ADR occurrence) and on-target interactions with other drugs.²³

Contrary to previous beliefs, it is evident that some Type B reactions are dose-dependent and immune-mediated through their “off-target” effects, where “off-target” is defined as being caused by mechanisms of action other than the intended primary pharmacologic mechanism of action of the drug. Due to the increasing recognition of the off-target effects of drug these types of ADRs are increasingly being recognized as relevant to clinical practice. Dose-independent IgE mediated immune reactions by which extremely small amounts of antigen are effectively amplified through an off-target IgE response represent the minority of ADRs. T-cell mediated drug reactions produce long-lived immune responses that are both dose dependent and genetically mediated and an off-target mechanistic basis for this through their non-covalent interactions with immune receptors has now been defined.^{28, 29,30} HLA risk alleles have now been defined for the severest of T-cell mediated reactions such as abacavir hypersensitivity (HLA-B*57:01) and carbamazepine Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). This has established that many of these so-called unpredictable Type B reactions can now be predicted and prevented through successful screening programs both as general guideline-based practice (abacavir and HLA-B*57:01) and more targeted in particular ethnic populations, including for therapies such as carbamazepine (HLA-B*15:02).^{31–34} Other off-target adverse reactions can present with symptoms of flushing, hives, angioedema and rash that are typically associated with IgE-mediated reactions but are differentiated by their dose dependency and lack of immunological memory. The molecular mechanism for a group of “non-allergic drug hypersensitivity/anaphylactoid” reactions was recently explored by McNeil *et al.*, who demonstrated that basic secretagogues and cationic small molecule drugs sharing a tetrahydroisoquinolone motif (e.g. fluoroquinolones) can directly bind the mas-related family of G-coupled protein receptors present exclusively on mast cells, and unlike true IgE mediated reactions, lead to non-IgE mediated dose-dependent mast cell activation.^{35–37} Also unlike true-IgE mediated reactions, these reactions can be medically managed with antihistamine pre-treatment/co-treatment or alteration of the mode of administration (slow-infusion), and do not preclude use of the agent. These concepts centered on clinical phenotyping are essential to the correct reconciliation of allergies in electronic medical

records (EMR), enabling decision support for prescribing to be based upon an accurate initial assessment. Improvements in the algorithms used to record allergies in the EMR and incorporating descriptive classifications, are required³⁸.

Key points

- A. Many antibiotic-associated ADRs are unlikely to be ‘true’ allergies that preclude drug dosing. Furthermore, examples now exist of immunologically mediated reactions that can be predicted and prevented through genetic screening and exclusion of risk populations. Allergists, immunologists and other clinicians need to ensure that mild “on-target” reactions (e.g. side effects) and “off target” reactions (non-IgE mediated mast cell activation) don’t lead to persisting AALs that impact antibiotic utilization.
- B. An increasing understanding of the molecular mechanisms of “on target” and “off-target” reactions, and their relevant pharmacogenomic associations and mechanisms, should be reflected in the re-taxonomization of ADRs and will lead to identification of more targeted therapeutics.

Cross-reactivity & Cross-checking: The importance of side chains

Side chains

An understanding of antibiotic cross-reactivity, especially between beta-lactams, is essential (Figure 2). Cross-reactivity between penicillins and cephalosporins can in part be predicted upon the presence of shared R1, and to lesser degree R2 side chains (Figure 3). Recent work by Romano *et al.* demonstrated patients with cephalosporin allergy commonly tolerated a different cephalosporin of varied R1/R2 side chain.³⁹ A recent survey of allergists, immunologists, pharmacists and infectious diseases physicians in Australia identified significant knowledge gaps regarding antibiotic cross-reactivity and absence of skin testing diagnostics to confirm,⁴⁰ echoed in surveys from the US and UK.^{41–43} The older literature also suggests erroneously high rates of cross-reactivity between penicillins and cephalosporins (10–25%).^{44, 45} Many of the early reports of cross-reactivity of up to 18%,^{46–48} are likely to reflect penicillin contamination of cephalosporin manufacturing, cross-reactivity rates based upon non-consecutive case reports and the fact that aminopenicillins and aminocephalosporins share a common R1 side chain.⁴⁹ In fact, cross-reactivity between carbapenems and penicillins or cephalosporins is as low as 1% and 0% with monobactams.^{39, 50–54} Whilst most of these reports of cross-reactivity are linked with immediate hypersensitivity, similar low rates of cross-reactivity have also been seen in observational studies of non-immediate hypersensitivity some of which have also suggested side-chain cross-reactivity.^{50, 55–58}

