CURRENT ALLERGY & CLINICAL IMMUNOLOGY

JOURNAL OF THE ALLERGY SOCIETY OF SOUTH AFRICA

VOL 28, No 4, December 2015

Adverse and allergic reactions to medicines

Adverse drug events – why we care

A clinical approach to drug-induced liver injury

Penicillin allergy – when is it ok to use a Cephalosporin?

Drug reactions associated with antituberculosis drugs

A South African multidisciplinary drug hypersensitivity clinic

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VOL 28, No 4, December 2015

CONTRIBUTION
The editors encourage articles, letters, news and photographs relating to the field of allergy and clinical immunology. Enquiries should be addressed to: The Editors, Current Allergy & Clinical Immunology, Allergy Society of South Africa, PO Box 88, Observatory 7935 South Africa.

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Accredited by the Department of Education
Indexed on SCOPUS and EMBASE

Cover: Photograph by Dr Harris Steinman
Printed by Tandym | ISSN 1609-3607

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SPONSORSHIP & SUPPORT
Current Allergy & Clinical Immunology is the official journal of the Allergy Society of South Africa and is produced as a service for the health care workers to improve understanding and communication in the field of allergy. Publication of the journal is made possible by the generous financial and other support offered by the following pharmaceutical and diagnostic companies.
The Allergy Society of South Africa gratefully acknowledges support from these companies:

Aspen Pharmacare | Astra Zeneca | Cipla Medpro | iNova Pharmaceutical | MSD Mylan | Pharma Dynamics | Takeda Thermo Fisher Scientific

Guest Editorial

ADVERSE DRUG REACTIONS: ALL OUR RESPONSIBILITY

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The WHO defines an adverse drug reaction (ADR) as any noxious, unintended, and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy.[1]

Phase 3 controlled clinical trials, required by the regulatory bodies, establish efficacy as well as ensuring that a drug does not cause unacceptable harm. Unfortunately, premarketing studies do not fully elucidate the harms that a drug can cause and have major limitations. They are often of short duration, small sample size, narrowly defined populations, narrow indications and limited comparison groups. Hence, the requirements for rigorous attention to the post marketing ADRs that may occur in order to fully describe the risk and benefits of a drug.

Six systematic reviews have estimated the proportion of adult medical admissions attributable to ADRs. The proportion ranges between 3.1% and 6.3%.[1-5]

A population-based study in three Swedish counties found that 3% of all deaths were suspected to be due to ADRs, making ADRs the seventh most common cause of death. This figure compares favourably with a systematic review which ranked ADRs among the top six causes of death in the USA.[2]

A recent publication from my research group revealed that 45% of ADRs resulting in admission were preventable and is in keeping with a 2012 meta-analysis which estimated that 52% of ADR-related admissions are due to preventable ADRs.[6] A study in three Swiss teaching hospitals reported an ADR-related mortality rate of 0.05% of admissions.[7] In another UK study, an ADR that developed in hospital was considered to have contributed to the deaths of 0.4% of the patients admitted (8.2% of in-hospital deaths).[8,9]

The economic impact of ADRs is substantial and potentially avoidable.

It is because ADRs represent an important public health concern and are often difficult to diagnose and manage, that my colleagues and I have written these various articles. We hope to share some of the important principles that will help readers navigate these drug related undesirable episodes and prevent future patient harm.

Dr Sarah Karabus has tackled the controversial topic, *Penicillin allergy: When is it ok to use a cephalosporin*. The article gives the reader a comprehensive understanding of the risk, the potential mechanisms of cross reactivity and then the important clinical advice of how one should proceed when faced with this patient scenario.

Drs Kakande and Lehloenya have collaborated on an article addressing the diagnostic dilemmas associated with anti-tuberculosis therapy, i.e. the clinical spectrum of cutaneous adverse drug reactions. They provide an in-depth analysis of the many clinical presentations, including photographs. This allows the reader to have an aide memoir to the various presentations. Drs Kakande and Lehloenya end the article with the vexed topic surrounding the challenges of drug rechallenge - an important read.

Dr Chughlay and his colleagues discuss a *clinical approach to drug-induced liver injury (DILI)*. The article highlights an overview of the current knowledge, risks factors, classification and clinical presentation of DILI. The authors use the common anti-tuberculosis treatment induced DILI in order to provide this approach. They also provide insights into when it would be appropriate to rechallenge a patient when they have suffered DILI, especially where there are limited treatment options.

Prof Blockman provides an overview of ADRs. His article discusses the epidemiology, classification and why they are a major burden to the healthcare system. He introduces the concept of pharmacovigilance, causality assessment and why ADR reporting is critical to the ongoing risk-benefit of medicine use.

Finally, Dr Peter and colleagues introduce the South African multidisciplinary drug hypersensitivity clinic. Their thesis is that many specialists often look after the same patient, as drugs cause varied immune-based pathology in patients with varying co-morbid disease. This may limit the ability to detect common clinical features and identify underlying immunopathogenesis linked to the pharmacological properties of the drug. To address this problem, they propose the multidisciplinary clinic model, including its pros and cons.

As healthcare workers, we have a duty to protect our vulnerable patients. Rational medicine use must underpin our therapeutic choices, with a major emphasis on adverse event recognition and prevention. We must remember that not only do drugs have benefits, they also have harms. Recognising these risks will inevitably lead to a reduction in patient harm.

Continued on page 256.

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CHAIRMAN'S REPORT: 2015 AGM

Di Hawarden

It is a great privilege and honour to stand before you all today as Chairman of our Society. I would like to thank everybody that has helped me to get this far, particularly my mentor, the late Cas Motala. Thank you to Paul Potter for guidance over the years, as well as to Eugene Weinberg, for those amazing pearls of wisdom he casually drops. Thank you to Ahmed and André for their wisdom and a special thank you to Sharon for all the time you have given me. Sorry Sharon, it is never just a quick phone call.

So here I am and what can I do that is perhaps different. I am not an Allergologist, I am not even a Specialist, but I am passionate about the society, particularly the members. I believe that as an Excom, we exist for our members, not for ourselves, or to further our own careers. As Chairman of this Excom, I will work to ensure that the best interests of our members are served. As our membership base also includes our sponsors, we will hear you too.

As you all know, Professor Robin Green resigned last year in December, as Chairman of the Society. I would like to thank him for his service to the society. Since then, we have re-designed our identity/logo and hope you like the new look. This logo works across many platforms, including print and digital.

EDUCATION AND TRAINING PORTFOLIO

DIPLOMA ALLERGOLOGY

In March 2015, two successful candidates passed the diploma, namely Dr Nonhlanhla Lunjani and Dr Makoma Moremi. The next exam will be in September 2015 in Durban and six candidates will be writing.

CERTIFICATE IN ALLERGOLOGY

University of Cape Town

Subspeciality – 4 posts available. Dr Talita van der Watt and Dr Jonny Peter will be filling two posts. Dr Van Der Watt is writing the certificate examination in September 2015 and Dr Peter in March 2016. Dr Thulja Trikamjee (Discovery Fellow from Durban) and Dr Elizabeth Kiragu (African Paediatric Fellowship programme from Kenya) started training at Red Cross Hospital in 2015.

DISTANCE LEARNING OPPORTUNITIES

Allergy in Africa webinars are available via UCTs website. Thirty three podcasts are currently available online.

JOURNAL

The journal continues to function well and we receive many submissions from not just South Africa but Africa. Advertising is at an all-time high and for that I would like to thank the industry for their support and Robyn Marais for driving this. Professor Matt Haus resigned as co-editor of the journal in December 2014 but Professor Eugene Weinberg will continue to edit our journal.

MEMBERSHIP

Ordinary members: 766
Honorary members: 41
Affiliated members: 17
New members in 2015: 53

RESEARCH

GENERAL

Since 2004, to date, ALLSA and our sponsors have supported 36 researchers in the field of allergy and asthma. For this we owe a sincere vote of thanks to all of our sponsors over the years. Our current sponsors are GlaxoSmithKline, CiplaMedpro and MSD.

RESEARCH AWARDS FOR 2014

We received 5 applications for research awards for 2014, all of them from UCT. Three applications were successful - Dr Craig Laurence, Dr Frank Kirstein and Dr William Horsnell.

APPLICANT	STUDY TITLE
CRAIG LAURENCE	Adaptation of inflammatory immune responses in Xhosa South Africans and the correlation between pro-inflammatory alleles and clinical and laboratory markers of allergy: Sub-study
UCT	
FRANK KIRSTEIN	Investigation of cellular and molecular mechanisms behind the progression from atopic dermatitis to allergic asthma in mouse models
UCT	
WILLIAM HORSNELL	Using helminths to protect from lung inflammation
UCT	

SPONSORS FOR 2015/16

We are in the fortunate position that all our sponsors have pledged their support for allergy research for 2015/2016. The awards are currently being advertised and the closing date is 31 October 2015.

- GlaxoSmithKline (R50,000)
- Cipla Medpro (R20,000)
- MSD (R25,000)

WEBSITE REPORT

The website has been redesigned and it shows our new logo. I would like to encourage members to log onto the website. There is also a free SMS service available to members. We are getting many international logons to our website, almost 500 just from Australia.

CONGRESS

2016 Congress will take place in September at the new Century City Conference venue. I look forward to welcoming you to Cape Town.

WAO REPRESENTATIVE

ALLSA is a member of the WAO. Mike Levin has been nominated as our representative for 2015/2016.

EAACI

South Africa was part of the African Allergy session at EAACI in 2015. Di Hawarden was co-chair of the session at which Mike Levin presented some novel South African research.

ELECTIONS

Thank you to all the members who participated in the recent ALLSA Excom elections. I am proud to introduce our new Excom members, who are here to serve you.

André van Niekerk	Vice-Chairman
Sarah Karabus	Treasurer
Shaunagh Emanuel	Secretary
Sharon Kling	
Ahmed Manjra	
Mike Levin	
Claudia Gray	
Debbie White	
Refiloe Masekela	

I would like to thank you for your attendance at this AGM.

Di Hawarden

Review Article

ADVERSE DRUG EVENTS - WHY WE CARE

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ABSTRACT

Adverse drug reactions (ADRs) play an important role in the rational and safe use of medicines. ADRs occur in 10% of patients prescribed a medicine in the primary health care setting. Approximately five percent of all hospital admissions are due to an ADR and 10% of patients in hospital will develop an ADR. ADRs are a major burden on often stretched healthcare systems, with substantial economic impact. Many ADRs are preventable and an awareness of these risks are paramount in terms of the prevention of patient harm.

This article will provide a broad overview of the epidemiology of ADRs, their costs to the healthcare system, a simple classification for ease of recognition, causality assessment and the importance of pharmacovigilance as well as ADR reporting.

INTRODUCTION

According to the World Health Organization, an adverse drug reaction (ADR) is any noxious, unintended and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy.[1]

EPIDEMIOLOGY OF ADRs

ADRs occur commonly. In the primary care setting approximately 10% of patients who are prescribed medicines will experience an ADR. ADRs are associated with an increase in morbidity, mortality as well as in hospitalisations.[2,3,4] A landmark study in ambulatory patients in the USA found that for every $1 spent on a drug, $1.13 was also being spent due to an ADR.[5,6] About 5% of medical admissions have been attributed to ADRs and about 10% of patients will develop an ADR in-hospital depending on the type of hospital, definition of an ADR, and the study methodology.[2,3,4,7,8] The incidence of serious and fatal ADRs in hospitalised patients has been reported to be as high as 6.7% and 0.32%, respectively.[8,9,10]

Although there is limited local ADR data, a recent hospital South African survey found that ADRs contributed to the death of 2.9% of hospitalised patients.[11] Studies emanating from high income countries indicate that ADRs are in the top 10 causes of death. Importantly, studies have shown that up to 50% of ADRs are potentially avoidable.[4,10] Common errors resulting in ADRs include failure to illicit patients' allergies, errors in prescribing or dispensing, inadequate monitoring of patients and failing to recognise important drug-drug interactions.[5,7,9,12]

The economic impact of ADEs is substantial and potentially avoidable.[8,13,14] ADRs and their subsequent comorbidities lead to increased hospital costs. Depending on facility size, hospital costs annually for all ADRs, are estimated to be as much as $5.6 million per hospital.[9,14] Patients who experience ADRs have longer, more expensive hospitalisations than patients who do not suffer ADRs. This leads to a large drain on resources, not only financial but human as well.[13,14,15]

CLASSIFYING ADRS

Although most ADRs can be anticipated, others are unpredictable, especially rare idiosyncratic reactions.

ADRs are categorised into type A, B, C, D, E and F reactions.[16,17] This paper will focus on the more common ADRs, i.e. A and B.

Type A reactions are expected amplifications of a drug's known pharmacologic effects. They usually are dose-dependent, predictable and in most cases, preventable. Type A reactions are responsible for the majority of ADRs encountered. Examples include hypotension with antihypertensive agents and anticholinergic effects with tricyclic antidepressants.[16,17,18] Type A reactions tend to occur in patients who have one of three characteristics. Firstly, the patients usually have received a higher than normal dose. Secondly, they may have received the normal dose of the drug, but they may metabolise or excrete the drug more slowly, leading to drug plasma levels that are too high, possibly due to concomitant disease or drug-drug interactions.[16,17] A good example would be the administration of simvastatin with the anti-retroviral protease inhibitor, ritonavir. This interaction, leads to a 25-fold increase in the simvastatin plasma level with the resultant increased risk of rhabdomyolysis.[19]

Thirdly, they may have normal drug plasma levels but are sensitive to their pharmacological effects, e.g. the elderly are more sensitive to the pharmacological actions of the neuroleptics. Most type A reactions are usually identified prior to drug marketing and may be listed in the package insert of the medicine.[16,17]

Type B reactions are idiosyncratic and tend to be unrelated to the known pharmacologic action of the drug. They are usually not related to dose, unpredictable, uncommon and potentially clinically more serious than type A reactions.[16,17,18] Type B reactions may be due to a hypersensitivity or immunologic reaction. These are characterised by immune-mediated organ disease. Haptenisation of the organ cells by the parent drug or metabolite occurs. Presentation via major histocompatibility complex class II leads to immune activation and cellular toxicity, by T/B-lymphocytes and Natural Killer cells.[20]

The *non-allergic* ADRs may involve the covalent binding of a reactive drug metabolite to cells causing cell death.[21]

These reactions often concentrate in certain body systems, including the liver, blood, skin, kidney and nervous system. A typical example of a type B ADR is anaphylaxis due to the administration of penicillin.

Because type B reactions are uncommon or rare, they are often only detected after marketing of a drug. Type B reactions represent a major focus of pharmaco-epidemiologic studies of ADRs.[16,17,18]

PHARMACOVIGILANCE

Because ADRs represent an important public health concern as well as cost, the science of pharmacovigilance has been developed.[18] Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines. It is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare workers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines with a view to:[18,22]

- Identifying new information about hazards associated with medicines;
- Preventing harm to patients.

There are important limitations of the safety data of newly marketed drugs. Pre-marketing randomised controlled trials are mainly performed for regulatory purposes. They lack sufficient power to detect uncommon or rare ADRs, and have strict inclusion criteria. These criteria exclude patients who will commonly be given the drug (e.g. elderly, those with kidney and liver impairment), and are unable to detect long term cumulative toxicity (e.g. the long term increased risk of cardio-vascular disease from non-steroidal anti-inflammatory drugs was only recognised after more than 50 years of use).[18,22]

Spontaneous reports of drug-related morbidity or mortality by healthcare workers are often the first signal of a new ADR. In some countries there is a strong culture of spontaneous reporting among healthcare workers, often with particular drugs selected by national regulatory bodies. Spontaneous reports of potential new ADRs are captured by an international centre to ensure maximum chances of detection.[6,18] Signals from spontaneous reports are usually studied with observational case-control or cohort studies. However, observational studies are limited by confounding, which is the possibility that the apparent effect of a drug exposure is due to other factors.[18] Only randomisation can control for confounding, but it is seldom possible to conduct a randomised controlled trial to confirm whether there is cause-effect relationship between exposure to the drug and an event.[18]

Current methods of pharmacovigilance responsible for ADR recognition and prevention, have failed to detect some serious adverse effects.[7,18,22] Strategies to prevent ADRs requires identification of the significant risk factors, while signal detection requires ongoing review of ADR reports and early causality assessments.[18]

Criteria have, therefore, been developed to help determine the strength of association between drug exposure and an adverse event. Several systems have been developed for causality assessment. A commonly used system is provided in Table I which may be helpful in clinical decision making.[22]

ADRs should also be classified by severity, which may help predict clinical and/or drug regulatory action.[18,22]

- *Minor:* No antidote, therapy or prolongation of hospitalisation is required;
- *Moderate:* Requires a change in drug therapy, specific treatment, or an increase in hospitalisations by at least 1 day;
- *Severe:* Potentially life-threatening, causing permanent damage, or requiring intensive medical care;
- *Lethal:* Directly or indirectly contributes to the death of the patient.

Regulatory actions include the addition of a new contra-indication and updated warnings or special precautions in order to allow for the safer prescription and administration of the drug. A further, but more difficult regulatory action would be the removal of a labelled indication when the risk-benefit profile is deemed to be unfavourable.

CONCLUSION

ADRs are an important cause of morbidity and mortality. They have major clinical, public health and economic implications. The majority of ADRs are related to the pharmacological action of the drug (type A) and are often preventable. This highlights the importance of rational drug selection, always weighing up the risks against the benefits.

TABLE I: ADR CAUSALITY ASSESSMENT SCALE

QUESTIONS	RESPONSE SCORE #	
	YES	NO
Are there previous conclusive reports on this reaction?	+1	0
Did the adverse event appear after the suspected drug was given?	+2	-1
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0
Did the adverse reaction appear when the drug was re-administered?*	+2	-1
Are there alternative causes that could have caused the reaction?	-1	+2
Did the reaction reappear when a placebo was given?	-1	+1
Was the drug detected in any body fluid in toxic concentrations?	+1	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0
Score interpretation	>9 = definite ADR 5-8 = probable ADR 1-4 = possible ADR 0 = doubtful ADR	

 # Score 0 if unknown or not done.
** Note that rechallenge is seldom justified*
(adapted from Naranjo CA et al. A method of estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239-45)

Increased awareness of ADRs and the requirement to report will undoubtedly decrease the burden of ADRs and improve patient outcomes.

DECLARATION OF CONFLICT OF INTEREST

The author has no conflict of interest to declare.

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Review Article

A CLINICAL APPROACH TO DRUG-INDUCED LIVER INJURY

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ABSTRACT

Drug-Induced Liver Injury (DILI) may cause substantial harm to patients and places a considerable burden on the healthcare system. DILI can be classified as non-idiosyncratic (predictable) or idiosyncratic (unpredictable). The focus of this review is on Idiosyncratic DILI. An update on the epidemiology of DILI will be presented. An overview of current knowledge of DILI risk factors, pathogenesis, classification and clinical presentation will be given. An approach to DILI diagnosis and management using DILI due to tuberculosis (TB) treatment, which is a common severe adverse drug reaction in South African patients, as a practical example, will be outlined.

INTRODUCTION

Drug-Induced Liver Injury (DILI) is liver injury due to prescription and non-prescription medicines, herbal or dietary substances.[1] Over the past decade there has been an increasing recognition of herbal and dietary substances as causes of DILI. There is variation in regional distribution of the offending agents, with antimicrobial, antiepileptic and psychotropic drugs most commonly implicated in North America, in contrast with Asia, where herbs and dietary substances are the common offending agents.[2] In South Africa, which has a high burden of both tuberculosis (TB) and Human Immunodeficiency Virus (HIV) infection, with substantial comorbidity, DILI is commonly associated with exposure to tuberculosis treatment (TB-DILI) and/or antiretroviral drugs.

EPIDEMIOLOGY

The incidence of DILI is estimated to be 14-19 per 100 000 persons.[3,4] However, the incidence may be underestimated in part due to underreporting and uncertainties regarding diagnosis.[1,2] Although local data is limited, DILI is reported to complicate TB treatment in 5 to 33% of patients.[5] DILI, as with adverse drug reactions (ADRs) in general, may be associated with considerable morbidity and mortality resulting in hospitalisation with associated costs.[6,7] ADRs are implicated in up to 18% of deaths in hospitalised patients worldwide.[8-12] In a recent survey of medical wards at four South African hospitals, ADRs contributed to the death of 2.9% of hospitalised patients. DILI, most commonly due to TB treatment, was the second most common ADR contributing to death of medical inpatients.[13] In addition, DILI has implications for drug development. Emerging evidence of hepatotoxicity is a common reason for drug developers deciding not to proceed further with the development and clinical trials of a new drug.[14]

CLASSIFICATION OF DILI

DILI is mechanistically divided into non-idiosyncratic and idiosyncratic reactions.[15] Non-idiosyncratic reactions are often predictable and tend to be dose-related, e.g. DILI due to paracetamol overdose. In contrast, idiosyncratic reactions are unpredictable, occurring in less than 1% of those exposed, and generally considered to be dose-independent.

RISK FACTORS OF IDIOSYNCRATIC DILI

Risk factors may influence the likelihood of developing DILI as well as the severity of DILI. DILI occurs more commonly in adults than children. Whether there is a true biological basis for the higher prevalence in adults, or whether it simply reflects greater drug exposure in adults, is not clear.[16,17] Females appear to be at higher risk of DILI than males. Genetic factors may contribute to risk of DILI due to a variety of mechanisms. Genetic differences in phase 1 and phase 2 drug metabolising enzymes within the liver may increase the risk of DILI, e.g. isoniazid DILI and N-acetyltransferase 2 gene polymorphism. Secondly, specific Human Leukocyte Antigen (HLA) haplotypes have been implicated in the development of DILI, e.g. HLA-*B5701 genotype and abacavir as well as flucloxacillin.[18] Underlying infection with hepatitis B or hepatitis C virus has been shown to be a risk factor for DILI in patients commencing antituberculous or antiretroviral drugs.[19,20] Malnutrition is thought to increase risk of DILI.[21] There is a

lack of data regarding whether or not concomitant alcohol exposure increases risk of development of idiosyncratic DILI.[1]

PATHOGENESIS OF DILI

The pathogenesis of DILI is complex and not entirely understood. DILI is thought to result from interplay between the individual, the drug, and the environment. The parent molecule or a drug metabolite may cause the initial insult culminating in hepatic injury. Idiosyncratic DILI may result from either immunologic (allergic) or metabolic (non-allergic) mechanisms, however, distinction is not always clear-cut and there may be an overlap.[22] Adaptation may explain why DILI occurs in a small percentage of individuals. Adaptation is characterised by transient minor abnormalities in LFTs without symptoms of DILI, occurring shortly after drug initiation, and resolving in the presence of continued drug exposure. A number of mechanisms are thought to explain adaptation, including optimised drug processing by the liver, development of tolerance by the adaptive immune system, as well as recruitment of antioxidant defences.[23]

ALLERGIC DILI

Allergic DILI is a drug hypersensitivity reaction characterised by immune-mediated hepatotoxicity. Haptenisation of hepatic cells by the parent drug or a metabolite leads to the formation of neoantigens. Subsequent neoantigen presentation via major histocompatibility complex (MHC) class II leads to immune activation and hepatocyte destruction mediated by T-lymphocytes, B-lymphocytes and Natural Killer cells.[24] Allergic DILI occurs within 1-8 weeks of exposure. Patients may present with features of a hypersensitivity reaction, such as fever, skin rash, arthralgia and eosinophilia but this does not occur in all cases. Recurrence of symptoms on repeat exposure is a key finding that is highly suggestive of allergic DILI.

NON-ALLERGIC DILI

Non-allergic DILI is thought to result from covalent binding of a toxic drug metabolite to hepatic cells, resulting in oxidative cell damage and eventual cell death. In contrast with allergic DILI, non-allergic DILI tends to have a long latency (months) before DILI occurs with a notable absence of systemic features of hypersensitivity. Rechallenge with the offending drug in non-allergic DILI generally does not result in recurrence.[15]

CLINICAL PRESENTATION OF DILI

SYMPTOMS

Symptoms may include:

- Malaise;
- Loss of appetite;
- Nausea;
- Vomiting;
- Abdominal or right upper quadrant pain;
- Jaundice;
- Features of drug hypersensitivity, e.g. fever and rash.

ABNORMALITIES IN LIVER FUNCTION TESTS

DILI presents with abnormalities in Liver Function Tests (LFTs) that reflect an underlying pattern of liver injury. The pattern of injury is categorised into hepatocellular, cholestatic, or mixed.[25] A markedly elevated alanine aminotransferase (ALT) is characteristic of hepatocellular injury, whereas, marked elevation in alkaline phosphatase (ALP) characterises cholestatic injury. The mixed presentation usually includes elevations in both ALT and ALP. Importantly, the serum bilirubin may be elevated across all presentations. The development of jaundice, in association with hepatocellular injury, has clinical significance. The physician Hy Zimmerman, observed a higher risk of mortality (>10%) in patients with DILI, if they developed jaundice in association with raised transaminases. “Hy’s law” refers to the increased mortality associated with an ALT ≥3 times the upper limit of normal (ULN) in combination with a serum bilirubin level ≥2 times the ULN.[26]

An awareness of the pattern of injury is of some utility in that some drugs tend to be associated with a specific pattern. Table I provides examples of drugs categorised according to their common pattern of injury.[25]

HISTOLOGY

DILI may be classified on the basis of histology and some drugs cause distinct histologic patterns of injury. Histologic patterns of injury include hepatocellular, cholestatic and steatosis. The limitation of histology in determining the cause of liver injury is that, as with derangements in LFTs, histological findings are generally not drug-specific. Nonetheless, the pattern of LFT derangement together with histological features may assist with causality assessment where there are multiple drug suspects.

APPROACH TO THE PATIENT WITH SUSPECTED DILI

Consultation with experts routinely involved in the management of DILI including hepatologists, clinical pharmacologists and infectious diseases specialists, is advised.

DIAGNOSIS

DILI is largely a diagnosis of exclusion. The aim is to exclude pre-existing liver disease and rule out other forms of liver disease.

The diagnostic work-up in suspected TB-DILI should give consideration to other potential causes of liver disease such as chronic and acute alcohol use, pre-existing liver disease, viral hepatitis, other hepatotoxic drugs, hepatic TB and Immune Reconstitution Inflammatory Syndrome (IRIS). In TB-DILI, isoniazid, rifampicin and pyrazinamide are the common offending agents. Asymptomatic elevations in serum aminotransferase levels may occur with

TABLE I: CLASSIFICATION OF DILI ACCORDING TO PATTERN OF INJURY

HEPATOCELLULAR *(ALT ELEVATED)*	CHOLESTATIC *(ALP AND BILIRUBIN ELEVATED)*	MIXED *(ELEVATED ALP AND ALT)*
Aspirin	Chlorpromazine	Amitriptyline
Allopurinol	Clopidogrel	Azathioprine
Amiodarone	Amoxicillin/clavulanic acid	Cyclosporine
Bupropion	Co-trimoxazole	Carbamazepine
Ciprofloxacin	Efavirenz	Clindamycin
Isoniazid	Erythromycin	Co-trimoxazole
Ketoconazole	Nevirapine	Enalapril
Losartan	Oral contraceptives	Erythromycin
Methotrexate	Phenothiazines	Phenobarbital
Nevirapine	Terbinafine	Phenytoin
NSAIDs		Sulphonamides
Paracetamol		Trazodone
Protease inhibitors		Verapamil
Pyrazinamide		
Rifampicin		
Risperidone		
Sertraline		
Statins		
Valproic acid		
Venlafaxine		

Adapted and expanded from: Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med 2006:16;354(7):731-739.

isoniazid and rifampicin. This reflects hepatic adaptation and does not require treatment cessation. In addition, rifampicin may also cause asymptomatic unconjugated hyperbilirubinaemia shortly after commencing treatment.

HISTORY AND CAUSALITY ASSESSMENT

A comprehensive history should be obtained in the patient with suspected DILI. The patient should be asked about co-morbidities and pre-existing liver disease. Moreover, there should be an evaluation of risk factors for DILI, as well as a thorough history of drug use that includes an assessment of the timing of all recent drug exposures.

For patients with suspected TB-DILI, it is essential to review the details of the TB diagnosis including results of drug susceptibility testing, and to determine if the patient is in the intensive phase or continuation phase of TB therapy. Patients should also be asked about exposure to other hepatotoxic drugs including HIV antiretrovirals, cotrimoxazole, as well as traditional or herbal substances and over the counter medication.

Various causality assessment tools have been developed to assist in the diagnosis of DILI. None replace the need to seek expert advice for complex cases.[27]

INVESTIGATIONS

We currently rely on abnormalities in LFTs (ALT, ALP and Bilirubin) to aid in the diagnosis and management of DILI. There is currently no universal definition for DILI on the basis of abnormalities in LFTs. However, the following definition of DILI requiring treatment interruption, is advocated for use in South Africa:[5,28]

- ALT level >3 times ULN and symptomatic (nausea, vomiting, abdominal pain, jaundice); or
- ALT level >5 times ULN and asymptomatic; or
- Total serum bilirubin concentration >2 times ULN.

Although indicative of liver injury, abnormalities in LFTs are not specific for DILI. The presence of a specific biomarker for DILI could aid in diagnosis and potentially improve our understanding of the pathogenesis of DILI.[22] However, there are currently no specific biomarkers for DILI. The search for specific biomarkers of DILI remains an active research area with liver-specific micro RNAs (miR-122 and miR-192) showing a great deal of promise.[1,22]

OTHER INVESTIGATIONS

Viral hepatitis is common in South Africa and needs to be excluded. Patients presenting with suspected DILI should be screened for Hepatitis A, B, C and E. The International Normalised Ratio (INR) is a marker of synthetic liver function and aids in assessing the severity of liver injury. The need for further investigations, including imaging modalities and/or liver biopsy, will be guided by the clinical presentation. Choice of investigations should be guided by advice from experts in DILI diagnosis and management.

In patients with suspected TB-DILI, additional investigations should be considered:

- Testing to confirm TB diagnosis if there is uncertainty regarding TB diagnosis;
- Review of available TB culture results and drug susceptibility testing;
- Request an abdominal ultrasound if the ALP or Bilirubin is elevated in order to exclude IRIS, disseminated TB and extrahepatic biliary obstruction.

MANAGEMENT

For DILI in general, management can be grouped into dechallenge, specific treatment and rechallenge.

For TB-DILI, there are specific considerations that impact on management decisions. These include severity of DILI, timing of onset of DILI (during initiation phase vs. continuation phase) and the use of concurrent HIV antiretrovirals and co-trimoxazole. In many cases causality assessment is complicated because of multiple drug suspects, which may include rifampicin, isoniazid, pyrazinamide, cotrimoxazole and a number of antiretrovirals, in particular efavirenz, nevirapine and protease inhibitors.

