

MULTIPLE-DRUG INTOLERANCE SYNDROME

Case records from the multi-disciplinary drug hypersensitivity clinic

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ABSTRACT

Multiple-drug intolerance syndrome (MDIS) is a condition where patients experience adverse drug reactions to three or more unrelated drugs. The immunological mechanism is unknown, hence the preferred labelling as 'intolerance' as opposed to 'allergy'. MDIS prevalence in South Africa is unknown, but may be as high as 2.1% according to international electronic medical record data. The majority of specialist physicians have encountered these complicated, sometimes frustrating, but always challenging patients.

MDIS patients have high rates of healthcare and medication use, and are highly prone to developing new adverse drug reactions. Risk factors include female gender and multiple non-life-threatening co-morbidities, but not atopy. Antibiotics, particularly cephalosporins and quinolones, together with NSAIDs are the common offending drug classes. The severity of reactions is often overestimated, but life-threatening anaphylaxis or severe cutaneous drug reactions are reported. Optimal management involves the judicious use of drug provocation testing in a safe environment to provide patients and treating physicians with safe drugs as and when medically indicated. Multiple costly *in vitro* and *in vivo* drug allergy testing should be limited.

This brief review first presents an illustrative case from our newly established multi-disciplinary drug hypersensitivity clinic and then provides a literature review on the risk factors, proposed mechanisms and optimal management of MDIS.

This article has been peer reviewed.

ILLUSTRATIVE CASE

A 38-year-old architect from a coastal town in South Africa was referred to our multi-disciplinary drug hypersensitivity clinic with the problem of multiple allergy reactions to different antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). The severity and diversity of adverse drug reactions (ADRs) had made her, her husband and her treating doctors very anxious: she felt that she no longer had any safe drug options to deal with her intermittent back pain or occasional antibiotic-requiring infection.

She has no chronic medical co-morbidities or history of atopy. She had a history of large local reactions to bee venom, and a delayed hypersensitivity reaction to Elastoplast®. She does not use chronic medication and last required analgesia (Adcadol® – paracetamol, codeine, caffeine and doxylamine; and Cataflam® – diclofenac) after a ligamentous injury to her right foot in 2015. Interestingly, both her mother and her maternal grandmother were intolerant to a number of drugs. During early childhood she tolerated intermittent antibiotic therapy for the occasional upper respiratory tract infection without problems, although she could not recall the specific drugs prescribed. She had her first ADR at age 15; she was given an antibiotic and

seconds later began to experience swelling of her feet and hands, with associated chest tightness. She was rushed to the general practitioner (GP) and treated successfully. She had a similar reaction at age 18 years, also requiring hospital treatment. She was uncertain of the precipitating drugs, but from that point on avoided antibiotics if at all possible. In 1998 she had her worst episode, after the family dog was prescribed an unknown antibiotic; very soon after handling it to give it to the dog, she started with tongue, hand and face swelling. She required emergency room admission and treatment. The most recent and severe reaction occurred during a general anaesthetic for maxillofacial surgery for a mandibular cyst last year. She was given an antibiotic and Cataflam® (diclofenac), together with the general anaesthetic, and developed a reaction 30 minutes into the procedure. She required treatment with adrenaline and antihistamines, and recovered quickly. On systematic enquiry, she described episodes of spontaneous urticarial-like 'heat rash', which would last about 15 minutes and respond to antihistamine cream; she has never had spontaneous angioedema. There were no dietary triggers of reactions. The only relevant finding on physical examination was dermatographism. A great deal of *in vitro* drug-allergy testing had been done prior to her being

