CURRENT ALLERGY & CLINICAL IMMUNOLOGY

JOURNAL OF THE ALLERGY SOCIETY OF SOUTH AFRICA

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Allergy, Immunology, Ethics and the Law

Patient Empowerment: creating effective partnerships between the patient and the healthcare delivery chain

Promoting access to safe medicines for children

Simulation-based education in allergology training: a South African perspective

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GUEST EDITORIAL

It is my privilege to edit this issue of *Current Allergy and Clinical Immunology*, the theme of which is 'Allergy, immunology, ethics and the law'. Thank you to Professor Eugene Weinberg and Dr Di Hawarden for their encouragement and support, and for entrusting me with this issue. I wish to express my thanks to the authors of the articles in this issue, and to the section editors for their contributions. I also wish to thank Mrs Robyn Marais, the production editor of the journal, for her professionalism and patience.

Ethics fascinates me. My interest in ethics was originally piqued by Professor Solly Benatar, and I was encouraged by many colleagues to do the wonderful MPhil in Applied Ethics offered by Professor Anton van Niekerk at the Centre for Applied Ethics at Stellenbosch University. Subsequently, Professor Weinberg encouraged me to establish the ethics section for *Current Allergy and Clinical Immunology*, and most of our allergy congresses have included ethics presentations.

Allergy, immunology, ethics and the law intersect in many ways. Studies and clinical trials in asthma and allergy are governed by research ethics and regulatory guidelines. Ethics impacts every aspect of clinical practice. Particular areas in allergy practice involve allergy prevention, food allergy, and access to investigation and treatment. It is, however, in the field of health policy that the Allergy Society can play a role. In 2014, I wrote:

> 'Where I do believe we need improvement, however, is in policy development and advocacy for patients with allergic problems. We must also advocate for equity of access to health care services and to appropriate treatment, including expensive therapies if necessary, for people with allergic diseases.'[1]

I am encouraged by the establishment of the Allergy Foundation of South Africa (AFSA), as I believe that this is the vehicle for advocacy and influencing healthcare policy. I would like to pay tribute to André van Niekerk, Mike Levin and Lynn Kampf for the enormous amount of effort and time they have put into AFSA.

In this issue of the journal we have four invited review articles around the theme. Professor Matthias Haus, who has had a long-standing interest in ethics and clinical and business governance, has written a masterly article titled; 'Patient empowerment: creating effective partnerships between the patient and the health care delivery chain.' In it he makes the point that patients have taken an increasingly greater interest in their health and the treatment options available to them. Professor Haus discusses the ethical dilemmas and emerging processes pertaining to promoting patient empowerment, as well as empowerment programmes which could benefit all stakeholders in the healthcare delivery chain. Professor Mariana Kruger, the Executive Head of the Department of Paediatrics and Child Health at Stellenbosch University, writes on a topic about which she is passionate: 'Promoting access to safe medicines for children.' In it she discusses the high prevalence of off-label medicine use in paediatrics, and makes suggestions as to how clinicians can advocate for children in this regard. Professor Alina Beyer is a medical doctor who has also trained in law and who is now teaching as an Associate Professor at a US international medical school. She has written an article on 'Simulation-based education in allergology training: A South African perspective'. She makes the point that using medical-simulation techniques in teaching can improve the ethical practice of allergy and immunology and can play an important role in preventing medical errors. I have written an article on 'Health professionalism and ethics – Is there a difference?' Professionalism is currently under the spotlight in South Africa, with healthcare professionals' transgressions publicised in the popular media. Numerous reports abound of healthcare professionals abusing patients or providing substandard care to them. Within the healthcare profession there is an attempt to renew our professional values, which have been eroded by the managed healthcare system and undermined by healthcare funders. Professionalism and ethics exist on a continuum, but there are important differences between them. Ethics, a branch of philosophy, provides a framework for reflection and discussion about deeper moral issues such as euthanasia, abortion, genetic testing and social justice.

This issue also includes a peer-reviewed article on the major allergens of the Asian Green Mussel by Yadzir and co-authors. In the always excellent series, 'Allergies in the Workplace', Hilary Carman addresses multiple chemical sensitivity. The PID section comprises an article on identifying patients with primary immune deficiencies by Sylvia van den Berg and Cathy van Rooyen, and one on Wiskott-Aldrich syndrome by Monica Esser. And, of course, the excellent ABC of Allergies by Shaunagh Emanuel and Di Hawarden never disappoints.

I hope you enjoy reading this issue as much as we enjoyed putting it together.

Sharon Kling
Guest editor

1. Kling S. Ethics and allergy practice. Current Allergy and Clinical Immunology 2014;27(4):268–270.

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Guest Review

PATIENT EMPOWERMENT: CREATING EFFECTIVE PARTNERSHIPS BETWEEN THE PATIENT AND THE HEALTHCARE DELIVERY CHAIN

Matthias Haus | MBChB, MD, DCH(SA), FCFP(SA), DipObst(SA), FFPM(RCP)

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SUMMARY

The delivery of healthcare has, over the past 2 500 years, been firmly entrenched in the domain of the physician. Since the 'Father of Medicine', Hippocrates (470 BC) created his vision for just, moral and ethical standards of administering and providing medical care for his patients, the information flow and decision-making responsibility has resided uniquely and solely in the formal and traditionally established physician-driven medical system. Patients were grateful, uninformed, unimpowered and entirely dependent on their physician's judgement, intent, knowledge and goodwill. In this role, the medical caregiver's image was akin to a god-like figure. Recently, however, during the explosion of the information and technology era, patients have been taking a more inclusive interest in their health and the various treatment options available to them. This article examines the benefits, risks, ethical dilemmas and emerging processes being offered to promote patient empowerment, and also proposes three different novel categories of empowerment programmes which could be to the benefit of all stakeholders in the healthcare delivery chain (HCDC).

INTRODUCTION

The medically trained physician has, for millenia, been the partisan purveyor and deliverer of healthcare, a situation described by some as '*le syndrome du bon Dieu*' (Jacque Kriel, personal communication) and often leading to a form of dysfunctional medical practice.[1,2] But, during the past 50 or so years, *parri-passu* with the emergence of today's technological age, the patient is becoming as well, if not better, informed about their various conditions. For example, self-help books were and are in every household's library (medical encyclopaedias, medical self-help books for families such as Dr Spock's childcare books). The advice of the local pharmacist (who now does screening cholesterol levels, random blood glucose tests, blood pressure measurements and even pregnancy and HIV screening) is freely asked for. In addition, the social power of a new generation of glossy magazines (brimming with healthcare advice and provocative advertising) and television medical 'chat' programmes (often poorly disguised marketing instruments sponsored by the manufacturers of commercially interested companies such as vitamin and mineral supplement alternatives) are extremely popular. People love the drama of health-related topics, especially if they can share in other people's misfortune. The power and reach of the new 'social media era' together with the explosion of the information technology boom through the powerhouse of the internet (with search engines such as Google) has changed the face of information access. Digital technology can now even assist diabetic patients with 'step counting', using various personalised devices to ensure that they exercise enough every day.

Consequently, the ready and rapid access to information has altered the mindset of patients completely. From being sterile, inactive recipients of healthcare, patients are becoming proactive and informed enough to demand a 'partnership' culture with their healthcare providers. Patients now have the tools and information access to become rapidly empowered.

According to Wikipedia's definition of 'patient empowerment' as a concept, the recent outgrowth of the global health movement asserts that '… to be truly healthy, people must themselves bring about changes in their social situations and in the environment which influences their lives, not only in their personal behaviour'. These advocates list the following as key tenets of patient empowerment:

1. Patients cannot be forced to follow a lifestyle dictated by others.
2. Preventative and curative medicine requires patient empowerment for it to be effective.
3. Patients as consumers have the right to make their own choices, and the ability to act on them.

In order to identify the appropriate platforms, interventions and novel tools to create a patient empowerment culture,

I use the following definitions for an 'empowered patient':

> *Archetype 1:* A patient who becomes well informed about their condition through various and diverse information channels, and who then works together subsequently in partnership with their physician to decide mutually on the most appropriate form of treatment, intervention and outcome options for the condition. The sanctity and authenticity of the patient's right to ultimately make their own choice for treatment is paramount and should be encouraged.
>
> *Archetype 2:* A patient, who is connected to various self-help and common community networks, in order to share experiences, develop a sense of common purpose and to engender a sense of 'belonging' with similarly afflicted patients, whatever their condition may be. These networks can be created by digital technology platforms, or can be sponsored and formed by academic bodies, pharma companies and socially initiated groupings.
>
> *Archetype 3:* A patient who becomes part of unique projects designed to give them back their self-esteem, the courage to bear their burden of disease with fortitude and to give them a sense of meaning and purpose in life, independently of the gravity or prognosis of their disease. Patients with diseases which hold a social stigma (such as HIV/AIDS, cancer, alcoholism, drug dependence and mental disease) are especially responsive to such interventions. Projects designed to give patients back their self-esteem and power often simultaneously create the conditions whereby they become powerful forces for change and renewal in their communities.

The paradigm shift in the HCDC is consequently now rapidly evolving. This evolution is creating both new problems, but then also many opportunities for those in the HCDC. New players such as healthcare funders, pharmaceutical companies, institutional and private hospital groups, 'over-the-counter' and alternative medicine manufacturers and traditional cultural healers have all become important stakeholders in what is today called the 'healthcare industry'. The value proposition and mandate of the historically dominant physician has consequently become co-owned by a plethora of new players, who are today an amalgam of providers of a wide range of services to the patient.

Regrettably, however, the patient is becoming increasingly confused by the explosion of facts and diverse proposed solutions, resulting in an even greater 'need-to-know' culture of information hunger.

Within this transformational turbulence, the value and cornerstone importance of both information and stakeholder connectivity remains central. One of the dilemmas is, of course, whether the required information availability is constantly and equally accessible everywhere (this connectivity differs between developed First World communities and emerging Third World communities) and whether it is validated and correctly interpreted by both patient and doctor in a balanced and scientifically relevant manner.

Nevertheless, the central premise is that the information and decision-making flow in terms of medical care today has reversed. It now runs in the opposite way, in that the patient is usually well (although not always wisely) informed of their condition and possible treatment options by the time they consult their doctor.

The question then begs as to whether the doctor today is redundant? An assessment of the average patient's opinion and faith in their information sources (other than that received through a medical consultation) has shown that patients put as much value on information and advice which they have obtained themselves, as they do by consulting their physician (personal communication, Hamelin). This is a growing reality. Medical information access channels available in the public domain are expanding exponentially, as both patients and healthcare providers are seeking new and reliable sources of information.

The explosion of health-related websites is a case in point. These sites vary in content and by sponsor. For example, the Governmental Agency for Healthcare Research and Quality of the US Department of Health and Human Services has created a website entitled www.ahrq.gov/questionsaretheanswer (accessed July 2012), where patients are instructed what to do before, during and after a consultation with their physician. They are encouraged to recognise that they cannot be forced to follow a lifestyle dictated to by others, and that they are entitled to make their own choices, together in an equal partnership with their physician, and act on them. Indeed, the concept of personal choice and co-responsibility in managing one's health is being incorporated into the discipline of Medical Ethics as a growing interest area in medicine. Even very young children now have well-defined choices in accepting or refusing treatment,[3] according to the Child Health Act of South Africa. The US website quoted above is aggressively advertised (*USA Today*, 23 November 2011) with full-page advertisements in globally circulated papers. Then there are therapeutically segmented sites, for instance, a website for patients with allergic disease, driven by the European Academy of Allergy and Clinical Immunology (www.infoallergy.com, accessed July 2012).

These are only two examples of governmental and organisational 'self-help' websites. There are thousands of other information channels. But regrettably, the quality of information and its relevance to any particular situation is, at best, fragmented and incomplete. Information on its own is worth very little.

Nevertheless, by the time a patient in a First World,

developed country sees their physician, they invariably know as much (if not more) about their condition than him or her. They are also eagerly prepared to litigate at any stage should there be any perceived or real act of omission or commission by the healthcare provider which leads to any adverse event or sequelae to treatment. Patient safety, with regard to the monitoring and tracking of side-effects and abnormal events after ingesting medication is therefore a growing concern, and physicians all now carry significant amounts of medical insurance cover (eg the Medical Protection Society, UK), far in excess of the situation years ago.

The question remains as to whether this empowerment, relating to the patient's own rights and choices, is balanced and augmented by the clear added-value benefits of their physician's judgement and an understanding of outcomes-based solutions which only a healthy and robust partnership with a physician will bring to any particular solution.

In addition, because of recently more stringent monitoring of organisational governance and ethical codes of behaviour between doctors, their patients and the global pharmaceutical industry, the terms of engagement and the unencumbered debate and discussion between these various stakeholders has become increasingly regulated.

It should be noted that patient empowerment and protection has also fallen under the spotlight in other areas. For example, the regulation of clinical development work with both new and established chemical entities has been tightened. The very fine ethical principles applicable to doing medical research on human subjects, as enshrined in the Declaration of Helsinki (World Medical Association General Assembly, Helsinki, 1964) has now gone through numerous additional iterations (the latest being in Seoul, Korea, in 2008). Some governments have been of the opinion that clinical trials have used patients as 'guinea pigs'[4] and new laws are constantly being promulgated to ensure the dignity, safety and empowerment of patients.

'What' then and, even more importantly, 'how' then, do the major stakeholders involved (see Figure 1) in the provision of optimal healthcare to patients develop and create an integrated, co-ordinated, relevant and structured partnership model which will increasingly empower patients within our regulated environment, while at the same time, ensure optimal healthcare and the elimination of risk?

EXISTING PLATFORMS AND INFORMATION SOURCES CURRENTLY AVAILABLE

These are broadly listed and discussed in the introductory comments of this article. These platforms are suitable for the Archetype 1 patient.

NEW EMPOWERMENT MODELS

There are three new categories of unique patient empowerment models which can be developed and integrated into a novel operating plan for both Archetype 2(a and b) and Archetype 3(c) patients.

a. Connectivity, networking and communication with common interest communities, using social networking media and telecommunications platforms. These novel and emerging adaptations of digital technology can be readily developed today, working closely with innovative and highly specialised digital agencies. The platforms, principles and marketing concepts used in creating common online communities are easily developed and are based on a software lifecycle methodology (SDLC) system.
b. Membership, participation and facilitation of therapeutic area interest groups, such as the disease-oriented patient empowerment (DOPE) programmes, encourage the patient to co-manage their disease in consultation with other similarly affected patient groups. This is a proposal and concept designed by Prof Robin Green, Professor and Head of Paediatric

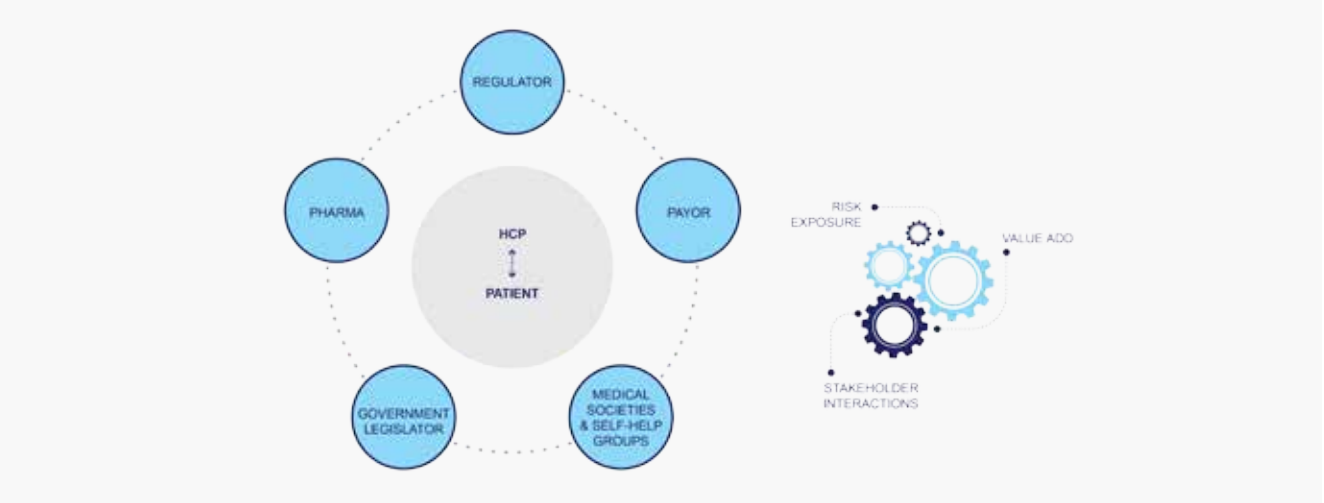

Figure 1: Stakeholder interactions

Pulmonology at the University of Pretoria, and past Chairman of the National Asthma Education Programme (NAEP) (Personal Communication).

c. Rolling out unique, therapeutically-based patient participation programmes, to elevate self-esteem and to create the optimum positive environment for mental and physical healing while the patients are dealing with their particular disease. The encouragement of patient advocacy and support is a cornerstone of this platform, such as the Moments in Time Project for example – a multidimensional project which connects oncologists, patients and our society at large. Apart from the passionate and artistically unique product deliverables, (visually appealing calendars, diaries and other products) the project has become extremely well branded, and has brought fundamental and meaningful support to hundreds of patients living with cancer. The project, which can be viewed on www.momentsintime.co.za (accessed March 2014), has influenced and changed the lives of thousands of patients living with cancer. The project can be presented as an example of patient empowerment and advocacy in the purist sense. One patient wrote:

   'Thank you for this magical and life-affirming opportunity. You have given us dignity, self-respect, a purpose to fight the battle and a meaning for life. Moments in Time is not only about honouring patients, but more about honouring and encouraging those patients and loved one's who will gain strength from this project. You have my deepest respect and fond love …'

This concept can be expanded and tailored to any therapeutic area.

GAME-BREAKERS

There are numerous potential game-breakers which need consideration before a risk-free and workable implementation programme can be implemented. Both the advantages and the disadvantages for each stakeholder need to be appreciated, as well as the impact between stakeholders. For instance, failure to appreciate that the governmental and secular legal framework, the commercial imperatives, the healthcare providers' ethical considerations, the funders actuarial and social complexities, the regulator's safety and gatekeeping role and the pharmaceutical companies governance and conduct prerogatives will all need to work in harmony.

So, is the promotion of patient empowerment desirable or an unmitigated risk? Is it really an attractive option to encourage the patient to play a greater role in choices regarding their welfare? Are the downsides of any such initiative perhaps not ultimately to the patients' detriment? Because clearly passengers do not fly jet planes nor do airline captain's practise surgery! Is there more benefit than risk in patients taking increasing responsibility for certain of their healthcare decisions?