DECHALLENGE

Immediate cessation of the offending drug or drugs is the first step following diagnosis of DILI. Dechallenge of the offending drug will usually result in improvement of liver injury. However, the rate of improvement following dechallenge can be variable. In cases of DILI with a predominantly cholestatic picture, the bilirubin can take many weeks or months to return to normal. In cases of TB-DILI in patients co-infected with HIV, antiretrovirals,

TB treatment and cotrimoxazole may all be implicated. All potential causes should be stopped.

TREATMENT

Treatment is largely supportive with regular monitoring of the patient to ensure recovery. Specific drug therapies for the treatment of DILI are limited and include N-acetylcysteine for paracetamol-induced DILI.[29] In addition, carnitine is used for valproic acid toxicity, although robust evidence is lacking.[30] There is a lack of robust evidence concerning the use of corticosteroids in the treatment of DILI, and their use is generally not recommended.

Patients with TB-DILI require ongoing combination treatment for their TB while recovering from the liver injury. Patients are switched to a background regimen including three antituberculosis drugs, generally, an aminoglycoside, fluoroquinolone, and ethambutol, for example:

Amikacin 15 mg/kg daily PLUS
Moxifloxacin 400 mg daily
OR
Levofloxacin 750 mg daily (weight <50 kg) or 1000 mg daily (weight >50 kg) PLUS
Ethambutol 800 mg daily (weight 40 kg to 54 kg) or 1200 mg daily (weight 55 kg to 80 kg)

This regimen should be continued throughout the duration of rechallenge (see below).

RECHALLENGE

Rechallenge should only be attempted after confirming the diagnosis of TB. As a rule, rechallenge with the offending agent causing DILI should be avoided in view of the possibility that DILI will recur, and may be more severe on recurrence. However, there are currently very limited options for TB treatment. If rifampicin and isoniazid are not included in the treatment regimen, protracted courses of therapy (up to 18 months duration) are required, and cure rates suffer. Therefore, patients are frequently rechallenged with first-line TB treatment, specifically rifampicin and isoniazid in South Africa. Pyrazinamide rechallenge is more controversial, but is performed in cases where benefit is thought to outweigh risk (e.g. disseminated TB). It is important to remember that rechallenge with TB drugs is only performed because of the lack of effective alternative drugs, and because of the high risk of morbidity and mortality associated with untreated or incompletely treated TB. Furthermore, unlike many other drugs, there is some evidence to support rechallenge with antituberculous drugs in patients with TB-DILI.[28,31,32] TB DILI recurs in 11% of patients rechallenged.[33] Rechallenge should always be performed with close supervision and monitoring, so that recurrence is detected early.

In patients with antituberculous DILI, rechallenge is usually undertaken once the ALT is <100 IU/l and total bilirubin has normalised. A small randomised controlled trial conducted in 175 patients in India, found no difference in recurrence rates between three approaches:

- Rechallenging with agents one by one with gradually incrementing dose;
- Rechallenging one by one with full doses;
- Rechallenging all drugs together.[32]

Rechallenging with individual drugs and gradually increasing the dose requires prolonged hospital stay. Rechallenging with all drugs together makes causality assessment in cases of recurrence very difficult. Therefore, in South Africa, the strategy of rechallenging in a stepwise fashion with full doses is frequently used. A commonly used first-line antituberculous drug rechallenge regimen is as follows:[5]

- Day 1: Rifampicin 450 or 600 mg daily (depending on weight);
- Day 3: Check ALT;
- Day 4-6: Add 300 mg Isoniazid daily;
- Day 7: Check ALT;
- Day 8: Consider a Pyrazinamide rechallenge (in cases of TB meningitis or intolerance/resistance to other drugs after discussing with an expert);
- Check ALT at Day 10 if Pyrazinamide is rechallenged;
- Monitor ALT twice weekly for the first 3 weeks, then every two weeks for a month, then monthly until 3 months.

In patients taking ARVs that were interrupted due to DILI, ARVs should generally only be reintroduced once TB drug rechallenge is complete.

CONCLUSION

DILI may be associated with substantial morbidity and mortality. Awareness of the clinical presentation and common offending agents is therefore important to facilitate early diagnosis, which may improve outcomes. Research into specific biomarkers is progressing and may hold the key to understanding the complex pathogenesis and aid in diagnosis. In view of the lack of specific therapies for DILI, management of DILI is primarily focused on withdrawal of the offending agent and the provision of supportive treatment. Rechallenge should rarely be done but is justified in many cases of DILI, due to first line TB treatment, because of limited alternative treatment options.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Continued from Marc Blockman's Guest Editorial on page 244.

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Review Article

PENICILLIN ALLERGY: WHEN IS IT OK TO USE A CEPHALOSPORIN?

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ABSTRACT

Penicillin and penicillin-based antibiotics are the most widely used antibiotics for common infections and are also the antibiotics which most often cause allergic reactions. Penicillins and cephalosporins share a common beta-lactam ring structure as well as similar side chains which could potentially lead to clinical cross-reactivity. IgE-mediated allergy to penicillins and cephalosporins may be due to the beta-lactam ring structure that is common to this group of drugs, or due to the R-group side chain that distinguishes the different penicillins from each other. After administration penicillin undergoes degradation resulting mainly in the formation of benzyl penicilloyl which is the major antigenic determinant to which the majority of allergic patients react. The beta-lactam ring may act as a hapten by covalently binding to tissue or serum proteins. When cephalosporins degrade, the beta-lactam ring as well as the R-group side chain are exposed. It is the R-group that is believed to play a more important role in the cross-reactivity between penicillins and cephalosporins. Most patients with proven penicillin allergy can safely receive cephalosporin antibiotics after a thorough history is taken and skin prick testing and a drug provocation test performed.

BACKGROUND

It is not uncommon for a skin rash to occur during a course of treatment with a penicillin antibiotic. This is often assumed to be due to penicillin allergy. In most cases no testing is performed in order to verify the diagnosis. Many individuals are simply labelled 'penicillin allergic'.

Penicillin and penicillin-based antibiotics are the most widely used antibiotics for common infections.[1] They are also the antibiotics which most often cause allergic reactions[2] with the frequency of life-threatening anaphylaxis estimated to be 0.01%-0.05%.[3] The incidence of self-reported penicillin allergy is from 1%-10% [4] but more than 80-90% of these have no evidence of IgE antibodies to penicillin on skin-testing.[5,6]

Penicillin-based antibiotics are usually less expensive and have fewer side effects than alternative broad-spectrum antibiotics. They are also more effective for certain infections. This is especially important among patients on long-term antibiotic prophylaxis or treatment such as those with rheumatic heart disease or bacterial endocarditis.

Patients with penicillin allergy have been shown to have longer hospital stays.[7] They are 23% more likely to have *C difficile* than controls and 30% more likely to have vancomycin resistant *enterococcus*.[7] Their mean antibiotic costs have been shown to be 63 times greater than those of non-allergic patients.[8]

Penicillins and cephalosporins share a common beta-lactam ring structure as well as similar side chains which may lead to clinical cross-reactivity.

ANTIGENIC COMPONENTS

It is helpful to review the potential allergenic components of these drugs in order to better understand how they may possibly cross-react in a clinical situation.

IgE-mediated allergy to penicillins and cephalosporins may be due to the beta-lactam ring structure that is common to this group of drugs or due to the R-group side chain that distinguishes the different penicillins from each other. The beta-lactam ring itself is too small to be antigenic but it can act as a hapten by covalently binding to tissue or serum proteins.[9]

After administration penicillin undergoes degradation resulting mainly in the formation of benzyl penicilloyl which is the major antigenic determinant to which the majority of allergic patients react.[9] Penicillin degradation also results in a range of molecules which can act as haptens. These so-called minor determinants are responsible for allergic reactions in about 15% of allergic patients. When

cephalosporins degrade, the beta-lactam ring as well as the R-group side chain are exposed. It is the R-group that is believed to play a more important role in the cross-reactivity between penicillins and cephalosporins.

CLASSIFICATION OF ALLERGIC REACTIONS

There are a number of ways to classify drug allergies. From a clinical perspective a practical method is to classify adverse drug reactions as 'immediate' and 'non-immediate' based on the time interval between administration of the drug and the reaction.

Immediate hypersensitivity reactions are IgE-mediated and occur within minutes up to 1 hour after administration. Non-immediate reactions are generally non IgE-mediated and manifest from 1-72 hours after exposure. Immediate reactions present with the typical IgE-mediated symptoms and signs which may include anaphylaxis, urticaria, angioedema and bronchospasm. Non-immediate allergic reactions may include contact reactions, serum sickness, haemolytic anaemia, morbilliform eruptions and Stevens-Johnson syndrome. Table 1 shows the classification of allergic reactions.

RISK FACTORS

A personal or family history of drug allergies predisposes to penicillin allergy[10] whereas a history of atopy does not.[11] Young adults between 20 and 49 years of age are most likely to be allergic and females report being allergic more than males. Older age predisposes to more serious reactions due to comorbidities and the use of other drugs, such as beta-blockers.[12] Concurrent viral infections such as HIV, EBV, HHV and CMV predispose to non-immediate reactions.

DIAGNOSIS

CLINICAL HISTORY

The signs, symptoms and severity of the reaction and any prior reactions should be documented. For example, urticaria and bronchospasm would suggest an IgE-mediated immediate drug reaction, whereas a vague history of minor gastrointestinal upset or a non-specific rash is much less suggestive.

The dose and route of administration are important. Prolonged parenteral administration is more likely to cause a hypersensitivity reaction than the oral or topical route, especially in non IgE-mediated allergy. A concomitant viral illness is important as this may cause a rash that is mistaken for penicillin allergy. The maculopapular rash induced by ampicillin or amoxicillin given to a child with Epstein-Barr virus infection is often mistaken for penicillin allergy.

QUESTIONS TO BE ASKED ABOUT HISTORY:

- Current and previous use;
- Dose;
- Frequency;
- Route of administration;
- Temporal sequence of events from initiation of treatment to onset of symptoms;
- Intercurrent illness, especially viral infections/HIV.

TABLE I: CLASSIFICATION OF ALLERGIC REACTIONS

TYPE	MECHANISM		TIME FRAME	CLINICAL CHARACTERISTICS	LIKELY CULPRIT DRUG
Type 1	IgE-mediated	IgE-drug complex binds to mast cells releasing inflammatory mediators.	Hours	Anaphylaxis, urticaria, angioedema, bronchospasm.	Penicillins
Type 2	Cytotoxic	IgM or IgG binds to drug-hapten coated cells.	Hours-days	Haemolytic anaemia, thrombocytopaenia.	Cephalosporins, penicillins, dapsone.
Type 3	Immune complex-mediated	Drug-antibody complexes deposited in tissues leading to complement activation.	Days–weeks	Serum sickness	Antitoxins, antivenoms, antibiotics.
Type 4	T-cell mediated		Days–weeks		
Type 4a		Monocytes		Contact dermatitis	Topical anaesthetics, topical antihistamines.
Type 4b		Eosinophils		Morbilliform rash, DRESS*	Anti-epileptics, sulfa-based agents, antidepressants, antibiotics.
Type 4c		CD4+ and CD8+ cytotoxic T-cell activation.		SJS/TEN*	Antibiotics, analgesics, NSAIDS, antiepileptics.
Type 4d		Neutrophil activation.		AGEP*	Penicillins, cephalosporins, quinolones.

**DRESS: Drug Rash, Eosinophilia and Systemic Symptoms*
**SJS: Stevens-Johnson Syndrome*
**TEN: Toxic Epidermal Necrolysis*
**AGEP: Acute Generalised Exanthematous Pustulosis*

The skin is the most commonly and prominently affected organ. Characterising the skin lesion is important. Skin manifestations may include maculopapular eruptions, urticaria, angioedema, fixed drug eruptions, photosensitivity, bullous lesions, vasculitis, erythema multiforme, DRESS, SJS and TEN.

INVESTIGATIONS

Blood tests are done based on the clinical picture (Table II).

TABLE II: INVESTIGATIONS

TEST	HELPFUL IN DIAGNOSING
Full blood count	Haemolytic anaemia, thrombocytopaenia, eosinophilia
Chest radiograph	Pneumonitis
ESR/CRP	Vasculitis
U&E/urine dipstix	Serum sickness/nephritis/vasculitis
C3/ANA/cANCA/pANCA	Vasculitis/drug-induced lupus/Churg-Strauss syndrome
Coombs test	Haemolytic anaemia
Tryptase	Acute anaphylaxis

Tryptase is a sensitive and specific marker of mast cell degranulation and is helpful in the context of anaphylaxis. Serum levels peak at one hour after a reaction and decline thereafter over hours. Samples taken at 0, 1 and 6 hours after the event may confirm anaphylaxis.

SKIN TESTING

Skin prick testing is the basic diagnostic tool for IgE-mediated reactions to penicillins. Clinical expertise is required in order to perform this test accurately. Skin tests are generally very safe but systemic reactions have been reported. They should, therefore, be done in a suitable setting.

A wheal of ≥3 mm greater than negative control is considered a positive result.

The skin test panel should include a positive and a negative control, benzylpenicillin, major and minor determinant mixture (Diater™, Madrid, Spain) and amoxicillin (20-25 mg/ml).[13,14,15]

If the offending drug is a cephalosporin, this is added to the above panel with the understanding that the negative predictive value of such a test is unknown. Skin prick tests have a specificity approaching 100% for IgE-mediated allergy.[15,16,17] The sensitivity is rather less (±70%).[15,16] If the skin prick test is negative, some go on to perform intradermal testing with various dilutions of the drug, injected intradermally on the volar surface of the forearm. Skin prick and intradermal tests are not useful for non-immediate reactions.

IMMUNOCAP

Specific IgE antibodies to amoxicillin, ampicillin, penicillin V, penicillin G and cefaclor can be measured to aid in the diagnosis. This test is highly specific (95%) but less sensitive (54%) than skin prick tests.[13]

OTHER TESTS

Patch testing: Patch testing has been used for investigation of non-immediate reactions. However, their use is not standardised, nor is the sensitivity fully validated. Sensitivity in some studies was only 9%.[18] Delayed reading of intradermal tests has been shown to be slightly more sensitive than patch tests, but less specific.[19,20]

Cellular Antigen Stimulation Test (CAST): This test measures the *in vitro* production of sulphidoleukotrienes by leukocytes when stimulated by the specific drug. The sensitivity and specificity are approximately 46% and 85% respectively.[14]

Basophil Activation Test: Limited to research settings.

Lymphocyte Transformation Test: Limited to research settings.

Drug Provocation Test (DPT): If the skin tests are negative and IgE antibody levels normal, a DPT should be performed provided resuscitation equipment and trained staff are available. A strongly suggestive history of immediate allergy coupled with a positive skin test and/or immunoCAP is generally sufficient to make the diagnosis of penicillin allergy without the need to perform a DPT.[15,16] A DPT is not usually performed if there is a history of anaphylaxis.

RESENSITISATION AFTER INVESTIGATIONS

There is no consensus with regards to the risk of re-sensitisation after performing skin tests and DPT. Recent studies suggest a low risk, however, the International Consensus on Drug Allergy suggests that retesting should be considered in those who have had a previous severe reaction.[21]

CROSS REACTIVITY WITH CEPHALOSPORINS

It was previously believed that up to 20% of patients with a history of penicillin allergy could have an adverse reaction to a cephalosporin,[22] most commonly with the first and second generation cephalosporins. Much of the evidence on cross-reactivity comes from retrospective studies. These studies were limited in that they lacked control groups. Many were based only on clinical history or on skin prick tests rather than on drug provocation challenges. In studies that did perform DPTs, most were carried out in an open fashion, rather than being blinded.[23,24]

First generation cephalosporins produced prior to 1980 are known to have contained traces of penicillin when they were initially manufactured. This may also have led to a

higher rate of cross-reactivity with these drugs.[25] A meta-analysis from 2007 showed a higher risk of cross reactivity with first generation but a negligible risk with second and third generation cephalosporins – around 2% overall.[26] There are no reported cases of cross-reactivity with fourth generation cephalosporins.

Cross-reactivity between these drugs is believed to be due to the drugs having similar R-group side chains and not due to the beta-lactam ring. For example, amoxicillin shares a side-chain with cephadroxil, cefotaxime with ceftriaxone and ampicillin with both cephalexin and cefaclor. Two studies of patients confirmed to be amoxicillin allergic, but not penicillin allergic, showed that up to 38% of patients reacted to cephadroxil as well.[27,28] Little is known about the cross-reactivity between penicillins and cephalosporins in non-immediate allergy.

RECOMMENDATIONS

For patient with reported, but not confirmed, penicillin allergy:

- Confirm penicillin allergy as above.

For patients allergic to penicillin and requiring a cephalosporin:

- Do a cephalosporin skin prick test;
- If this is negative, give the cephalosporin via graded challenge (see below for an example of a graded challenge);
- If the cephalosporin skin test is positive, the cephalosporin may be administered via a desensitisation protocol (Table III) or alternatively, avoided altogether.

For patients allergic to amoxicillin or ampicillin, but who tolerate penicillin, and require a cephalosporin:

- Avoid cephalosporins with identical side chains;
- If amoxicillin allergic, avoid cefadroxil and cefprozil;
- If ampicillin allergic, avoid cephalexin, cefaclor and loracarbef;
- Cephalosporins with dissimilar side-chains can be used;
- If a cephalosporin with an identical side chain is necessary, it can be administered via desensitisation.

For patients allergic to a cephalosporin and requiring penicillin:

- Do a penicillin skin prick test;
- If it is negative, give penicillin;
- If it is positive, avoid penicillin or administer penicillin via a desensitisation protocol.

For patients allergic to cephalosporin and requiring a different cephalosporin

- Use a cephalosporin with a different side chain and administer it via a graded challenge or desensitisation protocol depending on the severity of the previous reaction.

TABLE III: ORAL PENICILLIN DESENSITISATION PROTOCOL (SULLIVAN IN MIDDLETON)[30]

STEP*	PENICILLIN (MG/ML)	AMOUNT (ML)	DOSE GIVEN (MG)	CUMULATIVE DOSE (MG)
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.1	0.15
3	0.5	0.4	0.2	0.35
4	0.5	0.8	0.4	0.75
5	0.5	1.6	0.8	1.55
6	0.5	3.2	1.6	3.15
7	0.5	6.4	3.2	6.35
8	5	1.2	6	12.35
9	5	2.4	12	24.35
10	5	5	25	49.35
11	50	1	50	100
12	50	2	100	200
13	50	4	200	400
14	50	8	400	800

**Interval between doses is 15 minutes. After last dose, observe patient for 30 minutes. If no reaction occurs, the full therapeutic dose may be given.*

IF SKIN TESTING IS NOT AVAILABLE

If skin testing is not available, the clinical history of penicillin allergy should be carefully assessed and the likelihood of a serious IgE-mediated reaction estimated. If the symptoms are not suggestive, or the reaction was more than 10 years ago, the cephalosporin can be given in the usual way, provided that one with a different side-chain is used.

If there is a high likelihood because the reaction is more recent, or the symptoms are highly suggestive of an IgE-mediated reaction, a cephalosporin with a different side-chain may be given via a graded challenge. If the history of the reaction is consistent with anaphylaxis, rapid desensitisation should rather be performed.

Amoxicillin or ampicillin allergic patients should avoid cephalosporins with identical side chains or receive them via desensitisation. They are able to take cephalosporins with different side chains with no special precautions.

FOR CHILDREN WITH A MILD, NON-IMMEDIATE RASH OR MACULOPAPULAR ERUPTION

The first dose of the oral challenge should be given in hospital, followed by a 2-hour period of observation. The child then completes a 5-day course at home.[29]

TABLE IV: CEPHALOSPORINS WITH IDENTICAL SIDE CHAINS

Cefaclor Loracarbef Cephalexin	Cefadroxil Cefprozil	Cefepime Cefotaxime Cefpodoxime Ceftriaxone

GRADED CHALLENGE

A graded challenge does not modify the immune response, but rather is a more cautious method of administering a drug. A typical method for oral drugs is to give a 1/10 of the full dose, followed an hour later by the full dose. More caution is advocated should the drug be administered intravenously. In this case the starting dose is usually 1/100, followed an hour later by 1/10, and then the full dose an hour after that. For example, using cefuroxime give 2.5 mg, 25 mg and then 250 mg at 60 minute intervals.

CONCLUSIONS

Most penicillin allergic individuals are incorrectly labelled. This may result in the unnecessary use of more expensive and less effective antibiotics. It may also lead to the emergence of multi-drug resistant organisms. Accurate diagnosis is essential to avoid the morbidity, mortality and economic cost associated with unnecessarily withholding penicillin in non-allergic patients. A history of penicillin allergy is often unreliable, poorly documented or vague. Skin prick testing remains the standard practice for the evaluation of patients with immediate hypersensitivity reactions to penicillin. This, together with a thorough history, determination of IgE antibodies and a drug provocation test will pick up virtually all cases. Most patients with proven penicillin allergy can safely receive cephalosporin antibiotics.

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Review Article

DRUG REACTIONS ASSOCIATED WITH ANTITUBERCULOSIS DRUGS

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ABSTRACT

Tuberculosis continues to be a major cause of death worldwide, mainly driven by the HIV pandemic in Sub-Saharan Africa. Management of tuberculosis-HIV co-infection is fraught with challenges including a higher incidence of adverse drug reactions, complex drug interactions, overlapping toxicities and tuberculosis-associated immune reconstitution inflammatory syndrome. All first-line antituberculosis drugs can cause severe drug reactions. The limited number of effective antituberculosis drugs, compounded by lower efficacy and higher toxicity of second-line drugs, makes treatment of tuberculosis following adverse drug reactions a major challenge. In this review, the clinical spectrum of cutaneous adverse drug reaction to antituberculosis drugs, management of these reactions and challenges clinicians face in continuing tuberculosis treatment will be discussed.

BACKGROUND

Tuberculosis continues to be a major cause of death worldwide. The disease was directly responsible for 1.5 million deaths in 2013. The HIV pandemic has been a strong driver of the high incidence of tuberculosis. Approximately 13% of new cases of tuberculosis worldwide in 2013 were HIV co-infected. This figure climbs above 50% in sub-Saharan countries where there is a high HIV prevalence.[1] Management of HIV tuberculosis co-infection is fraught with management challenges including Adverse Drug Reactions (ADR), complex drug interactions, overlapping toxicities and tuberculosis-associated immune reconstitution inflammatory syndrome. ADR are significantly more common in HIV-infected persons.[2,3] Both first and second-line antituberculosis drugs are a well-established cause of ADR among those co-infected with tuberculosis and HIV.[4] The incidence of ADR in HIV has been estimated to be as high as 27% in a primary health care clinic in Cape Town.[3]

The spectrum of tuberculosis-associated ADR ranges from minor to life-threatening, including delayed-type Cutaneous Adverse Drug Reactions (CADR), immediate-type hypersensitivity reactions, drug induced liver injury, nausea and vomiting, arthralgia, peripheral neuropathy, vertigo, and psychosis.[4,5] In this review the focus will be on delayed-type CADR to antituberculosis drugs and their clinical presentations and management challenges.

CLINICAL SPECTRUM OF TUBERCULOSIS-ASSOCIATED CADR

The skin responds in a limited manner to a wide spectrum of insults. As a result, it is often difficult to correctly diagnose CADR. This has clinical implications as different subtypes of CADR carry different prognosis and are managed differently. The clinical spectrum includes Morbilliform (measles-like) Drug Eruption (MDE) commonly referred to as maculopapular eruption, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), Lichenoid Drug Eruption (LDE) and Fixed Drug Eruptions (FDE).

MORBILLIFORM DRUG ERUPTION

Morbilliform Drug Eruption (MDE), also called maculopapular rash, is the most common type of CADR. The rash usually spreads centrifugally with the lesions becoming progressively confluent. MDE are usually self-limiting without systemic involvement (Figure 1).[6] However, it can be difficult to differentiate MDE from early SJS/TEN and DRESS syndrome.

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, which is also commonly referred to as drug hypersensitivity syndrome, is the most common of the severe forms of CADR. It is characterised by pruritus, pyrexia, fever, oedema, lymphadenopathy, white cell abnormalities (leucocytosis, eosinophilia or atypical lymphocytosis) and hepatitis. The latency period usually exceeds three weeks. Apart from the liver, the other internal organs that may be affected include the lungs, pancreas, kidneys and the heart. The rash in DRESS

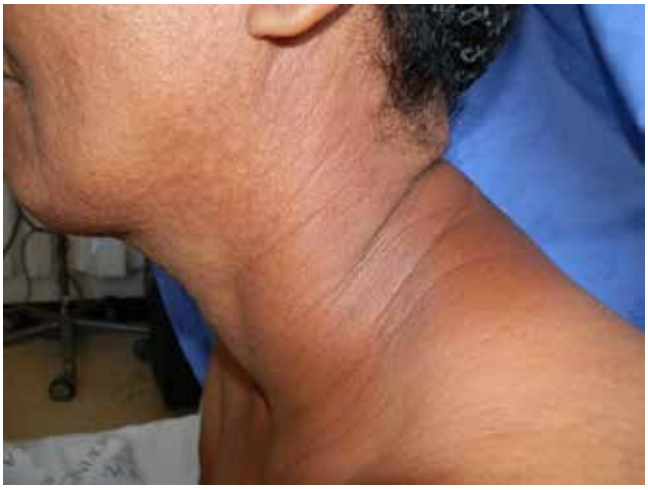

Figure 1: Morbilliform or maculopapular rash showing distinct papules in a background of erythema

syndrome has variable morphology, ranging from urticarial, maculopapular, vesicles, pustules, purpura, targetoid lesions, or erythroderma (Figure 2).[7] Deranged laboratory parameters may lag behind the rash by a few days. The differential diagnosis of DRESS syndrome includes viral exanthemata and inflammatory skin conditions. DRESS syndrome usually responds well to withdrawal of the offending drug and potent topical steroids. In severe cases with marked internal organ involvement, systemic steroids may be warranted. The most common causes of death in DRESS syndrome, estimated at 10%, are liver failure and sepsis.[7]

STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are considered to be a spectrum of the same disease. They are delineated by percentage body surface area of epidermal necrosis and stripping. In SJS, there is less than 10% of epidermal detachment and in TEN, there is greater than 30%. The SJS/TEN overlap lies between these two extremes.[8] Early SJS/TEN presents with fever, malaise, cough, stinging eyes, a sore throat and palmoplantar tenderness (Figure 3). This constellation of symptoms is often confused with upper respiratory tract infection and treated with antibiotics. These are subsequently blamed incorrectly as the offending drugs. Withdrawal of the offending drug and referral to a centre experienced in managing SJS/TEN improve outcomes.[9,10] Mortality in TEN, the more severe form of the disease, can be as high as 40%. Most commonly this results from skin and mucosal failure and subsequent bacterial systemic infections.[11,12] Management of SJS/TEN is controversial. Systemic corticosteroids, immunosuppressive therapy, and intravenous immunoglobulins have not defined their role in the management of SJS/TEN. Supportive therapy by a multidisciplinary team is the mainstay of treatment in most centres. Important aspects of supportive care include:

- Monitoring of vital signs for early detection of systemic infection;

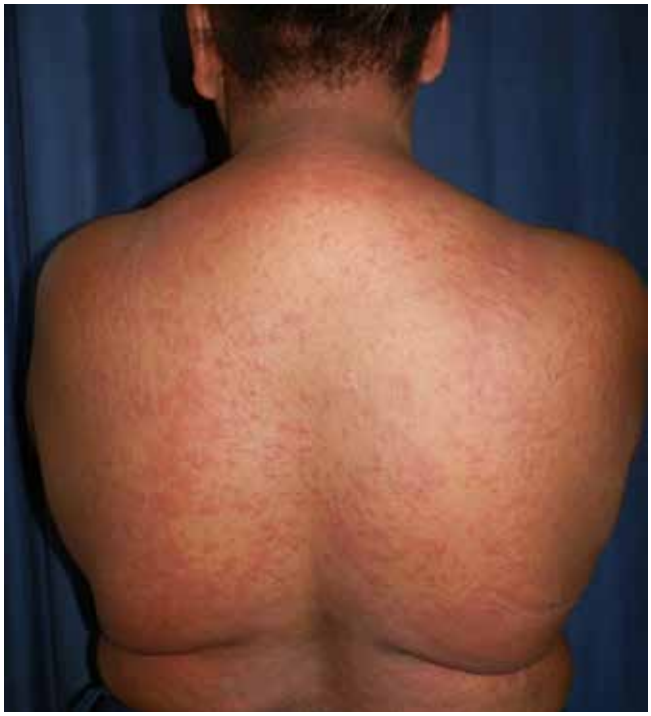

Figure 2: DRESS syndrome showing urticarial papules coalescing to form plaques

- Careful protection of the exposed dermis and early re-epithelialising skin with non-adherent sterile dressings;
- Pain management;
- Fluid balance;
- Temperature control;
- Early referral to ophthalmologists to prevent permanent eye damage;
- Genital care for females and uncircumcised males to prevent adhesions;
- Adequate nutrition, preferably non-abrasive, bland oral feeds at room temperature. Oral intake prevents oesophageal adhesions.[13]

LICHENOID DRUG ERUPTIONS

Lichenoid Drug Eruptions (LDE) present insidiously as pruritic purplish macules and plaques (Figure 4). The interval between drug initiation and a clinically detectable rash varies considerably in LDE. This, together with a lack of detectable acute blood markers, often makes it difficult to establish a temporal relationship with the offending drug and ascribe causality. This creates a major management challenge in setting of polypharmacy and limited number of effective drugs. This is illustrated in the treatment of tuberculosis where all first-line drugs can cause LDE, hindering identification and withdrawal of only the offending drug.