TABLE I: ILLUSTRATIVE CASE ALLERGY DIAGNOSTIC TESTING

FLOW CAST TEST POSITIVE	FLOW CAST TEST NEGATIVE
Penicillin MDM 37.9%	PPL
Amoxicillin 42.9%	Clindamycin
Cefuroxime 48.8%	Diclofenac
Clarithromycin 57.1%	Indomethacin
Co-amoxiclav 17.7%	Aspirin
Moxifloxacin 47.4%	Naproxen
Doxycycline 41.0%	
Ibuprofen 47.9%	
DIVERSE FLOW CAST	DIVERSE FLOW CAST
Telithromycin 80.0%	Tigecycline 2.19%
	Meropenem 1.4%
	Amikacin 1.12%
	Metronidazole 0.43%
SKIN/INTRADERMAL TEST POSITIVE	SKIN/INTRADERMAL TEST NEGATIVE
Metronidazole SPT 1:10 – 3/6 mm wheal/flare; IDT 1:100 no reaction, IDT 1:10 not done	Meropenem
Linezolid dilutions 1:100 – 2/4 mm wheal/flare	Ceftriaxone IDT 1:100

Abbreviations: CAST: Cellular antigen stimulation test; MDM: Minor determinant mix; PPL: Major determinant benzylpenicilloyl poly-L-lysine; SPT: skin-prick test; IDT: Intradermal test.

reviewed in our clinic, including multiple cellular antigen stimulation tests (CAST) and skin-prick and intradermal testing (see Table I). In addition, she had two normal baseline tryptase measurements, a normal full blood count and thyroid function, negative thyroid autoantibodies, and a negative stool antigen for *Helicobacter pylori*.

The history and test results were consistent with a diagnosis of multiple-drug intolerance syndrome. CAST testing suggested she was not sensitised to the beta-lactam ring, but rather to specific side-chains, although reactivity to many chemically distinct agents is hard to explain. CAST can be performed using the flow cytometry (see Table I) or ELISA methods; flow CAST measures that upregulation of basophil activation markers on patients' cells, whereas ELISA CAST measures leukotriene levels in cell supernatants, both following stimulation with a drug. Our management plan involved hospital admission for drug provocation testing with a focus on ensuring that she has safe oral and intravenous antibiotics that cover a wide microbiological spectrum, as well as a safe NSAID. During her four-day hospital admission she was successfully challenged to Cefexime (oral second-generation cephalosporin), Ceftriaxone (intravenous third-generation cephalosporin), metronidazole and aspirin. I stressed to her the limitations of *in vitro* drug-allergy testing, noting that, in the future, should she require a specific antibiotic for a resistant organism – for example, linezolid – graded drug challenge is highly recommended irrespective of her CAST results.

INTRODUCTION AND NOMENCLATURE

Drug-hypersensitivity reactions (DHR) affect approximately 7% of some populations, and therefore represent an important public health problem.¹ Up to one-third of patients presenting to drug allergy units report 'multiple-drug allergies', most of which are not validated.² The majority involve overuse of the term 'allergy'. Over-diagnosis of drug allergies can have a negative impact on the quality of medical care – for example, due to the use of non-preferred antibiotic therapy and resulting prolonged hospital stay.³ However, there are patients who react to multiple different drugs and these patients need to be identified, appropriately worked up and an optimal management plan developed for them.

In 1989, Sullivan et al⁴ first described the 'multiple-drug allergy syndrome' as drug allergies to two or more chemically different drugs (mainly antibiotics). The reactions were distinct from (i) cross-reactivity – due to structural similarities, common metabolic pathways or pharmacologic mechanisms; and (ii) flare-up reactions – exacerbations of existing drug-hypersensitivity reaction by the early switch of therapy to another drug.⁵

The name was revised to 'multiple-drug hypersensitivity syndrome' (MDH), but because the pathophysiological mechanisms remain poorly understood, the term has been used to describe a heterogeneous group of patients in the literature. Consequently, the term 'multiple-drug intolerance syndrome' was introduced to indicate that in many instances drug reactions might not be allergic.⁶ Undoubtedly, there is a group of patients that have multiple immunological reactions to chemically distinct drugs, confirmed with *in vivo* testing. Sullivan et al estimated that 1% of 437 penicillin-allergic patients reacted to non-beta-lactam antibiotics⁴ and Barbaud et al, in a large prospective study of severe cutaneous adverse reactions (SCAR), found that 18% of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) cases reacted to multiple drugs;⁷ these patients may be best labelled as experiencing MDH. In contrast, there is also a group of patients who report adverse drug reactions to three or more chemically, pharmacologically and immunogenically unrelated drugs, but who have negative skin (specifically IgE) testing and, in most instances, challenge testing. This patient group has labelled as experiencing 'multiple drug intolerance syndrome' (MDIS) and is the largest group of patients with multiple-drug reactions presenting to allergists, with an *estimated prevalence of 2.1%* in a large electronic health record study in the United States.⁸