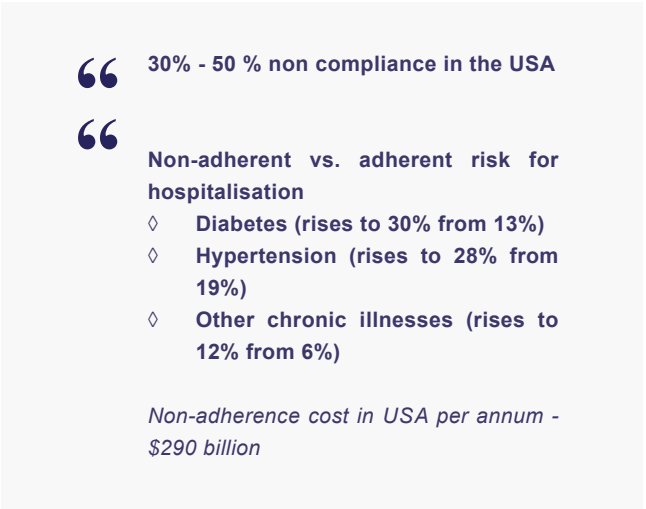

Figure 2: Patient compliance as a surrogate marker for empowered patients

Consequently, empowerment could be a negative development, although hardly avoidable in this era of modern information technology. 'Concern for impact' needs to be fully understood by all stakeholders. For instance, government agencies and licensing bodies for healthcare professionals (HCPs) could easily legislate against the use of electronic communication platforms between the HCPs and their patients. Equally, pharmaceutical companies would need to be aware of the risks when planning interventional strategies for their patients to avoid legal, regulatory and moral backlashes.

Questions should also be rightfully asked regarding the sources and validity of any information channels being accessed by the patient. Regulatory agencies may have legitimate safety and efficacy concerns regarding patient information leaflets for example, although websites and internet-based platforms are invariably not easily regulated.

Other than electronic and internet search engines, medical organisations and societies have begun to develop programmes which integrate educational advice into each patient contact. Some funders and medical aid organisations have begun to explore the facilitation of contact between HCPs and their own 'wellness programmes'. The largest medical aid in South Africa, Discovery Health, has offered financially incentivised 'reward' points to patients who join the National Asthma Education Programme (NAEP), who then receive discounts on a large number of health-related activities such as gym memberships, travel, etc. To date, this kind of access to medical information by bodies such as NAEP have been welcomed by the regulators, since the overall benefits to healthcare are obvious. While pharmaceutical companies cannot deal directly with patients, in this manner, they can directly influence this process by funding

Justice, integrity and morality will become the NEW order in our transitional world, in every aspect of human endeavour and striving…….

Figure 3: This is a process, not an event

NAEP and similar societies.

The downside of having patient information disseminated by the powerful press, television and the general print media is that these media often offer largely invalidated and unregulated sources of information.

PATIENT COMPLIANCE AS A SURROGATE MARKER FOR EMPOWERED PATIENTS

Data from the US healthcare system suggests that between 30–50% of patients do not take their prescribed medications. These non-compliant patients have significantly higher rates of hospitalisation and mortality compared to compliant patients. This is one positive reason for patient empowerment to be emphasised (Figure 2).

CONCLUSION

Using the principles, technologies and novel projects and platforms detailed above, in tandem with the existing information technology and internet-based search engines currently available, unique and mutually beneficial patient empowerment processes can be created and implemented by all the stakeholders concerned in the HCDC.

This momentum will become more relevant in the coming years, as the world moves into the new technology age (see Figure 3).

CONFLICT OF INTEREST AND FUNDING

The author has no conflict of interest to declare in the preparation of this article. He is currently a shareholder-appointed Independent Non-Executive Director of Adcock Ingram Holdings Limited, a Trustee of the Colleges of Medicine of South Africa and an Extraordinary Professor in the Department of Paediatrics, Faculty of Medicine, University of Pretoria. He has received no funding or support from any organisation for this paper.

This article has been peer reviewed.

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Guest Review

PROMOTING ACCESS TO SAFE MEDICINES FOR CHILDREN

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ABSTRACT

Children should have access to safe and efficacious medicines. Unfortunately, due to the lack of dedicated paediatric clinical trials, adult data is often extrapolated to children, leading to the common practice of prescribing off-label medicines to children. Off-label medicine use can be used to the advantage of children if clinicians, as part of their ethical responsibility to children, publish the outcome of off-label medicine use, as well as any adverse events or lack of efficacy. This article addresses the need for national policies to incentivise paediatric medicine research and registration. This has been done in the United States and Europe and should be done in South Africa. Furthermore, it is important to participate in collaborative, multicentre studies regarding paediatric off-label medicine use to generate the safety and efficacy data for these medicines in children. Finally, as part of our advocacy responsibility, healthcare workers dealing with children should pressurise pharmaceutical companies to register medicines, where paediatric efficacy data is available.

CURRENT OPINION

Children are often exposed to medicines that are not registered for them as there is a paucity of paediatric clinical trials, which are the gold standard for adult medicines preceding registration with national medicine-regulating authorities.[1–3] There are few incentives for pharmaceutical companies to conduct paediatric clinical trials, as these are not economically viable due to the small amounts of medicine needed by children.[4] Paediatric medicines, as well as medicines for rare diseases, are often described as 'therapeutic orphans' due to this lack of registered medicines. Since there is a lack of paediatric clinical trial data, healthcare workers have to rely on either adult data or expert opinion for the age group or clinical condition in therapeutic decision-making, leading to the practice of off-label medicine use.[1] 'Off-label medicine' refers to the use of medicines in a manner for which the medicine is not registered and therefore not indicated in the package insert.[3,5] Off-label use can be for either unapproved dosage, unapproved indication, unapproved age, unapproved frequency or unapproved formulation.[3,5] According to a review by Kimland and Odlind, the most common reason for off-label use in children is the lack of paediatric data.[5]

The use of off-label medicine does not imply any illegal or improper use or a lack of the necessary clinical experience, but only that the required safety and efficacy data are not yet available for registration purposes or data is extrapolated from adult data to assist in prescribing for children, since the sponsor of the medicine has not applied for registration. This could be due to the lack of paediatric clinical trials, especially as there is a lack of potential profit in the paediatric medicine market with little or no interest to the pharmaceutical industry.[1,5,6] As children are not young adults, they have age-related differences in physiology and disease pathophysiology, which necessitates dedicated clinical trials to generate the clinical safety and efficacy data needed for registration purposes.[6,7] These differences in physiology affect the absorption, distribution, metabolism and excretion of medicines and significant dose adjustments may be required to achieve target plasma concentration in children. It is crucial to generate scientifically-based, age-related dosing information, as treatment failure can result from subtherapeutic doses, as well as adverse effects without any therapeutic benefit from doses higher than required. Off-label use is especially true for neonates, young children and children with rare or chronic diseases. These populations of children are deemed particularly vulnerable in research, posing many challenges to their enrolment in clinical trials.[8]

In order to address the lack of registered safe and efficacious paediatric medicines, both the United States and the European Union have created regulatory frameworks to generate the necessary safety and efficacy data through paediatric clinical trials. The United States has promulgated the Best Pharmaceuticals for Children

Act (BPCA) and the Pediatric Research Equity Act (PREA) to improve paediatric medicine access which has led to increased paediatric labelling changes for more than 500 medicines since promulgation.[1,9,10] As an incentive, the BPCA specifically extends post-marketing exclusivity for six months if a pharmaceutical company submits data from paediatric clinical trials to the Federal Drug Administration (FDA) when applying for licensing or registration.[1,9] The PREA requires that all new medicines and certain approved medicines that may benefit children should be investigated in the paediatric population, except if there is an FDA waiver.[10] The European Union introduced a similar regulation, namely, the European Union 1901/2006 Paediatric Regulation in 2007, to increase the number of registered paediatric medicines. The regulation requires that all pharmaceutical companies submit a Paediatric Investigation Plan (PIP) if a medicine is of potential benefit to children.[11] This regulation has led to a marginal increase in the number of paediatric clinical trials, but has not always had the necessary positive effect, since the PIP is often driven by an adult indication.[12] Medicines are now available, for example, for very rare childhood cancers such as melanoma, whereas no new medicines have been developed for the common childhood cancer neuroblastoma.[12]

Globally, there are approaches to promote access to safe and efficacious medicines for children. One approach is the Essential Medicines List (EML) of the World Health Organisation (WHO), introduced in 1977 and regularly revised.[13,14] The EML includes medicines proven to be safe, affordable, of good quality, as well as cost-effective and provides a guideline for low- and middle-income countries (LMICs) for the treatment of common childhood conditions. The estimated cost of EML is US$13–US$25 per capita as a basic healthcare package, although LMICs spent less than US$13 per capita per annum resulting in the majority of the world's children still having inadequate access to these affordable EML medicines.[14] The WHO also adopted resolution WHA 60.20 in 2007 to encourage member states to undertake paediatric medicine research for new medicines, as well as to improve knowledge regarding paediatric dose and formulations for existing medicines as part of their priority area of improved medicines for children.[15]

The second approach is the orphan medicines model, which addresses the need for medicines for rare diseases. The United States promulgated the Orphan Drugs Act in 1983 and the European Union followed with their regulations in 2000 to investigate effective treatments for rare diseases, with acceptable safety profiles where the diagnosis of the rare disease is feasible and the necessary expert infrastructure is available.[16–18] Combining both the WHO initiative with the EML and the orphan medicines' approaches the International Society of Paediatric Oncology (SIOP) and Paediatric Oncology in Developing Countries (SIOP-PODC) clinicians, for example, have implemented modified treatment protocols using EML medicines to treat common childhood cancers in LMICs with great success.[19–21] Studies from Malawi and Brazil have proved these modified paediatric cancer therapies to be cost-effective, with the cost of treatment for Burkitt lymphoma being as low as US$50.[22]

To date, no clear regulation or policies have been identified in Africa in order to address the need for better paediatric medicines or medicines for rare diseases. This is despite Africa being one of the world's fastest growing economies with a pharmaceutical industry value of US$20.8 billion reported in 2013.[23] Of note is that South Africa has one of the top five pharma markets (together with Egypt, Algeria, Morocco and Nigeria) in Africa and the continent boasts more than 300 medicine manufacturing sites, one of which – Aspen Pharmacare – is currently one of the top ten generic companies in the world.[23,24] Such pharma activity necessitates a robust regulatory environment. In Africa, in general, this represents a challenge as the regulatory frameworks are subject to frequent changes, a lack of adequately trained employees and minimal guidance regarding marketing of medicines.[24] Pharmacovigilance in South Africa, also essential for regulating the safety and efficacy of medicines, needs strengthening while being subject to a lack of medicine-monitoring capacity, training opportunities and poor coordination of services.[25] The South African Medicines Control Council (MCC) is the first established regulatory authority in sub-Saharan Africa, but its working model has long timelines for reviews as the MCC relies on external reviewers from either research institutions or universities to assist in the registration process.[24] Again, no current MCC policy prioritises either paediatric medicines or orphan medicines (not found on the SA MCC website). As the South African MCC will be phased out in the near future and replaced by the South African Health Products Regulatory Agency (SAHPRA), which aims to streamline medicine registration process using in-house staff to undertake the majority of the work, it will be important to advocate for a policy that will incentivise paediatric medicine or orphan medicine registration.[24] It is of concern, however, that of 229 clinical trials conducted in South Africa between 2005 and 2010, with 60.1 per cent leading to market authorisation in either the European Union or the United States, there has been no new medicine application in South Africa.[26]

I therefore propose that we, as clinicians, consider it our ethical responsibility to promote access to better medicines for children in South Africa. As South Africa is a signatory to the Convention on the Rights of the Child, the country is compelled to adhere to article 3, which requires adequate healthcare provision for children, implying the availability of safe and efficacious paediatric medicines, an aim literally stated in Sustainable Developmental Goal 3.8.[27,28] One way of doing this is to publish our experiences with the use

of off-label medicines in children, especially outcome, lack of clinical efficacy, unsuitable medicine formulations and/or any adverse events. In this way it may be possible to generate the necessary evidence that may assist in future registration for paediatric use.[1] This is especially important when dealing with rare diseases, as one healthcare centre or individual clinical practice will not be able to generate such evidence single-handedly. If medicines for rare paediatric diseases are found efficacious, it should be included in the EML. At the same time, it is also important to pressurise pharmaceutical companies to apply for paediatric registration, if possible, as this is currently the route to follow for registration in South Africa.

In conclusion, it is the duty of all clinicians involved in paediatric healthcare's ethical responsibility to assist in ensuring improved access to efficacious and safe medicines for children. Clinicians should therefore advocate of children, especially by pressurising the pharmaceutical industry for paediatric medicine registration. We also need to pressurise South African policymakers to follow the example of the United States and the European Union by creating regulatory frameworks and policies, incentivising pharmaceutical industries to undertake paediatric clinical trials for paediatric medicine registration purposes in South Africa.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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Guest Review

SIMULATION-BASED EDUCATION IN ALLERGOLOGY TRAINING: A SOUTH AFRICAN PERSPECTIVE

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SUMMARY

In the past two decades, simulation-based education has moved medical teaching out of the lecture rooms, wards and emergency departments by creating a safe environment that provides the learners with life-like experiences, while shielding patients from novices' potentially unsafe medical practices.

Developing a curriculum based on simulation is a complex process that involves the acquisition of infrastructure and equipment as well as the employment of qualified personnel and faculty in order to support the training programme. Learning objectives are achieved by running simulated case scenarios followed by debriefing. The cases must be both realistic and relevant to the learners' practice area to motivate self-driven learning and, at the same time, to provide state-of-the-art training to the required competency standards. Debriefing through various techniques, such as the advocacy-and-inquiry with 'good judgement' approach is an essential component of the educational experience, focused on the learning phases of description, analysis and application of newly-acquired knowledge and skills.

Simulation-based education is particularly useful in fields of medical practice such as allergology, where trainees are not routinely exposed to critical cases and where communication skills are essential for successful chronic disease management through the development of a solid relationship between the medical team and the patient.

Motto: *'Knowing is not enough; we must apply. Willing is not enough; we must do.' - Johann Wolfgang von Goethe*

INTRODUCTION

Simulation-based education is recognised worldwide as an important teaching tool to be incorporated in the training of all healthcare professionals and across all medical specialties in order to improve the quality of care and patient safety.[1] Simulation allows for the 'deconstruction' of complex scenarios into simple tasks and for the application of new knowledge and skills in an environment where making mistakes is permissible, and the old 'learning through trial and error' adage is the norm, rather than a dangerous practice.[2,3] The extensive use of this powerful training tool has changed the traditional educational paradigm in acute and critical care. This is also the case in surgery, where trainees are required to have 'hands-on', repetitive experiences, before being allowed to practise on patients.[3] In these areas, simulation effectively facilitates the journey of a novice to the stage of medical expert without compromising patients' safety. However, other medical disciplines such as allergology may use simulation to enhance the trainees' learning experiences and ultimately improve the quality of healthcare. This article reviews the theoretical basis for simulation-based medical education and analyses possible frameworks for introducing this tool into the allergology training curriculum.

FOUNDATIONS OF MEDICAL SIMULATION: LEARNING THEORIES AND IMPLEMENTATION SCIENCE MODELS

Medical simulation educationalists focus on translating and implementing into medical practice evidence-based multidisciplinary theories, models, principles and methods such as business development, institutional management, psychology, error analysis, and even industrial engineering, to improve the quality and effectiveness of healthcare.[4,5] This approach of integrating the 'implementation science' (IS) into medical training facilitates the transfer of knowledge and the understanding of complex medical concepts. IS should result in an improvement in trainees' attitudes and problem-solving skills.[6]

The IS models may be used in simulation-based medical training to identify and pro-actively address performance gaps and barriers to implementation of learning, thereby

promoting positive change in key competencies and behaviours.[6,7] In addition, standardised methodology translated through the integration of IS in simulation-based training is used in assessment for the purpose of professional certification and licensing by several major accrediting bodies in the United States, Canada and the United Kingdom, such as the Accreditation Council on Graduate Medical Education (ACGME),[8] the Accreditation Council on Continuing Medical Education (ACCME),[9] the American Board of Medical Specialties (ABMS),[10,11] the Royal College of Physicians and Surgeons of Canada,[12,13] and the United Kingdom's General Medical Council.[14]

Current learning theories of individual change are incorporated in modern simulation-based medical education. This is a pro-active, intentional process, which depends on specific attitudes, perceptions, expectations that drive the learners' motivation and lead to reasoned action and planned behaviour.[15–17] However, when simulation is used in undergraduate training, effective teaching may be based largely on a non-negotiated curriculum that may promote change even when students are not yet aware of what cognitive or behavioural changes are needed for them to become competent medical professionals (the transtheoretical model).[18]

The Preceed/Proceed model[19] is another theoretical framework used in simulation. This model is aimed at reinforcing the learner's previous experiences before introducing new skills and competencies. The Pathman model[20] proposes customised education through negotiation with the individual adult learner, aimed at achieving mutually agreed objectives leading to long-lasting, self-driven practice changes.[20] Cognitive psychology strategies,[22–24] such as the enunciation of a general principle followed by multi-angled examples, redundant teaching and feedback, post-experiential reflection are widely used in simulation to increase the transfer of learning into practice.[24–26]

As a tool for system or team performance assessment in simulation-based training programmes, force-field analysis[27] has been used to identify a system's strengths and vulnerabilities by assessing the trainees' responses in simulated high-stake situations.[15] This approach may be used on a large scale, with the purpose of actively changing the healthcare culture and improving patient safety.[28] This model, applied in conjunction with the other IS tools, is especially valuable when the targeted outcome is the ethical and competent functioning of the individual learner within a team and within the healthcare system as a whole.[29] It is also used to build clinical resource management and leadership skills, as well as the capacity of the individual learner to identify, analyse and prevent medical errors.[30,31] Another error analysis model, which can be used in simulation debriefing, is the Ishikawa 'fishbone' diagram.[37] This 'root cause' analytical tool is a structured, team brainstorming process, seeking to identify positive and negative inputs (institutional policies, standardised operating protocols, infrastructure, equipment and materials, people and the environment) that led to a certain outcome.[37–38] Framework analysis, originally developed in the field of social policy research, has been incorporated in debriefing to improve the learners' and stakeholders' understanding of 'actionable outcomes', such as medical errors in acute care, for the purposes of proposing educational interventions to change behaviours and improve patients' safety.[32–36]

All these IS theories are applied in designing simulation-based medical education curricula and in measuring the impact of the subsequent change on the overall competencies required for safe and efficient medical practice.[39]

SIMULATION AS A POWERFUL LEARNING TOOL IN MEDICAL EDUCATION AND ALLERGY TRAINING

Simulation is lessening the inherent risks of allowing the trainees to learn through 'trial and error' and makes medical teaching more ethical, bringing it in line with the basic tenet of medicine: 'first do no harm'.[1] The ethical principle of non-maleficence ought to prevent novices from interacting with patients before they have perfected their skills to a degree that ensures patient safety. Trainees need the close supervision of specialised staff, which may be insufficient to ensure an acceptable level of patient safety. In addition, the overwhelming need to place the patient's wellbeing at the centre of medical care may result in more time spent with exclusive patient care, especially in emergencies, at the expense of the time available for teaching trainees.[1] Therefore, simulation-based teaching offers a controlled environment, where inexperienced trainees are able to learn from their own mistakes and achieve a competency level that ensures safe medical practice before their interaction with the patients. In addition, simulation is useful for the more experienced practitioners who wish to maintain their competencies and perfect or learn new skills.