FIXED DRUG ERUPATION

Fixed Drug Eruption (FDE) usually presents as solitary or numerous itchy, round well-circumscribed, erythematous macules or indurated plaques on the skin or mucosal surfaces. The lesions rarely become bullous. FDE tends

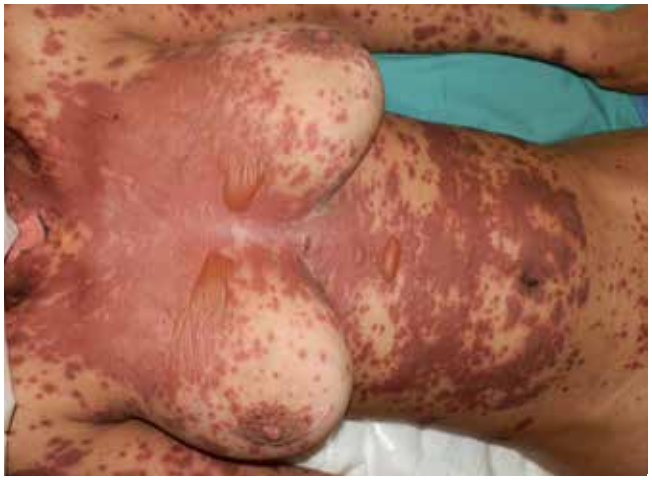

Figure 3: Toxic Epidermal Necrolysis showing areas of epidermal necrosis, blisters and stripping

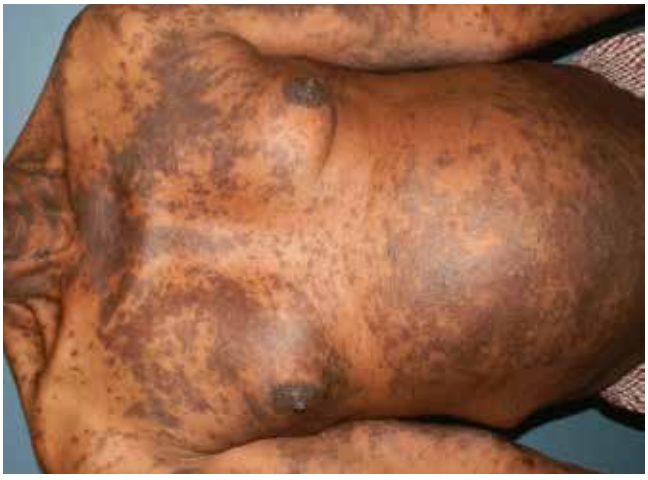

Figure 4: Ongoing Lichenoid Drug Eruption during tuberculosis treatment

to recur within hours on the same site when re-exposed to the drug, sometimes with new lesions erupting elsewhere (Figure 5). They typically resolve with persistent hyper-pigmentation of the involved sites.[14]

CHALLENGES IN THE MANAGEMENT OF ANTITUBERCULOSIS DRUG CADR

All the first-line antituberculosis drugs can cause multiple types of CADR, and a specific type of CADR can be due to any of the drugs. This makes identification of the offending drug a major challenge.

RECHALLENGE FOR FIRST-LINE DRUGS OR USE SECOND-LINE REGIMEN

The use of rifampin and isoniazid in any treatment regimen for tuberculosis is associated with superior outcomes.[15] The limited numbers of effective antituberculosis drugs and significant toxicities of the less effective second-line drugs, create a clinical management dilemma when first-line drugs cannot be used. There is abundant data that outcomes are sub-optimal when using second-line drugs in drug resistant tuberculosis.[16] Less is known about the outcomes of using second-line drugs in non-drug resistant tuberculosis. In a well-designed study, Suárez et al. showed that mortality, cure rates and compliance were all unfavourable when using second-line antituberculosis drugs, compared to standard therapy in a Peruvian population. This cohort included patients who had a failed response to first-line regimen and did not have drug resistant tuberculosis.[17]

The risks of tuberculosis-associated mortality, drug resistance, transmission of tuberculosis by infectious patients to other patients, staff and the community need to be balanced against the risk of a disabling or fatal rechallenge reaction. It has previously been shown that diagnostic rechallenge to pinpoint the offending drug is feasible and safe.[18] The safety of diagnostic rechallenge was further confirmed in the rechallenging of more than 150 cases of antituberculosis drug-associated CADR.[18,19] There were no long-term morbidities or deaths as a direct result of a rechallenge reaction. However, this was under close supervision in a hospital and an experienced multidisciplinary team managed the patients. Based on these data, tuberculosis outcomes are likely to be better if a rechallenge is undertaken and only the offending drug is removed from the treatment regimen.

MULTIDISCIPLANRY APPROACH

Tuberculosis-associated CADRs are multi-organ diseases that often require expertise ranging from hepatologists, infectious disease specialists, pulmonologists, dermatologists, dietitians and others. The best outcomes are attained using a multidisciplinary approach.

HOW SOON CAN RECHALLENGE BE INITIATED?

In tuberculosis treatment, interruption of therapy during the intensive phase is associated with a three times higher risk of death. The risk is even higher in HIV-infected persons.[20,21] This suggests that re-initiating therapy as soon as possible is advisable considering the relative safety of rechallenging.

ROLE OF *IN-VITRO*, PATCH AND SKIN PRICK TESTS

There is limited data on the efficacy of *in-vitro* tests to identify offending antituberculosis drugs. They are technically demanding, require expensive equipment and sterile cultures. These factors make them inaccessible, especially in resource-poor settings where tuberculosis is most prevalent.[4] The role of patch, skin prick and intradermal testing is yet to be fully determined for antituberculosis drug-associated CADR. The specificity and sensitivity of these tests is dependent on the phenotype of CADR, the drug being tested and the vehicle carrying the test drug.[22,23] It has recently been shown that in HIV-infected persons, patch and skin prick tests to antituberculosis drugs resulted in systemic reactions rather than localised reactions. The tests had low sensitivity. Using the Common Terminology Criteria for Adverse Events (CTCAE), a validated score used to grade adverse reactions, there was no difference in severity of rechallenge reactions resulting from patch

Figure 5: Bullous Fixed Drug Eruption

tests, skin prick tests and oral rechallenge, with the offending drug.[19,24,25] This suggests that in HIV-tuberculosis co-infection, cutaneous tests may not be beneficial in reducing the risk of rechallenge reactions.

ORAL PROVOCATION TESTING

Oral drug provocation tests are still considered the gold standard to identify the offending drug.[26] The risk of a rechallenge reaction must be balanced against the morbidity and mortality associated with sub-optimal therapy. There are few aspects of diagnostic oral rechallenge that are not fully defined. These include the use of bridging therapy before initiating rechallenge, whether rechallenge should occur at full dose or with incrementally increasing doses and the sequence in which the drugs are rechallenged.[4]

BRIDGE THERAPY BEFORE RECHALLENGE

To avoid mono-therapy and to minimise the risk of developing mycobacterial resistance during the prolonged rechallenge process with the individual drugs, a bridging therapy of three second-line drugs, to which the patient has not previously been exposed, is advised. The selection of drugs depends on local treatment guidelines, availability, toxicities and underlying co-morbidities. It has been established that almost a quarter of HIV infected patients with tuberculosis associated CADR develop multiple drug hypersensitivity to both first and second-line drugs. If rechallenge with first-line drugs is initiated too early, the overlapping clinical features of the rechallenge reactions and adverse reactions to the bridge therapy create confusion. Reactions to the bridge therapy usually develop within two weeks of their initiation. Based on this, it is recommended that rechallenge should only be undertaken two weeks into the bridge therapy.[27]

THE SEQUENCE OF DRUGS TO RECHALLENGE

Some authors believe that the most effective drugs, namely rifampicin and isoniazid, should be rechallenged first to minimise the risks of suboptimal therapy during the prolonged rechallenge process. Others suggest that the drugs least likely to cause a reaction should be rechallenged first.[4] It is well established that all first-line drugs cause CADR but there are no good studies quantifying the contribution of each drug. Thus, it is suggested to rechallenging with isoniazid and rifampicin first to minimise risk of developing drug resistant strains of tuberculosis, currently a major public health problem.

ESCALATING VERSUS FULL DOSES IN RECHALLENGING

In drug-induced hepatitis, Sharma et al. have shown that the severity and frequency of rechallenge reactions was not different when comparing full dose or incremental rechallenge.[28] There is currently no robust data supporting the safety of either method in CADR. Thus, it is suggested that dosing be escalated in rechallenge as recommended in the American Thoracic Society guidelines for reintroduction of antituberculosis drugs following drug-induced hepatitis.[29] An ongoing study to answer this question is currently underway.[19]

INTERVAL BETWEEN RECHALLENGING WITH FIRST-LINE DRUGS

The interval between the sequential reintroduction of the individual drugs is not well established. In an ongoing study it has been established that >90% of rechallenge reactions occur within 72 hours. Based on this, rechallenging with a new first-line drug every 96 hours is recommended while monitoring closely for features of a rechallenge reaction. The features of a rechallenge reaction in these studies was a variable combination of erythema, rash, pruritus, transaminitis, eosinophilia, fever, oedema and nausea.[18,19]

DURATION OF THERAPY AND FINAL TREATMENT REGIMEN

This depends on the offending drug(s), duration of treatment before interruption, drug sensitivities, co-morbidities and other drugs the patient is using. It is a complicated process requiring expert opinion, preferably by an infectious diseases specialist with experience in managing tuberculosis.

MANAGEMENT OF LICHENOID DRUG ERUPTIONS

Due to the lack of acute markers, it is difficult to pinpoint the offending drug in LDE. As a result, in HIV-infected patients the approach is to continue treatment under cover of potent topical steroids and phototherapy. However, this carries a risk of permanent dyspigmentation and should be discussed in detail with the patient and co-managed with a dermatologist.[30,31]

CONCLUSION

Tuberculosis is currently a major public health challenge. It is largely driven by the HIV pandemic. Tuberculosis

and HIV co-infection is associated with an increased risk of CADR. This often creates major challenges in the diagnosis and management of CADR, identification of the offending antituberculosis drug and selection of subsequent therapy for tuberculosis. Clinical subtypes of tuberculosis-associated CADR present different diagnostic and management challenges and clinicians should be able to identify each.

Elimination of first-line drugs results in poorer outcomes in the management of tuberculosis. This is even more so in HIV-tuberculosis co-infection. Thus, a diagnostic rechallenge following antituberculosis-associated CADR is often advisable to eliminate the offending drug from the treatment regimen. It has previously been shown that diagnostic rechallenge is safe and feasible in a controlled environment. However, rechallenge is associated with multiple pitfalls that need careful consideration before it can be attempted. With a rational multidisciplinary approach, outcomes in antituberculosis-associated CADR can be improved considerably.

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Review Article

A SOUTH AFRICAN MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC

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ABSTRACT

Immune function is not limited to a particular organ system and neither is immune-mediated pathology. Drug hypersensitivity reactions, having a diversity of pathophysiologic mechanisms, manifest with a range of clinical disorders. A particular drug can cause varied immune-based pathology in different individuals and to varying extents in the context of co-morbid diseases such as HIV. Consequently, a range of specialists care for the different reactions caused by a single drug. This may limit our ability to detect common clinical features and uncover unifying immunopathogenesis linked by the pharmacology of the particular offending drug. Furthermore, in South Africa with the ongoing TB/HIV epidemics, drug hypersensitivity reactions are common, occur in the context of polypharmacy and concomitant systems pathology and frequently require multidisciplinary input for optimal care within the constraints of limited therapeutic alternatives. To address this problem and in line with the global trend towards systems biology and personalised medicine, a multidisciplinary drug hypersensitivity clinic at Groote Schuur Hospital has recently been started – the first of its kind in South Africa. This article outlines the background to the formation of this initiative, the potential advantages and needs of a multidisciplinary drug hypersensitivity clinic and the focal starting point of this clinic to better understand the spectrum of immune-based hypersensitivity reactions to Rifampicin.

INTRODUCTION

South Africa, as one of the BRICS emerging national economies, is facing a health transition. Health systems remain burdened by the HIV and TB epidemics, yet non-communicable diseases are rising.[1] Prescribing practices, although still dominated by anti-retroviral and anti-tuberculous medicines, continue to expand to include an ever-increasing list of relevant chronic medications as well as novel small molecule and biologic therapies. Clinicians, already battling to keep up with the uses and predictable type A side-effects of this expanding medicinal armamentarium, need to be supported in managing the idiosyncratic Type B drug reactions. Many of these reactions are life-threatening with the majority being immune-mediated. In the context of HIV and TB, many occur in patients with multi-system co-morbidities and polypharmacy, thus requiring care from different sub-specialists. In addition, a cross-disciplinary effort is required to adequately surveil, respond, manage and research the patterns and dominant offending drugs within our local populations. It is out of this background that a multidisciplinary drug hypersensitivity clinic at Cape Town's Groote Schuur Hospital has been formed – a first for South Africa. In this brief review the rationale for the formation of this initiative will be outlined. The potential advantages and needs of a clinic of this nature will be discussed utilising as a focal starting point the spectrum of immune-based hypersensitivity reactions to rifampicin.

WHY A MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC?

There are two main drivers behind the formation of this multi-disciplinary drug hypersensitivity clinic:

I. A drug rather than clinical phenotype/organ-system focus; and
II. The complexity of patients with drug hypersensitivity reactions in South Africa.

A single drug can cause different immune-mediated drug hypersensitivity reactions (DHR) (Figure 1). For instance, beta-lactam antibiotics can cause urticaria, angioedema and anaphylaxis through an IgE-mediated type 1 reaction, leucocytoclastic vasculitis and serum sickness through an immune-complex type III reaction and a maculopapular rash and even a severe cutaneous adverse reaction

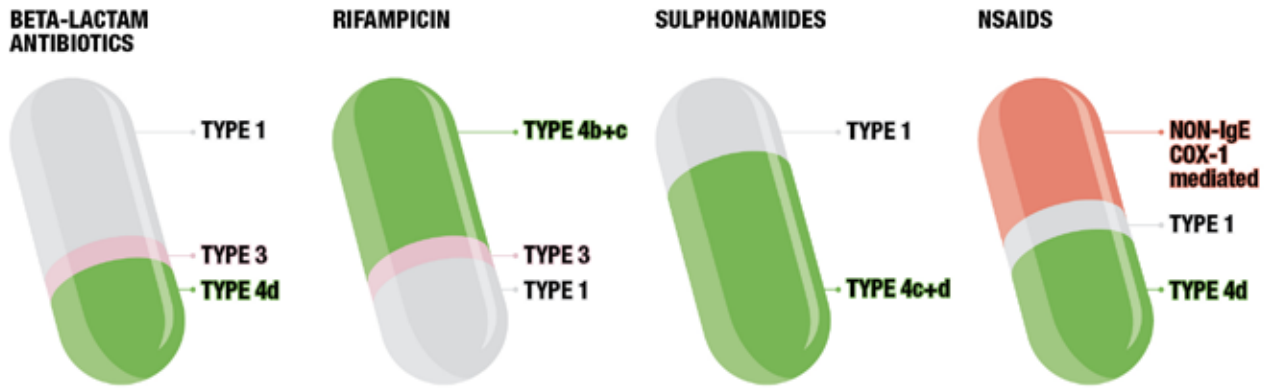

Figure 1: Drugs causing different types of immune-mediated pathology

(SCAR) via a T-cell mediated type IV reaction.[2] Currently, a patient with this spectrum of reactions would see an allergist, a rheumatologist, and a dermatologist with no required communication between them. This is an opportunity lost. In many instances the approach has been to blame a chemical without understanding that host factors may contribute as the underlining and perhaps unifying aetiology of these clinically diverse reactions. Important host factors may relate to pharmacogenomics, immunology or target organ susceptibility.

We have entered the era of systems biology. This is beginning to highlight the limitations of artificial clinical phenotypes. The move is towards phenotyping based on pathophysiological mechanisms. The immune system and its' pathologies, without a well-defined organ 'home' certainly lend themselves better to these mechanistic approaches. Thus, it is logical that a multidisciplinary drug hypersensitivity clinic, seeing the entire spectrum of a particular drug's immune-mediated reactions, will offer new insights and allow mechanistic approaches to best applied.

TABLE I: REQUIREMENTS FOR AN OPTIMAL FUNCTIONING MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC AND PLATFORM

PHYSICAL INFRASTRUCTURE:
1. Clinic
   a. Consultation rooms;
   b. Refrigeration for storage of skin/intradermal/patch drugs (4 degree);
   c. Consumables for patch testing, e.g. Finn Chambers;
   d. Photo patch testing equipment;
   e. Resuscitation equipment to treat anaphylaxis;
   f. Computing equipment required for admin and data capture.
2. Laboratory
   a. Centrifuge, sterile hood for processing human blood and tissue;
   b. -20 and -80 degree storage facility;
   c. Access to specialised equipment facilities including flow cytometer, ELISA readers, tissue culture facilities and luminex.

HUMAN RESOURCES:
1. Clinic
   a. Specialist clinicians including pharmacology, allergy, dermatology, infectious diseases, nephrology and hepatology;
   b. Nurses trained in performing and reading patch tests;
   c. Administration staff for clinic booking and paperwork.
2. Laboratory
   a. Technician (part-time) to process and store patient samples;
   b. Consumables for clinic and laboratory work.

Readers are encouraged for further illustrative examples and a more in-depth review of immune-mediated drug hypersensitivity in South Africa to refer to our article on this topic in the last edition of *Current Allergy and Clinical Immunology*.[3]

The most severe forms of SCAR are toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) with mortality over 35% and 10% respectively.[4,5] In the South African context, these most commonly occur secondary to nevirapine, cotrimoxazole and rifampicin usually in patients with HIV infection, advanced immunosuppression and disseminated TB.[6-8] These patients are often taking at least seven drugs at the time of their reactions and frequently have both TB and additional opportunistic infections. The natural history of TEN and DRESS can lead to the development of sepsis and liver/renal impairment or failure. The patient's nutritional, fluid and skin care requirements often need daily specialised attention. Thus, the optimal care of these patients requires input from multiple specialities - dermatology, intensive care, infectious diseases, hepatology, nephrology, nursing and dietetics. Identifying the offending drug/s requires admission and substantial resources and expertise, especially in the context of either sub-optimal or no available *in vivo* or *in vitro* tests. Consequently, the day-to-day care of these complex drug hypersensitivity reactions encourages multi-disciplinary care team collaboration. Added to this, there is a spectrum of less severe drug hypersensitivity reactions that should be able to access and benefit from multi-disciplinary outpatient services.

STRUCTURE AND NEEDS OF THE MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC

The drug hypersensitivity clinic will be staffed by specialists and trainee specialists including allergologists,

dermatologists, pharmacologists, infectious diseases, hepatologists and nephrologists. Specialist nurses trained in patch testing are already employed but the capacity in this area will be expanded. Both an in-patient referral service as well as an out-patient clinic will be used. The first successful clinic took place on the 11th September 2015. Fortnightly clinics will be started and frequency will be increased as the demand grows. Challenging cases from across the country will be discussed and readers are encouraged to email the authors for further discussions or if they are interested in being a part of this initiative to start a similar clinic in their own centres. The clinic will review any cases where a clinician is concerned about the possibility of an immune-mediated drug hypersensitivity reaction. The clinic will then manage and follow-up patients that fulfil current definitions for these reactions.

In order for a clinic of this nature to deliver an international standard of care, it will have certain basic requirements. Table I outlines these basic requirements under the headings of infrastructure, human resources and consumables. An important aspect for the clinic will be to develop the capacity to provide specialised *in vivo* testing for uncommonly used drugs or immunogenic excipients. For example, skin and intradermal testing protocols to test DHR to biologic therapies such as the TNF*α* blockers, e.g. infliximab, or access to photo patch testing equipment like Dermalight 80 MED and phototherapy units to elucidate photoallergic reactions to excipients such as titanium dioxide. Furthermore, to be fully actualised, the clinic will need to expand its research capacity by:

i. Developing a functional, simple and secure database to store patient information;
ii. Having the ethics and laboratory capacity in place to analyse data, collect and store relevant biological samples including tissue biopsies, peripheral blood mononuclear cells and DNA/RNA; and
iii. Establishing links with local and international collaborators that can help address complex basic science questions and train scientists in the many techniques needed to tackle the science of DHR.

These initiatives will require funding support and the clinic will need to think of innovative methods to acquire the necessary support in the current highly competitive funding environment.

ADVANTAGES OF THE MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC

From the above background and needs of a multidisciplinary drug hypersensitivity clinic, some of the key advantages are already evident. In Table II a summary of these and other additional advantages are listed. A multidisciplinary clinic of this nature is well aligned with the three core pillars of academic medicine:

i. Clinical service;
ii. Teaching; and
iii. Research.

It will be a leading example of inter-disciplinary service and collaboration. If adequately supported, the clinic will provide a platform for care to be delivered at an international standard, focused on locally relevant DHRs. Training for specialists from all the disciplines involved as well as the upskilling of specialist nursing staff will be easy to co-ordinate. It is also hoped that high quality, management-altering research outputs will soon follow as the clinic grows and fosters local and international collaborations.

A multi-disciplinary clinic of this nature will also offer a centralised unit to co-ordinate and fulfil important surveillance and advocacy roles around DHRs. For instance, at present no prevalence data on DHRs from South Africa is available

TABLE II: ADVANTAGES OF THE MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC

1. IMPROVED CLINICAL CARE AND PATIENT SATISFACTION:
   a. In-patient referral service to aid clinicians with diagnostic and management challenges;
   b. Capacity for cutting-edge evaluation of DHRs;
   c. Single clinic visit for management of patients with multiple clinical problems;
   d. Depth of experience built through centralisation of patients with uncommon DHRs.

2. CROSS-CUTTING SURVEILLANCE OF DHR SPECTRUM:
   a. Determining local prevalences and allowing the opportunity to identify new emerging reactions.

3. HUMAN RESOURCE CAPACITY BUILDING AND TRAINING:
   a. Training of specialists in managing DHR;
   b. Training of specialised nurses;
   c. Acquisition and training on state-of-the-art diagnostics (*in vivo* or *in vitro*);
   d. Development of translational laboratory tools.

4. RESEARCH PLATFORM DEVELOPMENT TO ELUCIDATING MECHANISMS AND IDENTIFY USEFUL PREDICTIVE BIOMARKERS:
   a. Hypothesis generation afforded from the opportunity to see the whole spectrum of a single drugs' hypersensitivity reactions;
   b. Systematic data-recording, patient follow-up and link to laboratory to allow optimal translational research platform;
   c. Pooled resources to improve success in accessing funding.

5. ADVOCACY, BOTH IN ACADEMIC AND PUBLIC SPHERES, TO RAISE AWARENESS TO THE BURDEN, MORBIDITY AND MORTALITY ASSOCIATED WITH SEVERE DHRS.

TABLE III: BRINGING IT ALL TOGETHER - THE RIFAMPICIN CASE STUDY

T-CELL MEDIATED DRUG HYPERSENSITIVITY REACTIONS:
1. Severe cutaneous adverse reactions (SCAR).
    b. Fixed drug eruptions;
    c. Lichenoid drug eruptions;
    d. DRESS;
    e. SJS/TEN;
    f. Acute generalised pustulosis.
2. Drug induced liver injury (DILI).
3. Tubular interstitial nephritis (TIN).

MULTIDISCIPLINARY CLINICAL APPROACH:
1. Joint patient review and clinical assessment to allow for the best possible clinical characterisation, with detailed clinical data collection.
2. Where clinically appropriate, ensuring pathological characterisation and tissue immunophenotyping through histology, blood compartment immunophenotyping and the storage of DNA and RNA.
3. Long-term follow-up data.

SAMPLE RESEARCH QUESTIONS THIS PLATFORM ALLOWS US TO TACKLE:
1. Are there any common predisposing factors or clinical characteristics to the above endotypes of rifampicin type IV hypersensitivity?
2. What are the immunological commonalities and differences that underlying the organ-specificity of rifampicin type IV hypersensitivity reactions?
3. Are there any predictive clinical or biomarkers when compared to control populations of HIV-infected and uninfected rifampicin exposed but non reacting patients?
4. What is the clinical and immunological cross-reactivity amongst the rifamycins?

for a number of commonly prescribed drugs including penicillins, rifampicin, or neuromuscular blockers. The lack of this information is a public health concern. In the USA, recent studies have begun to illustrate the consequences of incorrect pencillin allergy 'labelling'. Only about 1 in 20 patients self-reporting to doctors that they are penicillin allergic will have true hypersensitivity. The impacts of this has been shown to include increased antibiotic-related side-effects due to the use of alternatives, increased healthcare cost and length of hospitalisation.[9] It is unknown if there is a similar problem and public health impact in South African hospitals. Similarly, the anaesthetists are struggling with a lack of information about which agents are preferable for South African populations, e.g. which neuromuscular blocker. Is it similar to international data or population specific? Consequently, proposals are already been worked on, together with anaesthetic collaborators and the UCT medicines information centre, to develop a centralised service to link patients experiencing peri- or intra-operative anaphylaxis with allergy testing. A database where anaesthetists could potentially look-up previous DHRs will be developed where future anaesthesia is required. This may in time become a valuable, life-saving resource. Undoubtedly, the clinic will provide a focal point for these and other types of surveillance and advocacy activities.

RIFAMPICIN DRUG HYPERSENSITIVITIES: A STARTING POINT FOR THE CLINIC

South Africa has one of the highest rates of active TB in the world and over 60% of all incident TB cases are HIV co-infected.[10] Thus, TB drug induced hypersensitivity reactions are more common by virtue of increased exposure and hypersensitivity reactions are varied. For instance, rifampicin can cause the full spectrum of immune-mediated DHRs (Figure 1). However, the T-cell mediated type IV reactions are the commonest and usually most serious (Table III).[6] Consequently, the burden and complexity of these rifampicin T-cell mediated reactions are an excellent research area for the new clinic to focus on. In a recent pilot study, it was shown that in DRESS there is no cross-reaction with rifabutin, another equally effective rifamycin. If proven in larger studies, this has major implications in the retention of the more effective first-line regimen for treating TB.[11] In Table III a few of the key broad research questions have briefly been outlined and how the multidisciplinary clinic will address these questions. In addition, the clinic has an already expanding local and international collaborator base to develop the laboratory capacity. It is hoped that these collaborative efforts will be successful and either improve the management or predict the occurrence of these reactions.

CONCLUSION

It is exciting to embark on this new initiative of a multidisciplinary drug hypersensitivity clinic. It is felt that it is long overdue given the ongoing burden of drug hypersensitivity reactions, their varied presentation and complex specific investigation and management requirements. It is hoped that this new platform will allow better management of the needs of the local population and also break new territory in the understanding and preventing of the often disastrous consequences of the medicines that are prescribed.

Other centres in South Africa are encouraged to start similar clinics and a network be developed so that work can be harmonised nationally.

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RJ Green | S Kling | M Levin | E Weinberg

21 October 2015 will go down in the history of medicine in South Africa as an auspicious day. On this day, the first sub-specialist in Allergology passed her examination in the Certificate in Paediatric Allergology. Dr Talita Ferreira-Van der Watt is the first Paediatric Allergologist to achieve this status through examination in South Africa.

The sub-speciality in Allergology has come a long way. Allergology as a Division of Paediatrics started in Cape Town, at the Red Cross Children's Hospital, in the early seventies with Prof Eugene Weinberg joining the department. Prof Paul Potter was the first Fellow to train in Allergology in the early eighties. However, the idea of a formal sub-speciality in Allergology, started in the late nineties when Professors Weinberg and Potter lobbied the College of Medicine and HPCSA to register such a programme and examination. Then, over the last 15 years the work persisted with efforts by Professors Matt Haus, Sharon Kling, Mike Levin and Robin Green to make Allergology, as a recognised sub-speciality, a reality. A few years ago the HPCSA recognised Allergology as a sub-speciality of Paediatrics, Internal Medicine and Family Medicine. Since then just a handful of doctors have been credited as 'Grandfathers' in Allergology. However, much work has continued to formulate Rules and Regulations for examinations and setting up training facilities. Prof Mike Levin has led the charge to get Fellows trained and now Talita has achieved this landmark status.

The examination was in two parts – a written exam of two 3 hour papers in August 2015 and the oral/OSCE exam in October. The panel of examiners for this first exam were:

- Convenor and Examiner: Prof Robin Green
- Examiners: Prof Sharon Kling and Prof Mike Levin
- Moderator: Prof Eugene Weinberg

The examiners and candidate after the first successful Certificate in Paediatric Allergology

It was especially auspicious that Prof Weinberg was part of this first exam. He has brought Allergology to its natural crescendo. From today onward, we trust Allergology will take its place in the forefront of medicine and health, providing a service to needy South Africans with allergic illnesses.

Talita and Mike have set a very high standard in the training and examination of Allergologists. Now we move forward with the crusade to have Departments of Health, around South Africa, provide training posts and services in Allergology.

Peer Review Article

A REVIEW OF THE MANAGEMENT OF OCULAR ALLERGY

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ABSTRACT

The wide array of ocular allergy symptoms, its profound effect on the quality of life and economic burden on the sufferer, underline the need for adequate knowledge of its management options. Primary treatment algorithm includes measures to reduce allergen exposure while medication such as antihistamines, vasoconstrictors and mast-cell stabilisers remain the mainstay management of ocular allergy. Severe cases of ocular allergy may require corticosteroids or immunotherapy.

INTRODUCTION

Traditionally, ocular allergy has been defined as a group of type I and type IV hypersensitivity-mediated ocular surface diseases that include seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), contact dermatoconjunctivitis (CDC) and contact lens-induced papillary conjunctivitis (CLPC).[1] However, IgE and non IgE-mediated mechanisms are involved in the development of ocular allergic diseases.[2] In 2001, the European Academy of Allergy and Clinical Immunology (EAACI)[3] suggested a new classification that distinguishes between allergic and non-allergic hypersensitivity reactions, with allergic diseases being further divided into IgE- and non IgE-mediated hypersensitivities (Table I). The triggering event is the contact of the causative allergen with the conjunctival mucosa and ocular allergy is typically a type 1 IgE-mediated hypersensitivity reaction with cell-mediated Th-2 involvement in some types. SAC and PAC are IgE-mast cell mediated hypersensitivity reactions and are triggered mainly by pollen and dust mites respectively.[2] Both SAC and PAC are comorbidities of rhinitis and asthma[4] and are seldom followed by permanent visual loss.[1] However, the symptoms of SAC and PAC can lead to a significant reduction in quality of life for the patients and their families.[5] AKC and VKC are characterised by chronic inflammation with T-cell infiltration and can potentially cause severe visual complications.[6] CLPC represents chronic inflammation of the tarsal conjunctiva by mechanical trauma such as contact lenses and ocular prosthetics, with the induction of alterations in local inflammatory mediators.[7]

Ocular allergy is often underdiagnosed and undertreated until it reaches severe levels due to various reasons.[8] For example, some patients may seek attention for concomitant atopic disease (i.e. asthma, allergic rhinitis, urticaria, or eczema) and the clinician who is managing those comorbid conditions may overlook the patient's ocular manifestations,[9] contributing to suboptimal management of patients with ocular allergy. The International Study of Asthma and Allergies in Childhood study (ISAAC)[10] has reported allergic conjunctivitis as rhinitis associated with itchy eyes (allergic rhinoconjunctivitis) and not isolated ocular symptoms.[11] Although available prevalence data usually address ocular symptoms such as rhinoconjunctivitis, up to 40% of the population in developed countries have been reported to experience symptoms of ocular allergy.[11] The ISAAC study reported that the prevalence of ocular allergy in developing countries was low but did not assess the prevalence of isolated allergic conjunctivitis. However, the prevalence of allergic conjunctivitis has been reported to be 7.3% in children between 5 and 17 years of age in Nigeria,[12] 7.9% in Gambia,[13] and 9.1% in Ghana.[14] Recent hospital based studies in Nigeria suggest that the prevalence of allergic conjunctivitis is as high as 32%[15] and 42%,[16] suggesting that this is a widespread visual health challenge, affecting people of all ages.