RISK FACTORS AND USUAL OFFENDING DRUG CLASSES

History-taking is the cornerstone of diagnosis in MDIS because there is neither a biomarker nor a straightforward *in vitro* allergy test for confirmation. History-taking should

focus on identifying risk factors and ascertaining as detailed a description of each adverse drug reaction as possible in order to identify the list of possible offending drugs. Figure 1 provides a list of risk factors and the relevant frequencies of offending drugs as defined by the two largest studies of MDIS.^{6,8} The diagnosis is one of exclusion, where better-known conditions such as cross-intolerance to NSAIDs in patients with underlying spontaneous urticaria or cross-reactivity to structurally similar drugs – for example, beta-lactams – need to be excluded. Across the available literature, female gender is the most consistent risk factor.^{2,6,8} MDIS patients also tend to have multiple co-morbidities and use more medications and healthcare services; however, the prevalent diagnoses are frequently non-morbid conditions such as gastro-oesophageal reflux, dermatitis, hypertension and various forms of pain.⁶ An association with psychiatric disease, including depression and anxiety, has been suggested and should be enquired after, but is not consistent across studies.^{6,8,9} Proven anaphylaxis or a severe cutaneous drug reaction will increase the likelihood of positive allergy testing and the reproducibility of challenge (if indicated).

Omer et al examined the odds ratios (OR) for particular drugs being implicated in a large UK cohort of MDIS. Cephalosporin and quinolone ADRs were the most significant predictors of MDIS (OR of 11.3 and 11.1, respectively). In contrast, penicillin allergy was not associated with MDIS, while the likelihood of MDIS was lowest in those allergic to peanuts (OR 2.3), shellfish (OR 2.3), and aspirin (OR 2.6) compared to other NSAIDs (OR 5.4) and other non-beta-lactam antibiotics (OR >5).⁸

POSSIBLE MECHANISMS

The pathogenesis of neither MDIS nor MDH is clear, and it is likely that different mechanisms are involved across the heterogeneous patient group. First, in a number of instances the ADRs in MDIS may be non-allergic, possibly even known off-target actions of the drug (side-effects). Secondly, the reactions may be pseudoallergic – reactions with clinical features suggestive of mast-cell mediator release – for example, urticaria – but not antibody- (IgE) or T-cell-mediated. Recently, a novel mast-cell G-protein coupled receptor, Mrgprx, has been characterised and demonstrated to cause mast-cell degranulation in response to chemically distinct cationic drugs containing a common structural motif.¹⁰ Unpublished data suggest that this receptor is highly polymorphic with impacts on thresholds of activation; therefore it is reasonable to hypothesise that different individuals may have lower thresholds for activation. Further research into the reactions is required. Thirdly, other unidentified receptors or alternative non-IgE mechanisms may be associated with these ADRs. Lastly, there are patients with proven IgE-mediated or T-cell-mediated reactivity to multiple different drugs. Abnormalities of T-regulatory functions or increased frequency of certain effector T-cell populations has been implicated.²

MANAGEMENT

MDIS patients are a particularly challenging and often frustrating group of patients. They have frequently seen many doctors and have long lists of co-morbid conditions and ADRs. They consume disproportionate healthcare resources and present with complications arising from the inability of treating doctors to use preferred first-line medications. A clear step-wise strategy to allergy assessment and management is therefore advised and outlined in Box 1 below. Allergy management can be performed by all doctors trained to perform drug-provocation testing and in a hospital environment in which testing can be performed safely.