The benefits of simulation are obvious especially in high-risk areas of medical practice with an increased incidence of medical errors, by providing a safe framework that enables trainees to analyse incidents leading to adverse outcomes and to identify latent safety threats within the healthcare environment.[40] These competency requirements apply across medical specialties and are the main criteria in the evaluation of the quality of medical training for programme accreditation and certification purposes. Training programmes in Basic Life Support (BLS), but also Advanced Life Support (ALS) courses, such as Advanced Cardiovascular Life Support (ACLS) and Pediatric Advanced Life Support (PALS), expose the learners to simulated emergency cases within a safe environment. Theses programmes facilitate the development of an ethical approach to patient care,

efficient team work, closed-loop communication skills, accurate patient assessment, rapid management of most frequently encountered life-threatening causes of respiratory and cardio-respiratory arrest.[41,42] Repetitive use of simulated case scenarios, followed by appropriate debriefing, has proved to be more efficient in improving not only the purely cognitive and technical aspects of practice, but also the clinical reasoning process. In addition, the transfer of durable knowledge and skills into the real practice environment is more effective and more likely to prevent errors, compared to standard teaching.[43,44]

Simulation becomes particularly helpful when healthcare professionals, including allergology practitioners, are rarely exposed to emergencies and need to maintain or refresh their competency in managing life-threatening cases in tension-filled, complex situations.[45] This can be achieved through the creation of realistic and relevant scenarios that challenge the allergology practitioners and are designed to improve their capacity to deal efficiently and appropriately with life-threatening emergencies.[45–47]

As compared with traditional teaching methods, simulation-based education promotes standardised learning by repetitive experience, observation and reflection.[1,48,49] One of the most challenging tasks for traditional clinical medical teachers is to plan and structure their learning sessions with patients relevant for the learning objectives. Not only is the recruitment of the patients difficult, but their availability may often not coincide with learners' or teachers' schedules.[50] This results in a lack of uniformity to clinical exposures and unfairness in terms of unequal learning opportunities and preparedness for summative, high-stake assessments. Besides the qualitative and quantitative inequality in the learning experiences, involving real patients as a teaching resource raises critical ethical issues related to their autonomy and safety, especially when they are vulnerable.[50] Standardised patients (SPs) played by trained actors or the use of virtual patients (online models or mannequins) provide a fair and safe environment for teaching and assessment.[1,50,51]

In allergology training, simulation provides a safe environment for learning technical skills, such as epinephrine administration, intravenous and intraosseous fluid administration, airway management, through repetitive practice.

In addition, simulation based-education is appropriate for teaching and assessing professionalism and for training healthcare workers in effective, patient-centred communication.[1,51,52] Insofar as the diagnostic and management of allergic disease are concerned, an accurate, comprehensive history, which is focused on certain must-not-miss, generally applicable signposts, is necessary for developing a meticulous action plan, tailored to each individual patient's case. As with any chronic conditions, a close relationship of trust needs to develop between the allergology practitioner and the patient to ensure monitoring and good compliance with the medication. Therefore, when employing simulation for procedural skills or clinical management training, it is necessary to add a communication dimension to the case scenarios, and perhaps also involve trained SPs to aid in the improvement of communication skills.

Allergology practices are usually heterogenic, involving people with diverse backgrounds and professional experiences, and good communication is essential for a successful collaboration between team members. This is particularly important in life-threatening emergency situations, where good knowledge of protocols and well-coordinated team work were shown to improve patient outcomes,[1] therefore team work on various possible clinical scenarios may enhance the overall quality of performance, optimise the use of individual skills, improve communication and relationships, and ultimately ensure better patient care and safety.

At the same time, realistic, relevant simulated case scenarios may be used to enforce certain qualities that are always embedded in the 'hidden' medical curriculum such as honesty, openness, fairness and empathy.[1]

In addition, simulation is a powerful educational tool for management and leadership skills training, including environment awareness, error analysis and remediation, resource allocation, crisis control and conflict resolution.[1]

Health advocacy is critical in allergology practices, where patient education and cooperation are central to the successful treatment of allergic disease and prevention of allergic emergencies. Case scenarios specifically designed for patient education may assist in the creation and enforcement of behaviours that ensure good control of the baseline illness, as well to model the rapid sequence of symptom recognition and response in life-threatening emergencies, such as calling for help and epinephrine administration in anaphylaxis.

However, with all its advantages, when it comes to implementing a quality simulation programme in practice, there are many hurdles, especially in respect of finding the necessary financial and human resources. These pitfalls will be discussed in more detail in the context of the possible development of a simulation model for allergy training, based on Kern's approach to curriculum development.[53]

DEVELOPING A SIMULATION-BASED MODEL FOR ALLERGY TRAINING

In the United States, medical training is inconceivable without a simulation programme embedded in the curriculum of all medical schools.[54] Major universities such as Harvard

have developed large, interdisciplinary Simulation Centres that function autonomously from the medical schools and service a large array of medical professionals from the United States and abroad. The Simulation Centres appoint staff capable of aiding the medical schools and residency programmes with designing simulation-based curricula and simulation staff training. A similar approach has been adopted in Australia, Canada, Europe and the United Kingdom. Whether part of medical schools or affiliated to non-profit organisations- or hospitals, medical simulation centres have promoted a radical change in traditional educational paradigms.

From the experience reported by various programmes, the process of implementing a simulation-based medical curriculum involves several critical steps, adapted from Kern's approach to curriculum development.[53] The initial stage involves the problem identification and a general needs assessment, followed by the recognition of the targeted learner' needs assessment. The next step is setting out the programme's goals and objectives, followed by choosing the educational strategies to be adopted and the implementation of those strategies. Thereafter, there is a never-ending process of evaluation, adjustment and re-evaluation that ensure that the curriculum is at all kept times aligned with the identified needs, learning objectives and outcomes.

GENERAL AND TARGETED NEEDS ASSESSMENT

The paradigm shift towards replacing the traditional bedside teaching with simulation would be difficult without a persuasive presentation of the reasons for change. The process of assessing the relevance of a new simulation-based medical education programme to evaluate the benefits and drawbacks of moving away from the classic model, which uses actual patients for teaching clinical skills. In this context it may be argued that, taking into account all the various potential uses for simulation in promoting experiential teaching and learning in various medical systems, the movement towards replacing real patients with computerised mannequins or trained actors to educate medical novices is justified by not only by professional ethics, but also by versatility, efficiency and efficacy considerations.

While allergology practitioners at all levels are required to competently manage severe allergic diseases, such as anaphylaxis, angioedema and asthma, they are not routinely exposed to extreme situations. For many, unexpected emergencies are unfamiliar or even frightening. In this case, simulation may aid in the periodic refreshing of knowledge and practise of skills that increase the competence and confidence to act in critical situations.[54] The clinical management of life-threatening emergencies is taught most efficiently and effectively in a safe environment that allows for the reinforcement of concepts and repetition practical skills until the competency level is sufficient for actual patient interactions. In addition, the unique core communication skills that are at the root of an accurate diagnosis of allergic disease and ensure the appropriate patient-centred management and compliance monitoring are best taught through repetitive, standardised interviews with trained actors, followed by debriefing.

Another targeted group for simulation training in allergy may be the patients themselves, their families and school staff, since many severe allergies occur in the community and valuable time is wasted because bystanders are unable or not competent to administer life-saving treatment, such as epinephrine.

Therefore, an intervention directed at these groups will contribute to effective staff and public training in emergent allergic disease.

THE CURRICULUM BLUE-PRINT

Instructional design

An essential stage in the process of curriculum planning is focused on the identification of the learning goals and objectives of the course which must be in line with the general and targeted needs and, more specifically with the professional competencies defined by the authorised accreditation bodies.[53]

The strategies and methods for curriculum delivery in medical education must be appropriate, effective and efficient in meeting the specific requirements of the healthcare system, organisation and learners. The overall instructional design will depend on the level of learner and the targeted field of medical practice. Regardless of the educational strategy chosen, the success of curriculum delivery will depend on the congruence between the instructional design and the learning objectives.[54,55]

In the field of emergency medicine, technology-enhanced simulation, using mannequins, partial task trainers and other educational tools, was found as effective as traditional teaching methods in terms of knowledge acquisition, skill product, learner behaviour and effect on patient outcomes, its success relying significantly on the type of instructional design chosen to deliver the curriculum.[3,42,54–56] An innovative instructional design in acute-care training is the 'Emergency Medicine Milestones', based on the 'mastery learning model', where the learners have to achieve a certain level of competency in more basic procedures before moving on to the next, more complex or difficult tasks.[3,57,58] This approach allows for an objective evaluation of the learners' progress and makes possible the early identification and remediation of those who have failed to comply with a set of cognitive, behavioural and procedural requirements.[58] Furthermore, scenario repetition and the type of feedback or debriefing given during, or after the simulation session was found to significantly influence the learning outcomes. In procedural skills, closed supervision

and feedback provided using the 'pause-and-perfect' model improved performance and self-efficacy.[57–60]

The most important principle in incorporating simulation in the allergy training programme is to employ the most efficient teaching strategy to effectively achieve the learning objectives. The simulation sessions could focus either on acquisition of simple technical skills (intramuscular or intravenous epinephrine administration, rapid sequence intubation, skin-prick testing), non-technical skills (teamwork, leadership and communication) or overall patient interview, examination and management.

Use of simulation for formative and summative assessments

Medical education institutions and professional accreditation bodies consider simulation to be both a training tool and an instrument for competency assessment.[60] The assessment objectives, criteria and checklists must be aligned with the curriculum and adequate in terms of validity, reliability and general efficacy in evaluating performance.[60–62]

Instructional design signposts in simulation-based education: development of simulated cases and debriefing

Embedding simulation-based education in medical curricula involves the development of a 'case-scenario bank' that fulfils the all-important criterion of meeting the course's learning objectives. The cases must be both realistic and relevant to the learners' practice area.[44]

Pre- and post-simulation debriefing is an essential component of the learning experience and must be done skillfully, if the learning objectives are to be achieved and retained, while at the same time maintaining learner curiosity and motivation.[63–64] Modern debriefing methods, such as the 'debriefing diamond' used at the Simulation and Interactive Learning Centre and the King's Learning Institute, King's College London,[63] or the 'debriefing molecule' used by the Harvard Medical School Associated Center for Medical Simulation,[64] are based on the learning phases of description (knowledge), analysis and application, and are focused on the advocacy-and-inquiry with 'good judgement' approach.[64] The learning objectives targeted by debriefing are related to the development of non-technical skills, such as leadership, collaboration and task-prioritising.[63,64]

IMPLEMENTATION AND RESOURCES

The shopping list for establishing and maintaining a simulation training course could become expensive, which is one of the main drawbacks of using simulation in education. Nevertheless, solutions may be found when efforts are made to establish corporate partnerships or collaborations with other programmes, which facilitate sharing and exchanging facilities and equipment. Demonstrating a good 'return on investment' (ROI) and a positive change in patient safety is key to gaining acceptance of a simulation programme by the various stakeholders.[39] Rigorous feasibility studies are necessary to gauge the actual ROI when using simulation versus traditional training.

In this context, it may be argued that, given the high prevalence of allergic disease in South Africa, improving the quality of care offered to the affected patients through systematic training of healthcare professionals at all levels may be as much a priority as is the management of tuberculosis (TB) or HIV/AIDS.[65] Better diagnosis and management of allergic disease may result in a significant reduction in medical expenses and may decrease the incidence of preventable allergy-related deaths.

Infrastructure: *"in-situ"* simulation versus "off-site" simulation centres

Training 'in context' has proved to improve the quality of medical education, including retention of knowledge. Dedicated premises, whether within hospitals, medical schools or autonomous simulation centres, are meticulously designed to specifically organised areas that reproduce emergency rooms, wards, operating theatres and even radiology departments. Major hospitals affiliated with the Harvard Medical School in Boston have built up their own simulation centres, separate from the clinical premises. Other simulation programmes function from hospital premises in standardised rooms that are separate from the clinical patient care circuit. The 'in-situ' simulation is cheaper, easily accessible, comfortable, realistic, tailored according to the institutional needs and in an environment familiar to the learners. Training takes place in the vicinity of patients and their families, who are therefore reassured that the staff practises and trains regularly. On the other hand, the disadvantage is that patients lack privacy, may witness incidents that may cause them anxiety or discomfort, and may be exposed to safety risks such as accidentally using simulation equipment and materials. In addition, there are other disadvantages such as the difficult construction and maintenance of a safe environment for 'learning by trial and error' or the risk of interruption with requests for other work-related tasks.[66]

Technology and materials

Depending on the purpose, different simulation tools may be used with comparatively similar efficacy. The equipment available in the simulation market ranges from simple, low-tech or part task simulators to complex task trainers and realistic, high-fidelity patient simulators. Simulation programme creators and managers must evaluate various types of simulation equipment and method to achieve the learning objectives at the lowest cost.[3,67] In allergy training, learners may benefit from hybrid simulations, where a standardised patient provides the history and allows for the physical examination, while being attached to a simple task trainer, such as an airway management mannequin,

a lower limb for intramuscular epinephrine administration or intraossesous infusions, or an arm for intravenous fluids and medications.[68] Low-cost mannequins may not reproduce identically the relevant human structures, and often realism is difficult to achieve with task trainers, even in hybrid simulations. However, simulation is as close as one can get to practising new skills for the first time – short of experimenting them on a real patient.

Faculty and faculty training

Worldwide, as simulation-based training is increasingly used as tool in medical education programmes, there is a parallel increase in the need for appropriately skilled teachers.[69–72] Several training programmes for simulation instructors and technicians are in place in Australia, Canada, Spain, the United Kingdom and the United States. In the United States, the Society for Simulation in Healthcare sets out the standards for the certification of the Healthcare Simulation Educator.[73]

Medical simulation instructors need to develop expert-level skills in important areas, including curriculum development, evaluation and adaptation; designing and running realistic, effective and standardised simulated cases followed by an efficient and effective debriefing process, based on the learning objectives; insightful formative assessments and reliable, fair summative assessments and research aimed at improving the outcomes of medical education.[69–72] Ultimately, their selection and training are critical, having an important impact on the effective standardisation of simulation programmes, as well as on the way the programme is perceived by the learners.[52,72,73]

However, training simulation experts is expensive and time consuming. Where there is already a shortage of human resources in healthcare, removing clinical staff from patient care for training in simulation may not be an option. Therefore universities and hospitals in developing countries such as South Africa may have difficulties in setting up formal simulation instructor training programmes to regulate the certification of simulation educators and thereby ensure adequate professional standards. While collaborations with international instructor training programmes may be an alternative option, this is also not cheap and may not be necessarily tailored to the needs of the local healthcare stakeholders.

MECHANISMS FOR EVALUATION OF THE TRAINING PROGRAMMES

Kirkpatrick proposed a four-level conceptual model for curriculum evaluation, based on learners' participation or reaction to the educational experience, the degree of modification of attitudes or perceptions, modification of knowledge and (or) skills, and ultimately the transfer of the changes to the workplace.[75] This process takes place on an ongoing basis, closing the curriculum development loop, while at the same time leading to adjustments that address the gaps and adapt the content accessed at and methods to the changes in healthcare and learners' needs.[76]

CONCLUSION

In the past two decades, simulation moved medical education out of the lecture rooms, wards and emergency departments by creating life-like experiences that improve knowledge and facilitate the learning of behaviours and skills, while shielding the patient from being subjected to the novices' potentially unsafe medical practices.[39,46,55,69] Besides enhancing the effectiveness of experiential learning, simulation offers an efficient standardised instrument for competency assessment and accreditation.[58,60] In the United States medical and nursing schools have successfully incorporated simulation into their training programmes. Recently published reports have proved the usefulness of this powerful educational instrument in the training of allergologists in managing emergencies such as anaphylaxis.[68]

In the South African context, the process of incorporating a simulation-based curriculum into allergology training may prove to be complex and expensive. The programme promoters may, however, seek corporate partnerships and share resources with other medical specialties training programmes within universities, public and private hospitals. In the long run, this effort may result in better, safer, patient-centred allergology services.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

This article has been peer reviewed.

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ALLSA RESEARCH REPORT FEBRUARY 2017

Sharon Kling, Chair, ALLSA Research Subcommittee

The current ALLSA research subcommittee comprises Prof Refiloe Masekela (University of KwaZulu-Natal), Dr Debbie White (University of the Witwatersrand), Prof Sharon Kling (Stellenbosch University, Chair) and Mrs Ruwayda Adams, who provides administrative support and who liaises with the applicants and the sponsors. Mrs Robyn Marais, production editor of *Current Allergy and Clinical Immunology*, liaises with the sponsors for the advertisements to be placed in the journal.

All research applications are submitted electronically. Each application is assessed by two evaluators who are not blinded as to the researcher's identity, as well as by one of the subcommittee members. The scores are averaged and ranked, and final ratification is by the ALLSA Excom.

Between 1991 and 1999 ALLSA research awards have benefitted 30 researchers. From 2000 to date, ALLSA and our sponsors have supported 56 researchers in the fields of allergy and asthma. ALLSA prefers to fund an entire study or a significant part of a research study rather than supplementing the funds of a large study that has major funding; however, ALLSA will make exceptions for meritorious applications.

During the 2015/2016 cycle we received eight applications for research awards and four researchers were successful. The successful aplicants are Drs Jonny Peter (Prospective cohort study of peri-operative anaphylaxis at four hospitals in the greater Cape Town area), Frank Kirstein and Thulja Trikamjee (An analysis of aeroallergens and a comparative study of endotoxin and aeroallergens in dust samples from rural and urban cohorts and comparisons with prevalence of atopic diseases) and Kaarina Meintjes (A pilot study to implement primary healthcare management guidelines for childhood atopic eczema).

The awards were handed out to the successful applicants at the Gala Dinner during the ALLSA Congress at the Century City Convention Centre on 17 September 2016. Congratulations to these researchers; we wish them every success in their research endeavours.

We wish to acknowledge the ongoing support from our sponsors: GSK (the major sponsor over many years), Aspen, MSD and Cipla. Many of the ALLSA-funded research projects have led to local and international publications, and at least six previous recipients of ALLSA research awards have achieved PhD degrees. Among these is Dr Claudia Gray – a recipient of two ALLSA-GSK awards – who achieved her PhD in the field of food allergy and atopic dermatitis. We also wish to thank all our reviewers for their willingness to assist with the reviews, and for their thoughtful and constructive input into our award process.

Guest Review

HEALTH PROFESSIONALISM AND ETHICS – IS THERE A DIFFERENCE?

Sharon Kling

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ABSTRACT

Health professionalism has evolved as technology, managed healthcare and business considerations have influenced the healthcare system and milieu. Codes of ethics and the Charter on Medical Professionalism (known as the 'Physicians' Charter') emphasise the primacy of patient welfare and respect for patient autonomy, together with social justice, but health professionals frequently neglect the latter aspect. Complex ethical and moral problems require more intense discussion and debate by health professionals, and professional organisations have a limited role to play in this regard.

INTRODUCTION

The issue of health professionalism regularly rears its head in popular and medical literature. Two of the most publicised local cases involving medical professionalism are that of Dr Wouter Basson, who was found guilty of professional and ethical misconduct for his role in an apartheid-era chemical warfare programme, and Professor Tim Noakes, who was charged with unprofessional conduct by the HPCSA for providing 'unconventional advice' to a breastfeeding mother on Twitter. Professor Noakes' case has still not been resolved.

