



Australian Medical Student Journal

Melioidosis in the Torres Strait Islands



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Review

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Feature

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












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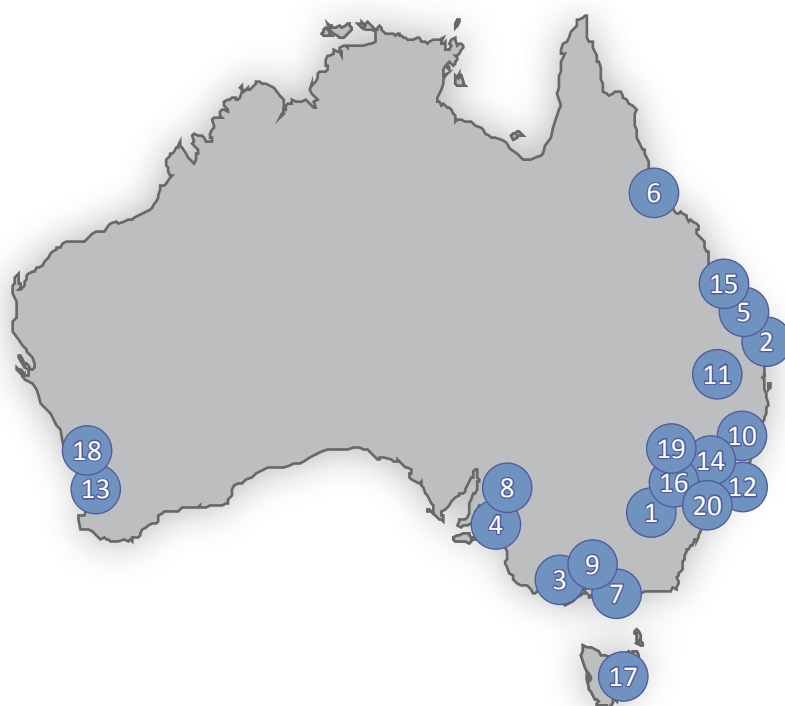
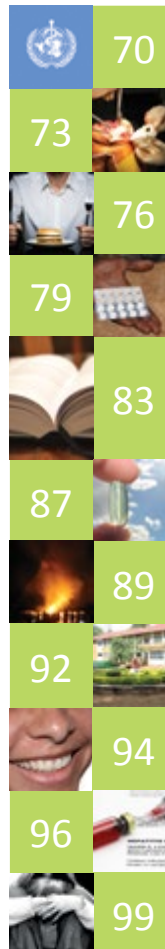
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Australian Medical Student Journal Volume 4 Issue 2: Editor's Welcome

Foong Yi Chao

Editor-In-Chief, AMSJ

Welcome to Volume 4, Issue 2 of the *Australian Medical Student Journal*.

Coming into our eighth issue, we are proud to announce that the journal continues to be a showcase of the outstanding quality of medical research done by students across Australia. We have continued to focus on the issues relevant to local medical students whilst maintaining a stringent peer review system. However, we feel that this is an opportune time to expand our horizons, and we're pleased to announce that from the next issue onwards we will be trialing online publication of suitable international submissions. These are exciting times for the AMSJ and we look forward to what the future brings for the journal

The number of submissions have continued to grow with each issue, with a number of high quality submissions. Highlights include a unique 11 year audit of melioidosis in the Torres Strait Islands and a timely letter on the high profile #interncrisis campaign. Given the rising importance of melioidosis as a cause of infective disease in Northern Territories and Far North Queensland, the article provides us with vital statistics regarding the situation in the Torres Strait Islands. Of note, the authors conclude that the incidence of melioidosis is one of the highest in Australia and internationally. Other notable submissions include an original research article on social phobia in children, reviews on the role of viruses in carcinogenesis and

the use of viruses as oncological treatment, a report on an internship at the World Health Organisation, and a case report on dynamic compression of the motor ulnar nerve branch in the hand caused by a mobile segment of the hamulus.

We have been fortunate to receive articles from respected Australians in this issue of the AMSJ, namely Dr Helen Caldicott, Professor John Mattick and Professor David Wilkinson. Dr Helen Caldicott is a prominent Australian physician and a leading anti-nuclear activist, who presents her opinions on the impact of the recent Fukushima nuclear crisis on global health. Professor John Mattick is the executive director of the Garvan Institute and a internationally recognised leader in the field of genetics, and his article provides us with timely and well-placed advice on the rise of genomic medicine. Last but not least, Professor David Wilkinson has a wealth of experience in medical education, and is currently the Deputy Vice Chancellor at Macquarie University. We believe that his article on medical student assessment will be of great interest and relevance to Australian medical students.

As a medical student journal, we are reliant on the voluntary work of our student staff. This issue is a culmination of many months of hard work by staff members all across Australia, who have managed to put together a high quality, peer-reviewed journal whilst



maintaining full time medical studies. A sincere thank you to all of our staff. I'd also like to take this opportunity to thank the previous Editor-in-Chief, Dr Michael Thompson, for his invaluable guidance and support, whilst wishing the incoming Editor-in-Chief, Saion Chatterjee, the best of luck with the following issue. We're also indebted to our peer reviewers, most of whom are full-time professionals who took time out of their busy schedules to review our articles. We're pleased to be able to acknowledge them in this issue, and look forward to working with them in future issues. Last but not least, we'd also like to thank our authors for their outstanding contributions, which provide the basis for the continued success of our journal. We hope you enjoy this issue of the AMSJ, and look forward to your feedback and future contributions.

Thank you to AMSJ Peer Reviewers

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International medical electives: time for a rethink?

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International medical electives (IMEs) are rapidly growing in popularity. A recent study by Law and colleagues [1] conducted across Australia reported that 53% of graduate entry program students and 35% of high school entry students undertook IMEs, of which just over half were in developing countries. In some medical schools the majority of students head overseas for their electives. [2] This phenomenon is not restricted to Australia; in the United Kingdom (UK) and United States (US) roughly 40% of students reported having spent some time in developing countries. [3,4] Many universities across Australia now have global health interest groups, and an increasing proportion of graduating medical students report having some experience in overseas health. [4] Traditionally, these electives are unstructured and arranged on an ad hoc basis between local partners and medical students.

There are undeniable benefits to practicing medicine in an unfamiliar, foreign setting. Students often describe IMEs as one of the highlights of their time at medical school, and it can be an opportunity for unparalleled personal and professional development. On a personal level, students report increased confidence, broadened perspectives, increased cultural competence, and improved communication skills. [5] Professionally, students benefit from being exposed to uncommon conditions and the opportunity for more hands-on experience. [6,7] IMEs also have the potential to influence future practice, with students more likely to enter public service, serve underprivileged populations, and participate in volunteering. [8,9]

However, the results of the aforementioned studies have to be interpreted with caution. Unlike other aspects of the medical course, IMEs tend to be student driven and lack a structured curriculum. Therefore many of the outcome measures are highly subjective and were assessed with unvalidated questionnaires. Given the observational nature of these studies, it is difficult to establish a causative relationship between IMEs and outcome measures. There is also the potential for selection bias (for example, where IME participants were chosen based on their commitment to global health) and publication bias in this area. [8,10] Given the subjectivity of the current literature, it remains unclear if there are indeed any long-term benefits for medical students.

Of note, much of the research on IMEs has revolved around medical students from OECD (Organisation for Economic Cooperation and Development) nations instead of host institutions or patients. Given the short term, transient nature of many IMEs, it seems unlikely that there will be any long term benefits to the local institution. There is potential for limited, temporary benefits such as increased supply of resources, incorporation of new teaching ideas, and positive support from local communities. [5] However, even this can turn out to be a double edged sword, as local institutions develop reliance on visiting medical students. Furthermore, there are cases where the donated equipment end up draining more of the hospitals resources in the long run, or are unable to be maintained. This is not to say that there are not examples of IMEs that have had a positive impact. [11] However, these programs tend to be structured, continuous partnerships between hosts and visiting students with a clear long-term goal. Unfortunately, the vast majority of IMEs lack such a structure.

A significant proportion of IMEs involve students from developed countries heading to less developed countries. These include pre-clinical students with little to no practical medical training. As students they require proper supervision and this puts added strain on already scarce resources in developing countries. In addition to this problem, many students perceive electives as a holiday, tending to be ill-prepared both culturally and medically for the experience. [3] In worst case scenarios, the student may be placed in a position where he expected to take on the role of a qualified physician and is given responsibility for their own patients. [12] There are several reports in the literature of junior medical students being asked to participate in potentially risky procedures such as lumbar puncture and tubal ligation. [13] Students often try to rationalise this by adopting a utilitarian viewpoint, arguing that no one would look after these patients if they did not step up to the plate. The moral boundaries in these situations are vague and to date there are few established guidelines. However medical students must bear in mind that practicing beyond one's competency is a serious breach of medical ethics. Students risk doing more harm than good, particularly when they may not be fully aware of the complexities associated with unfamiliar medical conditions and treatments.



To further aggravate this problem, patients in developing countries tend to be vulnerable and greatly disadvantaged. The risk of students developing their skills at the expense of vulnerable patients is a very real one that is probably under-reported in the literature. [14] Anecdotally, we often hear of medical students speak proudly about having been able to perform surgeries or risky procedures on their own with little supervision. There is often a lack of critical reflection surrounding this phenomenon, and clear ethical guidelines should be developed for students.

The motivation behind IMEs is slowly evolving. Traditionally, altruistic reasons were often quoted as the driving factor in medical students pursuing IMEs where students had a genuine interest in serving resource poor areas. [15,16] However, gaining a competitive advantage with the increasing demand for experiences in developing countries has become an important motivating factor. Global health programs look good on a CV and with training programs becoming more competitive, the proportion of students participating in IMEs for this reason will increase.

The threat to medical students' well-being during electives is often an aspect that is overlooked. Medical students are often drawn by the sense of adventure, opportunity for travel, and the chance for a unique experience different to that back home. At the turn of the century, there was strong concern due to the lack of preparation by visiting British medical students to areas with a high prevalence of HIV. [17] There are often reports of a range of infectious diseases, ranging from schistosomiasis, typhoid fever, malaria, and dysentery. [2] Literature now demonstrates that adverse events go beyond the risk of HIV and other infectious diseases.

Deaths and serious injury have occurred due to risks associated with overseas travel (such as road traffic accidents), suicide, crime and political issues. [18] Aside from physical harm, psychological trauma has also been reported. [18]

Numerous studies encourage pre-departure training as a way to increase awareness of ethical issues, encourage critical self-reflection, and practical preparation. [13,19] In spite of the physical dangers and ethical dilemmas that are sometimes posed by IMEs, studies have shown that basic practical and ethical preparations for students travelling abroad was low. [20] Only three quarters of Australian medical schools offer pre-departure training, however only half of these

are mandatory. [1] The average duration of pre-departure training was 4.7 hours. Only half of Australian medical schools offered post-elective debriefing, out of which roughly half was mandatory. [1] The average duration of post-elective debriefing was 1.2 hours. [1] Medical schools have a duty of care towards medical students and it seems surprising that there is a significant lack of preparation for what is often a unique and unusual experience.

With the increasing ease and affordability of international travel, IMEs will continue to have a growing appeal to medical students. However there is a dangerous lack of critical thought and reflection in terms of the ethical aspect of IMEs, as well as the possible threat

to student well-being. Given the strong consensus in the literature for more structured global health education, medical schools should consider developing training programs aimed at enabling students to conduct considered, structured and sustainable IMEs.

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Conflict of interest

None declared.

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National Leadership Development Seminar: developing the health care leaders of the future

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The vast field of medicine transcends the mere finding of cures for ailments, seeking approaches to prolonging life, and undertaking research in the pursuit of wellbeing, important as these duties are. However, medicine's empathetic pledge to the ill requires us to exercise leadership, amongst other qualities, as an important tool to advance the interests of both the individual and the population at large. Practical leadership and advocacy is the cornerstone of the increasingly complex environment in which 21st century healthcare is provided. Patients, institutions and communities often perceive doctors as agents of change i.e. leaders. However, some physicians may have been marginalised by the healthcare system because they either do not receive good leadership and management training, or they occupy positions that require leadership and managerial skills, which they initially do not possess. This apparent lack of appropriate leadership and management development may preclude doctors from participating in essential roles to shape the delivery of health services. [1] The problem can be traced back to medical school, where relatively little, or perhaps non-existent emphasis is given to nourish medical students' attitudes towards leadership. Current medical curricula offer students little leadership education of the kind considered necessary to develop competences essential in becoming actively involved in the planning, implementation and provision of patient care. [2]

The Australian Medical Students' Association (AMSA), being the peak advocating body for key affairs that concern medical students across the country, has identified this issue. It has responded by establishing the National Leadership Development Seminar (NLDS),

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an initiative aimed to assist motivated students interested in leading the medical profession. Each year, since its inception in 2005, NLDS attracts hundreds of applications from bright students who are keen to enhance their leadership skills. The seminar allows for approximately 90 applicants to participate annually. The NLDS program is carefully constructed to equip attendees with knowledge, skills and attitudes regarding leadership, advocacy and management, with a focus on current national health issues. The three-day seminar, which is held in Canberra, integrates guest speaker presentations, small group activities and interactive workshops to teach students how to link necessary leadership competencies with actual service opportunities.

The NLDS focus on leadership is closely aligned with *Health LEADS Australia*, a health professional leadership framework draft that has recently been published by Health Workforce Australia. The framework describes some of the most important leadership attributes that health workers who are involved in building a flourishing and sustainable health system should embrace and promote. This leadership framework is divided into five arms, including emotional intelligence and self-performance reflection, acknowledging the abilities of others whilst helping them to develop, and concentrating on achieving goals and pursuing innovative change. [3]

Although long term evaluation data is required to assess the effectiveness of NLDS (especially in meeting the key objective competences as outlined by *Health LEADS Australia* and Domain 4 of the Australian Medical Council's Graduate Outcome Statements [4]), this program offers an innovative model



of a leadership-based course. This can have a positive impact on leadership skills development among medical school students and can be incorporated into the medical school curriculum. We understand that NLDS has some limitations in terms of its primordial structure compared to other more established leadership programs in the realm of business and economics. These limitations include the program's exclusivity to only a minor number of students per year, non-exhaustive coverage of all aspects of what it takes to become a successful leader in the clinical arena, and lack of networking past the event's conclusion. Despite these drawbacks, NLDS is a unique national attempt to illustrate the importance of leadership in medical education. We invite medical schools to look at NLDS as a template whilst designing an innovative, socially accountable curriculum to engage students in the practices of advocacy, management and leadership.

Conflict of interest

None declared.

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What comes next after #interncrisis?

Dr. Michael Bonning
MBBS

Michael is a past President of the Australian Medical Students' Association and past Chair of the AMA Council of Doctors in Training. He currently works for the Royal Australian Navy.

Dr. William Milford
MBBS

William is currently completing Obstetrics and Gynaecology training in Queensland. He is actively involved in lobbying for postgraduate training places through roles on many professional and government committees.

Will last year be a turning point or just another chapter in the saga of medical workforce planning in Australia? The story, so ably publicised by the high profile grassroots #interncrisis campaign, [1] AMSA and the AMA, covered the lapse of planning by jurisdictional health authorities to provide graduates from Australian medical schools with internships. [2]

The reality was significantly more complex and will pose broader questions about the entire medical education continuum. As with many arguments in health, the complexity arises from the divide in funding, and therefore in control, of different levels of medical training.

Medical graduate numbers have increased by more than 200% in the last decade. [3] This increase was fuelled by both increases in Commonwealth supported places, and the unregulated expansion in international student numbers by many universities to cross-subsidise programs. Between 2003 and 2011, vocational medical training places have more than doubled in order to accommodate this growth. [3] However, capacity at all levels has supposedly been reached, with state and territory governments, who fund post-graduate training, now unwilling to match ongoing graduate increases. This has resulted in not only the well-publicised intern crisis but also a lack of post-internship prevocational positions in Queensland and the ever-increasing competition for specialty training places nationally. The disconnect between national and state medical workforce goals has never been clearer.

The crisis has far deeper themes than the simplistic media message typified by statements such as 'unemployed doctors driving taxis'. As shown with the recent deployment of 60 regional internships, funded by the Commonwealth Department of Health and Ageing, bonding mechanisms are being used to attain better workforce geographic distribution. The ultimate prize is solving the chronic maldistribution of the medical workforce, both in terms of location and specialty. The goal is to create

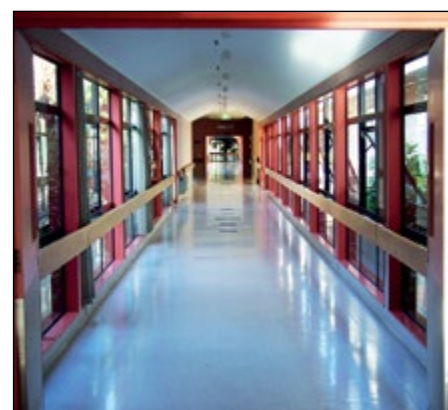
a sustainable medical workforce capable of delivering quality health care to the broader Australian community.

The events occurring at the end of 2012 contrast the conflicting goals of the Commonwealth with those of the states and territories. The Commonwealth Government considered the bigger picture of medical workforce reform and sought to retain the graduates of Australian medical schools, and yet was thwarted by the brinksmanship of the states and territories. The creation of additional medical internships was welcomed but ultimately, given the late hour, saw little uptake, as graduating students activated other plans. This was an opportunity missed but not one that should be forgotten as a new cohort nears graduation. The potential to partner with the private sector to open new pathways for training at both the prevocational and vocational levels is obvious, but, as always, will require funding.

It is clear that states and territories are planning and investing only for their own immediate need, and forgoing the potential of meeting Australia's medical workforce requirements for short-term budgetary reasons. These decisions will have real world consequences including limiting accessibility to core services, leading to poorer health outcomes and unnecessary hospital admissions, particularly for those already disadvantaged, especially by distance. [4]

There is abundant evidence to support the employment of all Australian medical graduates. Health Workforce 2025 modelled the future health workforce required for Australia and proposed a number of possible futures. [5] In the baseline scenario, based upon current graduate trends, Australia will be short of more than 2000 doctors by 2025. The geographic maldistribution of the medical workforce and poor alignment of training pathways to the health requirements of the community is anticipated to further amplify perceived shortages.

We agree that Australia's medical training system must change. Coordinating internship



allocation at a national level, addressing the bottlenecks of entry into specialty training, and ensuring that community need shapes the medical workforce is just the beginning. Students and doctors-in-training also have an integral responsibility for creating a balanced, responsive medical workforce in their choices of specialty and location of training and practice.

Some action is already underway, with jurisdictions agreeing to the creation of the National Medical Training Advisory Network, but this will not be a panacea. Standing Council on Health meetings need to move beyond perpetuating the blame game, and create a timetable for reform while opening a discourse to consult meaningfully with the profession.

Innovative solutions to training issues must be influenced and informed by the experiences of students and doctors-in-training if they are to have the intended impact on the future medical workforce. Moreover, as the issue descends on states, ensuring that members of parliament are aware of the issues and their implications for the future of health service delivery will be a key opportunity for students to support long-term reform.

Conflict of interest

None declared.

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End-of-life issues in the emergency department

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In AMSJ Vol. 3, Issue 2, Michael Li provided an insightful and personal dissertation on the futility of medical treatments and the potential of students to relate to and support patients and their families. [1] Li's article captures one of the most confronting situations faced by all health professionals, in acknowledging the futility of aiming for a cure, and instead allowing the patient to succumb to their illness. In these situations, clinicians may experience thoughts of frustration, feelings of being powerless, guilt, a sense of professional or personal failure, and an awakened sense of human fragility and mortality. [2] However, the challenges posed by end-of-life decision making across the divergent fields of medicine are not identical. Emergency medicine has long been held as a field of medicine centred upon recognising, treating and stabilising patients with acute illness before they receive definitive care. This is now changing and emergency physicians are experiencing an increasing responsibility for patients with acute, sometimes terminal, exacerbations of chronic, incurable disease. [3,4] Awareness of the values pertinent to end-of-life care, specifically within the emergency department setting, is critical to maintaining patient dignity and preventing unnecessary distress to the patient and their families.

The 24/7 availability of emergency departments and their functioning as the point of access to a range of hospital services, both therapeutic and diagnostic, often result in emergency doctors being the first medical personnel confronted by new or worsening symptoms in patients with advanced or terminal medical conditions. [3,5] Rosenwax *et al.* (2011) illustrated that emergency providers feature prominently in the care of patients with terminal illness, with 70% of a Western Australian cohort of 1071 patients with terminal illness visiting the emergency department at least once in their last year of life and 4% on their final day of life. [4] Such

exposure provides emergency physicians the opportunity to apply the tenants of palliative care in relation to patients with incurable, terminal disease, who are clearly suffering. [3] Despite its need, the decision regarding the extent of treatment appropriate is often a challenging one to make in the emergency setting. Emergency medicine is a field characterised by limited continuity of care and a highly mobile patient population, as highlighted by the national four-hour benchmark. [6] Consequently, emergency physicians rarely have the advantage of knowing a patient or their family and lack the background knowledge and unique rapport of a long-term therapeutic relationship. Physicians must also struggle against some ingrained cultural aspects and expectations tied to emergency medicine, where when in doubt aggressive resuscitation is the default. [7,8]

Strategies to increase the ability and confidence of emergency departments to manage patients nearing the end of life include increasing training and protocols around end-of-life care, improving the utilisation of palliative care services and improving access to palliative management information for novel situations. [3,9] Tasmania has recently instituted the Healthy Dying Initiative, a state-wide policy that includes 'Goals of Care' documentation. [10] A patient's Goals of Care are documented on admission and range from 'for all active treatment measures' to 'terminal', with a range of medical and surgical management options in between. They aid after-hours patient management, clearly outlining treatment expectations and goals, and provide a link between hospitals and the community. As always, clear communication between medical practitioners, patients, families and allied health professionals is an essential component of providing good medical care.

In some situations, treating with curative



intent may be futile, even harmful, but emergency doctors still have a major role to play in optimising patients' overall quality of life and relieving suffering. Worthwhile goals that may outweigh the simple prolongation of life include reducing pain or preserving a patient's independence, dignity or good neurological functioning. As Australian medical students, we are always progressing towards the moment when we take the lead responsibility for our patients. Considering how we can best benefit patients and their families when a cure is no longer an option and death appears imminent is a vital, if challenging, aspect of medical training. The emergency department is a setting we will all encounter during some stage of our training. While there may be unique challenges to achieving optimal end-of-life care in the emergency environment, awareness of these challenges and of the continuing importance of symptom relief across all domains of medicine will aid our practice as we endeavour to provide the best possible care and achieve the best possible outcome for each and every patient.

Conflict of interest

None declared.

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Lessons learned from internship

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Many medical students this year have asked me about what it is like to become an intern. The truth is, nothing you learn at medical school can fully prepare you for the transition to internship. In fact, 42% of newly qualified doctors feel their medical training does not adequately prepare them for starting work. [1] However, it's not all drama and chaos as shows like *House* would make you believe. Most internship work is spent on paperwork, requesting investigations and simple procedures like inserting cannulas and taking bloods.

From day one, interns are often rostered for after-hours work, something medical students often have very little exposure to. All of a sudden, new interns may find themselves looking after several wards overnight. Even though some, like me, are interested in critical care medicine, it can still be a challenging thought that over a hundred patients' lives are entrusted to your care. My first after-hours shift will always stick in my mind, having given me many valuable lessons that I have taken through internship. This is that night in my life:

It is 5pm and most of the doctors have already left. I turn on my pager, secretly hoping it will not beep. Two minutes into the shift, the pager sounds and anxiety kicks in. The nurse on the other side of the phone requests, "Doctor, can you please dose this patient's warfarin?" It feels strange to not have any other doctors nearby, and my first thought is to 'phone a friend'. However, I hold off, remembering that the answer lies in the hospital protocol for warfarin, found on all the computers. It reminds me that there is always an abundance of resources and guidance available to us as medical students and interns - if we are willing to ask and look for them.

For the next hour, the tasks are manageable. I re-chart medication charts and get a request to insert a cannula into an elderly lady for intravenous fluids. The team struggled to put the last one in, and her newest one has fallen out during a shower. The lady is thin

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with fragile veins, and after three painful attempts, the cannula still isn't in. She is tired of being poked and prodded, and I'm feeling frustrated. I decide to take a break and come back later.

The nurses then page urgently for a doctor. A patient has slipped and knocked his head, and now lies on the floor with a pool of blood beside him. When I arrive at the ward, I find a nurse beside the patient saying, "Everything's going to be OK, the doctor's here now," as if a miracle is about to happen. I do not feel like anyone's miracle worker, but as one of the first responders and because more senior help had not arrived yet, the nurses look to me for further instructions. My mind freezes, but kickstarts to life again when the basics of 'ABC' spring to mind. I feel incredibly grateful for the medical school hammering the ABC approach for such situations. I begin to assess and treat the patient. His airway is patent, cervical spine protected, breathing and circulation maintained. We apply pressure to the wound and perform an ECG and glucose. The few minutes waiting for help to arrive seem to last forever. When more help arrives, we give a huge sigh of relief. I notice that all this time, the patient's wife has been waiting outside and has been growing extremely worried. As the appropriate members are treating the patient, I take the opportunity to go to her, explain what is happening, and reassure her that her husband is being cared for. One of my consultants once told me that as a junior doctor, one of the best things to do in such situations is to communicate with the patient's family.

Just when I think that there has been all the excitement I'd need in one night, the pager beeps again. A patient is spiking a high fever, and the nurse is requesting antibiotics. I check through the patient's notes first and note that she has been spiking fevers in the last few days, cultures are negative, and the treating team thinks it may be viral. A septic screen has been done, and it was previously decided paracetamol should be sufficient. I reassess her and decide that she does not look too ill at this stage. She has been stable over the



last few days. I choose to leave her without antibiotics, as it does not seem likely that they will be beneficial. The next day, I will check on the patient and be relieved to see that the treating team did not decide to prescribe any antibiotics either.

Before the end of the shift, I go back to visit the elderly lady who still needs a cannula. If I fail, I'll need to call the duty anaesthetist, and I feel bad because it is getting pretty late in the night. I discuss with the patient, and she agrees for me to have one last opportunity to try. I aim for a small vein in her left hand, and by some stroke of luck, the cannula goes in and flushes smoothly. I breathe a sigh of relief and thankfulness. It reinforces to me that sometimes, just when we are feeling down and tired from trying, we can come back to the task and succeed.

Every day in the hospital, you learn something new. After completing my internship, I am able to reflect back on how much I have learnt in the past year. Completing medical school makes you a doctor, but that is far from the end of the journey. If I may offer some advice, it would be to stay calm in unfamiliar situations, stick with what you have been taught, and never be afraid to ask for help.

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The role of viruses in carcinogenesis

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It is accepted that populations in the so-called developed world have gone through an 'epidemiological transition' where chronic disease has replaced infection as the primary cause of death. However, there is mounting evidence that infections play a key role in certain chronic diseases such as cancer. Cancers of infectious origin provide the perfect opportunity for harnessing the advances that have been made in the control of communicable diseases to attempt the control of noncommunicable diseases. Worldwide, one in every five malignancies can be attributed to infections: this figure is considered conservative and expected to rise. About two-thirds of these cancers occur in less developed countries. The majority of these malignancies are recognised to be caused by viruses via mechanisms of chronic inflammation, immunosuppression or the expression of oncogenic proteins. An understanding of virally mediated carcinogenesis may provide new targets for the development of specified viral therapy that not only impacts on viral infections but human cancer as well. From a public health perspective, viral carcinogenesis is important because it shows potential for preventative and therapeutic programmes to reduce the burden of cancer, particularly in less developed countries.



summarised in Table 1.

The induction of cancer development by viruses requires persistent infection of the host. It is hypothesised that long-term infection initiates cellular changes that predispose to cancer progression. [3]

In addition to persistent infection, the specific actions of these viruses are discussed below and can be broadly grouped into viruses that induce cancer by (i) chronic inflammation (eg. HCV), (ii) immunosuppression (eg. HIV) and by (iii) direct actions of viral oncogenic proteins (eg. EBV, HPV). [3]

(i) Cancer associated with chronic inflammation: Hepatitis B and C Viruses

Once a viral infection is initiated, recovery requires the activation of the innate and adaptive arms of the immune system. Acute inflammation is usually a short process that eliminates the pathogen. However, chronic inflammation may result if acute inflammation continues unresolved and fails to eradicate the pathogen. Chronic inflammation itself may promote carcinogenesis via the release of many factors including nitric oxide, cytokines and chemokines thus mediating DNA damage and effecting cell proliferation and neoangiogenesis. [3]

HBV and HCV infections are examples of chronic infections associated with ongoing inflammation. HBV and HCV are responsible for 54% and 31% of human hepatocellular carcinoma (HCC) cases worldwide. [4,5] These hepatotropic viruses can induce cirrhotic livers from which HCC can arise. This review will focus on HCV.

In those infected with HCV, 80% will develop chronic infection, and in 30 years 10-30% of these chronic HCV infections will develop cirrhosis. The subsequent rate of cirrhotic HCV liver disease developing HCC is 1-3% per year. [6] Since current WHO estimates suggest that 3% of the world's population, or 150 million people, are HCV infected, this represents a significant virus-associated cancer burden.

HCV is a RNA virus of the *hepacivirus* family of the genus *Flaviviridae*. HCV does not integrate itself into the host genome and several viral

Introduction

The process of carcinogenesis involves multiple contributing factors. These include environmental, lifestyle, host factors, genetically inherited traits and infectious agents. Infectious agents are important from a public health aspect as they represent a significant and preventable cause of cancer. The infection-attributable cancer burden has been estimated at 1.9 million cases, or 17.8% of the total global cancer burden. [1] The percentage of infection-attributable cancer is higher in developing countries (26.3%) than in developed countries (7.7%), reflecting the higher prevalence of infectious diseases. Of these infection-associated cancers, viruses are the most common causative agents with 12.1% of cancers worldwide attributed to viral infections. [1]

This article aims to outline current knowledge of the role of viruses in mediating cancer, explore the main mechanisms involved and propose exciting preventative and therapeutic approach for virus-associated cancers in the 21st century.

Mechanisms by which viruses mediate cancer

The International Agency for Research on Cancer (IARC) recognises seven viral agents that have been linked with cancer: Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), Human Papilloma Virus (HPV), Epstein-Barr Virus (EBV), Kaposi-Sarcoma Herpes Virus (Human Herpes Virus 8), Human T-cell leukemia virus type I (HTLV-1) and Human Immunodeficiency Virus type 1 (HIV). [2] These seven viruses classified as 'carcinogenic to humans', and the recently discovered Merkel Cell Virus which has not yet been included by the IARC, are

Table 1. Human viruses associated with malignancies.

Taxonomic Grouping	Examples	Mechanism of Carcinogenesis	Cancers for which there is sufficient evidence in humans
DNA Viruses			
<i>Hepadnaviridae</i>	Hepatitis B	Potential HBx oncogene, chronic inflammation [3]	Hepatocellular Carcinoma [4,5]
<i>Herpesviridae</i>	Epstein-Barr Virus	Oncogenic proteins: LMP-1, BARF-1, EBNA [3,21]	Nasopharyngeal carcinoma, Burkitt's lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin's lymphoma [14]
	Kaposi-Sarcoma Herpes Virus (Human herpesvirus 8, HHV-8)	Oncogenic proteins: vGPCR [23]	Kaposi's sarcoma, primary effusion lymphoma [23]
<i>Papovaviridae</i>	Merkel Cell polyomavirus	T antigens [33,34]	Merkel Cell Carcinoma [33]
<i>Papillomavirus</i>	Papillo-mavirus (HPV-16, 18, 33, 35, 39, 45, 51, 52, 56, 58, 59)	Viral genes: E6 and E7 degrade tumour suppressor proteins p53 and pRb, inhibiting apoptosis and DNA damage response [28]	Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx and tonsil [24,25]
RNA Viruses			
<i>Flaviviridae</i>	Hepatitis C Virus	Chronic Inflammation [7]	Hepatocellular carcinoma, non-Hodgkin lymphoma [3]
<i>Retroviridae</i>	Human T-cell leukaemia virus type I	Insertional mutagenesis	Adult T-cell leukaemia and lymphoma [29]
		Oncogenic protein: Tax [30-32]	
		Immortalisation and transformation of T cells	
	Human Immuno-deficiency virus	Immuno-suppression [20]	Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma, cancer of the cervix, anus, conjunctiva [13,14]
		Oncogenic protein: Tat in colon cancer? [18]	

proteins (core protein and the NS3, NS4B and NS5A) have been suggested as potential oncogenic candidates *in-vitro*. For example, the HCV NS5A protein has been shown to bind and sequester the cellular p53 protein to the perinuclear membrane, and it may be

the be key to HCC development. [7] However, it is thought that HCC primarily occurs due to repeated rounds of hepatocyte destruction and regeneration from chronic inflammation, producing a procarcinogenic cirrhotic microenvironment, [3,8] rather than through the action of viral oncogenes. Cirrhosis appears to be the main risk factor for HCC, but exogenous factors could also play a role, such as chronic alcohol consumption, viral co-infection (such as HIV modulating immunosuppression), diabetes and obesity [4] highlighting the multifactorial triggers for the induction of cancer. [9]

HCV is also a well-established cause of essential mixed cryoglobulinemia, a lymphoproliferative disease that can evolve into B-cell non-Hodgkin lymphoma (NHL). [10] HCV has been suggested to be lymphotropic, but this is not well defined. [11] Again, since HCV has not been demonstrated to encode direct oncogenic proteins, the mechanisms of HCV-induced NHL are likely to be via chronic inflammation.

(ii) Cancer associated with immunosuppression and insertional mutagenesis: HIV

It is estimated that there are approximately 34.2 million individuals worldwide living with HIV infection, two-thirds of these being in sub-Saharan Africa. [12] People with HIV have a substantially higher risk of certain cancers compared with uninfected people of the same age. These cancers are termed AIDS-defining malignancies and include: Kaposi sarcoma, a mesenchymal tumour originating from lymphatic endothelial cells, cervical cancer and NHL. [13] Additionally, other types of cancer, such as Hodgkin's disease (HD), anal cancer, lung cancer and testicular germ cell tumours appear to be more common among HIV-infected subjects compared to the general population and are termed AIDS-associated cancers. [14]

HIV is an RNA *lentivirus* of the *Retroviridae* family. The members of this family all integrate into the host chromosome and thus have the potential to cause direct insertional mutations or activation of cellular oncogenes. Other members of the *Retroviridae* family, such as Mouse mammary tumour virus (MMTV) have a well-defined link with tumours in mice, which are likely mediated by insertional activation of cellular genes in breast tissue through hormone responsive elements in the MMTV promoter. [15] Similarly, insertional mutagenesis and the induction of lymphoma has been identified in humans treated with gammaretrovirus [16] and lentivirus vectors used in gene therapy. [17] In contrast, there is little evidence for an HIV oncogenic protein, although studies have suggested that the transactivator protein of viral gene expression, Tat, which has oncogenic potential, is secreted by HIV. It has also been suggested that Tat can re-enter non-infected cells blocking apoptosis and accelerating tumour formation. [18]

The above described AIDS-associated cancers are linked with low CD4+ T-cell counts, and this may lead to co-infections with other oncogenic viruses such as HPV (cervical cancer) and Kaposi's sarcoma-associated herpesvirus (Kaposi's sarcoma), or the reactivation of existing infections with opportunistic oncogenic viruses such as EBV (Burkitt's lymphoma). [18] However, the specific mechanisms by which depressed immunity may increase the risk for cancer are unclear, except for KS and most subtypes of NHL that are strictly associated with a low CD4 count. [19] Supporting the link between cancer and immunosuppression, the pattern of cancers in immunosuppressed organ transplant recipients is similar to people with HIV/AIDS. [20]

Thus, the evidence suggests that HIV can be associated with carcinogenesis through insertional mutagenesis. Moreover, HIV may indirectly cause cancers by inducing a chronic state of immunosuppression, reducing immunosurveillance for neoplastic cells, and increasing the risk of reactivation of latent oncogenic viruses as well as the risk of acquiring new oncogenic viral infections.

