

IMMUNE-MEDIATED ADVERSE DRUG REACTIONS IN SOUTH AFRICA

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ABSTRACT

In South Africa, adverse drug reactions have recently been implicated in 16% of deaths in medical wards. Immune-mediated hypersensitivity reactions (HSR) account for only a small fraction of this mortality. Immune-mediated reactions, however, are idiosyncratic, often with a rapid onset of life-threatening clinical features; this makes them feared by clinician and patient alike. The diverse clinical spectrum of HSR means that it presents across clinical disciplines, often with ultimate consultation to allergists, pharmacologists and dermatologists for a definitive diagnosis and plan for future management. The imperfect understanding of reactive drug immunogens and immunopathogenesis, together with the lack of robust *in vitro* and *in vivo* diagnostic tools, makes confident diagnosis and management challenging in many instances. This is especially true for uncommon Type 1 and the Type IV HSR occurring in the context of HIV-related immune dysregulation and polypharmacy (especially with TB co-infection). In this review we aim to contextualise immune-mediated drug hypersensitivity reactions within the epidemiology of ADRs in South Africa. Current conceptual models of immune activation by drugs, and the clinical spectrum of reactions are discussed. Finally, the diagnostic armamentarium and roles of allergist, pharmacologist and dermatologist in the management of these complex patients, stressing the need for multi-disciplinary clinics to provide optimum care and improve research in local priority areas, are highlighted.

EPIDEMIOLOGY, CLINICAL SPECTRUM AND CONCEPTUAL MODELS OF IMMUNE ACTIVATION IN DRUG-INDUCED HYPERSENSITIVITY REACTIONS

Worldwide, around 5% of adult medical admissions and about 3% of paediatric admissions are as a result of adverse drug reactions (ADRs).^{1,2} In a South African survey, ADRs were the cause of admission for 6.3% of adults admitted to medical wards, and an additional 6.3% of inpatients developed ADRs during their hospital stay.³ Recently, ADRs were implicated in 16% of deaths in the medical wards of four South African hospitals.⁴

ADRs are classified as Type A (the 'augmented' pharmacologic action of the drug such as insulin-related hypoglycaemia, which can affect anyone exposed to the drug), or Type B (an 'off-target' idiosyncratic reaction which only occurs in susceptible individuals). In hospital-based studies, Type B reactions constitute 15 to 20% of all ADRs. The true epidemiology of hypersensitivity reactions (HSRs) is unknown, with most studies either focused on a subset of HSRs (such as HSR to specific drugs, or specific

presentations such as anaphylaxis) or not distinguishing HSRs from other types of drug-related harms.⁵ An estimate of the frequency of drug HSRs outside of hospital wards came from the setting of a tertiary allergy and immunology outpatient clinic in the US, where 4.7% of consultations were due to suspected drug allergies.⁶ Also in the US, in a surveillance system for adverse drug events, ADRs caused 2.4 emergency room visits per 1 000 population per year (95% CI 1.7 to 3.0), of which drug allergies comprised one third.⁷ Local prevalence is likely to be significantly impacted on by prescribing habits, but overall SA data is sadly lacking.

Table I shows the spectrum of immune-mediated hypersensitivity reactions using an updated Gell & Coombs classification.⁸ The table illustrates the diverse effector immune mechanisms and consequent wide array of clinical manifestations. In clinical practice, Type II and III reactions are rare, e.g. 10/1 000 000 per year incidence of drug-induced thrombocytopenia⁹ and thus Type I and IV reactions constitute the majority of patients requiring assessment and management, usually presenting to the allergist and dermatologist, respectively.

TABLE I: CLASSIFICATION OF THE SPECTRUM OF IMMUNE-MEDIATED DRUG REACTIONS CATEGORISED BY MECHANISM AND CLINICAL FEATURES (ADAPTED FROM ⁹)