Box 1: Step-wise management approach for MDIS patients

1. History and examination.
2. Detailed documentation of each ADR with list of possible offending agents.
3. Specific enquiry about risk factors, tolerance to NSAIDs, and atopic disease.
4. Examination for dermatographism.
5. Identification of main healthcare providers and a decision, together with the patient, on priority drug requirements – this should dictate plans for testing and drug provocation.
6. Limited *in vivo* and *in vitro* diagnostic testing guided by severity of reaction and known diagnostic accuracy of testing to the particular offending agent.
7. Arrange for oral-provocation challenge in safe environment.
8. Detailed letter for patient (and to future doctors) to summarise allergy findings and encourage graded challenge or even desensitisation rather than exclusion of preferred medications where clinically indicated.

Abbreviations: MDIS: multiple-drug intolerance syndrome; ADR: adverse drug reaction; NSAIDs: non-steroidal anti-inflammatory drugs

A detailed history of ADRs, potential offending drugs and risk factors is the starting point, as highlighted above. Where possible, hospital records of previous ADRs, prescriptions from the pharmacies to identify exact drug preparation used and direct discussions with the treating clinician are optimal. The aim is to clarify the clinical symptoms and severity, the timing of onset and whether any confirmatory testing – for example, serial tryptase measurements – was performed. Once the list of offending drugs is available, possible unifying explanatory models/diagnosis should be considered – for example, NSAID cross-intolerance with underlying spontaneous urticaria – or cross-reactivity – for example, beta-lactam hypersensitivity. In addition, it is important to consider any hypersensitivity reactions to a common drug excipient; this may necessitate contacting the medicines information centre to make direct enquiries with pharmaceutical companies for a detailed list of ingredients, which is often not found in the package insert.

The most important question to ask in the work-up and management of MDIS patients is which drug therapy they require to optimally manage their co-morbidities, and what the impact is likely to be of

- avoidance of the possible offending drug class, and
- using an alternative agent.

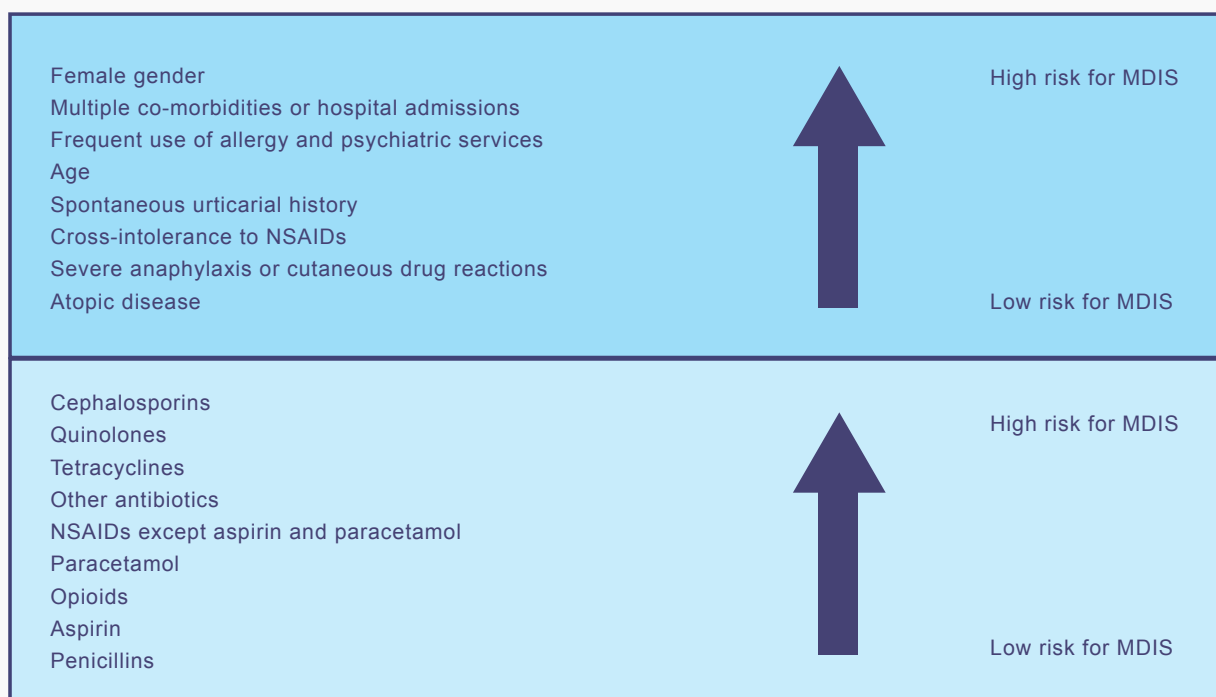


Figure 1: Factors and offending drugs to identify the MDIS patient

Abbreviations: MDIS: Multiple-drug intolerance syndrome; NSAIDs: non-steroidal anti-inflammatory drugs