(iii) Cancer associated with Oncogenic viruses

Of the identified and accepted carcinogenic viruses, EBV, HHV-8, HTLV-1 and HPV are tumour viruses that express viral oncogenic proteins to

exert carcinogenesis. HBV also produces the HBx protein that disrupts signal transduction and deregulates cell growth: however, HBV-associated carcinogenesis is believed to be mainly mediated through chronic inflammation as described for HCV. [3] Oncogenic viruses can transform cells by carrying viral oncogenes into a cell or by activating cellular proto-oncogenes. [5] The virally derived oncogenes produce transforming growth factors that deregulate growth control and proliferation, leading to malignant transformation. Specific examples are discussed below, with the oncogenic viruses divided into DNA and RNA tumour viruses.

DNA Tumour Viruses

EBV best illustrates DNA tumour viruses. EBV is a double-stranded DNA virus of the *herpesviridae* family, and causes infectious mononucleosis. Like all *herpesviruses*, EBV causes a life-long latent infection, and EBV is the primary cause of B-cell transformation in Burkitt's lymphoma. [14] This was the first human tumour associated with an infectious agent. Since then, EBV has been implicated in a number of other cancers (see Table 1).

In the case of EBV-lymphoma, expression of the viral oncogene, latent membrane protein-1 (LMP1), transforms cells into lymphoblasts by the disruption of cellular signal transduction. [3] In contrast, in most NPCs, the viral BamHI-A reading frame-1 (BARF1) gene is expressed. BARF1 has been identified as an important oncogene in NPC pathology. [21] Thus, EBV has a number of different oncogene expression profiles associated with different cancers. EBV is extremely widespread in prevalence affecting more than 90% of the world's population, [22] yet only a small fraction of the infected populations have a cancer attributable to EBV. Therefore, beside viral factors, host responses also play a role in the neoplastic transformation of EBV-infected cells.

HHV-8 is a DNA virus of the *herpesviridae* family, and HHV-8 infection is strongly associated with Kaposi's sarcoma. The mechanism, however, of HHV-8-induced carcinogenesis is very different to that of the related virus, EBV. HHV-8 infects endothelial cells and encodes a viral G protein-coupled receptor (vGPCR). This vGPCR has dysregulated signalling function and acts as an oncogene, inducing angioproliferative tumours. [23]

HPV is a DNA virus of the *papillomavirus* family, and there are 30-40 types. Approximately fifteen types of HPV are oncogenic viruses, causing 5.2% of total human cancers. [24] These cancers include those of the ano-genital mucosae (cervix, vagina, vulva, anus and penis), and the mouth and the pharynx. [24,25] The predominant transmission of these HPV infections is sexual. [26] While HPV is an accepted aetiological factor for oral and pharyngeal cancers, the major risk factors are tobacco and alcohol, with the effects of these exposures being multiplicative. [25] Oncogenic HPV can be detected by PCR in virtually all cases of cervical cancer, with specific genotypes HPV16 and 18 identified as the primary causes of cervical cancer. These viral genotypes have also been associated with 86-95% of HPV-associated non-cervical cancers. [26,27] These viruses infect the basal layer of the stratified epithelium and express two important viral oncoproteins, E6 and E7. [23] These proteins destabilise the cellular tumour suppressor genes, p53 and the retinoblastoma protein (RB). [28] This dysregulation of cellular growth directly leads to cell transformation and cancer.

RNA Tumour Viruses

HTLV-I is a retrovirus related to HIV, which is associated with adult T-cell leukaemia. Only 1% of HTLV-I infected individuals will develop leukaemia, and only after a long latency period of 20-30 years. [29] HTLV-I infection rates are elevated in certain Indigenous populations of Central and Northern Australia, as well as the southern islands of Japan, the Caribbean basin and South Africa. [14] Unlike HIV, HTLV-I infections are not associated with immunosuppression, but HTLV-I encodes an oncogenic protein; the viral Tax protein. [30,31] Tax is a transcription factor and is known to bind to a number of cellular genes

involved in cell cycle progression and growth regulation, such as NFkB and p53. [32] Via promotion of transcription and cell cycle progression, Tax is proposed to set up a self-stimulating loop that causes continuous proliferation of infected T-cells, and ultimately leukaemia.

The growing cancer burden attributable to viruses

While there are only seven viruses clearly recognised as carcinogenic to humans, this is conservative, with the discovery of new associations between infections, particularly viruses, and cancer anticipated.

MCV is a recently discovered DNA virus that is found to be associated with approximately 80% of Merkel Cell Carcinomas, an aggressive form of skin cancer. [33] MCV is a relatively common virus, yet only leads to cancer in rare circumstances. It is thought that this is because for MCV to become carcinogenic, two rare mutagenic steps must occur: viral integration and T antigen mutation. Integration of MCV is not a regulated event, unlike for HIV and HTLV-I, and occurs rarely. The integration, probably of only parts of the MCV genome into cells, renders the virus replication-incompetent, but allows parts of the virus, such as the T-antigens, to be maintained in these cells. [34] MCV T antigens can be oncogenic, and target cellular tumour suppressors and cell cycle regulatory proteins. Thus, the whole replicative virus may not be present, but the residual oncogenic T-antigen is, and can promote transformation of the cell leading to cancer.

Cancerous cells themselves are generally not transmissible. In humans, during the two known physiological routes for tumour cell transmission (pregnancy and organ transplantation), the immune system is altered. Transplacental transmission of lymphoma, acute leukaemia, melanoma and carcinoma have been observed, as well as acute leukaemia cells transmitted to the foetuses in multiple case pregnancies with the subsequent disease development in the newborn. [35] Similarly, in organ transplantation, donor derived tumour cells have been observed, with the immunosuppressive therapy following transplantation potentially facilitating the engraftment and growth of donor derived tumour cells. [35] Fortunately, these transmissible tumours are rare, with the development of donor-derived tumours in solid organ transplant recipients at 0.04%. [15] Additionally there have been rare case reports of human contagious cancers documented via needle stick (colonic adenocarcinoma), [36] and a surgeon contracting a malignant fibrous histiocytoma from a patient following an intraoperative cut to his left palm. [37]

Cancer prevention and public health strategies

In theory, the cancers resulting from viral infections represent an exciting potential for public health intervention strategies and therapeutics to prevent these cancers. In particular, the high number of cancers attributable to viral infections in developing countries presents a real need and opportunity for public health programs to reduce both infectious disease and cancer burden. [38]

The mode of transmission of the seven IARC-recognised carcinogenic viruses is provided in Table 2. The implementation of public health education, awareness, treatment and prevention programs to reduce the horizontal spread of these viruses and manage these viral infections in patients is a public health priority, but has the additional benefit of reduction in the associated cancer risks.

Public health programs should be prioritised to target vertical transmission of viral infections such as HBV and HIV. The WHO outlined targets and recommendations in 2010 with the prevention of mother to child transmission (PMTCT) strategy, targeting anti-retroviral therapy (ART) in pregnant women and providing guidelines for HIV in relation to infant breastfeeding. [39] Similar guidelines may be applicable to our Indigenous population afflicted by HTLV-I, which has a well described increased mother to child transmission rate associated with breastfeeding. [40] However, breastfeeding recommendations in resource poor settings need careful consideration. [41]

More outstanding, are the successful programs for screening and

Table 2. Infectious agents-associated with malignancy and their transmission modified from [3].

Viral Agent	Route of Infection	Preventative Strategy
EBV	Saliva	
HPV	Sexual	Vaccination, Safe Sex Programs, Screening Programs
HCV	Sexual/post-transfusion/IV drug user	Safe Sex Programs, Needle-exchange programs
HBV	Perinatal/Sexual	Vaccination, avoidance of breastfeeding, Safe Sex Programs
HHV-8	Sexual	Safe Sex Programs
HTLV-1	Sexual/perinatal/parenteral	Safe Sex Programs, avoidance of breastfeeding
HIV	Sexual/perinatal/IV drug user	Safe Sex Programs, Needle-exchange programs, administration of anti-virals during childbirth, avoidance of breastfeeding

management of viral infections associated with cancer. For example, the National Cervical Screening Program (NCSP) in Australia has had a huge benefit in reducing the mortality rates from cervical cancer from 3.9/100,000 in 1991 to 1.9/100,000 in 2007, [42], demonstrating that cancer prevention via monitoring oncogenic viral infections is a real possibility. [43] Additionally, such programs as the NSW Cancer Council 'B positive' program, implemented in 2008 aims to increase HBV awareness and the treatment and management of chronic HBV infection to reduce the risk of HCC. [44]

Vaccination and treatments to prevent cancer-associated viral infections

Historically, the world has experienced, with polio and smallpox, elimination or virtual elimination of viral diseases through vaccination. There are now vaccines available for both HBV and HPV, two major infectious causes of HCC and cervical cancer, respectively. The HBV surface antigen is the basis for the vaccine against the HBV, which was first available in the 1980s, and is the first vaccine for prevention of a human cancer. [45] Vaccination programmes of children with the HBV vaccine have already proved successful in protecting against chronic carriage and HCC, [46,47] and HBV vaccination has now been introduced into the Australian childhood immunisation schedule. Long-term and full coverage of newborns against HBV has the potential of reducing HCC by approximately 85%. [14]

The two currently marketed vaccines for HPV utilise the L1 coat protein in the form of virus-like particles to prevent persistent infection with HPV16 and HPV18. [48-50] These viral subtypes are estimated to cause 71.8% of all HPV-related cancers, cervical and non-cervical. [25] These vaccines need to be administered prior to exposure to HPV16 and 18, which makes delivery in a public health setting more difficult than an infant setting. In Australia in 2007, the National HPV vaccination Program was made available to teenage women, and is now part of the school age vaccination program. From 2013 will also be made available to 12-13 year old males. [51] However, the current cost is not practical for all groups, especially those in developing countries, [14] and although the HPV vaccination program in developing countries is supported by the WHO, the applicability and benefits of HPV vaccination have been

queried and recently suspended in India. [52] The efficacy of these HPV vaccines in preventing infections at sites other than the cervix, vagina and vulva should be assessed. [27] Specifically, research is required on the administration to high-risk groups (e.g. men who have sex with men and HIV positive people) for anal cancer. [24]

Unfortunately, the described RNA viruses associated with cancer, HIV and HCV, are highly genetically variable and therefore prove to be difficult candidates for prophylactic vaccines. For these viruses, anti-viral therapy appears to be more successful. For example, the risk of infection-associated cancers in HIV positive individuals is related to ongoing HIV replication. The use of suppressive highly active antiretroviral therapy (HAART) has dramatically reduced the risk for opportunistic infections and improved overall life expectancy in patients with HIV-infection and AIDS. [53] A significant decrease in the incidence of KS has been observed in patients treated with HAART. [19] Moreover, HAART and preserved CD4 count preferentially reduces the risk of malignancies associated with oncogenic infections. [54] Similarly, patients with HCV who were prescribed the anti-viral agent, interferon, showed regression of their splenic lymphoma. [55]

Recently approved HCV NS3-4A protease inhibitors are proving effective in clearing and curing HCV infection. In the future, this may significantly impact on HCV infection rates and subsequent incidence of HCC.

Exciting Therapeutic Targets

Our understanding of mechanisms of viral initiation of carcinogenesis has provided the opportunity to design innovative, targeted cancer therapies based on the pathways disrupted by the transforming viral genes.

For example, recent studies reveal that the cellular survivin oncoprotein is activated by MCV large T antigen protein via targeting the cellular Rb (p53) protein, and that survivin inhibitors can delay MCV-induced tumour progression in animal models. [56] Clinical trials are now in progress to determine whether these survivin inhibitors have any therapeutic benefits. Additionally, MCV is a target for cell-mediated immune responses, and so important research efforts are being focused on immunologic therapies that may benefit MCC patients. [56] These findings provide a proof of principle for specifically treating virus-associated cancers by targeting the mechanisms by which they induce oncogenesis. In the case of MCV, a promising rational drug target has been uncovered within only four years of the initial discovery of MCV as a causative cancer agent. Similarly, other new treatments for cancer might be rapidly developed should we identify new viral associations with malignancies.

Conclusion

Viruses are an important aetiological cause of human cancers, especially in the developing world where they lead to a significant burden of disease. Although viruses make an important contribution to human cancer development, it is often difficult to prove the association of viral infections with cancer, due to latency in tumour development and the multifaceted interaction with the host. It is reasonable to think that the calculations of cancers attributable to viruses are underestimates and that cancers other than the ones described may also be associated with viral infections. The viruses in this review exemplify the best-established human tumour viruses, but there are many other potential candidates. Undoubtedly, as our knowledge of carcinogenesis and viruses expand, further cancer-associated viruses will be discovered. From a public health point of view, infectious diseases are often preventable or treatable; therefore, cancers associated with infections are, or may become, preventable. Prevention may be in the form of vaccination, novel therapies to target the immune system or oncogenic proteins, or education and public health interventions.

Conflict of interest

None declared.

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A systematic review evaluating non-invasive techniques to diagnose genetic disorders in a human fetus and the ethical implications of their use

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Introduction: Genetic disorders are a significant cause of neonatal morbidity and mortality. [1] Diagnosing a genetic disorder currently involves invasive tissue sampling which carries an increased risk of miscarriage. The discovery of cell-free fetal DNA (cffDNA) in maternal plasma has enabled the development of non-invasive prenatal diagnostic tests (NIPD). [2,3] The scientific and ethical implications are examined. **Methods:** Medline, PubMed and Cochrane Library were searched for original research articles, review articles and meta-analyses focussed on screening and diagnosis of fetal genetic disorders. **Results:** 422 original research and review articles were assessed using processes in the Cochrane Handbook for Systematic Reviews of Interventions. [4] Using maternal plasma obtained during the second trimester, researchers were able to sequence the fetal genome with up to 98% accuracy. Clinicians reported the test will improve prenatal screening uptake, and reduce morbidity and mortality associated with genetic disorders. Ethicists argue it has implications for informed consent, rates of termination, reliability of future applications, inadvertent findings in clinical settings, commercial exploitation and inconsistent use of the technology internationally. **Conclusions:** Once NIPD tests utilising cffDNA are refined and costs reduced it is likely its implementation will affect both specialist genetic and routine antenatal services. However, given the complex set of ethical, legal and sociocultural issues raised by NIPD, professional education, public engagement, formal evaluation and the development of international standards are urgently needed. Health systems and policy makers must prepare to respond to cffDNA technology in a responsible and effective manner.

Introduction

Most pregnant women wish to be reassured that their unborn baby is healthy. [5] The aim of antenatal care is therefore to select screening and diagnostic tests that are accurate, safe and can be performed sufficiently early to allow parents to plan ahead or terminate the pregnancy in the event that fetal abnormality is diagnosed. [6] Genetic disorders are a significant cause (20%) of neonatal mortality. [1] At present, maternal serum screening, alone or in combination with ultrasound, is used to identify fetuses at risk of aneuploidy and other disorders. [7] Unfortunately, neither maternal serum screening nor ultrasound provide information on the genetic constitution of a fetus or allow a definitive diagnosis to be made. [8] For this, fetal cells must be invasively sampled from the placenta (chorionic villus tissue), amniotic fluid or fetal blood - all of which increase the risk of miscarriage. [9,10] This increased risk makes the decision to use invasive prenatal diagnosis difficult, particularly as there are still only very limited treatment options. [11] As a result, the medical community has sought to develop reliable and safe methods for achieving non-invasive prenatal diagnosis (NIPD), in addition to future treatment options. [12] Through NIPD, researchers hope to improve screening uptake, and reduce morbidity and mortality associated with genetic disorders. [1] Ethicists argue that NIPD transects existing distinctions between screening and diagnostic tests, and has implications for informed consent or choice. [12]

Methods

MEDLINE, PubMed and Cochrane Library were searched weekly between September 2012 and April 2013 for original research articles,



review articles and meta-analyses focussed on screening and diagnosis of fetal genetic disorders. MeSH headings used were: Genetics, Medical, Genetics Testing and Fetus. Search terms used were: non-invasive, whole-genome and sequencing. Results were limited to human studies written in English between 1995 and 2013.

Results

The search resulted in 422 articles being identified; these were subsequently examined. The majority of publications were original research and review articles, although there was one meta-analysis by Alfirevic *et al.* (2003). [6] Many publications (217) were excluded for their limited scope or irrelevance.

Maternal serum screening and ultrasound are current methods of choice for screening pregnancies at risk of genetic disorders. [8,13] However, both methods rely on measuring epiphenomena rather than core pathology. Consequently, both tests have limited sensitivity and specificity and can only be used within a relatively narrow gestational period. [14] To achieve a definitive diagnosis chorionic villi sampling (CVS), amniocentesis or cordocentesis must be used. [6,8]

CVS is an invasive diagnostic procedure performed after 10 weeks gestation that is used for karyotyping when first trimester screening suggests a high risk of aneuploidy. [8] It is also used for fetal DNA analysis if the parents are known to be carriers of an identifiable gene mutation, such as cystic fibrosis or thalassaemia. [9] The procedure involves ultrasound-guided aspiration of trophoblastic tissue using either the trans-cervical or trans-abdominal routes. The tissue is then analysed with fluorescence *in situ* hybridisation polymerase chain reaction (FISH PCR). Like CVS, amniocentesis involves ultrasound-guided aspiration of amniotic fluid but is performed after 15 weeks gestation. [6] Cordocentesis involves direct sampling of fetal blood from the umbilical cord but is rarely performed and will not be discussed further in this article.

The benefit of CVS is that it can be performed at an earlier gestation, facilitating earlier diagnosis and providing the opportunity to terminate the pregnancy by suction curettage of the uterus. The benefits of amniocentesis include the lower background rate of miscarriage and the avoidance of isolated placental mosaicism occurring in 1% of samples. [8] The primary risk with CVS and amniocentesis is miscarriage. The level of risk is similar for the two tests (reported

risk ranges from 1% to 1 in 1600) and is operator dependent. [6,7] Researchers have attempted to reduce this risk by developing a NIPD that allows the direct analysis of fetal genetic materials. [2,12,14-22] Better screening tests will achieve a higher detection rate combined with a lower false positive rate, resulting in less invasive testing and fewer procedure-related miscarriages.

Much of the early work on NIPD focussed on the isolation of fetal nucleated cells that had entered into the maternal blood. [14] However, the concentrations of these cells were low, meaning the tests had low sensitivity and specificity. [15,22] Later methods were inspired by the presence of tumour-derived DNA in the plasma of cancer patients. [23,24] In 1997, Lo *et al.* (1997) observed an analogous phenomenon was present in pregnancy by identifying Y chromosomal DNA sequences in plasma of women carrying male fetuses. [25] Replication of this study has concluded that 10% of cell-free DNA (cffDNA) in a pregnant woman's plasma originates from the fetus she carries. [14,17,18,20] Since then, several groups have developed NIPD tests but most were only capable of detecting gross abnormalities such as aneuploidies, and were limited by small sample size and substandard accuracy. [17,18,22,26,27] In June 2012, Kitzman *et al.* (2012) reconstructed the whole-genome sequence of a human fetus using samples obtained relatively noninvasively during the second trimester, including paternal buccal DNA and maternal and cffDNA from the pregnant mother's plasma. [2] Predicting which genetic variants were passed from mother to fetus was achieved by resolving the mother's haplotypes - groups of genetic variants residing on the same chromosomes - and combining this result with shotgun genome sequencing of the father's DNA and deep sequencing of maternal plasma DNA. [19] Comparing the results of this method with cord blood taken at delivery found inheritance was predicted with 98.1% accuracy. The study sequenced only two fetuses at a cost of \$50,000 each, and is yet to be reproduced. Researchers from Stanford University were able to sequence the fetal genome without a paternal saliva sample although this was less accurate than the method used by Kitzman *et al.* (2012). [18] This latter method forms the basis of commercially available NIPD tests being offered by laboratories. [28] In Australia, NIPD testing is currently limited to Trisomy 21, 18, 13 and abnormalities of sex chromosomes, is not eligible for a Medicare rebate and costs upwards of \$1,250. [29] It is anticipated that analysing samples for NIPD locally will reduce the cost and drive demand. [30,31]

Discussion

Clinicians report that non-invasively diagnosing genetic disorders will reduce infant mortality and morbidity. [31] Ethicists argue the technology raises concerns for informed consent, rates of termination, reliability of future applications, inadvertent findings in clinical settings, commercial exploitation and inconsistent use of the technology internationally [12,32-36].

Informed Consent and Informed Choice

Ethicists believe NIPD testing transects existing distinctions between screening and diagnostic tests and has implications for informed consent and choice. [12] An example is screening for Down's syndrome, a common genetic disorder. Although a significant number of women may not already achieve informed choice for screening, at least a subsequent invasive diagnosis provides another opportunity for reflection as they consent to the procedure (CVS or amniocentesis). [34,35] Replacing this multi-step screening process with highly-predictive cffDNA testing may reduce opportunities for exercising informed choice. [12] In addition, despite the belief that introducing cffDNA testing will promote parental reproductive choice, it may indeed make proceeding with an affected pregnancy more difficult for two reasons: First, the decreased risks associated with cffDNA might lead women to feel 'pressured' into agreeing to the tests, or undergoing testing without informed consent, even if they potentially lead to outcomes with which they disagree. [33,36] Second, the lower risks might cause a shift in the extent to which society is supportive of

those who chose to have disabled children. [10] In turn, worries over social disapprobation could prompt a loopback effect, where women feel more pressured to test and to terminate their pregnancies.

Termination of pregnancy (TOP)

In Australia, there is broad agreement that TOP is ethically and legally permissible in some circumstances. [11,33,37] However, the laws are notoriously unclear, outdated and inconsistent between states and territories. [38,39] In many jurisdictions it is legally defensible for a clinician to perform a TOP at any gestation if they can justify the harms of continuing with the pregnancy outweigh the risks of termination. [40] For this reason, access to TOP is very much dependent on the clinician, which may be problematic if cffDNA testing becomes more widespread and moves outside the existing setting of medical genetics, where high standards of relevant ethical practice and the professional duty of non-directive counselling are firmly entrenched. [12]

Accuracy and reliability of NIPD

Despite improved accuracy by utilising fetal nucleic acids, the sensitivity and specificity of even the most accurate method is still less than 100%. [2] Maintaining an acceptably high sensitivity and specificity will also be a challenge, as researchers discover an ever-increasing number of sequences associated with pre-existing diseases. [12] To do this will require careful monitoring within different applications. [33] Without it, the personal, sociocultural, legal and ethical ramifications of false positives and negatives may be devastating. For example, additional invasive testing may be undertaken, healthy fetuses may be terminated, and children may suffer psychologically should they discover their parents would have terminated them if they had known of their diagnosis. [34]

Inadvertent findings in clinical settings

The Kitzman *et al.* method requires paternal buccal DNA to sequence the fetal genome and may therefore inadvertently disclose misattributed paternity. [41] However, so too may the Stanford University method that forms the basis of commercially available NIPD but that does not require paternal buccal DNA. [18] In a trial of 18 subjects, researchers using the latter method were able to predict 70% of the paternally inherited haplotypes in the fetus with 94-97% accuracy. [18] Of course, the correlation of these findings to the clinical setting would likely still require paternal buccal DNA to confirm paternity. The potential for inadvertent disclosure of misattributed paternity would be a particular concern if cffDNA testing were ever incorporated into routine antenatal screening as a greater number of women who may not have been adequately forewarned would be exposed to the risks such information may bring.

Commercial and international uses

The likely increase in the accessibility of NIPD using cffDNA tests made available via the internet has major implications, particularly for fetal sex selection. [12] In China [42] and India, [43] population skewing has already been observed as a result of unlawful sex selection practices favouring male children. Some ethicists believe cffDNA could significantly aggravate or extend this problem. [44] The development of cffDNA technology within the commercial sector is also a concern as some companies choose only to sell the service rather than invest in research and development eg: babygendermentor.com. The provision of testing direct-to-consumers raises a complex set of issues relating to the role of 'gatekeepers' in prenatal testing and access to non-clinical applications of the technology. [33] In addition, it may even impact upon the provision made through Medicare for ongoing care, including diagnostic confirmation, interventional procedures (such as TOP) and medical advice. [5] Having commercial players involved may result in elements of professional practice, including informed consent and counselling, being difficult to enforce considering international legislative and regulatory boundaries. [12] The cultural context is also highly relevant to how consumers access cffDNA testing. For example, its use in countries where access to safe TOP is limited or absent is

ethically questionable and could cause significant social and medical problems. [45]

Conclusion

The utilisation of cffDNA for safe and reliable NIPD has opened the way for accurate sequencing of the fetal genome and the ability to diagnose an ever-increasing number of genetic anomalies and their clinical disorders. Once methods such as those by Kitzman *et al.* and researchers at Stanford University are refined and costs reduced it is likely the implementation of cffDNA testing will affect both specialist genetic and routine antenatal services, improve screening uptake, and reduce morbidity and mortality associated with genetic disorders. As a result of the pace of development, there is concern that cffDNA testing transects existing distinctions between screening and diagnostic tests, having implications for informed consent, termination rates and commercial. Given the complex set of ethical, legal and sociocultural issues raised by NIPD, both professional education

and public engagement are urgently needed. Formal evaluation of each test should be required to determine its clinical accuracy, and laboratory standards should be developed alongside national best practice guidelines to ensure that cffDNA testing is only offered within agreed and well-supported pathways that take account of the aforementioned issues. This development has the potential to deliver tangible improvements in antenatal care within the next 5-10 years, and health systems and policy makers around the globe must now prepare to respond to further developments in cffDNA technology in a responsible, effective and timely manner.

Conflict of interest

None declared.

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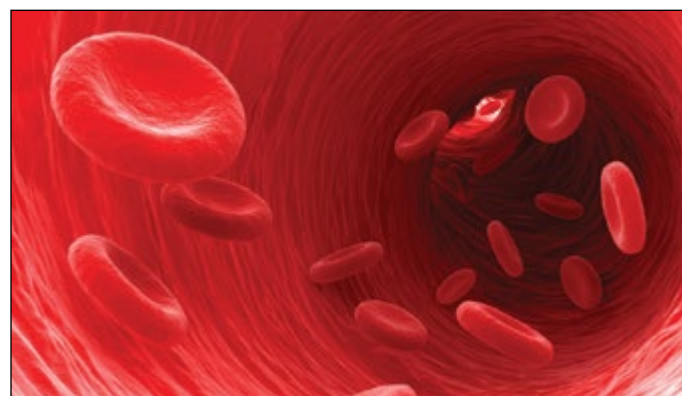
Is plasmapheresis the optimal treatment option for acute pancreatitis secondary to hypertriglyceridemia? A systematic review

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Background: Hypertriglyceridemia is an uncommon cause of acute pancreatitis, which is a life-threatening illness. Conventional management involves fasting, lipid-lowering medication, insulin and heparin. Plasmapheresis is an approach which is used occasionally to achieve rapid lowering of triglyceride levels in patients where conventional management is unsuccessful. It is currently unclear whether plasmapheresis improves outcome in patients with hypertriglyceridaemia-induced pancreatitis. **Aim:** A literature review and critical analysis was conducted to assess the effectiveness of plasmapheresis in improving patient outcomes in patients with acute pancreatitis secondary to hypertriglyceridemia. **Methods:** The PICO model (Population, Intervention, Comparator, Outcomes) was used to synthesise a research question. Thereafter, a search was conducted through the Scopus database (includes complete MEDLINE coverage) applying the terms 'plasmapheresis' OR 'plasma exchange' OR 'lipid apheresis' AND 'pancreatitis' AND 'hypertriglyceridemia' OR 'hyperlipidaemia' OR 'hyperlipidemia'. Article titles and/or abstracts were screened for relevance to the topic. Original research articles assessing the efficacy of plasmapheresis in hypertriglyceridaemia-induced pancreatitis were included. **Results:** To date, no randomised controlled trials have been published assessing the efficacy of plasmapheresis in this population. Two retrospective primary research studies were identified. Both studies demonstrated a rapid reduction in triglyceride levels following plasmapheresis in the magnitude of 65.8-80%. The studies showed no significant clinical benefit in terms of mortality and morbidity, but were limited by small sample size and study design. **Conclusion:** Current evidence demonstrates that plasmapheresis in the setting of hypertriglyceridemia-induced pancreatitis reduces triglyceride levels by 46-80%. [1] However there is insufficient data to suggest a beneficial effect on clinical outcomes. Well-designed prospective studies with adequate follow-up are required to elucidate whether plasmapheresis is associated with reduced morbidity and mortality in this population.



morbidity and mortality. Current management includes fasting, lipid-lowering medication (such as fenofibrate), and insulin and heparin, used to 'accelerate lipoprotein lipase activity'. [2,4] These interventions have shown limited efficacy in reducing inflammation and life-threatening complications associated with severe acute pancreatitis. Novel therapies are needed to improve patient outcomes. [5]

Plasmapheresis is defined as 'removing the plasma and replacing it with donor plasma or a plasma substitute'. [6] The term plasmapheresis is used interchangeably with the term 'therapeutic plasma exchange'. The use of plasmapheresis in patients with hypertriglyceridemia can be traced back to a case report in 1978. [3] However, it is not widely utilised in this patient population at present. Given that plasmapheresis provides rapid removal of the triglycerides responsible for underlying inflammation in hypertriglyceridemia-induced pancreatitis, it is expected that this intervention may prove highly effective in reversing this sub-type of acute pancreatitis. The aim of this review was to assess the effectiveness of plasmapheresis in achieving positive patient outcomes (as per Table 1) in patients with acute pancreatitis secondary to hypertriglyceridemia.

Table 1. PICO model.

Population	Patients with acute pancreatitis secondary to hypertriglyceridemia
Intervention	Plasmapheresis/therapeutic plasma exchange
Comparator	Conventional treatment for hypertriglyceridemia-induced pancreatitis (as defined above)
Outcomes	<ul style="list-style-type: none"> • Symptomatic relief • Complications secondary to acute pancreatitis • Mortality • Lowering of triglyceride levels

Introduction

Hypertriglyceridemia is an uncommon cause of acute pancreatitis, accounting for 1.3-3.8 % of cases with an incidence of 18/100,000 per year in the United States of America. [1,2] Primary (genetic) and secondary causes, such as uncontrolled diabetes mellitus, hypothyroidism, alcohol, obesity, certain medications, and pregnancy, are associated with hypertriglyceridemia-induced pancreatitis. [1,3] The mechanism for severe hypertriglyceridemia-inducing pancreatitis remains unclear, [3] although triglyceride levels exceeding 10 mmol/l (1000 mg/dl) can trigger a bout of pancreatitis. [3,4] One postulated theory involves the idea that pancreatic lipase hydrolyses excess triglycerides to produce free fatty acids around the pancreas. These free fatty acids can damage the pancreatic acinar cells and pancreatic vascular endothelium, resulting in ischaemia and inflammation. The acidic environment can further amplify the free fatty acid toxicity in a vicious cycle. [3,4]

Hypertriglyceridemic pancreatitis is a life-threatening illness with a mortality rate of 7-30%. [5] Complications include sepsis, pancreatic necrosis, abscess formation and renal insufficiency; which account for the high mortality seen in this disease. [3] Optimal management of hypertriglyceridemia-induced pancreatitis is essential to reduce

Methods

The PICO model was used to synthesise the research question. [7]

Search Methodology

The literature search was conducted on Scopus, which is one of the

largest databases of abstracts and citations of research literature, and includes complete coverage of the MEDLINE database. [8] The following search terms were used: ("plasmapheresis" OR "plasma exchange") AND "pancreatitis" AND ("hypertriglyceridemia" OR "hyperlipidaemia" OR "hyperlipidemia"). The initial database search yielded a total of 139 documents, of which 110 were written in English. After further limiting the search query to include only 'articles' or 'reviews', a total of 86 documents were found. The documents were then sorted by relevance, and titles and abstracts were screened to identify articles that reported on the use of plasmapheresis in the management of hypertriglyceridemia-induced acute pancreatitis. A total of 28 relevant articles were identified: one primary research study, one review paper, one guideline (the 2010 American Society for Apheresis (ASFA) guideline), eleven case-series (62 patients), and fourteen individual case studies (Figure 1). Review of the references and citations of these studies yielded an additional two articles: one original retrospective study and one review. Focused searches revealed no additional relevant articles. The inclusion criterion for this review was limited to primary research studies only.

Results

Two cohort studies meeting the pre-specified inclusion and exclusion criteria were included. No randomised-controlled trials were identified, and are probably not feasible given the low incidence of hypertriglyceridemia-induced pancreatitis.

Chen *et al.* [9] conducted a retrospective cohort study to compare the mortality and morbidity in patients with hyperlipidaemic pancreatitis before and after the introduction of plasmapheresis in Shin kong Wu-Ho-Su Memorial Hospital, Taiwan, in August 1999. This study separated the patients into two cohorts: group I (pre-August 1999) and group II (post-August 1999). There were 34 patients in group I and 60 patients in group II, of which twenty patients received plasmapheresis. The cohort was recruited appropriately with all patients fitting the time-frame criteria (pre- or post-August 1999). There was no statistical difference between the demographics of group I and group II, including mean age, gender distribution, initial mean triglyceride level, diabetes mellitus, alcohol consumption, Ranson's score ≥ 3 and Balthazar grade D or E. [9]

Furthermore, patients with severe hypertriglyceridemic pancreatitis (defined by Ranson's score ≥ 3) were analysed separately, comparing Group A (those who received plasmapheresis) and Group B (those who did not receive plasmapheresis). There were ten patients in Group A and nineteen patients in Group B. Morbidity was defined in terms of systemic complications, including acute renal failure, upper gastrointestinal bleeding, shock and acute respiratory distress syndrome; and local complications, in particular abscess and pseudocyst formation.

The results were analysed using a t-test and chi-square test. There was no statistical significance (defined as $p < 0.05$) between the mortality and complications of patients with severe pancreatitis who received plasmapheresis, compared to those who received conventional therapy. Similarly, there was no significant difference (defined as $p < 0.05$) between the clinical outcomes of pre-August 1999 and post-August 1999 samples. Interestingly, Chen *et al.* found that the mean serum concentration of triglycerides and lipase were markedly reduced after plasmapheresis, with a 65.8% reduction of triglyceride levels and 88.8% reduction of lipase levels. [9]

Gubensek *et al.* [4] also carried out a retrospective cohort study. They looked at two sets of patients. The first sample consisted of 50 patients who were treated with plasmapheresis between 1992 and 2008 at a tertiary-care hospital (University Medical Center Ljubljana, Slovenia), and the triglyceride and total cholesterol levels before and after plasmapheresis were compared. The demographic characteristics of these patients revealed a gender bias, with 92% of the sample being male. The second set of patients included 40 patients treated between 2003 and 2008 with plasmapheresis. The Acute Physiology and Chronic

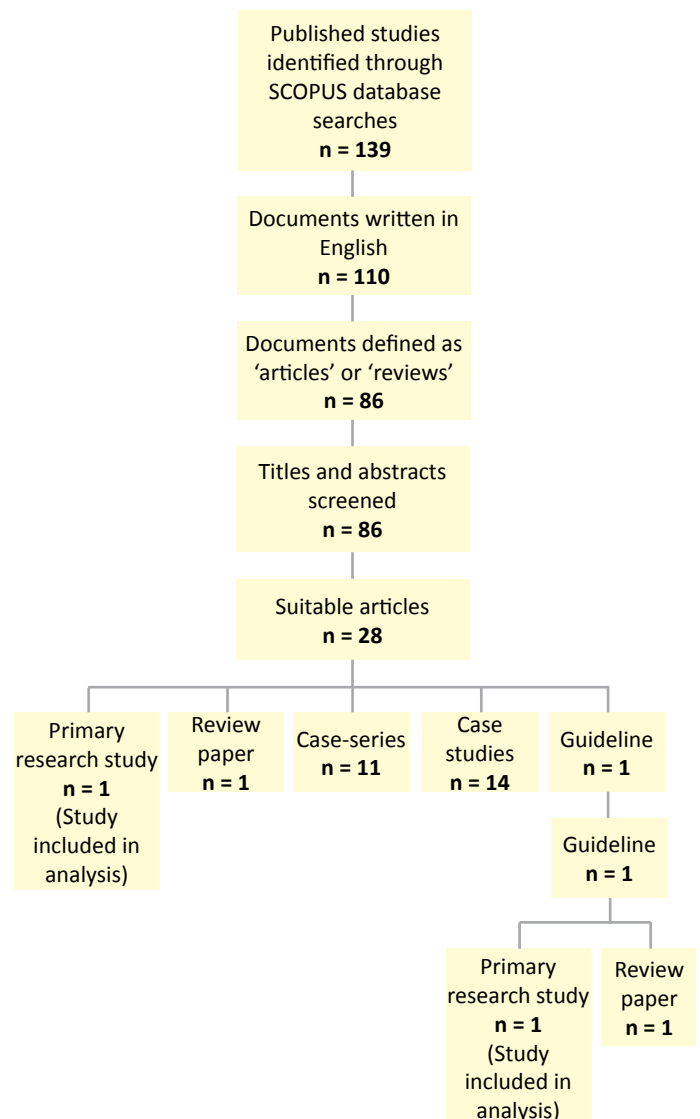


Figure 1. Flow diagram showing search methodology. 139 published studies identified through SCOPUS database searches. 28 suitable articles were found which assessed the role of plasmapheresis in hypertriglyceridemia-induced acute pancreatitis. Out of these 28 articles, one primary research study was found which has been included for analysis along with another primary research study identified through references of the 2010 ASFA Guidelines on the Use of Therapeutic Apheresis in Clinical Practice.