GELL & COOMBS CLASSIFICATION	IMMUNE MECHANISM	CLINICAL FEATURES	EXAMPLE DRUGS
TYPE I	IgE-mediated, immediate reaction	Urticaria*, angioedema*, anaphylaxis*, Bronchospasm*	Beta-Lactam antibiotics, neuromuscular blockers, e.g. rocuronium, latex, radio-contrast media (see Table II as commonly present to allergist)
TYPE II	IgG/M-mediated cytotoxic reaction	Anaemia, cytopenia, thrombocytopenia	Heparin, methyldopa
TYPE III	IgG/M-mediated immune complexes	Vasculitis, lymphadenopathy, fever, arthropathy, rashes, serum sickness	Procainamide, quinidine, minocycline, Beta-lactams
TYPE IVA	Th1 cells activate monocyte/macrophages via IFN-g and TNF-a	Contact dermatitis, bullous exanthema	Topical antibiotics and antihistamines, local anaesthetics
TYPE IVB	Th2 cells drive eosinophilic inflammation via IL-5, IL-4, IL13, eotaxin	Maculopapular and bullous rashes such as DRESS: Drug reaction (or rash) with eosinophilia and systemic symptoms	Rifampicin, pyrazinamide, isoniazid
TYPE IVC	CD41/CD81 cytotoxic T cells kill targets via perforin, granzyme B, FasL	Contact dermatitis, maculopapular, pustular and bullous exanthemata (Stevens Johnson Syndrome and Toxic Epidermal Necrolysis)	Thioacetazone, Nevirapine, abacavir, rifampicin, pyrazinamide, isoniazid, carbamazepine, sulfonamides
TYPE IVD	T cells recruit and activate neutrophils via CXCL-8, GM-CSF	Acute generalised exanthematous pustulosis (AGEP)	Sulfonamides, tetracyclines, cephalosporins, penicillins, hydroxychloroquine, NSAIDs, terbinafine, azoles

*These can also be non-immune mediated

Figure 1 shows the three current conceptual frameworks for understanding how drugs activate the immune system resulting in HSR. Traditionally drugs were considered too small (<1 000 daltons) to be able to activate the immune system alone, giving rise to the hapten/prohapten model, whereby a drug (in the form of a reactive intermediary) is required to bind irreversibly to a protein, and only this hapten-protein complex (e.g. Benzylpenicilloyl poly-L-lysine [PPL]) can result in immune activation following antigen-processing and presentation. Some drugs, however, do not form intermediaries, certain reactions occur more swiftly than the time required for antigen presentation and without prior sensitisation; consequently, the pharmacological interactions (p-i) concept was suggested.¹⁰ In this model, certain individuals have *de novo* reactive T-cell clones, possibly of a memory phenotype, that is stimulated by parent drug without the need for hapten-protein complex formation. This model also

fits with the observed higher incidence of drug HSR associated chronic infections which expand the T-cell compartment, e.g. herpes and HIV, because of the likely concomitant expansion of reactive T-cell clones.¹⁰ The last, most recent model, elucidated during research into the association of Abacavir hypersensitivity and HLA-B*57:01,¹¹ is known as the altered peptide repertoire model. Binding of drug in the groove of the MHC molecule leads to a conformational change in peptide binding, and consequently immune reactivity to previously tolerated self-peptides.¹¹ Given the diversity of drug HS, it is likely that all three models are accurate, featuring in different degrees depending on the specific drug and type of hypersensitivity reaction.

THE ALLERGIST IN DRUG-RELATED HYPERSENSITIVITY REACTIONS

Drug HSR manifesting with features typical of Type 1 hyper-

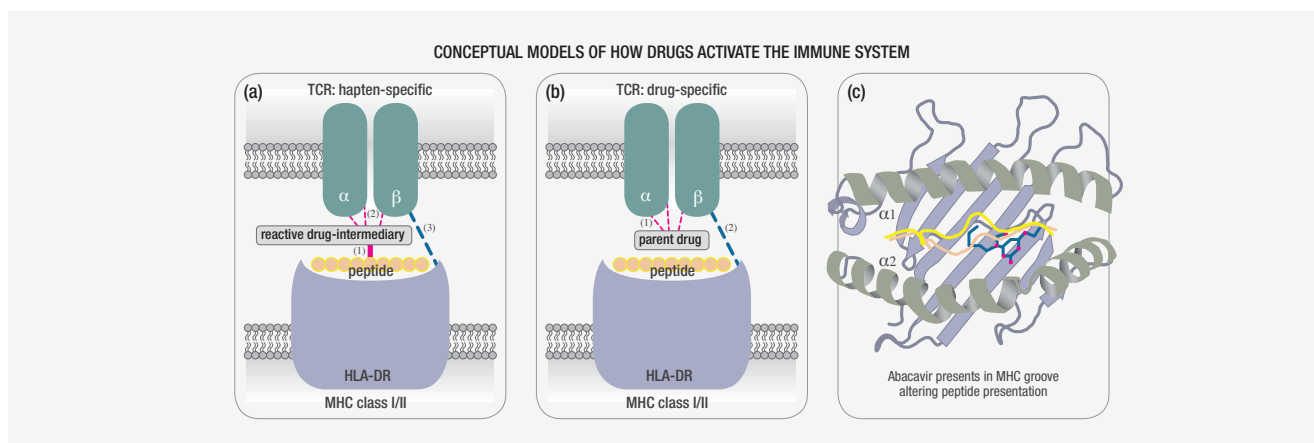


Figure 1: Conceptual models of how drugs activate the immune system, a) Hapten-protein complex, b) P-I concept, and c) Altered peptide repertoire