Key points

- A. In a patient with confirmed penicillin allergy (skin test positive to one of penicillin G, major penicillin determinant or minor penicillin determinant), other penicillins should be avoided.

- B.** Third generation cephalosporins can be employed in patients with a history of non-immediate or non-life-threatening allergy to penicillin.
- C.** Carbapenems can be employed in patients with a history of immediate penicillin allergy. Due to the 1% rate of cross-reactivity, in cases of previous life-threatening allergy to penicillin a risk/benefit assessment must be undertaken.
- D.** Monobactams can be employed in patients with any history of penicillin allergy.
- E.** Both immediate and non-immediate reactions appear to be commonly associated with the side-chain structures of the drugs. In the case of immediate reactions selective de-labeling strategies appear possible. In the case of severe T-cell mediated delayed reactions such as DRESS or SJS/TEN to-date antibiotic class avoidance has been the preferred management.

Immediate (IgE) allergy skin testing

Penicillin skin prick and intradermal testing (SPT/IDT) in combination with a single or graded oral challenge can successfully remove the label of penicillin allergy in the >90% of those tested.^{59, 60} Often the accessibility to such testing and reagents has been the rate-limiting steps. The negative predictive value of penicillin skin testing with major [benzylpenicilloyl-poly-L- lysine (PPL)] and minor determinants [benzylpenicillin, sodium benzylpenilloic acid, benzylpenilloic acid] is reported to be 97–98%.^{61, 62} Whilst some centers use SPT only, the modern practice is to include IDT and oral provocation to improve sensitivity for immediate hypersensitivities.^{43, 63, 64} There does remain a lack of consistency across skin testing practices, recently demonstrated in a survey of European allergy service providers.⁴³ Adverse reactions following SPT/IDT, whilst often feared, are infrequently reported, and are potentially the result of incorrect drug volume or concentration.^{65–68} The concept of re-sensitization following a negative SPT/IDT and oral provocation to antibiotics, whilst often feared, is a rare event, hence re-testing prior to each treatment is therefore not recommended.^{69, 70}

Despite the haptens for other penicillins and beta-lactams being relatively unknown, the parental form is commonly used for *in vivo* skin testing practices.^{71, 72, 51, 58, 73–84} Consensus regarding administered concentrations also remains elusive.^{85–87} The negative predictive value (NPV) of cephalosporin SPT/IDT is also less than that seen with penicillin testing (sensitivity 30–86%)^{72, 88–90} and may be lost over time (68% positive at 1 year).⁹¹ Romano *et al.* demonstrated that patients with cephalosporin allergy can frequently tolerate alternative cephalosporins with different R1 side chains.³⁹

Delayed (T-cell) allergy skin testing

Antibiotics, especially beta-lactams, sulfa antimicrobials and glycopeptides are common causes of severe cutaneous adverse reactions (SCAR).⁹² A long held belief is that skin testing should not be performed in patients with non-immediate (T-cell mediated) hypersensitivity, due to the risk of reactivation, and lack of reliable information. Whilst IDT may be associated with an increased risk of systemic events,^{93, 94} patch testing (PT) in severe cutaneous adverse reactions (SCAR) is considered safe.^{95–98} Guidelines suggest IDT can be performed, only after a negative PT and at least 6 weeks post skin healing.⁹⁹