Health Evaluation II (APACHE II) score was used as a prognostic tool, with a score of < 8 indicating mild pancreatitis and a score of ≥ 8 indicating severe pancreatitis. A comparison of mortality rates was made between these two groups. The mortality rate was 4% and 42% respectively, with statistically significant differences between the two groups ($p < 0.001$).

The results of the first cohort in the study by Gubensek *et al.* [4] showed a statistically significant (defined as $p < 0.001$) reduction in triglyceride and cholesterol levels after plasmapheresis within 24 hours. On average, a reduction in serum triglyceride levels of approximately 80% was achieved by plasmapheresis. The analysis of the second cohort showed a significantly higher mortality in patients who had an APACHE II score of ≥ 8 (42% vs. 4%). The overall mortality was 15%, which the authors acknowledged as 'considerable'.

Discussion

The efficacy of plasmapheresis in hypertriglyceridemia-induced pancreatitis has been unclear. In an attempt to clarify this, we conducted a systematic review of published studies and guidelines investigating the benefits of this therapy. Studies by Chen *et al.* and Gubensek *et al.* reported on different populations; however both

highlighted that a significant reduction in serum triglyceride levels can be achieved by plasmapheresis in patients with hypertriglyceridemic pancreatitis. Chen *et al.* [9] showed a reduction in triglyceride levels by 65.8%, and Gubensek *et al.* [4] demonstrated an average reduction of 80% in triglyceride levels. It should be highlighted that a rapid reduction in triglyceride and cholesterol levels does not necessarily imply a clinical benefit to the patient. The exact pathophysiology of hypertriglyceridemia-induced pancreatitis remains unclear. During a prolonged episode of acute pancreatitis cellular injury can occur which may remain irreversible regardless of lowering of triglyceride levels, although further pancreatic destruction and recurrent episodes may be reduced. [5,10-11] Admission triglyceride levels have not been associated with severity, complication rates or clinical course. [5] Therefore more research is required to look at the effect of the rapid lowering of triglyceride levels on patient outcomes.

The weaknesses of both studies are the small sample size and sub-optimal study design. Chen *et al.* only looked at a small number of patients from a single hospital, and no definitive conclusions could be reached based on the limited statistical power of the study. Moreover, Chen *et al.* [9] compared group I and group II outcomes, despite group II comprising of 40 patients who had not received plasmapheresis in addition to the twenty patients who had received plasmapheresis. Therefore, since group II comprised of a mixed sample of patients receiving plasmapheresis and those receiving conventional treatment, the outcomes do not give a true picture of the effect of plasmapheresis only. A statistical comparison between group I and group II only accentuates that there was no benefit in terms of mortality and morbidity between patients presenting with acute pancreatitis secondary to hypertriglyceridemia before August 1999 or after August 1999 at that specific hospital. Thus, any conclusion on the effectiveness of plasmapheresis at reducing patient morbidity and mortality using these statistical results is invalid.

On the other hand, Chen *et al.* [9] should be commended on their detailed explanation of the apheresis procedure performed, which was well controlled. However, replacement fluid was either fresh frozen plasma (N=8) or isovolumetric 5% albumin solution (N=12). The authors did not adjust their results for this potentially confounding variable. The mean serum concentration of triglycerides and lipase were markedly reduced after plasmapheresis, with a 65.8% reduction of triglyceride levels and 88.8% reduction of lipase levels. However, the time period in which these reductions occurred post-procedure is unclear, and no comparisons were made with the reduction in serum lipase and triglycerides in patients presenting pre-August 1999. The authors did not follow the patients over a considerable time period and were unable to assess recurrence of acute pancreatitis or mortality between patient samples.

The research study by Chen *et al.* [9] is essentially the only study comparing the use of plasmapheresis and conventional treatment in acute pancreatitis due to hypertriglyceridemia. This study found no differences in mortality and morbidity between conventional therapy and plasmapheresis, but the results need to be carefully evaluated, as mentioned above. A review of this study by the 2010 ASFA Guidelines highlight that 'adequate information was not provided to ascertain the comparability of the two groups'. [1] Chen *et al.* stated that earlier intervention might provide positive outcomes for plasmapheresis, given that the median time for starting plasma exchange was three days for their patients. [9] This is a possible explanation for the results, and further studies are needed to evaluate the relationship between the time of initiating plasmapheresis and patient outcomes. A review by Tsuang *et al.* reported that 'early initiation of treatment for hypertriglyceridemic pancreatitis is likely to be beneficial', [3] based on findings from the retrospective case series by Kyriakidis *et al.*, who reported positive patient outcomes in eight out of nine patients treated with plasmapheresis within 48 hours of diagnosis. [2]

The study by Gubensek *et al.* is also limited, in that it did not compare

the effect of plasmapheresis with conventional treatment options. No comparison was made with the mortality rate of patients who were treated conventionally. The study makes a strong point on the effectiveness of plasmapheresis in acutely reducing serum triglyceride and cholesterol levels, but does not determine whether there is any clinical benefit of this to the patient.

The indications and criteria for applying plasmapheresis was not consistent across the literature. Plasmapheresis is commonly used in settings where there is inadequate outcomes achieved using conventional management. [5] However, the patients treated with plasmapheresis in Chen *et al.* [9] and Gubensek *et al.* [4] include those with mild to moderate pancreatitis as well as severe pancreatitis (evaluated using Ranson's scores or APACHE II score), but no information was given about any conventional treatment prior to the initiation of plasmapheresis. Therefore, it is unclear whether any prior conventional treatment had an effect on patient outcomes.

Neither study reviewed the potential symptomatic relief from plasmapheresis. A possible reason could be due to the subjectivity in measuring this outcome and the retrospective nature of the studies. Evaluation of potential symptomatic relief from plasmapheresis may be useful in minimising the severe pain associated with hypertriglyceridaemic pancreatitis.

ASFA [1] conducted a literature review to evaluate the rationale for plasmapheresis in patients with hypertriglyceridemic pancreatitis. This review is consistent with the findings of studies by Chen *et al.* and Gubensek *et al.*, and reported no randomised controlled trial evaluating the effectiveness of plasmapheresis in these patients. Their search on PubMed yielded twelve case-series and 28 case reports, with sample sizes ranging from 100-300. The ASFA have given a Category III indication to the use of plasmapheresis in patients with hypertriglyceridemic pancreatitis, which implies that the optimum role of apheresis therapy in these patients is not established. ASFA highlight the role of clinicians in making individualised decisions due to the weak evidence in this area. [1]

There is clearly a need for stronger evidence to determine the effectiveness of plasmapheresis in patients with hypertriglyceridemic pancreatitis. However, the low incidence of this disease means that randomised controlled trials may not be feasible. Gubensek *et al.* [4] argue that it would be questionable to perform a randomised controlled trial, given the large reduction in triglyceride levels by plasmapheresis. The ethical issues and feasibility of performing a randomised controlled trial on a small sample are barriers in answering this question. Nevertheless, large cohort studies with sufficient follow-up and appropriate adjustments for population stratification should provide immense support either in favour or against the use of plasmapheresis. Furthermore, appropriate studies assessing the effectiveness of rapidly lowering triglyceride levels on patient outcomes should be conducted.

Conclusion

There is insufficient evidence to confirm that plasmapheresis is a beneficial treatment option for patients with acute pancreatitis secondary to hypertriglyceridemia. Current literature shows that plasmapheresis promotes a rapid reduction in triglyceride levels of 46-80% [1], however its effect on patient outcomes remains unclear. Adequately powered prospective studies with long term follow-up are recommended to elucidate whether plasmapheresis is associated with reduced morbidity and mortality in this population.

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Conflict of interest

None declared.

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Examining the pathological nature of Hepatitis C and current drug therapies used in an Australian general practice context

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Aim: This review aims to examine the pathological nature of Hepatitis C and review current drug therapies relevant to Australian health practitioners. **Methods:** Terms *hepatitis C, Australia, pathogenesis* and *current treatment* were searched using MEDLINE and CHINAL databases to identify research articles and systematic reviews. Constraints were used when researching drug developments to include only full-length papers, on humans published between 2009 and 2013. Literature was analysed to identify shared themes. Sixty-eight articles were analysed and fifty-two chosen based on relevance to objective, reputable data sources and current information. Two websites and five books were included upon cross referencing data to journal articles. Four Australian guideline publications were included due to relevance to topic and general practitioners. **Results:** The aetiology, clinical significance and molecular pathogenesis of hepatitis C virus were examined to provide Australian practitioners with a basis of knowledge for presentation of both acute and chronic stages of hepatitis C infection. This understanding was further linked to current drug treatments available in Australia and potential future therapeutic options. **Conclusion:** The consequences of Hepatitis C infections will burden the Australian healthcare system in the next few decades as the chronic nature of HCV infection leads to complications of liver failure, cirrhosis and hepatocellular carcinoma in many patients. Practitioners must equip themselves with knowledge of HCV pathogenesis which forms the basis of current and future treatments in order to provide best quality care at all levels of prevention and management.

Introduction

The recognition of viral hepatitis can be dated as far back as the fifth century BC to Babylonian records. [1] Our understanding of Hepatitis C gained remarkable ground when previously non-A non-B hepatitis infections were attributed to the hepatitis C virus discovered by Choo *et al.* in 1989. [1,2] Since then efforts have been made to develop drug treatments to combat the virus which progresses to chronic infection in up to 80% of patients, increasing their risk of cirrhosis, liver failure and hepatocellular carcinoma. [3,4,5] Chronic hepatitis C infection is currently the leading cause of liver transplantation in Australia. [6,7,8]

Hepatitis C is a major health concern for Australian practitioners with 260 000 Australians infected in 2010 and an estimated 12 000 new infections occurring annually. [4,7] The dominant mode of transmission of the hepatitis C virus (HCV) is parenteral exposure to infected blood and thus the epidemic of HCV infection in Australia continues to escalate predominantly through people who inject drugs (PWID). [7]

This review aims to summarise the aetiology, transmission and life cycle of HCV as well as examine the most recent literature regarding current and future drug therapies to provide the Australian general practitioner with a contemporary understanding in emerging hepatitis treatments.

Aetiology of Hepatitis C

Transmission in the Australian context

Hepatitis C is a blood-borne viral infection and is most commonly spread in Australia via shared injecting equipment (up to 80% acquiring the infection via this route). [7] Other means of transmission include unsterile tattooing, needle-stick injuries and vertical transmission



from mother-to-infants from trauma during pregnancy and/or birth. [9,10] About 5% of all cases in Australia arise from HCV contaminated blood transfusions and blood products prior to screening introduced in February 1990. [7]

Virological Structure

Hepatitis C is caused by a small, positive-stranded RNA virus of the *Flaviviridae* family. The RNA strand is enveloped by a protein capsid which is further surrounded by a lipid bilayer envelope studded with E1 and E2 heterodimer proteins. The genome contains a 5' noncoding region required for viral translation, followed by an open reading frame terminated by a 3' noncoding region necessary for replication. The open reading frame translates into a 3000 amino acid polyprotein which is cleaved into structural (core, E1, E2) and non-structural (p7, NS3, NS4A, NS4B, NS5A, and NS5B) proteins. [11-15]

The NS5B protein is a RNA-dependent RNA-polymerase which lacks proofreading function. This combined with a high replication rate (10^{12} virions/day) results in rapid mutations driving genetic diversity. [16] Thus within a host, HCV circulates as a population of extremely closely related, but not identical variants called quasispecies. [17] This feature has contributed to difficulty in developing a vaccine as well as implications for pharmacological therapies. HCV is classified into seven major genotypes which differ genetically by at least 30% with over 100 subtypes. [11,13] The prevalence of genotypes differ with geographical distribution. Genotype 1 mostly dominates Australia, the Americas, Japan and Europe with genotypes 2 and 3 also prevalent in these areas. Genotype 7 was only recently discovered in a small proportion of people in Central Africa. Disease association is largely similar across genotypes, however genotype 3 has been correlated with a higher risk of hepatic steatosis and progressive liver disease. [13,18]

Life Cycle

The main stages of the HCV replication cycle are binding and entry, uncoating, translation and replication of RNA, assembly into new particles, maturation and secretion. [11,19] Several host factors have been identified aiding entry of HCV including heparan sulphate and low-density lipoprotein receptor. Other host factors CD81, scavenger receptor B1 and tight junction proteins claudin-1 and occludin allow for clathrin-dependent endocytosis which delivers the virus to early endosomes, which become acidified causing fusion of the viral envelope, uncoating and release of the viral RNA into the cytoplasm. [12,19] HCV replication induces a membranous web concentrating

lipid-rich structures that aid the replication process. Hepatocyte-specific microRNA-122 has been shown to bind to target sites on the 5' untranslated region of the HCV genome which forms a complex that protects the HCV genome from nucleolytic degeneration and innate host immune responses. [20] Lipid droplets interact with the core and NS5A viral proteins allowing viral assembly. The newly synthesised viral proteins can then exit the cell in a manner similar to the hosts' very low-density lipoprotein (VLDL) export pathway by utilising cofactor ApoB and microsomal triglyceride transfer protein to form low-density viral particles termed lipo-viral particles. [11,12,18] ApoE is involved in HCV particle morphogenesis and infectivity. HCV particles exist in the serum as a mixture of complete low-density infectious lipo-viral particles and an excess of apoB-associated empty non-infectious particles complexed with anti-HCV envelope antibodies. [18]

The mechanism responsible for onset and progression of chronic hepatitis are not fully understood but it is currently believed that HCV establishes persistent infection by impairing host innate and adaptive immunity. [1,21] The infected hepatocytes recognise Pathogen Associated Molecular Patterns (PAMPs) through receptors known as Pattern Recognition Receptors (PRRs) which include Toll like receptors (TLRs) and RIG-1 like receptors (RLRs). Upon sensing HCV via TLR3 and RIG-1, intracellular signalling cascades result in the induction of type I and type III interferon and pro-inflammatory cytokines which establish an antiviral state in infected and neighbouring cells. [21,22] Resident antigen presenting cells, such as dendritic cells residing in the liver migrate from infected tissue to lymph nodes where they prime T and B cell activation to induce adaptive immunity. [11]

Recent studies have established multiple routes whereby HCV impairs immune functioning so as to coexist and replicate in the host. [23] NS3/4A protease cleaves intracellular pathway protein TRIF and CARDIF to impair TLR3 and RIG-1 receptors. [11] Furthermore, the HCV enveloped particle is not detected by TLR-2 and TLR-4 which also contribute to antiviral states. HCV has been shown to up regulate MHC Class I molecules on infected hepatocytes which suppresses Natural Killer cell activity. [23] Finally generation of quasispecies carry mutations to evade B and T-cell recognition as well induce hypermutation in B cell receptors to lower affinity allowing the virus to escape immune surveillance. [11]

Clinical Implications

The World Health Organisation estimates 170 million people are infected with Hepatitis C globally. [1,24] Hepatitis C is thus the leading cause of chronic liver disease worldwide and is a growing burden on healthcare systems, including within Australia. [3,25] Infection is characterised by a wide range of clinical manifestations and propensity to develop into chronicity. Up to 80% of infected patients will develop a chronic infection. [1,3] Persistent infection and chronic hepatitis are the hallmarks of HCV infection with severity varying widely from asymptomatic chronic infection with normal liver function tests to severe cases leading to cirrhosis and hepatocellular carcinoma. [2,14]

Acute Hepatitis

Acute HCV infection is often asymptomatic due to a mild immune response and reversible cellular injury seen at the microscopic level. [9] Where symptoms occur they tend to be minimal involving jaundice and flu-like malaise. [5] Strong immune responses during the acute infection are associated with clearance of the virus however in the majority of cases milder initial infections lead to chronic viral persistence. [5,26]

Chronic Hepatitis

Cirrhosis develops in as many as 20% of chronic HCV patients and is associated with hepatocellular failure. Patients may present with portal hypertension manifested as splenomegaly, variceal bleeding or ascites. [9,26] Primary hepatocellular carcinoma is thought to result from the continual division of infected hepatocytes attempting to

regenerate in the presence of injury. [5] Once cirrhosis has established, patients have a 5% annual risk of developing hepatocellular carcinoma. [27] Extra-hepatic diseases such as mixed cryoglobulinemia and glomerulonephritis are also believed to be caused by HCV induced antibody complex depositions in small vessels causing vasculitis, however the pathogenesis of this is not fully understood providing an area for investigation in the future. [28,29]

Current drug therapies

Current standard of care treatment of HCV genotype 1 is triple therapy with pegylated interferon- α (cytokine), ribavirin (antiviral) and a direct acting antiviral (NS3/4A protease inhibitor) - either telaprevir or boceprevir. [2,8,30] The combination of pegylated interferon (PEG-IFN) and ribavirin remain the recommended treatment for HCV infection with genotypes 2, 3, 4, 5 and 6. [19] The aim of treatment is a sustained virological response (SVR), defined as the absence of detectable HCV RNA for 6 months after treatment cessation. [31] SVR is associated with crucial end points, particularly survival and protection from the complications of chronic hepatitis C such as cirrhosis and hepatocellular carcinoma. [19,30]

For reasons that remain elusive, interferon-based therapies result in a SVR of 80% in genotype 2 and 3 infections but only 45% in genotype 1 and 4 infections. [4,13] With the approval of boceprevir and telaprevir in 2011 by the US Food and Drug Administration, triple therapy has enabled the SVR to increase in patients with genotype 1 from 45% in 2010 to ~66% in 2011 and is expected to be >75% by 2014. [4,26]

The SVR is also influenced by a myriad of host factors such as ethnicity, gender, age and insulin resistance. [13,32] Furthermore, new biomarkers such as serum IP10 levels and genetic tests to determine polymorphisms in the gene encoding IFNL3 (formerly known as IL28B or IFN- λ 3) and recently discovered IFNL4 show strong value with respect to interferon-based therapy as predictors of treatment outcome. [1,13,30]

In Australia, hepatitis C treatment is available for all eligible patients over 18 years of age who have chronic HCV infection with compensated liver disease and are using effective forms of contraception. Treatment is subsidised by the government under the Highly Specialised Drugs (HSD) program, section 100 (\$100) of the *National Health Act 1953* (Cwlth). [8]

Pegylated Interferon- α

Interferons are naturally produced by immunological cells in response to tumour or infectious organism. They are glycoproteins with antiviral, anti-proliferative and immunomodulatory functions. [31]

Upon administration of IFN- α , the type I interferon binds to IFNAR-1 and IFNAR-2 receptors on cell surfaces initiating a complex intracellular signalling pathway resulting in activation of genes coding for proteins which inhibit intracellular viral replication. Proteins include RNA-dependant protein kinase (PKR) which inhibits RNA translation and oligoadenylate synthetase (OAS) which mediates RNA degradation. IFN- α also stimulates T_H1 cell production while reducing suppressor T_H2 cells as part of its immunomodulation. [31,33]

Pathogenesis of HCV occurs as a result of the virus' ability to prevent host cells from responding to natural levels of interferon. As previously discussed, HCV blocks TLR3 and RIG-1 receptors reducing type I IFN production. [5,11] Thus overwhelming host cells with high levels of injected IFN allow normal cellular mechanisms to control the virus. [5,13] Replacement of standard interferon with pegylated interferon (interferon- α conjugated to polyethylene glycol) improves pharmacokinetics and efficacy and has allowed its administration as a once weekly subcutaneous injection. [30]

Ribavirin

Unlike pegylated interferon- α , whose function was unravelled due to developments in cell culture models, the mechanism of action

of ribavirin against HCV is unknown. [33] Ribavirin was originally synthesised as a guanosine analogue that could inhibit viral polymerases by chain termination. The process by which this is thought to occur is when the polymerase incorporates the nucleotide but cannot add more after inserting the analogue, hence preventing viral replication and transcription. [5]

However there is much debate about the mechanism of ribavirin activity in chronic hepatitis C. Despite showing in vitro activity against some RNA and DNA molecules, studies conducted with ribavirin as a monotherapy against HCV reflect no effect on HCV RNA levels or improvement of hepatic histology following 12 months of therapy. [33] Yet analysis of the current literature shows multiple studies where combination therapy of IFN- α and ribavirin is significantly more effective than IFN- α alone. [34-36] Furthermore, the anti-HCV activity of ribavirin occurs at much lower doses than expected for the chain termination theory to occur. [5] This suggests other mechanisms of action are at work.

Greenblatt presents two possibilities. [5] One involves ribavirin as depleting the cell's reservoir of normal guanosine to interfere with viral RNA synthesis. Secondly she proposes a mutagenic theory in which ribavirin incorporation into viral genomes renders them functionless. [5] Other theories propose that ribavirin induces IFN-stimulated genes or may have immunomodulatory functions which like IFN- α , push patient cytokine profiles towards T_H1 types which are more effective against viral infections than type 2 Helper T cells. [13,31]

Telaprevir and Boceprevir

Telaprevir and boceprevir are first generation peptidomimetic, reversible inhibitors of NS3/4A protease. [30] The HCV NS3/4A serine protease is essential for viral replication by cleaving polyproteins into mature non-structural proteins. [13] Thus by inhibiting this protease, telaprevir and boceprevir are the first direct-acting antivirals (DAAs) approved for use against HCV genotype 1.

Despite both drugs having similar mechanisms of action and thus sharing most clinically relevant strengths and weaknesses, there are discrepancies between telaprevir-based regimens and boceprevir-based regimens. [1,30] These differences are in the timing and duration of combined therapy. Typically, telaprevir is given in triple therapy with PEG-IFN and ribavirin for the first 12 weeks of therapy, PEG-IFN and ribavirin are then continued for the remainder of treatment (either 24 or 48 weeks) without the protease inhibitor. Duration of treatment is dependent on virological response (response-guided therapy). Boceprevir, however is started 4 weeks after commencement with PEG-IFN and ribavirin and is continued for the remaining treatment duration of 28 or 48 weeks depending on response. [19] Telaprevir-based regimen is stopped in patients with a HCV RNA level greater than 1000 IU/ml at week 4 or 12 and all three drugs should be discontinued. For the boceprevir-based regimen, patients with HCV RNA levels greater than 100 IU/ml at week 12 should discontinue treatment. For both treatments, if HCV RNA is detectable at 24 weeks of therapy, all three drugs should be stopped. [19]

Side effects profile – pegylated interferon- α and ribavirin

These can be quite distressing and contribute to low tolerance and compliance in patients. The major effects of interferon include depression, constant flu-like symptoms, thrombocytopenia, leucopenia, thyroid dysfunction, retinopathy and alopecia. [25,37] Ribavirin is highly teratogenic and can lead to haemolytic anaemia and autoimmune disorders. [37]

Psychiatric status as well as full blood count, kidney and liver function tests should be monitored continuously throughout therapy. Furthermore, precautions should be taken with patients with depressive histories, thyroid dysfunctions, diabetes, autoimmune disorders and renal impairment. [38] Finally pregnancy in female patients or the partners of male patients must be avoided during treatment, and owing to the long half life of ribavirin, also 6 months

after cessation of treatment. [39]

Side effects profile – telaprevir and boceprevir

Although triple therapy is more efficacious in HCV genotype 1 infections, there are additional side effects compared to traditional dual therapy and thus management of hepatitis C patients has become more complex. Common side effects of telaprevir include rash and anorectal discomfort while dysgeusia (altered taste sensation) and neutropaenia are associated with boceprevir. The most challenging side effect of both drugs is marked anaemia (haemoglobin level < 10 g per decilitre) occurring in 36-50% of patients. [19,30] Erythrocyte-stimulating agents have some success in managing this complication however are not approved for routine use in chronic hepatitis C patients due to serious side effects and cost. Some studies have shown that reduction in the dose of ribavirin can effectively manage anaemia in this setting and this is the current recommended first line approach. [19]

Due to the highly variable nature of HCV with the error-prone RNA polymerase, drug resistance is also an issue with these protease inhibitors and can develop as early as day 4 upon use in monotherapy. Consequently, these drugs are not to be used in isolation. Because of the similar mechanism of action, resistance to one protease inhibitor can result in other drugs within the same class to be ineffective. Once the drug is stopped, the frequency of resistance-associated variants within the quasispecies slowly decreases until they disappear, most likely because they do not replicate as effectively as the wild-type virus. [19,30] General practitioners can play a crucial role in patient education to ensure adherence to the prescribed regimen in order to limit the development of resistance-associated variants.

The third major consideration with these new drugs is the issue of drug-drug interactions. Both telaprevir and boceprevir are inhibitors of the cytochrome P450 3A (CYP3A). CYP3A enzymes are involved in the metabolism of numerous drugs such as statins, antidepressants, antiarrhythmics, anticonvulsants, analgesics and sedatives. [19] As such, these are all contraindicated in patients undergoing treatment with telaprevir and boceprevir. This has important implications for general practitioners who are frontline prescribers of such agents. Efforts are being made to make such complex information widely available to the medical community through platforms such as the 'Hepatitis Drug Interactions' website from the University of Liverpool, UK. [30,40]

The future of hepatitis C

With the exponential increase in knowledge of life cycle and replication of HCV due to breakthroughs in cell culture systems in 2005, there is fierce competition to develop medicines that will replace PEG-IFN, ribavirin and first generation protease inhibitors. [30] About two-thirds of agents in Phase II and III trials are directed against the NS3/4A and NS5B viral proteins called second generation protease inhibitors and polymerase inhibitors respectively. [19,30] The current challenges in drug development are decreasing side effects and drug interactions, exploring combinations for genotypes 2-6, exploring individualised drugs to specific genetic polymorphisms, and eradicating the need for interferon and ribavirin in treatment.

A number of drugs are currently being developed for genotypes 2-6. A preliminary phase 2a study in New Zealand involved combining sofosbuvir, an oral nucleotide inhibitor of HCV polymerase, and ribavirin in various interferon and interferon-sparing regimens for 12 weeks. [41] Patients with HCV genotype 1, 2 and 3 were investigated. In this early trial sofosbuvir showed a promising result with 100% rate of SVR among patients with genotype 2 or 3 infection. [19,26,41] However phase 3 studies of sofosbuvir fall short of the results produced by the phase 2a study. [42,43,44] One noninferiority trial looked at sofosbuvir plus ribavirin compared to standard peginterferon alfa-2a plus ribavirin in 499 patients with HCV genotype 2 or 3 infection. The results revealed the same SVR rate of 67% in both the sofosbuvir-ribavirin and peginterferon-ribavirin group at 12 weeks after cessation

of therapy. [43] Two further phase 3 trials (POSITRON and FUSION studies) investigated sofosbuvir-ribavirin therapy in patients for whom peginterferon treatment was not an option (due to pre-existing psychiatric or autoimmune disorders) and in those who did not have a response to previous interferon treatment. The POSITRON trial was a randomized, blinded, placebo-controlled study that compared 12 weeks of sofosbuvir-ribavirin treatment with matching placebo in patients who had previously discontinued interferon therapy due to adverse events or concurrent medical condition. In this group, 78% had a SVR at 12 weeks after treatment compared to 0% in the placebo group. [42] The FUSION study looked at patients who had failed a sustained response to interferon-based therapy and compared 12 and 16 week regimens of sofosbuvir-ribavirin therapy. Results showed that four additional weeks of therapy made a difference with an increase in the SVR from 86% to 94% in patients with genotype 2 infection and from 30% to 63% in genotype 3 infections. [42,44] All three phase 3 studies with sofosbuvir-ribavirin showed better SVR rates in genotype 2 infections compared to genotype 3 infections. [42,43,44]

Nonstructural 5A (NS5A) protein is also a target of recent drug development. [45] The functions of the NS5A protein are not yet fully understood with in vitro studies suggesting it has a role in viral replication and assembly and release of infectious particles. [45] Daclatasvir is a potent NS5A inhibitor which has shown early promising results for use in interferon-free combinations with rapid decline of extracellular HCV titres upon administration. [45] In a phase 2a trial, patients who had not had a response to previous therapy received daclatasvir and a protease inhibitor (asunaprevir) for 24 weeks. [46] Four out of eleven patients had a SVR at 12 and 24 weeks after treatment ended, suggesting a cure may be possible with an all-oral interferon-ribavirin free treatment. [45,46]

Another group of host targeting antiviral agents are arising. Miravirsin is a drug undergoing development which targets miR-122. Liver specific miR-122, as discussed previously is a microRNA which all strains of HCV use to survive and replicate in liver cells. [11,12] A recent phase 2a study by Janssen et al, dose-dependent reductions in HCV RNA levels were found without viral resistance. [20] The study was limited by a small sample of 36 patients and only moderate levels HCV RNA reduction which rebounded once miravirsin was stopped in patients who had not begun interferon and ribavirin. [20,47] Normally miR-122 is involved in controlling cholesterol levels independent of its effect on HCV. In the study, there was a sustained decrease of serum cholesterol levels by ~25% which lasted 14 weeks after the final injection. [47] Given statins are contraindicated in the current triple therapy treatment of HCV genotype 1 infections, there is potential in the future to develop liver-targeting nucleic acid drugs which can be used intermittently for both HCV treatment and other co-morbid conditions.

Furthermore, the future of HCV treatment is trending towards highly individualised regimens which consider not only the viral genotypes but also the patient's genetic polymorphisms. For instance, easy-to-treat patients have been identified as treatment-naïve, IL28B CC. [30] Patients with a favourable interleukin-28B genotype (CC variant as opposed to CT or TT) have shown sustained virologic responses up to 80%. [19] It is theorised that these patients could receive PEG-IFN and ribavirin first, minimising the adverse effects of triple therapy. [19] Although testing for the IL28B genotype is not currently the approved standard of care, in the future Australian general practitioners may be managing care of these 'easy-to-treat' patients while more complex cases, such as patients with IL28B TT with decompensated cirrhosis are managed at tertiary centres using a cocktail of tailor made drug regimens. [30]

Implications for Australian health practitioners

Accessing and treating hepatitis C infection in PWID – the role of the general practitioner

Advances made in the development of better tolerated interferon

free HCV treatment will remain negligible as long as access to therapy cannot be expanded to the most affected and underserved risk groups. [48,49,50] People who inject drugs act as a virus reservoir, as the burden of HCV-related liver disease in this group is increasing but treatment uptake remains low. [49,50] There are a number of barriers to accessing care at the level of the patient, practitioner and system. [48,50,51] New guidelines have been published with recommendations for the management of HCV infection among PWID which aim to overcome these barriers by providing evidence-based treatment recommendations. [50] Analysis of the literature revealed a common theme supported by high quality evidence which was the use of multidisciplinary care teams in enhancing treatment uptake in PWID. [49,50] General practitioners can play a crucial role in co-ordinating multidisciplinary care between specialists, drug and alcohol support services, psychiatric services, social work and other social supports such as peer-based groups. [49] In an Australian community-based study, hepatitis C positive patients who had seen a general practitioner about HCV in the last 6 months were four times more likely to be assessed for therapy by a specialist. [50] Furthermore, a prospective cohort study using telehealth technology in supporting and training GPs was compared to HCV treatment provided at a tertiary centre. Similar rates of treatment success were achieved in both groups. [49,51] From these studies, it was seen that general practitioners not only co-ordinated care but provided a more patient-centred approach necessary in dealing with the complex psychiatric and substance abuse co-morbidities which required individualised models of care. Enhanced personal contact provides an ideal environment for pre-therapeutic assessment of housing, education, cultural and social issues, supports, finances, nutrition, drug and alcohol use and psychiatric evaluation. [50] Merging different disciplines into one general practice model may be a simple and effective model in the future for a sub-population of PWID with HCV but will require commitment by motivated and

Table 1. Hepatitis C and the role of the General Practitioner. [8,26,50,52].

Primary Measures
History – ask about risk factors. People who have never been tested before and:
<ul style="list-style-type: none"> • Ever injected drugs • Ever been in a correctional facility • Received a blood transfusion in Australia prior to 1990 • Received blood products overseas • Born in a country of high prevalence of hepatitis C • Mother with hepatitis C • Ever had a tattoo or body piercing • Multiple sexual partners • Partner with hepatitis C • Needle stick injury
Investigations
<ul style="list-style-type: none"> • Test blood for HCV-specific antibodies and HCV RNA • Full blood count, liver function tests and thyroid function • Screen for HBV and HIV co-infection in patients with risk factors
Counsel patients with detectable levels of HCV RNA to eliminate transmission-prone practices
Counsel patients and partners with regards to effective contraception forms prior to initiating treatment
Secondary Measures
Vaccinate for hepatitis A and B virus
Education and support to reduce / eliminate drug and alcohol use
Education regarding safe injecting and needle sharing practices
Treat with antivirals – referral to liver clinic
Management and continued follow up of adverse effects
Surveillance of drug interactions
Long term follow up and multidisciplinary care in conjunction with liver clinic

supported GPs who have undergone further training in addiction and HCV medicine. [49]

The role of general practitioners in assessment and management of HCV infection

As stated previously, hepatitis C may be present in patients unknowingly for decades before symptoms of liver failure prompt a seeking of treatment. At this stage of irreversible cellular damage, treatment options are limited, often associated with distressing side effects and yield less efficient results in certain genotypes. The onus is on health practitioners, armed with an understanding of the pathogenesis of HCV, to identify high risk patients and test for anti-HCV antibodies and HCV RNA levels as a secondary preventative strategy to provide early detection and referral. There are a number of useful international guidelines which can assist general practitioners in managing newly diagnosed hepatitis C patients in regards to indications for treatment as well as first-line treatment recommendations. [3,24] Furthermore, primary prevention strategies whereby educating the public about transmission, symptoms and progression of the disease can be effectively implemented in a consultation setting.

In regards to treating chronic hepatitis C patients, this review aims to equip the general practitioner with an up-to-date understanding of the molecular and immunological aspects of HCV pathogenesis to aid in diagnostic tools as well as provide a platform of knowledge for future

pharmaceuticals. We are entering an exciting new era of hepatitis C treatment where interferon-free therapies are likely to dominate the therapeutic landscape within the next 5 years [19] and so an understanding of their mechanism of action in hepatitis C is crucial for continuing treatment and management.

Conclusion

From the ancient observations to the discovery of hepatitis C virus 24 years ago, up until recent advances in cell model systems, our understanding of the pathological nature of hepatitis C has grown exponentially. With this growth have come parallel developments in treatment, both in understanding mechanisms behind current drug therapies but also providing a platform for future pharmaceuticals to target aspects of HCV pathogenicity. These developments come at a timely point, as the burden of an escalating epidemic of hepatitis C in Australia will have major impacts on our healthcare system within the next few decades as the chronic nature of the disease will come into play.

Conflict of interest

None declared.

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Oncolytic Virotherapy: The avant-garde approach to oncological treatment via infectious agents

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Kok-Ho's interest lies in infectious diseases and oncology; in particular, the use of microbial therapeutics in cancer treatment. Kok-Ho's primary motivation in medicine is to find a novel therapy for cancers with poor prognosis so that cancer patients who are incurable now may potentially have a new lease of life in the near future.

Over the past twenty years, advances in translational medicine have resulted in new and exciting treatments in the area of oncology. New modalities have arisen out of the need to address existing limitations in conventional treatments such as chemotherapy and radiotherapy. What started out as an outrageous idea in the 20th century to use potentially dangerous infectious agents such as viruses to kill cancer cells has gradually evolved into a maturing field, which has the promising potential to incorporate conventional and immunological aspects of treatment within a microbial-based system. Finally, in 2006, the introduction of the world's first approved oncolytic virus by China heralded a milestone in the clinical application of this approach. This article will examine use of oncolytic viruses in cancer treatment with emphasis on its current status and strategies, possible immune mechanism and future considerations.