TABLE II: DRUGS CAUSING THE MAJORITY OF ADVERSE REACTIONS REFERRED TO ALLERGY CLINICS**ANTIBIOTICS**

- Penicillins and other Beta-Lactams
- Non-Beta Lactam antibiotics, e.g. tetracyclines, macrolides

REACTIONS DURING GENERAL ANAESTHESIA DUE TO*

- Neuromuscular blockers
- Anaesthetic agents, e.g. propofol
- Exposure to latex or cleaning solutions, e.g. chlorhexidine or iodine

ACE inhibitors

Aspirin and other NSAIDs

Local anaesthetics, e.g. lignocaine

Radio-contrast media

Others including: insulin, opiates, vaccines, heparin, plasma expanders

*Peri-operative antibiotics still a major cause of drug reactions during general anaesthesia

sensitivity reactions, such as urticaria, angioedema, bronchospasm and anaphylaxis, tend to be referred to allergy clinics, and the usual drugs implicated are highlighted in Table II, but the specific agents will vary depending on local prescribing practices, e.g. aminopenicillins versus penicillin V. It is important to note that these clinical signs may in fact result from non immune-mediated mechanisms. An example would be of angioedema presenting to emergency rooms, which is actually ACE-inhibitor associated angioedema, mediated through the vasodilator effects of bradykinin (most common cause (30%). Although not immune-mediated, due to the frequent referral to allergy clinics, its key features are outlined in Table III.

At the initial clinical encounter of a patient with suspected drug HSR, a detailed history is critical to both diagnosis and management. Key information necessary to formulate an assessment is provided in Table IV. It is also useful to be aware of drug and host risk factors that may increase the likelihood of a drug HSR. Important risk factors include: i) drug factors, such as prolonged or higher doses, parenteral therapy and specific drug chemistries, e.g. High Molecular Weight, and ii) host factors such as HIV co-infection, female gender and specific genetic polymorphisms e.g. HLA types.⁸ In cases where a drug of a similar class has been previously tolerated, actual medication package inserts should be reviewed and it should be remembered that reactions can occur to both the active pharmaceutical agent and excipients. Excipient-related adverse drug reactions were reviewed in the previous edition of this journal.¹² Similarly, in cases of anaphylaxis during general anaesthesia it is paramount to review in detail the anaesthetic records to consider all possible culprit drugs.

Diagnostic work-up should consider the likely culprit drug, and the best available *in vitro* or *in vivo* testing method to confirm such reaction where appropriate. Table V outlines the available diagnostic armamentarium indicating where tests are available in SA, their major utilities (IgE- and non IgE-mediated reactions) and a few important comments pertaining to use. *In vivo* testing should always be conducted in facilities where full resuscitation equipment is available, given the small risk of serious reactions with skin testing, and

TABLE III: ACE-INHIBITOR ASSOCIATED ANGIOEDEMA IN SA

1. ACE-inhibitor associated angioedema (ACEI-AE) is a vasodilatory effect to bradykinin and other molecules, not immune-mediated (in SA patients association found with bradykinin 2 receptor polymorphism²⁰).
2. Most common cause of drug-related angioedema in SA, occurring in 0.7-1% of treated patients (increased in African ethnicity).
3. No diagnostic test available in allergy clinics to prove/disprove ACEI-AE.
4. Management involves:
 - Airway management always the priority in emergency situation;
 - Immediate discontinuation of ACE-inhibitor if suspected;
 - In severe situations icatibant (bradykinin receptor antagonist) has shown to be beneficial but is expensive.
5. Prescription of alternative anti-hypertensives, including angiotensin-receptor blockers can be used with close monitoring for angioedema.

especially intra-dermal testing (SPT, IDT).⁸ Allergists conducting *in vivo* testing should use or determine non-irritant drug concentrations for testing, and where possible should have experience in the interpretation of a specific agents' reactivity. Details on specific testing for individual agents is beyond the scope of this manuscript, but readers are referred to current guidelines and other recent reviews which cover common culprit agents including:

- i. Beta-lactam antibiotics;¹³
- ii. Anaphylaxis during general anaesthesia;¹⁴
- iii. Contrast-related HSR;¹⁵ and
- iv. Excipient-related ADRs.¹²

It is also indicated to conduct diagnostic testing for alternative drug therapies to which cross-reactivity may be present and important. For instance, in a patient presenting with anaphylaxis to a 3rd generation cephalosporin, penicillin SPT would be indicated.¹³