A 59-page document on the website of the Health Professions Council of South Africa (HPCSA) details the judgments against healthcare practitioners found guilty of unprofessional conduct during 2016, together with the punishments meted out to them, ranging from reprimands, to fines, to being struck off the roll of practitioners.[1] Booklet 2 of the HPCSA guidelines defines 'profession' as 'a dedication, promise or commitment publicly made'.[2,3]

A study done by the Ethics Institute of South Africa (EthicsSA) in 2001 revealed that almost two-thirds of the doctors surveyed said that they had observed cases of medical misconduct by a colleague, but that they feared the consequences to themselves if these instances were to be reported.[4] Many of the respondents also indicated that over-servicing of patients was common among their colleagues.[4] In a survey of 1 662 specialists in the United States, 96% agreed that impaired or incompetent colleagues should be reported to the relevant authorities. However, 45% of the doctors who had knowledge of such colleagues did not report them.[5] A 2009 survey of 1 891 practising doctors in the United States found that most of the respondents agreed that patients should be fully informed about the risks and benefits of interventions and that their confidentiality should be respected. However, many of the doctors admitted to not always being truthful to patients, to withholding information regarding serious medical errors, and almost 40% did not believe it was important to disclose their financial relationships with drug and device companies to patients.[6]

HEALTH PROFESSIONALISM – A SOCIOLOGICAL AND HISTORICAL PERSPECTIVE

The terms 'profession' and 'professional' are derived from the Latin *professio* – a public declaration that carries the power of a promise. One of its meanings was the taking of religious vows. The Merriam-Webster online dictionary[7] defines 'profession' as:

- a calling requiring specialised knowledge and often long and intensive academic preparation;
- a principal calling, vocation, or employment;
- the whole body of persons engaged in a calling.

Generally speaking, groups that declare themselves to be professions guarantee that their members will behave in certain ways and the groups will exercise appropriate control over those members.[8] The hallmarks of a profession (quoted from Jonsen[8]) are:

1. Competence in a specialised body of knowledge and skill.
2. An acknowledgement of specific duties and responsibilities towards the individuals it serves and toward society.
3. The right to train, admit, discipline and dismiss its members for failure to sustain competence or observe the duties and responsibilities.

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Health professionals 'are granted the social privilege of self-governance and internal maintenance of high professional standards', and the public place a great deal of trust in the health professional.[9] The following considerations, which impose an additional obligation on health professionals, differentiate healthcare from other occupations: the power differential between the vulnerable, ill patient and the health professional; the knowledge and learning acquired from research and clinical training performed on ill people; and the traditional oath taken at graduation, in which the graduating health professional acknowledges the service aspect of the profession.[10]

The origins of medical professional ethics lie in the Code of Hammurabi (2000 BCE) and the Hippocratic Oath (5th century BCE). Variations of the latter still form part of graduating medical students' pledges. In medieval and early Renaissance times guilds were formed to protect the interests of skilled workers and craftsmen, and lawyers and doctors were quick to use the guilds to protect their working circumstances and income.[11] Doctors saw themselves as part of the elite, as they had trained at universities, and so used the term 'profession' to distinguish themselves from 'lower-order practitioners' such as surgeons and apothecaries.[12] In the 18th century two doctors who were also ethicists, John Gregory and Thomas Percival, designated medicine as a profession. They were also the first to use the word 'patient' instead of 'the sick'. Gregory shifted the emphasis of medicine away from the doctor towards the patient, and he also stressed the importance of doctors' competence, warned against self-interest, and coined the idea that medicine is a public trust and not a merchant guild.[12] Percival used the term 'medical ethics' to evaluate doctors' behaviour and professionalism in hospitals. Many organisations of doctors subsequently established codes of ethics to define the character traits and ideal behaviour expected of a doctor.[12]

THE EVOLUTION OF MEDICAL PROFESSIONALISM

Medical professionalism has evolved further over the past few years. In 2002 the American Board of Internal Medicine (ABIM), the American College of Physicians-American Society of Internal Medicine (ACP-ASIM) and the European Federation of Internal Medicine (EFIM) jointly published the Charter on Medical Professionalism (known as the 'Physicians' Charter'), a product of a working group on medical professionalism. The charter contained three fundamental principles and ten commitments.[13,14] The fundamental principles were (i) the principle of primacy of patients' welfare; (ii) the principle of patients' autonomy, and (iii) the principle of social justice. These principles were complemented by a 'set of professional responsibilities', involving the following commitments:

i. professional competence;
ii. honesty with patients;
iii. patients' confidentiality;
iv. maintaining appropriate relationships with patients;
v. improving the quality of care;
vi. improving access to care;
vii. just distribution of finite resources;
viii. scientific knowledge;
ix. maintaining trust by managing conflicts of interest, and
x. professional responsibilities.

The professionalism project was stimulated by doctors' frustrations at changes in the healthcare setting that they believed eroded the values of medical professionalism. Some of these changes included advances in technology, the commodification of medicine and the advent of managed healthcare organisations that employ doctors. The aim of the Physicians' Charter was to endorse the values and ideals of medical professionalism which doctors felt were being challenged. The working group acknowledged the diversity and globalisation of medicine, but felt that common themes around the concept of the healing profession unite all physicians.[13,14] Interestingly, the charter makes no mention of the term 'compassion', which most health professionals would view as an essential component of the professional–patient relationship.[15]

In an article commemorating the 10th anniversary review of the Physicians' Charter, Cassel et al stated that the charter had been endorsed by more than 130 organisations worldwide, had been translated into 12 languages and was being widely used by medical schools.[16] Their analysis was that the principles of patient autonomy and protecting patients' welfare have been embraced by the medical profession, and professional organisations have espoused fair distribution of healthcare resources. However, most doctors believe that their first obligation is to the individual patient and not to society, and that they have a limited role to play in controlling healthcare costs and just distribution of healthcare in society. I believe that the same applies to South Africa, where doctors advocate for individual patients and do not always take the impact of their investigations and treatment on other healthcare users into consideration.

How then has medical professionalism evolved? Stanton et al advocate for a new professionalism that emphasises accountability, with professionals engaging with the wider health and healthcare systems, and promoting quality improvement.[17] An undertaking to improve the quality of patient care is a central tenet of this new professionalism, together with clinicians working with other members of the healthcare team. The individual doctor–patient relationship is no less important in this model, but it is further augmented by the clinician actively working towards improving the healthcare environment.

HEALTH PROFESSIONALISM AND ETHICS

The key aspect of professionalism is self-regulation by a professional organisation. In this respect the HPCSA appropriately oversees the undergraduate curricula and programmes offered by the training institutions, the admission of graduates into the professions, postgraduate

training and specialisation, and other regulatory issues in South Africa.

However, when it comes to ethical issues such as abortion, euthanasia and assisted suicide, genetics and other 'value-laden existential questions', such a regulatory body has a limited role to play. Grappling with these issues requires more than medical expertise, and this is where philosophers and social scientists have become involved in bioethics debates.[11] Vogelstein argues that professional organisations ought not to dictate on controversial ethical issues within healthcare.[18] He believes that health professionals cannot claim to have the skills and knowledge necessary for moral reasoning, which requires knowledge of ethical theory and deliberation.[18] As an example of the limitation of organisational engagement with difficult ethical issues, both the HPCSA and the South African Medical Association (SAMA) pronounced very strongly against the assisted-suicide judgment in the *Stransham-Ford* case, with the HPCSA joining the appeal for the Supreme Court of Appeal to rescind Judge Fabricius' order.[19,20] The danger in professional organisations pronouncing on such controversial issues is that the discussion and debate may be guided 'by arguments from authority rather than sound reasons and considered, critical thought'. Vogelstein draws a distinction between actual, genuine and false ethical controversies, with actual controversies existing when there is substantial disagreement on a particular issue; and genuine controversies where there are good arguments on both sides of the debate. A false controversy is an actual controversy in that there is substantial disagreement between the two sides, but it is not a genuine controversy because the one side's arguments are so weak.[18]

ALLSA, ALLERGY PROFESSIONALS, PROFESSIONALISM AND ETHICS

The Allergy Society of South Africa (ALLSA) has a constitution and a governance charter, but no code of ethics for our members. I do not believe that this is a problem, as our governance charter and policies cover the major issues that would appear in a code of ethics. As a professional organisation we ought to acknowledge our reliance on the pharmaceutical industry for our establishment and continued existence, and the potential conflict that this could create for the executive committee and members. Our members are aware of and take seriously their professional responsibilities in advocating for our patients and in trying to improve the health and healthcare systems for patients with long-term health conditions such as allergy and asthma. This was also one of the main incentives for the creation of the Allergy Foundation of South Africa (www.allergyfoundation.co.za). The society's contribution to engaging with ethical controversies is through journal club discussions, congress presentations and articles in this journal.

CONCLUSION

In concluding, I wish to quote Bauchner et al:

> 'Medicine is a privileged profession. Caring for patients and helping them stay well and become well is a most noble calling. However, much is at stake in the evolving health care system and the current debates about educational reform, training issues, maintaining skills, and the cost of health care. As increased transparency reveals many aspects of medicine that have formerly been hidden from patients (such as conflicts of interest and costs of care), as more physicians are employed, as the economic stakes for patients and their families are greater, and as the belief that medicine should be more personalised becomes integrated into practice, it is incumbent on the leaders of medicine to reexamine the organisational, governance, and self-regulatory structure of the profession.'[21]

The ideas expressed in the preceding paragraph apply to all health professionals, not only to doctors. Professionalism is important, but it has to be distinguished from ethics in healthcare. As Salloch states:

> 'A critical eye must, therefore, be kept on the narrowing of ethics and professionalism in public discussion and in medical education. Morally contentious topics in modern societies should be open to a participatory and inclusive discussion which is not dominated by traditional elites, but is particularly focused on the voices of those who have often been overlooked in the past.'[11]

A renewed sense of and commitment to professionalism in healthcare is required, and vigorous debate should be encouraged around difficult moral and ethical issues. Regulation of the health professions should go hand in hand with an ethics of personal responsibility and a commitment to individual patients as well as to changing the health systems within which we work.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest with respect to the content of this article, with the exception of being a Director of the Allergy Foundation of South Africa.

This article has been peer reviewed.

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ALLSA EDUCATION REPORT

Professor Michael Levin, Chair, ALLSA Education Subcommittee

The Colleges of Medicine of South Africa (CMSA) convenes two examinations that are aimed at increasing skills in allergy for generalists and specialists as well as graduating certified subspecialist allergologists.

The Diploma in Allergology, housed in the College of Family Physicians, commenced in March 2003 and the first graduates were Dr Gloria Davis, Dr George du Toit, Dr Gustav Joyce, Dr Ahmed Manjra and Dr Adrian Morris. Including our latest graduates for 2016, Drs CX Dearden, W Dicks, E Kiragu, O Odusote, AC Swartz, N De Villiers and M Naidoo, 81 diplomates have now graduated from the college.

The diploma aims at empowering doctors with the knowledge and skills required to practise in all aspects of allergy commonly seen in primary care. It has been written predominantly by paediatricians, but other categories of doctors include general practitioners, ENT surgeons, internal medicine specialists, family physicians and emergency medicine physicians.

The Eugene Weinberg medal is awarded to candidates who have performed exceptionally well that year. The full list of recipients is Dr AI Manjra (2003), Dr TJ Urquhart (2006), Dr T Moodley (2007), Dr A Gouws (2009), Dr DA White (2010), Dr S Abbott (2011), Dr TC Kerbelker (2012), Drs Dr J Holtzhausen and Dr WC Lewis (2013), Dr AC Jeevarathnum (2014), Dr M Moolla (2015) and Dr E Kiragu (2016).

The subspecialty of allergology was gazetted in 2012, with the base specialties being paediatrics, internal medicine and family medicine. Allergologists were 'grandfathered' into the subspecialty based on a standardised set of criteria, to identify postgraduate teachers and examiners sufficiently competent in the subspeciality of Allergology and to be committed to the training of future allergologists.

Candidates for the subspecialty examination are required to be registered as a specialist with the Health Professions Council of South Africa (HPCSA) as a paediatrician, internal medicine specialist or specialist family physician. These candidates are required to have completed two years of training in an HPCSA-accredited training programme.

Currently, the only allergy service registered for training by the Colleges of Medicine of South Africa is situated in the Western Cape at the University of Cape Town and training at Red Cross War Memorial Children's Hospital and Groote Schuur Hospital. Four training numbers are shared between paediatrics and internal medicine; however, only one registrar training post is funded by the Department of Health. Other tertiary units providing allergy services exist in Pretoria, Johannesburg, Tygerberg, 1 Mil, 2Mil, Durban and Bloemfontein. There is an acute need for specialised allergology training units at these tertiary hospitals and for the establishment of further centres in Polokwane and in the Eastern Cape.

ALLSA would like to congratulate our newly graduated allergologist, Dr Thulja Trikamjee, who passed her examinations at the end of 2016. She joins Dr Talita van der Watt as the first two allergologists trained and examined under the new subspecialty regulations in South Africa.

Through the specialist and subspecialist training programmes, ongoing CME events in allergy and the conference held each year, ALLSA is making great strides towards increasing the numbers of doctors with skills and interest in allergy, as well as supporting the training of the first generation of fully accredited allergologists.

ALLSA 2016
ASTHMA & ALLERGY RESEARCH GRANT

IN ASSOCIATION WITH Cipla RESPIRATORY

As a further commitment to providing quality medical care to all South Africans, Cipla Medpro has granted an amount of **R20 000** to the Allergy Society of South Africa for research in the field of asthma and allergic rhinitis.

Applications will be considered for research projects relating to asthma and allergic rhinitis, whether basic or applied; however conventional drug trials will not be acceptable.

CLOSING DATE FOR APPLICATIONS
30 APRIL 2017

Application details can be obtained from the ALLSA office. Please visit the ALLSA website at www.allergysa.org/awards to submit your electronic application.

PLEASE NOTE THAT ONLY ELECTRONIC SUBMISSIONS FROM FULLY PAID-UP ALLSA MEMBERS WILL BE PROCESSED

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Original Research

IDENTIFICATION OF TROPOMYOSIN AND TROPONIN C AS THE MAJOR ALLERGENS OF *PERNA VIRIDIS* (ASIAN GREEN MUSSEL) AND THE EFFECT OF COOKING ON THEIR ALLERGENICITY

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ABSTRACT

Objectives: To identify major allergens of Asian green mussel (*Perna viridis*) and to investigate the effect of different cooking processes on the allergenicity of this mussel.

Methods: Raw, boiled, fried and roasted extracts of mussel were prepared. Protein profiles were analysed using sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and two-dimensional gel electrophoresis (2-DE). Major allergens and allergenicity patterns of all extracts were then determined by immunoblotting with sera from patients with positive skin-prick tests (SPT) to the raw mussel extract. Mass-spectrometry was used to identify the major allergens of this mussel.

Results: SDS-PAGE of raw extract showed 21 protein bands. Smaller numbers of protein bands were detected in the boiled, fried and roasted extracts. The 2-DE gel profile of the raw extract further separated the protein bands to ~50 protein spots. Immunoblotting of raw extract exhibited 16 IgE-binding proteins with two proteins of 36 and 18 kDa as the major allergens, whereas the cooked extract revealed 2 IgE-binding proteins. 2-DE immunoblotting of raw extract demonstrated 10 IgE reactive spots. Mass-spectrometry analysis led to identification of two important allergens: tropomyosin (36 kDa) and troponin C (18 kDa).

Conclusions: The process of cooking resulted in reduced mussel allergenicity by reducing the number of IgE-reactive bands. The order of allergenicity of mussel from lowest to highest, was demonstrated to be, raw > boiled > fried ≈ roasted. The two major allergens of *Perna viridis* were identified as tropomyosin and troponin C.

Key words: cooking processing; major allergen; *Perna viridis*; tropomyosin; troponin C

INTRODUCTION

The Asian green mussel, *Perna viridis*, belongs to the Mytilidae or true mussels (Mollusca; Bivalvia; Lamellibranchia; Mytiloida; Mytilidae) and is widely distributed and extensively cultured in the Indo-Pacific region as an important protein source.[1,2] In Malaysia, *Perna viridis* is one of the popular bivalves consumed. Unfortunately, our earlier study among atopic patients demonstrated that mussel sensitivity is present.[3]

Exposure to mussel allergens can occur through ingestion of mussel-containing meals or by inhalation or skin contact while cooking or working.[4–6] Mussel allergy symptoms are more or less similar to that of other shellfish allergies. Target organs for mussel allergy include the cutaneous, respiratory, gastrointestinal tract and the cardiovascular system. The frequently observed symptoms include angioedema, urticaria, allergic rhinitis, rashes on the skin, swelling of the tongue or throat and asthma.[4,7,8] In severe cases, life-threatening anaphylactic reactions can occur.[9,10]

Allergies to mussels are diagnosed similarly to other shellfish allergies. The diagnosis relies upon a careful evaluation of history, the presence of appropriate clinical signs and confirmed with *in vivo* or *in vitro* tests to demonstrate the presence of allergen-specific IgE.[4] The only proven therapy for mussel-induced allergies is strict avoidance.[4] Unfortunately, strict avoidance is not always possible because accidental consumption is almost unavoidable. Consequently, allergens must be identified in a particular mussel species in order to improve the diagnosis of mussel allergy and subsequent management of mussel-allergic patients.[4,11,12]

Previously, tropomyosin was the only well-recognised allergen in mussel.[13] Tropomyosin with molecular masses of 34 to 38 kDa has been widely identified as a major and cross-reactive pan-allergen in various species of invertebrate including crustaceans, molluscs, mites and cockroaches.[14–24]

Most mussels are cooked either by boiling, frying or roasting, all of which can be considered a form of thermal treatment. Thermal treatment promotes protein denaturation, aggregation and structure disruption and therefore has a potential to modify the allergenic properties of proteins. In some cases, thermal treatment has been shown to decrease allergen reactivity,[25–27] yet in other cases, thermal treatment increases allergen potency,[28–30] possibly by exposing new IgE-binding sites. Therefore, an understanding of the allergenic properties of mussel as affected by the cooking process is of the utmost importance, especially for mussel-allergic individuals. The aims of the study were to evaluate how the cooking process may alter the allergenicity of mussel and aimed at identifying the major allergenic proteins of the mussel (*Perna viridis*).

METHODS

ALLERGEN EXTRACTION

The mussel shell was split open and the inner muscle tissue was removed and used for extraction. Approximately 20 g of the muscle mass was homogenised in 200 ml of 0.1 *M* phosphate-buffered saline (PBS), pH 7.2 for 10 minutes using a Waring blender. This homogenate was then agitated overnight at 4˚C, followed by centrifugation at 4 500 and 14 000 rpm, for 30 and 15 minutes, respectively. The clear supernatant was then recovered and sterilised by passage through a 0.22 µm syringe filter, frozen and lyophilised. The lyophilised extracts were stored at −20˚C until used. The boiled mussel extract was prepared by boiling muscle tissue with 0.1 *M* PBS (pH 7.2) for 10 minutes at 100˚C before homogenisation in a Waring blender. The fried mussel extract was obtained by frying the muscle tissue in vegetable oil for 10 minutes at 120˚C and subsequently dried on filter paper to remove the oil. The fried mussel muscle was then homogenised in 0.1 *M* PBS (pH 7.2) and extracted as above. The roasted mussel extract was obtained by roasting at 180˚C for 10 minutes followed by homogenisation using the same protocol as above. Protein concentration of the extracts was determined using the total protein kit (Sigma-Aldrich, US), according to the manufacturer's instructions. Bovine serum albumin (BSA) was used as the protein standard.

ALLERGEN TESTING AND COLLECTION OF SERA

Sera from 20 mussel-allergic patients were used in this study. The sera were obtained from patients referred to the Allergy Clinic, Kuala Lumpur Hospital. Allergic response was confirmed on the basis of the patient's clinical history and characterised by a positive SPT to the raw mussel extract. Serum from non-allergic individuals was used as a negative control. All sera were stored at −80˚C until use. This study was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia and informed consent was obtained from the patients or their relatives.