Performed with the highest-non-irritating concentrations of drug, both patch and delayed intradermal testing are highly specific and can be helpful in some cases for elucidating causes of non-immediate hypersensitivity; the utility, however, varies between studied region (e.g. North America versus Europe)^{100–103}. It is important to note that the sensitivity of testing methods varies for the approach, the underlying clinical phenotype and the implicated drug. Patch testing sensitivity varies, highest for drug reaction with eosinophilia and systemic symptoms ([DRESS] 32–80%)^{98, 104} and acute generalized exanthematous pustulosis ([AGEP] 58–64%)^{98, 105} and lowest for SJS/TENS (9–24%)^{98, 105} and MPE (10–40%).^{95, 104} The sensitivity is also dependent on the implicated antibiotic, lowest with sulfa antimicrobials and fluoroquinolones, and highest with abacavir, beta-lactams and pristinamycin.^{98, 106, 107} Along with causality assessment this type of testing is most useful when multiple drugs (antibiotics and non-antibiotics) were implicated at the same time. The importance of identification and correct labelling in patients with SCAR is highlighted by Finkelstein *et al.* who demonstrated that 42% of patients with SCAR were hospitalized with a subsequent episode of SJS or TEN.¹⁰⁸ *Ex vivo* diagnostics, such as T-cell enzyme linked immunospot (ELISPOT)^{109–116} and lymphocyte transformation testing (LTT),^{94, 117–120} and flow assays may improve the sensitivity and specificity of current testing and provide additional insights into immunopathogenesis. In some cases of appropriately selected phenotypes (MPE) and implicated antibiotics (penicillin or aminopenicillin), direct oral challenge without skin testing has been safely employed to exclude non-immediate hypersensitivity.^{121, 122} Prior studies have previously demonstrated that childhood antibiotic associated exanthems or non-immediate hypersensitivities were difficult to reproduce on oral challenge.⁹⁶ The “pickup” of non-immediate hypersensitivity has been improved when a prolonged oral challenge (5–7 days) has been employed.¹²³

Key points

- A.** SPT/IDT combined with single dose oral challenge is a validated testing strategy to exclude immediate IgE-mediated penicillin allergy and should be employed.
- B.** SPT/IDT can also be applied for antibiotics outside penicillin including cephalosporins and other beta-lactams however, skin testing to these agents has a significantly lower NPV and should for appropriate labeling should always be followed by single or multi-step ingestion challenge.
- C.** Resensitization is rare (<1%) following routine use of oral antimicrobials and therefore re-testing following negative testing skin testing and oral provocation is not recommended.
- D.** Delayed intradermal skin testing and/or patch testing has utility in selective phenotypes of T-cell mediated adverse drug reactions (DRESS/AGEP >> SJS/TENS) and if positive these are helpful. However, the negative predictive value of these tests still falls significantly short of 100% and clinical history remains the gold standard. The use of delayed intradermal testing may vary based upon regional preferences and practices.

- E.** Currently *ex vivo* cellular studies (i.e. Enzyme linked immunospot assay [ELISpot]) appear promising but have not been validated in large scale studies and they remain as research tools.

Collaboration– New pathways and partnerships

Antibiotic allergy knowledge and the electronic medical record (EMR)

Assessments of antibiotic allergy knowledge amongst immunologists, allergists, general practitioners, and infectious diseases physicians have demonstrated deficiencies in drug allergy knowledge.^{38, 124–128} Education programs aimed at hospital providers can increase knowledge of penicillin skin testing and preparedness to investigate allergy histories.¹²⁶ Sastre *et al.* demonstrated that 40% of physicians do not verify the AAL during a hospital admission.⁵ Fehily *et al.* identified that only 38% of hospital doctors were aware of their patients' penicillin ADR history.¹²⁵ 'De-labelling' patients via any of these means is only half the battle, as both clinicians and patients often revert to the pre-test labels post-assessment.^{63, 129, 130} Although penicillin allergy may be recorded in 8% of inpatients, a description in the EMR is often missing (36%).³⁸ Updating electronic medical records (EMR) and ensuring correct AALs are reinforced or removed post testing is also essential to effect change,³⁸ yet studies evaluating the impact of the EMR on antibiotic allergy are missing.