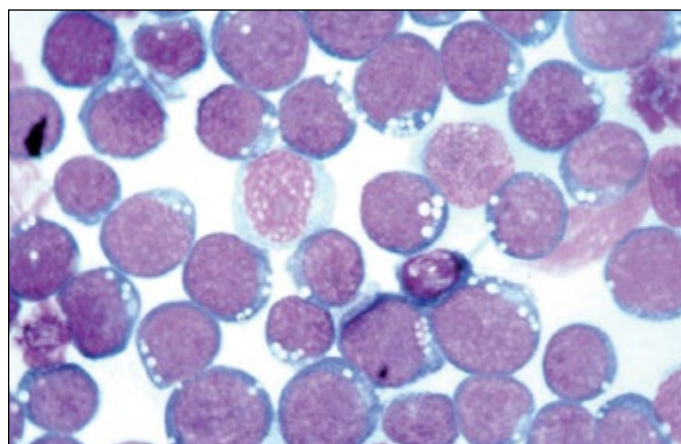
Introduction

Oncolytic viruses are self-replicating viruses which can target and lyse cancer cells specifically. [1] Since the early 1900s, it was recognised that natural viral infections in cancer patients are sometimes associated with tumour regression. Indeed, case reports noted instances where influenza or measles infections in leukemia patients resulted in remissions. [2] Interest in utilising these 'cancer-killing' viruses peaked in the 1950-60s but the rise of chemotherapy and radiotherapy meant that progress in this field stagnated until the 1990s, when genetic engineering and better understanding of viruses and tumours revived the development of oncolytic viruses. [3] A breakthrough in the clinical translation of oncolytic viruses finally came in 2006 with the world's first approved oncolytic virus- H101 (a genetically modified adenovirus) for head and neck cancers. [4]

Why oncolytic virotherapy?

Conventional treatments such as chemotherapy and radiotherapy have been the cornerstone of oncological management for many years. While we have achieved a considerable amount of success in many cancers, there are often criticisms against conventional treatments in terms of their limitations (e.g. transient effects against metastasis) and flaws (e.g. poor toxicity profile). [5] In recent years, gene therapy and immunotherapy have emerged as alternatives but results have been mixed. In 2002, the development of leukaemia in x-linked severe combined immunodeficiency (X-SCID) patients due to insertional mutagenesis has severely affected public confidence in gene therapy. [6] While immunotherapy remains promising, the current emphasis on specific targeting neglects the ability of tumour cells to mutate and change antigen profiles, resulting in variable clinical outcomes. [7]

In view of these insufficiencies, there has been renewed interest in oncolytic virotherapy, an interesting cross-disciplinary approach to treatment based virology, genetic engineering and immunology. The initial thinking behind this approach was simple- certain viruses exhibit tropism for cancer cells, which either express specific receptors for viral entry or lack anti-viral mechanisms that are normally intact in normal cells. [8] Once viral entry is achieved, replication of viruses continues until cell lysis occurs; allowing their progeny to infect other cancer cells. If viral spread is homogenous, the oncolytic effect can be



amplified many times and this effectively destroys the whole tumour. [8] As therapeutic genes encoding pro-apoptotic and immune effectors can be incorporated into the viral genome, an effective anti-tumour response may be initiated and magnified with each replication. [9] The ingenuity of this idea is that it exploits the infectious nature of viruses and uses it as a carrier and amplifier of other therapeutic agents. The latter may be crucial in exploiting synergistic anti-tumour effects between distinct treatment modalities.

Current status of oncolytic virotherapy

A variety of natural occurring and genetically modified viruses have been tested in clinical trials (Table 1).

Table 1. Summary of major oncolytic viruses in clinical trials.

Naturally occurring oncolytic viruses	Genetically-modified oncolytic viruses
Vesicular stomatitis virus (VSV)	Adenovirus (Ad)
Reovirus	Herpes simplex virus (HSV)
Newcastle Disease virus (NDV)	Vaccinia virus (VV)
Myxoma virus	Measles virus

Natural occurring oncolytic viruses are chosen for their low pathogenicity and inherent specificity for tumour cells. [10] Conversely, genetically modified viruses are those that are modified to promote tumour specificity, for example through use of tumour-specific promoters and gene deletions, or reduce pathogenicity by serial passage through cell culture. [8] Based on clinical data, it has been shown that virotherapy has a favourable toxicity and safety profile as compared to conventional treatment; the most common side effects being fever, flu-like symptoms and safety issues mainly concerning viral shedding and mutation-induced pathogenesis. [1,11] For the latter, dosing limitations and use of pro-drug activating suicide genes have addressed many of these issues. [1,6]

A straightforward dose-response relationship is not often observed as viral replication occurs in a heterogeneous tumour microenvironment and depends on factors such as availability of cell surface receptors

and anti-viral responses. [12] Efficacy varies between different viruses but is reasonable at this early stage of development. The clinical trial for H101 reported complete remissions and partial responses in three and eleven out of forty-six patients respectively while another modified adenovirus- ONYX-15 was also used in head and neck cancer trials and achieved tumour growth stabilisation in eight out of twenty-two patients and tumour necrosis in five out of twenty-two patients. [11,13]

It appears that limitations in efficacy were due to certain barriers. Firstly, viruses are not adept at surviving in the circulation. They are subjected to neutralising antibodies, complement and sequestration by the reticuloendothelial system. [8] In some cases, previous viral exposure may result in pre-existing anti-viral antibodies. For example, almost all individuals have antibodies to measles while reovirus infections are prevalent in about half the population. [14,15] Potent anti-viral responses such as type 1 interferons (IFNs) may also inhibit viral replication within the tumour. [8] Secondly, viruses have to endure acidotic and hypoxic conditions, transverse necrotic tumour regions and areas of poor vasculature in order to survive and infect tumour cells. [1] Thereafter, the availability of cell receptors may become a limiting factor in viral entry. [8] These obstacles are expected as viruses are foreign but this does not mean they are unsuitable therapeutic agents. On the contrary, viruses have the advantage of alerting the immune system to attack their infected target(s).

Enhancing oncolytic virotherapy via protective strategies

Protective strategies are aimed at improving delivery of viruses and avoiding viral clearance. The systemic delivery of viruses can be improved by preventing uptake of viruses by liver Kupffer cells (specialised macrophage cells). In mouse studies, viral delivery can be enhanced by clodronate-containing liposomes. [1] Clodronate is a selective macrophage-depleting agent that can temporarily inhibit viral uptake by Kupffer cells, thereby allowing more virus particles to reach the tumour site. [1] Recent interest is focused on cell-carrier based delivery of oncolytic viruses, which aims to protect viruses from systemic and intra-tumoural barriers by packaging within a cell carrier that supports viral replication and targets tumour cells, its microenvironment or the tissue/organ in which the tumour resides. [16]

Cell-carriers targeting tumour cells include tumour-infiltrating lymphocytes (TILs) and cytokine-induced killer (CIK) cells. [16] TILs are T cells which accumulate in tumours and possess T cell receptors (TCRs) that recognise tumour-associated antigens (TAAs) in the context of major histocompatibility complex (MHC). [17] Since TILs are inherently cytotoxic to T cells, using such a carrier synergistically enhances the anti-tumour effects of oncolytic viruses. Highly-specific TAAs are rare and use of less-specific TAAs may lead to non-specific targeting of normal cells. [18] Production of TILs against TAAs is also an expensive and tedious process, which argues against its widespread clinical application. [16] Conversely, although cytotoxic lymphocytes like CIKs have a lower tumour-specificity, these cells are non-MHC dependent and can proliferate *ex vivo* without antigen stimulation. [18] Thorne *et al.* injected vaccinia virus-containing CIKs into nude mice and found that the VV/CIK combination was able to accurately target tumour cells and also improved the survival rate of mice as compared to VV administration alone. [19] To improve specificity, Yoon *et al.* engineered Her-2/neu expressing CIKs which can target ovarian cancer cells in nude mice with high affinity. Results suggest that this approach was more effective in killing cancer cells than administering Herceptin alone. [20] Nonetheless, mechanisms underlying the tumour-specificity of CIKs remain unclear and should be studied further.

In comparison, cell carriers targeting the tumour microenvironment have well-studied. Examples include mesenchymal stem cells (MSCs) and tumour-associated macrophages (TAMs). [18] MSCs are often attracted by inflammatory chemokines expressed in the microenvironment while TAMs tend to accumulate in hypoxic areas

and regions of chronic inflammation in the tumour. [16] Mader *et al.* reported that in mouse studies, intra-peritoneal injection of a measles virus-MSC combination can prolong the survival period of mice with ovarian cancer. [21] Similarly, a clinical study found that intravenous injection of autologous MSCs carrying the modified adenovirus-ICOVIR 5 into four children with metastatic neuroblastoma was found to induce a complete clinical response in one child who also achieved complete remission within 3 years. [22] However, as MSCs are potentially tumourigenic, there is a trade-off between exploiting its propensity for tumour accumulation and the risk of enhancing tumour growth. The main criticism against targeting the tumour microenvironment relates to the inability of these cell carriers to deliver viruses directly into tumour cells. However, modifying the microenvironment through the engineering of viruses containing genes encoding pro-apoptotic and pro-inflammatory cytokines may circumvent this limitation by disrupting tumour-promoting interactions between the microenvironment and cancer cells. [16] Furthermore, the administration of proteases such as relaxin to degrade the extracellular matrix or fusogenic membrane glycoproteins to promote cell-to-cell fusion before oncolytic therapy may facilitate intratumoural spread of viruses. [23,34]

Lastly, the targeting of tumour-associated tissues and organs is also achieved by carriers such as dendritic cells (DCs) and peripheral blood lymphocytes (PBLs). [18] These carriers are attractive because they circulate through lymphoid organs such as the lymph nodes and spleen, which are sites of micrometastases and T-cell priming. [16] DC or PBL mediated delivery of VSV and reoviruses have been shown to purge metastases in lymphoid organs. Qiao *et al.* found that a VSV/PBL combination partially purged B16 metastases in mice 2-3 days after administration. [25] The oncolysis of metastatic cells by VSV also primed anti-tumour T cell responses effectively and probably contributed to fast purging. [16] Targeting of tissues/organs is the least specific but this negates the requirement for highly-specific tumour markers. In addition, the circulatory paths of these cell carriers are well-characterised, allowing better prediction of their tumour trafficking patterns. [18]

The mechanisms of viral loading, amplification and transfer are equally important in enhancing cell-carrier based strategies. Willmon *et al.* suggested that the loading of viruses depends on the multiplicity of infection (MOI), which is the ratio of infectious agent to infection target (i.e. cell carrier). [16] In high MOI loading, a higher viral loading density may be achieved but many viral particles will be stuck to the cell's external surface and become susceptible to neutralising antibodies. [26] Conversely, in low MOI loading, most viral particles will be internalised although the viral loading density may be lower. [26] This approach may help avoid neutralisation and is suitable for individuals who have pre-existing antibodies against the oncolytic virus (e.g. measles and reovirus).

The carrier's ability to support viral replication determines the amount of virus delivered. As viral replication can be affected by intact IFN responses in normal cells and also requires synchronous timing with carrier bursting, tumour cells have been implicated as possible carriers. [27] A successful example has been shown in the use of VSV-infected carcinoma cells to target lung metastases in mice but safety issues concerning the tumourigenicity of tumour cell-based carriers remain. [28]

The transfer of virus from cell carrier to tumour cells is crucial as exposed viral particles are susceptible to neutralisation. In some viruses such as human immunodeficiency virus (HIV), viral spread is mediated by a virological synapse (a specialised form of immunological synapse) between TCRs on T cells and MHC on adjacent cells. [29] By identifying viruses which utilises a virological synapse, oncolytic viruses can transfer safely between cells.

Besides cell-carrier based strategies, immunosuppression has been considered as a means of inhibiting anti-viral immunity. In rat glioma

models, cyclophosphamide and cyclosporin A (CPA) have been shown to enhance HSV-mediated oncolysis by inhibiting tumour-mediated phagocyte infiltration. [30] However, recent studies suggest that such agents can be immunostimulatory and there is increasing recognition that anti-viral immunity also contribute to effective anti-tumour responses; implying that immune mechanisms of oncolytic virotherapy may need to be examined further. [31]

Immune mechanisms of oncolytic virotherapy

The direct oncolytic effects of oncolytic virotherapy are well appreciated. Successful infection and efficient spread of oncolytic viruses determine the extent of tumour lysis; leading to emphasis on developing viruses that replicated robustly and extensively. [31] However, the lack of a straightforward dose-response relationship suggests that other oncolytic mechanisms are present. The immune system may play paradoxical roles in enhancing or impeding anti-tumour responses mediated by oncolytic viruses. [32]

Innate immune responses have been shown to inhibit viral replication in rat glioma models as indicated by rapid decrease in HSV/VV titers with concomitant increase in natural killer (NK) cell infiltration following oncolytic virotherapy. [30,33] However, viral-mediated recruitment of NK cells is advantageous as NK cells are cytotoxic and associated with tumour regression. NK cells and DCs are also involved in reciprocal interactions. [31] In vitro experiments involving Mel888 melanoma cell lines showed that reovirus-infected DCs induced IFN- β production, which in turn activated NK cells. [34] Activation of NK cells resulted in cytotoxic effects against Mel888 cells and reciprocal maturation of DCs. [34] As DCs are involved in antigen presentation to T cells, DC maturation may also promote adaptive anti-tumour responses. However, DC functions are virus-dependent as studies showed that wild-type measles and adenoviruses are inhibitory and neutral respectively. [31] It appears that the timing of viral clearance is crucial and prolonging this therapeutic window by immunosuppression may be beneficial. This is because some immunosuppressive agents may suppress anti-viral responses while stimulating anti-tumour responses. For example, similar to HSV, rat glioma studies indicate that CPA may promote VV replication while inducing a cytokine storm, which enhances activity of tumour-associated cytotoxic lymphocytes. [35]

Adaptive anti-tumour responses may be shaped by two models of immune activation: the infectious non-self (INS) and 'danger' models. [31] The former refers to the provision of pathogen-associated molecular patterns (PAMPs) such as viral nucleic acids to pattern-recognition receptors (e.g. toll-like receptors) on antigen-presenting cells (APCs) while the latter refers to the release of endogenous 'danger' signals such as TAAs to APCs. [31] In the INS model, the presence of viral PAMPs induces activation and proliferation of antibodies and T cells upon antigen presentation. Infection of tumour cells is therefore not a pre-requisite for anti-tumour responses, which may instead be due to bystander effects of anti-viral responses. This was illustrated by Breitbach *et al.* in a murine colorectal cancer model whereby administration of HSV and VV infected only a small number of cancer cells but triggered massive destruction of non-infected cancer cells. [36] Conversely, the 'danger' model is more in line with oncolysis of tumour cells. Greiner *et al.* showed that an attenuated VV was capable of lysing human melanoma cells with subsequent development of an anti-TAA response. [37] These two models are not mutually exclusive, suggesting that the actual anti-tumour effect may be mediated by both, with their relative contributions dependent on the immunogenicity of the oncolytic virus or the tumour. [31] It is therefore apparent from an immunological perspective that effective oncolytic virotherapy may capitalise on the use of highly immunogenic viruses in a bystander effect or alternatively, promoting efficient anti-TAA responses via engineering of TAA-expressing viral vectors in poorly immunogenic viruses. [31,38]

The mechanisms involved in oncolytic virotherapy are summarised in Figure 1.

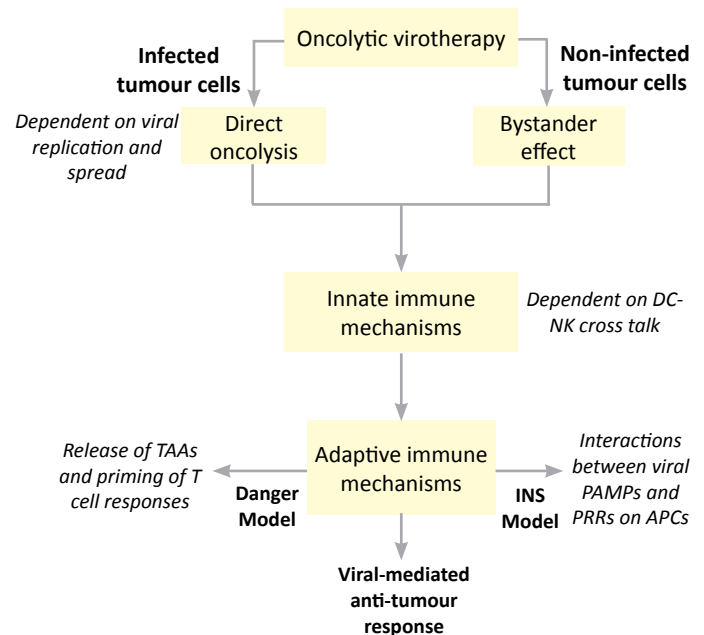


Figure 1. Anti-tumour effects of oncolytic virotherapy. Oncolytic virotherapy results in direct and bystander effects depending on infection state. Direct oncolysis requires efficient viral replication and spread while bystander effects are not infection-dependent. Innate immune mechanisms are mediated via cross-talk between DCs and NK cells. Depending on the danger or INS model, release of TAAs or viral PAMP-PRR interactions may contribute to the viral-mediated anti-tumour response differentially.

Future work

The current development of oncolytic virotherapy is based on rational designing but this approach may not always lead to the most selective and potent viruses. Buazon and Hermiston suggested that directed evolution might help researchers identify viruses with these desired characteristics. This involves growing diverse viruses in conditions that enhance diversity and passing them through conditions mimicking the tumour microenvironment. [39] Application of directed evolution to colon cancer cell lines resulted in the adenovirus ColoAd1, which was 2-3 logs more potent than the advanced ONYX-15 and also had a therapeutic window 3-4 logs greater than the standard Ad5. [4,40] Furthermore, ColoAd1 is more sensitive to the anti-viral cidofovir (CDV) than either of its parents (Ad11p and Ad3) and this was due to directed evolution. [41] Thus, such an approach has a promising safety profile.

Integrating oncolytic virotherapy with existing treatments must be considered. Current studies have indicated promising results with radiotherapy and chemotherapy. A combination of modified HSV and radiotherapy have shown additive cell-killing effects in colorectal cancer assays and increased tumour regression in human glioma xenograft models. [42,43] It was suggested that radiotherapy could have improved viral replication and spread through irradiation-induced cellular changes. Similarly, pre-clinical studies have indicated that combination of ONYX-15 with cisplatin and 5-fluorouracil in oesophageal cancers had a 39% increase in response rate as compared to chemotherapy alone (79% versus 40%). [44] Although both radiotherapy and chemotherapy are immunosuppressive to some extent, synergistic effects can be achieved by selecting the right virus and radiation/drug dosage. Combination of immunotherapy and virotherapy is at an early stage but success has been seen with VSV therapy combined with IL-2 and regulatory T cell (Treg) depletion in terms of enhanced NK cell activity and increased viral delivery. [45]

In the short term, the conflict between intra-tumoural and intravenous/intra-peritoneal administration of oncolytic viruses needs to be resolved. Mastrangelo *et al.* showed that intra-tumoural injection of a GM-CSF-modified VV was able to induce regression in distant non-injected metastatic sites in melanoma patients but systemic effects were absent in intra-tumoural injections of ONYX-15 or reovirus. [46]

Intravenous administration of the latter viruses was efficacious but resulted in thrombocytopenia and transaminitis respectively. [47] Therefore, when deciding the route of administration, a clear clinical endpoint must be established (targeting primary tumour or metastatic sites) and this will guide the type of virus used and effects (beneficial and detrimental) observed, and eventually how the patient is managed.

To conclude, oncolytic virotherapy has its antecedent in early observations and experiments detailing viral-mediated tumour regressions. Despite being neglected for decades, its resurgence reflects a current trend towards exploring new oncological treatments

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and a genuine hope that it can deliver better clinical outcomes. Encouraging early results and the increasing availability of solutions to its problems suggest that it is well-poised to be the avant-garde of next-generation cancer therapeutics.

Conflict of interest

None declared.

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Sugammadex – the solution to our relaxant problems?

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Sugammadex is the first of a class of selective relaxant binding agents. It acts by binding with high affinity to steroidal non-depolarising neuromuscular blockade drugs terminating neuromuscular blockade (NMB) through 1:1 encapsulation. Reversal of NMB has traditionally been performed by acetylcholinesterase inhibitors however these drugs have their drawbacks and are therefore not ideal. This review examines the indications and advantages of sugammadex as well as the potential risks and shortcomings associated with its use. Sugammadex is a relatively new drug that has been shown to be efficacious with an improved side effect profile as compared to its alternatives however several factors associated with its use have yet to be determined. These shortcomings have relevance on a therapeutic level as well as on a health economics level.

Introduction

NMB has been an important development in anaesthetic practice improving operative scenarios through patient paralysis. Muscle relaxation facilitates endotracheal intubation, ensures patient immobility and improves conditions for laparoscopic abdominal surgery. [1] Broadly speaking, the two classes of agents used are the depolarising NMB agents, of which there is only one in use, and the non-depolarising NMB agents. One of the significant problems with the non-depolarising NMB agents is their propensity to cause post operative residual blockade. This side effect of the drug has both patient safety implications and economic implications. The perfect solution to post operative residual blockade is absolute reversal of a non-depolarising NMB agent. This is routinely performed by cholinesterase inhibitors. These drugs however are less than perfect, as will be discussed and come with their own side effects. [11] A relatively new drug that has appeared on the market is sugammadex, a selective reversal agent that is considered far superior. Given the recent arrival of sugammadex to the market, its use is yet to be perfected and its risks are yet to be fully understood. Furthermore it is a very costly drug raising questions regarding cost effectiveness. This review article will look at the extent to which sugammadex is the solution to the problems associated with muscle relaxant in anaesthesia.

Method

The study was performed through review of existing literature on sugammadex and its use. Searches were performed using Ovid MEDLINE and the Cochrane Database of Systematic Reviews using the following terms: sugammadex, rocuronium, pancuronium, neostigmine, vecuronium, neuromuscular block, neuromuscular blockade, post operative residual block, post operative residual curarisation, post operative residual paralysis and economic assessment. Titles and abstracts were read and assessed for relevance to the paper. Bibliographies of the identified articles were hand searched to find additional relevant studies. Searches were limited to: humans and the years 2000 to current.

Results

The Ovid MEDLINE search identified 1832 articles. Of these, 15 articles were identified as pertinent to this review. The Cochrane Database of Systematic Reviews identified one systematic review. A remaining six articles were identified from bibliographies. Therefore, a total of 21 articles were included in the final analysis.



Discussion

Neuromuscular Blockade

Neuromuscular blocking agents are used on certain patients undergoing anaesthesia in addition to an anaesthetic agent and an analgesic agent. The drugs have significant risks. They pose the hazard of post-operative residual blockade which will be discussed. They are also the most common cause of anaphylaxis during anaesthesia accounting for between 60% and 70% of cases. The most commonly offending agents are rocuronium and suxamethonium. [5]

Neuromuscular blocking agents aim to totally paralyse the surgical patient by creating a blockade at the neuromuscular junction. This is not a therapeutic intervention but is rather used to facilitate endotracheal intubation, to eliminate spontaneous ventilation and to provide abdominal muscle relaxation for laparoscopic surgery. [4]

There are two classes of neuromuscular blocking drugs; depolarising agents and non-depolarising agents. Depolarising agents work by binding to nicotinic receptors causing depolarisation. They are not metabolised by acetylcholinesterase unlike acetylcholine thus prolonged activation of the receptor is produced causing paralysis. The only clinically approved depolarising agent is suxamethonium, a very short acting non-reversible drug. [22]

The other class is the non-depolarising agents. These are competitive antagonists that bind to post-synaptic nicotinic receptors preventing access and depolarisation by acetylcholine. [22] There are numerous agents under this class, notably pancuronium, rocuronium, vecuronium and mivacurium. These drugs are categorised by their length of action; pancuronium is long acting, rocuronium and vecuronium are intermediate acting and mivacurium is short acting. They are used in different scenarios depending upon procedural requirements.

Rocuronium

Rocuronium is a commonly given non-depolarising neuromuscular blocking agent and is the primary target agent of sugammadex. It has a quick onset of action of 1-2 minutes and if given in high doses can mimic the rapid onset of suxamethonium. This is useful when considering rapid sequence induction for Caesarean section. If given in such high doses however its duration of action is lengthened behaving in a manner similar to pancuronium increasing the risk of postoperative residual blockade. It has a good side effect profile and has a 30 to 50% quicker recovery rate than pancuronium. [2,4] The problem with non-

depolarising NMBDs is the risk of postoperative residual curarisation or residual NMB and the significant but small risk of anaphylaxis.

Post-operative residual neuromuscular blockade

Post-operative residual NMB presents a very real risk to surgical patients. It is a potentially reversible condition and should be avoided where possible. It has the potential to impair the integrity of an airway and can contribute to patient death. [6] Classic signs include airway obstruction, inadequate ventilation and hypoxia. Evidence suggests the incidence of adverse respiratory events is from 1.3 to 6.9% with one study suggesting the figure as high as 88% during the post anaesthetic care period. [7,8] The reason for such great variability in figures is in part due to the different definitions and methods of detection. In addition to patient risk, there is also evidence to suggest residual NMB has economic consequences contributing to operating theatre congestion and a bottleneck in patient flow. [9]

Postoperative residual blockade can be minimised through two strategies: 1) pharmacological reversal of NMBD effects and 2) optimisation of NMBD dosing through careful monitoring and titration of the relaxant. [11]

Neuromuscular Blockade Monitoring

Neuromuscular monitoring is routinely practiced, most commonly with train of four (TOF) ratios¹. Classically a TOF of <0.7 was the criteria for residual NMB. This, however, has been discredited by Murphy *et al.* (2009) with evidence suggesting a TOF <0.9 is required to ensure a recovery. [7] Despite increasing stringency of neuromuscular monitoring the methods are not sufficiently objective or accurate. Naguib *et al.* [10] found in their meta-analysis the difference in residual NMB between TOF monitored and non-monitored patients with intermediate acting NMB agents was not statistically significant ($P=0.314$); however, incidence was increased with long acting NMB agents as compared with intermediate NMB agents. [10] Further methods of NMB monitoring include tidal volume, vital capacity, sustained tetanus, head lift and hand grips however all are considered inferior to TOF. [2]

Neuromuscular Blockade Reversal Agents

The other strategy for the prevention of residual paralysis is the use of pharmacological measures. Kovac *et al.* (2009) postulated that

"An ideal NMB reversal agent would; (1) have rapid onset; (2) be 100% effective and predictable; (3) reverse any degree of NMB; (4) be effective in the presence of potent anaesthetics; and (5) have minimal or no side effects." [1]

Neostigmine

The common class of drug for NMB reversal agents are cholinesterase inhibitors, the most commonly used being neostigmine. [1,2] Cholinesterase inhibitors prevent the breakdown of acetylcholine in the neuromuscular junction, increasing neuromuscular transmission. [12] Neostigmine does not have a rapid onset, with the mean time to muscle recovery being 50.4 minutes. [16] The drug cannot reverse deep NMB with TOF<0.1. [13] The drug also has a ceiling dose and can only reverse drugs of certain potencies and of certain doses. [2] Duration of action is limited and consequently residual paralysis may still be evident or paralysis may reappear post administration. [3] The drug also has significant parasympathetic side effects due to excessive stimulation of muscarinic receptors. Side effects include bradycardia, arrhythmias, nausea, vomiting, increased GIT motility, bronchospasm and excessive secretions. To prevent these side effects, anticholinergic drugs are co-administered, notably glycopyrrolate or atropine, which have their own side effects, notably tachycardia, altered cardiac conduction, dysrhythmias and urinary retention. [1,12] In addition

¹ TOF ratio – a technique used to monitor neuromuscular blockade. Muscular twitches are induced at 2 Hz (ie. 0.5 seconds apart). The ratio between the 4th and 1st twitch as measured by an accelerometer is used to measure the depth of neuromuscular block. [13]

to the side effects, anticholinesterase drugs have further limitations including their lack of predictability and unreliability. [13]

As discussed, there are significant issues with residual NMB that are clinically underappreciated. The standard reversal agents that are routinely used are not without their drawbacks; their onset is slow, their side effect profile is significant and their efficacy is insufficient in particularly deep NMB. Furthermore, monitoring methods for residual blockade are inaccurate and technically difficult.

Sugammadex

Due to the limitations of the current class of NMB agents, sugammadex has become of interest. It is a modified cyclodextrin that has a high affinity with steroidal NMB agents (rocuronium>vecuronium>>pancuronium). [1,12] Cyclodextrins are oligosaccharides arranged in a circular shape surrounding a central cavity that can be used to bind molecules within the cavity, eliminating the target's pharmacological action. In the case of sugammadex, cyclodextrins are modified to have a rocuronium inclusion complex. It will bind to all non-depolarising NMB agents, although with a decreased affinity. [23]

One of the major benefits of sugammadex is that unlike the anticholinesterase inhibitors, it does not interfere with the receptor systems but rather acts on the NMB agent itself, meaning there are little to no muscarinic side effects. The drug binds to the respective NMB agent rendering it unavailable at the neuromuscular junction. [12] A high dose can be given if required without a high risk of cardiovascular effects, as with neostigmine. Furthermore it does not need to be given with a muscarinic agonist, unlike anticholinesterase agents, eliminating the potential for further adverse events.

The drug is currently approved for use in Australia and the European Union; however, it is yet to be approved by the FDA in the United States. In August 2008, a not-approvable letter was issued not due to lack of efficacy but rather due to the risk of hypersensitivity and allergic reactions that had not been adequately determined. Further studies are currently being performed by Schering-Plough. [1]

The efficacy of sugammadex is well established by several significant studies. It has been shown to be a very effective NMBD reversal agent of non-depolarising NMB. Puhlinger *et al.* (2010) reported an improvement in NMB reversal from rocuronium and vecuronium as compared with placebo, however these results represented trends and were not statistically significant. Mean rocuronium reversal times were 96.3 min with placebo and 1.5 min with sugammadex. Mean vecuronium reversal times were 79min and 3 min respectively. [20] One study by Lee *et al.* (2009) found that reversal of profound high dose rocuronium induced NMB with sugammadex reversal, and was substantially quicker than the use of the short acting suxamethonium. [18] Jones *et al.* (2008) found in a randomised comparison that sugammadex reverses profound rocuronium induced NMB significantly faster than that of neostigmine. [16] Alvarez-Gomez *et al.* (2007) made a similar finding in their study comparing the two drugs. [19] Sugammadex is also thought to halt relaxant induced anaphylaxis as it encircles the relaxant drugs theoretically preventing further immune reactions. However, this has not been sufficiently studied to confirm. [5] The drug has also been used successfully to reverse rocuronium induced NMB in a 'can't intubate can't ventilate' scenario. [21]

That being said there are adverse events as have been reported in 30 studies looking at 2000 patients. The most frequently reported side effects with an incidence greater than 2%, were hypotension, bronchospasm, QTc prolongation greater than 400msec, constipation, hyperactivity and altered taste sensation. Less common side effects included cough, dry mouth, temperature changes, parasthesia, parasomnia, mild erythema, abdominal discomfort, increased creatinine phosphokinase, bradycardia and dizziness. These adverse events did not appear to have a dose-response relationship. [1] While generally well tolerated, the adverse events one ought to be aware of are procedural pain, nausea and vomiting. [3]

Sugammadex can serve a purpose in rapid sequence induction. Traditionally, suxamethonium was used due to its quick speed of onset and short duration of action. However, this drug comes with a substantial list of side effects. [4] Instead, rocuronium can be given in high doses to quicken onset and can be quickly reversed at the close of the operation with sugammadex, although this is still considered second line.

The risks of residual NMB, as discussed previously, can be eliminated with the use of sugammadex. There are still some concerns for its regular use. Many studies have been conducted on the drug, looking at factors such as side effects and suitable dose ranges; however, more studies need to be conducted with larger cohorts to fully appreciate the risks. Patients with poorer health and who are more predisposed to adverse events have yet to be studied in great detail. [3]

While the cost of sugammadex is of no therapeutic relevance it needs to be taken into account from a health economics point of view. The cost is significant with a 200mg/2mL vial costing AUD188.90 and a 500mg/5mL vial costing AUD477.80 (cost sourced from FRED Dispense®, accessed 9th August 2013). It is not covered by the PBS and must be bought privately. Two systematic reviews have been performed in the UK on the cost benefit of sugammadex, both published in the British Journal of Anaesthesia. Both studies acknowledge that there could be cost benefit both from mortality and morbidity reduction point of views and with regards to optimisation of theatre time and post-anaesthetic care. However, the studies conclude that it would not be feasible to make an accurate economic assessment due to a lack of evidence. [14,15] It should be noted that these studies are UK relevant and apply differently to Australian practice. Zhang *et al.* (2008) found in their preliminary study of cost benefit that there is an appreciable decrease in postoperative time spent in an operating theatre improving cost efficiency; however, this failed to take into account the drug cost itself. Furthermore the study is applicable to the US health system and again may lack relevance to the Australian health system. [17]

The impetus for this paper came from an episode that occurred in theatre. A middle aged female due to receive a cholecystectomy was in an extremely anxious state before entering the operating theatre. She was convinced to go ahead with the procedure, which was uneventful. She was paralysed with rocuronium which was reversed with sugammadex. Upon reversal, the patient had a sudden severe reflexive episode going into a tonic-clonic contracture causing her jaw to occlude the endotracheal tube, in turn causing her oxygen saturation levels to fall. She had to be re-paralysed with suxamethonium to allow for manual respiration with bag and mask.

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An episode as described above is not an uncommon event and can occur during the emergence from anaesthesia; however the episodes are rarely so severe. It is very possible the sugammadex can be partly blamed for the reflexive episode, with a sudden return of muscle tone increasing afferent input through the muscle and tendon stretch receptors causing the biting. Because the standard reversal agents are not as effective as sugammadex, similar reflexive episodes that have taken place will have not had the severity seen here. The drug is still very new and anaesthetists are perhaps yet to fully understand its use. With experience such events will become increasingly rare through improved use.

It has been shown convincingly that sugammadex is a superior NMB reversal agent to the cholinesterase inhibitors in terms of efficacy, although it has a significant side effect profile. Despite the considerable research that has been performed on the benefits and risks of the drug's use, there are still many gaps in the literature which require further research.

There was no case report or evidence of similar cases to that in the clinical scenario discussed earlier. A case report of this incident may be of value. The patient's response may have been due to incorrect dosing or indeed a rare reaction that is yet to be clinically identified.

Conclusion

This paper examined the use of sugammadex and its role in anaesthetic, focussing both on the risks and benefits of use. Having studied the available literature, there is a clear therapeutic benefit in the reduction of postoperative residual NMB, a preventable event that poses significant risk to patients. It presents a superior alternative to the current first line anticholinesterase NMB reversal agents. The benefit of the drug from a health economics point of view is yet to be determined, having regard to its high cost. Furthermore, the potential adverse effects and hypersensitivity reactions have not been adequately studied. The true side effect profile may require a very long period of testing or long term routine use before there is a good understanding. Sugammadex does have a role in very specific anaesthetic scenarios, however, given its significant cost and gaps in the literature, it cannot be recommended suitable for routine use.

Conflict of interest

None declared.

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Factors that influence Australian medical graduates to become General Practitioners

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Karan is a third year medical student at James Cook University. He has been the recipient of the GPSN First Wave Scholarship which gave him the opportunity to explore his research interests. He hopes to become a rural generalist when he graduates and has an immense passion for research.

Aim: To determine the factors that influence Australian medical graduates to become general practitioners. **Method:** A literature review was conducted. Medline, PubMed and Cochrane Library were searched using the terms; "Australia", "medical", "graduates", "interns", "students", "choice", "specialty", "general", "practice", "factors" and "influencing". **Results:** The factors were grouped into intrinsic (age, gender, personality and skill set,) and extrinsic influences (lifestyle, income, stress, location and role models), with extrinsic influences regarded as the most influential. Most importantly, 72% of the Australian medical graduates viewed work culture as important, while 56% prioritised flexibility of working arrangements and hours of work. **Conclusion:** There are a variety of both intrinsic and extrinsic factors influencing medical graduates to choose General Practice over others. This can be seen as an opportunity for Australian workforce planners and policy makers to target the extrinsic factors with the aim of balancing the medical workforce to combat the shortage of rural general practitioners.



widely and include both qualitative and quantitative studies.