The imperfect understanding of immunopathogenesis and/or pharmacology, together with the rarity of some reactions means that in a number of instances, diagnostic testing is either unavailable or provides false negative results. Allergists must then consider management carefully. Options include drug provocation (single or multiple dosing) in an appropriate clinic setting, which if performed in correctly selected patients, should produce a low positive rate.⁸ Alternatively, if clinical history is highly suggestive and reaction severe, the culprit agent should be avoided and an alternative therapy used. Where therapy is mandatory, e.g. penicillins for neurosyphilis or aspirin post myocardial infarction, desensitisation should be considered and protocols are widely available.

THE DERMATOLOGIST IN DRUG-RELATED HYPERSENSITIVITY REACTIONS

Type IV drug HSR have a myriad of clinical presentations but most involve the skin. Severe cutaneous adverse drug reactions (SCAR) can either be confined to only the skin or be part of a multisystem disorder. Morbiliform eruptions are usually mild, while the severe end of the spectrum includes Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (considered a spectrum of the same disease), drug rash with eosinophilia and systemic symptoms (DRESS), lichenoid drug eruptions, acute generalised exanthematous pustulosis (AGEP) and cutaneous vasculitis.¹⁶

TABLE IV: KEY INFORMATION REQUIRED TO COLLECT WHEN ASSESSING OR REFERRING A PATIENT WITH SUSPECTED DRUG ALLERGY

1. Detailed description of the reaction:
 - Clinical features, sequence, duration and severity;
 - Treatment required and outcome of therapy;
 - Witness description;
 - Photographs.
2. Timing of symptoms in relation to drug administration.
3. Has the patient had the suspected drug before this course of treatment?
 - a. How long had the drug(s) been taken before reaction?
 - b. When was/were the drug(s) stopped?
 - c. What was the impact of stopping?
 - d. Has the patient tolerated drugs of the same class or other preparations with the same parent drug, e.g. generics?
5. Illness for which the suspected drug was being taken, i.e. underlying disease which may have caused symptoms; alternative treatment options which may be able to be utilised.
6. List of all drugs taken at time of the reaction (including over-the-counter medicines) **NB!** In assessment of anaphylaxis during general anaesthesia the anaesthetic charts should be looked at for a detailed list of drugs given.
7. Previous history of other drug reaction, allergies and co-morbidities.

Management of Type IV drug HSR is most challenging in the setting of poly-pharmacy and a limited number of effective drugs typified by current HIV and tuberculosis pandemics in sub-Saharan Africa. In tuberculosis-associated SCAR an individual drug can cause multiple types of SCAR, and a specific type of SCAR can be due to any drug. In many patients, these are self-limiting with minor consequences, however, there may be considerable morbidity, mortality (up to 25%) and significant treatment interruption or a change in regimen. HIV-associated immunosuppression has both driven the high incidence of tuberculosis co-infection as well as increasing the frequency of drug HSR. Initiation of highly active antiretroviral therapy (HAART), *Pneumocystis jirovecii* pneumonia prophylaxis with

co-trimoxazole and anti-tuberculosis therapy all around the same time further complicates matters, as does the occurrence of the immune reconstitution inflammatory syndrome soon after HAART commencement.¹⁶

In this setting of limited alternatives, the ability to eliminate only the offending drug is important. This is usually based on a number of factors including:

1. the type of SCAR;
2. the temporal relationship to the initiation of the drug;
3. the response to drug withdrawal and rechallenge;
4. possible alternative causes for the reaction;
5. the placebo response;