Antibiotic allergy testing outside the outpatient clinic

Patient AALs often drive inappropriate antibiotic use in the operative setting.¹³¹ Trautmann *et al.* demonstrated that allergy testing could successfully aid drug causality assessment and safe antimicrobial prescribing in subsequent anaesthesia.¹³² However, the impact of such a program on reducing restricted antibiotics in the operating theatre has yet to be explored. Inpatient penicillin skin testing has been used to improve appropriate antibiotic use.¹³³ A pilot prospective study and retrospective review of inpatient testing, predominately of patients with remote penicillin allergy, demonstrated cost savings and reduction in non-beta lactam use with the implementation of inpatient penicillin skin testing.^{134–136} In a small retrospective case series of infective endocarditis, inpatient skin testing allowed the implementation of the preferred beta-lactam therapy in 15 of 16 patients.¹³⁷ The use in acute care and intensive care settings, where the highest numbers of antibiotics are employed, has not been extensively studied. The potential for a false negative result in acutely unwell patients, has limited this application to date.^{138, 139} The safe use of penicillin skin testing in the ED setting was demonstrated by Raja *et al.*¹⁴⁰. Antibiotic allergy re-challenge protocols, examined in before/after studies, can increase simple beta-lactam uptake, reduce glycopeptide usage and improve patient outcomes.^{126, 141, 142}

Antibiotic allergy and Antimicrobial Stewardship (AMS)

The Infectious Diseases Society of America Antimicrobial Stewardship Guidelines raise awareness of the need for further study of antimicrobial allergy testing and its incorporation into stewardship programs.¹⁴³ Further reports have called for the incorporation of antibiotic allergy services into antibiotic stewardship programs.^{71, 144, 145} Small pilot studies have demonstrated pharmacy led referral systems, antibiotic allergy stewardship rounds, and

direct oral provocation programs can safely increase simple beta-lactam use and reduce restricted antibiotic usage and hospital costs.^{14, 63, 126, 135, 146–152} Recent published experiences with inpatient allergy testing, either pharmacist, allergist or infectious diseases led, have also demonstrated improved uptake of preferred beta-lactam therapies.^{134, 153–155} Targeted antimicrobial stewardship programs have demonstrated a reduction in restricted antibiotic usage, with such an intervention.^{152, 156, 157} A limitation of these studies has been a focus on aztreonam use, without an examination of other restricted antimicrobials, such as carbapenems and fluoroquinolones. Pharmacist engagement is potentially under utilized, as Wall *et al.* demonstrated that a pharmacist-led allergy testing service was well received by physicians and reduced unnecessary antibiotic usage.¹⁵⁸ Incorporation of decision support software into AMS regarding antibiotic choice in patients with beta-lactam allergy was shown to reduce unnecessary anti-pseudomonal penicillin and increased 3rd generation cephalosporin use.¹⁵⁹ Addressing the allocation of resources is an important step in the collaborative approach, determining who would most benefit from testing based upon antibiotic need(s), rather than simply allergy history (e.g. preference for an immunocompromised patient with multiple infective complications over an otherwise well patient with multiple drug hypersensitivities). Developing targeted testing via an integrated AMS model is likely to lead to improved patient outcomes (e.g. utilization of beta-lactam therapies in invasive staphylococcal infections) in addition to preventing *C. difficile* and antimicrobial resistance generation.⁴

Key points

- A. Antibiotic allergy testing, if made readily available to physicians, may aid ‘de-labelling’ initiatives and improve antibiotic usage. The impact of a multidisciplinary antibiotic allergy ‘de-labelling’ model, that engages the entire healthcare team and involves the expertise of allergists/immunologists, pharmacists, infectious diseases physicians and AMS teams on long-term antibiotic prescribing, antibiotic appropriateness and patient AALs is yet to be fully evaluated.
- B. The impact of EMR systems on antibiotic allergy labelling has currently been under investigated.