DIAGNOSIS

Ocular allergy is usually diagnosed based on the findings from the patient's history and clinical examination, particularly with a personal or family history of systemic allergic diseases.[17] These characteristic features are important for the clinician to know because they may require different management strategies.

HISTORY

An accurate diagnosis of ocular allergy requires a thorough medical history to elicit characteristic signs and symptoms,

Figure 1: Seasonal and perennial allergic conjunctivitis: mild chemosis and hyperaemia of the palpebral and bulbar conjunctiva

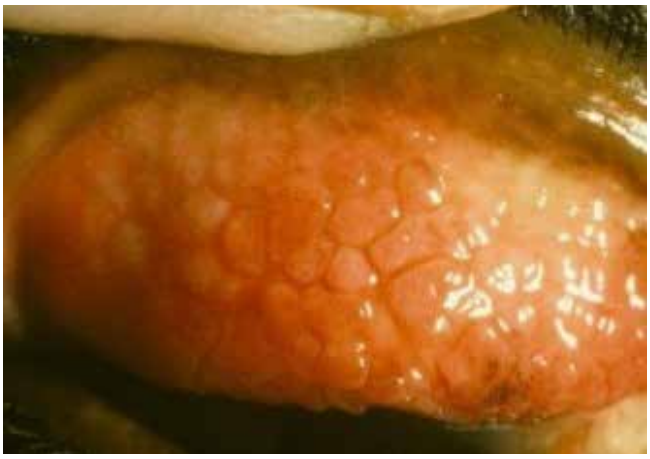

Figure 2: Vernal keratoconjunctivitis: giant papillae of the upper tarsal conjunctiva which can be seen easily by 'flipping' the upper eyelid

the offending agent, the presence of autoimmune and other allergic disorders and medication use for controlling allergy.[17] The clinical presentations include itching, burning, stinging, redness, and swelling/chemosis. Tearing, redness and itching are the most common symptoms and a diagnosis of allergic conjunctivitis should be considered if any patient presents with a chief complaint of itching, together with red, irritated eyes.[18] Itching, particularly aggravating in the nasal quadrant, is the hallmark symptom of ocular allergy. Patients with blepharitis, dry eye and irritative, non-allergic conjunctivitis may also complain of itching that is localised to the eyelids or periorbital skin.[17] Most patients with ocular allergy will also have nasal symptoms (nasal itching, congestion or a runny nose) because the nasal and ocular mucosal tissues react to allergens in a similar way.[17] Allergic conjunctivitis is associated with a watery discharge, which may sometimes contain a small amount of mucus, making a stringy or mucoid discharge. The mucoid discharge can lead clinicians to make an erroneous diagnosis of bacterial conjunctivitis.[17]

TABLE I: DIFFERENTIATING FEATURES OF VARIOUS ALLERGIC EYE DISEASES[2,5,20]

	SAC	PAC	VKC	AKC	CDC	CLPC
HISTORY OF ATOPY	Rhinitis Asthma	Rhinitis Asthma	Variable	Rhinitis Asthma Dermatitis	Variable	Variable
ALLERGIC MECHANISM	IgE-mediated	IgE-mediated	IgE- and non IgE-mediated	IgE- and non IgE-mediated	Non IgE-mediated	Non-allergic
PRESENTATION	Intermittent	Persistent	Persistent ± intermittent exacerbations	Chronic	Chronic ± intermittent exacerbations	Persistent
PREDOMINANT CELL TYPE	Mast cell Eosinophil	Mast cell Eosinophil	Lymphocytes Eosinophil	Lymphocytes Eosinophil	Lymphocytes	Lymphocytes Eosinophil
VISION INVOLVEMENT	Minimal	Minimal	Mild	Severe	Minimal	Minimal
SEASON	Spring, Autumn	Perennial	Spring, Autumn or perennial	Any	No	Any
DISCHARGE	Clear mucoid	Watery	Stringy mucoid	Stringy mucoid	Watery	Clear white/ mucous
CHEMOSIS	+	+	±	±	-	±
CONJUNCTIVA	Follicles and/or papillae	Follicles and/ or papillae	Giant papillae	Papillae ± fibrosis	±Hyperaemia Follicles	Giant papillae
CORNEA	-	-	Superficial punctate keratitis ± Ulcer ± Vernal plaque	Superficial punctate keratitis Ulcer, Plaque, Opacities, neovascularisation	-	Rare
EYELIDS	Oedema	± Oedema	Oedema Pseudoptosis	Eczema + meibomitis blepharitis	Erythema, eczema	-
LIMBUS	-	-	± Thickened + Trantas dots	± Thickened ± Trantas dots	-	Hyperaemia
ITCH	+	+	++	++	+	++
GRITTINESS	±	±	±	±	-	+

Figure 3: Atopic keratoconjunctivitis: chemotic eyelid skin with a fine sandpaper-like texture

A history of medication can explain an incomplete clinical picture of allergy in a patient with active disease and identify an underlying cause for problems with dry eye or contact lens discomfort.[17] For example, patients who are using an oral histamine medication may not have prominent itch, but may be suffering from the ocular drying effects of those medications. Asking specifically about agents purchased without a prescription is important considering a large number of clinical and experimental studies have revealed that preservatives in topical ophthalmic medications have been demonstrated to produce effects from inflammation or hypersensitivity to permanent cytotoxic effects involving all structures of the eye.[19]

CLINICAL EXAMINATION

The examination of patients with suspected ocular allergy should involve the inspection of the eyelids, conjunctiva and cornea. SAC and PAC are the most common forms of ocular allergies.[2,5] The signs and symptoms of PAC and SAC are the same, the only difference being the specific allergens to which the patient is allergic.[2,5] Redness (conjunctival injection) and chemosis (conjunctival swelling) tends to be mild to moderate (Figure 1). Itching is a fairly consistent symptom of SAC and PAC and corneal involvement is rare (Table I).

The hallmark sign in VKC is giant cobblestone papillae that appear in the upper palpebral conjunctiva (Figure 2) and patients with VKC may also complain of severe photophobia.[2] Trantas dots appear as small gelatinous nodules at the limbus and consist of clumps of necrotic eosinophils, neutrophils and epithelial cells.[5]

The most characteristic sign of AKC is an oedematous or thickening of the periorbital skin (Figure 3). There is some overlap between the clinical features of VKC and AKC (Table I). For example, a shield ulcer, which is due to the breakdown of the epithelial barrier function, can be seen in both chronic forms of VKC and AKC.

Contact keratoconjunctivitis (CDC) is a form of contact dermatitis that involves the ocular surface, eyelids and periocular skin and can manifest in both atopic and non-atopic individuals.[2] Contact lens induced papillary conjunctivitis (CLPC) is not a true allergy (the stimuli are inert substances rather than allergens) but is an inflammatory disease characterised by papillary hypertrophy of the superior tarsal conjunctiva.[2] The appearance of CLPC is similar to vernal conjunctivitis (Figure 2), but unlike VKC, there is no significant corneal involvement in CLPC (Table I). The differentiating features of various types of ocular allergic diseases in the form of epidemiology, history, and clinical features are summarised in Table I.

MANAGEMENT

The management of ocular allergy is aimed at inhibiting the release of mediators of allergy, controlling the inflammatory cascade and symptoms, and preventing ocular surface damage.[21] Management involves non-pharmacologic and pharmacologic strategies to minimise the negative impact of ocular allergy on the individual's quality of life.[21] It is, therefore, important for the clinician to identify what type of ocular allergy is present, assess the severity, comorbidity and long term risks before instituting an appropriate treatment plan.

NON-PHARMACOLOGIC MANAGEMENT

The first line treatment in most ocular allergic conditions is to identify and avoid the offending allergen.[21] However, the identification and complete avoidance of the offending allergen is not always possible.[21] Table II provides a summary of practical avoidance measures (which focus primarily on environmental control) for common allergens implicated in ocular allergic diseases. In addition to strategies for allergen avoidance, other non-pharmacologic interventions include the use of cold compres ses, cooled preservative free artificial tears or isotonic saline.[21] Cold compresses act as natural decongestants against non-specific irritants and are effective in mild to moderate symptoms of ocular allergy.[21] Frequent dosing (4-8 times a day) with over-the-counter preservative free ocular lubricants, such as artificial tears, improve symptomatic relief by diluting and flushing away allergens[21] and encouraging vasoconstriction to reduce eyelid swelling, chemosis and hyperaemia.[8] Clinicians should advise patients with ocular allergy to use preservative free formulations to avoid any potential hypersensitivity reactions. Similarly, the refrigeration of these products is also helpful as the cold solutions are both soothing and counteract the elevated tissue temperature associated with ocular inflammation.

TOPICAL OCULAR PHARMACOLOGIC MANAGEMENT

ANTIHISTAMINES

Topical antihistamines are the most commonly used agents in the pharmacological management of ocular allergy and are available alone or in combination with vasoconstrictors.[21] Newer generation topical antihistamines, such as emedastine, are more potent, have a longer duration and are well tolerated.[21] The mode of action, effects, dosage and common side effects of topical antihistamines are shown in Table III.

TABLE II: PRACTICAL ALLERGEN AVOIDANCE MEASURES[21]

ALLERGEN	CONTROL MEASURES
POLLEN	Remain indoors with windows closed at peak pollen times. Wear closely fitting, wrap around style sunglasses when outdoors. Use air-conditioning, where possible. Install car pollen filter.
MOULDS	Ensure dry indoor conditions; Use ammonia to remove moulds from bathrooms and other wet spaces.
HOUSE DUST MITES	Provide adequate ventilation to decrease humidity; Wash bedding regularly at 60°C; Encase pillow, mattress and quilt in allergen impermeable covers; Use vacuum cleaner with HEPA filter; Dispose of feather bedding; Remove carpets; Remove curtains, pets and stuffed toys from bedroom.
COCKROACHES	Eradicate cockroaches with appropriate gel-type, non-volatile, insecticides; Eliminate dampness, cracks in floors, ceilings, cover food, wash surfaces, fabrics to remove allergen.
PETS	Remove pets from bedrooms or from the entire home; Vacuum carpets, mattresses and upholstery regularly; Wash pets regularly; Avoid rubbing eyes or nose after being in contact with animals; Wash hands after and clothes which have been in contact with animals.

VASOCONSTRICTORS

Naphazoline, is the most common vasoconstrictor and is also available in a higher strength by prescription.[22] One to 2 drops in each affected eye, 2 to 3 times daily, are required to reach therapeutic levels.[22] Caution should be taken when prescribing vasoconstrictors to patients with hypertension, cardiovascular disease, arrhythmias, diabetes mellitus, hyperthyroidism, or angle-closure glaucoma.[22] They also tend to cause rebound hyperaemia or conjunctivitis medicamentosa with chronic use.[22]

ANTIHISTAMINES/VASOCONSTRICTOR COMBINATIONS

Topical antihistamines (e.g. antazoline or pheniramine) combined with a vasoconstrictor (e.g. naphazoline, tetrahydrozoline, oxymetazoline or phenylephrine) are more effective for the treatment of allergic conjunctivitis, have a quick onset and limited duration of action.[8] However, they are contraindicated in patients with narrow anterior chamber angles as they exhibits the anti-cholinergic effect of mydriasis, which could enhance angle-closure glaucoma attack.[21] Given the potential adverse effects, these products should be used with caution in cases with hypertension, cardiovascular disease and poorly controlled diabetes, and are recommended only for the temporary relief of itching and redness and makes them inappropriate for long-term use.[23]

ANTIHISTAMINE/MAST CELL STABILISER COMBINATIONS

New anti-allergy drugs, such as olopatadine, ketotifen, and azelastine are potent antihistamines and also have mast cell stabilising effect and other activities.[21] Azelastine and epinastine demonstrate mast-cell stabilising and anti-inflammatory properties and have a rapid onset of action.[24]

MAST CELL STABILISERS

Mast cell stabilisers are preventative medications, and therefore, cannot relieve ongoing allergic reactions once histamine and other mediators have been released from mast cells.[21] For example, sodium cromoglycate is a classic mast cell stabiliser with a relatively excellent safety profile and is suitable for long-term prophylaxis and therapeutic management of SAC, vernal keratitis, VKC and GPC.[21] A loading dose is required, following which recommended dosing is 4 to 6 times daily at regular intervals, tapered to three to four daily when symptoms subside.[25] Lodoxamide tromethamine has a faster onset of action and is 2500 times more potent than sodium cromoglycate but has a maximum usage of only 4 weeks.[8] Newer mast cell stabilisers include pemirolast potassium and nedocromil.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDS have no effect on other allergic inflammatory mediators such as histamines and leukotrienes and therefore, their use in the treatment of ocular allergy is limited.[21] Diclofenac sodium, ketorolac, indomethacin, pranoprofen may be an alternative to steroids use due to their effect on itching.[21] NSAIDS should be used with caution in patients who have a triad of asthma, nasal polyposis and aspirin sensitivity because of their risk of causing NSAID-induced respiratory distress in this group.[21]

CORTICOSTEROIDS

Topical corticosteroids are considered most appropriate in chronic ocular allergic conditions.[21] Loteprednol etabonate is regarded as a “soft” steroid due to its safety profile and is a treatment option for patients with allergic ocular inflammation.[21,26] Prednisolone acetate is effective for the treatment of severe inflammatory disorders while the fluorometholone-based steroids are used to treat mild and chronic forms of ocular allergy.[26] Cream-based steroids such as triamcinolone and hydrocortisone are effective in the treatment of periocular inflammation in contact ocular allergy.[26] Steroids are associated with the development of serious ocular adverse effects (Table III) and patients who are prescribed a topical corticosteroid should therefore be carefully monitored by an ophthalmologist, and therapy should be slowly tapered over several days once the condition is under control.[22]

TOPICAL OCULAR IMMUNOSUPRESSIVES

Topical immunomodulators such as cyclosporines and tacrolimus are gaining increasing popularity in the long term treatment of severe allergic eye disease.[1] Topical cyclosporine A 0.05% is lipophilic and therefore requires to be dissolved in an alcohol-oil base, which causes ocular irritation such as burning, tearing, erythema,

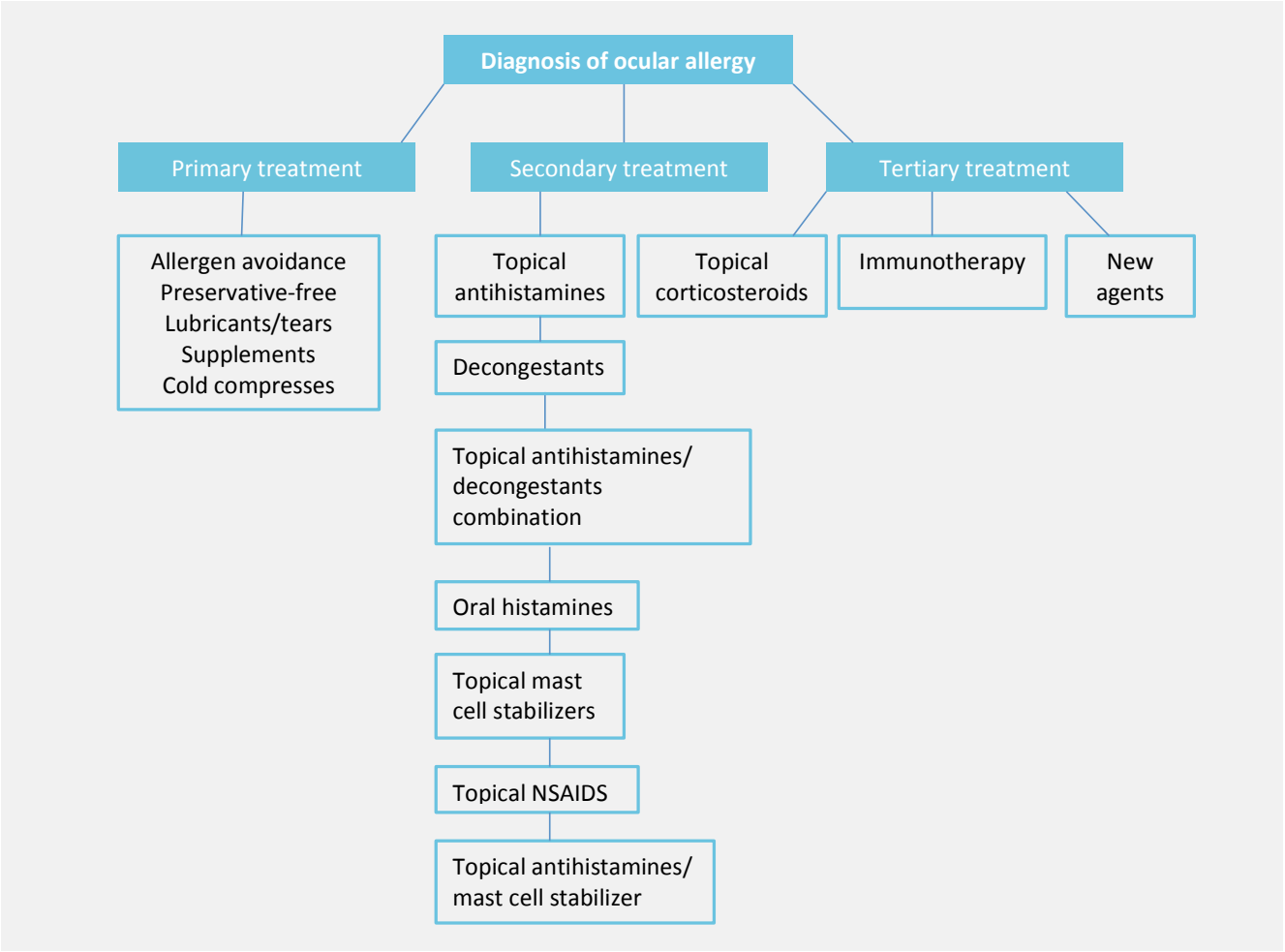

Figure 4: Stepwise approach for the treatment options of various types of allergic ocular disease[1,17]

itching, and headaches after instillation.[1] However, these side effects are not seen with the commercially available cyclosporine A 2% because it is a neutral, hydrophobic cyclic undecapeptide metabolite of the fungus *Tolypocladium inflatum*.[1]

SYSTEMIC PHARMACOLOGIC TREATMENT

ORAL ANTIHISTAMINES

Oral antihistamines are more effective when they are combined with other topical anti-allergic agents.[5] Systemic antihistamines reduce tear production due to their anti-muscuranic action and exacerbates discomfort in the already irritated eye.[5] They should not be used at all in the absence of systemic allergic disease, e.g., rhinoconjunctivitis and patients who are taking systemic antihistamines should be advised to use lubricants eye-drops to sooth the eyes.

SYSTEMIC IMMUNOSUPRESSIVES

In severe cases, resistant to conventional therapy, systemic treatment with T-lymphocyte signal transduction inhibitors such as cyclosporines A or tacrolimus may ameliorate both the dermatologic and ocular manifestations.[27] For instance, systemic cyclosporine A, dosed 2.5 mg/kg/day in divided doses, has been successfully used for the treatment of severe AKC and dry-eye disease.[27] However, potential toxicity restrict long term use of these products.[27]

ANTI-IgE RECOMBINANT

Anti-IgE therapy used in the treatment of allergic rhinitis and asthma may have potential implications for the treatment of ocular allergy.[28] Humanised monoclonal antibodies against IgE such as omalizumab have been reported to be an effective treatment of moderate-to-severe allergic asthma, and for nasal and ocular symptoms of allergic rhinitis.[28] Williams and Sheppard[29] reported that five of their six patients with AKC, that they treated with once or twice monthly omalizumab injections, had a significant improvement of symptoms and only one did not show remarkable changes. Similarly, Sánchez and Cardona[30] reported that use of biweekly injections of omalizumab was effective in a 15-year old boy with VKC who was unresponsive to conventional therapy. Side effects include headaches, hypersensitivity, itching, runny nose, pain or tenderness around the eyes and cheekbones.[28]

SPECIFIC ALLERGEN IMMUNOTHERAPY

This involves exposing the patient to doses of the offending allergen over time to desensitise mast cells, essentially inoculating the patient and resulting in immunity and

TABLE III: DRUGS USED FOR THE TREATMENT OF OCULAR ALLERGIC DISEASES[2,5,17]

CLASS	EXAMPLES	MECHANISM OF ACTION	EFFECT	INDICATIONS	DOSAGE	COMMON SIDE EFFECTS
Antihistamines	Levobastine Emedastine	Histamine receptor antagonist	Relieves itching and redness	PAC, SAC, VKC, AKC	Tds-qid	Ocular burning, dry mouth, somnolence, tiredness and itching, headache (emedastine)
Vasoconstrictors	Oxymetazoline, Naphazoline	Stimulates alpha-adrenergic receptor	Decongestion	PAC, SAC	Tds	Rebound hyperaemia, follicular conjunctivitis, eczematous blepharoconjunctivitis, increase IOP
Antihistamines/ Vasoconstrictor	Pheniramine maleate/ naphazoline	Histamine receptor antagonist and decongestant	Relieves itching and redness	PAC, SAC, VKC	Qid	Conjunctival injection and chemosis, mydriasis, ocular irritation, hypersensitivity, hypertension
Antihistamine/Mast cell stabiliser	Olopatadine, Ketotifen, Epinastine, Azelastine	Histamine receptor antagonist, stabilisation of mast cell degranulation and suppression of activation and infiltration of eosinophils	Relieves itching, redness and oedema with immediate effect	SAC, VKC, AKC	Bd	Headaches (olopatadine) conjunctival injection, headache, and rhinitis (ketotifen), ocular burning, headache, bitter taste (azelatine)
Mast cell stabiliser	Sodium cromoglycate, Lodoxamide	Blocks the release of allergy mediator, chemokines and cytokines by suppressing mast cell degranulation	Used for prophylaxis	SAC, VKC, GPC	Tid-qid	Hyperaemia and blurred vision (lodoxamide). Ocular irritation and burning, stinging, and itching (rare)
NSAIDS	Ketorolac tromethamine	Inhibits prostaglandin and thromboxane synthesis by blocking the cyclooxygenase pathway	Reduces conjunctival hyperaemia and pruritus	PAC, SAC, VKC	Tds-qid	Ocular burning, stinging and itching
Corticosteroids	Loteprednol etabonate, Prednisolone acetate, Dexamethasone	Suppresses migration of polymorphonuclear leukocytes and reverses capillary permeability	Reduces inflammation and cellular infiltrates	Severe allergic diseases	Bd-qid	Cataract, glaucoma, infections, delayed wound healing
Oral antihistamines	Cetirizine, Loratadine, Ebastine, Levocetirizine	H1 receptors antagonists and inhibits ICAM1 and PAF	Reduces pruritus, oedema vasodilatation	Severe allergic conditions	Od, bd	CNS and GIT effects (with 1st generation), dry eye (especially with 2nd generation)
Immunosuppressive	Cyclosporin, Tacrolimus	Cyclosporine inhibits eosinophil infiltration. Tacrolimus blocks T-cells action	Relieves signs and symptoms and reduces steroid use	AKC, VKC	Tds	Burning during instillation

Od = once a day, Bd = two times a day, Tds = three times a day, Qid = four times a day, ICAM = intercellular adhesion molecule, PAF = platelet factor, CNS = central nervous system, GIT = gastrointestinal tract

a decrease in the amount of pharmacotherapy needed.[25,31] Specific allergen immunotherapy treatment has been shown to be more effective than topical and oral medications in the control ocular allergy symptoms.[32] Sublingual immunotherapies have better safety profiles and significantly reduce symptoms in patients with ocular allergy.[33] Reported adverse effects of specific allergen immunotherapy include increased local reactions, anaphylactic reaction and serum sickness (rare).[33] These symptoms can usually be eliminated by adjusting the dosage.[33] However, studies on allergen immunotherapy have predominantly been about rhinoconjunctivitis and have not differentiated the different types and severity of ocular allergy. The authors have acknowledged the deficiencies with the data available for their meta-analysis.[33]

Common ocular allergy drugs, their mode of action and effects, indications, dosage and adverse effects, used in various types of ocular allergy are summarised in Table III and the step by step treatment algorithm is illustrated in Figure 4.

CONCLUSION

Ocular allergy remains a growing public health problem in Africa and many other countries. Environmental factors including changing climatic conditions and extent of pollution (which comes along with urbanisation) may contribute to the increasing prevalence of the condition in Africa. It has also been reported that one of the most commonly seen entities in HIV/AIDS patients is allergic conjunctivitis.[34] Therefore, when a patient with no previous history of ocular allergies presents with new-onset allergic conjunctivitis, it is important for the clinician to rule out underlying HIV. The choice of ocular allergy treatment depends on the severity of the symptoms. The use of non-pharmacological management is not always adequate so anti-allergic medications may become necessary to prevent

and alleviate symptoms. Currently available medications such as antihistamines, vasoconstrictors, mast cell stabilisers, NSAIDS, steroids, and others provide safe and effective management of most cases of ocular allergy. Familiarity with topical ocular and non-ocular pharmacologic treatment, systemic pharmacologic treatments and immunotherapy can result in significant benefits for patients with ocular allergies.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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Consensus Document

THE DIAGNOSIS AND MANAGEMENT OF ALLERGIC RHINITIS: SUMMARY OF RECOMMENDATIONS BY THE SOUTH AFRICAN ALLERGIC RHINITIS WORKING GROUP (SAARWG) 2015

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The SAARWG meeting was sponsored by Aspen Pharmaceuticals.

ABSTRACT

Background: Allergic rhinitis (AR) is a common chronic condition which is often unsatisfactorily diagnosed or treated. Relevant allergens are area-specific hence the need for careful selection for relevance and cost-effectiveness. In this document, the South African Allergic Rhinitis Working Group (SAARWG) aims to address several diagnostic and therapeutic issues related to AR in the South African context.

Recommendations: The diagnosis of AR relies on a sound clinical assessment together with laboratory tests for allergic sensitisation. Tailored screening panels for relevant allergens in South Africa have been devised and are discussed. X-rays and CT scans are generally unnecessary in uncomplicated AR. Component testing can differentiate between allergen-specific and cross-reactive components and aid in the selection of suitable patients for immunotherapy.

Management: The management of AR entails allergen reduction, pharmacotherapy and immunotherapy. Intranasal corticosteroids are the pharmacological treatment of choice for AR and alleviate immediate as well as delayed symptoms. The role of second generation antihistamines and montelukast as add-on treatment for AR is discussed. First generation antihistamines are generally discouraged owing to their unfavourable side-effect profile. Systemic steroids and food restrictions are not recommended in the routine management of AR. Referral to an ear, nose and throat surgeon is recommended in treatment-resistant or complex cases to rule out anatomical or inflammatory complicating factors.

Immunotherapy is the only treatment modality which can alter the natural course of the disease, but is currently unlicensed in South Africa and supply issues remain a concern.

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1. INTRODUCTION

Allergic rhinitis (AR) remains one of the most common and expensive chronic conditions in South Africa and internationally, but as yet remains largely underdiagnosed and inadequately treated.[1] Although AR per se is not a serious condition, its consequences can be serious, including exacerbation of asthma symptoms,[2] increased susceptibility to viral illnesses, comorbidities such as rhinosinusitis and otitis media, disturbance in taste and smell, sleep deprivation and marked reduction in quality of life with reduced productivity at work and school.[3]

In March 2015, the SAARWG met to discuss diagnostic and therapeutic issues related to AR, with the aim of improving overall diagnosis and management of this condition in the South African context. Despite diagnosing and treating patients according to best practice guidelines, both locally and internationally, a significant number of patients remain dissatisfied with clinical outcomes. This meeting aimed to explore this problem.

2. CLINICAL DIAGNOSIS OF ALLERGIC RHINITIS, ASSESSMENT OF SEVERITY AND TREATMENT RESPONSE

2.1 CLINICAL DIAGNOSIS OF ALLERGIC RHINITIS

The diagnosis of AR relies chiefly on a sound clinical assessment together with laboratory tests for allergic sensitisation. The clinical assessment should include a thorough history, taking into account frequency, duration, seasonality and severity of symptoms.[4,5] In South Africa, the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines are widely applied,[2,6] despite a recognition of some of its weaknesses.[7] These guidelines divide symptoms into intermittent or persistent and severity into mild, moderate or severe (Figure 1). A clinical examination should assess for signs of atopy, nasal signs of inferior turbinate swelling/pallor and concomitant allergic diseases such as eczema and asthma. Comorbidities such as rhinosinusitis, otitis media and hearing loss should be assessed for. Equally important is examining for co-existing factors that can also cause nasal obstruction such as nasal polyposis, nasal septal deviation, other internal and external nasal deformities or midfacial hypoplasia. Such factors will be discussed further in Section 7. It is also important to note that nasal obstruction is a late chronic symptom in AR.

Plain film sinus X-rays have no place in the routine diagnosis of AR. Imaging in the form of CT scanning should be reserved for those with poor response to treatment or those with suspected chronic sinus disease and those in whom surgery may be contemplated.

2.2 ASSESSING RESPONSE TO TREATMENT

In assessing the response to treatment, assessments such as **visual analogue scales or allergic rhinitis control tests** could be applied.[8] Ideal control tests need to be reproducible, quick and easy to perform in routine clinical practice and focus on the disease's impact on everyday life. The aim of control tests is to monitor treatment response, detect adverse effects and gauge the need to adjust treatment. Several control tests are available, including the "Control of Allergic Rhinitis and Asthma Test" (CARAT), "Rhinitis Control Assessment Test" (RCAT) and "Allergic Rhinitis Control Test" (ARCT). All are validated but have not been compared in head-to-head trials. The clinician should use the same validated control test consistently and regularly in a patient to monitor the AR.

Nasal patency is a complex clinical issue that can involve mucosal, structural and psychological factors. The perception of nasal obstruction is subjective and does not always correlate with nasal examination. Therefore, a number of more objective measures of nasal patency are available, including:[9]

- Peak Nasal Inspiratory Flow Rate (PNIFR);
- Rhinomanometry;
- Acoustic Rhinometry;
- Optical Rhinometry;
- Allergen-specific Nasal Provocation Testing (ASNPT);
- Mucociliary clearance.

The above tests are generally not easily reproducible or widely applied.