Results

The primary influential factors involved in the selection of a particular specialisation can be separated into intrinsic and extrinsic factors.

Intrinsic Factors

Intrinsic factors include age, personality and gender. Individuals have little or no control over such factors. [8]

Age is an intrinsic factor that plays a role in the selection of a particular specialty. The majority of medical students in Australian universities are under the age of 24. [9] Despite this, there has been an increase in the number of 'mature age' students over the past two decades. One Australian study, that compared the career choices of medical graduates, found that older students were more likely to specialise in a primary care field such as General Practice. [3]

An individuals' personal set of skills and the satisfaction they receive from using these skills are intrinsic factors which play a large role in influencing medical graduates to undertake General Practice. In 2005, Harris et al examined the factors influencing the choice of specialty of 4259 Australian medical graduates. [3] The study showed that 79% of graduates considered their own skills and aptitude to be of importance when selecting General Practice. Personal satisfaction was also linked to choosing General Practice as a specialty. Laurence and Elliot supported this in their 2007 study which concluded that personal satisfaction arises from procedural skills, activities involved and patient contact. [4] All of the 54 Pre-Registration Junior Medical Officers (PMJOs) interviewed in South Australia, agreed with this however, this was only a small sample size.

Gender has been shown by studies to be a vital influencing factor for Australian medical graduates when choosing General Practice as a specialty. Whilst the responsibilities of raising children have evolved over the past few decades, Prideaux *et al* found that Australian female medical graduates are more likely to become specialists in General Practice due to child bearing responsibilities and family commitments. [10] It has been noted the Australian literature that female doctors tend to work shorter hours and have a preference for working shorter hours due to family commitments. [11] Despite this, there has been a rise in male doctors choosing to work fewer hours due to family reasons. [10] This reflects the fact that both partners now commonly work.

Introduction

In the field of medicine, a specialty is simply a specific study of medical science. [1] Dermatology, Obstetrics and Gynaecology, Cardiology, Neurosurgery and General Practice are just a few of the vast array of medical specialties that medical graduates must decide between before embarking on a long, strenuous but nevertheless, highly rewarding journey. Students endure four to six years of medical school, only to begin a new journey as junior doctors. Internship is followed by residency, and the pathway after this depends upon the choice of specialty. [2] Medical students and junior doctors are faced with the tough challenge of selecting a specialty. This review seeks to precisely identify the factors influencing medical graduates to undertake General Practice.

This narrative review aims to explore the intricate complexities that invade the mind of medical graduates faced with the dilemma of choosing a specialty; in particular, what influences them to choose General Practice. The aims of this literature review are to highlight the spectrum of factors that play a role in medical students and interns choosing to undertake General Practice, and present medical colleges, recruitment agencies, workforce planners and national organisations with a platform upon which they can correct the imbalances in the medical workforce.

Methodology

This literature review covered recent literature that has focused on the factors influencing choice of medical specialisation (in particular General Practice) in Australia. Medical and social science databases were searched for publications from 1990-2013. Medline, PubMed and Cochrane Library were searched using these terms; "Australia", "medical", "graduates", "interns", "students", "choice", "specialty", "general", "practice", "factors" and "influencing". 7670 papers were identified through the database searches. These were then reviewed to only include studies conducted in Australia and concerning Australian medical graduates, which narrowed it down to 25 papers. 9 of these papers were excluded because they were not completely relevant to the topic. In addition, the bibliographies of articles were searched for further relevant publications. Studies referred to in this review vary

Extrinsic Factors

Extrinsic factors include stress, work hours, family commitments, lifestyle and mentors. They are variables that may be controlled. [8]

Lifestyle plays the greatest role in influencing medical graduates to choose particular specialties over others. Laurence and Elliot found that 100% of the 54 South Australian PMJOs interviewed regarded lifestyle as a vital factor in choosing General Practice as a specialty. [4] This included hours worked, stress, career potential and potential for travel (55%). Most participants described their ideal job as having shorter working hours and less time on call. Most PMJOs also wanted a certain amount of control over hours and hence chose anaesthesia and GP practice. Wanting a life outside of medicine (85%) for example, spending more time with family and friends was also important. [4] Similarly, Harris et al also rated extrinsic factors as the most influential factors of choosing a medical specialty in Australia. [3] Seventy two percent of the Australian medical graduates viewed work culture as important, while 56% prioritised flexibility of working arrangements and hours of work. In contrast, Thomas concluded that only 28% of Australian medical graduates saw work life balance and lifestyle as important to selecting General Practice as their specialty. [7] However, this study had a small sample size and focused on only one specialty (General Practice).

Location is of importance when choosing a medical specialty. Stagg et al found that key influences on choosing a rural pathway specialty were mentors and undergraduate rural exposure. [6] In contrast, Ward et al, in a longitudinal study that followed 229 UWA medical graduates, showed that a rural background is the most important predictor of rural general practice. [5] Clearly, there factors that influence an individual to undergo a rural generalist pathway are multifactorial and more research is needed in this area.

The studies used in this literature review all stressed the importance of role models in influencing Australian medical graduates to choose particular specialties. Laurence and Elliot studied when, what and how SA pre-registration junior medical officers made their career choice. [4] Fifty four percent of the 54 graduates perceived the role of mentors, supervisors and consultants to be of importance in selecting General Practice as a specialty. Their interaction with 'mentors' was through observing and asking questions. Role models were seen to demonstrate specific characteristics admired by the students. [12]

Discussion

The results confirm that choosing General Practice as a specialty is a complex decision strongly influenced by personal qualities (intrinsic factors), individual experiences and opportunities (extrinsic factors), and domestic circumstances. Whilst parenting dynamics have changed over the last century, there is still a trend for females to choose General Practice over other specialties due to flexibility and option of part time employment, which may be helpful when choosing to start a family. [13]

The most important extrinsic factors include lifestyle, work experience since graduation, flexible hours, influence of mentors and hours of work. [3] In Australia, it was concluded that factors relating to lifestyle and job satisfaction were the most important influencing factor. [4] This is consistent with the belief that recent graduates regard lifestyle factors as more important than income. [14] The younger generation of graduates also prioritise potential for travel. These graduates are influenced by their experience of General Practice and confirm that work experience is helpful for developing knowledge within medical. [3]

The results also suggested that trainees in different specialties prioritised certain influencing factors over others. Surgical trainees viewed mentors and role models as more important than trainees in

other specialties. Additionally, General Practice trainees were more likely to prioritise flexibility, whilst this factor was of less importance to trainees in Adult Medicine. [15] Compounding this notion is the fact that surgical and emergency trainees found it extremely important to do procedural work compared to trainees in other programs. [3]

Clearly, there is not one single factor that influences an individual to undertake a particular career path, rather a vast array of factors. A medical graduate's choice of career is dependent upon a wide range of intrinsic and extrinsic factors. [3] Whilst there is not much chance of altering intrinsic factors, the nature of extrinsic factors allows for an interventionist approach. [16]

The main goal of medical workforce agencies and groups is to ensure a balance of doctors across a vast array of specialties to provide equal, effective and holistic medical care to the community. For 80% of doctors, the decision about choice of specialty has to be made by the end of the third postgraduate year (PGY3). [3] As such, training programs, teaching facilities and recruitment agencies involved in medical workforce planning should aim to educate medical students and graduates up until PGY3 and allow them to make an informed decision. Given the importance of extrinsic factors, there should be a review of the work culture typical of specialties that are under-represented. [13] Training providers can therefore implement strategies that attempt to increase entry to less well-represented specialties. [4]

This literature review has a number of limitations. Firstly, this review was limited to articles concerning the Australian medical workforce. This review excluded international medical graduates, which may have given greater insight into the factors influencing the specialty choice of graduates. A comparison study could be done in the future, comparing the mindset of Australian medical graduates to overseas graduates. Secondly, whilst certain conclusions can be made concerning the factors which influence choice of General Practice as a specialisation, this review did not focus on the factors that influence doctors to change specialties or even the percentage of medical students that graduate without having made a decision about their future career. Research on the factors influencing General Practice specialty choice could be improved by including a larger number of schools and students, studying trends over several years, and using validated measures and outcomes.

Conclusion

The main factors which were identified as influencing medical graduates to choose General Practice included both intrinsic and extrinsic factors. Additionally, a career choice that is made when an individual is young may not represent how they will feel as they progress through life and their priorities will often change. While there remains a continuous need for valuable research in the area of factors affecting medical specialisation, it appears that we need to use this information to prevent imbalances and skews in medical workforce planning. There is a great opportunity for governments, health authorities and the medical profession to influence extrinsic determinants of choice of specialty. [13]

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Conflict of interest

None declared.

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The impact of the nuclear crisis on global health

Dr. Helen Caldicott

Dr Helen Caldicott is an Australian physician and a leading anti-nuclear activist. She is a widely respected lecturer and authority on the topic, and played an integral role in the formation of the organisations Physicians for Social Responsibility and International Physicians for the Prevention of Nuclear War. The latter was awarded the Nobel Peace Prize in 1985. She has won numerous prizes for her efforts, such as the Humanist of the Year award from the American Humanist Association.

Due to my personal concerns regarding the ignorance of the world's media and politicians about radiation biology after the dreadful accident at Fukushima in Japan, I organized a 2 day symposium at the NY Academy of Medicine on March 11 and 12, 2013, titled 'The Medical and Ecological Consequences of Fukushima,' which was addressed by some of the world's leading scientists, epidemiologists, physicists and physicians who presented their latest data and findings on Fukushima. [1]

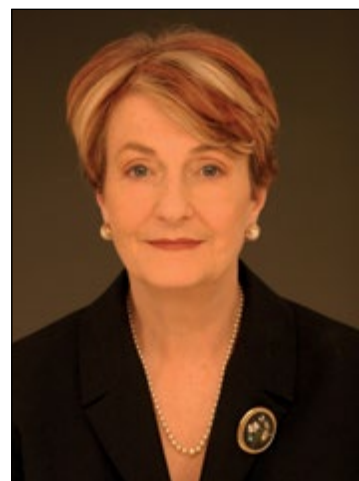
Background

The Great Eastern earthquake, measuring 9.0 on the Richter scale, and the ensuing massive tsunami on the east coast of Japan induced the meltdown of three nuclear reactors within several days. During the quake the external power supply was lost to the reactor complex and the pumps, which circulate up to one million gallons of water per minute to cool each reactor core, ceased to function. Emergency diesel generators situated below the plants kicked in but these were soon swamped by the tsunami. Without cooling, the radioactive cores in units 1, 2 and 3 began to melt within hours. Over the next few days, all three cores (each weighing more than 100 tonnes) melted their way through six inches of steel at the bottom of their reactor vessels and oozed their way onto the concrete floor of the containment buildings. At the same time the zirconium cladding covering thousands of uranium fuel rods reacted with water, creating hydrogen, which initiated hydrogen explosions in units 1, 2, 3 and 4.

Massive quantities of radiation escaped into the air and water - three times more noble gases (argon, xenon and krypton) than were released at Chernobyl, together with huge amounts of other volatile and non-volatile radioactive elements, including cesium, tritium, iodine, strontium, silver, plutonium, americium and rubidium. Eventually sea water was – and is still – utilized to cool the molten reactors.

Fukushima is now described as the greatest industrial accident in history.

The Japanese government was so concerned that they were considering plans to evacuate 35 million people from Tokyo, as other reactors including Fukushima Daiichi on the east coast were also at risk. Thousands of people fleeing from the smoldering reactors were not notified where the radioactive plumes were travelling, despite the fact that there was a system in place to track the plumes. As a result, people fled directly into regions with the highest radiation concentrations, where they were exposed to high levels of whole-body external gamma radiation being emitted by the radioactive elements, inhaling radioactive air and swallowing radioactive elements. [2] Unfortunately, inert potassium iodide was not supplied, which would have blocked the uptake of radioactive iodine by their thyroid glands, except in the town of Miharu. Prophylactic iodine was eventually distributed to the staff of Fukushima Medical University in the days after the accident, after extremely high levels of radioactive iodine – 1.9 million becquerels/kg were found in leafy vegetables near the University. [3] Iodine contamination was widespread in leafy vegetables and milk, whilst other isotopic contamination from substances such as caesium is widespread in vegetables, fruit, meat, milk, rice and tea in many



Source: www.helencaldicott.com

areas of Japan. [4]

The Fukushima meltdown disaster is not over and will never end. The radioactive fallout which remains toxic for hundreds to thousands of years covers large swathes of Japan and will never be "cleaned up." It will contaminate food, humans and animals virtually forever. I predict that the three reactors which experienced total meltdowns will never be disassembled or decommissioned. TEPCO (Tokyo Electric Power Company) - says it will take at least 30 to 40 years and the International Atomic Energy Agency predicts at least 40 years before they can make any progress because of the extremely high levels of radiation at these damaged reactors.

This accident is enormous in its medical implications. It will induce an epidemic of cancer as people inhale the radioactive elements, eat radioactive food and drink radioactive beverages. In 1986, a single meltdown and explosion at Chernobyl covered 40% of the European land mass with radioactive elements. Already, according to a 2009 report published by the New York Academy of Sciences, over one million people have already perished as a direct result of this catastrophe. This is just the tip of the iceberg, because large parts of Europe and the food grown there will remain radioactive for hundreds of years. [5]

Medical Implications of Radiation

Fact number one

No dose of radiation is safe. Each dose received by the body is cumulative and adds to the risk of developing malignancy or genetic disease.

Fact number two

Children are ten to twenty times more vulnerable to the carcinogenic effects of radiation than adults. Females tend to be more sensitive compared to males, whilst fetuses and immuno-compromised patients are also extremely sensitive.

Fact number three

High doses of radiation received from a nuclear meltdown or from a nuclear weapon explosion can cause acute radiation sickness, with alopecia, severe nausea, diarrhea and thrombocytopenia. Reports of

such illnesses, particularly in children, appeared within the first few months after the Fukushima accident.

Fact number four

Ionizing radiation from radioactive elements and radiation emitted from X-ray machines and CT scanners can be carcinogenic. The latent period of carcinogenesis for leukemia is 5-10 years and solid cancers 15-80 years. It has been shown that all modes of cancer can be induced by radiation, as well as over 6000 genetic diseases now described in the medical literature.

But, as we increase the level of background radiation in our environment from medical procedures, X-ray scanning machines at airports, or radioactive materials continually escaping from nuclear reactors and nuclear waste dumps, we will inevitably increase the incidence of cancer as well as the incidence of genetic disease in future generations.

Types of ionizing radiation

1. X-rays are electromagnetic, and cause mutations the instant they pass through the body.
2. Similarly, gamma radiation is also electromagnetic, being emitted by radioactive materials generated in nuclear reactors and from some naturally occurring radioactive elements in the soil.
3. Alpha radiation is particulate and is composed of two protons and two neutrons emitted from uranium atoms and other dangerous elements generated in reactors (such as plutonium, americium, curium, einsteinium, etc - all which are known as alpha emitters and have an atomic weight greater than uranium). Alpha particles travel a very short distance in the human body. They cannot penetrate the layers of dead skin in the epidermis to damage living skin cells. But when these radioactive elements enter the lung, liver, bone or other organs, they transfer a large dose of radiation over a long period of time to a very small volume of cells. Most of these cells are killed; however, some on the edge of the radiation field remain viable to be mutated, and cancer may later develop. Alpha emitters are among the most carcinogenic materials known.
4. Beta radiation, like alpha radiation, is also particulate. It is a charged electron emitted from radioactive elements such as strontium 90, cesium 137 and iodine 131. The beta particle is light in mass, travels further than an alpha particle and is also mutagenic.
5. Neutron radiation is released during the fission process in a reactor or a bomb. Reactor 1 at Fukushima has been periodically emitting neutron radiation as sections of the molten core become intermittently critical. Neutrons are large radioactive particles that travel many kilometers, and they pass through everything including concrete and steel. There is no way to hide from them and they are extremely mutagenic.

So, let's describe just five of the radioactive elements that are continually being released into the air and water at Fukushima. Remember, though, there are over 200 such elements each with its own half-life, biological characteristic and pathway in the food chain and the human body. Most have never had their biological pathways examined. They are invisible, tasteless and odourless. When the cancer manifests it is impossible to determine its aetiology, but there is a large body of literature proving that radiation causes cancer, including the data from Hiroshima and Nagasaki.

1. Tritium is radioactive hydrogen H^3 and there is no way to separate tritium from contaminated water as it combines with oxygen to form H^3O . There is no material that can prevent the escape of tritium except gold, so all reactors continuously emit tritium into the air and cooling water as they operate. It concentrates in aquatic organisms, including algae, seaweed, crustaceans and



Iniencephaly as a result of radiation exposure (Photograph with permission from Dr Wladimir Wertelecki).

fish, and also in terrestrial food. Like all radioactive elements, it is tasteless, odorless and invisible, and will therefore inevitably be ingested in food, including seafood, for many decades. It passes unhindered through the skin if a person is immersed in fog containing tritiated water near a reactor, and also enters the body via inhalation and ingestion. It causes brain tumors, birth deformities and cancers of many organs.

2. Cesium 137 is a beta and gamma emitter with a half-life of 30 years. That means in 30 years only half of its radioactive energy has decayed, so it is detectable as a radioactive hazard for over 300 years. Cesium, like all radioactive elements, bio-concentrates at each level of the food chain. The human body stands atop the food chain. As an analogue of potassium, cesium becomes ubiquitous in all cells. It concentrates in the myocardium where it induces cardiac irregularities, and in the endocrine organs where it can cause diabetes, hypothyroidism and thyroid cancer. It can also induce brain cancer, rhabdomyosarcomas, ovarian or testicular cancer and genetic disease.
3. Strontium 90 is a high-energy beta emitter with a half-life of 28 years. As a calcium analogue, it is a bone-seeker. It concentrates in the food chain, specifically milk (including breast milk), and is laid down in bones and teeth in the human body. It can lead to carcinomas of the bone and leukaemia.
4. Radioactive iodine 131 is a beta and gamma emitter. It has a half-life of eight days and is hazardous for ten weeks. It bio-concentrates in the food chain, in vegetables and milk, then in the the human thyroid gland where it is a potent carcinogen, inducing thyroid disease and/or thyroid cancer. It is important to note that of 174,376 children under the age of 18 that have been examined by thyroid ultrasound in the Fukushima Prefecture, 12 have been definitively diagnosed with thyroid cancer and 15 more are suspected to have the disease. Almost 200,000 more children are yet to be examined. Of these 174,367 children, 43.2% have either thyroid cysts and/or nodules.

In Chernobyl, thyroid cancers were not diagnosed until four years post-accident. This early presentation indicates that these Japanese children almost certainly received a high dose of radioactive iodine. High doses of other radioactive elements released during the meltdowns were received by the exposed population so the rate of cancer is almost certain to rise.

5. Plutonium, one of the most deadly radioactive substances, is an alpha emitter. It is highly toxic, and one millionth of a gram will induce cancer if inhaled into the lung. As an iron analogue, it combines with transferrin. It causes liver cancer, bone cancer, leukemia, or multiple myeloma. It concentrates in the testicles and ovaries where it can induce testicular or ovarian cancer, or genetic diseases in future generations. It also crosses the placenta where it is teratogenic, like thalidomide. There are medical homes near Chernobyl full of grossly deformed children, the deformities

of which have never before been seen in the history of medicine.

The half-life of plutonium is 24,400 years, and thus it is radioactive for 250,000 years. It will induce cancers, congenital deformities, and genetic diseases for virtually the rest of time.

Plutonium is also fuel for atomic bombs. Five kilos is fuel for a weapon which would vaporize a city. Each reactor makes 250 kg of plutonium a year. It is postulated that less than one kilo of plutonium, if adequately distributed, could induce lung cancer in every person on earth.

Conclusion

In summary, the radioactive contamination and fallout from nuclear power plant accidents will have medical ramifications that will never cease, because the food will continue to concentrate the radioactive elements for hundreds to thousands of years. This will induce epidemics of cancer, leukemia and genetic disease. Already we are seeing such pathology and abnormalities in birds and insects, and because they reproduce very fast it is possible to observe disease caused by radiation over many generations within a relatively short space of time.

Pioneering research conducted by Dr Tim Mousseau, an evolutionary biologist, has demonstrated high rates of tumors, cataracts, genetic mutations, sterility and reduced brain size amongst birds in the exclusion zones of both Chernobyl and Fukushima. What happens to animals will happen to human beings. [7]

The Japanese government is desperately trying to "clean up" radioactive contamination. But in reality all that can be done is collect it, place it in containers and transfer it to another location. It cannot be made neutral and it cannot be prevented from spreading in the future. Some contractors have allowed their workers to empty radioactive debris, soil and leaves into streams and other illegal places.

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The main question becomes: Where can they place the contaminated material to be stored safely away from the environment for thousands of years? There is no safe place in Japan for this to happen, let alone to store thousands of tons of high level radioactive waste which rests precariously at the 54 Japanese nuclear reactors.

Last but not least, Australian uranium fuelled the Fukushima reactors. Australia exports uranium for use in nuclear power plants to 12 countries, including the US, Japan, France, Britain, Finland, Sweden, South Korea, China, Belgium, Spain, Canada and Taiwan. 270,000 metric tons of deadly radioactive waste exists in the world today, with 12,000 metric tons being added yearly. (Each reactor manufactures 30 tons per year and there are over 400 reactors globally.)

This high-level waste must be isolated from the environment for one million years – but no container lasts longer than 100 years. The isotopes will inevitably leak, contaminating the food chain, inducing epidemics of cancer, leukemia, congenital deformities and genetic diseases for the rest of time.

This, then, is the legacy we leave to future generations so that we can turn on our lights and computers or make nuclear weapons. It was Einstein who said "the splitting of the atom changed everything save man's mode of thinking, thus we drift towards unparalleled catastrophe."

The question now is: Have we, the human species, the ability to mature psychologically in time to avert these catastrophes, or, is it in fact, too late?

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Genomic medicine

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John joined the Garvan Institute as the Executive Director in January 2012. He has made a significant contribution to the understanding of genetics and genomics through his farsighted theories on 'junk' DNA, the large non-coding sections of the human genome that do not code for proteins. Most recently John was the Professor of Molecular Biology and NHMRC Australia Fellow at the Institute for Molecular Bioscience, University of Queensland. John was educated at St Patrick's College Strathfield, the University of Sydney and Monash University, where he obtained his PhD. He has subsequently worked at Baylor College of Medicine in Houston, the CSIRO Division of Molecular Biology in Sydney, and the University of Queensland, where he was based from 1988-2011. He has also spent research periods at the Universities of Cambridge, Oxford, Cologne and Strasbourg. He was Foundation Director of the Australian Genome Research Facility and the Institute for Molecular Bioscience.

The last decade has seen an extraordinary revolution in the technology of DNA sequencing. This has meant that the cost of sequencing a human genome has dropped from nearly a billion dollars in 2001, when the first draft of a human sequence was completed, to less than \$10,000 today (Figure 1). [1] We're now seeing the first prototypes of sequencing machines that promise the capacity to sequence a human genome in a few hours for less than \$1000.

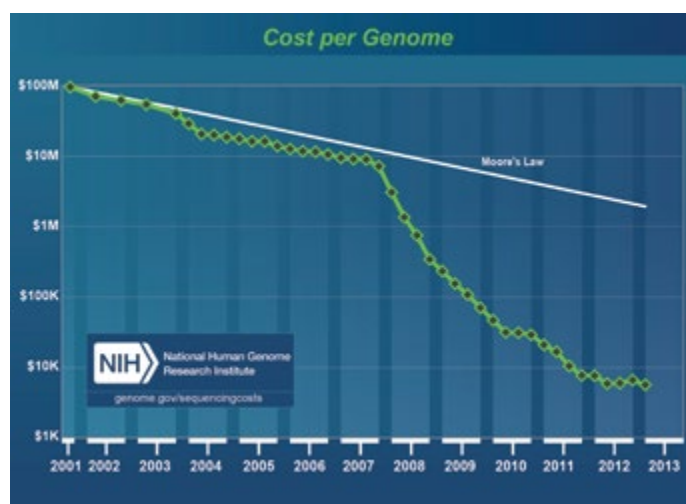


Figure 1. Cost per (human-sized) genome. Credit: NHGRI.

Even at current costs, this acceleration in sequencing has enabled a whole suite of studies into human variation at the genetic level. In the cancer arena, the international cancer genome projects—with which we've been involved—show that cancer is a heterogeneous disease. While there are differences in the distribution of mutations in cancers from different tissues, a surprisingly high percentage have mutations in common. [2] This is not obvious from the pathology and can, in many cases, productively inform treatment options and save lives. However, this is just the tip of an iceberg. There are large numbers of human genomics studies around the world producing an explosion of information about how individuals vary in physical and, to some extent, psychological characteristics. These studies are also identifying idiosyncrasies in our DNA that can leave us at risk for complex diseases.

Taking advantage of that information can be useful even at this early stage. In a recent *Cell* paper [3], the Chair of the Stanford University genetics department gave himself a battery of medical tests and analysed his own genome. By integrating this information, he was able to successfully identify his own type 2 diabetes and take steps to manage its impact.

Genomic stratification – to identify the underlying mutations in cancer – is quickly becoming the standard of care in cancer. Some of these mutations are considered 'actionable' because there are existing drugs that have been developed to treat the same mutations in other



tissue contexts. Others may predict outcomes in response to existing therapies.

Usage of partial or whole genome sequencing in diagnosing monogenic diseases is also moving quickly. While monogenic diseases, which have catastrophic mutations in protein-coding sequences, are usually individually rare, they collectively account for more than 1% of births in our population. Faster, cheaper sequencing provides the opportunity to analyse an individual's DNA sequences very quickly. As a result, there are an increasing number of examples in the literature where such information has transformed clinical treatment and the health of the individual.

The bottom line is that we are going through the most extraordinary exploration of human genetic programming and genetic diversity in history. This will have an enormous impact on medical practice. Eventually, everybody's genome will be sequenced and incorporated into their medical record. Clinicians and physicians of the future will be referring to this information as part of standard care for their patients, in conjunction with contextual information such as diet, economic and cultural circumstances.

Where many of the treatments that we traditionally use were pitched at the average of the population, it is now possible to personalise care. This begins with making judgments about people's drug responses and tuning those accordingly to get the best effective dose and avoiding side effects. It is expected to extend to assessing an individual's risk of complex diseases like diabetes, osteoporosis and stroke and helping them to take ameliorative behavioural, lifestyle, dietary or pharmaceutical strategies as appropriate to reduce those risks.

There is going to be an extraordinary cultural and operational transition from treatment to health optimisation. The challenge is to translate the literally millions of differences between individual whole genome sequences into simple, lucid, clinically-actionable information

that can be accessed at point of care. This means, I think, that in the background, we're going to see the development of national and international genotype-phenotype databases that will assemble and collate evidence-based information about how human genetic variation indicates disease risk and health futures.

Rather than suggest that this is a threatening development, I think this is a wonderful opportunity for young clinicians to empower medicine

through the integration of genomic information with other aspects of practice and care. This is an extraordinary time of technical, intellectual and conceptual change, which offers medical students the opportunity to embrace a career in research and to invest their futures with a major medical research institute. Genomic medicine will have as big an impact on health as antibiotics, and it will be your generation that takes this forward.

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A new paradigm for assessment of learning outcomes among Australian medical students: in the best interest of all medical students?

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This work was done while Professor Wilkinson held a National Senior Teaching Fellowship funded by the Office of Learning and Teaching, Department of Industry, Innovation, Science, Research and Technology, Australian Government.

Truism: a claim that is so obvious or self-evident as to be hardly worth mentioning, except as a reminder or as a rhetorical or literary device.

Assertion: a proposition that is repeatedly restated regardless of contradiction.

"Medical education in Australia is a world-class system, and produces doctors of the highest capability."

Truism or assertion? I suggest more assertion than truism. I ask you to consider: "how do we know if this statement is true?" How do you know how good you are; whether you have met the necessary learning outcomes from your medical program?

Introduction: the need for change

Most of us involved in medical education would agree that – broadly speaking, across the sector – what we do in Australian medical education is indeed world class. However, most of us would also say that we could always do better, and that we should always be trying to improve the system.

Despite having a rigorous accreditation system, developed and delivered by the Australian Medical Council (AMC), we do not have explicit measures – across the system – of the *outcomes* of the educational process at our medical schools. [1] This gap first became apparent to me when preparing my school for AMC accreditation a few years ago. We were asked to provide data on the *outcomes* of the education (including what our graduates had gone on to achieve) and I found this challenging. We did source some data from Royal Colleges that suggested our graduates performed at a similar level on College exams to other school's graduates, and we had some data on rural practice, but overall the picture is patchy. Does this gap in the outcomes data matter? I think it does – I suggest that this is in fact a major issue for the sector to consider, and I suggest that medical students need to engage with this issue. Luckily I believe we have a simple solution, and one that is within our grasp.

Some unanswered questions

As a medical dean, I wanted to know – in a quantitative and systematic way – how my students and my school perform. Specific questions I asked myself were:

1. How do my students and my school perform against a defined national or international standard?
2. How do my students and my school perform against other medical schools (nationally and globally)?
3. How can I gather this type of data and use it to improve the educational experiences of our students so that they become even better doctors?
4. How can I provide quantitative reassurance to my university, the profession and to society that we are doing what we can to fulfil our social responsibility, in terms of graduating competent doctors.

I was not, and am not, particularly interested in our performance in a ranking or league table sense.



Source: www.mq.edu.au

Current state of play

Currently in Australia each medical school designs and delivers its own examinations. There is some, but limited collaboration in the design, delivery, evaluation, and quality assurance of the exams in Australian medical schools. Certainly there is no externally focussed data or reporting that affirms the quality and outcomes of our medical degree programs. Firstly, we do not have a national standard against which to assess our students; we do have very clear AMC standards but they do not include examination against a defined set of national competencies. Nor do we have an explicit statement of what knowledge, which clinical skills, and which professional competencies, our graduates are expected to display. Although there are projects underway, some under the auspice of Medical Deans Australia and New Zealand (MDANZ), there is no explicit set of expectations.

Not a national licensing exam

I do *not* argue for a national licensing exam. [2] Indeed I argue against a national licensing exam. [3] And, the broad view of medical deans seems to be that a national exam would be very expensive, time-consuming and could risk undermining the flexibility and diversity that exists within Australian medical programs. Thus, although the USA and Canada, by way of example, have rigorous national licensing exams, medical deans in Australia are not keen to go this route. Many of us see suggesting a national licensing exam as being overly simplistic, a knee-jerk reaction, not necessary to fix the existing gaps, and potentially damaging.

So, what is it we really need? If we are to provide a level of quantitative reassurance to society, to the profession (in the form of the Medical Board of Australia, and the AMC, for example), to our universities and – very importantly – to our students, we do need a more collaborative approach to assessment of medical student competency, and we need some common exam questions, and hence some data that can be used to compare performance across students and schools.

Nothing new under the sun: collaborations already underway

This is not a new idea, and indeed there is an impressive collaboration of medical schools working within AMSAC (Australian Medical Schools

Assessment Collaboration) that has been doing this since 2009. [4] In 2012, 11 of the 19 medical schools in Australia (comprising 2492 students) took part in AMSAC. The “AMSAC exam” comprised 49 multiple choice questions in 2012, including 19 testing ‘structure’ and 30 testing ‘function’. Even with this relatively modest number of questions a substantial amount of high quality data can be generated that provides significant insight into the performance of the collaborating schools.

Other collaborations are in place across Australia, each with a slightly different focus. For example the ACCLaIM collaboration is focussing on the OSCE exam, developing common OSCE stations and common approaches to marking, among a group of schools. The IDEAL collaboration is a global network of schools that all contribute to a very large database of exam questions. Other “item banks” that have been used, and could be used, include the AMC items used in the examinations taken by international medical graduates.

In contrast to AMSAC, which focuses on assessment of the biomedical sciences around the midpoint of undergraduate medical training, the AMAC (Australian Medical Assessment Collaboration) group has its focus on testing knowledge and application of knowledge at the end of medical school training. Funded initially by the Australian Learning and Teaching Council [5] and now by the Office of Learning and Teaching with the Department of Industry, Innovation, Science, Research and Technology, AMAC now includes the majority of medical schools and has already piloted an ‘end of course common exam’. AMAC’s focus is on developing a strong collaborative culture among Australian medical schools, who will share a commitment to working together on assessment. Figure 1 shows one of the data outputs from AMAC, demonstrating how performance of the collaborating schools varied in the pilot trial. In the future I anticipate that some schools will choose to share a common exam, or part of an exam, while others will (at least initially) work within the group on identifying, developing and quality assuring individual items for the item bank.

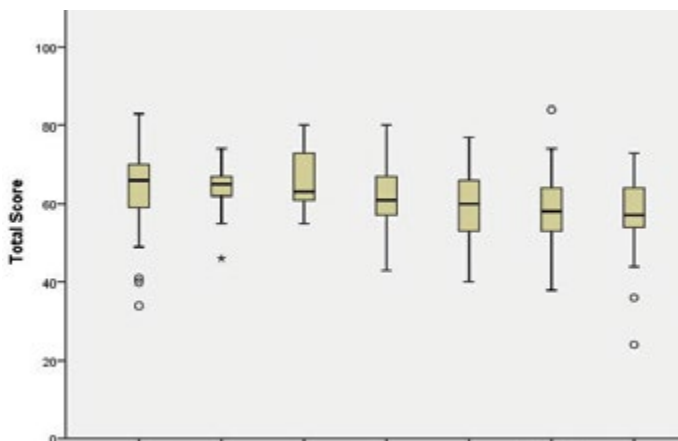


Figure 1. Distribution of AMAC pilot exam scores by school (2012). Overall a total of 513 students from eight medical schools in Australia and New Zealand participated in the AMAC pilot, with seven involved in the 2012 formal trial. The numbers of students representing each school ranged from 13 to 124. The box in the plots below are the interquartile range of the sample for each participating medical school. The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the line in the middle represents the 50th percentile (or the median). The whiskers (the lines that extend out the top and bottom of the box) represent the highest and lowest values that are not outliers or extreme values. Outliers (values that are between 1.5 and 3 times the interquartile range) are represented by a small circle and extreme values (values that are more than 3 times the interquartile range) are represented by an asterisk.

Strengthening our medical schools

It is vital to point out here that the underpinning philosophy is one of cooperation and collaboration. This is about schools working together to strengthen their own assessment capacity and capability, and to help others do the same. It is not at all about withdrawing

responsibility for assessment from schools, nor about undermining each school’s capacity to change its assessment practice. By making appropriate use of common exam questions, schools can measure and benchmark performance. These data can inform schools of areas of weakness and strength, and hence lead to curriculum development. I suggest this approach is actually an essential part of a broad quality assurance process that should underpin Australian medical education.

This is not about league tables – and such a counter-productive approach can easily be avoided by making comparisons between schools completely anonymous, which is the way that AMSAC functions (Figure 1).

Shall we go global?

In 2012, medical schools at The University of Queensland (UQ) and The University of Sydney, both delivered the International Foundations of Medicine (IFOM) Clinical Sciences Exam (CSE) to final year medical students, as a required formative assessment. A detailed report on the UQ experience has been submitted for publication. The IFOM CSE is a 160 question multiple-choice exam that tests knowledge and application of knowledge across most of the clinical disciplines. It is effectively an international version of United States Medical Licensing Exam (USMLE) and as such provides a “global standard” against which we can test ourselves. Now, let’s be careful about language here: I am not suggested that the USMLE is *the* global standard, but it is *a* global standard, and indeed the IFOM is being designed and developed to be *one* explicit global standard that students and schools can make use of (should they wish). Of course, good practice would have us formally blueprint any exam against our own curriculum, and this is not possible for the IFOM. The exam is produced by the National Board of Medical Examiners (NBME) [7] in the USA, under strict security constraints, and while a high level blueprinting is done by the international committee that oversees IFOM development, local level blueprinting is not possible. Further research and evaluation is needed to explore how important this is.

So, having delivered IFOM CSE once, we now have high quality data that shows how our medical students performed against one global standard, against the USMLE, and against our colleagues at The University of Sydney. All the information we have gathered is new, is insightful, and is stimulating a range of thoughtful conversations. Of course the data is not definitive, it is not a “magical, gold standard” but it is important data that is giving us important pause for thought.

Peering into the future

So, we are on a journey – a journey that I firmly believe is in the best interests of students, medical schools and all our stakeholders, most importantly your future patients. Just 2-3 years ago while several innovators were working on some of the collaborations described here, the importance of sector-wide change was not on the Deans’ agenda; now it is. What might it look like in the future?