SODIUM DODECYL SULFATE POLYACRYLAMIDE-GEL ELECTROPHORESIS (SDS-PAGE)

SDS-PAGE was carried out in a 12% polyacrylamide separating gel with a stacking gel of 5%. Electrophoresis was performed using a Mini Protean 3 Apparatus (BioRad, US) at 120 mA for 45 minutes. Each sample was dissolved in Laemmli sample buffer (BioRad, US) in the presence of 5% 2-mercaptoethanol, heated at 97˚C for 4 minutes and subjected to electrophoresis. Precision plus protein standards (BioRad, US) were used as reference molecular weight standards. Gels were stained with Coomassie brilliant blue R-250 and recorded using Imaging densitometer GS800 and Quantity One Software (BioRad, US).

IMMUNOBLOTTING

Following SDS-PAGE, the separated proteins were electro-transferred onto nitrocellulose membrane using a Mini Transblot System (BioRad, US) at 100 V for 70 minutes. The membrane was washed with Tris-buffered saline (TBS) containing 0.05% Tween 20 (TTBS), incubated with 5% non-fat milk in TBS and incubated with 20 individual patient's serum diluted overnight at 4˚C. IgE-binding proteins were detected using biotinylated goat antihuman IgE-antibody (Kirkergaard and Perry Laboratories, UK) diluted 1:1 000 in TBS with 5% non-fat milk, followed by incubation with streptavidin-conjugated alkaline phosphatase solution (BioRad, US) for 30 minutes at room temperature. Finally, Alkaline Phosphatase Conjugate Substrate Kit (BioRad, US) was used for colour development according to manufacturer's instructions. To investigate the allergenicity of the cooked extracts which include boiled, fried and roasted extracts, seven patients' sera were chosen based on having IgE-binding to raw extracts. A strip without a serum sample was used as a blank, while serum from a non-allergic individual was used as a negative control.

TWO-DIMENSIONAL GEL ELECTROPHORESIS (2-DE)

The lyophilised raw mussel extract was mixed with a rehydration buffer containing 8 M urea, 50 mM DTT, 4% chaps, 0.2% carrier ampholyte pH 3-10, 0.0002% bromophenol blue. For the 7 cm immobilised non-linear pH 3-10 gradient strip (BioRad, US), 50 µg of protein sample was applied for rehydration overnight (12–14 hours). Isoelectric focusing was performed at 20˚C using Protean IEF Cell apparatus (BioRad, US) with the following voltage/time gradient: 100 V for 1 minute, 250 V for 30 minutes, 4 000 V for 2 hours and 4 000 V for 10 000 V-hours (V-hr). Before transferring the IPG strip onto the second dimension electrophoresis step, the strip was equilibrated sequentially for 10 minutes in a buffer containing 65 mM dithio-threitol and then 135 mM iodoacetamide in 125 mM Tris-HCl, pH 6.8, 6 M urea, 2% SDS, 30% glycerol and 0.01% bromophenol blue. After equilibration, the strip then was placed on 12% polyacrylamide separating gel and sealed in place using Ready Prep Overlay Agarose (BioRad, US). Proteins were separated using Mini Protean 3 apparatus (BioRad, US) for 45 minutes or until the bromophenol blue dye reached the bottom of the gel. Protein spots profile was visualised with Coomassie brilliant blue (CBB) R-250 dye.

2-DE IMMUNOBLOTTING

A nitrocellulose membrane blotted with 2-DE-separated raw mussel components were subjected to a procedure similar to immunoblotting analysis.

MASS SPECTROMETRY ANALYSIS

The Coomassie-stained protein spots corresponding to those recognised by the above sera were manually excised and transferred to microcentrifuge tubes. These protein spots were analysed using mass-spectrometry analysis by First Base Laboratories Sdn Bhd, Malaysia. Protein samples were trypsin digested and the peptides were extracted according to standard techniques. These peptides were analysed by matrix-assisted laser desorption-ionisation time of flight (MALDI-TOF) mass-spectrometer using a 4 800 Proteomics Analyser. Spectra were analysed to identify the protein of interest using Mascot sequence-matching software (Matrix Science) with Ludwig NR Database and taxonomy set to other metazoa.

RESULTS

COMPARISON OF PROTEIN FRACTIONS IN RAW, BOILED, FRIED AND ROASTED MUSSEL BY SDS-PAGE

Protein profile of raw mussel extract revealed approximately 21 protein bands at various molecular weights between 10 and 250 kDa, whereas the boiled extract contained 11 protein bands. Several protein bands between 13–15 kDa, 40–42 kDa, 55–90 kDa and 180–250 kDa were sensitive to heat and therefore were no longer detected in the boiled extract. On the other hand, most of the protein bands in fried and roasted extracts were completely denatured. However, proteins of 18 and 36 kDa were conserved in all the extracts regardless of the cooking process employed (see Figure 1).

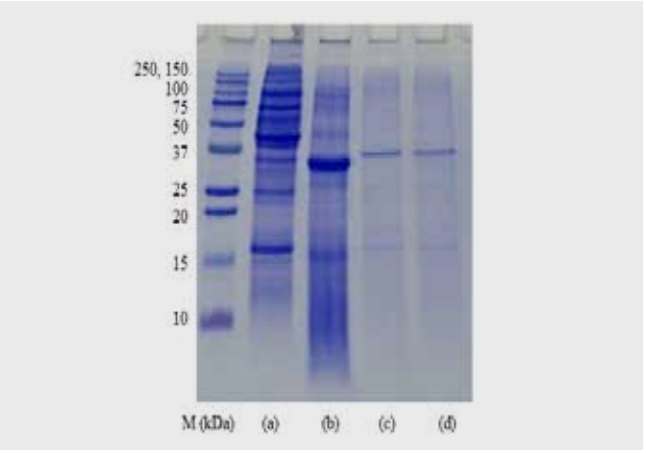

Figure 1: SDS-PAGE profiles of raw (a), boiled (b), fried (c) and roasted (d) extracts of Perna viridis (Asian green mussel). Lane M, molecular mass markers.

COMPARISON OF IGE-BINDING TO MUSSEL COOKED IN DIFFERENT WAYS

In general, immunoblotting experiments revealed that the raw mussel extract had a higher number of IgE binding proteins than the cooked extracts (see Figure 2). A total of 16 IgE-binding proteins were detected by the immunoblot of the raw mussel extract. The 36 kDa protein showed the highest frequency of IgE-binding (95%) followed by 18 kDa protein (55%), therefore identified as the major allergens of mussel. In addition, other IgE-bindings were detected at proteins of 42, 50 kDa (45%), 25 kDa (40%), 30, 40, 55 kDa (35%), 37, 65, 75, 90, 100 kDa (30%), 150, 250 kDa (20%) and 180 kDa (15%).

The allergenicity of the cooked extracts which include boiled, fried and roasted extracts were further studied using seven allergic patients' sera, as shown in Figure 2b, 2 and 2d. These patients' sera were selected because their IgE binds to the proteins of the raw extract seen in the immunoblot above. The identified bands were at 18 kDa (patients 2, 11 and 19), and 36 kDa (patients 5, 11, 12, 15, 19 and 20). None of the mussel proteins showed binding with the negative control serum.

IDENTIFICATION OF THE 18 AND 36 KDA PROTEINS, THE MAJOR ALLERGENS OF MUSSEL

Coomassie blue staining of the separated components showed ~50 distinct spots, whereas immunoblotting showed at least 10 different reactive spots with molecular masses of 10–250 kDa and isoelectric point (pI) values ranging from 4.0 to 8.0 (see Figure 3). This study focused on further identification of the allergenic spots of 18 and 36 kDa proteins, the major allergens of mussel. Therefore, spot number 1 (36 kDa/pI 4.7) and 2 (18 kDa/pI 4.1) were selected for mass-spectrometry analysis. No IgE-binding

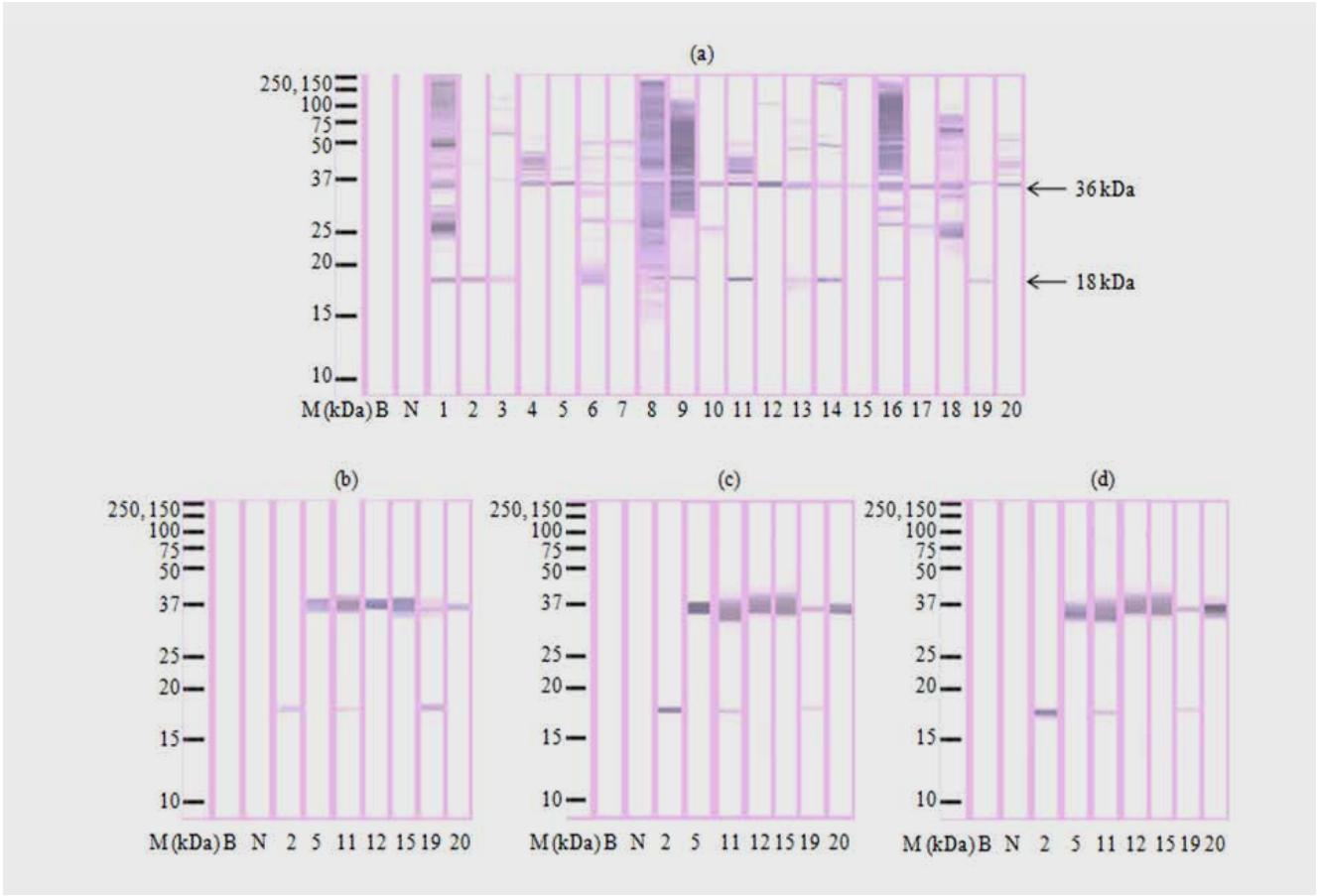

Figure 2: Immunoblotting of raw (a), boiled (b), fried (c) and roasted (d) extracts of Perna viridis (Asian green mussel). Lane M, molecular mass markers; lanes 1–20, immunoblots showing binding of IgE from different serum samples; lane N, immunoblot using serum from a non-allergic individual; and lane B, blank.

spots were detected by immunoblotting using a control serum from a non-allergic subject (result not shown). Table I summarises the mass-spectrometry analysis of the spots. Sequence comparisons of a 36 kDa (spot 1) and 18 kDa (spot 2) with known protein sequences in databases have identified these spots as tropomyosin and troponin C, respectively.

DISCUSSION

Cooking appears to affect the allergenicity of mussel allergens. Our study demonstrated that the process of cooking by boiling, frying or roasting, produces changes in the SDS-PAGE protein profile of mussel allergens. Compared to the raw extract, boiling causes a remarkable reduction in the number of protein bands due to denaturation of proteins. Both frying and roasting showed a similar protein profile, with most of the bands clearly eliminated compared with those of the raw and boiled extracts. The loss of the proteins in boiled, fried and roasted extracts may be related to the effects of heat on protein structure, since heat may disrupt secondary and tertiary protein structures and lead to random-coiled aggregation and insolubility.[18,31]

Regarding IgE reactivity, immunoblotting experiments revealed that the raw mussel extract had higher IgE binding than the cooked extracts. These results were consistent with previous studies of other bivalve allergens, that is, cockle, clam and oyster.[14–16] Moreover, several studies proved that bivalves are allergenic in both raw and cooked states.[4–6,32,33] This is a significant finding as local mussel is commonly consumed in both forms. This was also seen in this study as patients' sera demonstrated IgE reactivity to both raw and cooked mussel extracts. In contrast, Kamath et al[34] reported that none of the raw bivalve extracts (i.e. blue mussel and oyster) reacted to monoclonal antibodies. IgE reactivity was observed only in the heated extracts, with very faint monoclonal antibodies reactivity for oyster.

Allergens can be defined as being either major or minor. Major allergens mean proteins that elicit IgE-binding in the majority (more than 50%) of patients; while those, which elicit allergic reactions only in a minor fraction (less than 50%) of patients allergic to the specific source, are regarded as minor allergens.[35] In this study, two IgE-binding proteins were recognised by more than 50% of patient sera: 18 and 36 kDa. Both proteins are heat-stable because they retain their IgE reactivity in immunoblots of extracts from cooked mussel. So far, the only known mussel allergen is a tropomyosin. Tropomyosin with a molecular weight around 34 to 38 kDa, comprises a group of highly conserved actin-binding proteins present in muscle and non-muscle cells and plays a central role in muscle contraction. Similarly, our

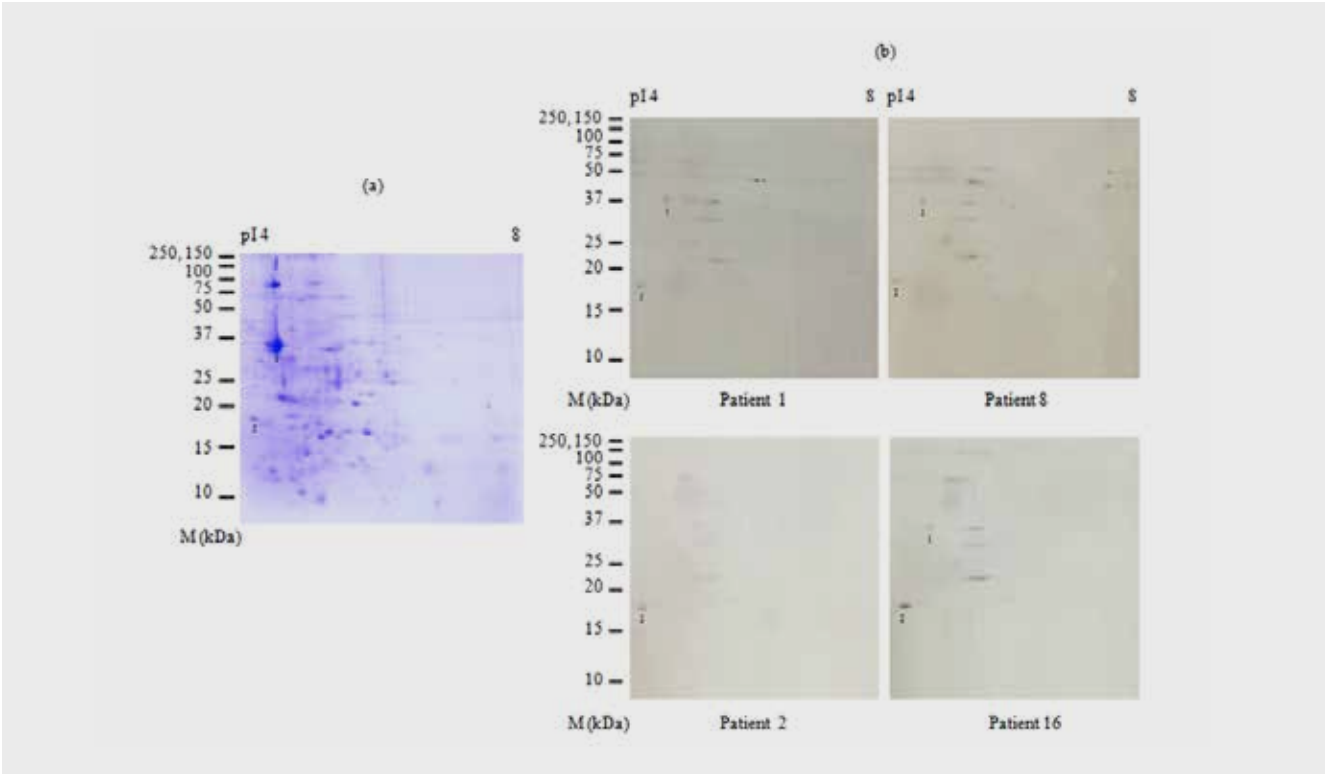

Figure 3: Two-dimensional electrophoresis and immunoblot analysis of Perna viridis (Asian green mussel) (a): Coomassie blue stained blot; (b): Immunoblot with individual patients' sera. Spots number 1 and 2 were sent for mass spectrometry analysis. Lane M, molecular mass markers.

study has also identified the 36 kDa protein as tropomyosin by mass-spectrometry analysis.

Results of the present and some of the earlier investigation from our laboratory indicate the antigenic stability of tropomyosin toward heat treatments.[14–16,18–20] Immunoblotting of the cooked mussel extracts revealed more intense and high-yielding IgE-binding of the tropomyosin. This suggests that this protein is highly heat-stable and cooking altered the epitopes of the allergen by unmasking the epitopes with more surfaces accessible, resulting in an increased IgE affinity.[36–38] The ability of tropomyosin to withstand heat treatment and most known types of food processing technique can be attributed to its exceptionally stable alpha helical coiled-coil secondary structure.[24,34]

Another major allergen identified in this study was troponin C. Our study is the first to report troponin C as the second major allergen of mussel. Troponin C is a subunit of troponin which involves in calcium-dependent muscle contraction in skeletal and cardiac muscle.[39] Prior to this study, troponin C has already been identified to be one of the allergens in crustacean and some invertebrates such as shrimps or prawns,[40,41] cockroach[39] and mite.[42]

In this study, minor allergens were detected only in the raw extract. This suggests that all these allergens were heat-sensitive proteins. The process of cooking may have altered the allergen extracts in that cooking may have fragmented the proteins to small peptides not observed on the gel. Heat treatment may also alter the allergen extracts as a result of changes in protein conformation by masking the allergenic epitopes. Therefore, allergen recognition was reduced and so was allergenicity.[36-38]

CONCLUSION

Cooking may be viewed as an important way of preventing allergy in susceptible individuals. The process of cooking results in reduced mussel allergenicity by reducing the number of IgE-reactive bands. The order of allergenicity of mussel from lowest to highest, was demonstrated to be, raw > boiled > fried ≈ roasted. The two major allergens of *Perna viridis* were identified as tropomyosin and troponin

TABLE I: IDENTITIES OF PROTEIN SPOTS OF *PERNA VIRIDIS* IDENTIFIED BY MALDI-TOF

Spot No.	MW (kDa) and pI of matched proteins: observed/ predicted	Protein identification	Organism	Accession No.	Residue numbers of matched regions	Coverage of protein sequence
1	36/32.7 kDa, 4.7/4.6	Tropomyosin	*Tresus keenae*	B7XC69	91–105, 134–146, 168–178, 206–217	17%
2	18/17.3 kDa, 4.1/4.0	Troponin C	*Venerupis philippinarum*	H6B8P0	16–24, 33–39, 86–108	26%

C. Therefore, allergens found in this study would help in mussel allergy diagnosis and treatments.

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DECLARATION OF CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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ABC of Allergy

SOYA (OR SOY) ALLERGY

Shaunagh Emanuel & Di Hawarden

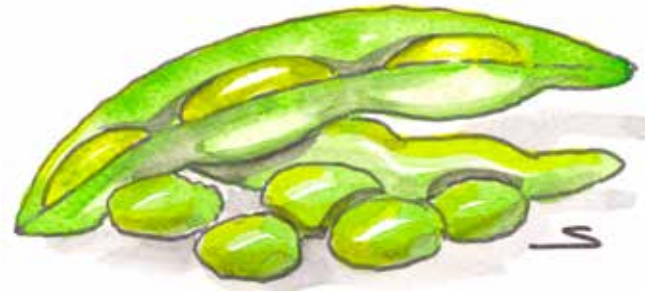
Dr Do-a-lot asks her students to find answers to questions on soya allergy. These are their answers:

Dried Soya Beans

What is soy, and is it different from soya?