3. LABORATORY TESTING FOR ALLERGIC RHINITIS

Careful history taking remains essential to the diagnosis of allergy and can identify specific triggers in the patient's environment. However, in many patients there may be uncertainty about the allergen or triggers involved in an allergic reaction and a rational and cost-effective approach to laboratory allergy testing should be adopted.

3.1 LABORATORY TESTS AVAILABLE FOR ALLERGEN DETECTION IN ALLERGIC RHINITIS

Clinicians may use the following laboratory tests to assist in the diagnosis of allergic conditions:[10-12]

- Skin prick testing (SPT);
- Specific IgE ELISA tests/"ImmunoCAP" tests (originally referred to as "RAST" testing or radioallergosorbent tests but this terminology is no longer used as the methods have changed to normal ELISA platforms);
- Component testing by specific IgE or microarray (see Section 4);
- Cellular allergen stimulation tests (CAST) for non IgE-mediated allergies (see Section 5).

Total IgE is not a relevant screening test for AR and its use is to be discouraged.[12,13] The choice of SPT versus specific IgE (ImmunoCAP) tests depends on availability, cost and other factors such as concomitant medications. SPT are cost-effective and provide a point-of-care answer, yet need an antihistamine and steroid washout period and are operator- and technique-dependent. For this reason, SPT should be performed by trained clinical personnel

or accredited laboratories in a standardised fashion after adequate antihistamine washout. Specific IgE by ImmunoCAP test are more expensive and results may take a few days or even weeks to be available, yet are standardised, do not require a medication washout period and may be added on to an existing sample within 48 hours if necessary. Both SPT and specific IgE, at cut-off levels of 3 mm and 0.35 kU/L respectively, are considered sensitive for allergy detection, but are not specific (specificity 50%), hence the relevance of low-positive results should be interpreted in the light of history of symptoms.

3.2 SCREENING PANELS FOR ALLERGIC RHINITIS

Previously published local South African allergy guidelines[10-13] have emphasized the regional variability of prevailing aero-allergens and the cost effective use of blood tests, especially when looking for groups or mixes of allergens to assist clinicians and patients to reach a diagnosis and effective treatment as quickly as possible.

The traditionally used "Phadiatop®" blood test is a screening test for aeroallergens designed to differentiate between atopic and non-atopic patients by screening for IgE antibodies to common inhalant allergens. The Phadiatop® test is designed for international use and has not been modified to include the most relevant allergens in South Africa.

The South African Rhinitis Working Group (SAARWG) recognised the need to provide new updated panels of inhalant allergies in the South African setting and created a task force to do this. This task force, the Allergy Diagnostic Working Group (ADWG), consists of representatives from the Allergy Society of South Africa (ALLSA), the National Pathology Group (NPG) and the SAARWG. The taskforce set up a recommended basic screening panel, based on countrywide statistical analysis of laboratory test outcomes and available aeroallergen data.[10] The basic screen should include:

- Bermuda grass;
- Rye grass;
- *Dermatophygoides pteronyssinus;*
- *Blomia tropicalis;*
- *Alternaria alternata;*
- *Cladosporium herbarum;*
- *Aspergillus fumigatus;*
- Cat;
- Dog.

This approach should logically replace the Phadiatop®.

Further testing should be symptom-driven and based on specific geographical regions. For example, in the Western Cape, *Epicoccum* mould and the German cockroach should be considered and in KwaZulu-Natal the oriental cockroach. In the Highveld, Free State and Northwest regions consider adding maize pollen, eucalyptus and weed pollen mix (cosmos and khaki-bush). If patients have *seasonal exacerbations* during springtime, additional testing for tree pollen IgE may be requested (appropriate tree mix screen or the individual tree pollens allergens in the environment).

Food allergy testing should not routinely be performed for allergic rhinitis, unless the patient gives a history of acute reactions to foods involving multiple systems, not just nasal. The clinician should be alerted to the fact that false positive food allergy tests may occur secondary to cross-reactivity between various foods and aeroallergens (e.g. grass pollen can cross-react with wheat, soya or peanut).

3.3 RECENT ADVANCES IN LABORATORY TESTING FOR ALLERGIC RHINITIS AND RELATED CONDITIONS

3.3.1 South African Tree Pollen test

A cost effective tree pollen test strip has been developed by Lancet Laboratories in consultation with one of the leading allergy test manufacturers in Germany (Euroimmun). Advice on which South African trees should be included was obtained from clinical specialists and the SAARWG. One test blot or strip allows a screen of 18 different trees including alder, birch, oak, elm, olive, plane, willow, poplar, ash, white pine, eucalyptus, acacia (salinga), cypress, mulberry, lilac syringe, jacaranda, karee and stinkwood.

3.3.2 Mast Cell Tryptase

Tryptase is a protease released by mast cells and basophils during degranulation. Measuring acutely elevated levels of serum mast cell tryptase (in the active β-form) is diagnostic of anaphylaxis and can help distinguish it from other disorders with similar clinical symptoms.[14,15] Typically, serum mast cell tryptase peaks 1-2 hours after

Figure 1: ARIA Classification of allergic rhinitis

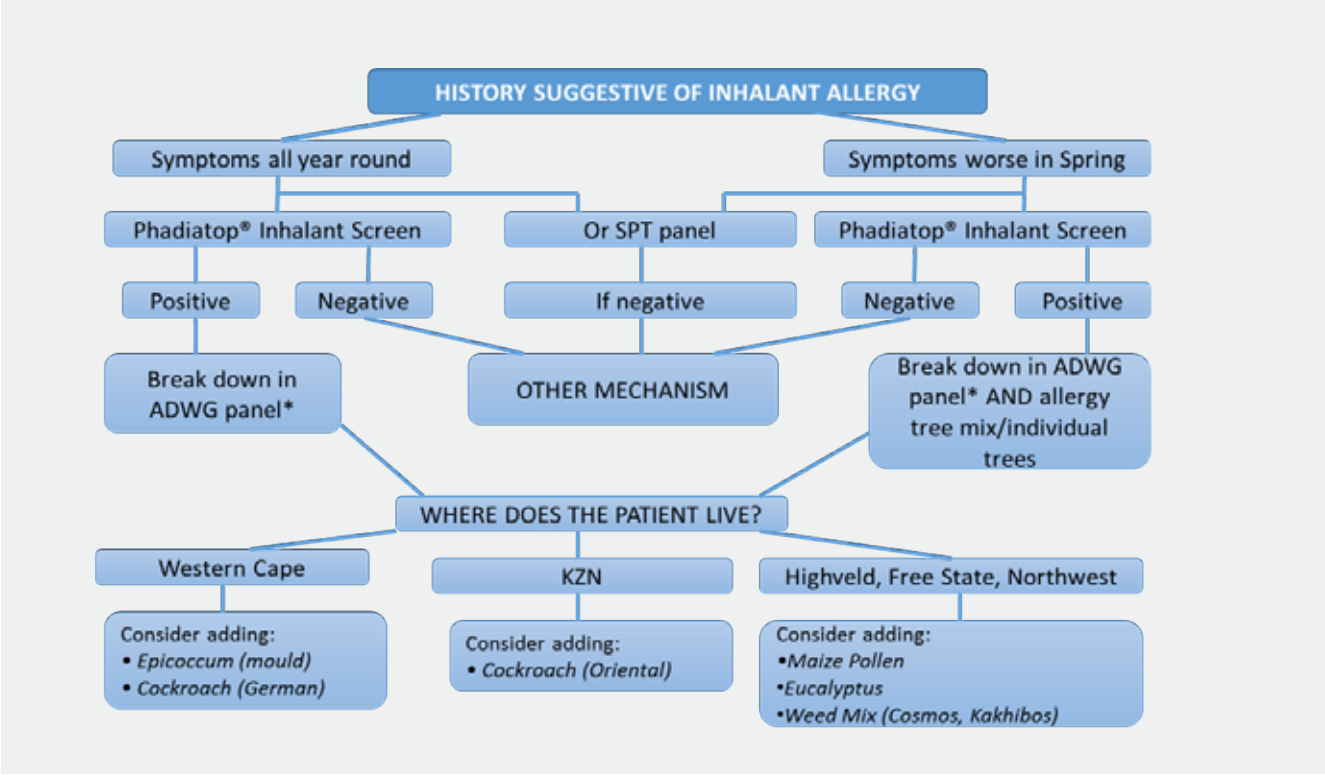

*Figure 2: Suggested Aeroallergen Testing Algorithm (*ADWG panel: Bermuda grass, Rye grass, Dermatophygoides pteronyssinus, Blomia tropicalis, Alternaria alternata, Cladosporium herbarum, Aspergillus fumigatus, cat, dog*

onset of symptoms and remains elevated for 4-6 hours but sometimes up to 12 hours after an episode. Serial levels should be performed. Mast cell tryptase is stable and may be ordered on stored blood to confirm the diagnosis of anaphylaxis.

3.3.3 Molecular Allergology

The role of molecular allergology/component-resolved diagnostics in AR is discussed in detail in Section 4.

4. ROLE OF COMPONENT TESTING IN ALLERGIC RHINITIS

Component tests are available in the form of ImmunoCAP tests for specific components - these need to be requested specifically - or as a microarray test such as the ISAC test (Immuno Solid Phase Allergen Chip test), which tests for 112 food and aeroallergen components simultaneously. These should not form part of screening panels. This testing should stay in the hands of the trained allergists and clinicians with the relevant expertise. Component testing can differentiate between allergen-specific components and cross-reactive components, which in the context of AR, can serve one of the following purposes:[10,16,17]

- Identify and manage cross-reactivity syndromes, e.g. pollen fruit syndrome;
- Identify true positive versus false positive food allergy tests in patients with aeroallergen sensitisation;
- Help in the selection of patients most likely to respond to immunotherapy.

These situations will be elaborated on below.

4.1 IDENTIFICATION OF CROSS-REACTIVITY SYNDROMES, E.G. POLLEN FRUIT SYNDROME[16]

Cross-reactivity may occur when a particular antigen causes an allergic reaction to an unrelated antigen because of amino acid sequence similarities. Patients with pollen allergies are often sensitised to cross-reactive components that occur in pollens as well as foods of plant origin. This can be clinically relevant. Such components include, in increasing order of allergenicity: CCD (cross-reactive carbohydrate determinants), profilins, PR-10 proteins and LTPs (lipid transfer proteins). These components are the cause of the oral allergy syndrome, otherwise known as pollen-fruit syndrome. In this syndrome, the patient usually experiences local oral symptoms upon ingestion of the food which has a cross-reactive component with a pollen, however, systemic symptoms may occur in some cases.

4.2 IDENTIFYING TRUE POSITIVE VERSUS FALSE POSITIVE FOOD ALLERGY TESTS IN PATIENTS WITH AEROALLERGEN SENSITISATION[16]

Certain foods such as peanut, soya and wheat can also share cross-reactive components with pollen allergens and thus come up as a false positive in food allergy testing in patient with AR. In this situation, a good history is critical. Tolerance on regular consumption of the food in question will exclude a true food allergy and the patient should be advised to continue eating the food despite a positive food-specific IgE test.

If there is uncertainty about tolerance to the food,

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E	G	U	I	B	T	S	H	D	X	L	A	C	L	E
J	M	P	R	X	Z	C	Q	R	I	A	X	N	L	K
D	B	R	Y	F	K	F	E	Q	K	Z	P	W	E	X
P	O	K	T	B	N	E	X	O	M	I	S	T	C	W
P	B	Y	K	R	O	M	V	U	X	H	V	N	E	N
Z	E	W	Q	D	D	A	S	P	D	P	X	G	T	G
D	C	P	F	L	O	M	I	S	T	V	M	S	P	Q
U	L	U	O	K	M	Y	W	L	L	F	I	C	R	S
R	A	L	O	R	A	L	E	X	S	D	X	O	H	Z
B	T	W	D	S	Z	U	N	N	Y	M	P	H	H	M
F	E	X	O	C	P	P	T	K	P	J	G	W	U	U
K	X	L	E	Z	F	P	E	B	Q	Q	K	K	Z	O

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component testing may help, e.g. for peanut allergy, the storage components Ara h 1,2,3,6 are more likely to reflect a true allergy, whereas the cross-reactive components Ara h 5,8,9 may represent a false positive cross-reactivity. For soya, positive Gly m 5 and 6 are more likely to reflect true allergy than the component Gly m 4, a PR-10 protein. For wheat, omega-5 gliadin is most likely to reflect a true wheat allergy.

4.3 HELPING IN THE SELECTION OF PATIENTS MOST LIKELY TO RESPOND TO IMMUNOTHERAPY[17]

Grass pollen immunotherapy: Specific markers indicate the likelihood of success of grass pollen immunotherapy:

- Cyn d 1 or grass group 1 allergen for Bermuda grass allergy;
- Phl p 1 or grass group 1 and Phl p 5 or grass group 5 for Timothy grass allergy. However, there is a lot of similarity between the group 1 and group 5 grass pollen allergen components in other grass species, especially those belonging to the Pooidae subfamily, e.g. Timothy and Rye grass. Patients sensitised to Phl p 1 only and not to any of the other allergen components in Timothy grass, are probably sensitised to Bermuda grass and/or maize pollen and not to Timothy or Rye grass.

Cat: Fel d 1, cat uteroglobin is a marker of primary sensitisation and predicts successful immunotherapy. Fel d 2 (cat serum albumin) is likely to cross-react with most other mammalian albumins and Fel d 4, a lipocalin, cross-reacts with horse, dog and cow. If a patient is Fel d 2 or 4 positive in the absence of Fel d 1 positivity, immunotherapy is not recommended.

Dog: Can f 1 and Can f 2 are lipocalins and are associated with primary sensitisation to dog. Can f 1 sensitisation predicts successful immunotherapy. Can f 5, a prostatic allergen secreted by male dogs only, is also an indicator of primary sensitizer to male dogs, but immunotherapy is not recommended in the absence of Can f 1 positivity.

Horse: Equ c 1, a horse lipocalin, is the major allergen in horse dander, but results should be interpreted in correlation with the clinical history, as there is some cross-reactivity with mouse and cat lipocalin.

House dust mite: Sensitisation to D pter 1 (cysteine protease) and D pter 2 (NPC protein) indicate true house dust mite sensitisation. D pter 10 (tropomyosin) cross-reacts with shellfish and other insects - immunotherapy is not recommended if D pter 10 is positive but D pter 1 and 2 are negative.

Blomia tropicalis does not cross-react significantly with other house dust mites, hence a separate B. Tropicalis vaccine is needed for Blomia tropicalis positive patients. The component Blo t 5 is currently only available on ISAC testing.

5. ROLE OF OTHER TESTS IN AEROALLERGEN SENSITISATION

The use of alternative basophil-activation based tests such as the CAST (Cellular Antigen Stimulation Test) may be considered for non IgE-mediated mechanisms of aeroallergen sensitisation.[10] However, these tests need further validation on a larger scale level before they can be routinely recommended.

6. MANAGEMENT OF ALLERGIC RHINITIS

Management of AR consists of the 3 pillars of:

a. Allergen reduction strategies;
b. Pharmacological treatment:
    - Topical intranasal corticosteroids;
c. Antihistamines;
    - Leukotriene inhibitors;
    - Antibiotics;
    - Other.
d. Immunotherapy.

Allergen reduction strategies have previously been described and are not further discussed in this document.

6.1 PHARMACOLOGICAL TREATMENT OF ALLERGIC RHINITIS

6.1.1. Intranasal corticosteroids

Intranasal corticosteroids are recommended as first line treatment for AR in both adults and children. This recommendation comes from the ARIA revised guidelines (2010) as well as more recent guidelines such as the American "Guidelines on the Management of Allergic Rhinitis" published in February 2015.[18]

Intranasal corticosteroids are effective for both intermittent and persistent AR, as well as for other chronic nasal conditions.[19] They have a profound effect on inflammatory response by suppressing many elements of the inflammatory cascade, reducing eosinophil infiltration and suppressing cytokine production. Their clinical efficacy begins after 1-3 days of use and peaks after 2-3 weeks. Intranasal corticosteroids inhibit both the immediate and delayed phases of the allergic response in AR. Placebo-controlled clinical trials demonstrate their effectiveness in the reduction of nasal symptoms including sneezing, itching, rhinorrhoea and congestion, in both adults and children with AR. They are the treatment of choice in patients with any element of nasal congestion. Combination therapy is generally not much more effective than monotherapy with intranasal corticosteroids, but can be tried in patients with severe or persistent symptoms.

The efficacy of available intranasal corticosteroid molecules is generally comparable, with reduction in symptoms of 40-80% achieved in most clinical studies.[20]

Intranasal corticosteroid molecules available in South

Africa include:
- Beclomethasone;
- Budesonide;
- Triamcinolone;
- Mometasone;
- Fluticasone proprionate;
- Fluticasone furoate;
- Ciclesonide.

No single molecule has been consistently deemed better than another. All are consistently superior to placebo.[20] Many clinicians and patients are reluctant to use intranasal steroids because of the concern of local and systemic side effects. The available molecules are all considered generally safe with minimal local side effects (e.g. stinging, nose bleeds occurring in 5-10% of patients) or systemic side effects.[21] The more lipophilic the molecule, the more increased the local binding and reduced systemic availability is. Systemic bioavailability of swallowed topical intranasal steroid is low (<1%) for fluticasone, mometasone and ciclesonide and higher (30-40%) for beclomethasone and budesonide.[22]

Suppression of the HPA axis is generally considered negligible with intranasal steroid sprays, although the molecule beclomethasone may have an effect on growth velocity.[22] Safety aspects should be taken into consideration especially in children and in those on multiple sources of topical steroids (such as inhaled corticosteroids for asthma, topical corticosteroids for the skin) which may have a cumulative effect.

Cushing's syndrome has been described with the chronic use of beclomethasone drops.[23] The long-term use of intranasal beclomethasone, particularly in the drop form with its higher nasal and pharyngeal absorption and bioavailability, should be discouraged.

Higher dose intranasal corticosteroid "nasules" with extremely low reported bioavailability, e.g. fluticasone, may be used where rhinitis is difficult to control and anatomical issues have been excluded.

6.1.2 Antihistamines

Histamine is pivotal in the allergic response and antihistamines act as inverse agonists to dampen the effects of released histamine.[24]

The first generation antihistamines (chlorphenamine, promethazine, hydroxyzine) have poor receptor selectivity and a high propensity towards central nervous system side effects. They have no place in routine management of AR.[24,25] Recently their anti-muscurinic effect has been identified as a factor accelerating cognitive decline in Alzheimer's disease.[26]

The second generation antihistamines have fewer side effects, better receptor selectivity and no tachyphylaxis and are the antihistamines of choice in the management of AR.[27,28] Antihistamines are particularly useful when pruritis, sneezing and rhinorrhoea are predominant symptoms. Generally, the reduction in symptoms achieved by antihistamines for congestion (nasal obstruction) is significantly less than that achieved by intranasal corticosteroids.[29]

Antihistamines can be used as add-on treatment to intranasal corticosteroids to aid in the pruritis and rhinorrhoea control.[30] Antihistamines may be needed as a first line treatment in certain situations such as when there is reluctance to take intranasal corticosteroids (e.g. in children), predominant itch/sneeze symptoms and also as rescue therapy when symptoms are severe. Their onset of action is generally fast (between 1-3 hours), however, maximal effect is reached only after 2 weeks of continuous use.

Most second generation antihistamines have a prolonged action and need once daily dosing. The exception is in young children <6 years age, who have faster elimination and may need twice daily dosing for certain antihistamines such as cetirizine and levocetirizine.[31]

Available second generation antihistamines in South Africa are:
- Cetirizine;
- Levocetirizine;
- Loratadine;
- Desloratadine;
- Fexofenadine;
- Rupatadine.

Efficacy studies show a clear benefit over placebo for all of the above antihistamines. Currently, no one antihistamine has been found to be consistently more efficacious than another.[32] Rupatadine, a molecule newly available in SA, has a dual antihistamine as well as antiplatelet activating factor (anti-PAF) effect. A theoretical advantage is reduced nasal congestion but in clinical practice this has not been proven as superior to other antihistamines.[33]

If the patient has an inadequate response to a particular antihistamine, another second generation antihistamine may be tried.

Choice of antihistamine should be affected by:[27,28,32]
- Side effects profile: In the second generation antihistamines up to 30% of drug may pass through the blood brain barrier, so somnolence may still be an issue. This is greater for cetirizine and lower for fexofenadine. Patient variability is high with regards to central nervous system side effects.
- Metabolic interactions: Loratadine, desloratadine and rupatadine are metabolised in the liver utilising the CYP450 enzyme system and are thus more prone to

TABLE I: DIAGNOSTIC CRITERIA FOR ACUTE BACTERIAL RHINOSINUSITIS

Anterior/Post nasal discharge .
OR
Nasal obstruction
±
Facial pain/pressure
±
Change in sense of smell

Together with:
- Severe lasting purulence or fever;
- Worsening of symptoms (2nd sickening) starting usually within 10 days of onset of illness;
- With symptoms lasting a total of >10 days and <3 months.

drug interactions with enzyme inhibitors. Fexofenadine can be bound by aluminium and magnesium-containing antacids.
- Cost and reimbursement.
- Special situations: All of the above-listed antihistamines are licensed for use in children in South Africa,[34,35] some for younger children (e.g. from 6 months onwards for fexofenadine) and some currently for older children (e.g. over 12 years for rupatadine).
- In pregnancy, cetirizine, loratadine and levocetirizine are considered safe but more studies are required. Fexofenadine and desloratadine have been shown to cause reduction in size in animal foetuses, hence, are currently not recommended during pregnancy.

Antihistamines do not prevent asthma in children with AR and/or eczema. Antihistamines should not be used in the treatment of viral upper respiratory tract infections. The SA Allergic Rhinitis Working Group particularly discourages the use of older generation antihistamines in combination with oral corticosteroids or systemic decongestants for the treatment of "colds." These carry a serious risk of side effects.

6.1.3 Montelukast

The leukotriene receptor antagonists are licensed in South Africa for the use of AR in patients with concomitant asthma. In general, montelukast is better than placebo but not as effective as intranasal corticosteroids or antihistamines.[36,37] Therefore, they should not be used as first line agents for AR, or as monotherapy. They do play a potential role as an add-on therapy in patients with predominant symptoms of nasal congestion, with some studies showing better improvement in night-time symptoms and congestion compared with antihistamines.[38-41] In this situation, they should be tried for periods of at least 4-6 weeks to assess their effect. Antihistamine plus montelukast combination is very costly with minimal benefit over the individual therapies.

Recent concerns have been published about central nervous system (e.g. sleep disturbance) and psychiatric side effects (e.g. depression) with montelukast in a small percentage of paediatric patients.[42] This is rare but the clinician should be aware of such side effects. Cost-benefit ratio also needs to be taken into consideration.

6.1.4 The role of antibiotics in the management of allergic rhinitis and its complications

Uncomplicated AR does not benefit from antibiotic treatment. However, antibiotics are recommended for the co-morbidity of acute bacterial rhinosinusitis. In adults, antibiotic treatment is recommended for a minimum of 5 days and for children 7-10 days. In adults, the number needed to treat for clear benefit with antibiotics is 13 for acute rhinosinusitis. The diagnostic features and guidelines for antibiotics of choice for acute bacterial rhinosinusitis are depicted in Tables I-III.[43]

Antibiotics, specifically macrolides, can be used for their anti-inflammatory effect, anti-neutrophilic effect as well as for promotion of mucociliary clearance in the following situations:[44]

TABLE II: ANTIBIOTICS RECOMMENDATIONS FOR ADULTS WITH ACUTE BACTERIAL RHINOSINUSITIS

IMMEDIATE CHOICE		FAILURE OF TREATMENT (AFTER 48-72 HOURS)	
RECOMMENDED DRUG OF CHOICE	ALTERNATIVE IF PENICILLIN ALLERGIC	RECOMMENDED DRUG OF CHOICE	ALTERNATIVE TREATMENT
Amoxicillin (1 g twice daily for 5 days)	Telithromycin (800 mg daily) Gemifloxacin (320 mg daily) Levofloxacin (500 mg twice daily or 750 mg daily) Moxifloxacin (400 mg daily) ALL 5 DAYS	Amoxicillin-clavulanate (2 g SR twice daily if not used previously) Gemifloxacin (320 mg daily) Levofloxacin (500 mg twice daily or 750 mg daily) Moxifloxacin (400 mg daily) Clindamycin (450 mg three times daily) ALL THE ABOVE 7-10 DAYS, or Ceftriaxone (1-2 g daily for 3 days IV/IM)	Refer to ENT specialist for further evaluation and management.
OR			
Amoxicillin-clavulanate (2g SR twice daily OR 1 g amoxicillin-clavulanate+1g amoxicillin BD) Cefuroxime (1 g twice daily) Cefpodoxime (400 mg twice daily) ALL FOR 5 DAYS			

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- Recurrent upper respiratory infections (e.g. in those with immune deficiencies);
- Those at high risk of lower respiratory tract infections (e.g. cystic fibrosis, recurrent bronchitis);
- Chronic rhinosinusitis;
- Nasal polyps.

Dosing regimens in these situations are not standardised and the minimum duration of therapy should be 6 weeks. The impact of long term macrolide use on antibiotic resistance warrants careful monitoring.

6.1.5 Other treatment modalities in allergic rhinitis

Nasal douching or use of saline nasal sprays is encouraged in both AR and acute or chronic rhinosinusitis. Saline use is of particular benefit to rinse the nose before the use of intranasal corticosteroids.

Any form of systemic steroids or over-the-counter first generation antihistamine combinations is to be strongly discouraged in the routine use for AR treatment. Avoidance of certain foods such as wheat or dairy is generally discouraged for AR in the absence of other clear signs of food allergy involving other systems.

6.2 IMMUNOTHERAPY

Immunotherapy to aeroallergens is the only possible treatment with disease-altering effects in AR. Immunotherapy should be considered in patients who have an inadequate response to pharmacotherapy and avoidance techniques and in whom a thorough nasal examination has failed to reveal structural issues that could be hampering management. It is especially useful in mono-sensitised patients. Immunotherapy for aeroallergens is available in the subcutaneous and (increasingly popular) sublingual forms. Sublingual drops/sprays are currently not licensed in South Africa but available with special Medicines Control Council (MCC) approval.

Patients on immunotherapy should be monitored regularly for efficacy and side effects. Side effects are generally mild and localised and the treatment can usually be continued.[45] However, recent local supply problems with sublingual immunotherapy as well as subcutaneous immunotherapy have hampered their use and threatened the continuity of treatment. The SAARWG endeavours to promote the continued availability of sublingual immunotherapy in South Africa. Of promise is oral immunotherapy tablets for grass and house dust mite. The ideal situation would be obtaining MCC licensing status in South Africa for immunotherapy, which will make immunotherapy much more readily available.

7. POSSIBLE REASONS FOR TREATMENT FAILURE IN ALLERGIC RHINITIS

Poor compliance, incorrect choice of medications, incorrect administration of medications, incorrect diagnosis or confounding diagnostic factors should be considered in poor treatment response in AR.[46] A vital part of AR diagnosis and follow-up is a thorough nasal examination as well as examination of facial features and shape. Poor response to a good treatment regime should prompt referral to an ENT specialist for further evaluation and nasal endoscopic examination of the nose and adenoids. Lateral plain film X-rays of the neck are unreliable for nasal and adenoidal

TABLE III: ANTIBIOTIC RECOMMENDATIONS IN CHILDREN WITH ACUTE BACTERIAL RHINOSINUSITIS (± ACUTE OTITIS MEDIA)

IMMEDIATE CHOICE		FAILURE OF TREATMENT (AFTER 48-72 HOURS)	
RECOMMENDED DRUG OF CHOICE	ALTERNATIVE IF NON-TYPE 1 PENICILLIN ALLERGIC	RECOMMENDED DRUG OF CHOICE	ALTERNATIVE TREATMENT
Amoxicillin (80-90 mg/kg/day in 2 divided doses) <2 yr: 7-10 days >2 yr: 5-7 days	**Azithromycin** (10 mg/kg/day for 3 days) **Clarythromycin** (7.5-15 mg/kg twice daily for 5-7 days) **Erythromycin estolate** (40 mg/kg twice daily for 7-10 days)	**Amoxicillin-clavulanate** (90 mg/kg/day amoxicillin + 6.4 mg/kg/day clavulanate in 2 divided doses) <2 yr: 10 days >2 yr: 7 days	**Ceftriaxone** (50 mg/kg/day IM or IV for 3 days) **Clindamycin** (30-50 mg/kg/day in 3 divided doses for 5 days) ± 3rd generation cephalosporin
OR	ALTERNATIVE TREATMENT IF PENICILLIN ALLERGY TYPE 1	OR	ANTIBIOTIC FAILURE/SEVERE TOXICITY/ PROGRESSIVE MIDDLE EAR INFECTION
Amoxicillin-clavulanate (90 mg/kg/day amoxicillin + 6.4 mg/kg/day clavulanate) in 2 divided doses) **Cefuroxime** (30 mg/kg/day in 2 divided doses) **Cefpodoxime** (16 mg/kg/day in 2 divided doses) <2 yr: 7-10 days >2 yr: 5-7 days	**Levofloxacin** (10-20 mg/kg/day in 1-2 divided doses for 5-7 days)	**Ceftriaxone** (50 mg/kg/day IM or IV for 3 days)	Refer to ENT specialist for further evaluation and management.

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TABLE IV: POSSIBLE REASONS FOR POOR RESPONSE TO TREATMENT[46]

1. Compliance issues.
2. Poor management choices:
   - Incorrect/inappropriate choices or administration technique;
   - Choice of drug, dose and combinations.
3. Poor Diagnosis:
   a. Inadequate knowledge base/skills.
4. Anatomical issues:
   a. Syndromes (e.g. Downs, cleft palates, choanal atresia, brachycephaly);
   b. Common anatomical issues such as septal deviations or nasal shape.
5. Inflammatory diseases which may also co-exist with allergic rhinitis.
   a. Inflammatory rhinitis:
      - Mucosal & mucociliary defects including cystic fibrosis;
      - Immune defects;
      - Non-allergic rhinitis including irritant exposure at work and during leisure (e.g. swimming);
      - Smoking;
      - Substance abuse – including rhinitis medicamentosa;
      - Alcohol;
      - Traumatic rhinitis including surgery.
      - Adenoidal hypertrophy.
      - Chronic sinusitis with polyposis.
      - Chronic sinusitis without polyposis.
      - Granulomatous disease (e.g. TB, Sarcoid, Wegener's, HIV).
6. Traumatic injury to the nose
   a. Septal;
   b. Nasal supra-structure;
   c. Adhesions;
7. Tumours.
8. Foreign Bodies.

pathology. A CT scan of the sinuses is recommended before any sinus surgery is planned.

Possible reasons for failure of adequate response to AR treatment are outlined in Table IV.