The ideal scenario that would develop over the next few months and years is as follows:

- A formal, voluntary, collaboration between as many medical schools in Australia and New Zealand as possible, run under the auspice of MDANZ as the peak body representing these medical schools
- A formal, inclusive, governance structure would be in place, with appropriate representation of all members
- A proper business plan to support the collaboration would be developed and managed through the governance structure
- The outputs of the collaboration would be used by each medical school in a way that it sees fit, and the activities and outputs could include:
 - o Annual meeting on assessment practice and strategy

- o A common clinical sciences exam of 100-200 multiple choice questions, covering all core clinical sciences that schools that wish to use a common exam would take up
- o An item bank of MCQs and OSCE stations: schools might choose to use some common OSCE stations in their own clinical exams
- o A range of innovation projects to develop new assessment practices
- Analysis and statistical support would be provided to allow schools and students to understand how they are performing in comparison with a defined national or global standard

- Anonymous reports would be available to schools that provide benchmarking data, which could be used in accreditation reports to reassure the AMC, MBA, and society about learning outcomes.

Importantly, students need to be a part of this process. Medical students are deeply engaged in all aspects of medical education in Australia, and rightly so. Surely it is in the students' best interests to know that their schools are working to improve their educational experience, and their educational outcomes all the time?

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Case Report

A case of solid pericardial metastases causing constrictive pericarditis in a patient with non small cell lung cancer

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Final Year Medicine (Graduate)

Monash University

BSc (Molecular Biology and Genetics)

Joyce recently did her elective in oncology. She is interested in pursuing a career in women's health.

Ruwan Wijayaratna

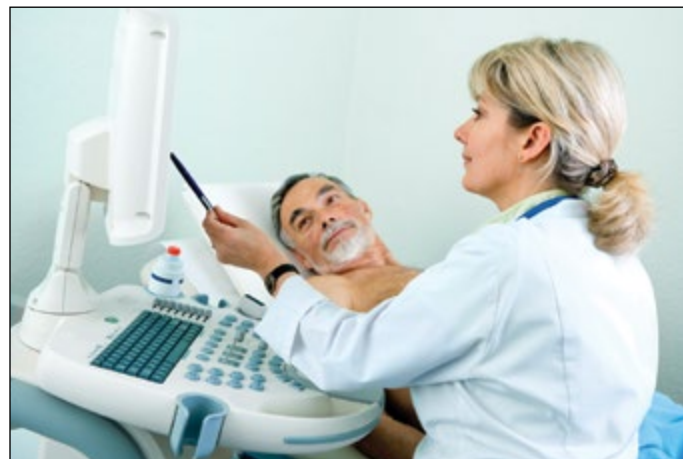
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Introduction: Cardiac metastases are rarely diagnosed in patients with cancer despite being a common finding at autopsy. We report on a case of pericardial metastases in a patient with non small cell lung cancer (NSCLC) in the setting of coexisting direct tumour invasion into the superior vena cava (SVC) and right atrium. **Case:** We present a case of a 61-year old gentleman with metastatic adenocarcinoma of the lung. He presented with 2 - 3 days of progressive dyspnoea associated with pre-syncope. His physical examination was significant for bilateral elevated jugular venous pressure (JVP), bilateral arm oedema and hypotension. These clinical signs were explained by solid pericardial metastases causing constrictive pericarditis in the absence of significant pericardial effusion, and direct invasion of tumour into the SVC and right atrium producing SVC obstruction. His admission was complicated by an episode of supraventricular tachycardia (SVT), presumably caused by compromise of the electrical conduction system within the right atrium. **Discussion:** Cardiac metastasis is a common occurrence in advanced neoplastic disease, but is often clinically silent. The mechanism of cardiac metastases is believed to be primarily through lymphatic channels and metastasis is most commonly located in the pericardium. Symptoms of cardiac metastasis can be understood with respect to their anatomical position and are best diagnosed using transoesophageal echocardiogram (TOE). The most concerning complication of metastasis to the heart is pericardial effusion leading to life-threatening cardiac tamponade. This is an oncological emergency and is treated with pericardiocentesis and follow up preventative measures. Ultimately, cardiac metastasis signals advanced disease and poor prognosis.



and was attenuating the SVC and compromising the right atrium. Metastases to the liver, the right sternoclavicular joint and the 4th, 9th and 10th ribs were also identified.

Pathology from the bronchoscopy biopsy demonstrated that the tumour was p63 negative and Thyroid Transcription Factor 1 (TTF-1) positive via immunohistochemical staining, consistent with adenocarcinoma of the lung. Epidermal Growth Factor Receptor (EGFR) screening was negative, hence the tumour was not sensitive to treatment to EGFR tyrosine kinase inhibitors. His management plan, following multidisciplinary team discussion, was radiotherapy to his chest and clavicle for pain management, and palliative chemotherapy (carboplatin/paclitaxel).

Three months post initial diagnosis, restaging CT of the chest, abdomen, pelvis and lumbar spine was organised after completion of radiotherapy and two cycles of chemotherapy. CT scans of the chest, abdomen and pelvis showed disease progression with new right adrenal metastases and new pericardial metastases (Figures 1 and 2). CT of his lumbar spine revealed disease in L1-2 and S1. In light of his latest CT results, radiotherapy to the lumbar spine and pericardium was planned.

Medications and Allergies

At time of admission the patient's medications included oxycodone/naloxone, omeprazole and dexamethasone. He was allergic to penicillin.

Inpatient Admission

The patient was admitted after worsening dyspnoea was noticed during radiotherapy to his lumbar spine. Initial physical examination revealed mild bilateral pitting oedema at the ankle and no other signs. His initial investigations included full blood examination (FBE), urea, electrolytes and creatinine (UEC), liver function tests (LFTs), and calcium, magnesium and phosphate (CMP). All were normal except for a decrease in haemoglobin (Hb: 83). A provisional diagnosis of anaemia secondary to chemotherapy or neoplastic disease was made based on

Introduction

Cardiac metastases occur in 20-30% of patients with non small cell lung cancer (NSCLC) [1] but are clinically silent in the majority of cases. [2] We report on a case of constrictive pericarditis caused by solid pericardial metastases concurrent with direct invasion of tumour into the superior vena cava (SVC) and right atrium. The clinical picture was complicated by SVC obstruction and right atrial compromise causing supraventricular tachycardia (SVT).

The case

The patient was a 61-year old store worker with a previous 60 pack-year smoking history. He was admitted with progressive dyspnoea over 2-3 days, associated with pre-syncope, on a background of metastatic NSCLC (T4N0M1b).

Past Medical History

The patient initially presented with a six month history of pain when abducting his right arm, which was associated with dyspnoea and a productive cough. A chest computed tomography (CT) identified a large right hilar lesion causing right middle lobe bronchus occlusion and collapse of the right lung. The tumour had invaded the mediastinum,

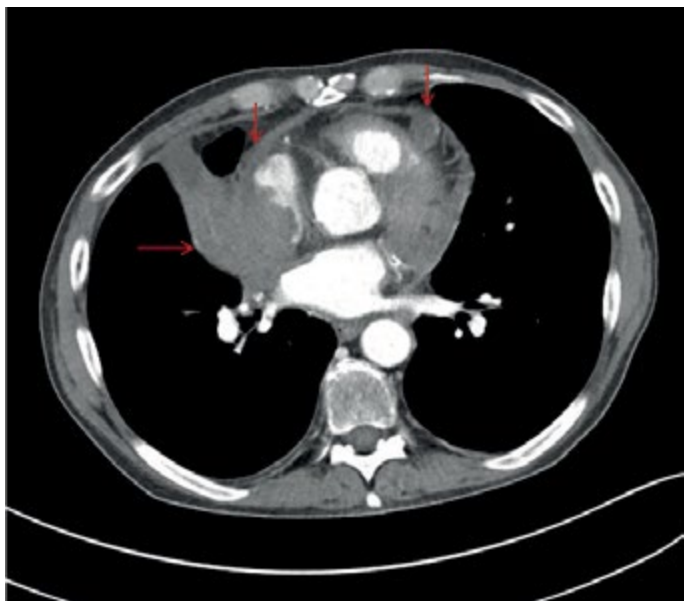


Figure 1. Axial view of CT chest showing, with arrows from left to right: a) solid pericardial metastasis measuring 17mm at its widest b) pericardial thickening and c) space occupying lesion in right atrium.



Figure 2. Coronal view of CT chest showing tumour compression of the SVC (red arrow).

his haemoglobin, and he was given two units of packed red blood cells.

The following morning, the patient's dyspnoea had not improved with transfusion. On examination, his jugular venous pressure (JVP) was elevated bilaterally at four centimetres, his arms were swollen bilaterally and his blood pressure (BP) was 95/55. He was not tachycardic. An urgent electrocardiogram (ECG) and transthoracic echocardiogram (TOE) was performed to exclude cardiac tamponade. ECG was normal and a pericardial effusion, though noted on TOE, was trivial and deemed insufficient to cause cardiac tamponade. However, the echocardiogram demonstrated pericardial metastases overlying the left and right ventricular apex as well as the lateral left ventricular wall and inferior right ventricular wall. Significant echocardiography findings consistent with constrictive pericarditis included abnormal septal motion with marked septal bounce, annulus reversus on tissue Doppler, and left diastolic dysfunction with shortened deceleration time.

On day three of his admission, the patient had an episode of supraventricular tachycardia. His tachycardia was asymptomatic and he was treated conservatively with fluid hydration. Fluid resuscitation was unsuccessful and he remained tachycardic and hypotensive. Amiodarone 200mg was delivered and his heart rate and BP normalised gradually over eight hours. Electrolyte replacement was also initiated after UEC and CMP results revealed mildly decreased potassium and magnesium.

Outcome

The patient remained as an inpatient for a further two weeks, amiodarone was gradually reduced from 200mg three times daily to 200mg daily and he had no further episodes of SVT. He completed radiotherapy to his lumbar spine and pericardium. Chemotherapy was ceased due to disease progression and functional decline.

Before discharge, the patient enquired about his prognosis which was carefully explained to him and communicated to his family. He was discharged to a palliative care unit, where he died six days later.

Discussion

Cardiac metastases are rare clinical ante-mortem diagnoses, as they are silent in more than 90% of patients. [2] Most cases of cardiac metastases are diagnosed post-mortem and, as a result, most epidemiological data regarding cardiac metastases are from autopsy results. The reported incidence according to the literature up to 15% [3] in oncology patients. An increased incidence has been reported

due to modern diagnostic tools and improved survival of cancer patients, secondary to improved treatment and change in the natural cancer history. [2]

In theory, any primary malignancy has the potential to spread to the heart. The rates of metastasis in different tumour types were reported by Bussani *et al.* in 2007 [4] in a review of post-mortem studies performed at the University of Trieste, Italy, where over 80% of in-hospital deaths are examined by autopsy. They reviewed data from 1994 to 2003 and their reported rates of cardiac metastasis in different tumour types is summarised in the table below (Table 1). Currently, the only tumours which have not been demonstrated to metastasise to the heart are central nervous system tumours. [5]

Table 1. Rates of cardiac metastasis in different tumour types, as reviewed by Bussani *et al.* (2007). [4]

Tumour Type	Rates of cardiac metastasis (%)
Pleural mesothelioma	48.4
Melanoma	27.8
Lung adenocarcinoma	21.0
Undifferentiated carcinomas	19.5
Lung squamous cell carcinoma	18.2
Breast carcinoma	15.5
Ovarian carcinoma	10.3
Lymphomyeloproliferative neoplasm	9.4
Bronchioalveolar carcinoma	9.8
Gastric carcinoma	8.0
Renal carcinoma	7.3
Pancreatic carcinoma	6.4

Tumours can spread to the heart via one of four routes: 1) direct invasion, 2) haematogenous spread, 3) lymphatic spread and 4) intracavitary diffusion. [4] Tumours which originate near the heart, such as bronchial and oesophageal tumours, can directly invade the heart. Lymphatic channels facilitate pericardial metastases, whereas haematogenous routes seed myocardial metastases. [5] Endocardial metastases arise from a combination of haematogenous and intracavitary diffusion through other layers of the heart. [4]

The most common site of cardiac metastases is the pericardium, followed by the myocardium and endocardium. [4-7] With a preference for lymphatic spread, lung and breast carcinomas commonly spread to the pericardium, whereas lymphomas, leukaemias, sarcomas and malignant melanomas spread haematogenously and seed in the myocardium. [5] Only in isolated cases has there been tumour spread to the valves. [4,7]

Clinical evidence of cardiac metastases is variable ante-mortem. However, common presenting symptoms of cardiac involvement include dyspnoea, cough, palpitations, syncope and chest pain. [2] Presentations of cardiac metastases may be obscured by symptoms of advancing primary malignancy, but they can also present as life-threatening emergencies, such as cardiac tamponade, myocardial rupture, ventricular arrhythmia and, rarely, acute myocardial infarction. [2] In some cases, the rise of symptoms from cardiac involvement may be the only indication of an underlying malignancy. [8,9]

In our case, cardiac metastases presented with dyspnoea and elevated JVP. Relevant differentials for dyspnoea associated with elevated JVP included intracardiac SVC obstruction, cardiac tamponade, constrictive pericarditis, radiation pericarditis and restrictive cardiomyopathy. CT chest demonstrated SVC obstruction, and echocardiography findings were suggestive of constrictive pericarditis caused by solid pericardial metastases. As such, the patient's dyspnoea and elevated JVP were likely to have been caused by a combination of tumour compression of the SVC reducing venous return to the right atrium and impaired diastolic filling due to an inelastic pericardium in constrictive pericarditis.

Presentations of cardiac metastases can be explained by the anatomical position of the metastases. Pericardial lesions cause pericarditis, which lead to serosanguineous or haemorrhagic pericardial effusions and, in most cases, cardiac tamponade. [5] Replacement of the myocardium and endocardium with tumour can cause systolic or diastolic heart failure, particularly if the ventricles are involved. [4] Myocardial infarctions occur when a neoplasm-induced embolus occludes the coronary circulation, or when coronary arteries are directly compressed or invaded by tumour or pericardial effusion. [4] Arrhythmias are common in the setting of any neoplastic involvement of the heart. [10]

The investigation of choice in detecting cardiac metastases is transoesophageal echocardiography. [5] Pericardial involvement is strongly indicated by a thickened pericardium, or in some cases, as a cauliflower-like projection into the pericardial fluid space. [11] Pericardial effusions can be detected with high sensitivity, and pericardiocentesis can be immediately performed under ultrasound guidance, quickly verifying the diagnosis of metastatic disease. Other imaging modalities such as MRI and CT can determine the size and extension of the tumour more precisely, and provide information on the characteristics of the lesion. [5,12] As such, myocardial metastases are better demarcated by CT and MRI over ultrasonography.

ECG findings in cardiac metastases are non-specific, although more

than two thirds of patients with cardiac metastases show some degree of abnormality. [2] Similarly, chest radiography has limited use, but may reveal an increased cardiac silhouette from pericardial effusion or pericardial tumour. Chest radiography may demonstrate a primary lung tumour or pleural effusion resulting from heart failure. [5] There have been rare cases of osteogenic sarcoma metastases to the heart which contained bone and were visualised on the chest radiography. [13]

Biopsy of cardiac metastases is rarely indicated, as less invasive imaging techniques are usually adequate to suggest tumour type and determine if surgery is feasible. However, biopsies of the heart can be done using fluoroscopy- or ultrasound-guided techniques, or through open surgery. [5] Coronary angiogram studies have value in surgical planning. However, the above techniques are rarely utilised in secondary cardiac tumours, and are more significant in the evaluation of likely primary tumours. [5,14]

Surgical treatment of cardiac tumours is uncommon and reserved for those with good long-term prognosis. Radiotherapy is commonly used to relieve local symptoms, provide local control and obtain haemodynamic stability. [2] Chemotherapy is also employed if the tumour is chemo-sensitive, as in the case of lymphomas, leukaemias and germ cell tumours. The life expectancy of pericardial metastases without treatment is reported to be 1.75 weeks. [15] With treatment, namely radiotherapy and pericardiocentesis when necessary, life expectancy was extended to 22.5 weeks. [15]

Immediate treatment is required in patients presenting with pericardial effusions leading to life-threatening cardiac tamponade. Drainage of the pericardial fluid by pericardiocentesis is required, but effusions return in up to 60% of cases. [16] Thus, treatment of the initial effusion is combined with prevention of recurrence, which can be achieved with prolonged catheter drainage, obliteration of the pericardial space or creation of a permanent pericardial window which drains into the pleural or peritoneal cavity. The utilisation of sclerosing agents and instillation of chemotherapeutic agents in the pericardium have also been shown to prevent effusions. [2]

Conclusion

This case demonstrates salient features of cardiac involvement in metastatic lung cancer, including primary invasion into the SVC and right atrium as well as metastatic involvement of the pericardium. While most cardiac metastases are silent, or obscured by advanced disease, this case has highlighted clinical complications of cardiac involvement, including SVC obstruction, SVT and constrictive pericarditis. Suspicion of cardiac metastases should always be high in oncology, as it allows prompt treatment and optimal comfort of the patient.

Consent declaration

Informed consent was obtained from the patient for publication of this case report and accompanying figures.

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Conflict of interest

None declared.

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Case Report

Acute viral bronchiolitis in the setting of extensive family history of asthma

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Glenn is a fourth year medical student at Monash University. He has a keen interest in researching areas of medicine outside the textbooks. He has a great interest in critical care medicine, a field he hopes to specialise in the future.

This case report describes a previously healthy eleven-month old ex-preterm female with a severe presentation of acute viral bronchiolitis with an extensive family history of asthma. The link between viral bronchiolitis and asthma has always been controversial despite extensive research. Several studies have linked respiratory syncytial virus (RSV) bronchiolitis to the development of persistent wheezing or asthma later in childhood, even suggesting that a dose-response relationship may exist between the two entities. Some studies have also demonstrated that severe lower respiratory infections in the first year of life are important contributors to asthma, particular in those sensitized during infancy. On the other hand, it has also been studied as to whether an individual at risk of asthma has any impact on the severity of bronchiolitis. Despite numerous studies, results have largely been inconclusive, and the question of whether it is RSV that directly results in asthma, or if the susceptibility to RSV is conferred due to predisposing pulmonary pathology, still remains unknown.



otitis media with amoxicillin by her general practitioner, but began to worsen over the subsequent 24 hours, with laborious and wheezy breathing, coupled with a persistent fever of 38.4°C. Despite two doses of salbutamol, her breathing continued to deteriorate, leading to her presentation at the ED. There were no apnoeic or cyanotic episodes, rigors or any associated inspiratory stridor. During this period, Sally was anorexic, with subsequently fewer nappy changes, and was reported by her parents to be far less active than usual. She was previously well, with no known sick contacts, and her vaccinations were up-to-date.

Sally had a similar episode of bronchiolitis in at eight months of age but was treated then as an outpatient. There was an extensive family history of asthma (Figure 1), and both the patient's siblings had bronchiolitis as infants. At eleven months, Sally was meeting all the developmental parameters for her age. There were no known drug

Case

Sally was an eleven-month old ex-preterm (35 weeks) female who presented to the Emergency Department (ED) with symptoms of fever, coryzal symptoms and a wheeze, subsequently diagnosed as viral bronchiolitis.

History

Sally had become acutely febrile two nights prior to presentation, developing coryzal symptoms the following morning. Sally was initially treated for an upper respiratory tract infection (URTI) and acute

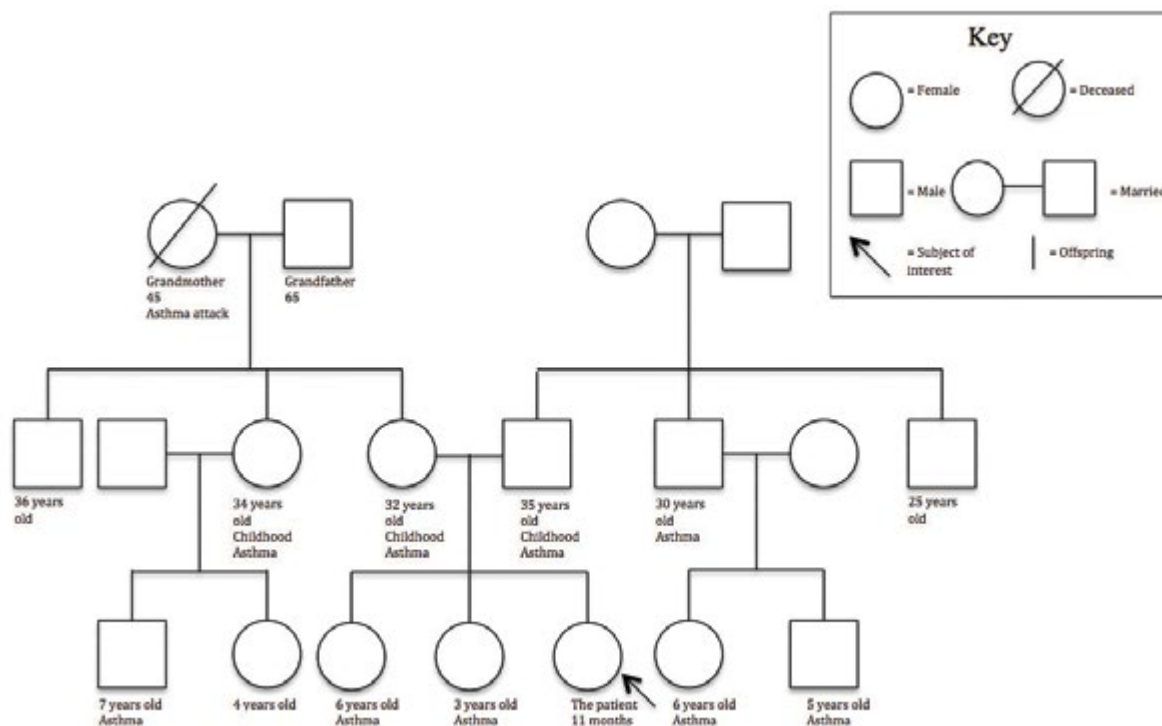


Figure 1. Family pedigree of asthma.

allergies and other than salbutamol PRN, the patient was not on any other medication. There was no remarkable social history.

Examination

Sally appeared lethargic and was in respiratory distress, with tachypnoea, an audible wheeze and classical signs of increased breathing effort (nasal flaring, tracheal tug and subcostal recession). She had a respiratory rate of 78 and was saturating at 100% on 8L supplementary oxygen, which decreased to 90% on room air, and was febrile at 38.5°C. She was tachycardic at a heart rate of 170. There were no clinical signs of dehydration. On auscultation, air entry was reduced bilaterally, with an expiratory wheeze and diffuse crackles present. There was no evidence of stridor, increased vocal resonance, or dullness to percussion. An ear, nose and throat examination revealed an erythematous pharynx but was otherwise unremarkable. All other examination findings were unremarkable.

Workup and Progress

The presenting symptoms suggested a diagnosis of acute viral bronchiolitis. However, with the extensive family history of asthma, Sally's presentation could be her first virus-triggered asthma attack. While the clinical presentation suggested otherwise, there were concerns over the possibility of pneumonia, which had to be ruled out in the workup. In consideration of the severity of her initial presentation and the likely further deterioration until its peak at day 2-3, basic investigations were ordered. These included a full blood count, urea, electrolytes and creatinine parameters, a chest X-ray and a nasopharyngeal aspirate. There were no abnormal findings.

Sally was commenced on immediate supportive therapy. An IV line was inserted and she was commenced on 75% maintenance fluids as per guidelines to avoid Syndrome of Inappropriate Antidiuretic Syndrome. [1] She was also commenced initially on 2L oxygen as per guidelines for respiratory distress, [2] but failed to saturate appropriately until given 8L of humidified oxygen via nasal prongs, where she maintained 100% O₂ saturation. While the efficacy of short-acting beta agonists (SABAs) in the acute management of bronchiolitis has been inconclusive despite extensive research, current guidelines recommended a trial of bronchodilators in infants >6 months. [3] Sally was administered six puffs of Salbutamol MDI (100mcg/puff) via spacer [1] but with no results, hence the regime was discontinued.

The Royal Children's Hospital (RCH) provides further guidance regarding management based on clinical signs and symptoms. Admission to the intensive care unit (ICU) was indicated for Sally to allow continuous cardiorespiratory monitoring and supportive management. Observations were performed hourly and with only supportive management, her oxygen requirements were weaned down to 2L over 24 hours.

Discussion

Bronchiolitis during infancy and asthma in childhood - is there a causal link? Should infants at high risk of asthma receive Palivizumab immunization?

Several studies have linked respiratory syncytial virus (RSV) bronchiolitis to the development of persistent wheezing or asthma later in childhood. In a long-term prospective cohort study, there was a relative risk of 2.8 of developing wheezing at 5.5 years in children who had had bronchiolitis. [4] Sigurs *et al.* (2005) also reported a ten-fold excess of asthma in a similar study. [5]

It has also been suggested that a dose-response relationship exists between bronchiolitis and asthma. In a study involving 90,341 children, Carroll *et al.* (2009) demonstrated that the odds ratios (OR) for asthma as a child were 1.86 (95% CI, 1.7-2.0), 2.41 (95% CI, 2.2-2.6) and 2.8 (95% CI, 2.6-3.0) in the outpatient, ED, and hospitalization groups, respectively, compared to children without bronchiolitis. [6] Henderson *et al.* (2005) also noted an OR of 2.5 (95% CI 1.4-4.3) of developing asthma with hospitalization for RSV bronchiolitis, [7] as

did two prospective studies, which showed a 30-40% likelihood of subsequent asthma. [8]

RSV bronchiolitis as a direct cause of asthma

In an extensive seven-year REBEL prospective cohort study, Bacharier *et al.* (2012) reported that increased Chemokine (C-C motif) Ligand 5 (CCL5) expression in nasal epithelial cells during RSV infection carried an OR of 3.8 (95% CI, 1.2-2.4) for developing asthma. [9] This is in concordance with studies demonstrating increased CCL5 levels in subjects with asthma, [10] as well as in vitro studies demonstrating increased expression and transcription by RSV. [11] Unfortunately, the study failed to measure CCL5 levels prior to infection and thus the causal relationship has not been established. Hence, whether it was RSV that directly resulted in asthma, or if the susceptibility to RSV was conferred due to predisposing pulmonary pathology, [12] still remains unknown.

A five-year cohort study on children at high risk of atopy by Kusel *et al.* (2007) demonstrated that severe lower respiratory infections in the first year of life are important contributors to asthma, particular in those sensitized during infancy. [13] These findings suggest that protecting high-risk individuals from infection during infancy may be considered for long-term asthma prevention.

Effect of family history of asthma or atopy on severity of bronchiolitis

It has also been studied whether an individual at risk of asthma has any impact on the severity of bronchiolitis. This was particularly relevant in the Sally's case, with her significant family history of asthma. Results in this field have been conflicting, with most studies not eliciting any significant association. However, Gurwitz *et al.* (1981) demonstrated that hospitalized cases were associated with a higher incidence of first-degree relatives with bronchial hyper-responsiveness. [14] A study by Trefny *et al.* (2000) also demonstrated similar results. [15]

Should high-risk atopic individuals receive Palivizumab immunization during RSV season for prevention of asthma?

Passive immunization with Palivizumab is currently recommended only for high-risk infants to prevent serious complications arising from RSV infections. [16] However, a recent double-blinded RCT in the Netherlands has begun examining its preventive effect on recurrent wheeze in healthy preterm children 33-35 weeks gestational age (MAKI trial), based on a non-randomized trial suggesting a prevention of wheeze in 50% of preterm children. [17] Such a study would complement this case study's patient profile, and would be especially relevant in the context of her rich family history of asthma which puts her at high risk, and the abovementioned association but inconclusive causation between bronchiolitis and asthma.

From an economic standpoint, studies assessed the cost-effectiveness of Palivizumab, albeit in the context of high-risk premature infants (32-35 weeks). Unfortunately, the predisposition of these infants to a higher disease burden and costlier hospitalizations constitutes a higher cost per QALY [18] compared to this case study's patient, but even then there is still considerable controversy over its cost-effectiveness, especially across various healthcare systems.

Conclusion

In summary, this was a case of severe viral bronchiolitis warranting ICU admission for supportive management, on a background of an extensive family history of asthma. While studies have shown a clear association of bronchiolitis with asthma, causation has not been conclusively established, with family history of atopy possibly interacting in the development of asthma. Current research is lacking in the area of Palivizumab prophylaxis in the interest of asthma prevention in healthy children, but the evidence would suggest that it is likely to be cost-ineffective.

Conflict of interest

None declared.

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Adult Onset Still's Disease – a diagnostic dilemma

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Adult Onset Still's Disease (AOSD) is a rare systemic inflammatory disorder that predominantly affects young adults aged 16 to 35. The following case highlights the diagnostic complexities and challenges of AOSD following an Epstein Barr Virus (EBV) infection. Although having overlapping clinical manifestations with that of systemic Juvenile Idiopathic Arthritis (JIA) and rheumatoid arthritis, AOSD is a separate clinical entity with an unknown aetiology. Several pathogenic theories have been postulated which will be discussed and will serve as a basis for outlining targeted therapies for this condition.

Introduction

AOSD is characterised by fever, an evanescent skin rash, polyarthralgia, hepatosplenomegaly, leucocytosis, liver enzyme elevation and a high serum ferritin level. [1,2,3] It is a difficult diagnosis to make, as there is no pathognomonic test for the disease and it is a great mimicker of other conditions, such as autoimmune disorders and haematological malignancies.

Despite being a separate clinical entity to JIA and rheumatoid arthritis, there is evidence to suggest that AOSD as well as JIA are triggered by viral infections. [2,3,4] The following case demonstrates a young man who was diagnosed with AOSD following an infection with Epstein Barr Virus. This is impetus for a discussion of the interplay between AOSD and a viral aetiology, and the innate and adaptive immune responses in guiding effective therapy.

Case Presentation

In 2012, a previously healthy 20 year old male presented with a sore throat, malaise, tender cervical lymphadenopathy and fever, consistent with infectious mononucleosis. He was transferred to a secondary referral hospital where paired EBV serology was positive for an active infection despite a negative monospot test. The patient's travel history and past medical history were unremarkable apart from regular alcohol binge drinking.

After being discharged, he began to experience intermittent fevers and night sweats. In addition to this, he had ongoing malaise and was forced to stop work as a mechanic. Weight loss of 10kg occurred during a two month period, along with a persisting microcytic anaemia, with a haemoglobin level of approximately 8.0 g/dL.

His polyarticular pain was distributed mainly to his ankles, knees, shoulders and wrists, and associated with morning stiffness and visible swelling. The pain was partially responsive to regular ibuprofen. He also complained of intermittent pleuritic chest pain. Over a course of two months, his weight stabilised and night sweats improved, but his anaemia and polyarthralgias persisted.

Approximately two months after his initial diagnosis of infectious mononucleosis, the patient represented to hospital with severe polyarthralgias and was unable to walk. During this admission, he was afebrile but had some mild tender cervical lymphadenopathy with no hepatosplenomegaly. A pleural rub was auscultated. He had a salmon-coloured non-blanching rash on the medial aspect of both legs that felt like a 'sunburn'; this was biopsied. Although the diagnosis of AOSD had previously been considered, the patient was investigated for other causes for these symptoms. The results of these investigations are



presented in Table 1. His investigations included a bone marrow and trephine biopsy, which revealed a markedly hypercellular bone marrow. The skin biopsy of the rash on his legs showed a leucocytoclastic vasculitis with perivascular neutrophilic invasion, but negative staining for complement. This finding is non-specific to the condition and can occur due to drug reaction, immune-complex deposition or be idiopathic. [5] As test results did not indicate another likely cause for his symptoms, the patient was commenced on treatment for AOSD and was referred to a rheumatologist.

Case Discussion

This case illustrates the unique clinical and laboratory picture of AOSD, with its intermitting and remitting fevers, polyarthralgias, myalgias, lymphadenopathy, transient macular rash and pleuritis. It is likely that the patient had a degree of pleuritis, as suggested clinically with a pleural rub and on CT imaging. Serositis manifesting as pleuritis, pleural effusions or pericarditis can be encountered in AOSD, but is rare. [3,6] The rash is fleeting and may only last for hours or days, and skin biopsies generally reveal a non-specific perivascular inflammation. [1] Our patient's thrombocytosis and markedly elevated serum ferritin are reactive changes. The serum ferritin level has been suggested as a predictive marker for AOSD as it is invariably elevated and often higher than levels found in other autoimmune or inflammatory diseases, with a five-fold increase in serum ferritin being 41% specific and 80% sensitive as a diagnostic test. [9] The markedly high ferritin level in AOSD has been attributed to hyper-production by the reticuloendothelial system or hepatocyte damage, and is unrelated to iron metabolism. [8] The patient's blood results illustrated a microcytic anaemia, although the iron studies point towards an inflammatory reaction.

The leukocyte count appears to correlate well with the activity of illness. The underlying mechanism of this is probably bone marrow granulocyte hyperplasia, as demonstrated on bone marrow biopsy in our patient. It is not uncommon to see marked reductions in red cell counts, weight loss and hypoalbuminaemia in active disease. [8]

In our patient, causes of fever of unknown origin with or without rash were considered, such as endocarditis, haematological malignancies and systemic vasculitides. The single cytopenia, normal LDH and bone marrow biopsy excludes leukaemia, lymphoma and myelodysplasia. It is unlikely he had a protracted course of EBV due to the nature of his symptoms and degree of anaemia, in addition to the negative EBV

Table 1. Laboratory and imaging results on admission.

Parameter	Patient's result	Normal range
Haemoglobin	7.7 g/dL (microcytic anaemia)	13.0-18.0 g/dL
Haematocrit	26%	40-54%
MCV	76 fL	80-96 fL
Reticulocytes	2.77% (appropriate)	
Leucocytes	20 x 10 ⁹ /L	4.0-11.0 x 10 ⁹ /L
Neutrophils	16 x 10 ⁹ /L with left shift	2.0-8.0 x 10 ⁹ /L
Platelets	857 x 10 ⁹ /L	150-450 x 10 ⁹ /L
Erythrocyte sedimentation rate	118 mm/hour	<15 mm/hour
C-Reactive Protein	268 mg/L	<10 mg/L
Blood culture	Negative	
Fe studies		
Serum Iron	3 micromol/L	10-30 micromol/L
Transferrin	1.9 g/L	2.2-3.7 g/L
Transferrin saturation	8%	13-47%
Ferritin	3051 microgram/L	20-300 microgram/L
Serum folate	2159 nanomol/L	>630 nanomol/L
Rheumatoid Factor, Antinuclear Antibodies and ANCA antibodies	Negative	
Haptoglobin	4.51 micromol/L	4.10-16.5 micromol/L
Direct antiglobulin test	Positive	
Creatine Kinase	125 U/L	0-240 U/L
Serum protein electrophoresis	Polyclonal hypergammaglobulinaemia	
Complement		
C3	High	
C4	Normal	
Liver function tests		
AST	95 U/L	<40U/L
ALT	102 U/L	<55 U/L
GGT	72 U/L	<50 U/L
ALP	158 U/L	35-110U/L
Albumin	26 g/L	38-50 g/L
Kidney function	Normal	
Hepatitis Serology		
A	Negative	
B	Negative	
C	Negative	

Parameter	Patient's result	Normal range
Cancer markers		
LDH	232 U/L	240-480U/L
B-2-microglobulin	2.2 microgram/L	0.8-2.5 micrograms/L
EBV serology	IgM detectable, IgG positive (seroconverted)	
Barmah Forest Virus	Negative	
Ross River Virus	Negative	
Leptospirosis	Negative	
Chlamydia trachomatis	Negative	
Neisseria gonorrhoea	Negative	
Imaging		
Ultrasound abdomen	No hepatosplenomegaly, no free fluid	
Echocardiogram	Normal	
CT chest/abdomen/pelvis	Minimal inflammatory change at left lung base. Tiny amount of ascites in the pelvis. No enlarged lymph nodes	

IgM serology. Given the recent heavy rainfall, migrating polyarthritic conditions such as Ross River and Barmah Forest viruses were considered in the differentials.