The challenge in many instances, such as the illustrative case, is that patients appear allergic to 'all antibiotics'. In these situations, it is important to decide on a few essential medications that the patient/doctors wish to use in the near to medium future – for instance, an oral antibiotic for uncomplicated upper respiratory tract infection. *In vitro* testing should be tailored to the list of offending drugs and alternatives to be used as part of drug challenge. It is inappropriate and costly to perform *in vitro* testing on multiple drugs that the patient may or may not require in the future. The reason for this is that the diagnostic accuracy and predictive value of *in vitro* drug allergy testing when compared to gold standard drug provocation testing is highly variable, and in many instances unknown, for individual drugs. Where necessary, the clinician should discuss testing with a drug-allergy specialist or laboratory.

Judicious use of drug-provocation testing is the optimal management strategy for patients with MDIS if avoidance is neither safe nor convenient. The reasons for this approach include:

- the unknown aetiology of ADRs in MDIS;
- the limited utility of *in vitro* and *in vivo* drug-allergy testing for many offending drugs;
- the context-specific factors associated with a particular ADR that led to allergy labelling.

Schiavino et al performed 1 808 challenges in 480 patients – 84.4% female, mostly ages 40–60, with histories of ADRs to at least three unrelated medications. Only 224 (12.4%)

challenges were positive, and in almost all those patients either the offending medication or an alternative was safely tolerated.¹¹ Raman et al performed 350 challenges in 23 MDIS patients, with only three positive challenges, all to NSAIDs.¹² Despite the infrequency of reactions, drug challenges should always be performed in settings where full resuscitation equipment is available and staff are trained in anaphylaxis management.

In all instances, following allergy work-up and testing, a detailed letter and tailored bracelet should be organised for the patient. Importantly, allergy labelling should be as focused as possible so as not to unnecessarily exclude the future use of potentially life-saving medications. Patients should be told, and letters should detail, that in hospital a challenge or desensitisation may be possible should the patient require life-saving medications, especially certain antibiotics, in the future.

CONCLUSION

Patients with intolerance to multiple drugs are a challenge to both the attending physician and the allergist. They are a heterogeneous patient group, and undoubtedly certain patients do have proven immune-mediated hypersensitivity to multiple structurally unrelated drugs. However, in many instances allergic reactions are not validated, yet cause considerable distress to both patient and provider, increase healthcare use and jeopardise their optimal medical care. In these patients with MDIS, detailed and step-wise allergy work-up and, where appropriate, drug-provocation testing,

are invaluable in ensuring that patients safely access the therapies they need.

DECLARATION OF CONFLICT OF INTEREST
The author declares no conflict of interest.