8. CONCLUSIONS/SUMMARY

- Allergic rhinitis (AR) is an under-recognised and undertreated chronic condition.
- The diagnosis of AR relies chiefly on a sound clinical assessment together with laboratory tests for allergic sensitisation. There is no place for routine X-rays in diagnosis of AR or adenoidal hypertrophy. CT scan of the sinuses and nose should be considered in co-morbid cases or when sinus surgery is planned.
- Response to treatment should be monitored by regular clinical assessments, visual analogue scales or AR control tests.
- Total IgE is not recommended for AR diagnosis.
- Specific sensitisation to aeroallergens can be identified using either skin prick tests or serum specific IgE tests (ImmunoCAP tests).
- The Allergy Diagnostic Working Group (ADWG) suggests that, in South Africa, the basic screening test should include: Bermuda grass, Rye grass, *Dermatophygoides pteronyssinus, Blomia tropicalis, Alternaria alternata, Cladosporium herbarum, Aspergillus fumigatus,* Cat and Dog. Further testing should be symptom-driven and based on specific geographical regions.
- Component testing can differentiate between allergen-specific components and cross-reactive components, which in the context of AR, can help in identification of pollen-food cross-reactivity and also in the selection of suitable patients for aeroallergen immunotherapy.
- Management of AR depends on the 3 pillars of allergen reduction, pharmacotherapy and immunotherapy.
- Intranasal corticosteroids are the treatment of choice for AR and alleviate symptoms in the immediate as well as delayed phases of the AR response. Molecules available are largely equivalent in their efficacy and should be chosen based on side effect profile, cost and patient choice.
- Second generation antihistamines can be used in addition to intranasal corticosteroids, and in some situations as monotherapy (especially when itch and rhinorrhoea rather than congestion are predominant symptoms). They can also be used in shorter courses as rescue therapy due to their quick onset of action.
- Efficacy of second generation antihistamines is generally comparable and choice of drug depends on side effect profile, potential metabolic interactions, cost, age of patient and availability.
- First generation antihistamines are generally discouraged in AR owing to their unfavourable side effect profile.
- Antihistamines are not effective for the common cold and are not effective in the prevention of asthma in children with atopic disease.
- Montelukast may be used in addition to other treatment modalities as an anti-inflammatory, especially in patients with concomitant asthma. It should not be used as a first line agent in AR.
- Systemic steroids are not recommended for the routine management of AR.
- There is no evidence for dietary restrictions in the management of AR.
- Immunotherapy is the only treatment modality which can alter the natural course of the disease. Currently there are supply issues with immunotherapy. Registration and licensing with the MCC remains a problem adding to logistical and cost issues.
- If response to treatment in AR is inadequate, the clinician should consider factors such as treatment choice, adherence to treatment, concomitant anatomical or inflammatory conditions or trauma/tumours.
- Referral to an ENT surgeon is recommended in treatment resistant or complex cases to rule out anatomical or inflammatory complicating factors.

DECLARATION OF CONFLICTS OF INTEREST:

The SAARWG meeting was sponsored by Aspen Pharmaceuticals. The authors declare no conflict of interest.

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Allergies in the workplace

OCCUPATIONAL ALLERGIC RHINITIS IN A LABORATORY WORKER DUE TO MOULD CONTAMINATION IN A WATER-DAMAGED HOSPITAL BUILDING

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ABSTRACT

Mould exposure from water-damaged buildings and indoor dampness has been associated with allergies, infections and irritation, however, the immune mechanisms are complex. Occupational rhinitis is referred to as an inflammatory disease of the nose characterised by intermittent or persistent symptoms (nasal congestion, sneezing, rhinorrhoea, itching) and/or variable airflow limitation and/or hypersecretion attributable to a particular work environment and not to stimuli encountered outside the workplace. The purpose of this case report is to highlight the challenges in evaluating the relationship between mould exposure in water-damaged buildings and suspected allergic rhinitis.

The case report is one of probable occupational rhinitis caused by sensitisation to *Alternaria alternata* and *Aspergillus sp.* The 52-year-old patient experienced recurring nasal polyps and sinus infection and underwent several operations. Patient serum tests to the mould mixture and specific moulds using the UniCAP system (Pharmacia, Sweden) revealed moderate to elevated IgE levels for various mould allergens. Paint scrapings and swab samples collected from her work environment revealed the presence of *Aspergillus sp* and *Alternaria* amongst other moulds, which she was sensitised to. Her condition improved after the building was repaired.

INTRODUCTION

Allergic rhinitis is the most common chronic disease caused by a nasal reaction to allergens, (e.g. pollen and fungal spores) through an IgE-mediated inflammation.[1,2,3] The prevalence of allergic rhinitis is increasing globally[4] affecting approximately 10-40% of the population[1] and is a common and persistent disease in South Africa.[4,5]

Work related rhinitis (Figure 1)[6] can be occupationally caused as a result of exposure to specific agents in the work environment or work-exacerbated when pre-existing rhinitis is worsened by non-specific workplace exposures. These could be irritant agents, (e.g. chemicals, dusts, fumes), physical factors (e.g. temperature changes), emotions, second hand smoke and strong smells (e.g. perfumes).[6] Symptoms can be intermittent or persistent and include nasal obstruction (congestion or blockage), sneezing, rhinorrhoea, nasal itching and post nasal drip.[1-2,5-8] Nasal congestion is the most common and troublesome symptom which occurs in up to 90% of patients.[3,7] Patients can also suffer from insomnia, fatigue, irritability, memory and/or learning deficit.[3]

There is increasing evidence that the work environment contributes significantly to the burden of rhinitis and asthma worldwide, negatively affecting the quality of life, work ability and socioeconomic status.[9]

Various studies have reported an association between exposure to fungal (mould) spores and allergic rhinitis.[10]

Excessive moisture in buildings promotes mould growth and is associated with an increased prevalence of allergy, infection and irritation.[11] The most common airborne moulds implicated include species of *Alternaria*, *Aspergillus*, *Cladosporium* and *Penicillium*. Atopic individuals exposed to aerosolised moulds develop an IgE-mediated response due to spores infiltrating the sinuses.[12,13] A study conducted by Seedat et al. at Universitas Academic Hospital in Bloemfontein reported a high prevalence of sensitisation to moulds (26%) in patients with allergic rhinitis.[7] Studies in the United States and elsewhere, report that sensitisation to *Alternaria* is common[14] and is strongly associated with allergic rhinitis.[10] Evaluations in clinical practice are challenging since damp building related illnesses have similar symptoms to other clinical conditions such as rhinitis, asthma, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis and allergic fungal sinusitis (AFS).[15,16] In general, the diagnosis of allergic rhinitis is based on a positive history, clinical signs, assessment of atopy, initial *in vitro* or *in vivo* screening (measurements of specific IgE antibodies and/or by skin prick tests (SPT) with allergens. For example, fungal extract mixtures using the most common species (*Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria alternata* and *Candida albicans*) known to induce allergic reactions. This should be followed by confirmatory tests or nasal provocation challenges, e.g. with single specific mould extracts to define the specific cause of sensitisation.[5-7,9] In an individual with symptoms of rhinitis and a suggestive occupational history, accompanied by positive immunological tests to the specific allergen known to be present in the workplace, a diagnosis of probable occupational rhinitis should be considered.[9] The purpose of this case report is to present a case of probable occupational allergic rhinitis due to mould exposure in a laboratory known to have a leaking roof predisposing it to damp and mould contamination.

CASE REPORT

PATIENT HISTORY

The patient is a 52-year-old female with atopic asthma. She is a non-smoker and has been employed for 5 years as a manager in a medical laboratory which is situated inside a public hospital building. Her main job task is managing and working in the haematology laboratory. In November 2012, she presented to the National Institute for Occupational Health (NIOH) Clinic complaining of intermittent blocked nose and headaches. She was using a corticosteroid nasal spray (27.5 mcg fluticasone furoate). She reported suffering from allergic symptoms for the past 10 years but her symptoms flared up in the preceding 3 years of her current presentation. The symptoms usually lasted for a number of hours while at work and decreased substantially when at home. She had consulted an otolaryngologist since 2009 and was diagnosed as having chronic allergic fungal sinusitis (AFS). On further enquiry there appeared to be insufficient clinical evidence from the clinician to support this diagnosis (information of findings from CT scan, nasal polyp histology, etc. were not reported).[17,18] She experienced recurring nasal polyps and sinus

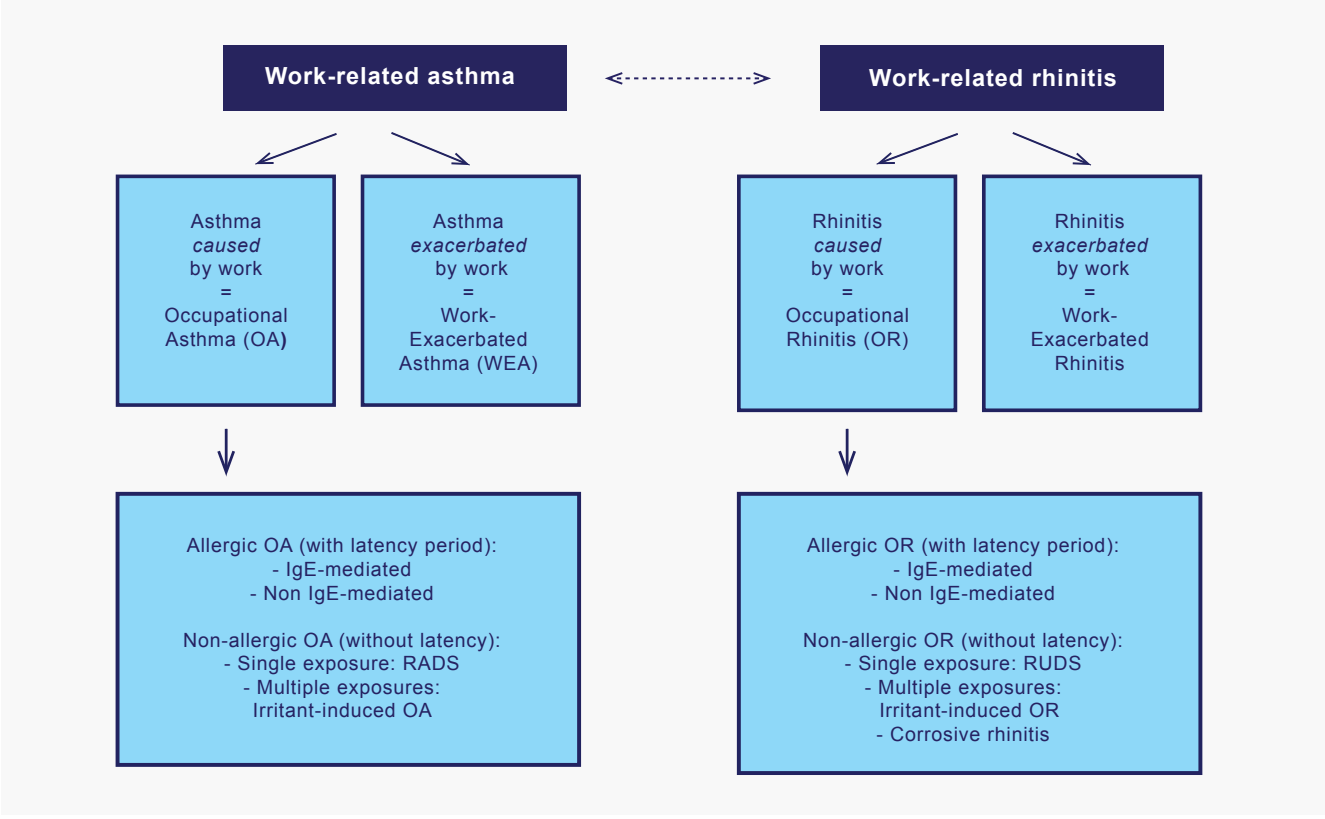

Figure 1: Classification of occupational rhinitis and asthma[6]

TABLE I: PATIENT SERUM IgE PROFILE FOR SENSITIVITY TO MOULD MIXTURE INHALANT AND SPECIFIC MOULD ALLERGENS BEFORE (2012) AND AFTER (2015) WATER DAMAGE REPAIR WORK

TEST	PATIENT IgE LEVELS (IU/ML)				CUT OFF RANGE (IU/ML)
	2012	INTERPRETATION	2015	INTERPRETATION	
TOTAL IgE	282	high	ND	ND	0.0-22*
MOULD MIXTURE (*P.notatum, C.herbarum, A.fumigatus* and *A.alternata*)	12.4	high	ND	ND	<0.35
ASPERGILLUS#	1.63	moderate	0.26	Very low	<0.35
ALTERNARIA ALTERNATA	12.5	high	5.74	Moderate	<0.35

** Age of 10 years and older; ND: not done; # Aspergillus fumigatus*

infection according to the clinician's report. The report also stated that she had undergone repeated surgery to her sinuses and had been on corticosteroids (nasal spray) for extended periods to alleviate her symptoms. In 2012, the patient underwent two operations and had her blood tests referred to a laboratory for further analysis.

IMMUNOLOGICAL ASSESSMENT: SERUM IgE

As part of the clinical evaluation, IgE to inhalant allergens (mould mixture) and specific serum IgE tests were performed to determine the patient's sensitisation to various mould species. The inhalant screening laboratory results using the UniCAP system (Pharmacia, Sweden) revealed moderate to elevated IgE levels for various allergens tested (Table I). The mould mixture used for testing consisted of *Penicillium notatum, Cladosporium herbarum, Aspergillus fumigatus* and *Alternaria alternata* mould species.

EXPOSURE ASSESSMENT OF THE PATIENT'S WORKING ENVIRONMENT

a. Paint scrapings

The building walkthrough inspection conducted by the employer's safety health and environment (SHE) team and management revealed evidence of structural damage from water leakage on the roof (Figure 2). The laboratory is situated in a public hospital building. Paint scrapings collected in July 2012 from different areas in the laboratory were cultured on Malt Extract Agar (MEA) plates and incubated at 25°C ±2 for 5-7 days for mould presence. *Penicillium* and *Cladosporium* species were isolated in the tearoom; *Ulocladium* species from the TB room; *Aspergillus nidulans* in the receiving office; *Cladosporium* and *Syncephelastrum* species from the air conditioner in the administration area; *Alternaria* and *Moniliella* species from the passage and *Aspergillus terreus* in the patient's office.

b. Air sampling

Air samples were collected in July 2013 from selected rooms within the laboratory complex including the microbiology and flow cytometry laboratories, storeroom, the patient's office and tearoom. Duplicate samples were collected using the MAS 100 air sampler (Merck Pty; Germany) by impaction method on Malt Extract Agar (MEA) at a flow rate of 100 L/min. The plates were incubated at 25-30°C for 7 days and moulds were identified to genus level using lactophenol staining and microscopy. All indoor fungal counts were less than outdoors, except the tearoom. *Cladosporium* species was isolated from both indoor (all laboratory areas sampled) and outdoor samples, with the tearoom levels being higher than other rooms. Other moulds that were identified were *Penicillium* from the other rooms and *Curvularia* species from the patient's office.

A clinical diagnosis of probable occupational allergic rhinitis was made at the time and the leaking roof was repaired. In 2014, she presented to the otolaryngologist for a follow up and reported a significant improvement in her symptoms and decline in her specific IgE results in 2015. She was negative to *Aspergillus* and the IgE levels for *Alternaria alternata* reduced from 12.5 to 5.74 IU/ml. She is still using a corticosteroid (fluticasone) nasal spray when necessary, but currently has no other respiratory symptoms. The nasal provocation test was not performed for this patient, hence a diagnosis of probable allergic rhinitis was concluded. The current condition is compensable according to COID Act circular instruction No 27216 of 2005 with 15% disablement awarded if sensitisation persists.[19]

DISCUSSION

Allergic sensitisation to moulds is not a new condition, although work-related cases are not widely reported in South Africa, when compared to those reported in the general population. In the current case of probable occupational allergic rhinitis to mould, the patient had highly elevated IgE to *A.alternata* species and moderate IgE to *Aspergillus* species. These findings concur with a study at the Universitas Academic Hospital, which demonstrated a higher prevalence of sensitisation to one or more mould allergens (34%), with *A.alternata* being the most prevalent (28%) followed by *A.fumigatus* (8%).[20]

Figure 2: Water-damaged walls and ceilings observed during an inspection in some of the work areas of the patient: (a) tearoom, (b) patient's office, and (c) laboratory.

Aspergillus, Alternaria and *Cladosporium* species are three highly allergenic moulds[10,21-22] and were all identified in different areas of the patient's work environment.

These results suggest that *Alternaria* and *Aspergillus* species were primarily responsible for the patient's allergic rhinitis as these moulds were detected in the environment (paint scrapings) and in her serum samples. *Cladosporium* identified in air samples was also present in the previous paint scrapings. Air sampling is the preferred measure of exposure to surface sampling and bears relevance to mode of transmission since inhalation of airborne mould spores leads to fungal hypersensitivity. It is plausible that *Penicillium* and *Cladosporium* species detected in the air samples could have contributed to the patient's sensitisation as these species are known to cross-react with *Aspergillus sp.*, a complex phenomenon complicating the diagnosis of fungal sensitisation. There is widespread consensus that most mould sensitised patients are monosensitised (>75%), with *Alternaria* being the most common due to the major allergen Alt a1. It is very rare (<1%) in other species (*Aspergillus*, *Cladosporium*, *Penicillium* and *Saccharomyces*) due to high cross-reactivity of these species. The study by Mari et al. 2003 showed a higher prevalence of reactivity to two or more fungal allergens with *Aspergillus and Cladosporium* being the most common (>80%) followed by *Penicillium* (~50%) illustrating the high potential of cross reactivity among these fungal species.[23]

It can be deduced from the current case report that the patient also demonstrated polysensitisation suggesting possible cross-reactivity as has been reported in the literature. However, this was not specifically investigated by ELISA inhibition experiments.

Allergic Fungal Sinusitis (AFS) is the most common form of non-invasive fungal sinusitis with approximately 5-10% of all chronic rhinosinusitis cases undergoing surgery.[12,18] Atopic hosts exposed to aerosolised moulds develop an allergic reaction (Type 1, IgE-mediated) from spores which infiltrates the sinuses, resulting in AFS.[12] The diagnostic criteria for AFS vary in the literature as there is currently no universally accepted criterion, however, Bent and Kuhn is regarded standard criteria and includes:

1. Type 1 hypersensitivity to moulds and elevated total serum IgE;
2. Formation of nasal polyps;
3. Characteristic computed tomography (CT) scan findings;
4. Eosinophilic mucin within the nasal cavity and sinuses without invasion; and
5. A positive fungal stain of sinus content removed during surgery and the exclusion of fungal rhinosinusitis.[12,17,18]

Although allergic sensitisation is the fundamental requirement for diagnoses of AFS and assessment of atopy by *in vitro* measurements of specific IgE were done for this case,[18,21] the Bent and Kuhn criteria was not met for this case, thus the previous AFS diagnosis was not supported. Occupational Rhinitis (OR) has been getting little attention, although there is increasing acknowledgement that the burden of this condition is underestimated.[6] This case will bring awareness to employers, employees and clinicians on probable OR from potential mould exposure, which is commonly not reported, especially in SA.

After a six year period of disabling symptoms, the patient's health improved following the repair of the leaking hospital roof. This highlights the importance of undertaking an immediate response to repairing water-damaged building problems, thereby alleviating ill-health complaints. The patient's follow-up visit to the otolaryngologist in August 2014 showed no growth or fungal infection from her sinuses. The patient also reported a relief of upper airway symptoms and an improved quality of life. These findings are consistent with the recent meta-analysis, which showed that dampness and visible mould presence are important determinants of allergic rhinitis and emphasise that prevention and remediation of indoor dampness and mould problems are likely to reduce allergic rhinitis.[24] However, although moisture problems are common, not all are associated with increased health risk. Should there be no visible growth but health complaints are received

from workers, then full investigations must be conducted by a multidisciplinary team to define the extent of the water damage, the exposure assessed and clinical outcomes ascertained. Minimising exposure to the sensitisers are important to prevent persisting symptoms and the risk of poor work ability outcomes.[25] Effective preventive measures can be achieved through several remediation steps. These may include cleaning the visible mould growth by experienced specialists, repairing water leaks and damage, applying an antifungal paint to walls and ceilings, improving the ventilation, preferably fresh air supply with extraction in occupied areas to reduce airborne mould spores and lastly, maintaining indoor relative humidity to below 60% to minimise mould growth.

CONCLUSION

This case report has demonstrated that water-damaged buildings can be a source of exposure to mould spores which can cause allergic rhinitis in exposed workers. Therefore, buildings should be properly maintained and remediated if there is any visible or musty odour from mould growth and/or water damage to prevent excessive exposure of workers. Clinicians should also recognise the potential of workplace exposures to cause allergic rhinitis and have a high index of suspicion, which will more likely lead to appropriate diagnosis and effective management. There is a need for improved awareness of employers, workers and clinicians on occupational allergic disorders specifically caused by moulds, to develop effective preventive strategies.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT

The author would like to thank the patient for allowing them to use her case for the publication and Ms Z Kirsten and Ms E Ratshikhopha for coordinating the retesting of the patient samples.

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Case Study

FOOD ALLERGY PRESENTING AS A SURGICAL ABDOMEN IN A NEONATE

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INTRODUCTION

Food allergies, especially of the non IgE-mediated variety, can masquerade as a number of other conditions in the young child. The following case report illustrates how a neonate with cow's milk induced enteropathy was misdiagnosed initially as pyloric stenosis and subsequently as sepsis, leading to unnecessary diagnostic tests and surgery.

CASE STUDY

A six-week old baby presented with a history of severe, intractable vomiting, present intermittently since day two of life. The infant had not been breast fed, by choice, but was placed onto a cow's milk formula, which resulted in vomiting on the second day of life. A stomach wash out was performed and the condition settled. He was discharged on day three.

At home, he developed intractable vomiting and was taken back to the paediatrician where he was diagnosed with lactose intolerance and placed onto a lactose free formula, which resulted in a slight improvement of the vomiting. In his third week, the vomiting recurred and when the vomiting continued, a second opinion was sought at 6 weeks of age. On examination, he was pale, dehydrated and ill looking and was immediately admitted to hospital.

A workup for sepsis was performed but the blood test results were non-specific. The abdominal x-ray revealed some air fluid levels throughout the bowel. The classical x-ray features of upper abdominal obstruction were not demonstrated. A barium swallow was performed two days later and a diagnosis of pyloric stenosis was made. Subsequently a surgical opinion was sought and the baby was taken to theatre for repair of the pyloric stenosis. The baby was then discharged home on soya milk formula, which was better tolerated in comparison to the cow's milk based formula.

At a later date, two independent radiologists at differing centres, with no clinical history provided, reviewed the radiology studies and in both circumstances they were reported as normal.

The vomiting began again after a week of appearing well post discharge. The mother reported poor sleeping, incessant crying, arching of the back, frequent runny stools and cramping. A return to the paediatrician resulted in a diagnosis of colic and gastroesophageal reflux disease. The milk was then changed to an anti-reflux formula and a proton pump inhibitor was prescribed. Advice was given to provide regular small feeds.

This regime was adhered to for two weeks, but the baby continued to vomit and pass frequent stools. No weight gain was noted during this period. The child continued to deteriorate and presented to the third paediatrician in extremis. Clinical examination revealed a critically ill child that was pale, dehydrated, mottled and hypothermic. Additionally, there was evidence of failure to thrive with his weight being similar to his birth weight.

A preliminary diagnosis of sepsis was made and treated as such. The baby responded well to the fluid resuscitation. Initial haematological testing revealed a lymphopaenia with a thrombocytosis of 553 000/mm^3. The C-reactive protein (CRP) was within normal limits. There was pre-renal picture of renal dysfunction, with an elevated creatinine of 74 µmol/l. His serum albumin was low at 30 g/dl. Cerebrospinal fluid (CSF) revealed 3 polymorphs/µl. The urine dipstix revealed no abnormalities, stool microscopy demonstrated a few pus cells, but no organisms were isolated on microscopy or culture.

In view of the clinical presentation and his previous admissions into hospital, he was diagnosed as having nosocomial sepsis and treated with empiric antibiotics for three days. These were subsequently stopped when the blood and CSF cultures returned negative.

During this period he remained well until day four when his anti-reflux formula was reintroduced. Within four hours of feeding, intractable vomiting developed together with bloody diarrhoea. He was clinically shocked with signs of mottling, lethargy, and had cold peripheries with delayed capillary refill. Blood pressure was not recordable and following resuscitation he was transferred to the intensive care unit (ICU). Initial blood gas measurement

demonstrated a normal anion gap metabolic acidosis. The delta ratio suggested a hyperchloraemic metabolic acidosis (pH: 6.9; pCO_2: 15 mmHg; pO_2: 80 mmHg; HCO_3: 5.6 mmol/l; BE: minus 17 mmol/l; Na^+: 143 mmol/l; K^+: 3.5 mmol/l; Cl^-: 119 mmol/l; Ca^{2+}: 1.19 mmol/l) .

The differential diagnosis at this stage was:

- Inborn error of metabolism;
- Shock from gastrointestinal losses;
- Renal tubular acidosis;
- Lactic acidosis;
- Sepsis;
- Renal insufficiency.

Haematological testing included a metabolic screen, lactate, pyruvate, ammonia and organic acids as well as a screening for renal tubular acidosis. All these test results were ultimately found to be normal.

In the ICU, the baby remained on intravenous fluids with only $NaHCO_3$ replacement. On day seven, oral fluids sips were started and his formula was changed to an amino acid based formula, which was well tolerated with no further episodes of vomiting and diarrhoea.

By day twelve of hospitalisation, our little patient was on full feeds for his age, and he demonstrated an appropriate weight gain. A differential diagnosis of cow's milk protein enterocolitis, possibly of the food protein induced enterocolitis syndrome (FPIES) variety, was made pending the outcome of the metabolic screen. A food allergy screening ImmunoCAP RAST test (FX5) and Phadiotop test also performed at this time, were negative.

Prior to discharge, he was given an oral challenge of 10 mls anti-reflux formula and within twenty minutes it was vomited. Consequently, all cow's milk protein was removed from his diet and the mother was advised to keep him on an amino acid formula until further review.
During this time the metabolic screen result returned as normal and the patient remained well, with appropriate growth, on the amino acid based formula.

At the four month follow up, the child was well and thriving, but waking up frequently to feed. The mother felt that the new formula was no longer satisfying him and it was decided to start him on a rice-based cereal.

Two hours after ingestion of the rice-based cereal, he was admitted to hospital with severe gastrointestinal symptoms and shock. Feeds were stopped and the mother was advised to continue the amino acid formula until age six months.

A definitive diagnosis of FPIES to multiple foods was made at this stage and the dietician was consulted to help with the weaning process.

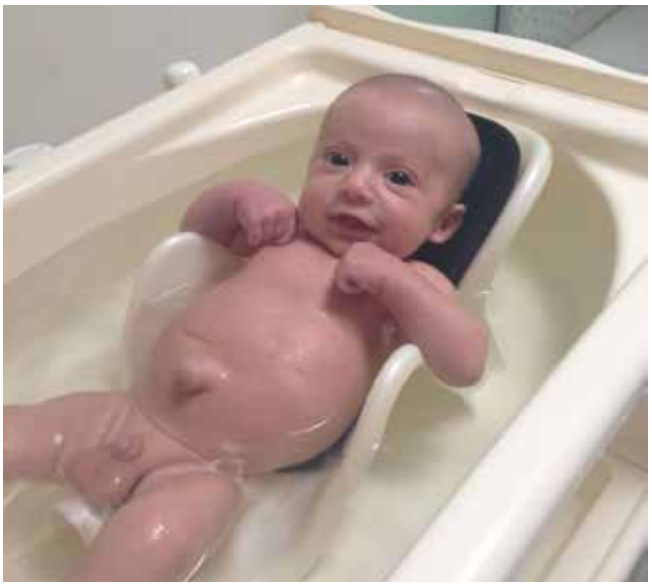
At six months, he was weaned on to vegetables, which were well tolerated. Sweet potato was then added to his diet at seven months and he was once again admitted for diarrhoea and vomiting. Stool cultures were negative and sweet potato was removed from the diet.

Over the following month's oats, lentils, chicken and eggs were also identified as triggers of gastrointestinal symptoms and these were removed from his diet. At this point, he had not been exposed to any nuts or shellfish.

At twenty months he continues to grow well, and his milestones are appropriate for his age. He continues to see the dietician for nutritional support, and a food challenge is under consideration. The photographic sequence of this little

Four weeks of age

Seven weeks of age



Post-operative scar following surgery for pyloric stenosis

20 months old well child

one's life is reflected below.