TABLE V: IN VIVO AND IN VITRO DIAGNOSTIC TESTING AVAILABLE IN SA FOR THE ASSESSMENT OF DRUG HYPERSENSITIVITY REACTIONS

DIAGNOSTIC TEST	AVAILABILITY IN SA	MAJOR UTILITY	COMMENTS
Tryptase	Widespread	Confirmation of anaphylaxis (Cannot distinguish IgE- from Non IgE-mediated mast cell degranulation).	Requires sampling immediately after reaction, at 2 hours (up to 6 hours still useful) and then a baseline for comparison (> 24 hours after reaction or at follow-up).
Skin prick tests (SPTs)	Limited to clinics where resuscitation equipment and experienced staff are available.	Provides evidence of clinical sensitisation to drug. Useful for beta-lactams, and neuromuscular blockers.	Useful when parent drug or metabolite causing reaction is known and used in testing. Predictive value/utility undetermined with drugs where relevant immunogen is unknown, e.g. clindamycin. Parenteral or commercial preparations should be used skin prick testing.
Intradermal testing (IDT)	Limited to clinics where resuscitation equipment and experienced staff are available.	Improves the sensitivity of SPT for same agents where SPTs are reliable, e.g. beta-lactams.	Require extensive experience to perform and interpret. Non-irritant drug concentrations must be known and matching patient controls should be used to confirm non-irritating drug concentrations to reduce risk of false positives.
Serum specific IgE testing	Widespread although available drugs vary between major SA laboratories.	Useful to confirm sensitivity in severe reactions where SPT/IDT testing may be dangerous.	Not available for many drugs. Uncertain sensitivity and specificity; mainly useful if positive to confirm suspected culprit drug and prevent the need for further testing in severe anaphylactic reactions or to add further confidence when negative to progress to drug challenge test.
Cellular Antigen Stimulation Testing (CAST) ELISA	ADCRU (performs testing on samples referred to Pathcare and NHLS services)	Adjunctive <i>in vitro</i> testing in severe reactions encompassing IgE and non IgE mechanisms of reactions.	Measures leukotrienes after peripheral blood cell stimulation with drug. Not validated in large prospective studies with many drugs despite commercial availability. Useful for testing of drug excipients and specific drug formulation. Expert knowledge of local laboratory experience required for appropriate test interpretation.
FlowCAST	Ampath	Adjunctive <i>in vitro</i> testing in severe reactions encompassing IgE and non IgE mechanisms of reactions.	Measures basophil activation (CD63) markers after peripheral blood cell stimulation with drug. Useful for testing of drug excipients and specific drug formulation.
Patch testing	A number of dermatologists and dermatology clinics offer testing.	Useful for investigating Type IV, usually cutaneous drug reactions, e.g. rifampicin.	Experience required to prepare patches with appropriate drug concentrations and interpret the results at 24, 48 and 96 hours.

6. drug levels in body fluids or tissues;
7. the dose response relationship;
8. drug notoriety; and
9. confirmation by *in vitro* or *in vivo* testing.¹⁷

For instance, there are some drugs that are known to cause SCAR and are of such significant notoriety that they can safely be eliminated, based solely on clinical features and a temporal relationship. A good example is thioacetazone, which was identified early on as a common cause of SJS/TEN in tuberculosis and HIV co-infected patients leading to a decline in its use. Nevirapine, an antiretroviral that was used extensively for the management of HIV infection, is following a similar path. Many clinicians are comfortably replacing nevirapine, used as part of triple therapy, with another drug while continuing the other two in cases as severe as TEN. However, in many cases of SCAR, matters are not as simple and there is a need for more objective evidence to identify the offending drug. *In vitro* methods are preferable in severe SCAR, as *in vivo* methods, mainly a rechallenge with the offending drug, carry a risk of recurrence, possibly even more severe. Unfortunately though, *in vitro* assays are not widely available and are still considered experimental. There is an acute need to develop rapid, affordable, drug specific and sensitive laboratory tests to identify culprit drugs in drug HSR. These tests should, ideally be applicable to all ethnic populations as many SCAR and underlying pathogenesis are increasingly being shown to be population-specific.

In the absence of reliable *in vitro* tests a lot of parallel work is being done to determine utility of patch tests, skin prick tests

and oral rechallenge for various drugs. In HIV-tuberculosis co-infection this has been fraught with unexpected twists. It is emerging from our current work that roughly a third of HIV-infected patients who are rechallenged with first-line anti-tuberculosis drugs soon after a SCAR develop multiple drug hypersensitivity syndrome, to both first and second-line drugs, although not previously exposed to the latter.¹⁸ It is also emerging that patch tests to first-line anti-tuberculosis drugs can induce systemic rather than only localised reactions to the patch test area in HIV-infected persons, in contrast to those who are HIV-uninfected.¹⁹ This is another unexpected finding requiring further investigation.

CONCLUSION

Administering drugs as therapies is the mainstay of clinical medicine, and clinicians must constantly evaluate the risk-benefits of each medication in an individual patients. The unpredictable, often severe nature of immune-mediated drug HSR unsettles this decision-making and is thus appropriately feared. In South Africa, Type IV HSR related to the syndemics of HIV and TB are predominant over the better characterised Type I drug HSR. Furthermore, very little fundamental work has been done in uncovering the mechanisms of drug HSRs in local populations. To this end, we are in the process of establishing a multidisciplinary immune-mediated adverse drug reaction clinic involving pharmacologists, dermatologists, allergists and basic immunologists. We hope that this will provide a platform for us to identify important causative drugs, mechanisms and clinical manifestations of local drug HSR, and in so doing optimise patient care.

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