There is no difference between soy and soya. In the USA the term soy is typically used, whereas in Europe the legume is called soya. The terms refer to a type of legume that is native to East Asia, but is now grown extensively worldwide. Products made from soya (or soy) include soya milk, tofu and fermented soya products like bean paste or soya sauce. Soya beans may be ground to make soya flour. They may be further processed to make Textured Vegetable Protein, or TVP. Soya oil may be found in margarines, spreads and oil mixtures. Processed foods often contain soya, usually in the form of soya lecithin or soya concentrate, or isolated soya protein where it is used as an emulsifier or stabiliser. Soya is cheap to grow, highly nutritious and rich in protein. Fresh soya beans are often called edamame beans.

Is soya allergy always immunoglobulin E (IgE) mediated?



Edamame Beans

No, delayed type reactions that are non-IgE mediated may be caused by soya. IgE mediated reactions usually have a quicker onset after allergen exposure than non-IgE mediated reactions.

Is allergy to soya as common as allergy to milk, egg, peanut or fish?

Soya is listed amongst the most frequent human food allergens, which include milk, eggs, fish, crustacea, wheat, peanuts, tree nuts and soya, however allergy to soya is less common than allergy to foods like milk, egg, peanut and fish which contain proteins which are typically more allergenic. Because soya is a legume, it is possible for people to react to other legumes like peas and lentils if they are allergic to soya. Peanuts are legumes, but patients who are allergic to soya will not necessarily be allergic to peanuts. Soya beans are not related to tree nuts like almonds or cashews. It is also possible for patients who are allergic to soya to react to birch pollen due to cross reactivity to shared proteins.

Soya Infant Formula

In the case of children with milk allergy, is soya milk a possible alternative (where breastfeeding is not an option)?

In children who tolerate soya milk it is a suitable alternative. In cases where soya milk is not tolerated an extensively hydrolysed formula or an amino acid formula may be required.

What symptoms are common in soya allergy?

Typically, the allergic manifestations of IgE mediated soya allergy are mild and usually affect the skin (e.g. pruritis, mild dermatitis. urticaria or angioedema), especially in children.

However symptoms may also include the gastrointestinal tract (e.g. vomiting, abdominal pain, diarrhoea) and the respiratory system (e.g. rhinitis, bronchospasm, cough), and anaphylaxis may occur.

In a patient who has developed IgE mediated allergy to soya, there is no way to predict for certain how severe possible subsequent reactions will be. In non-IgE mediated allergy to soya, reactions tend to be delayed (typically by more than 2 hours), usually localised to the gastrointestinal system and include symptoms like abdominal pain, diarrhoea, vomiting, reflux and colic. In these patients it is not uncommon for the diarrhoea to be bloody. Food Protein Induced Enterocolitis Syndrome (FPIES) is an example of a non-IgE mediated reaction that may occur in patients with soya allergy.

What tests are used to make the diagnosis of soya allergy?

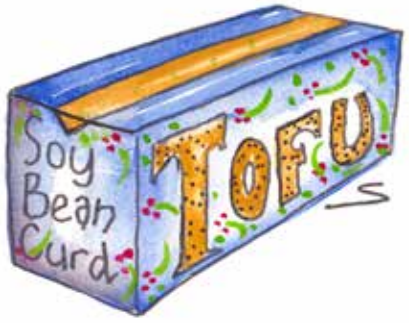
Skin prick testing may be performed in patients who have not had anaphylaxis to soya protein. Specific IgE blood tests may be helpful. An elimination diet with subsequent reintroduction of soya may aid diagnosis. This is best done under the supervision of a dietician. A food challenge test (under controlled circumstances in a medical facility with experienced staff) may be necessary to confirm the diagnosis where there is uncertainty.

How is soya allergy treated?

Avoidance of soya is the cornerstone of management. Patients must be taught to read food labels and learn to recognise soya-containing ingredients. They need to be pro-active in questioning waitrons and chefs at restaurants to ensure that soya is not used in food preparation. Consultation with a dietician is recommended as the avoidance of soya requires thorough education, and in patients where soya products are relied upon as a protein source (for example in vegan patients) dietary advice may be needed to find adequate protein substitutes.

Soya Sauce

Patients may need to carry an adrenaline auto-injector, especially if they have had a previous episode of anaphylaxis or have asthma. They must wear a medical identification bracelet or necklace clearly stating their allergy to soya. Asthma control must be optimised.



Tofu or Soya Bean Curd

What are some commonly eaten foods that may contain soya?

Soya sauce, tofu, tempeh, miso, breads and baked goods, energy bars, infant foods, mixed oils, margarine, spreads, processed foods, nut butters, canned soups, canned tuna and some medicines may contain soya.

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PID123

Primary Immunodeficiency

WISKOTT-ALDRICH SYNDROME (WAS)

Dr Goodheart is a paediatrician whom we met in previous versions of PID 123. She is seeing a seven-year-old boy called Enrico in her clinic. Enrico's mother is quite worried because her son has had a rash on his legs for a couple of weeks, which does not heal. Enrico is also coughing all the time.

Dr Goodheart examines the child. Enrico is growth-retarded and underweight for his age. The eczema on his legs is diffuse and appears infected. On investigation of the chronic cough, Dr Goodheart hears crackles in both lungs.

Dr Goodheart is alerted by these findings of apparent chronic illness and takes a more detailed history: The family lives on a farm. Mother, father and one brother appear all healthy. From the records, Dr Goodheart recognises an **abnormal frequency of upper respiratory** tract infections for a little boy living in an otherwise healthy farming environment.

Enrico presented to the hospital earlier in the year with pneumonia, septicaemia and lung empyema. At that time thrombocytopenia was also investigated. Bone marrow investigations revealed no clues to a possible cause. Enrico was treated with steroids to which he did not respond. Dr Goodheart's colleague considered a splenectomy at the time but this was delayed because of the ongoing respiratory infections, requiring repeated antibiotics. However, apart from intermittent nose bleeds, he did not have major bleeding problems.

Dr Goodheart admits Enrico to have a chest X-ray taken, which shows infiltration and consolidation in both lungs and starts IV antibiotics. She also initiates a number of blood tests.

The following day she is contacted by a concerned laboratory technologist. Enrico has a low platelet count of 40 000 x $10^9/\ell$ and the pathologists noted **small platelet size**. Enrico is also mildly anaemic.

The severe and recurrent nature of Enrico's respiratory infections in combination with the **eczema** and the low and small platelets alarm Dr Goodheart to the possibility of a primary immune deficiency (PID). She, therefore, calls her colleague, Dr Bala, to request a transfer to her hospital for further management and assessment for possible PID.

After admitting Enrico to her ward, Dr Bala initiates a basic immune screen which includes a laboratory confirmation of the low platelet count. Other results show normal neutrophil and normal lymphocyte counts. Immunoglobulins IgG, M, A are also within normal range. The total complement screen shows normal activity. Vaccine antibodies to pneumococcus as well as to tetanus and diphtheria toxoids are not protective. A chest X-ray is suggestive of bronchiectasis in both lower lobes.

After three days of intravenous antibiotics, Enrico is much better and is discharged on oral antibiotics and vaccine boosting. His platelets, however, still remain in the low range and his parents are given information on his possible bleeding tendency caused by the low platelets.

A follow-up in four weeks is scheduled for his pneumonia and general health, as also repeat vaccine antibody studies and monitoring of platelet count. The option of intravenous immunoglobulins to prevent recurrent infections may have to be considered.

Dr Bala has also stored blood for genetic testing as she strongly suspects **Wiskott-Aldrich Syndrome (WAS)**, for which Enrico fits all the clinical and laboratory criteria (see Box). She also obtains consent to put Enrico on the PID register with this provisional diagnosis and contacts the molecular laboratory.

Some days later she receives the results from exome sequencing which confirms the diagnosis of WAS. At this stage, she phones Dr Goodheart about these latest results.

Dr Bala will keep a watchful eye on other complications associated with WAS such as malignancies and auto-immune manifestations.

She discusses a splenectomy with colleagues from haematology, however, this is delayed since platelets are currently not critically low. Dr Bala also consults with dermatology for control of eczema. Enrico is also discussed for a possible bone-marrow transplant once 'stabilised', however, the evidence of chronic lung disease makes this a difficult decision.

Enrico's parents are very grateful to now have a diagnosis to explain their son's frequent illness. Prompt treatment of infections and the eczema will help to improve his quality of life significantly.

Wiskott-Aldrich Syndrome (WAS) is an X-linked recessive primary immunodeficiency disorder caused by various mutations affecting the WAS protein (WASp).
There is a classical triad of:

- recurrent infections (otitis media, pneumonia, sepsis, meningitis);
- bleeding (thrombocytopenia and platelet dysfunction);
- eczema (often mimicking atopic dermatitis).

However, WAS patients may present with a wide range of symptoms and disease severity with only one third displaying the 'typical' triad. There may also be autoimmune manifestations and malignancies.

Treatment includes antimicrobial treatment of infections and prophylactic antibiotics. Especially severe and persistent eczema requires ongoing care. Since many WAS patients have abnormal vaccine responses, immunoglobulin replacement therapy may be considered. Splenectomy may be considered in patients with particularly low platelet counts. Many WAS patients receive bone-marrow transplants, which considerably extend life expectancy.

SUGGESTED READING

Wiskott-Aldrich Syndrome. Chapter 10 in Immune Deficiency Foundation Patient & Family Handbook for Primary Immunodeficiency Diseases. 5th edition. Immune Deficiency Foundation. 2013

Ochs HD. Wiskott-Aldrich syndrome. UpToDate 2016

Wikott-Aldrich Syndrome. International Patient Organisation for Primary Immunodeficiencies (IPOPI)

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MULTIPLE CHEMICAL SENSITIVITY – TWO ILLUSTRATIVE CASE REPORTS

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ABSTRACT
Multiple Chemical Sensitivity was first proposed as a disease entity 50 years ago and, although still surrounded by controversy, is increasingly being accepted as such. The condition is also known as Idiopathic Environmental Intolerance. It is a chronic disease in which low levels of chemicals invoke a multiplicity of unrelated symptoms. The cause is not known but the condition will present to physicians, allergologists, ear, nose and throat surgeons and, most especially, occupational health practitioners. Symptoms may be mild or totally disabling, and multiple organs may be affected. No objective or measurable features aid the diagnosis and no definitive management options are available. Two case histories are presented which conform to the criteria that were established in 1999 and modified in 2005. In both cases the condition caused severe disability, with devastating consequences for the sufferers, especially their ability to continue working. This article aims to bring the existence of this condition to the attention of health practitioners.

INTRODUCTION

Multiple Chemical Sensitivity (MCS) as a disease entity was proposed 50 years ago and has elicited scepticism from scientists amid much controversy. It is described as a chronic condition with multi-organ symptoms that occur in response to exposure to a range of chemicals. Symptoms include headaches, burning eyes, nose or throat, concentration or memory lapses, nausea, muscle pain, dizziness, breathing problems and fatigue. The disease is debilitating and causes social isolation and hardship. Because the symptoms are subjective and there are no objective signs of disease or of allergy, the diagnosis is difficult. No adequate treatment is available.[1]

BACKGROUND

Germany was the first country *formally* to recognise MCS, and in 2000 classified it with an ICD-10 code (T78.4) as a physical disease associated with an unspecified allergy. Austria, Luxembourg and Japan followed suit.[2] Denmark and Switzerland followed in 2010 and 2012, and Spain in 2014.[3] The United States, Canada and South Australia recognise MCS as a disabling occupational condition and it is therefore compensable.[4]

Although MCS is not specified as an occupational disease in South Africa under Schedule 3 of the Compensation for Occupational Injuries and Disease Act 181 of 1993, and is therefore not readily accepted by the Department of Labour as a compensable work-related condition, both the cases presented were accepted by their professional insurance company *as having a disabling disease* and *were granted disability pensions.*

The consensus criteria for the definition of this condition, established in 1999 and still recognised, are these:[5]

- It is a chronic condition.
- Symptoms recur reproducibly.
- Multiple organ systems are affected.
- It occurs in response to low levels of exposure.
- Multiple unrelated chemicals seem causative.
- Symptoms improve or resolve when incitants are removed.

These criteria were modified by Lacour et al in 2005,[6] as follows:

- It is a chronic condition lasting more than six months and causing a deterioration of lifestyle and bodily functions.
- Symptoms recur reproducibly and affect the nervous system, with a characteristic hypersensitivity to odours.
- The central nervous system and at least one other organ system is continuously involved.
- Responses are induced after low levels of exposure.
- Responses are to multiple unrelated chemicals.
- Symptoms improve or resolve when incitants are removed.

In 1996, the International Programme on Chemical Safety (IPCS) held a conference at which the preferred term

TABLE I: EXPOSURES COMMONLY CAUSING SYMPTOMS IN PEOPLE WITH MCS (ADAPTED FROM CARESS & STEINEMANN[11] AND MAGILL & SURUDA[13])

TYPE OF EXPOSURE	SPECIFIED AGENTS
Cleaning agents	Tile cleaner, floor cleaner, furniture polish, dry-cleaning fluid, laundry detergent
Pesticides	Insect repellents, insecticides
Perfume	Cosmetics, shampoos, aerosol deodorants, air fresheners, aftershave lotion
Tobacco smoke	Cigar and cigarette smoke
Car/diesel exhaust	*Exhaust emissions*
Beauty salons and barber shops	Nail polish, nail-polish remover, hairspray, shampoos
New carpets or furniture	*Volatile organic compounds*
Fresh ink	Marker pens
Other industrial agents	Asphalt, tar odour from road or roof, oil-based paint, varnish, shellac, lacquer, paint thinners, chlorine in water

Idiopathic Environmental Intolerance (IEI) was proposed since the term MCS implies a causal relationship with chemicals that has not been established.[7] IEI has been defined as:

- an acquired disorder with multiple recurrent symptoms;
- being associated with diverse environmental factors tolerated by the majority of people;
- not explained by any known medical, psychiatric or psychological disorder.

Despite the consensus decision, MCS is still the term most used to describe this complex syndrome.

The aetiology is unknown and whether exposure to chemicals is the actual cause is doubted, although a number of different theories have been suggested.[8] Broken down into concepts, these include:

- disruption in immunological or allergic processes;
- an alteration in nervous system functioning;
- changes in biochemical or biotransformation capacity;
- changes in psychological or neurobehavioural function.

Immunological and allergic processes seem the least likely to be causative. Several avenues of investigation are being explored. Pall[9,10] postulates elevated nitric oxide levels activated by organic solvents that cause neural sensitisation whereas Bell et al postulate dysfunction of the olfactory–limbic system.

Of 120 patients with MCS examined in an environmental medicine department, the authors found that in 100 (83%) of these at least one psychiatric diagnosis was made.[10] The authors concluded that many of these patients suffer from somatoform disorders but also from other well-known psychiatric conditions.

The prevalence of this condition varies with its definitions and is uncertain. Among a randomly selected sample of 1 582 respondents from the general population in a geographical area in metropolitan Atlanta,[11] 199 (12.6%) reported hypersensitivity to common chemicals and 49 (3.1%) reported that they had actually been diagnosed with MCS. Moreover, 29 (13.5%) reported losing their jobs because of hypersensitivity. The authors concluded that both men and women are affected, although women make up the majority of patients (more than 70%). The condition was reported by individuals of different ages and educational levels.

Among general cohorts of Gulf War veterans, the rate of chemical sensitivity was reported to be 36–38% and the rate of MCS was 2–6%.[12]

Exposures most commonly reported as causing or triggering symptoms are listed in Table I.

Many and varied symptoms involving multiple organs have been described in the literature.[14] Some of those more commonly reported on are listed in Table II. It is the vagueness of the symptoms experienced, and their variety and seeming unrelatedness, that *are* important and that should alert the clinician to MCS. The symptoms are unique to each person and do not seem to be precipitated by any specific exposure.

In this article, two cases of MCS are presented. An insurance company referred both of them to a dermatologist working

TABLE II: SYMPTOMS FREQUENTLY REPORTED BY PATIENTS WITH MCS

Neuropsychological	Fatigue
	Difficulty concentrating
	Depressed mood
	Memory loss
	Weakness
	Dizziness
	Headaches
	Heat intolerance
Ear, nose and throat	Dry mouth, sore throat and nasal congestion
Respiratory	Shortness of breath
	Difficulty breathing
	Coughing
Skin	Irritation and redness (not documented by doctor)
Miscellaneous	Arthralgia, chest and abdominal pains

in an occupational setting for disability assessment. Both had consulted many medical practitioners. The first case had been eventually diagnosed with MCS by an occupational health practitioner.

The aim of this presentation is to bring the existence of this condition to the attention of medical practitioners in South Africa.

CASE PRESENTATIONS

Case 1

The patient was a 48-year-old woman. She worked as a dentist in private practice and had rooms at her home. She had worked as a dentist since 1984 and as such was in contact with many chemicals – especially acrylates. The consultation with this patient was prolonged and the information conveyed confusing and difficult to correlate.

She stated that her 'allergic problems', as she believed them to be, had started in 2005 after she had been exposed to glass ionomer cement, a material used in dental fillings that is a combination of silicate and polyacrylate cement system and which may also contain acrylate monomers. She had an 'acute reaction' and 'felt terrible'. Thereafter, she experienced intolerance to all smells, not only those in the work environment, and this persisted until the consultation.

She described having blocked ears, a thick sensation in her head, sleepiness, tiredness, memory loss, difficulty with concentrating, stiffness, loss of sensation, difficulty with seeing, a tight chest and a 'gevoel van benoudheid' (feeling of anxiety). She was examined by medical practitioners, homeopaths and physicians. She was tested extensively for allergies: patch tests and the Cellular Allergen Stimulation Test (CAST); the Memory Lymphocyte Immunostimulation Assay (MELISA) tests using various dental materials were negative. However, for the duration of the patch tests (48 hours), she complained of a burning mouth, weak muscles, rash and sore joints. She was diagnosed as type 1 urticaria on the basis of her symptoms but the reactions were not witnessed. She was prescribed oral steroids and a Ventolin® inhaler, which were ineffective. At this time she stopped working in her rooms and employed a locum. However, she found the smell intolerable even though she did not go into the consulting rooms. She got rid of all the dental materials and had the offices thoroughly washed. Nonetheless, when she went near them, she experienced the same symptoms.