The diagnosis of ASOD is made after taking into account the patient's medical history and risk factors for other infectious agents, environment and relevant infectious diseases epidemiology. Although being a diagnosis of exclusion, there are two commonly used clinical criteria in practice, that being Yamaguchi (Table 2), which has been shown to be most sensitive (93.5%) followed by Cush's (80.6% sensitivity). [7,8]

Table 2. Yamaguchi classification criteria for ASOD, modified from [8].

ASOD diagnostic criteria (Diagnosis requires ≥five criteria, two of which must be major)	
Major criteria	
Fever of at least 39 degrees, intermittent, lasting one week or longer	
Arthralgia or arthritis, lasting two weeks or longer	
Skin rash	
Leucocytosis with ≥80% granulocytes	
Minor criteria	
Sore throat	
Recent development of significant lymphadenopathy	
Hepatomegaly or splenomegaly	
Abnormal liver function	
Exclusion criteria	
Infections	
Malignancies	
Other rheumatic diseases	

In regards to the aetiology of AOSD, there have been numerous case reports of AOSD following viral infection, [4,10] with one citing an older female patient diagnosed with AOSD after EBV infection. [2] Other implicated viruses include rubella, mumps, cytomegalovirus, parainfluenza, human herpes virus 6, echovirus, parvovirus B19, and bacterial infections like mycoplasma pneumoniae, chlamydia

pneumonia, yersinia enterocolitica and borrelia. [2,8] Although relevant to our patient, the link between infections and AOSD has not been robustly established from an aetiological perspective, [10] and probably only forms part of the multifaceted pathogenesis, that being a dysregulated immune system combined with susceptible HLA loci. However, no consistent associations between AOSD and particular HLA loci have been elucidated, although HLA-B17, HLA-B18, HLA-B35 and HLA-DR2 have been implicated. [6]

It does appear that pathogenesis of the condition overlies autonomous activity of both innate and adaptive immune systems. Patients with AOSD often show hypercomplementaemia, and serum levels of IL-1 β , IL-6, IL-18, TNF α , IFN γ and macrophage-colony stimulating factor (M-CSF) have been found to be considerably higher than compared with controls. [6,7,11] These cytokines also appear to share a role in increasing the production of ferritin. [1,12] IL-18 is predominantly secreted by macrophages and has been implicated in hepatotoxicity [13] and joint disease, [7] and may be the cause of liver enzyme derangement characteristic of AOSD. Serum IL-18 levels also appear to correlate significantly with serum ferritin levels. [8] Furthermore, IL-18 may be seen as the part of the bridge between activation of the innate and adaptive immune systems in AOSD, as it facilitates the Th1 response and induces other cytokines like IL-1 β , TNF α and IFN γ . [6] Pro-inflammatory cytokines such as IL-6, TNF α and IFN γ also increase the expression of Toll-like receptors (TLR), and high circulating levels of cytokines leads to a higher sensitivity of TLR to anti-microbial or viral peptides, thus creating a self-perpetuating cycle of inflammatory response and augmentation. [14]

On the adaptive immunity side of the pathogenesis, the role of T cells in pathogenesis has been well documented. [11,14] Dysregulated production of a particular subset of T helper cells, called Th17 cells, that secrete IL-17 have been implicated in the development of autoimmune diseases. [15] Significantly higher levels of Th17 cells and serum IL-17 levels were found in both AOSD and SLE patients, and there was a parallel decrease with clinical remission. [10] IL-17 stimulates monocytes to produce IL-6 and IL-1 β , which are also principle cytokines involved in the differentiation of CD4+ T cells into Th17 cells. [6] These therefore augment and maintain the inflammatory cascade. [16]

Non-steroidal anti-inflammatory drugs (NSAIDs) had previously been the first line medication for ASOD, despite only being effective monotherapy in less than 15% of patients. [10] The benefits of corticosteroids are higher when patients have more pronounced joint disease, with a response rate of two thirds of the patient population. [10]

Highlighting the implicated cytokines, namely IL-1 β , IL-6 and TNF α , [17,18] will guide the use of targeted therapies such as the disease modifying anti-rheumatic drugs (DMARDs). There have been favourable results with corticosteroids, and more than two thirds of patients require corticosteroids after NSAIDs are attempted as symptom relief. [6] The use of DMARDs are indicated where the condition is refractory to corticosteroids without signs of remission, or in combination as corticosteroid-sparing agents. This includes methotrexate, which has indirect actions on TNF α and IL-6. Although there is a lack of robust evidence regarding TNF in the pathogenesis of ASOD compared to rheumatoid arthritis, the use of etanercept and infliximab have shown significant improvement in disease in several

case series. [10] Of particular note, there is increasing evidence to suggest that anakinra, an IL-1 receptor antagonist, is well tolerated, and several case series have yielded positive results in ameliorating the disease at a haematological, biochemical and cytokine level. An excess of IL-1 β inducing factor has been demonstrated in JIA, a condition that also shares similar pathogenesis to that of AOSD. [6,19]

The clinical course of AOSD is heterogeneous, with patients falling into one of three clinical patterns. The first group which affects about 60% of patients [8] is a monocyclic systemic group with only one episode of systemic manifestations, with complete remission within one year of the onset of symptoms. The second group is polycyclic systemic, whom experience more than one episode which is followed by partial or total remission. The third group is a chronic articular group, with persistent polyarthritis lasting longer than 6 months. [6] In the chronic group, the average duration of disease is 10 years, the symptoms appear to be less permanent than other rheumatological diseases and the disease shows less propensity to interfere with social functioning or time off from work despite disability and the need for long-term medication. [20]

Patient outcome

The patient improved satisfactorily with regular ibuprofen and prednisolone 20 mg daily and was discharged after day 7 with a tapering steroid dose.

He was able to resume work, but continued to experience mild intermittent polyarthralgias with no other significant systemic symptoms. Six months post-admission, deterioration in arthritic symptoms prompted the addition of methotrexate.

Key points

- Adult Onset Still's Disease is a rare systemic inflammatory disorder that mainly affects people aged 16-35 years old.
- It is a difficult diagnosis to make, and one that must be questioned continually, as it is a mimicker of other disorders, including other causes of fever of unknown origin, infectious diseases and malignancy.
- It is characterised by both clinical and laboratory manifestations like fever, evanescent rash, polyarthritis and polymyalgias, microcytic anaemia, leucocytosis, thrombocytosis and marked hyperferritinaemia.
- Treatment is based on clinical course and is similar to that of rheumatoid arthritis. A more targeted biological disease modifying therapy should be chosen with consideration of likely pathogenic pro-inflammatory cytokines.

Consent declaration

Consent from the patient was gained for the writing and distribution of this article for education purposes.

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Conflict of interest

None declared.

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Case Report

Mobile segment of the hamulus causing dynamic compression of the motor ulnar nerve branch in the hand

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This paper is the first to document the mechanism of how a mobile segment of the hook of hamate can dynamically compress the motor branch of the ulnar nerve. Presented is the case of a professional golfer who experienced pain on the ulnar aspect of his right hand that he attributed to weakness and inability to control his hand. Imaging revealed the rare condition of os hamulus proprius causing a dynamic compression of the ulnar nerve when in power grip. Provided is a review of wrist anatomy with particular focus on the peculiar case of the bipartite hamulus.

Introduction

Anatomy of the wrist

The wrist comprises a proximal and distal carpal row. The distal carpal row consists of the trapezium, trapezoid, capitate and hamate and acts as a base for the metacarpals. The proximal carpal row consists of the scaphoid, lunate, triquetrum and pisiform bone. These function as an intercalated segment, balancing the hand on the radius and ulna. [13]

Hamate anatomy and function

The hamate articulates with the triquetrum proximally and the bases of the 4th and 5th finger metacarpals distally. The hook of the hamate is an important structure in the hand. Protruding from the volar surface of the hamate, it anchors the distal transverse carpal ligament, acting as a pulley for the ulnar flexor tendons and protecting the motor branch of the ulnar nerve. This branch of the ulnar nerve courses dorsally and distally around the hook of the hamate to supply nearly all the intrinsic muscles of the hand. [14]

Guyons Canal and the Ulnar Nerve

Felix Guyon described a potential space [15], which is a fibro-osseous tunnel, protecting the ulnar nerve and artery and veins as they enter the hand. The boundaries of Guyon's canal are the pisiform bone, the tip of the hook of the hamate, the piso-hamate ligament and the transverse carpal ligament.



ossification center in the hook of the hamate does not unite with the primary ossification center in the body of the hamate. [2] When the tip of the hook of the hamate does not fuse with the body of the hamate the result is a separate ossicle known as the os hamulus proprius or a bipartite hamate. Whilst an os hamulus proprius or bipartite hamate is often congenital a similar appearance can sometimes be the result of a non-union of a fracture of the hook of the hamate. [3]

Ossification of the hamate is not complete until the early teenage years. [4] Bone growth and maturation usually takes place via a single ossification center. However, a secondary ossification center independent from associated underlying bone occasionally develops giving rise to an accessory ossicle. [9] This lack of fusion has been observed involving the hamulus and the hamate and is known as either os hamulus proprius or bipartite hamate. Such cases are often congenital in nature; however, depending on the patient's history, trauma or degenerative etiology should be considered. [10]

A study [5] conducted in 2005 on 3,218 hand radiographs revealed that variations are more prevalent than previously thought. 96 participants were found to have variations of the hook of hamate of which 42 patients had a bipartite hook, 50 had a hypoplastic hook and 4 had an aplastic hook. Furthermore, 93 of these cases presented with carpal tunnel syndrome symptoms.

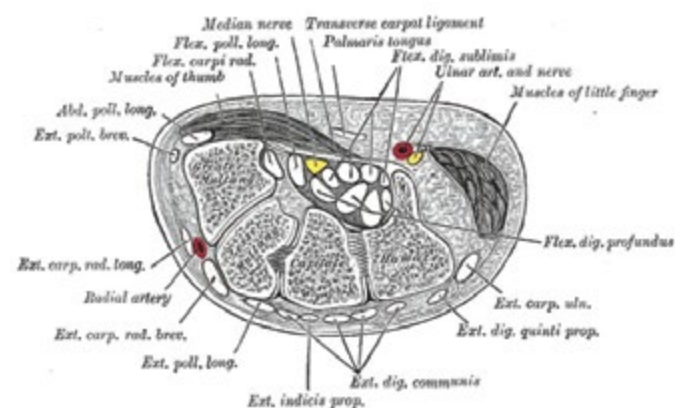
In 1981, Greene *et al.* [6] identified a single case of bipartite hamate with ulnar tunnel syndrome. However, since then there have been no other accounts of the os hamulus proprius, associated with dynamic ulnar neuropathy.

Case Study

History

The patient was a 37 year old professional right handed golfer with an unremarkable medical record.

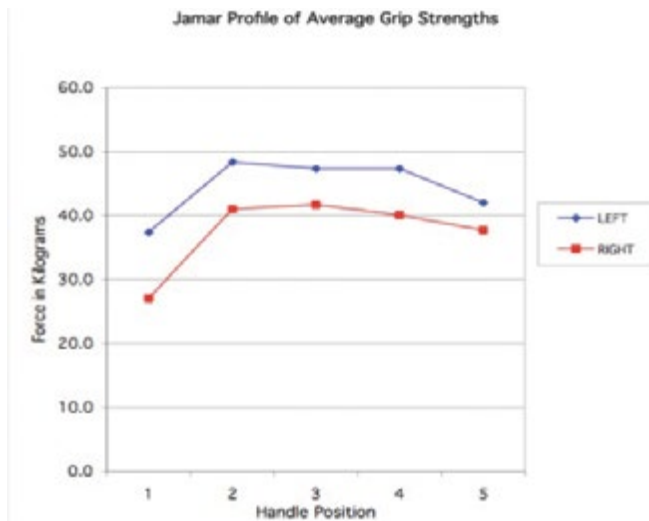
He presented with an eight-week history of pain in the ulnar side of the right hand with loss of fine motor control requiring the use of his contralateral left hand to perform activities of daily living. The patient reported no other neurological symptoms at the time.



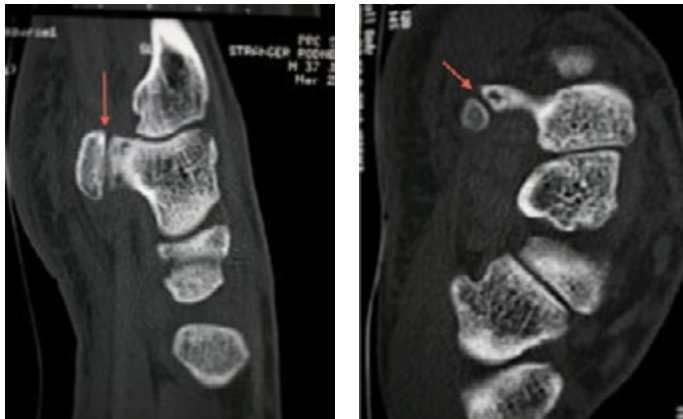
Os Hamulus proprius

The os hamulus ossifies from a primary ossification center in the body of the hamate; however, occasionally a secondary ossification center in the hook of the hamate is also present. [1] Rarely, the secondary

Physical examination revealed wasting of the intrinsic muscles of the right hand, most pronounced in the first dorsal interosseous muscles with weak intrinsic movements when compared to the left side. Following initial examination a series of investigation and imaging was conducted:



Electromyography: ulnar nerve neuropathy involving motor branch in the hand.



Imaging: CT scan was interpreted as demonstrating an os hamulus proprius.

It is not uncommon for golfers to fracture the hook of hamate based on the type of grip and dynamics of the golf swing. Furthermore, they can develop stress fractures of the hook of the hamate, which subsequently do not unite. [11,12]

Whilst this may have been the mechanism for the development of injury, an alternative explanation implicates a congenital anomaly where the primary ossification center the hamate fails to unite with the hook of the hamate giving rise to a bipartite bone (os hamulus proprius). [3]

Findings

This patient had a well-established long-standing asymptomatic non-union of the hamate or an os hamuli proprius, which subsequently became symptomatic following a motor vehicle accident in January 2005 resulting in an acute eight-week history of fine motor control deficit in the right hand.

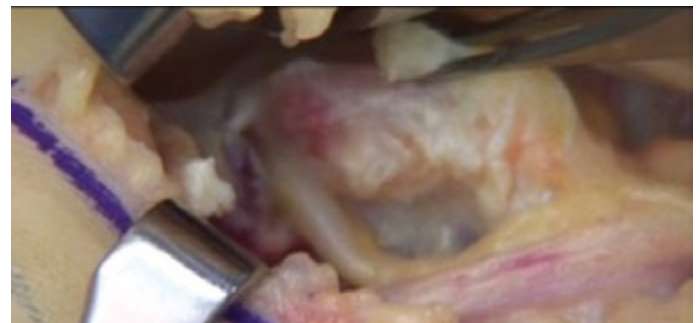
Surgical intervention

A mobile segment of the hook of the hamate was identified. Pressure over the mobile segment of the hook of the hamate compressed the motor branch of the median nerve as it traversed around the ulnar and distal hook of the hook of the hamate. The motor branch of the median nerve was swollen proximal to the point where the mobile segment of the hook of the hamate dynamically impacted on the nerve. This had the appearance of a 'neuroma in continuity' commonly seen from failure of regenerating nerve growth cone to reach peripheral targets.

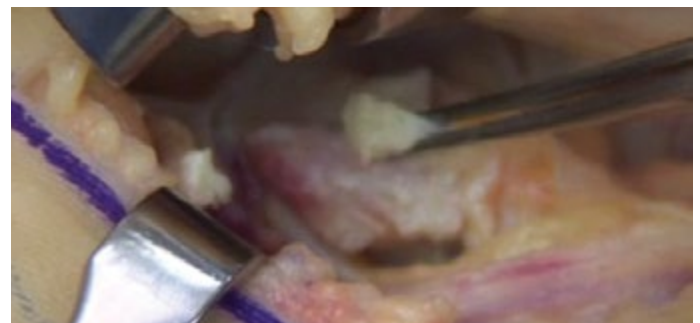
The ulnar nerve was released in Guyon's Canal. The motor branch of the ulnar nerve was identified and dissected as it coursed around the hook of the hamate. The hook of the hamate was very mobile and unstable. Manipulation of the mobile hook of the hamate demonstrated how it impacted and compressed the motor branch of the median nerve distal to the swollen segment of the motor branch of the median nerve. This was surgically excised.

The patient noticed a marked improvement of symptoms within two days post-operatively commenting on a return of 'power and movement'. Following rehabilitation through daily grip strength exercises; this was further demonstrated on clinical examination at eighteen days confirming a return of intrinsic muscle power in the right hand.

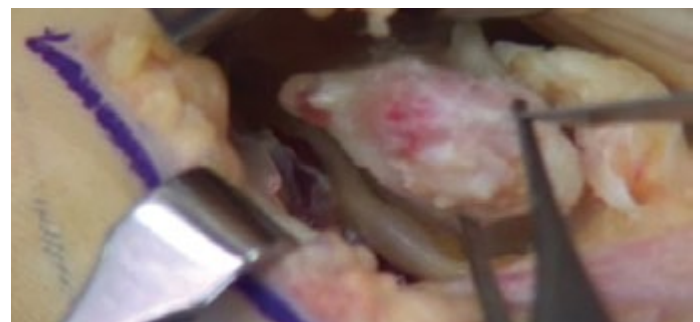
The following five images describe the surgical repair of Os Hamulus Proprius as performed in this case.



Dynamic compression of the motor branch of the ulnar nerve by mobile segment of hamulus (os hamulus proprius).



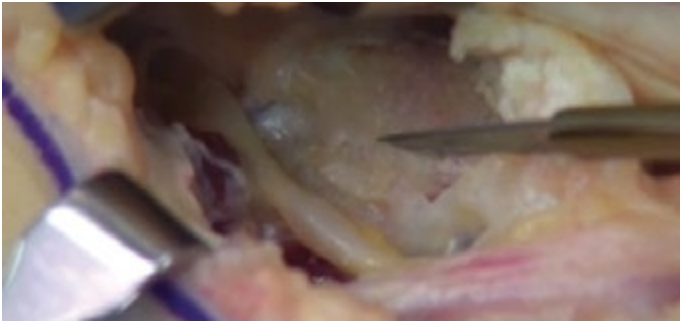
Neuroma of ulnar nerve proximal to the site of compression unmistakably swollen and enlarged.



Excised mobile segment of hamulus.



False Joint: view of the hamulus and secondary ossification fragment.



Decompression and release of ulnar nerve.

Discussion

The hook of the hamate is an important structure providing mechanical stability on the ulnar aspect and protecting the motor branch of the ulnar nerve as it traverses deep into the hand from Guyon's canal. It is also an important structure for insertion of the flexor retinaculum and as a result the muscles on the ulnar side of the hand. [16]

It is very likely that this abnormality of the hook of the hamate was present prior to his injury. The most likely explanation is that it is a secondary ossification center of the hook of the hamate (os hamulus proprius) which went on to unite. However, it is not possible to completely rule out that this represents a long standing non-union of the hook of the hamate and at some stage in the past he may have sustained a stress fracture which resulted in a non-union. [1,3,6,8,11,17]

Clinical examination plays a crucial role in isolating cases of os hamulus proprius. Patients will often present with clinical signs suggesting ulnar neuropathy such as intrinsic muscle weakness and altered sensation of the hand. In differentiating a case of bipartite hamulus, there will also be marked local tenderness over the hook of hamate with symptomatic pain due to dynamic compression such as when performing a power grip. Further hand and upper limb evaluation can compliment the diagnosis by quantifying and comparing loss of strength in the hand. [17]

The patient had marked motor (intrinsic hand muscles) weakness and some minor impairment of sensation in the ulnar distribution, which is consistent with the electrophysiological abnormalities in the hand. Surgery to remove the mobile segment of hamulus resulted in major improvement - particularly in terms of the level of his symptoms and restoration of normal power to the intrinsic muscles of the hand. Excision of the mobile os hamulus proprius has restored control and

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sensation of his left hand and enabled him to resume his career as a professional golfer.

Ulnar nerve compression in the hand could be due to a multitude of factors, including a tumour, a ganglion cyst, a fracture of either the pisiform or the hamate, compression in Guyon's Canal, and an aneurysm of the ulnar artery. [18] To discriminate between a congenital bipartite hamulus or a non union of the hook of the hamate five criteria [17] have been described:

1. Bilaterally similar bipartite hamulus
2. Absence of history or signs of previous trauma
3. Equal size and uniform signal intensity of each part on imaging
4. Absence of progressive degenerative changes between the two components of the hamate or elsewhere in the wrist
5. Smooth well corticated and rounded margins of the hamate and mobile separate hook

Treatment

There are a limited number of options to treat a mobile hamulus segment causing ulnar nerve compression. [8] Initial splinting of the hand can be trialed to prevent dynamic compression of the nerve in the hope that pain and weakness resolve. [5] Furthermore, avoidance of sports relying on grip strength may provide symptomatic relief. If these interventions do not result in the resolution of symptoms, then there is the option of surgically excising the accessory ossification center on the tip of the hook of the hamate with subsequent decompression and release of the ulnar nerve such as presented in this case.

Consent declaration

Informed consent was obtained from the patient for publication of this case report and accompanying figures. IMAGE ONE is taken from <http://upload.wikimedia.org/wikipedia/commons/3/31/Gray422.png>. This image is in the public domain because its copyright has expired. This applies worldwide.

Acknowledgments

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Conflict of interest

None declared.

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Melioidosis in the Torres Strait Islands: an 11 year audit 2001-2012

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Melioidosis is an infection of concern to global health. It is caused by the intracellular gram-negative bacterium *Burkholderia pseudomallei*, which is found in the soil and fresh waters of endemic regions. This study identified the average annual incidence of melioidosis in the Torres Strait region between 2001-2012, and compared this to one other similar study, which identified the average annual incidence between 1995-2000. Patient demographics, clinical presentation, outcomes and risk factors were compared to other available studies. In this retrospective study of melioidosis in the Torres Strait, 31 cases were identified over an 11-year period, representing an annual incidence of 37 cases per 100,000 population. Of these cases, 84% recovered, 16% required intensive care unit (ICU) admission, 3% had a relapse and two patient deaths occurred. The mortality rate was 6.4%. Pneumonia accounted for fifteen presentations (48%) and splenic abscesses for ten presentations (32%), with nine patients presenting with septic arthritis of a joint (29%). Other presentations included hepatic (19%), prostatic (19%), renal (10%), skin (6%), pancreatic (3%), scrotal (3%) and spinal abscesses (3%). Four presented with bacteraemia alone (13%) and one case presented with urethritis (3%). Risk factors included diabetes mellitus (68%), excessive alcohol intake (35%), renal disease (12%), autoimmune disease (6%), malignancy (4%) and the use of immunosuppressive medication (2%).



highlights the significant relationship between the transmission of melioidosis and certain environmental factors, such as rainfall level. [1,2]

The transmission of melioidosis most commonly occurs through percutaneous inoculation, and less commonly through inhalation, aspiration and ingestion. [2] A range of host and environmental factors must also exist for an individual to be infected. This includes reduced host immunity and the significant environmental exposure to the pathogen which occurs in endemic regions. [1] This was demonstrated in the study by Kanaphun *et al.* conducted in northeast Thailand, in which serological studies of 80% of the population exhibited positivity for antibodies against *B. pseudomallei* by four years of age. [18] There is clear significant environmental exposure in populations of northeast Thailand, yet only 20% of these children developed a symptomatic infection. [1,18] In addition, of the adults infected with symptomatic melioidosis, over 80% displayed reduced host immunity, with most affected by diabetes mellitus or renal failure. [8] In comparison, studies conducted in Australia demonstrated that most individuals were affected by excessive alcohol consumption and diabetes mellitus. [9]

The clinical syndrome associated with the infection of *B. pseudomallei* is diverse and can affect a variety of organs. Both domestic and international literature overwhelmingly demonstrated the lung as the most commonly affected organ, with pneumonia being the most common clinical presentation of melioidosis. [7,9] Other clinical presentations include symptoms of septicaemia such as fever, malaise, pain in the joints or abdomen, which may be the result of abscess formation in the liver, prostate, kidney, skin or pancreas.

The incubation period varies, as *B. pseudomallei* can remain dormant for a prolonged period of time. This makes it difficult to establish the exact period of infection. In most cases, a diagnosis of melioidosis is made through positive cultures demonstrating the growth of *B. pseudomallei*. Serological evidence can also be used to demonstrate past infections, or the presence of rising titres can provide a diagnosis in the absence of positive cultures. [2]

Recurrence of melioidosis can occur in 15% of individuals within ten years of the primary infection, with 50% of these occurring within the first twelve months. [10] Overall, 25% of individuals with recurrence will die. [10] Risk factors for recurrence include severity of initial

Introduction

Melioidosis is an infection caused by the intracellular gram-negative bacterium *Burkholderia pseudomallei*, which is found in the soil and fresh waters of endemic regions. [1] Endemic regions include Southeast Asia and Northern Australia, with peaks of infection occurring during the wet seasons. [2] Melioidosis is of global public health significance, and may be thought of as an emerging infection across tropical regions. [3]

The Torres Strait is a tropical region comprised of 274 islands between the Cape York Peninsula of mainland Australia and Papua New Guinea (PNG). According to the 2006 Australian Bureau of Statistics (ABS) census data, the region has a total population of 7,624, with 82.5% identifying as Indigenous. [4] Half of this population is clustered within the central island group located closest to Thursday Island (TI), which is the commercial and governmental centre of the region. Hospital services are also centralised at TI, however, the closest tertiary referral centre for the Torres Strait region is the Cairns Base Hospital, located 800km south of TI.

Melioidosis is endemic in the Torres Strait, with the most recent average annual incidence reported to be 42.7 cases per 100,000. [5] This is significantly greater than other centres such as Darwin, where the annual incidence was noted to be 19.6 cases per 100,000 between 1986 and 2008. [6] However, during periods of extreme climate, such as during years of significant heavy rainfall, this incidence dramatically increases. This was observed in Darwin between 2009 and 2010, during which the annual incidence increased to 50.2 cases per 100,000, as a result of a heavy wet season. [7] The variability in annual incidence

infection, treatment regime and compliance, and short treatment duration. [10]

Within Australia, it was noted that the mortality rate was similar across the Torres Strait, North Queensland and Darwin. The most recent study conducted in the Torres Strait demonstrated a 22% mortality rate, [5] whilst a larger study in Darwin exhibited a similar mortality rate of 19%. [6,9]

The literature demonstrates the importance of melioidosis to the Torres Strait region. Its seasonal, wet, tropical location and its burden of chronic disease make it a prime location for *B. pseudomallei*. Furthermore, the most recent examination of this condition in the area is ten years old, highlighting the need for more recent data. This study aims to retrospectively examine all melioidosis cases between the year 2001 and 2012, in order to understand the current burden, risk factors and disease pattern of melioidosis in the Torres Strait.

Methods

This study aimed to conduct a retrospective audit of all patient data between 2001 and 2012, with diagnosis of melioidosis confirmed by isolation of *B. pseudomallei*. Patients who had been coded as having a diagnosis of a melioidosis infection within this period were identified. All patients who had a positive culture or serology for melioidosis were identified through Queensland Health Pathology. Electronic records were accessed for confirmation of diagnosis and to collect patient medical history, social history and medication lists. Electronic data was accessed through the Queensland Health Electronic Discharge Summary (EDS) program and via clinical notes in Best Practice. AusCare was accessed to confirm positive blood or swab cultures.

Positive serological diagnoses without supporting positive cultures were excluded. Patients with negative pus or blood cultures were excluded. Patient records were de-identified and analysed for demographical data, risk factors, clinical presentation and outcomes. All cases identified were acquired within the Torres Strait region.

Patient transfer to a tertiary hospital for further management and treatment did not result in exclusion of the patient. Once stabilisation was achieved in tertiary centres, patients returned to the TI Hospital to complete treatment, and were not listed as an additional case in the study.

Annual incidence rates were calculated using the 2006 ABS population census data of the Torres Strait region. [4] Recognised risk factors for melioidosis were utilised to aid in analysis of patient records. Data were compared to previous studies from both the Torres Strait and other similar regions within Australia, to determine similarities and differences across these areas.

Patient occupational data was not included in this study, as they were not reflective of environments which would cause significant increased exposure to *B. pseudomallei*.

Results

Melioidosis was confirmed in 31 cases by isolation of *B. pseudomallei* from any clinical sample. Of the 31 cases, 28 cases were confirmed by blood culture and two cases were confirmed by swab culture of pus, one from a septic ankle and the other from an epidural abscess. These two cases did not culture *B. pseudomallei* in serological samples. This represented an average annual incidence of 37 cases per 100,000 of melioidosis within the Torres Strait region.

The majority of individuals affected were male (65%), of Torres Strait Islander decent (Figure 1), with a median age of distribution between 40-49 years (Figure 2). Most patients presented from outer islands (71%), in particular Badu Island. Ninety percent of presentations occurred during the wet season months of the Torres Strait, between January and May.

Many patients had more than one risk factor, and diabetes mellitus

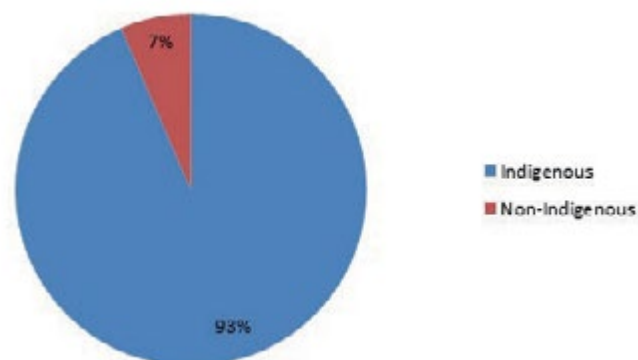


Figure 1. Proportion of Indigenous vs Non-Indigenous people infected with melioidosis between 2001-2012.

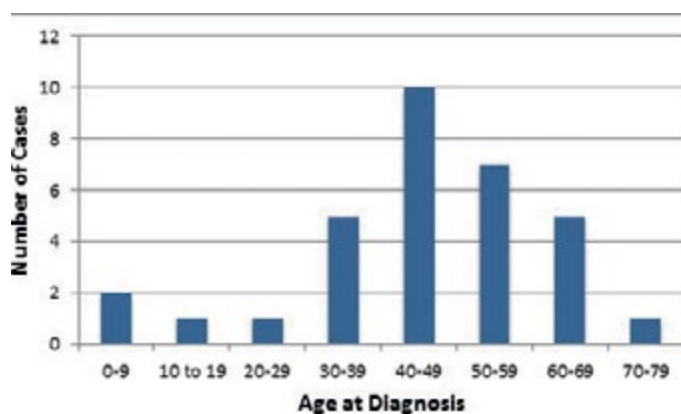


Figure 2. Age of distribution of confirmed melioidosis cases in the Torres Strait 2001-2012.

was by far the most common, present in 21 cases (68%). Excess ethanol intake (35%) and renal disease (12%) were also identified as significant risk factors in this study. Autoimmune disease (6%), malignancy (4%) and the use of immunosuppressive medication (2%) were considered minor risk factors (Figure 3). Significant risk factors were defined as those that represented a higher percentage in the population as extrapolated from data. Obesity, heart disease and COPD were not identified as significant risk factors in this study.

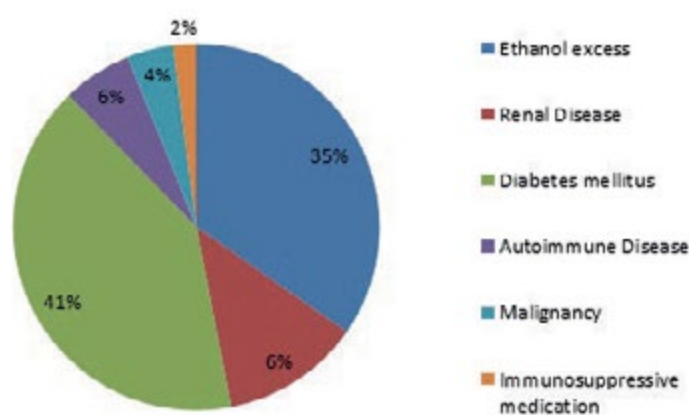


Figure 3. Risk factors for melioidosis infection in the Torres Strait 2001-2012.

Of all cases, pneumonia was the most common presentation (48%), closely followed by splenic abscesses (32%) and septic arthritis of a joint (29%). Other presentations included hepatic (19%), prostatic (19%), renal (10%), skin (6%), pancreatic (3%), scrotal (3%) and spinal abscesses (3%). Four presented with bacteraemia alone (13%), and one case presented with urethritis (3%) (Figure 4). The majority of patients (84%) recovered with a total of five ICU admissions (16%), two patients had long-term disability and there were two deaths, giving a mortality rate of 6.4%. Two of the 31 cases occurred in children, one

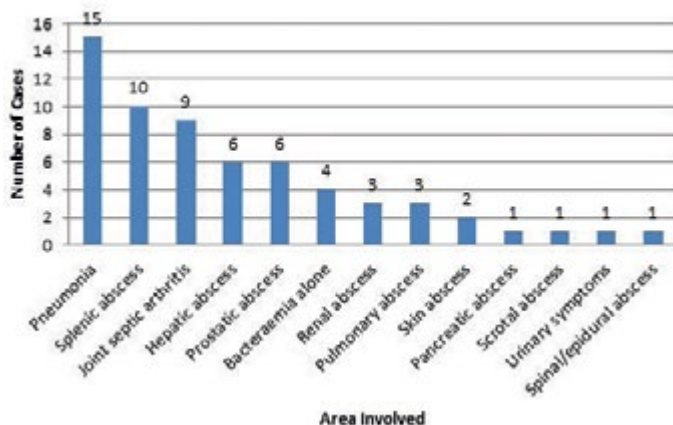


Figure 4. Clinical presentation of melioidosis in the Torres Strait 2001-2012.

in a five-week old infant with the outcome of death, and one in a five year old child who was not of Aboriginal or Torres Strait Islander origin, who presented with pneumonia and septicaemia. One case of relapse was identified in a 30-year old male from Badu Island who was non-adherent with treatment following discharge from ICU at the Cairns Base Hospital.

Discussion

To date, this study is the largest retrospective study of melioidosis within the Torres Strait. It highlights that melioidosis continues to be a disease of significance in the region, despite a larger public profile in recent years. [3] The average annual incidence reported in this study is 37 cases per 100,000 between 2001 and 2012, less than that reported in a previous study examining 1995 to 2000, in which a total of 24 cases were reported, giving an annual incidence of 42.7 cases per 100,000. [5] The incidence of melioidosis in the Torres Strait remains one of the highest in Australia, excluding the seasonal peak in Darwin between 2009 and 2010. [6] The finding of this study is high compared to international figures, such as those reported in Thailand, where the annual incidence of melioidosis is 5.5 per 100,000. [10]

The high incidence reported here could be attributed to a number of environmental and population factors unique to the Torres Strait region. Climate is a major factor, as the Torres Strait region has very high rainfall during the seasonal wet months from December to May. [5] This reinforces the seasonal distribution of melioidosis, as 90% percent of cases identified occurred within these months. This strong association between the incidence of melioidosis and the rainfall patterns highlights an opportunity for public health intervention to be focussed on the annual wet period in the Torres Strait. In addition, melioidosis incidence was highest on TI (26%), closely followed by Badu Island (23%), which creates additional target locations for public health intervention.

In alignment with the literature, our study demonstrated an over-representation of the Indigenous population presenting with melioidosis. Out of the 31 cases, 28 identified as Indigenous (93.5%), and only three as non-Indigenous. This could be attributed to the generally poorer health status of Indigenous Australians, and the higher rates of chronic illness such as diabetes mellitus, resulting in this population being more susceptible to melioidosis infection. [11] The higher incidence of melioidosis may also be attributed to the cultural differences in the Indigenous population of the Torres Strait. This population has been anecdotally noted to rarely wear shoes, and to spend much of their time in outdoor activities such as fishing. This results in a significant higher environmental exposure to *B. pseudomallei*.