Conclusions

The high prevalence of antibiotic allergies coupled with the potential adverse downstream effects on antibiotic appropriateness, antibiotic resistance, heightened risk of *Clostridium difficile* infection and other adverse drug effects has brought the problem of antibiotic allergy over-labelling into the spotlight. Addressing key areas of accurate allergy labelling, diagnosis and novel management strategies remains key to reducing the burden. Correct labelling of an adverse drug reaction, as a manageable side effect due to a pharmacologically predictable effect of the drug versus a severe potentially life threatening immunological event is likely help allergy label phenotyping in terms of defining those who could be exposed to the drug in the future with a specific management versus those who should permanently avoid the drug. A greater understanding of side-chain cross reactivity is likely to lead to more appropriate antibiotic selection and aid medication safety. Broadening the

evidence base of antibiotic de-labelling strategies that include combinations of skin testing and/or ingestion challenge and incorporation into infectious diseases programs, such as antimicrobial stewardship, is also a potential avenue to reducing the impact of AALs on antibiotic prescribing.

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Figure 1. Re-classification of Adverse Drug Reactions
Adapted from Peter¹⁶⁴, White *et al.* 2015²⁴ and Phillips *et al.* 2015²³

Figure 2. Beta lactam structure and cross reactivity

A. Beta-lactams are classified as 'penicillin' if they have a beta-lactam ring fused to a thiazolidine ring. A dihydrothiazine ring in cephalosporins replaces this thiazolidine ring. Monobactams and carbapenems have an alternative adjacent ring structure, a monocyclic ring and five-membered ring respectively. In patients that have a penicillin allergy it is possible to remain sensitised to other 'penicillins', including aminopenicillins (amoxicillin, ampicillin) and anti-staphylococcal penicillins (flucloxacillin, oxacillin, dicloxacillin, methicillin, piperacillin-tazobactam, ticarcillin-clavulante), via the thiazolidine ring ('penicillin ring'), rather than beta-lactam ring.

B. Isolated allergy to single penicillin (e.g. amoxicillin) is also possible if a side chain is involved (e.g. "R" side chain). The true rates of overall penicillin-cephalosporin cross-reactivity are dependent on the generation of cephalosporin: <5% with 1st generation, 2–5% with 2nd generation and <1% with 3rd generation^{165, 166}. If cross-reactivity does persist it is most likely the result of shared "R" side chains (Figure 3)^{167, 168}. Cross-reactivity between penicillins and cephalosporins with the same R1 side chain such as aminopenicillins and aminocephalosporins is reported as 14–38%^{88, 165, 167}. Some cephalosporins such as cefazolin do not share R1 or R2 groups with any other beta-lactam. Cross-reactivity between cephalosporins is usually based on the shared side chain structures (typically the R1 group) and not the shared cephalosporin dihydrothiazine ring. (36–48%)^{90, 168}.

[illegible]

Figure 3. Common penicillins, aminopenicillins and cephalosporins that share an identical or similar R₁- and R₂-group side chains

Note: Aminopenicillin/aminocephalosporin cross-reactivity: cefaclor, cefadroxil and cephalexin share an identical R1 group with ampicillin; cefadroxil shares an identical R 1 group with amoxicillin.