If exposed to any smell, such as occurred when she passed a nail bar in a mall or when she bought new, varnished furniture, the symptoms recurred. She bought a new house and moved away from her home and rooms.

The diagnosis of MCS was made by an occupational health practitioner. The condition caused her disability such that she was unable to continue with her chosen profession. She has continued to suffer in her normal life in spite of no longer being exposed to dental materials.

Case 2

A 64-year-old man had worked as a pharmacist since 1969 and as a manufacturing pharmacist since 1989. He was in contact with a host of different chemicals and was forced to retire in 2009 on account of his symptoms.

He stated that he was allergic to penicillin and also to cut grass prior to the onset of the MCS. He had never suffered from asthma, hayfever or flexural eczema.

He developed his problem in 2006 and dated the onset of his condition from exposure to turpentine. He developed 'sensitivity' to various drugs with which he worked. He listed them as Zithromax®, Taquin®, Antistine-Privine®, Tobrex®, Vita-thion, estomycin (erythromycin) and herbal medications. In addition, he found perfumes worn by women, mosquito repellent, citronella, solvents, paints, toluene, theatrical smoke and ammonia intolerable.

His symptoms were vague, many and incapable of being clearly attributed to a single cause. They included red rashes, a tight chest, coughing and a hoarse voice, irritation of his upper respiratory tract, itch, erythema and distress. He also suffered from headaches, aches and pains. His symptoms resolved over weekends, only to recur on returning to work on Mondays.

He had consulted a number of practitioners, including a pulmonologist, who could find no abnormality. The total IgE and the radio-immune test (RAST) for inhalants (Phadiotop®) were normal. He was patch tested with the European standard series of allergens and these were unreactive.

The diagnosis was MCS from the chemicals that he was exposed to both at work and in his city environment. He was disabled in that he was unable to continue in his occupation. After retiring in 2009, he continued to experience symptoms in the city suburbs in which he lived. He moved to live with his son in the Bushveld, where there were no triggering smells and he was able to live normally and contentedly.

DISCUSSION

What was striking about these two cases was the similarity between them. Both individuals were highly skilled professionals who had worked for many years in their professions and felt forced to stop working against their will.

The consultations were long and confusing and there was no recognisable pattern to the multiple symptoms involving many organ systems which they described. Both displayed great distress and discomfort. In a long and circuitous submission, Case 1 pleaded: 'Help my asseblief om hierdie nagmerrie in my lewe af te sluit.' ('Please help me to end

this nightmare in my life.')

Both had been extensively investigated for physical disease and especially for allergy, with negative results. Both described an aversion to a wide variety of odours. Neither had cause to malinger; both had retired before their consultation. The differential diagnosis includes various psychiatric disorders, since in some of the literature MCS is regarded as a special subgroup of somatoform disorder.[15] Physical disease and allergy had been excluded through extensive investigation prior to the consultation.

Both patients fulfilled the Lacour criteria for the diagnosis of MCS:

- Symptoms in both patients had persisted for many years and both found their lives intolerable. Many of their symptoms were similar to those described in the literature (see Table II). However, they were vague and legion and peculiar to each person. Neither was able to continue working.
- Both patients, on exposure to various chemicals, complained of the odour that caused discomfort and of numerous somatic complaints.
- They experienced psychological distress as well as headaches, non-specific aches and pains, and respiratory symptoms.
- The levels of chemicals that induced the symptoms were low. For instance, Case 2 reacted with distress to another patient in the office who was wearing perfume. Case 1 reacted to nail chemicals inside a mall but outside of the shop.
- In both cases a number of unrelated chemicals induced the response.
- In Case 2, the patient improved after leaving work and living in the Bushveld. The patient in Case 1 still experiences discomfort on exposure to solvents, although, having stopped work, she is no longer exposed to dental chemicals.

The diagnosis had not been made in the case of patient 2 prior to referral for disability assessment; but an occupational health practitioner who was aware of this syndrome was able to make the diagnosis in patient 1. Both cases were accepted by the insurance company as having a disabling disease and were awarded disability pensions.

The question remains whether MCS can be classified as an occupational disease and, most importantly, whether compensation can be obtained for sufferers. It is not listed in Schedule 3 of the Occupational Health and Safety Act 181 of 1993[16] as a compensable occupational disease. However, since MCS may be triggered by chemical exposure at work, submission of a claim should be considered. This is provided for in Chapter VII Occupational Diseases, paragraph 64, sentence 1(*b*) which states that an 'employee shall be entitled to the compensation provided for and prescribed in this Act if it is proved to the satisfaction of the Director General' that the disease, even if not listed in Schedule 3 'has arisen out of and [in] the course of his or her employment'.

CONCLUSION

The existence of this condition as an entity has been controversial but it is increasingly being accepted. The cause or causes are not known but are being extensively researched. Both these patients conformed to all the criteria laid down in 1999 and again in 2005. Clinicians need to be aware of the syndrome, especially in view of the devastating effect it has, in severe cases, on the ability of patients to work and earn a living. No effective treatment other than the avoidance of chemicals was available, and both patients therefore claimed and were awarded disability payouts. Medical practitioners should be patient and sympathetic when confronted with such cases and should motivate for compensation if the work environment has played a causative role.

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

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Primary Immune Deficiency

WE CAN DO MORE TO IDENTIFY PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

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Primary immunodeficiencies (PIDs) remain largely undiagnosed and underreported in South Africa.[1] PIDs are inherited, non-communicable disorders that involve a defect in one or more components of the immune system. Immunodeficiencies comprise more than 250 heterogenous disorders that cause either an absent, defective or weakened function of the immune system.[2] These disorders are mostly associated with recurrent infections that can present very early in childhood, but depending on the defect, also in later childhood and even in adulthood.

In early childhood, the immune system encounters antigens for the first time, mounting immune responses and acquiring memory. Young children mix with other family members and other children and are therefore exposed to many pathogens, making them vulnerable to infections. Recurrent infections are therefore quite common.[3,4] The delay in early PID diagnosis could be explained by a perception that recurrent infections are a normal part of childhood development.

The diagnosis of PIDs is therefore not always easy, especially among the many sick children seen in daily practice by general practitioners and paediatricians. These children often present with very common and non-specific complaints. It remains challenging to decide when to treat symptomatically and when to start investigating a patient for PID. Furthermore, a decision should be made about appropriate, cost-effective laboratory testing, correct

TABLE I: A SELECT GROUP OF THE MORE COMMON IMMUNODEFICIENCIES TAILORED FOR THE SOUTH AFRICAN PRACTITIONER – CONSTRUCTED WITH REFERENCE TO GEHA ET AL[5] AND AL-HERZ W, BOUSFIHA A, CASANOVA J ET AL[17]

PRIMARY IMMUNODEFICIENCIES	CLINICAL FEATURES
ANTIBODY DEFICIENCIES	**MUCOPURULENT SINOPULMONARY INFECTIONS**
• XLA • CVID • Specific antibody deficiency • Transient hypogammaglobulinaemia of infancy	
Combined T-/B-cell deficiencies • SCID • Omenn's Syndrome/Leaky SCID • Hyper-IgM Syndrome	Bacterial, fungal, viral infections, protozoal infections with/without failure to thrive and diarrhoea
NEUTROPHIL FUNCTIONAL DEFICIENCY	
• CGD	Abscesses and infections of parenchymal organs and lymph nodes
COMPLEMENT FUNCTIONAL DEFICIENCIES	
• Terminal complement pathway deficiency (most common)	Terminal complement deficiency with risk of meningococcal disease
IMMUNODEFICIENCY SYNDROMES	
• Wiskott Aldrich Syndrome	Bacterial and viral infections; thrombocytopaenia with small platelets; eczema; lymphoma/autoimmunity
• Ataxia Telangiectasia	Progressive ataxia/telangiectasis/immune deficiency
• Di George Syndome	Mostly mild/no immunodeficiency May present with incomplete T-cell defects with varying levels of CD4 cells Occasionally complete Di George: SCID-like presentation
• Hyper-IgE syndrome	AD form: Boils/pneumatocoeles/eczema-like skin rash/abnormal facies/failure to lose primary teeth AR form: severe and recurrent herpes viral infection. Persistent/recurrent molluscum contagiosum

CVID: common variable immunodeficiency; SCID: severe combined immunodeficiency. SLE: Systemic lupus erythematosus. AD: Autosomal Dominant. AR: Autosomal Recessive. MBL: Mannan Binding Lectin. CGD: Chronic granulomatous disease. XLA: X-linked agammaglobulinemia

AMPATH LABORATORIES

Diagnosing PID

Primary immunodeficiencies are like chameleons

Presenting with Severe, Persistent, Unusual and Recurrent infections

Disguised as HIV, allergies and other chronic diseases

Are you not dealing with a humoral, cellular, combined immunodeficiency, complement or neutrophil defect?

Confirm your suspicions with the appropriate LABORATORY TESTING

ANTIBODY DEFECTS

- IgG, IgA, IgM
- IgE
- IgG subclasses
- Lymphocyte subsets (B cell numbers)
- S.pnemonia antibodies
- H.influenzae antibodies
- Tetanus antibodies
- Diphtheria antibodies
- Memory B cells
- Brutons Tyrosine Kinase

T-CELL DEFECTS

- Lymphocyte subsets (T cell numbers)
- Naïve and memory Cells CD4
- Naïve and memory Cells CD8
- Alpha beta/gamma delta T cells
- Common Gamma Chain
- Lymphocyte proliferation test against mitogens/recall antigens
- CD 40 Ligand

NEUTROPHIL DEFECTS

- Neutrophil antibodies
- Oxidative burst
- Chemotaxis
- Phagocytosis
- Leukocyte adhesion studies

NK DEFECTS

- Lymphocyte subsets
- NK cell cytotoxicity

NEWBORN SCREENING FOR SEVERE IMMUNO-DEFICIENCIES

- TREC & KREC Qualitative PCR

COMPLEMENT DEFECTS

- Classic & Alternative pathways
- Mannan Binding Lectin
- C3, C4

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TABLE II: FINDINGS SUGGESTIVE OF IMMUNODEFICIENCY

Persistent lymphopaenia (<1.5 × 10^9/ℓ in older children and <2.5 × 10^9/ℓ in younger children)
Unexplained, excessive frequency and/or severity of infection • Eight ear infections, two sinus infections per year (especially with mucopurulent discharge) • Two episodes of pneumonia within one year or chronic suppurative chest infection • Rare or unusual complications, for example, complicated varicella
Dependence on or refractory to antibiotic treatment • Need for intravenous antibiotics to clear infection • Two or more months on antibiotics to little effect
Infectious syndromes • More than one organ involved • Recurrent deep skin or organ abscesses • Two or more deep-seated infections (eg sepsis, meningitis, pneumonia)
Organisms • Less virulent or opportunistic causative agent • Persistent oral thrush or cutaneous candidiasis (especially in children older than four months) • *Neisseria meningitides* meningitis. In certain settings such as the Western Cape, it may be appropriate to screen with total haemolytic complement
Constitutional symptoms • Failure to thrive • Persistent, extensive, atypical dermatitis or erythroderma • Chronic diarrhoea
Clinical examination • Lymph nodes and tonsils may be absent in severe PID • Evidence of chronic ear infection • Evidence of bronchiectasis
Family history • PID • Unexplained sudden death in infancy • Consanguinity
Age and gender • SCID presents in early infancy • Profound antibody deficiency usually presents in first year of life • Severe immunodeficiencies more commonly affect boys
Unexplained fever or autoimmunity
Additional features in infants include: • Delayed umbilical separation (>30 days) • Congenital heart defects • Hypocalcaemia • Absent thymic shadow on CXR

timing of these tests, proper interpretation thereof and what constitutes sufficient testing.[3,5]

A recent survey in the United States assessed management of PIDs by family practice physicians. Only a few family practice physicians were aware of professional guidelines for diagnosis and management of PID (4 vs 79% of subspecialist immunologists).[6] It is commonly assumed that PIDs are rare childhood disorders, but common variable immunodeficiency (CVID) has an estimated prevalence of 1 : 10 000–1 : 50 000 and is mostly an adult disorder. Diagnosis of combined immunodeficiencies may even be delayed into adulthood.[7] A population-based, newborn screening programme in the United States reported an overall incidence of severe combined immunodeficiency (SCID) at 1 : 33 000 and T-cell lymphopaenia of 1 : 6 600.[8]

The question therefore arises: What more can we do to recognise these patients timeously in order to treat them quickly and sufficiently and to prevent complications?

TABLE III: FINDINGS AGAINST PID

- Recurrent infection of one organ only
- Another explanation or known exposure that predisposes to infection
- Failure to find a causative pathogen despite repeat testing (consider non-infective cause of symptoms)

BE AWARE THAT THEY EXIST

The field of PID has evolved and an increasing number of PIDs are now recognised.[9,10,11] Most immunodeficiencies are caused by an antibody (B-cell) deficiency or a combined antibody plus cellular (T-cell) deficiency. Isolated T-cell deficiencies, complement and phagocytic cell deficiencies are much less common.[12]

The more common and/or serious PIDs observed in clinical practice are summarised in Table I.[13,14]

PIDs can present to a variety of clinicians with various symptoms and increased awareness should therefore be taught on a pregraduate and postgraduate level.

KNOW THE RED FLAG SIGNS

Pattern recognition of a constellation of clinical findings over a period of time or certain immediate clues should be used to alert clinicians to the possibility of an underlying immune deficiency. A limited set of easily available laboratory investigations can then be used to further guide in the initial workup.[15]

A constellation of red flag signs, in isolation or in combination, should prompt one to look for an immunodeficiency (Tables II and III).[13,16]

Any one of the following is regarded as the most suggestive of an underlying immune deficiency: a family history of a PID including history of an early infant death due to an infection, sepsis in children requiring intravenous antibiotics and failure to thrive.[16] In the South African context, bacillus Calmette-Guérin (BCG) dissemination, paralytic poliomyelitis, recurrent meningococcal infections, PJP (*Pneumocystis jirovecii* Pneumonia) in HIV-negative patients and infections with atypical mycobacteria should be additional highlighted warning signs.[1] An acronym to assist with the diagnosis of PID was endorsed by the Primary Immunodeficiency Network of South Africa (PINSA), namely, SPUR: Severe, Persistent, Unusual and Recurrent (SPUR) infections.[5]

Secondary causes of immunodeficiencies should always be excluded and include HIV/AIDS, malignancies, infections, immunosuppressive medication, diabetes mellitus, dialysis and ureamia, protein-losing conditions, liver disease, malnutrition, trauma and burns, ionising and ultraviolet radiation, toxic chemicals, pregnancy, old age and severe stress.

TABLE IV: IMMUNODEFICIENCIES AND ASSOCIATED PATHOGENS

PATHOGENS AND INFECTIONS	ASSOCIATED PID
Recurrent sinopulmonary infections with encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Moraxella catarrhalis)*	B-cell disorders
Recurrent pneumococcal infections	Humoral, complement or innate deficiency
P neumocystic jirovecii pneumonia	T-cell deficiencies including SCID, CD40 ligand deficiency
Pseudomonas aeruginosa	Severe phagocytic, humoral or T-cell deficiencies, also cystic fibrosis, neutropaenia and soft tissue injury
Enteroviral meningo-encephalitis	Agammablobulinaemia or severe CVID
Recurrent infections with *S aureus*, Coagulase Negative Staphylococci, *Serratia marcescens*, *Chromobacterium violaceum* or *Aspergillus spp.*	Phagocyte dysfunction
Recurrent Staphylococcal skin infections, abscesses, lung cysts or pneumonia	Hyper-IgE syndrome
Recurrent herpes viral infections, including HSV, CMV and EBV	NK cell deficiencies and combined T-cell defects including DOCK 8 deficiency
Infections with live vaccines (including BCG, oral polio vaccine, measles, rota virus, varicella)	Severe primary immunodeficiencies, including SCID and XLA
Prolonged or recurrent Candida infections involving the mucous membranes	T-cell immunodeficiency, immune dysregulation syndromes including APECED
Recurrent invasive Neisserial infections	Late component complement deficiency
Systemic or deep infections with nontuberculous mycobacteria	Interferon gamma or interleukin receptor deficiency
Recurrent molluscum contagiosum and/or persistent/extensive/recurrent warts	T-cell defect, innate immune defect or combined defect called WHIM

BCG: BacilleCalmette Guerin; DOCK 8: Dedicator of cytokinesis 8; APECED: Autoimmune Polyendocrinopathy-candidiasis-ectodermal dystrophy; CVID: Common variable Immune Deficiency; XLA: X-linked agammaglobulinemia; SCID: Severe Combined Immune Deficiency;HSV: Herpes simplex virus; CMV: Cytomegalovirus infection; EBV: Epstein-Barr virus; BCG: BacilleCalmette-Guerin; WHIM: Warts, hypogammaglobulinaemia, infection, myelokathexis syndrome

KNOW THE SENTINEL ORGANISMS

The type of organism can also provide clues as to the nature of the underlying immune deficiency (Table IV).[17] Being well-versed in local infectious diseases is, therefore, paramount for PID recognition, making well-trained local paediatricians crucial for early PID diagnosis.[18] Infections with certain organisms should set off the alarm bells. These include infections with organisms that we find in the context of HIV infection. A negative HIV test with/without a low CD4 count with an infection of an unusual organism therefore does not equate to laboratory error or an insignificant finding – think PID.

Antibody deficiency disorders often present with encapsulated invasive bacteria and patients with low IgA levels (ie IgA deficiency or CVID) may often have protracted diarrhoea caused by the parasite *Giardia lamblia*. Patients with agammaglobulinaemia are especially susceptible to infections with enteroviruses, which may lead to chronic meningo-encephalitis. They may also suffer from severe infections with intracellular bacteria, including *Mycoplasma pneumoniae* and *Ureaplasma urealyticum* arthritis.

Recurrent viral, fungal, mycobacterial or protozoal infections may suggest a T-cell defect. The opportunistic pathogens that one usually finds in the context of HIV/AIDS, namely, *Pneumocystis jirovecii* and *Mycobacterium avium intracellulare,* are clues that an underlying T-cell defect may exist.

Lymphadentis and recurrent abscesses caused by low-virulence, gram-negative bacteria including *Escherichia coli*, *Burkholderia cepacia*, *Serratia spp* or *Klebsiella spp* and recurrent *Staphylococcus aureus* infection or invasive Aspergillosis may indicate abnormalities in granulocytes such as chronic granulomatous disease.[17]

In addition to being of help in establishing the diagnosis, PID patients are also more susceptible to develop these infections once diagnosed. It is therefore important to have a high index of suspicion and to do appropriate cultures and PCRs in consultation with a microbiologist to ensure adequate sampling and testing procedures are followed, in order to identify and treat infections appropriately.