DISCUSSION

Food protein induced enterocolitis syndrome (FPIES) represents an interesting spectrum of non IgE-mediated food allergy disorders,[1] and can masquerade as a number of clinical entities.[2]

FPIES is a cell mediated, non IgE-mediated, gastrointestinal food hypersensitivity that is commonly caused by cow's milk protein or soy. It signifies the severe end in the spectrum of protein induced gastrointestinal disease in the neonatal period and infancy.[3,4] There are, however, a number of other gastrointestinal disorders that can be attributed to food proteins allergy and the entire gastrointestinal tract can be affected.[5-9]

FPIES

Non IgE-mediated gastrointestinal food-induced allergic disorders include FPIES, food protein induced allergic proctocolitis (FPIAP), and food protein induced enteropathy (FPE). FPIES is currently the most actively studied non IgE-mediated gastrointestinal food allergic disorder.[10] This disease was described in the 1940's by Rubin, who described intestinal bleeding in neonates fed on cow's milk.[3] Similarly Grybowski[11] and Powell[12] described a condition in infants within the first six weeks of life, which presented with recurrent vomiting, bloody diarrhoea, and abdominal distension following ingestion of cow's milk. Feeding with cow's milk-based formula would cause recurrence of severe emesis within 1-3 hours, as well as elevation of the peripheral neutrophil count that would peak at six hours following food ingestion.[11-13]

PATHOPHYSIOLOGY OF FPIES

The mechanisms through which FPIES develops are poorly defined. Although FPIES is predominantly considered to be a T-cell mediated disorder, there is little evidence to support this viewpoint. Equally, humoral responses in FPIES, are not understood.[3] Symptoms have been produced with purified milk allergens that included casein, β-lactoglobulin (BLG), *α*-lactoglobulin (*α*-LG) and bovine serum albumin (BSA).[14,15]

Symptoms resolve following a complete elimination diet. Unlike IgE-mediated cow's milk allergy, in which baked milk products are often tolerated, in FPIES denaturing the milk proteins with heat does not seem to abate symptoms. Moreover, the threshold to induce symptoms in patients with FPIES is in the gram range, but for IgE-mediated food hypersensitivity, the range is in milligrams.[1]

FPIES may also be precipitated by foods, other than milk or soy, including fish, wheat, and eggs. Food allergens such as rice, oats, banana, sweet potato, green peas, beef and chicken may also trigger FPIES. Therefore, a wide variety of common foods have the potential to induce FPIES and the resolution of symptoms over time suggests that FPIES is an inappropriate adaptive immune response to foods.[1]

Villous sampling suggests that villous atrophy, subsequent to milk exposure, is responsible for the malabsorption syndrome in the more "chronic" FPIES presentation. Avoidance of milk results in normalisation of the intestinal architecture, whereas reintroduction of milk leads to partial villous atrophy. Lymphocyte numbers increase in the epithelium, with a large number of them expressing T-cell intracytoplasmic antigen (TIA1), a marker of cytotoxic granules.[16,17]

The humoral response in FPIES is poorly understood. FPIES is typically a non IgE-mediated food allergy, yet some patients have been found to have low levels of IgE against the precipitating food allergen. This is termed atypical FPIES. The presence of IgE to the triggering food by blood

or skin test is thought to be a marker for persistent FPIES.[1]

CLINICAL PRESENTATION

In its acute form, FPIES can present with recurrent severe vomiting, typically 1-3 hours after ingestion of the offending food. Diarrhoea, lethargy, pallor and dehydration usually follow. In its extreme form (15-20% of cases), it may be associated with hypotension, hypothermia and abdominal distension.[2,3]

The laboratory findings may mimic that of sepsis, with an elevated neutrophil count and thrombocytosis, but typically no increase in the CRP. Blood gas analysis may reveal a metabolic acidosis, which in combination with the clinical presentation, is often diagnosed as a metabolic disorder.[2,3] Methaemoglobinaemia is present and may be caused by severe intestinal inflammation and reduced catalase activity resulting in increased nitrites.[2,3]

In typical FPIES, there is a negative IgE test to the trigger foods.

Radiological assessment is rarely useful in making the diagnosis and may only assist if a surgical cause for the clinical presentation is being considered.[3]

Chronic FPIES can present with intermittent, chronic vomiting, watery diarrhoea (bloody, mucoid or both), lethargy, pallor, dehydration, abdominal distension, weight loss and failure to thrive.

ATYPICAL FPIES

A group of individuals with “Atypical FPIES” has been identified. These infants and children fulfil the clinical diagnostic criteria for FPIES, but develop positive specific IgEs to some trigger foods. The disorder is still considered to be essentially cell-mediated, but these individuals have a more prolonged course of FPIES. They also have the capacity to develop anaphylaxis. A large number of individuals with FPIES also develop atopic diseases, like atopic dermatitis, atopic rhinitis and asthma.[4]

DIAGNOSIS

The diagnosis of FPIES is based upon the history and the typical repetitive clinical symptoms of FPIES after exposure to specific allergens. Complete resolution of symptoms occurs with withdrawal of the culprit food(s) and significant clinical deterioration with exposure to the same food. Laboratory and radiographic findings are not diagnostic of FPIES.

Oral food challenge (OFC) is the gold standard for diagnosis of FPIES. Infants generally do not require OFC testing, as the diagnosis can generally be made on history, together with symptom resolution following the removal of the culprit food from the diet. In circumstances where the history is unclear, a specific food trigger needs to be identified, or where the presentation of FPIES is atypical, or when development of tolerance is being investigated, a specifically designed, prolonged OFC should be performed under clinical supervision in a hospital setting.[2, 3]

CONCLUSION

The diagnosis of FPIES is often not considered in the neonatal period as the symptoms of diarrhoea, vomiting, abdominal distension, poor feeding, lethargy, apathy, and hypotension are non-specific and are usually attributed to a variety of other neonatal conditions such as sepsis or intestinal obstruction. In the absence of a definite diagnosis, the astute clinician should consider food allergy as a cause of such non-specific symptoms in the neonate and infant.

The parents of this baby have given permission to publish the photos without hiding the identity of the baby.

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PID123 Treatment 4

Primary Immunodeficiency

This is the fourth in our series on primary immunodeficiency.

We continue the story of 3-year old Anathi who has been diagnosed with X-linked agammaglobulinaemia (XLA, or Bruton's disease) which affects Anathi's ability to produce antibodies and makes him susceptible to bacterial infections. **Patient education** and **counselling** is an important aspect of the success of treatment in PID. Dr Goodheart spends time with Nomhle, Anathi's mother, explaining the treatment plan recommended by the clinical immunologist, Dr Bala.

Drinking water should be boiled

1. Managing infections

Anathi was treated with antibiotics for pneumonia. He recovered well, but shows signs of early lung damage which makes him even more susceptible to further infections.

Dr Goodheart explains the importance of **preventing future infections**. The family must practice good handwashing habits. They must only drink water that has been boiled and it is important that they follow a healthy diet.

A healthy diet is important

Dr Goodheart explains that Nomhle should immediately report any signs of infection to his doctors, as all infections must be treated promptly.

Culture and sensitivity of infectious organisms should be obtained, where possible, for the appropriate antibiotic choice. Chronic infection with gut parasites (e.g. **Giardia**) must also be anticipated and treated. Signs of meningitis or encephalitis in early life may be indicative of an **enteroviral** infection.

Prophylactic antibiotics have been prescribed for Anathi. (Dr Goodheart learned from Dr Bala that these may be prescribed without immunoglobulin replacement to prevent infections in some milder forms of antibody deficiencies).

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Patient Support Group in South Africa: www.pinsa.org.za

Prophylactic antimicrobials may differ depending on the form of primary immune defect. For example, prophylactic Cotrimoxazole, with or without antifungal treatment, is used in severe combined immunodeficiency (SCID) before bone marrow transplantation.

Prophylactic antifungal agents and Cotrimaxozole is also recommended for Chronic Granulomatous Disease (CGD).

Antibiotics are used prophylactically

Antibody deficiencies may present with autoimmune symptoms along with the infections and these may require specific treatment.

2. Immune augmentation

In many cases of antibody defects, such as Anathi's, **Immunoglobulin Replacement Therapy (IRT)** is indicated. IgG antibodies pooled from the plasma of blood donors confer passive immunity with the aim of maintaining normal antibody levels to prevent infections. In Anathi's case intravenous treatment with immunoglobulins (IVIG), has been commenced. (Weekly subcutaneous home treatment is another option, which may be considered for him in future).

Whole blood from a donor

IgG antibodies are pooled from the plasma of blood donors

For Nomhle and Anathi, the intravenous treatment involves regular visits (every 3-4 weeks) to Dr Goodheart's clinic, with monitoring and adjustment of serum IgG levels for optimal stable levels. These are expected to be obtained following about 3 months of treatment. Dr Goodheart educates Nomhle on **adherence** which is important if Anathi's IVIG treatment is to be successful as chronic IRT is challenging and expensive.

Anathi receives IVIG

Vaccinations are not indicated for Anathi while he is on IRT. Dr Goodheart suggests preventive vaccination for Anathi's close relatives against influenza and pneumococcus (although not with live vaccines).

Inactivated and live vaccines

For other antibody deficiencies (e.g. deficient vaccine antibody responses) **vaccine boosting** may be recommended and used diagnostically to measure antibody levels.

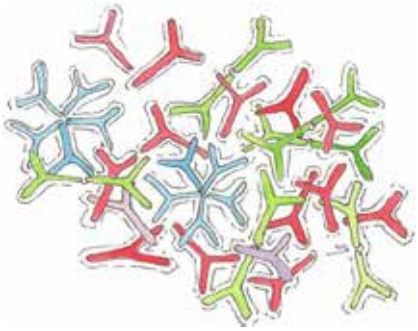
Care must be taken with vaccines in patients with certain immune defects, for example, live vaccines such as the oral polio vaccine should be avoided in major B and T cell defects (see table).

In practice, many children like Anathi will have received all scheduled vaccinations by the time they are diagnosed with PID. A history of adverse responses to these vaccines may give a clue to PID diagnosis.

Vaccination in PID – basic approach

(Modified after **Shearer et al.**, 2014)

Immune deficiency	Do not use	Recommended	Comments
B lymphocyte (antibody) defects	Certain live vaccines such as oral polio vaccine (OPV)	Pneumococcal (MMR)	Effectiveness uncertain; IRT may interfere
T cell defects	Live vaccines (incl. MMR, OPV, BCG)	Pneumococcal (meningococcal, Hib)	Vaccines likely to be ineffective
Complement defects	N.A.	Pneumococcal, meningococcal	Routine vaccines effective
Phagocyte defects	Live bacterial vaccines such as BCG	Pneumococcal	Likely to be safe and effective



Immunoglobulins

3. Immune repair

Hematopoietic stem cell transplantation (HSCT) is used successfully in a wide range of PIDs, such as SCID or CGD, to replace non-functional patient immune cells with functional donor cells. However, this has proven unsuccessful to date with XLA, and is therefore not a treatment option for Anathi.

Gene therapy is an emerging option which may be employed in the treatment of ADA-SCID but it is currently not offered as routine therapy.

4. Counselling

Dr Goodheart books an appointment with the **Clinical Genetic Service** for counselling, where investigations will be performed. Anathi and his family will be screened for the specific BTK mutation responsible for his agammaglobulinaemia. The aim is to identify possible carriers of the mutation among female family members, like Anathi's sister. This has implications for pregnancy and family planning.

Anathi will also attend check-up visits with the immunology specialist, Dr Bala, who will supervise and monitor the management of the immune deficiency and obtain consent for his inclusion in the PID registry.

Lastly, Dr Goodheart discusses with Nomhle the importance of informing school teachers and relatives about Anathi's condition and puts her in contact with the local **patient support** group.

PID Article

A DIAGNOSTIC APPROACH TO RECURRENT RESPIRATORY TRACT INFECTIONS IN CHILDHOOD: COULD IT BE PRIMARY IMMUNODEFICIENCY?

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SUMMARY

The recurrence of respiratory tract infections is a common problem in paediatric practice. Parental concerns around recurrent respiratory infections (RRTI) contribute significantly towards doctor visits. RRTI are also the most frequent presenting feature of primary genetic immunodeficiency (PID). There is a surprising lack of evidence, guidelines and appropriate ICD10 coding for RRTI. Many of the children who present with RRTI are immunologically "normal" children but it is important to recognise the features of a possible immune deficit or other underlying serious disorder.

The evaluation of children who present with RRTI requires close attention to the history and clinical findings in order to differentiate those who warrant more extensive investigations from those who need reassurance directed toward their concerned parents. PID may be responsible for around 10% of RRTI in children. More than 50% of these are due to antibody defects and the majority can be diagnosed and treated effectively. The question that arises is when to start more extensive investigations and when to accept that this child is otherwise healthy.

The purpose of this review is to assist the clinician with a diagnostic approach to differentiate the "normal" child from the child with a more serious underlying aetiology of RRTI, necessitating investigation.

INTRODUCTION

Respiratory tract infections (RTI) are common in young children and they are a frequent reason for consulting a doctor. Children who attend day-care centres may even suffer a 3-8 times higher burden of RTI. These consultations usually come with a parental low tolerance for symptoms such as an irritating cough, high expectations of prevention of further RTI, a demand for antibiotics, confusion created by a multitude of ineffective over-the-counter remedies and expectations of rapid improvement of the child so that the parents can return to work.

The differential diagnosis for RRTI in childhood is broad and the evaluation time consuming. There are no clear guidelines or evidence based data to advise clinicians on an approach to this common problem. Many children who present with RRTI will turn out to be "normal", while some may need further investigation to elicit a serious underlying cause. A serious diagnosis must not be missed as it may result in significant morbidity and even shortened lifespan. This review strives to offer a simplified aetiology based diagnostic approach towards childhood RRTI in the South African setting.

WHEN SHOULD RRTI RAISE CONCERN?

It is difficult to draft comprehensive guidelines for RRTI management due to the numerous features of RRTI that should alert the clinician towards further examination. An expert opinion based review by Bush[1] suggests the features that should suggest a need for further investigation. Some of these are summarised in Table I. It is however, not only the frequency or recurrence of RTI that should warn of a need for further investigation but relevant aspects of the history, including especially a family history, history of allergy, different social backgrounds and ethnicity, access to healthcare, specific clinical findings such as failure to thrive and dysmorphism, specific organisms identified and failure of infections to resolve to appropriate therapy.

With lack of evidence based guidelines, clinicians are

often prompted to investigate those RRTI that are too frequent in number, too severe, last too long, fail to resolve with standard treatment or which result in complications.[2] Parental concern must always be considered too. The decision on when to investigate, or when to stop investigating, relies on a good knowledge of the differential diagnosis, thorough history taking, sound clinical judgement and a sound understanding of the context of the problem. The same rules apply to the specific investigations that will be requested.

An aetiology based diagnostic approach to RRTI is discussed here.

AETIOLOGICAL BASED DIAGNOSTIC APPROACH TO RRTI

A number of different approaches may be followed when a child presents with RRTI. An aetiology-based diagnostic approach offers a simplified stepwise model for the clinician. The first step is to consider a possible secondary reason for RRTI such as human immunodeficiency virus (HIV)-related disease, protein losing diseases, diabetes mellitus and immunosuppressive treatment. The second step considers the three scenarios discussed below. According to Stiehm et al[2] approximately 50% of the children who present with recurrent infection, are actually "normal" children. A further 30% of recurrences result from underlying allergic inflammation, 10% from PID and the remaining 10% are caused by a variety of non-immune related chronic conditions (Figure 1).

The three scenarios encountered are:

1. The "normal" child with RRTI (50%) where it is important to avoid unnecessary investigations and treatment and to inform and address the anxiety of the parents.
2. The child with a non-immune related cause (10%) and RRTI in need of investigation to identify and manage a possible more sinister problem.
3. The child with dysregulated immune function and RRTI where it is equally important to make a diagnosis for effective management. Immune dysregulations usually manifest with either "over activity" or allergy (30%), or "under activity" or PID (10%) or combinations of both. "Misdirected immunity" or auto-immunity may be noted in later life.

The goal of a thorough history and clinical evaluation should be to identify the most likely scenario for RRTI and to guide further investigation and ideally lead to the correct diagnosis. These different scenarios will be discussed briefly, however, it is beyond the scope of this article to offer a detailed review of each differential diagnosis.

SCENARIO 1: THE "NORMAL" CHILD WITH RRTI

Acute respiratory infections (ARI), especially viral colds and infections of the upper respiratory tract, occur

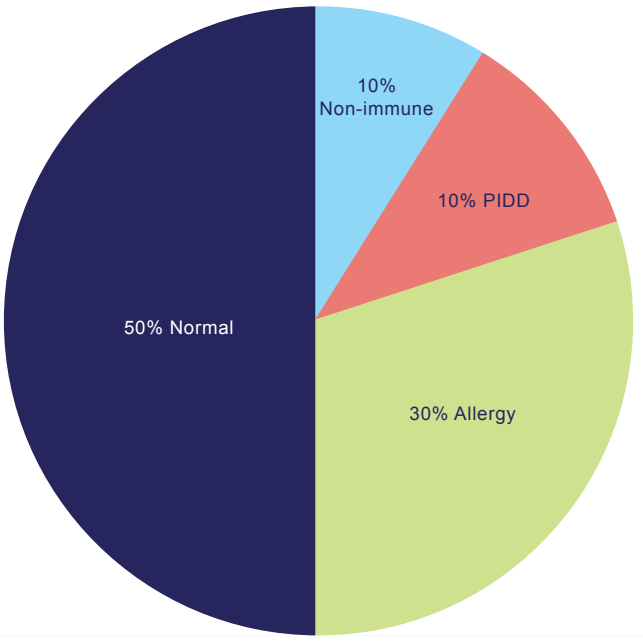

Figure 1: Aetiologic based diagnostic approach to RRTI

frequently in "normal" children. The average child suffers 4-8 respiratory infections per year.[3] The symptoms of an uncomplicated ARI last an average of 8-14 days and 10% of children may still cough at 25 days post infection.[4] The number of respiratory infections can increase 2-8 fold with larger group exposure such as in day-care settings. Characteristics of the "normal" child with RRTI include: milder and often self-limiting infections, complete recovery between episodes, normal growth and development and the absence of findings that would suggest an underlying chronic illness. Recurrent infection that is always limited to the respiratory tract, and not of other systems, further supports a more innocent aetiology.

The management of such a child and family is mainly supportive and has to be reviewed in the context of the child's environment and include allowance for possible excess anxiety of parents. The reassuring advice of the doctor is often sufficient to alleviate parental concern of the otherwise "normal" child.

SCENARIO 2: THE CHILD WITH A NON-IMMUNE RELATED CAUSE AND RRTI

Non-immune RRTI **may account for 10%** of causes and may result from various conditions (Table II). Most of these are important to diagnose promptly and therefore deserve a high index of suspicion.

Cystic fibrosis (CF) is caused by compromised cystic fibrosis transmembrane conductance regulator (CFTR) protein channel function resulting in decreased hydration of secretions. Nearly 2,000 gene mutations have been identified that may code for changes in the production, transport, membrane expression and activity of the CFTR channel.[5] The clinician that only considers CF in

TABLE I: WHEN SHOULD RRTI RAISE CONCERN? FEATURES THAT MAY POINT TOWARDS AN EARLIER NEED FOR INVESTIGATION

FINDING	POINTERS FOR FURTHER INVESTIGATION
Marked chronic upper airway symptoms	Snoring, stridor, chronic rhinitis, chronic sinusitis
Early onset of symptoms	Onset of symptoms since birth or soon after birth
More severe symptoms	Continuous, unremitting or worsening symptoms
Vomiting & choking	Pain on feeding or On or after feeds
Viral cold	≥ 15 episodes per annum
Acute tonsillitis	≥ 7 episodes in 1 year or ≥ 5 episodes per annum in 2 consecutive years or ≥ 3 episodes per annum in 3 consecutive years
Acute otitis media	≥ 3 episodes in 6 months or ≥ 4 episodes in 1 year
Acute sinusitis	≥ 2 episodes in 1 year requiring IVI antibiotic treatment
Acute pneumonia	≥ 2 hospital admissions in 1 year or ≥ 2 episodes of radiologic shadowing in 1 year or ≥ 3 episodes in total
Persisting cough	Daily for > 4 weeks Persisting wet cough
Mucus	Persisting and coloured mucus
Wheeze	High frequency and severe Non-remitting and not responsive to correctly administered asthma medication Asymmetric Fixed monophonic Young age of onset
Abnormal findings on general examination	Inadequate growth, failure to thrive or weight loss Digital clubbing Anaemia Absence or exuberance of lymph tissue
Clinical features of allergic disease	Atopic eczema Allergic conjunctivitis Allergic rhinitis Food allergy Asthma
Involvement of different systems	Respiratory infections accompanied by infections of other systems
Cardiac abnormality	Signs of cardiac disease
SPUR infections	Severe, persistent, unusual and recurrent infections

a "traditional" presentation of severe CFTR dysfunction will under diagnose this important and relatively frequent condition in South Africa. CF is not limited to Caucasians and the CF phenotype is heterogenous. The severity of CF varies according to the underlying CFTR mutations, environmental factors and modifier genes that interact with CFTR mutations.[6] CF should always be considered in RRTI and especially in the setting of RRTI with failure to thrive or as a mimic of young onset asthma. Sweat tests should be requested in all children where RRTI is further investigated. There are many good reviews on this topic and the 2013 South African CF consensus document offers further guidance. [7]

TABLE II: EXAMPLES OF SCENARIO 2 - THE CHILD WITH NON-IMMUNE RELATED CAUSE AND RRTI

MECHANISM	CONDITION
Ineffective mucus clearance	Primary ciliary dyskinesia (PCD) Cystic fibrosis (CF) Nervous system and muscular abnormalities with ineffective cough Bronchiectasis
Airway obstruction	Eustachian tube dysfunction Sinus ostia obstruction Tonsil and adenoid hypertrophy Lymph node hyperplasia Tumours Foreign body aspiration Vascular rings Airway malacia
Increased pulmonary blood flow	Cardiovascular abnormality
Congenital airway abnormality	Developmental abnormalities of the airways and lungs
Chronic infection	Mycobacterium tuberculosis Persistent bacterial bronchitis (PBB)
Recurrent re-infection	Day-care attendance
Exposure to irritants	Cigarette smoke Gastro-oesophageal reflux disease (GORD)

Primary ciliary dyskinesia (PCD) is generally under diagnosed and seldom considered. The reported prevalence is 1:10,000-20,000.[8] Important reasons for under diagnosis include a misconception that situs inversus will be present and the limited availability of reliable special investigations. Mirror image organ arrangement and other forms of heterotaxy is only present in 40-50% of PCD.[8] Chronic rhinorrhoea from birth, unexplained respiratory distress in the term baby, repeated upper and lower airway symptoms, chronic muco-purulent otorrhoea, nasal polyps and early loss of hearing should be warning signs of possible PCD.[1]

Gastro-oesophageal reflux (GOR) and gastro-oesophageal reflux disease (GORD) is often over diagnosed as a reason for RRTI. GOR is a physiologic phenomenon in healthy infants and children[9] and there is controversy over whether the cough is the reason for GOR or whether GOR the reason for the cough. GORD, and associated pulmonary aspiration, should be considered as a cause of RRTI in children with neurodisability, swallowing dysfunction, CF and previous tracheoesophageal fistula fistula repair. Associated findings may include chronic vomiting, frequent choking, failure to thrive, pain during feeding, Sandifer posturing and dental caries.

Protracted bacterial bronchitis (PBB) has recently been recognised as an important entity and cause for RRTI.[1] It often follows after an initial viral airway infection in younger children and manifests with an isolated wet cough that lasts for longer than 4 weeks. The cough is usually more prominent on reclining, in the early morning hours and during exercise. PBB patients may cough for the entire night and suffer from disrupted sleep. It is a neutrophil

disease with associated biofilm production in the airway. Non-typable *Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis* are the most frequent colonising bacteria. PBB patients are commonly misdiagnosed as being asthmatic. Associated findings include wet rattles in both lung fields, stained sputum and other biofilm manifestations like chronic middle ear effusion and sinusitis. It remains a diagnosis of exclusion and should be differentiated from bronchiectasis and chronic suppurative lung disease. Recurrent PBB raises concern, as underlying risk factors to PBB may be present. Detailed investigation is needed in children who present with recurrent PBB.[10]

SCENARIO 3: THE CHILD WITH DYSREGULATED IMMUNE FUNCTION AND RRTI

Allergy accounts for 30% of causes of RRTI and is a common finding in paediatric practice. Clinicians should pay special attention to history and clinical findings that may indicate allergic rhinitis, asthma and comorbidities. The symptoms of allergic rhinitis and asthma are often mistaken for those of viral ARI. Importantly allergic children, especially if poorly controlled, also suffer from increased susceptibility to RRTI due to a number of factors. These include enhanced adherence of pathogens to inflamed epithelium, decreased muco-ciliary clearance, increased mucosal permeability and altered host immune response to pathogens.

There are also overlaps between allergy and PID with co-existing allergy in 31% of PID patients.11 Allergic features may be a component of selective IgA (sIgA) deficiency, common variable immunodeficiency (CVID), chronic granulomatous disorder (CGD) and Di George syndrome (22q deletion syndrome). Elevated IgE is seen in the Hyper IgE syndrome (HIES), Wiskott Aldrich syndrome, Omenn syndrome and immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX).

TABLE III: SIGNATURE INFECTIONS - HELPFUL IN ALERTING TO DEFICIENCIES IN THE RESPECTIVE PATHWAYS OF THE IMMUNE SYSTEM

PIDD DEFECT	SIGNATURE INFECTION
Antibody (B-cell) deficiency: - XLA - IgA, IgG subclass - Specific antibody - CVID	*H. influenzae* *S. pneumoniae* *G. lamblia* ECHO virus Salmonella spp. *M. pneumoniae*
T-cell deficiency & SCID: - ADA deficiency - Hyper IgM syndrome - Major histocompatibility complex deficiency - Wiskott-Aldrich syndrome	Herpes simplex, zoster CMV, EBV, measles, RSV *P. jiroveci* Streptococci, *H. influenzae* Candida, Aspergillus Mycobacteria Cryptosporidium
Phagocyte defects: - Chronic granulomatous disease (CGD) - Familial, cyclical or auto-immune neutropenia - Leukocyte adhesion defects - Hyper IgE syndrome	*S. aureus* Streptococci Candida, Aspergillus Enteric Gram-negative bacteria
Complement deficiency: - Complement deficiency - Mannose binding lectin deficiency (MBL) - C3 or C5 deficiency	*S. pneumoniae* *H. Influenzae* *N. meningitides*

PID, although only accounting for 10% of RRTI, must be excluded, as it most frequently presents with symptoms of RRTI. This group of conditions causes significant morbidity and mortality and must be diagnosed early and treated appropriately. PID is still regarded as rare, however, a population based prevalence study in the United States has revealed a frequency of up to 1:2,000.[12] The hallmark of PID related infections are captured by the acronym SPUR, which stands for Severe, Persistent, Unusual or Recurrent infections and is modelled on the more extensive Jeffrey Modell Foundation 10 warning signs.[13] These hallmark or warning signs of PID have to be evaluated against the very different social background of South African patients.

Although the classification of PID has evolved far beyond the traditional 4 categories of immune function deficit, it is still useful for an initial approach to start with the 4 basic immune category abnormalities. For updated PID classifications the reader is referred to the IUIS classification or clinical diagnostic guidelines.[14] Recurrent viral or bacterial infections may point to different deficiencies of the immune system within the domain of B-cell abnormalities (50-65%), T-cell abnormalities (20-30%), phagocyte deficiencies (18%) and complement deficiencies (2%). This distribution of PID seems to also apply to the South African situation as reflected on the South African PID Registry.

Specific organisms are helpful in alerting to deficiencies in the respective pathways of the immune system referred to as the “signature“ infections of PID (Table III).[15]

A family history of PID or early infant death to infection is a most important and useful alerting feature, which may be present in 30% of patients with PID. This is even more frequently elicited in regions with consanguineous marriages. Other important PID warnings include persistent lymphopaenia and low globulin fractions, failure to thrive, chronic muco-purulent secretions, lethargy and absenteeism, recurrent diarrhoea, skin and soft tissue infections, two or more severe infections, dysmorphic features, absence or exuberance of lymph tissue, skin rashes, complications from a live vaccine and auto-immune disease. However, if PID cannot be diagnosed through basic screening with full blood count and differential count, serum immunoglobulin levels, vaccine antibody responses and total complement level in the face of SPUR infections, the child must be referred to a specialist centre. Other PID such as innate immune defects, immune defects relating to dysregulated immunity and overlapping deficiencies may then need to be evaluated further.

CONCLUSION

RRTI are common in paediatric practice. The differential

diagnosis is broad. The challenge is to not over-investigate or over-treat the normal child, but also not to miss important causes with significant morbidity and potential of shortened lifespan. Such conditions include allergy, genetic primary immune deficits and non-immune chronic conditions. An aetiological diagnostic approach helps to guide a targeted history, clinical evaluation and relevant investigations. Sound clinical judgement is crucial for the correct diagnosis and management of RRTI. The clinician who keeps these scenarios in mind can be more confident in the management of patients with RRTI.

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PRODUCT NEWS

The Range of Products and Benefits for your Respiratory Patients - From AstraZeneca

For asthma

The long-term goals of asthma management are to achieve good control of asthma symptoms in order to maintain normal activity levels as well as to minimise future risk of exacerbations, fixed airflow limitation and side effects.[1] At each treatment step in asthma management, AstraZeneca has several different medication options available, classified as 'preferred' medication by GINA guidelines[1]:

- Step 1 treatment is with an as-needed short-acting beta-2-agonist (SABA) alone such as Bricanyl® Turbuhaler®.
- Step 2 treatment is a regular daily low-dose inhaled corticosteroid (ICS) such as Pulmicort® Turbuhaler® + SABA as needed.
- Step 3 treatment for persistent symptoms and/or exacerbations despite low-dose ICS is a combination ICS/long-acting beta-2-agonist (LABA) such as the fixed-combination dry powder inhaler (Symbicord® 80(160)/4,5 Turbuhaler®), the fixed-combination metered dose inhaler Vannair® 80(160)/4,5 Inhaler or the use of separate inhalers i.e. Pulmicort® Turbuhaler® together with the LABA in Oxis® Turbuhaler®. The use of low-dose budesonide/formoterol as both maintenance and reliever therapy, such as Symbicord® SMART, has been shown to reduce the risk of exacerbations, compared with maintenance controller treatment plus as-needed SABA.
- Step 4 treatment is with medium- or high-dose ICS together with a LABA such as Symbicord® 320/9 Turbuhaler® or Vannair® 160/4,5 inhaler.

For COPD

Appropriate pharmacologic therapy can reduce chronic obstructive pulmonary disease (COPD) symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.[2] Each treatment regimen needs to be patient-specific as the relationship between tolerance of symptoms, airflow limitation and severity of exacerbations will differ between patients.[2] The choice between beta-2-agonist, anticholinergic, theophylline or combination therapy depends on availability and individual patient response.[2]

- Bronchodilator medicines are given either on an as-needed basis with a SABA such as Bricanyl® Turbuhaler® or on a regular basis with a LABA such as Oxis® Turbuhaler® to prevent or reduce symptoms.[2] LABAs are more convenient for patients and more effective at producing maintained symptom relief than SABAs.[2]
- An ICS/LABA combination such as Symbicord® Turbuhaler® or Vannair® Inhaler is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to severe COPD.[2]

For allergic rhinitis

Intranasal corticosteroids (INS) such as Rhinocort® Aqueous Nasal Spray are first-line therapy for moderate or severe and/or persistent allergic rhinitis (AR).[3] An INS relieves all the major nasal symptoms of AR, especially nasal blockage, but also itching, sneezing and rhinorrhoea.[4]

SMART – Symbicord® Maintenance and Reliever Therapy

References: 1. Global Initiative for Asthma. (GINA). Global Strategy for Asthma Management and Prevention. 2014. Available at: http://www.ginasthma.com/GuidelinesResources.asp Last Accessed: 13/08/2014. 2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2014. Available at: http://www.goldcopd.org/ Last Accessed: 13/08/2014. 3. Green RJ, Hockman N, Friedman E, *et al*. Allergic rhinitis in South Africa: 2012 guidelines. *S Afr Med J* 2012;102(8):693-696. 4. South African Allergic Rhinitis Working Group. Allergic rhinitis in South Africa – diagnosis and management. *S Afr Med J* 1996;86(10):1315-1328.