REFERENCES

- Gomes E, Cardoso MF, Praca F, Gomes L, et al. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004;34(10):1597–1601.
- Chiriac AM, Demoly P. Multiple drug hypersensitivity syndrome. *Curr Opin Allergy Clin Immunol* 2013;13(4):323–329.
- Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin 'allergy' in hospitalized patients: A cohort study. *J Allergy Clin Immunol* 2014;133(3):790–796.
- Sullivan T, Remedios C. Studies of the multiple drug allergy syndrome. *J Allergy Clin Immunol* 1989;83.
- Pichler WJ, Daubner B, Kawabata T. Drug hypersensitivity: flare-up reactions, cross-reactivity and multiple drug hypersensitivity. *J Dermatol* 2011;38(3):216–221.
- Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol* 2012;108(2):88–93.
- Barbaud A, Collet E, Milpied B, Assier H, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. *Br J Dermatol* 2013;168(3):555–562.
- Omer HM, Hodson J, Thomas SK, Coleman JJ. Multiple drug intolerance syndrome: a large-scale retrospective study. *Drug Saf* 2014;37(12):1037–1045.
- De Pasquale T, Nucera E, Boccascino R, Romeo P, et al. Allergy and psychologic evaluations of patients with multiple drug intolerance syndrome. *Intern Emerg Med*. 2012;7(1):41–47.
- McNeil BD, Pundir P, Meeker S, Han L, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* 2015;519(7542):237–241.
- Schiavino D, Nucera E, Roncallo C, Pollastrini E, et al. Multiple-drug intolerance syndrome: clinical findings and usefulness of challenge tests. *Ann Allergy Asthma Immunol* 2007;99(2):136–142.
- Ramam M, Bhat R, Jindal S, Kumar U, et al. Patient-reported multiple drug reactions: clinical profile and results of challenge testing. *Indian J Dermatol Venereol Leprol* 2010;76(4):382–386.

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References continued from page 144.

- with mild persistent asthma. *J Allergy Clin Immunol* 2007;120:1043–1050.
- Kaiser SV, Huynh T, Bacharier LB, Rosenthal JL, et al. Preventing exacerbations in preschoolers with recurrent wheeze: A meta-analysis. *Pediatrics* 2016;137(6):e20154496.
- Brand PLP, Caudri D, Eber E, Gaillard EA, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J* 2014;43:1172–1177.
- Sekhsaria S, Alam MA, Sait T, Starr B, et al. Efficacy and safety of inhaled corticosteroids in combination with a long-acting beta2-agonist in asthmatic children under age 5. *J Asthma* 2004;41:575–582.
- Kocevar VS, Bisgaard H, Jönsson L, Valovirta E, et al. Inpatient cost among pediatric patients with asthma in four Nordic Countries. *ECACI* 2001 (abstract)
- Gerritsen J, Koeter GH, Postma DS, Schouten JP, et al. Prognosis of asthma from childhood to adulthood. *Am Rev Respir Dis* 1989;140:1325–1330.
- Kelly WJ, Hudson I, Raven J, Phelan PD, et al. Childhood asthma and adult lung function. *Am Rev Respir Dis* 1988;138:26–30.
- Martin AJ, Landau LI, Phelan PD. Asthma from childhood at age 21: the patient and his disease. *Br Med J (Clin Res Ed)* 1982;284:380–382.

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References continued from page 150.

- follow up. *Thorax* 2003;58:322–327.
- Bara I, Ozier A, Tunon de Lara J-M, Marthan R, et al. Pathophysiology of bronchial smooth muscle remodelling in asthma. *Eur Respir J* 2010;36:1174–1184.
- Bumbacea D, Campbell D, Nguyen L, Carr D, et al. Parameters associated with persistent airflow obstruction in chronic severe asthma. *Eur Resp J* 2004;24:122–128.
- Brutsche MH, Downs SH, Schindler C, Gerbase MW, et al. Bronchial hyperresponsiveness and the development of asthma and COPD in asymptomatic individuals: SAPALDIA Cohort Study. *Thorax* 2006;61:671–677.
- Hardin M, Silverman EK, Barr RG, Hansel NN, et al. The clinical features of the overlap between COPD and asthma. *Respir Res* 2011;12:121–127.
- Andersén H, Lampela P, Nevanlinna A, Säynäjäkangas O, et al. High hospital burden in overlap syndrome of asthma and COPD. *Clin Respir J* 2013;7:342–346.
- Menezes AM, Montes de Oca M, Pérez-Padilla R, Nadeau G, et al. Increased risk of exacerbation and hospitalisation in subjects with an overlap phenotype: COPD-asthma. *Chest* 2014;145:297–304.
- Miravittles M, Soriano JB, Ancochea J, Muñoz L, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir Med* 2013;107:1053–1060.
- Global Strategy for Diagnosis, Management and Prevention of COPD. Updated 2016. www.goldcopd.org (accessed 10 May 2016).