KNOW WHICH DIAGNOSTIC TESTS TO ORDER

A stepwise approach to the diagnosis of PIDs was proposed and developed by the Jeffrey Modell Foundation (JMF) and modified for use in South Africa (Table V).[18,19] Most of the laboratory testing is widely available and the more specialised tests can be offered by some private laboratories in consultation with the immunology pathologists. Many of these specialised tests are functional assays and should ideally be performed at a stage when the patient is infection-free. Antibody levels should be measured before immunoglobulin replacement therapy has been instituted. A tiered approach should be followed and be directed towards the most likely immune deficiency as directed by clinical history and examination.[19]

TABLE V: A STEPWISE APPROACH TO THE LABORATORY DIAGNOSIS OF PID

	TEST	ASSOCIATION
	EXCLUDE HIV	
First-line investigations	Assessment for atopy	As indicated on history
	Full blood count • Differential count for neutrophil and lymphocyte numbers • Platelet count and morphology	Lymphopaenia is an important indicator of possible SCID Small platelets seen in Wiskott-Aldrich syndrome
	Serum (IgG, M, A and E),	IgE should be tested in patients who may be at risk of hyper-IgE syndrome
	CF screening	Suspected on history and clinical examination
	Investigation for active TB	
Second-line investigations	Specific antibody response • Targeted to polysaccharide-specific antigens (*S pneumoniae*) and protein antigens (tetanus, diphtheria and *H influenzae*)	**Indicated with recurrent bacterial infections, even in the presence of normal immunoglobulins**. Patients have to be off immunoglobulin replacement therapy for six months. If these antibody levels are decreased, the patient should be revaccinated and antibody responses should be repeated four weeks after vaccine boosting to determine an appropriate increase in specific antibody responses. Please note that an unconjugated pneumococcal vaccine, for exmaple Pneumovax® should be given to determine an appropriate polysaccharide antigen response.
	Lymphocyte subsets • B-cell numbers (CD19) cells should also be measured.	Absent in XLA-linked agammaglobulinaemia when all immunoglobulin isotypes are severely reduced
	T-cell numbers (CD3). T-helper (CD4) and T-suppressor (CD8)	Reduced in T-cell defects, combined immunodeficiencies and occasionally CVID
	Natural killer cells (CD16 and CD56)	Isolated NK-cell deficiencies may be associated with recurrent herpes virus infections
	Neutrophil function • Neutrophil oxidative burst	CGD
Third-line investigations	Lymphocyte proliferation studies • Response to mitogens, for example PHA, PMA, PMA +ionomycin, anti-CD3, anti-CD3+IL2 or to recall antigens, for example Candida, tetanus, varicella	T-cell deficiencies including SCID, Chronic mucocutaneous candidiasis. Specialist input valuable as to when to request a certain mitogen/s or recall antigen/s
	Neutrophil antibodies	Auto-immune and alloimmune neutropaenia
	Lymphocyte maturation panel: naïve and memory T-cells	Diagnosis of SCID and combined T-cell defects
	Recent thymic emigrants (T-cells)	Very low in SCID Can be used to monitor bone marrow regeneration post transplant
	Memory B-cells	Memory B cells categorise subsets of CVID patients
	Alpha/beta, gamma/delta T-cell receptor type	Abnormal in leaky SCID, hypomorphic SCID, T-cell defects with oligoclonality
	TRECs and KRECs (can also be considered as a first-line investigation – see text)	Used for neonatal screening for SCID and XLA on blood monospots – useful to do prior to giving live vaccines at birth
	Total haemolytic complement • Classic complement pathway • Alternative complement pathway	Complement deficiencies
Fourth-line investigations	• Genetic studies	Maybe appropriate as third-line test in some patients
	• T-regulatory cells	Fox P3 deficiency: decreased in IPEX syndrome
	• Th-17 cells	Decreased in HIGE syndrome
	• Surface markers for X-linked SCID: CD132, IL-7Rα	Diagnosis of X-linked SCID
	• HLADR	Absent in MHCII deficient SCID
	• BTK (diagnosis of XLA)	Absent in most boys with XLA
	• CD40L	Absent in most boys with X-linked HIGM
	• CD40	Absent in some patients with HIGM
	• MBL	Low MBL levels may predispose patients to upper respiratory tract infections and they may have a higher risk for severe menigococcal or pneumococcal infections
	• NK-cell cytotoxicity assay	Markedly reduced in FHL. Abnormal in primary NK-cell defects
	• Neutrophil studies for leukocyte adhesion, chemotaxis and phagocytosis	
	• CD11 and CD18	Leukocyte adhesion defects

Adapted from M Esser and B Eley[18] and MS Suchard, S Buldeo, S van den Berg and C van Rooyen[20,21]

TREC: T-cell receptor excision circles; KREC: Kappa receptor excision circles; SCID: severe combined immunodeficiency; BTK: Brutons tyrosine kinase; CGD: Chronic granulomatous disease; XLA: X-linked agammaglobulinaemia; PMA: PhorbolMyristate Acetate; CD3 = Cluster of differentiation 3; IL2 = Interleukin 2; CVID = Common Variable Immune Deficiency; CGD = Chronic Granulomatous Disease; MBL: Mannan Binding Lectin; CF: Cystic fibrosis; PHA: phytohaemagglutinin; HLADR: Human Leukocyte Antigen - antigen D Related; MHCII: Major histocompatibility complexclassII; HIGM: Hyper IGM; HIGE: Hyper IGE; FHL: Familial haemophagocytic lymphohistiocytosis

TABLE VI: INCIDENTAL LABORATORY FINDINGS THAT MAY BE ASSOCIATED WITH A PID	
LABORATORY FINDING	CLINICAL IMPLICATION
BIOCHEMISTRY	
Low immunoglobulins	Humoral and combined immunodeficiencies. Secondary immunodeficiencies
High immunoglobulins	May implicate HIV, autoimmune disorders, chronic inflammation and granulomatous disease
Low IgA during Coeliac disease serology	Specific IgA deficiency has a higher prevalence in patients with coeliac disease
High IgE (10 × upper limit for age)	Hyper-IgE syndrome, WAS, IPEX, DOCK 8 deficiency, etc, although the majority remain secondary to atopic disease
Low IgE (<2 IU)	May represent antibody deficiency in 7% of patients
Serum calculated globulin fraction (total protein – albumin)	Antibody deficiencies can reduce the globulin fraction – usually <19g/ℓ
Serum protein electrophoresis	Hypogammaglobulinaemia without a monoclonal protein may indicate a possible antibody deficiency
HAEMATOLOGY	
Lymphopaenia	Persistent unexplained lymphopaenia may be a key clue suggesting PID
Persistently absent or very low monocyte count	GATA-2 deficiency that predispose to human papilloma virus and/or atypical mycobacterial infection and high risk of myelodysplasia and acute myeloid leukaemia
Low platelet count	ITP may be a presenting feature of immunodeficiency. Similarly, also autoimmune haemolytic anaemia and autoimmune neutropaenia. ITP can be present in up to 6% of patients with CVID[23]
Low platelet volume	This is strongly suggestive of the rare Wiskott-Aldrich syndrome
CYTOGENETIC TESTING	
A failed cytogenetic test (ie lymphocytes fail to proliferate after mitogen stimulation)	Prompt consideration of SCID
MICROBIOLOGY/VIROLOGY TESTING	
Failed vaccine responses	Clinical episode of measles in a patient fully vaccinated, failure to respond to Hepatitis B vaccination (may occur in 10–15% of the normal population) and rubella vaccination
Unusual or recurrent positive cultures Recurrent *S pneumoniae* and *H influenzae* Gastrointestinal infection with *G lamblia* and *Campylobacter jejuni* Recurrent or severe Candida infections *P jirovecii* pneumonia Recurrent, unexpected or severe viral infections, for example CMV, HPV	See Table IV for immunodeficiencies and associated pathogens
HISTOPATHOLOGY	
Unexplained granulomata	CVID and chronic granulomatous disease should be considered
Absent germinal centres on lymph node biopsy	This should prompt measurement of lymphocyte subsets and immunoglobulins
Villous shortening	May be associated with *G lamblia* infection which is a common infection in antibody deficiencies
Absence of plasma cells in biopsies, for example GIT	May be seen in humoral immunodeficiencies

WAS: Wiskott-Aldrich syndrome; IPEX: Immune dysregulation, polyendocrinopathy, enteropathy and X-linked syndrome, DOCK 8: Dedicator of cytokinesis 8; ITP:Immune thrombocytopenic purpura; CVID: Common variable immunodeficiency;SCID: Severe combined immunodeficiency; GIT: Gastro-intestinal tract

The first- and second-line investigations will detect the majority of common PIDs and will warrant sufficient investigations in the majority of settings. Functional testing may be challenging for peripheral centres that are not close to the referring laboratories, as sample stability during transit may be problematic. Genetic testing may be considered to bypass logistic challenges inherent to functional testing.

CONSIDER IMMUNODEFICIENCY WHEN INTERPRETING ABNORMAL PATHOLOGY TESTS UNDERTAKEN FOR OTHER REASONS

Abnormal laboratory results may indicate a possible immunodeficiency as demonstrated in Table VI.[22] This may prompt additional clinical and laboratory investigations to exclude or confirm a suspected immunodeficiency.

AIM TO IDENTIFY PATIENTS PRIOR TO THE ONSET OF CLINCIAL SYMPTOMS

Newborn screening for severe PIDs involving the cellular and humoral immune system allows early detection and treatment, potentially saving the lives of babies affected by the disease. PCR assays to detect T-cell receptor excision circles (TRECs) and Kappa-deleting receptor excision circles (KRECs) in newborn blood have been available in South Africa since 2013. These assays

have been developed to detect diseases hallmarked by the absence of T- or B-lymphocytes, classically seen in severe combined immunodeficiency (SCID) and X-linked agammaglobulinaemia (XLA)/Bruton's disease. Babies with SCID appear healthy at birth, but without early treatment, most of these babies die before the age of one year. Research indicates that infants with SCID who receive haematopoietic stem-cell transplants in the first 3.5 months of life have a better chance of survival as compared with infants receiving this treatment after 3.5 months (95% vs 76%). It is crucial to make this diagnosis as early as possible, before the patients receive live vaccines or present with infections. This is because live vaccines and infections can be fatal, as well as greatly diminish the success rate of the bone-marrow transplant.[24]

Patients with XLA usually present later in life due to protective maternal antibodies, but are at great risk to develop infections after receiving live vaccines such as oral polio, which can lead to fatal infections. These patients are also at risk of severe infections, especially pulmonary infections. Pulmonary complications are the most common cause of mortality and morbidity in these patients. Early identification can prevent the administration of live vaccines and aid in early initiation of immunoglobulin replacement therapy, which can prevent pulmonary and other infectious complications.[25,26]

Newborn screeing for SCID is available on request in the private healthcare setting. Routine newborn SCID screening using existing methodology may be costly to implement in the public healthcare setting, but high-volume testing using alternate methods can drive costs down substantially and make newborn screening for SCID a cost-effective option.

JMF has developed a working algorithm or 'decision tree' for the implementation of newborn screening programmes for SCID. This algorithm has been validated by peer-reviewed scientific literature, and is intended for use by public health departments and health ministries in countries throughout the world. This decision tool allows for local or regional data to be applied to measure the threshold and economic impact of implementing newborn screening for SCID and T-cell lymphopaenia. This can be applied in the South African healthcare setting to evaluate the cost-efficacy of newborn screening for SCID.[8]

AIM TO MAKE A DEFINITIVE DIAGNOSIS

More than 250 genetic defects may result in PID.[2,9] Genetic testing can establish or confirm a suspected diagnosis and may predict future disease risk, inform reproductive decision-making and guide in selecting the most appropriated therapies. One should, however, be aware of testing limitations and patients and their families should be properly informed and counselled.[27]

TABLE VII: IMMUNODEFICIENCIES COVERED BY A PID GENETIC PANEL AVAILABLE IN SOUTH AFRICA

• SCID
• Hyper-IgM syndrome
• Hyper-IgE syndrome
• Immune dysregulation
• CVID
• Lymphoproliferative syndromes, including autoimmune lympho-proliferative syndrome
• CGD
• MHC Class I and MHC Class II deficiencies
• Anhidrotic ectodermal dysplasia with immunodeficiency
• Autoimmunity with lymphoproliferation
• Antibody deficiencies
• T-regulatory cell defects
• FHL, including FHL with hypopigmentation
• Chemokine signalling defects
• Innate immunity defects
• Complement deficiencies
• Isotype deficiencies
• Thymic defects with congential abnormalities

SCID: Severe combined immunodeficiency; CVID: Common variable immunodeficiency; CGD: Chronic granulomatous disease; MHC I and II: Major histocompatibility complex class I and II; FHL: Familial haemophagocytic lymphohistiocytosis

Genetic testing available in South Africa includes a private commercial genetic panel (Table VII), Whole Exome sequencing (WES) at the University of Stellenbosch and private laboratories, PID gene panels from international centres, for example the GOSH panel from Oxford, and various research collaborations involving WES.

If a PID gene panel is negative, further steps of exome and genome sequencing can be undertaken.[1]

TRAINING OF PRE- AND POSTGRADUATE MEDICAL STUDENTS IN IMMUNOLOGY

Appropriate training of pre- and postgraduate medical students in Immunology is essential to ensure adequate diagnosis and management of patients with PID. Clinical Immunology is not offered as a postgraduate training programme in South Africa, although Clinical Immunology is recognised as a postgraduate medical qualification in many countries including United States, the United Kingdom and other African counties. The need for pre-and postgraduate training in Clinical Immunology in South Africa needs to be addressed to facilitate improved diagnosis and care of PID patients.

ACCESS TO CARE

If a clinician suspects a PID on clinical grounds or the basis of an abnormal laboratory test, the available referral pathways for clinicians include Steve Biko/University of Pretoria, Stellenbosch University and University of Cape Town specialist PID centres. PINSA is a valuable resource

of information for patients and clinicians and can advise on routes of access to care.

REPORTING PATIENTS WITH PID ON THE SA PID REGISTRY

The South African PID registry is part of an ethically approved confidential research project to estimate the prevalence of PID in South Africa. This registry helps create awareness of PIDs in South Africa and information in this registry plays an important role in research and lobbying. The registry provides objective evidence needed to change policies, inform medical aids and improve patient outcomes through data-sharing.[1] Lack of access to care is one of the main reasons why PID remains largely under-diagnosed and underreported in South Africa.

CONCLUSION

Most children with recurrent infections have a normal immune system, but it is important to recognise the child with an immunodeficiency in order to manage and treat timeously and appropriately. Humoral immunodeficiencies often present in adult patients and PIDs are therefore not only paediatric disorders. It cannot be overemphasised that a high index of suspicion should always be maintained for possible immunodeficiencies, as untreated immunodeficiencies are life-threatening. In this regard, MA Slatter and AR Gennery have stated:

> '... the question to be asked in a patient presenting with recurrent infections is not "Who should be investigated for primary immunodeficiency ?" but "What are the reasons for not investigating further?"'[28]

As immunodeficiencies may be complex and difficult to diagnose, it is recommended that advice be sought from clinical immunologists, paediatricians, physicians, ENT surgeons, pulmonologists and the immunology laboratory in the workup of difficult patients.

DECLARATION OF CONFLICT OF INTEREST

Dr S van den Berg and Dr C van Rooyen are employed at Ampath Laboratories.

This article has been peer reviewed.

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RECOMMENDED FURTHER READING

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PATIENT EMPOWERMENT: CREATING EFFECTIVE PARTNERSHIPS BETWEEN THE PATIENT AND THE HEALTHCARE DELIVERY CHAIN

1. *True or false:* Litigation by empowered patients against their health care providers is becoming less frequent.
2. *True or false:* Even very young children have the right to decide whether or not to accept or reject treatment.
3. *True or false:* Patient empowerment increases treatment compliance and disease morbidity.
4. *Choose the **incorrect** answer:*
   a. Patient empowerment is detrimental to their effective treatment by their doctor;
   b. The Information and Technology revolution has assisted in creating empowered patients;
   c. Self-help groups and common community networks have a valuable role to play in supporting those with chronic illnesses;
   d. Patients put as much value on information which they have sourced themselves as they do on their doctor's advice.

HEALTH PROFESSIONALISM AND ETHICS – IS THERE A DIFFERENCE?

5. *True or false:* The Ethics Institute of South Africa survey revealed that doctors feared the consequences to themselves if they reported medical misconduct by a colleague.
6. *True or false:* A profession is defined as a calling requiring specialised knowledge and long and intensive academic preparation.
7. *True or false:* One of the hallmarks of a profession is the right to self-regulation.
8. *True or false:* In medieval times guilds were established to protect the interests of skilled workers, and these were the forerunners of the professions.
9. *True or false:* Surgeons and apothecaries had university training in medieval times, and were therefore seen as professionals.
10. *True or false:* The Physician Charter, a product of a working group on medical professionalism, contained three fundamental principles and ten commitments required of professionals.

PROMOTING ACCESS TO SAFE MEDICINES FOR CHILDREN

11. *True or false:* The Convention on the Rights of the Child states that governments should ensure adequate health care provision for children.
12. *True or false:* The Essential Medicine List includes only medicine for infectious diseases in low- and middle income countries.
13. *True or false:* Off label medicine use in children is a criminal offence.
14. *Choose the **incorrect** answer:* Advocacy for better medicines for children includes the following:
    a. Encourage doctors to undertake clinical trials with paediatric patients for medicines commonly used off-label in children.
    b. Restrict paediatric clinical trials as it is exploitation of vulnerable individuals who cannot take care of themselves.

c. Advocate to policy makers for the need for incentives to the pharmaceutical industry to undertake paediatric clinical trials.
d. Pressurize pharmaceutical companies to apply for registration of medicines for children if the necessary safety and efficacy data are available.

SIMULATION-BASED EDUCATION IN ALLERGOLOGY TRAINING: A SOUTH AFRICAN PERSPECTIVE

15. *Choose the **correct** answer:* Identify the competency which is the least likely to be included as a learning outcome in simulation-based curricula in allergology training:
    a. Sound medical knowledge and procedural skills;
    b. Team-work and leadership skills;
    c. Video editing for electronic media educational material;
    d. Patient-centred medical practice;
    e. Good knowledge of principles of medical ethics;
    f. Communication skills;
    g. Environment awareness and resource management skills.
16. *Choose the **correct** answer:* Which of the following resources may be used as teaching tools in simulation?
    a. Computer-based case scenarios;
    b. Standardised patients;
    c. Low fidelity mannequins;
    d. Partial task trainers;
    e. High-fidelity mannequins;
    f. All of the above.
17. *Choose the **correct** answer:* All of the statements below describe the advantages of an in-situ simulation program, except:
    a. Cheaper for the institution and comfortable for the trainers;
    b. Safe, allowing the mock equipment to be used in medical care when there are shortages;
    c. Realistic and tailored according to the institutional needs;
    d. Reassuring the patients that the staff is training regularly;
    e. Easily accessible, in an environment familiar to the learners.

MULTIPLE CHEMICAL SENSITIVITY (MCS) - TWO ILLUSTRATIVE CASE REPORTS

18. *True or false:* Patients with MCS often present to occupational health doctors.
19. *True or false:* The condition as an entity is controversial but has been accepted in some countries, including Germany and allocated an ICD-10 code.
20. *True or false:* MCS has been shown to be a purely psychological disease and is a quack diagnosis.
21. *True or false:* MCS is an allergic disease and all patients should be fully investigated for allergies.
22. *Choose the **incorrect** answer:* Lacour's expanded definition of Multiple Chemical Sensitivity includes:
    a. A chronic condition that lasts for at least 6 months and causes significant life-style or functional impairments;
    b. Symptoms occur only on exposure to high levels of chemicals;
    c. Responses to multiple unrelated chemicals;
    d. Improves or resolves when incitants are removed.

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