S4 Vannair® 80:4.5 (Inhaler). Reg. No: A39/21.5.1/0506. S4 Vannair® 160:4.5 (Inhaler). Reg. No: A39/21.5.1/0507. Each single actuation contains as active constituents, Budesonide 80 or 160 µg and formoterol fumarate dihydrate 4,5 µg. PHARMACOLOGICAL CLASSIFICATION: A 21.5.1 Corticosteroids and analogues. INDICATIONS: Asthma: VANNAIR® 80:4,5 & 160:4,5 µg/dose is indicated in the treatment of asthma in adults and children 6 years and older where continued use of a combination (inhaled corticosteroid and long-acting beta-2-agonist) is appropriate. COPD: VANNAIR® 160:4,5 µg/dose is indicated in the regular treatment of patients with moderate to severe chronic obstructive pulmonary disease (COPD), with frequent symptoms and a history of exacerbations. For full prescribing information refer to the package insert approved by the medicines regulatory authority.

S3 Pulmicort® Turbuhaler® 100 µg/dose (Inhaler). Reg. No: Y/21.5.1/171. S3 Pulmicort® Turbuhaler® 200 µg/dose (Inhaler). Reg. No: Y/21.5.1/172. S3 Pulmicort® Turbuhaler® 400 µg/dose (Inhaler). Reg. No: Z/21.5.1/266. Each metered dose contains 100 µg, 200 µg or 400 µg budesonide. Free from propellants, lubricants, preservatives, carrier substances or other additives. PHARMACOLOGICAL CLASSIFICATION: A 21.5.1 Corticosteroids and analogues. INDICATIONS: Prophylaxis of the symptoms of asthma. For full prescribing information refer to the package insert approved by the medicines regulatory authority.

S4 Oxis® Turbuhaler® 9 (Inhaler). Reg. No: 32/10.2.1/0168. Each dose delivers: formoterol fumarate dihydrate 9 µg. The corresponding metered dose contains 12 µg formoterol fumarate dihydrate. PHARMACOLOGICAL CLASSIFICATION: A 10.2.1. Bronchodilators (inhalants). INDICATIONS: Add on therapy to maintenance treatment with inhaled corticosteroids for the prophylaxis and treatment of reversible airways obstruction in asthma, chronic bronchitis and emphysema and prevention of bronchospasm in exercise-induced asthma, when adequate treatment with corticosteroids is not sufficient. For full prescribing information refer to the package insert approved by the medicines regulatory authority.

S3 Rhinocort® Aqua 32 (Nasal Spray). Reg. No: 32/21.5.1/0608. S3 Rhinocort® Aqua 64 (Nasal Spray). Reg. No: 32/21.5.1/0609. Each metered dose contains budesonide 32 µg or 64 µg. Contains potassium sorbate 0,12 % m/v as preservative. PHARMACOLOGICAL CLASSIFICATION: A 21.5.1 Corticosteroids and analogues INDICATIONS: Seasonal and perennial allergic rhinitis in adults and in children 6 years and older. For full prescribing information refer to the package insert approved by the medicines regulatory authority.

S2 Bricanyl® Turbuhaler® 0,5 mg/dose (Inhaler). Reg. No: X/10.2/155. Each dose contains: terbutaline sulphate 0,5 mg. PHARMACOLOGICAL CLASSIFICATION: A 10.2 Bronchodilators. INDICATIONS: Bronchial asthma, chronic bronchitis, emphysema and other lung diseases where bronchospasm is a complicating factor. For full prescribing information refer to the package insert approved by the medicines regulatory authority. .

S4 Symbicord® Turbuhaler® 80:4.5 µg/dose (Inhaler). Reg. No: 35/21.5.1/0404. S4 Symbicord® Turbuhaler® 160:4.5 µg/dose (Inhaler). Reg. No: 35/21.5.1/0405. S4 Symbicord® Turbuhaler® 320:9 µg/dose (Inhaler). Reg. No: 38/21.5.1/0187. Each delivered dose contains Budesonide 80/160/320 micrograms and formoterol fumarate dihydrate 4,5/4,5/9 micrograms. PHARMACOLOGICAL CLASSIFICATION: A 21.5.1 Corticosteroids and analogues. INDICATIONS: Asthma: SYMBICORD® TURBUHALER® 80:4,5 and 160:4,5 µg/dose is indicated in the treatment of asthma in adolescents and adults where use of a combination (inhaled corticosteroid and long-acting beta-2-agonist) is appropriate. SYMBICORD® TURBUHALER® 320:9 µg/dose is indicated in the treatment of asthma in adolescents and adults needing inhaled corticosteroids where continued use of a high dose combination (inhaled corticosteroid and long-acting beta-2-agonist) is appropriate. COPD: SYMBICORD® TURBUHALER® 160:4,5 and 320:9 µg/dose is indicated in the regular treatment of patients with moderate to severe chronic obstructive pulmonary disease (COPD), with frequent symptoms and a history of exacerbations. For full prescribing information refer to the package insert approved by the medicines regulatory authority.

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Ethics Article

ETHICAL ISSUES IN ANAPHYLAXIS

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INTRODUCTION

Anaphylaxis is "a serious, generalised or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal."[1] All international guidelines on anaphylaxis, including the South African one, emphasise the importance of early administration of adrenaline, either by intramuscular injection or auto-injector, into the outer thigh muscle. The International Consensus on (ICON) anaphylaxis published in the WAO Journal lists a number of unmet needs in anaphylaxis, one of which is that increased awareness of anaphylaxis is required, not only among health professionals, but also among patients, caregivers and the general public.[1]

CASE SCENARIO

Henry, a 3-year-old boy, is enrolled at a crèche. He is allergic to peanuts and his mother asks the staff to inform the other children's parents not to give them peanut butter sandwiches to bring to the crèche. The staff refuse to do so, and Henry's mother consults you as his doctor. What are Henry's rights in this scenario and how would you advise his mom?

RISK, UNCERTAINTY AND ALLERGY

The key question in this scenario is to try to identify the risk of a severe reaction should Henry be exposed to peanuts and/or peanut butter at school. To this end, a careful and detailed history is required, together with appropriate allergy testing. Depending on the history of previous reactions to peanuts, the most appropriate test may be specific IgE to peanuts (including rAra h2) or a skin prick test. A food challenge may be necessary if the history and allergy tests do not suggest that Henry is at risk of a severe reaction to peanuts. As it is often challenging to quantify the risk of peanut allergy, the risk of anaphylaxis is difficult to estimate. This causes severe anxiety and uncertainty when counselling families of affected children as to this potential risk. The clinician has to weigh up what is in the best interests of the peanut allergic child (beneficence) against the potential harm that may be caused by singling the child out and the stigmatisation that may result (non-maleficence). To what extent should clinical decisions include the preferences of the parents (respect for parental autonomy)? Making parents the primary decision makers may result in excessive parental anxiety and reduced quality of life.

The parental uncertainty is illustrated by two cases quoted by Wendy Hu and her co-authors.[2] The first case involved a 20-month-old boy who developed urticaria on his face after contact with peanut butter, but without any systemic symptoms, at the age of 12 months. He subsequently avoided peanuts, although his family continued to eat them. His skin prick test to peanut was positive (9 mm; ≥3 mm considered positive). He did not receive an adrenaline auto-injector, a decision with which his mother was comfortable. The second case was that of a 23-month-old boy who also developed facial urticaria and swelling of the lip and eyes after contact with peanut butter at the age of 9 months. He too did not develop systemic symptoms, but was given adrenaline at the local hospital. His skin prick test to peanut was 9 mm but an adrenaline auto-injector was prescribed for him, and his mother felt this was the safer option.[2] Underpinning the different management decisions of these two children is the uncertainty regarding the risk of anaphylaxis to peanuts.

How can health professionals, patients and parents cope with this uncertainty in allergy practice? Where possible, evidence-based medicine should be practised. If this is not available, as illustrated by the cases above, then the health professional should communicate the relevant information to the patient/parents, explaining the risks and benefits, together with a recommended management plan, and the final plan should be decided upon through shared decision making.[3]

FOOD ALLERGY AND ANAPHYLAXIS IN SCHOOLS

The tension around the management of food allergy in schools involves respecting the confidentiality of the food allergic child and avoidance of stigmatisation, while also avoiding risk and harm to him/her. The food allergic child has the right to be educated in a safe environment and exposure to food allergens may cause harm. At the same time, it is important to respect the rights of other (non-food allergic) children.[4]

Most guidelines on food allergy policies in schools address two issues:

1. Management of an emergency situation (anaphylaxis); and
2. Prevention of exposure to and/or accidental ingestion of a food allergen.[4]

The school should have an established policy and guidelines on the management of anaphylaxis. The policy has to address the training of staff to recognise the emergency

and to treat anaphylaxis by means of injectable adrenaline. Educators and staff have a right to be informed about the allergic problems of the children in their care and to be properly trained in managing allergic emergencies. The policy should also include indemnification of the person administering the injection.

Prevention of exposure to food allergens may be achieved by strict policies that forbid any sharing of food or food containers between children and the creation of "allergen-free" areas in canteens or classes. Completely banning food allergens such as peanuts from schools or crèches is usually not effective. Although this may well reduce allergen exposure, it infringes on other (non-food allergic) children's rights.

The ethical principle of respect for autonomy and its co-rollary of confidentiality applies to the food allergic child. These children are frequently the targets of bullying, dis-crimination and harassment.[4] Experts advise that care should be exercised to prevent the isolation of the food al-lergic child from other children. A number of studies from a group in Canada have looked at the issue of stigmatisation of children with food allergies in school.[5,6,7] When asked to depict their experiences through drawings, the children il-lustrated their feelings of being different, excluded, "other" and panicky when other learners brought in allergenic foods or had food fights in the school cafeteria.[5] They were unable to join their friends at school camps and felt robbed of spending time with them. "A life-saving tool (e.g. EpiPen) represented a differentiating object that meant disclosure was more challenging. Hiding food allergies to fit in, through non-disclosure or concealing life-saving tools, placed children at higher risk and very often resulted in them feeling more anxiety."[6] The children understood that their food allergy was a potentially life-threatening condition, which made it "a big deal".[6]

An ethical framework that would encompass safety con-cerns of food allergic children in schools is that of public health ethics. Here the concern is more the health of populations (children with food allergy) rather than that of individuals. Behrmann explains that this means that schools have to sanction policies to prevent the adverse health outcomes associated with food-induced anaphylaxis, just as other public health policies are enacted to protect other populations with health risks.[4] This includes adequate prevention policies as well as training of staff to manage anaphylaxis emergencies.

SABRINA'S LAW

Sabrina Shannon from Ontario, Canada, was 13 years old when she died from an anaphylactic reaction to peanuts in 2003. She knew she was allergic to peanuts, dairy and soya, with a high risk of anaphylaxis. She was also asthmatic. She was a very responsible young woman who had even participated in a documentary on food allergies when she was 10 years old. On the fateful day of 29 September 2003, Sabrina elected not to take her usual home-made hypoallergenic lunch to school, opting instead for the school cafeteria's French fries. She had eaten them without incident the previous week and once again ascertained that they had been cooked in vegetable, not peanut, oil. Unbeknown to her, however, the tongs that were used to dish up the chips had been contaminated by cheese curds.[8]

After lunch Sabrina started to wheeze in class, but she thought it was an asthma attack. By the time her teacher had retrieved her EpiPen from her locker, Sabrina had collapsed and arrested. She was successfully resuscitated but suffered severe neurological damage and was removed from life support on 30 September 2003.[8]

Subsequently, the Chief Coroner for Eastern Ontario called for comprehensive anaphylaxis management plans to be implemented in all schools in Canada and Sabrina's Law was finally promulgated on 1 January 2006. The re-quirements of this law are that schools have to have adrenaline auto-injectors available in the school office and that staff and teachers have to be trained to recognise and manage anaphylactic emergencies, including administering the auto-injector.[8] Similar legislation has been passed in Australia and the United States of America.

Although Sabrina's Law aimed to protect students with a potentially life-threatening health condition in the school environment, it initially resulted in the stigmatisation of the very children it was intended to protect. A study by Dean et al. revealed "the tension between balancing physical safety with social well-being in a system that often finds the two mutually exclusive due to the disclosure process".[7] The authors believe that Sabrina's Law was ultimately suc-cessful in creating awareness about severe food allergy and that this has been of benefit to the children and families affected by it. Awareness of a condition results in reduced stigmatisation and discrimination and eventual acceptance of such children as "normal".[7]

DISTRIBUTIVE JUSTICE, RESOURCE ALLOCATION AND ANAPHYLAXIS IN LIMITED-RESOURCE COUNTRIES

Access to highly specialised allergy services and inves-tigations for anaphylaxis may be difficult in a limited-resource country such as South Africa. As an example, if every child with peanut allergy, regardless of risk, has to be issued with two adrenaline auto-injectors, the cost implications would be prohibitive. If, in addition, we advocate that every school should have an adrenaline auto-injector, the costs escalate. We would have to consider alternative options such as adrenaline ampoules and syringes, or pre-filled unsealed syringes, in guidelines. At the same time, we ought to advocate for increased resources for allergy in South Africa and also engage with the pharmaceutical

industry to make affordable emergency care available to patients and schools.

LEGAL ISSUES AND ANAPHYLAXIS

The legal issues involved in anaphylaxis include some of the discussion above, particularly with regard to schools' responsibility in preventing and managing anaphylaxis. Other issues have been previously addressed in *Current Allergy and Clinical Immunology*.[9] They include medical liability and negligence in cases of fatal or near-fatal anaphylaxis. If a person dies as a result of anaphylaxis, especially where it is as a result of a medical intervention such as administration of an antibiotic, it is important to express regret and be empathetic, but not to admit liability without first consulting an authority skilled in risk management and/or legal advisor.[9]

Labelling of foods requires accurate information about the allergen content of foods in the public interest and legislation is required to enforce accurate labelling and testing by independent laboratories.[10]

CONCLUSION

Anaphylaxis is a potentially life-threatening allergic condition and its management includes both ethical and legal dilemmas. The main issues involve the degree of uncertainty regarding the risk of anaphylaxis and therefore, avoidance of harm. From a practical point of view, schools play a vital role in the avoidance of exposure to allergens and the emergency management of anaphylaxis in children. The health professional has an important role to play in advising patients and families about potential risk and the management options and in training patients, families and school staff in managing anaphylaxis. Another aspect of the health professional's role involves advocacy for food allergic patients. This role requires engagement with legislators, educational authorities, other health professionals and the pharmaceutical industry to ensure safe environments for food allergic people and affordable treatment of anaphylaxis.

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PRODUCT NEWS

CPD QUESTIONNAIRE

Earn 3 CPD points after you have read the journal by completing the following questionnaire online on the ALLSA website at www.allergysa.org. To earn points you need to log in to the member section to access the questionnaire (contact ALLSA office if you do not know your user name and password). There is only one correct answer and you will have only two opportunities to submit the questionnaire, so please check answers carefully. A pass of 70% or higher is required to gain 3 points.

ADVERSE DRUG EVENTS: WHY WE CARE

1. *True or False:* All adverse drug reactions (ADRs) are unpreventable.
2. *True or False:* An anaphylactic reaction is an example of a Type B ADR.
3. *True or False:* A patient's allergy history plays no role in ADR prevention strategies.

A CLINICAL APPROACH TO DRUG-INDUCED LIVER INJURY

4. *True or False:* Adaptation is characterised by transient minor abnormalities in LFTs without symptoms of DILI, resolving in the presence of continued drug exposure.
5. *True or False:* DILI may mimic other types of acute and chronic liver disease and is, therefore, a diagnosis of exclusion.
6. *True or False:* Corticosteroids are always indicated in the management of DILI.
7. *Choose the correct answer:* The timing of allergic DILI is typically:
   a. 1 to 8 weeks after drug exposure;
   b. 3 to 6 months after drug exposure;
   c. 6 to 12 months after drug exposure;
   d. More than 1 year after drug exposure.

PENICILLIN ALLERGY: WHEN IS IT OK TO USE A CEPHALOSPORIN?

8. *True or false:* The beta-lactam ring acts as a hapten by binding to tissue or serum proteins.
9. *True or false:* Minor determinants are the allergen in 51% of penicillin allergy cases.
10. *True or false:* The specific IgE for penicillins has a high specificity.
11. *Choose the correct answer:* Cephalosporins with identical side chains include:
    a. Cefaclor, Loracarbef, Cephalexin;
    b. Cefepime, Cefotaxime, Cefpodoxime, Ceftriaxone;
    c. Cefadroxil and Cefprozil;
    d. All of the above.

DRUG REACTIONS ASSOCIATED WITH ANTITUBERCULOSIS DRUGS

12. *True or false:* Rifampicin is the only antituberculosis drug that causes Lichenoid drug eruption.
13. *True or false:* The duration of treatment after eliminating the offending drug from the tuberculosis regimen should always be standard 6 months.
14. True or false: Rifampicin and isoniazid should be rechallenged first, as they are the most effective antituberculosis drugs.
15. *Choose the correct answer:* Ninety percent of rechallenge reactions following tuberculosis-associated CADR occur within:
    a. 20 minutes;
    b. 8 hours;
    c. 48 hours;
    d. 72 hours.

A SOUTH AFRICAN MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC

16. *True or false:* The formation of a multidisciplinary drug hypersensitivity clinic at Groote Schuur Hospital is the first clinic of this kind started in South Africa.
17. *True or False:* Anticonvulsant drugs such as carbamazepine and sodium valproate are the commonest causes of toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS) in South Africa.
18. *True or False:* A multidisciplinary drug hypersensitivity clinic of this kind offers an opportunity to consider the entirety of an individual drug's immune-mediated reactions.
19. *Choose the correct answer:* Rifampicin causes hypersensitivity reactions by a number of immune mechanisms including:
    a. Type 1;
    b. Type 4b;
    c. Type 3;
    d. All of the above.

Ethics CPD Questionnaire

ETHICAL ISSUES IN ANAPHYLAXIS

Ethics articles are accredited for ethics CPD points. Log in to the ALLSA website (www.allergysa.org) and click on "My CPD" to submit your answers. Kindly send submissions or suggestions for topics to the section editor, Prof Sharon Kling at sk@sun.ac.za

INDICATE TRUE OR FALSE

1. It is often difficult to quantify the risk of anaphylaxis in a child with food allergy. This causes uncertainty as to what is in that child's best interests, i.e. the principle of beneficence applies.
2. Evidence-based medicine ought to guide treatment plans in peanut allergic individuals, but it is not always available.
3. The ethical dilemma in managing the food allergic child at school is in weighing up the risk of non-disclosure of the food allergy against respecting his/her confidentiality.
4. The food allergic child's needs should always take precedence over the rights of other children at school.
5. Confidentiality in medicine is derived from the principle for respect for autonomy.
6. The framework of public health ethics may be applied to the population of food allergic children.
7. Sabrina's Law, promulgated in Canada after the death of Sabrina Shannon, requires schools to have auto-injectors available in every classroom.
8. Sabrina's Law, although designed to protect food allergic children in school, actually worsened the stigmatisation of these children.
9. Distributive justice requires a health system to allocate resources fairly, taking into account the individual's need but balanced against the needs of others.
10. If a patient dies as a result of anaphylaxis to an antibiotic, the doctor ought to apologise to the family and take full responsibility for the death of the patient.

The 24th ALLSA Congress Report

Two hundred and ninety two delegates attended the 2015 ALLSA Congress, which was held at the elegant Boardwalk Hotel in Port Elizabeth. The 2015 congress was structured around the theme "Basics and Beyond" and parallel sessions covered the clinical and the immunological aspects of allergy and asthma, by means of lectures and workshops. The International invited speakers were Dr Klaus Warnatz, Senior Consultant in Rheumatology and Clinical Immunology at The University Medical Centre in Freiberg, Germany and Dr Rosan Meyer, a dietician from London, United Kingdom. Local invited speakers included Sister Lucia Volkwyn, Drs Gloria Davis, Shaunagh Emanuel, Ray Friedman, Claudia Gray, Di Hawarden, Sarah Karabus, Tamara Kerbelker, Ahmed Manjra, Jonathan Peter, Mike Urban, Sylvia van den Berg, Talita van der Watt, Cathy van Rooyen and Debbie White and Professors Monika Esser, Robin Green, Sharon Kling, Mike Levin, Paul Potter, André van Niekerk and Eugene Weinberg.

Dr Ray Friedman, an Ear, Nose and Throat specialist and Honorary Consultant in the Department of Otorhinolaryngology at Johannesburg Academic Hospital, University of the Witwatersrand, provided a comprehensive overview of the anatomy and physiology of the nose. He discussed the reasons that patients do not respond to treatment and illustrated his talk with case studies and a nasal endoscopy video clip. He continued with a second talk on Polyposis and Epistaxis and gave practical guidelines for the treatment of these syndromes.

Drs Di Hawarden and Shaunagh Emmanuel discussed the practical aspects of immunotherapy, skin prick tests and intranasal corticosteroids, spirometry, metered dose inhalers and dry powder Inhalers and spacers. They gave simple but extremely important advice, from shaking the inhaler canister to more complicated guidance on the correct use of spacers, which should be adjusted for size as young patients grow. Technique was demonstrated, supported by slides showing diagnostic tests such as skin prick test wheals and they cautioned against the incorrect use of technique. Poor compliance was discussed. All of these relaxed, informative sessions were work-shopped and interactive. During the next session they gave a detailed overview of anaphylaxis and reviewed the management regimes of anaphylaxis. Drs Hawarden and Emanuel teamed up with Professor Mike Levin for a session, during which the practical aspects of allergy were demonstrated and discussed, from the wearing of medic alert bracelets to the use of adrenaline auto-injectors and the importance of action plans in the treatment of allergy.

Emeritus Professor Eugene Weinberg reviewed the diagnosis of asthma using a metaphorical fairy tale character as his asthmatic patient and deftly interweaving the story line with the symptoms, diagnosis and treatment of asthma. He held everyone rapt, as he worked through each step of the diagnosis of this fictional character, interacting with his audience, encouraging them to think about each choice and using flow charts to illustrate the route to the diagnosis of asthma and the exclusion of other syndromes. He stressed that many other conditions mimic asthma and gave guidelines for the selection of age appropriate tests.

Dr Debbie White discussed the modalities used in the treatment of asthma, using detailed charts and guidelines to examine the diagnosis and assessment of asthma severity. She listed stepwise treatment actions and stressed the importance of patient education.

Dr Sarah Karabus discussed Chronic Spontaneous Urticaria in depth, noting how important it is to moisturise the skin and **Dr Claudia Gray** took her audience through a discussion of eczema, stressing the role of a defective skin barrier. She emphasized the association of food allergy and eczema and stressed that food allergy may not be the direct cause of eczema and said that oral food challenges are essential in diagnosing this allergy in patients with eczema. This talk was followed by a practical demonstration of the topical treatment and wet wrapping of the child with eczema, by Sister Lucia Volkwyn, who used a doll as her demonstration model. Dr Gray interviewed Sister Volkwyn and the discussion during this demonstration, was informative and extremely practical.

Drs Tamara Kerbelker, Talita van der Walt and Claudia Gray presented case reports.

Dr Rosan Meyer discussed the importance of selecting hypoallergenic milk formulae for a child with cow's milk allergy and followed this with a discussion of the dietary requirements for the child with multiple allergies.

Dr Klaus Warnatz covered many aspects of Primary Immunodeficiency, in detailed presentations which covered B-cells, memory B-cells and autoimmunity. He illustrated his talks with relevant case histories, describing syndromes such as transitory hypogammaglobulinaemia and interstitial lung disease.

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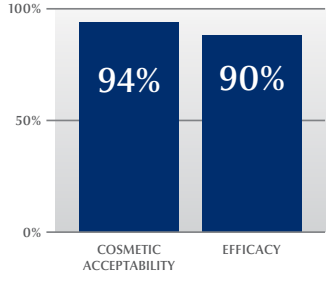

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Dr Sylvia van den Berg discussed the principles of flow cytometry.

Dr Monika Esser discussed the Immunoglobulins and the difficulties that arise when interpreting immunoglobulin laboratory levels and autoantibody laboratory results.

Dr Jonny Peter added to these sessions with discussions ranging from the role of T-reg cells to the diagnosis of PID using flow cytometry and Ig replacement and maintenance was outlined by Drs Esser and Peter. Case discussions brought these sessions into focus and Dr Jonny Peter illustrated the danger of misinformation in adverse drug reactions when describing a case of anaesthesia anaphylaxis, where the consultant had not been given the correct facts.

Dr Cathy van Rooyen discussed gluten sensitivity and coeliac disease.

Professor Sharon Kling took her audience through the difficult decisions that need to be made when the clinician's innate morality is at odds with the ethical code. She gave examples from other countries where dire or fatal consequences have been the result of adhering to the refusal to sell scheduled drugs without a prescription, to a patient with anaphylaxis, or where guidelines had not been in place for the protection of schoolchildren with severe food allergy in school canteens. She covered the modes of morality that are described when making these decisions.

Professor Paul Potter emphasised the importance of hidden food allergens, when the culprit food is obscure. He illustrated this lively presentation with a case history of a patient who developed severe symptoms after eating a particular brand of ice cream, of a variety that she had eaten many times before. On taking a careful history he discovered that she had chosen ice cream in a cone that included lupin flour as an ingredient and that lupin was proven, using laboratory tests, to be the hidden allergen. His second case history concerned a farmer/game hunter who had killed and eaten porcupine. The patient was "a bit of a cowboy" he told his audience who believed that large doses of antihistamines would counter adverse food reactions and needed to be educated about the management of his food allergy.

Dr Skumbuzo Ngozwana delivered the keynote address, explaining how drug therapy as we know it, would change in the future and be tailored to fit the needs of the individual. He stressed that Africa has specific needs and the pharmaceutical needs of the African Healthcare Renaissance would have to be met. He warned that with the volatile economic environment changing from day to day, it would be well for pharmaceutical companies to manufacture drugs in Africa, as imported drugs were likely to become unaffordable, even those imported from Asia.

Professor Robin Green gave the Eugene Weinberg lecture and discussed the complex interaction between respiratory infection and allergies and the role of viruses (Rhinovirus, Respiratory Syncytial Virus and Influenza virus) and bacteria in the development of atopy.

Professor André van Niekerk discussed the management of persistent airway infections, stressing the role of biofilm in thwarting drug therapy and stressed the importance of the correct diagnosis of recurrent infections which might begin with allergic rhinitis and then move on to infection and asthma. This was followed by a discussion on immune related causes for chronic and recurrent airway infections by **Dr Monika Esser.**

Dr Cathy van Rooyen outlined the correct choice of tests for the diagnosis of recurrent and chronic airway infections.

Professor Mike Levin covered advances in food allergy, neatly changing hats as he moved from his urban experience in an academic hospital, to the vastly different reality of food challenges in a rural Transkeian village, where children and farm animals mingle freely. He illustrated his talk with slides, explaining how he and his team set up a laboratory in the bush ('the tented waiting area goes up in one minute') and described how he managed food challenges in this population group.

Dr Gloria Davies took her audience back to the 1960's when she was a young mother, struggling to manage an asthmatic child in Port Elizabeth. There were few guidelines in place for the diagnosis and treatment of asthma and allergy in those days and she described her relief when she eventually met a young doctor named Eugene Weinberg at Red Cross Children's Hospital. He was one of the clinicians who played a pivotal role in changing her son's life, so that he was able to become an excellent sportsman. Dr Davis emphasised the importance of the environment in allergy and encouraged her colleagues to be aware of the role of aeroallergens. She detailed the history of the treatment of asthma and allergy in a talk titled: "Ethics: An Odyssey - from the abyss to the abuse."

CAS MOTALA MEMORIAL LECTURE

Emeritus Professor Eugene Weinberg paid tribute to Professor Cas Motala, his former registrar, colleague and friend, describing the many aspects of this man of great humility and humanity. His lecture was titled: "Protracted Bacterial Bronchitis in Children: The Role of Biofilm". He explained that biofilm encapsulates bacteria such as *Haemophilus influenza* in lung tissue, protecting these bacteria from antibiotics. He warned that a wet cough of 3 weeks duration that does not respond to medication is an important symptom in this syndrome and he paid tribute to Dr André van Niekerk who had alerted him to the role of biofilm.

Dr Ahmed Manjra comprehensively covered the role of the

mast cell in the pathogenesis of allergic disease.

Dr Mike Urban gave a comprehensive update on the practical applications of Primary Immune Disease and Allergy, outlining new findings and applications.

CONGRESS DINNER

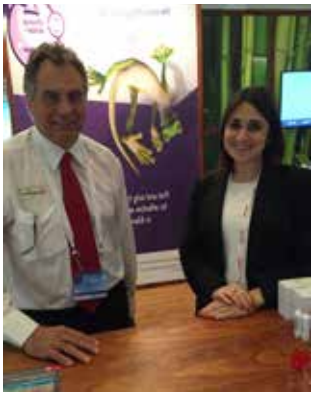
The dress code for the gala dinner was black and white and the elegantly attired delegates enjoyed a fun filled evening, with live music, energetic dancing and a beautifully presented banquet. Di Hawarden, the newly elected ALLSA chairperson was an able compere and insisted that her committee members dance onto the stage one by one, as their names were announced. Each newly elected committee member did this with good humour, demonstrating that the ALLSA Excom are as varied in their individual dancing styles as they are in their fields of expertise.

ALLSA Research Awards were presented to Frank Kirstein, Craig Laurence and William Horsnell. ALLSA Honorary Awards were conferred on Dr Rosan Meyer, Dr Klaus Warnatz, Dr Skhumbuzo Ngozwana, Dr Gloria Davis and Dr Marcelle Groenewald.

ALLSA Journal Awards went to Shaunagh Emanuel for the best picture and Debbie White for the best article. The awardee for the best Free Presentation was Debbie Parris. The trophy for the best exhibition stand went to Beiersdorf-Eucerin.















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Are the symptoms really signs of allergy?

Nasal congestion/sneezing, itchy/watery eyes and nose:

- **65%** of patients diagnosed as having allergic rhinitis and prescribed antihistamine may not be allergic. [1, 2]

Wheezing, coughing, breathing problems:

- **90%** of children and **60%** of adults with asthma have allergy. [3-5]

Dry skin, pruritus, scratching:

- **90-70%** of infants and young children with eczema have underlying allergy. [3, 6]

Rule in or rule out allergy early – add a Phadiatop® blood test to increase certainty

Phadiatop® measures IgE antibodies to a well-balanced mixture of common inhalant allergens. These tests help you to:

- differentiate IgE mediated atopic allergy from other allergy-like symptoms [7-13]
- identify patients that need Specific IgE testing for allergen identification and continued allergy care [7-13]

Reveal the secrets behind the allergy-like symptoms

A single blood test that helps you to rule in or rule out allergy

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