Table 1

Classification of target antibiotic allergy and recommended testing

ADR Type ^a	Immunological mechanism	Timing	Clinical	Commonly involved Antibiotics	Testing ^b
<i>Gell/Coombs Class I</i> Type B ADR	IgE mediated	Immediate or accelerated (30m – 1 h and less commonly 6–48 hours)	Pruritis/urticaria Angioedema/Laryngeal edema Bronchospasm Anaphylaxis	Beta-lactams Sulfa antimicrobials Macrolides Fluoroquinolones	<i>RAST/ImmunoCAP IgE^c</i> SPT IDT Drug provocation ^d
<i>Gell/Coombs Class II</i> Type B ADR	Cytotoxic IgG mediated	Accelerated or non-immediate (5h – > 72 h)	Hemolytic anemia Thrombocytopenia	Sulfa antimicrobials Ritampin Dapsone Beta-lactams Vancomycin	G6PD (for deficiency) Drug-specific anti-platelet antibodies
<i>Gell/Coombs Class III</i> Type B ADR	Immune complex IgG mediated	Accelerated or non-immediate (3h – > 72h)	Serum sickness	Beta-lactams Sulfa antimicrobials Minocycline	None
<i>Gell/Coombs Class IV</i> Type B ADR	T cell mediated IVa: Macrophage IVb: Eosinophils IVc: T-cells IVd: Neutrophils	Non-immediate (24h – > 72h) ^d	Contact dermatitis, SCAR (DRESS/DIHS/HSS/SJS/TEN, AGEP) DILI, AIN, FDE Non-specific (maculopapular) exanthem	Beta-lactams Sulfa antimicrobials Fluoroquinolones Tetracyclines Macrolides Antiretrovirals (abacavir, nevirapine and other NNRTIs) Dapsone Vancomycin Anti-tuberculous drugs Telaprevir (hepatitis C)	LTT/ELISpot/ICS ^c Patch testing Delayed IDT Drug provocation Pre-prescription HLA screening ^e
Non-allergic drug hypersensitivity reactions					
G-protein coupled receptor-mediated mast cell activation	Mast cell degranulation via receptor <u>MRGPRX2</u>	Immediate or accelerated (30m – 1 h and less commonly 6–48 hours)	Pruritis/urticaria Angioedema/Laryngeal edema Bronchospasm Anaphylaxis (Dose Dependent)	Fluoroquinolones	No direct testing but patients may tolerate low-dose oral challenge (differentiates from IgE mediated). Also reactions are responsive to antihistamines or slower infusion.
Non-G-protein coupled receptor mast cell activation	Unknown receptor Non-IgE mediated mast cell degranulation	Immediate or accelerated (30m – 1 h and less commonly 6–48 hours)	Pruritis/urticaria Angioedema/Laryngeal edema Bronchospasm (Dose Dependent)	Vancomycin Polymyxin B Miconazole Minocycline	None

Adapted from^{35, 71, 160–163}

^aType B adverse drug reactions (ADR) – immunologically mediated allergies, further sub-classified into Classes I-IV based on updated Gell & Coombs classification^{160,161} and newer classification of G-protein coupled receptor-mediated mast cell activation³⁵. Type A adverse drug reactions (ADR) – common and predictable drug reactions that are dose dependent and based on pharmacological properties

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^g Combination *in vivo* testing recommended, SPT/IDT & oral provocation is considered gold standard.

^c RAST/ImmunoCAP IgE screening only (specific not sensitive) and not available in all countries. The negative predictive value of RAST/ImmunoCAP IgE is poor and it should not be used in isolation as the basis for re-challenge in patients with a history suggestive of an IgE mediated reaction. LTT and ELISpot not recommended for IgE mediated drug allergy testing but can be used for Type IV mediated reactions.

^d Can occur from 1–2 days [in the presence of previous exposure] to 8 weeks following drug. Otherwise, with first exposure, onset is usually from day 5–7. May be a more rapid/severe on 2nd exposure

^e HLA associations have been described for antimicrobials however currently screening is only routine for abacavir with HLA-B*57:01

Abbreviations: Ig, immunoglobulin; m, minutes; h, hours; DRESS, drug reaction with eosinophilia and systemic symptoms; DIHS, drug-induced hypersensitivity syndrome; HSS, hypersensitivity syndrome; AGEP, acute generalized exanthematous pustulosis; DILL, drug induced liver injury; SPT, skin prick testing; IDT, intra-dermal testing; BAT, Basophil Activation Testing; LTT, Lymphocyte transformation test; ELISpot, enzyme-linked immunospot.