The incidence of diabetes mellitus within the Torres Strait is one of the highest in Australia, with one third of the population affected. [11] Diabetes mellitus is considered to be one of the most significant risk

factors for melioidosis infection, both in Australia and abroad. [10] This was confirmed in this study, with 68% of the case patients identified as having type 2 diabetes mellitus. In comparison to studies in Thailand and Malaysia, 60.3% and 70.4% of their case participants, respectively, were identified as having diabetes mellitus. [12,13] Alternatively, in Darwin, a 20-year prospective melioidosis study from 1989 to 2009, which included 540 cases, identified 39% with underlying type 2 diabetes mellitus. [3] Similarly, a 10-year prospective study in northern Australia identified 37% with diabetes mellitus. [4] Other important risk factors for melioidosis identified were excessive alcohol use (35%) and renal disease (12%). These have been previously identified however alcohol use was considered to be a more significant risk factor for melioidosis in Australia, and renal disease a more significant risk factor in South East Asia. [7,10]

Melioidosis presentation in this study commonly included pneumonia, septic arthritis, and hepatic, splenic and prostatic abscesses. Of these, pneumonia was the most common form of presentation (48%), which reinforces aerosol inoculation as an important transmission route. This finding was similar to that found in numerous studies [3,4]; however, genitourinary infections (3%) were not as common in our study. Genitourinary infections represented 15% of presentations in studies conducted in northern Australia [4] and 14% of presentations in studies conducted in Darwin. [3] Further differences existed in cases presenting with bacteraemia. In our study, 13% of cases presented with bacteraemia alone, compared with 46% of cases presenting with bacteraemia in a north Australian 10-year study. [3] The mortality rate in our study was 6.4%, which was also lower than the north Australian study which reported a mortality rate of 19%. [3] International mortality rates are significantly higher than in Australia, and were reported to be 63% in a Malaysian study and 49% in a Thailand study. [10]

For future follow up and extension of this study, another similar audit would be beneficial to complete for 2012-2022. A future audit would create continuity of data, and would provide further analysis of melioid disease patterns. Melioid disease patterns may be observed to decrease in incidence as a result of increased public awareness, improved access to health care and improved infrastructure, as most of the outer islands currently consist of unpaved roads. Alternatively, the suggested effects of climate change on weather patterns and increased rainfall could lead to an increase in melioidosis incidence, due to the strong environmental links. [1,15-17]

Another type of study that would be beneficial for the Torres Strait region would be to investigate the levels of *B. pseudomallei* exposure patterns. This would involve environmental sampling, to determine the concentration of *B. pseudomallei* present in the soils, waters and grasses across different islands. [14] This data could then be cross-referenced with our study data, which identified specific islands as having a higher number of clinical cases. Environmental studies could provide and explanation for the higher incidence of melioidosis present on particular Torres Strait islands. For example, if a decreased concentration of *B. pseudomallei* was found in the soils, waters and grasses of Badu Island, the health status of the population may be considered as a more weighted risk factor for melioidosis relative to environmental exposure.

Finally, a cost analysis study of the financial burden of melioidosis could be completed. Our study identified that the majority of patients required long stay admissions at TI Hospital and tertiary centres, and that a significant proportion of cases (16%) required ICU stay. This financial burden of melioidosis on the public health system needs to be addressed, as it may provide further incentive to fund greater public health programs aimed at the primary prevention of melioidosis.

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Conflict of interest

None declared.

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Social phobia in children – risk and resilience factors

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Introduction: Anxiety disorders account for one third of psychiatric complaints that young people present to their general practitioners with. Social phobia (SP) is one of the most prevalent of these disorders, in children and adolescents. **Methods:** Sixty nine patients with carefully defined SP and a control group of 129 typically developing (TD) children were recruited through the Academic Child Psychiatry Unit, Royal Children's Hospital. All completed the McMasters Family Assessment Device, Hopkins Symptom Checklist, and the Spanier Dyadic Adjustment Scale. **Results:** There were no clinically meaningful differences in family functioning between the SP group and TD group. Parents of children with social phobia reported higher rates of anxious ($\eta^2 = 0.10$), obsessive compulsive ($\eta^2 = 0.12$) and depressive ($\eta^2 = 0.13$) symptoms, compared to parents of the control group. Furthermore, the relationships of parents with children who have SP appeared to be unhappier ($\eta^2 = 0.15$) and they reported working together less ($\eta^2 = 0.14$) than their counterparts. **Discussion:** Although family functioning per se is not associated with an increased risk of SP in children, the presence of dysfunction tends to lead to protracted SP. Moreover, the stress of having a family member with a mental illness can impact on the parental relationship, causing problems. This may or may not be related to parents of young people with SP displaying symptoms of anxiety, obsessive-compulsiveness and depression. This supports the need to consider both the parents and children when constructing a management plan, which can be initiated and executed by general practitioners.



is an emerging association between SP and Bipolar Disorder (BPAD), while comorbid alcohol abuse in patients with BPAD and co-morbid SP seems to be recognised. [9-11] Interestingly, to date, there are no replicated findings about the impact of parental relationship factors on SP specifically.

Aim

The aim of this study is to investigate the potential risk and resilience factors in children with SP in the domains of family functioning, parental psychopathology and parental relationship. The McMasters Family Assessment Device (FAD), Hopkins Symptom Checklist (HSCL) and Spanier Dyadic Adjustment Scale (DAS) were used to explore these three respective domains.

Hypotheses

The hypotheses that the research addresses are 1) that family functioning between the SP and TD groups would not differ; 2) that parents of children with SP would show features of SP and other anxiety disorders and 3) that parental relationship factors would not have a clear association with SP compared to TD young people.

Methods

This research represents a cross-sectional study and was conducted at the Academic Child Psychiatry Unit (ACPU), Royal Children's Hospital (RCH) in Melbourne. The ACPU is a clinical research unit that provides comprehensive, standardised assessments and treatment for children and adolescents with internalising and externalising disorders. Prior to the assessments, informed consent was obtained from the parents and children, and a consent form was signed. The data used in the analysis were obtained from standardised questionnaires and structured clinical interviews completed by the parents and young people.

An ethics approval was not required for this paper as both the data analysis and the questionnaires used in this research did not involve the use of identifying information. In addition, the questionnaires utilised for the data are part of the full standard assessment that all patients referred to the ACPU are required to undertake as part of their management. Furthermore, this research project is not part of a Doctoral or Master's degree.

Introduction

Mental health problems are prevalent amongst young people, with almost one in four experiencing some impairing difficulties in their adolescence. [1] While the first port of call for Australian children tends to be their general practitioners (GP), it is estimated that out of the 25% who seek help, there are at least twice as many who actually have mental health issues, since most young people present with somatic complaints. [1,2] Anxiety disorders are one of the commonest psychiatric problems and over a third of young people who present to their GPs have symptoms of anxiety and depression. [1-3] Social phobia (SP) is a social situation-dependent condition, characterised by persistent and exaggerated fear of embarrassment or humiliation in front of others. [2] It is among the most prevalent of anxiety disorders in children and adolescents, and can be significantly distressing and debilitating to its sufferers, causing social and academic impairment resulting in isolation, school avoidance and refusal. [2,3] Some studies have even shown a more serious side to this condition: anxiety disorders, including SP, are associated with increased risk of suicide attempts and deliberate self-harm. [4,5]

Existing literature found that family functioning is not associated with SP, but the persistence of SP in young people is greater when family functioning is dysfunctional. [6-8] Furthermore, parents of children with SP are likely to suffer from SP themselves, [6-8] there

Family Functioning

In order to assess family functioning, the McMasters Family Assessment Device (FAD) was used. Devised in the 1980s by Epstein and colleagues, the FAD described seven aspects of family functioning through a 52-item questionnaire: problem solving, communication, roles, affective responsiveness, affective involvement, behaviour control and general functioning. [12] The selection of responses for each item ranged from 1 to 4, where 1 = strongly agree, 2 = agree, 3 = disagree, 4 = strongly disagree. [13] The positively oriented items were then recoded and the total score could range from 12 to 48, where higher scores represent better functioning. [13]

Parental Psychopathology

To measure parental psychopathology, the 58-item Hopkins Symptom Checklist (HSCL), a self-report symptom inventory, was utilised. It was scored on parental distress from 1 to 4, where 1 = not at all and 4 = extremely, and it was reported from the five symptom dimensions of somatization, obsessive-compulsive, interpersonal sensitivity, depression and anxiety. [14] The outcome of the survey was in the form of raw data, i.e. mean factor scores and standard deviations, calculated using average-unit weight methods, which made it better geared towards use in clinical research. [14]

Parental Relationship

The Spanier Dyadic Adjustment Scale (DAS) is a 32-item, widely used measure of relationship quality between couples. [15] For the purpose of this study, the abbreviated seven-item version of this instrument, which has shown good internal consistency and is deemed psychometrically sound, was used. [16] The DAS-7 consists of six-point Likert-type scales with end-points of "always agree" to "always disagree" or "all the time" to "never". [16] The last item on the questionnaire rates relationship satisfaction on a seven-point scale, with end-points of "extremely unhappy" to "perfectly happy". [16]

Statistical Analysis

Age, social adversity status (SAS) and full-scale IQ (FSIQ) were analysed using univariate analysis of variance, while gender was controlled using the chi square test. The HSCL, FAD and DAS variables were analysed using univariate analysis of covariance, controlling for SAS and FSIQ. Partial eta squared was used to ascertain effect sizes for variables that differed between the groups. The value at which a sample is considered to be clinically significant or large, was set at $\eta^2 \geq 0.10$.

Results

The 69 children diagnosed with SP and 129 TD children were identified using the Anxiety Disorders Interview Schedule for Children (A-DISC), which is a semi-structured interview conducted by clinically-trained interviewers. [17] The A-DISC comes in a parent (A-DISC-P) and child (A-DISC-C) form and is designed specifically to diagnose anxiety and other related disorders in individuals from 6-16 years of age. [17] Based on the parent and child account of the most distressing or interfering symptoms, the children are given a principle diagnosis and any other diagnoses fitting the criteria, as determined by the A-DISC. [17] Patients with Full Scale IQ less than 70, and children living away from their parents were excluded. Patients with any coexisting DSM-IV-TR Axis I diagnosis were also excluded.

The SP and TD groups did not differ in their age or gender: mean age of the children with SP was 11.01 while the mean age of the TDP was 10.50 years. Out of the experiment group, 40 of them were males and 29 females. Similarly there were more boys in the control group at 70, compared to girls, of which there were 53.

Family functioning

There were no clinically meaningful family functioning differences between the families of children with SP and the TD young people. This was based on scores of $\eta^2 = 0.06$ for general functioning, $\eta^2 = 0.02$ for problem solving, $\eta^2 = 0.03$ for communication, $\eta^2 = 0.03$ for roles and $\eta^2 = 0.03$ for behaviour control, all of which are not clinically significant.

This suggests that families from both groups were able to effectively solve problems together and communicate, from a clinical standpoint. Furthermore, the results implied that the established roles and execution of those roles within families of either group were not dissimilar. Also, the way in which the expression and maintenance of behavioural regulation is achieved in the two groups was not different from a clinical perspective.

Parental psychopathology

The data revealed some interesting results in this regard, supporting previous literature that traits of anxiety are significantly present in parents of socially phobic children ($F = 16.62$, $p < 0.0005$, $\eta^2 = 0.10$). Furthermore, it was found that parents of the control group displayed symptoms of an obsessive-compulsive ($F = 20.08$, $p < 0.0005$, $\eta^2 = 0.12$) and depressive ($F = 22.01$, $p < 0.0005$, $\eta^2 = 0.13$) nature. In addition, the effect size of the total HSCL score between the groups was $\eta^2 = 0.14$.

This demonstrated that parents with children with SP also tended to have manifestations of anxiety, e.g. restlessness, nervousness, tension or even somatic signs like trembling. Moreover, these individuals tended to experience the presence of unwanted thoughts, impulses or actions more often than their counterparts. Interestingly, parents of SP children also appeared to suffer from more dysphoria, anhedonia, avolition and hopelessness than parents of the control group. Overall, the data showed that parents of socially phobic children seemed to have more symptomology of mental health problems than parents with TD children.

Parental relationship

Contrary to the hypothesis on parental relationship, the effect size of the total DAS scores of the two groups proved to be $\eta^2 = 0.11$. Additionally, there were clinically significant problems with the happiness in the relationship ($F = 20.41$, $p < 0.0005$, $\eta^2 = 0.14$) and ability of spouses with SP children to work together ($F = 22.62$, $p < 0.0005$, $\eta^2 = 0.15$) compared to the control group.

This non-hypothesised result suggested that in families with children with SP, the relationships between the parents tended to be more strained, and they did not often collaborate on projects together.

Discussion

In general, the results of the data analysis were largely similar to the hypotheses put forth at the beginning of this paper. As supported by Knappe and colleagues in both their 2009 publications, family functioning was not associated with a risk of having offspring with SP. Earlier studies by Lieb *et al.* nearly a decade before also agreed that there was no connection between a child with SP and family functioning.

They did, however, discover that other parental factors, which were outside the scope of the measures used in this project, were associated with greater persistence of SP in children with the diagnosis. For instance, in cases where parents also had SP, negative parental rearing styles like parental overprotection coexisted (DSM-IV threshold SP: Beta = 0.23, $T = 2.06$, $p = 0.043$; at least sub threshold SP: Beta = 0.22, $T = 2.07$, $p = 0.042$). [8] In situations where there was an absence of disorders in parents, parental rejection (Beta = -0.42, $T = -2.18$, $p = 0.032$) also caused the persistence of SP in their offspring. [8] Furthermore, it was noted that, when families were dysfunctional in their functioning, SP tended to be more persistent in the children. [8]

According to the data produced in this study, parents of children with SP tend to have traits of anxiety and obsessive compulsive disorders themselves. Interestingly, the results also showed that a clinically significant portion of these also suffered from depressive symptoms.

It is well known in the literature that parents with SP themselves are at greater risk of having offspring with SP. [6-8] One study supported the findings of this paper, showing the risk of children developing SP is greater when their parents have SP (OR = 3.3, 95% CI: 1.4-8.0), other anxiety disorders (OR = 2.9, 95% CI: 1.4-6.1), depression (OR = 2.6, 95%

CI: 1.2-5.4), and even alcohol use disorders (OR =2.8, 95% CI: 1.3-6.1). [7]

This was not the first time alcohol abuse has been associated with SP. Studies by Perugi *et al.* found that patients with SP and co-morbid Bipolar Affective Disorder Type II (BPAD II) tended to develop alcohol abuse problems. [10] In that situation, however, they argued that the co-existence of BPAD and SP led to protracted anxiety in social situations, which may have explained their increased susceptibility to using alcohol as a social lubricant. [10-11]

Future research should seek to uncover whether the symptoms experienced by the parents are a direct result of raising children with SP, or whether their own psychopathology has contributed to their children's condition. Longitudinal study designs are needed.

It was hypothesised that the parental dyad would not be affected as a result of having a child with SP, due to the fact that SP, like many anxiety disorders, are internalising conditions. However, in this study these individuals ranked lower in relationship satisfaction and working on joint projects together. One explanatory theory could be that behavioural difficulties in children with SP, such as school refusal and poor academic performance, indirectly cause discord in the relationship of their parents. Conversely, a troubled parental relationship could potentially exacerbate or even contribute to symptoms of SP that their child.

Although no prior studies have been conducted exploring the use of the DAS as a parental relationship measure, the findings are not unreasonable. A study in 1997 by Friedman *et al.*, which examined adaptive functioning in the families of patients with psychiatric disorders, agreed with this. Their research found that, regardless of diagnosis, having a family member in an acute phase of a psychiatric illness was a significant stressor and put them at risk of poor family functioning. [18]

It may be reasonable to conclude then, that having an offspring with SP puts stress on the family as a whole, and can therefore lead to difficulties within the parental relationship. For instance, the demands of caring for a child with SP in addition to other responsibilities may result in less time spent together as a couple, and hence less time spent working together on projects. Given enough time, this may lead to relationship dissatisfaction. Ideally, future research will recreate or produce more modern data looking into this area, allowing for better interpretation.

Relevance to general practice

As alluded to earlier in this paper, there is a darker side to suffering from SP: namely the risk of suicide and self-harm. Even if one disregards this aspect of the condition, it is undeniable that an individual's development will be impaired if they are unable to fully participate with their peers socially and academically when growing up. In addition, this research supports the fact that the parents and family unit should not be forgotten when it comes to managing SP in young people. [1]

One of the more effective treatments for SP is Cognitive Behaviour Therapy (CBT). [3,19] In addition to treating SP in children, CBT is also useful in managing adult depression and anxiety disorders. [19] Also within the scope of CBT is dealing with issues related to marital distress. [19] CBT is a type of talking-therapy where a person's emotions, thoughts and behaviours as linked to particular circumstances e.g. social situations, and negative thought patterns are challenged. [19]

While traditionally seen as a time consuming form of psychotherapy in

the GP context, a recent article by Harden encourages GPs to reconsider. [19] She argues that CBT is among the least consuming of psychological therapies, due to its highly structured nature. [19] Furthermore, where CBT was once the domain of psychologists and psychiatrists, Harden outlines several resources for GPs to undergo training in basic CBT techniques, which will enable them to utilise this skill. [19]

Post-training, GPs should be well-equipped to handle the milder forms of SP and family dynamics, and still retain their ability to refer complex cases to specialists. [19] Moreover, they can serve as a bridge for more complex patients who are waiting for specialist appointments. [19] These GPs can gain satisfaction from enabling their patients to develop problem solving techniques, take more responsibility and make better choices. [19] As an added bonus, GPs trained in psychotherapy now receive greater rebates from the government as an incentive to participate in mental health care. [19]

Exposure therapy is another form psychotherapy which effectively manages SP, which GPs are able to execute. [2,20] This behavioural intervention, which incorporates activity scheduling, graded task assignment, distraction and relaxation, can be easily learned by both GPs and patients to a level of competence comparable to treatments conducted by mental health specialists. [2]

Another way to manage SP is using drug therapy, e.g. sertraline with or without psychotherapy. [20] Blomhoff and colleagues found that sertraline was one of more 'GP-friendly' psychiatric drugs, owing to its effectiveness and tolerability. They recommended a blend of sertraline and exposure therapy to manage SP in general practice, the latter more so in patients unsuitable for drug treatment or who do not respond to sertraline alone. [20]

Conclusion

In summary, although family functioning per se is not associated with an increased risk of SP in children, the presence of dysfunction can lead to protracted SP. Moreover, the stress of having a family member with a mental illness can impact on the parental relationship, causing problems. This may or may not be related to the parents of young people with SP displaying greater symptoms of anxiety, obsessive-compulsiveness and depression. These interplaying factors make it necessary to consider both the parents and child, when constructing a management plan.

The field of primary care is well-equipped to aid with the management of patients with SP and their families through the use of psychotherapies e.g. CBT and exposure therapy, as well as medications e.g. sertraline. This will be extremely beneficial due to the debilitating and sometimes serious nature of this problem.

Future research should be geared towards producing more modern data and exploring the areas of parental relationship and parental psychopathology in the context of SP, in more detail.

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Conflict of interest

None declared.

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Chocolate, Cheese and Dr Chan: Interning at the World Health Organization Headquarters, Geneva

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Introduction

In early 2013, Ban Ki-Moon, Margaret Chan and Kofi Annan had something in common: they may be completely unaware of it, but I saw them speaking in Geneva, and not merely because I lurked around Palais de Nations. Rather, wielding my very own blue United Nations (UN) ID card as an intern at the World Health Organization headquarters (WHO), I became a de facto insider to events on the international stage.

Between January and March, I undertook an 11 week internship with the WHO Emergency and Essential Surgical Care (EESC) Program in the Clinical Procedures Unit, Department Health Systems Policies and Workforce. The WHO is the directing and coordinating authority for health within the UN. It is responsible for providing leadership on global health issues, setting the research agenda, setting and articulating norms, standards and evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends. [1] At some point during your studies, you will encounter material developed and disseminated by the WHO. You may have cited WHO policies in your assignments, looked up country statistics from the Global Health Observatory before your elective, or at least seen the ubiquitous *Five Moments for Hand Hygiene* posters, which emerged from WHO guidelines. [2] In other words, if you haven't heard of the WHO or don't recognize the logo, then I suggest taking a break from textbooks and click around the many fascinating corners of their website. Perhaps watch *Contagion* for a highly stylized (but filmed partially on location) view of an aspect of their work. [3]

The WHO and Surgery

The WHO established the EESC Program in 2005, in response to growing recognition of the unaddressed burden of mortality and morbidity caused by treatable surgical conditions. [4] This reflects the lack of prioritization of surgical care systems in national health plans and the ongoing public health misconception that surgical care is not cost-effective and impacts only upon a minority of the population. [5] These misconceptions apply as much to those in the field of public health, as well as to surgeons on the ground and in the literature, let alone those at other agencies. This was reflected by the question I all too commonly faced when explaining my internship: "The WHO is involved in surgery?"

In reality, surgical conditions contribute to an estimated 11% of the global burden of disease. It is a field that cuts across a number of public health priorities. [6] For example, progress on many of the Millennium Development Goals demands the prioritization of surgical care systems, most obviously in connection with maternal and newborn care. [7] Timely access to surgical interventions, including resuscitation, pain management and caesarean section, are vital to reducing maternal mortality. [8] Even in its most basic forms, surgical procedures can play a role in both preventative and curative therapies, from male circumcision in relation to HIV control to the aseptic suturing of wounds. However, surgery also has a very real impact on poverty by addressing the underlying causes of disability which often contribute to unemployment and debt. These include the management of congenital and injury incurred disabilities and preventable blindness. [9] Surgery can be a complex intervention because it relies upon numerous elements of the health system to be functioning completely.



There is little point in having access to basic infrastructural amenities like electricity, running water and oxygen, when at the moment of an emergency it is unavailable. Similarly, having equipment and supplies alone are insufficient when there is a shortage of a skilled workforce to wield them.

The WHO EESC is dedicated to supporting life-saving surgical care systems in the areas of greatest need, through collaborations between the WHO, Ministries of Health and other agencies. The WHO Global Initiative for Emergency and Essential Surgical Care (GIEESC) is an online network linking academics, policy makers, health care providers and advocates across 100 countries. Together, they developed the WHO Integrated Management for Emergency and Essential Surgical Care (IMEESC) toolkit to equip health and government workforces with WHO recommendations, skills and resources, focusing on emergency, trauma, obstetrics and anaesthesia, in order to improve the quality of, and access to, surgical services. [4]

In terms of my role, let me begin with the caveat that, as an intern, one can be called upon to conduct a wide variety of tasks within the huge scope of the WHO. My experiences differed greatly from those of colleagues and are not necessarily reflective of what one may encounter in other departments, or even in the same program at different times of year. I applied through the online internship application, but amongst my colleagues, this was in fact a rarity. [10] By far the majority of interns had applied directly or through their university to the specific areas of the WHO that aligned with their interests.

I undertook both administrative and research tasks, working very closely with my supervisor, Dr. Meena Cherian. There is a paucity of evidence capturing the surgical capacity, including infrastructure, equipment, health workforce and surgical procedures provided, across facilities in low- and middle-income countries. Through the GIEESC network, the WHO Situation Analysis Tool captures the capacity of first-referral health facilities to provide emergency and essential surgical care. [4] One of my key roles was in data collation and analysis. In terms of tangible outcomes, in the span of my internship I was able to contribute to two research papers for submission. In terms of my education, however, it was the administrative roles that demonstrated many of the key lessons about working in international organizations, and for which I am most grateful. Although menial tasks like photocopying and editing PowerPoint presentations can seem futile, carrying those documents into meetings allows one to witness the behind-the-

scenes exchanges that drive many international organizations. This deepened my understanding of the WHO's functions, strengths and limitations. In my experience, exacerbated by funding limitations and the rise of game-changing new players from the non-government sector, such as the Bill and Melinda Gates Foundation, attracting and justifying resource allocation to marginalized areas like surgery becomes a full-time job in itself. Opportunities for collaboration with such NGOs can result in successful innovation and programming, as with the polio eradication campaign. However, although inter-sector and inter-department collaboration is seemingly an obvious win-win, the undercurrents of turf wars and politicization of health issues can make such collaborations seem like a delicate diplomatic performance. Effective WHO engagement with external stakeholders cannot come at the cost of its intergovernmental nature or independence from those with vested interests. [1] Such are the limitations imposed on international organizations by the international community and the complex relationships between member states.

Ultimately, learning to collaborate with colleagues across cultural, economic, resource and contextual barriers under the tutelage of my supervisor has implications for any future endeavor in our increasingly globalized workplaces. Learning to navigate such competing social and political interests is as applicable to clinical practice as it is to public health. Furthermore, the *Experts for Interns* program initiated by the WHO Intern Board provides bi-weekly lunchtime seminars specifically designed to broaden the scope of the intern experience by facilitating discussion with experts in various fields. [11] These were particularly valuable as an opportunity to ask direct questions, challenge preconceived notions and reexamine the historical development of public health, global health and the role and scope of the WHO.

Personal Highlights and Challenges

Geneva is an international city, home not only to WHO HQ and the United Nations in Europe, but also to a number of other UN Agencies and international non-governmental organisations, including Médecins Sans Frontières and the International Committee of the Red Cross. This means that, at any given time, there are a huge number of international and cultural events occurring. During my stay alone, there was the WHO Executive Board Meeting, the Geneva Human Rights Film Festival, a number of conferences, the UN Human Rights Council and some truly high profile speakers. Hans Rosling, the rock star of epidemiology and a founder of GapMinder, has put together a great TED Talk, but seeing him speak in person was one of my most lively, educative and stimulating experiences. [12,13] It is a memory I will treasure and return to for motivation, particularly when rote learning another fact for an exam seems impossible. For many of us who aspire towards a career in global health, seeing these famous faces and learning firsthand about their work and career pathways is more than just inspiring, it can become a *raison d'être*.

From a slightly more cavalier perspective, Switzerland is centrally located in Europe, and Geneva as an international city is a great base from which to travel. It is easy to find sale flights to major European destinations, and the train to Paris takes only three hours. As an unpaid intern, your weekends are your own and most supervisors are generous about allowing travel grace. The opportunity to explore a new city every weekend is alluring, and with options like the *demi-tarif*, the half-priced fares on Swiss trains, it's certainly a possibility. The Geneva and Lac Lemman region features charming villages and cities with the sort of breathtaking mountain views that makes everything look like a postcard, not least if it's covered in a blanket of pristine white snow. This is the other key attraction of Geneva in winter: if you're into snow sports, you will be based within an easy day trip to some of the best *pistes* in the world. Indeed, the Swiss penchant for such trips seems to be why Sundays find Geneva a ghost town of sorts. Aside from the odd museum, absolutely nothing is open on Sundays, to the point where if you make my mistake of arriving on Sunday, it may be difficult to even find food.

Even if you can find food on a Sunday, affording it and anything else in Geneva is not easy. The cost of living is high, and, despite the high turnover of ex-pat staff, finding a place to stay is extremely difficult. As Australians we have it luckier than most, by being able to make use of OS-HELP loans while studying overseas. There is an ongoing discussion about paid internships within the UN, and there are varying practices amongst agencies. Some, notably the International Labor Organization, pay interns, while the WHO and others do not. This has become an advocacy issue amongst interns, as it severely limits access to the educative and career-oriented experiences internships provide for those from middle- and low-income nations. However, it seems unlikely that this will change in the near future. Nonetheless, with careful saving, planning and some basic austerity measures, finances should not deter you from this experience.

Another potential challenge is that Geneva is in francophone Switzerland; it is geographically surrounded on most sides by France. Many WHO staff and interns live, or at least shop, across the French border, where I discovered amazing supermarkets with entire aisles devoted to Swiss and French cheeses and chocolate. As a hopeless Francophile, this was a delicious highlight. I took classes and developed my French while safely working in a predominantly anglophone environment. If you have never studied French, then learning basics pre-arrival would be recommended, though it is possible to get around Geneva without, as the locals are very generous in this regard. However, there were often times when my linguistic limitations perpetuated anglophone dominance, forcing colleagues to transition into my language of choice. Such language barriers can also contribute to cultural misunderstandings. For example, early on I committed the fauxpas of being too casual in the more hierarchical workplace, where professional titles were used even in personal conversations. Coming from the more egalitarian Australian context, this can come as something of a culture shock, though it varies considerably between different offices and departments.

As a result of my experiences, I am now both more cynical and more hopeful about the future of global health. The bureaucratic limitations of the WHO are also where its authority lies. Sifting through convoluted Executive Board meetings, it is easy to become skeptical about the relevance of this 65-year old organization. However, this belies the power of health mandates supported by member state consensus, whether in regards to the Tobacco Free Initiative or the Millennium Development Goals. Such change and reform, though slow, is broad reaching and invigorating.

Finally, the most significant and meaningful experiences I shared during my internship were not with the famous faces of global health, but with my peers. Across the various organizations based in Geneva, there are a huge number of interns from all over the world. Making connections with these kindred spirits, who shared my interests and a similar desire for an international career, was such a privilege. Even when our areas of interest did not intersect, it was amazing to learn from the expertise of fellow interns and students. For example, a fascinating experience was encountering a student at CERN (*Conseil Européen pour la Recherche Nucléaire*, better known to us non-physicists as the home of the Large Hadron Collider) with whom I was able to have a sticky beak at the labs and lifestyles of modern physics' greatest thinkers. Just as he is progressing towards becoming a *don* of theoretical physics, at some point in the next few decades many of the friends I've made through this internship are going to become the next generation of global health leaders. More importantly, creating such networks across continents and across specializations has been instrumental in shaping my sense of self and perspective, and has left an indelible mark in the form of new education, career and lifestyle aspirations.

Where to from here for you

There is an online intern application through the WHO website. Although I completed this as my elective term, I also encountered

a number of students from Australia for whom this was a summer opportunity to experience the organization, or as part of their research. I would strongly urge any student with interests in public health, global health, policy or research to consider applying for this opportunity, and to do so by contacting the departments of your interests directly.

In terms of surgery and global health, please visit the EESC program website at www.who.int/surgery for further information, and to become a GIEESC member.

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Patient Specific Total Knee Arthroplasties: A technological solution to the ageing population

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David is enjoying returning to study and is looking forward to the challenge of clinical years.

Australia is faced with an ageing population and is bracing for the significant health challenges of this changing demographic. Individuals born during the post-war population boom of the late 1940s are now progressing into the over 65 age bracket, which has led to the emergence of a number of unique health and economic challenges. While the majority of older adult Australians continue to live at home, caring for the ageing population will inevitably require additional healthcare resources.

Of today's older Australians, nearly half of the individuals aged 65-75 will have five or more long term physical health conditions. [1] By 2050, it is expected that the number of individuals aged 65-84 will have doubled, and the number of people aged over 85 quadrupled. [2]

The full challenge of the ageing population will be faced by today's generation of medical students. The future health system will not simply need to deliver more of the same services, but do so in a more efficient manner, making use of the most advanced technologies in a cost and time-efficient manner. The system will need to adapt to the complex needs of the elderly patient, optimising coordinated care between primary and tertiary health care facilities.

Currently, within the population of Australia some 15% (3.1 million) are affected by arthritis, with osteoarthritis being the leading cause. [1] Being a degenerative condition, the incidence of osteoarthritis increases with age, and accounts for the primary cause of approximately 97% of total knee arthroplasties (TKAs) performed in Australia. [3] The dramatic increase in the population aged over 65 represents an immense increase in the numbers of individuals at risk of osteoarthritic knee changes. Given the inevitable wave in those requiring joint arthroplasty, are we fully prepared for this expected number?

In 2011, a total of 40,470 TKAs were performed in Australia. [3] This represents an increase of 5.7% on the previous year and a further increase of 83.7% since 2003. [3] There is also a growing trend of patients requiring TKAs at an earlier age, further adding to the workload of surgeons and hospitals. [3] Given the growing demand and expected increase in the patient population, there is a clear impetus to evaluate novel surgical approaches used in total knee arthroplasties.

Patient specific total knee arthroplasties (PSTKA) are one possible solution to this growing demand. They provide an anatomically individualised approach to surgery based on pre-operative computer tomography (CT) or magnetic resonance imaging (MRI). Following imaging, a patient specific cutting block is manufactured from a digital 3D reconstruction of the patient's joint. The cutting blocks are then used to guide intra-operative bone resection, followed by installation of a pre-sized prosthesis. [4]

After initial assessment, the surgeon will decide upon the use of CT or MRI, based on personal preference. The scans are sent electronically to a manufacturing company of choice, where they are converted into a digital 3D reconstruction of the patient's anatomy using computer-aided design. At this stage, the surgeon will review the digital reconstruction and finalise coronal and rotational alignment parameters. The review process allows the surgeon to make changes prior to manufacture, specific to the patient's functional requirements. Following this process, the custom designed disposable cutting blocks are then authorised for fabrication. Intra-operatively, the cutting blocks are attached to the distal femur and proximal tibia to accurately

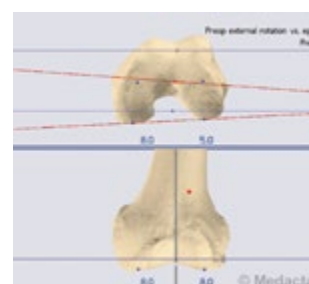


guide bone resection prior to the insertion of a customised prosthesis. [4] The primary advantage of the fabricated cutting blocks is their ability to accurately guide the quantity of bone resection, maintaining the desired coronal and rotational alignment for optimal prosthesis placement. [4]

Companies such as Medacta in Sydney, NSW, currently offer this service. From the time of the initial scans, the patient specific cutting blocks can be reviewed, and manufactured ready for use in as little as three weeks. Review prior to manufacture is a fully online process, allowing the surgeon to log in via any computer and make the necessary changes before authorising the cutting blocks for production. The time taken by the surgeon to review the specifications can range from 5-15 minutes, depending on the complexity of patient anatomy and individual skills. [5]



CT imaging



Digital 3D reconstruction



Functional design

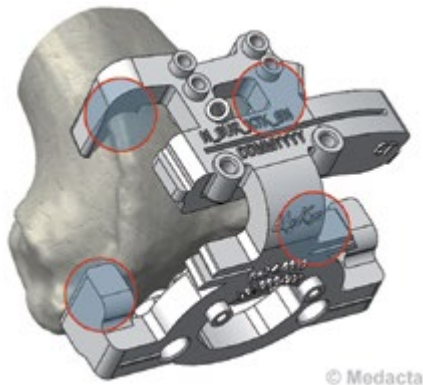


Manufacture

Figure 1. Critical steps in the manufacture of Patient-Specific Total Knee Arthroplasties.

By finalising operative procedures prior to surgery, there is less demand for intra-operative decision making by the surgeon, further

streamlining the process. [6] The individualised planning allows finalisation of prosthesis size, position and alignment prior to the first incision being made. [4] While this process may require additional out-of-operating commitments by the surgeon, overall it may lead to a reduction in the total theatre time per patient.



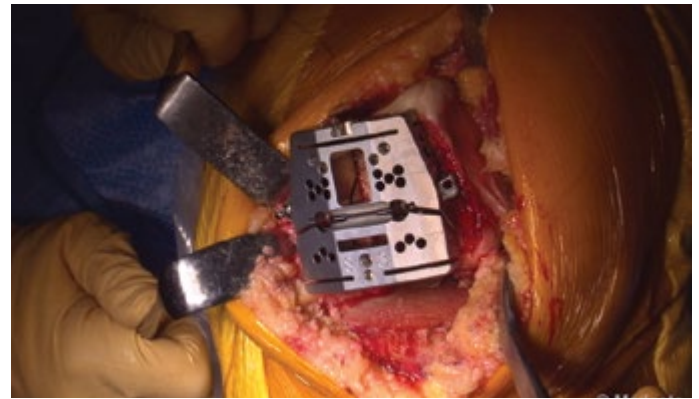
Manufacturers of this technology propose a number of positive outcomes. Advantages include reduced operative time when compared to conventional techniques, [4] pre-operative sizing of prosthesis, reduced bone resection [6] and optimal alignment of the tibia and femur post-surgery. [7-9] This method also does not require violation of the intramedullary canal as used in some conventional TKA methods. [4] Additional costing benefits may also be found in a reduction in the number of instrument trays required for surgery, leading to reduced setup time and sterilisation cost. Conventional methods require an average of 7.3 intra-operative instrument trays, compared to 2.5 used in PSTKA ($p < 0.001$). [14]

A sensitive indicator of the success of TKA is prosthesis survival, measured in years post surgery. This idea is supported in research by Berend *et al.* (2004), who demonstrated that a tibial varus deformity greater than three degrees was associated with implant failure at rates 17 times greater than seen in patients with tibial deviation of less than three degrees post surgery. [10] In the literature, alignment of the tibia on the femur within three degrees in the coronal plane remains a consistent indicator of surgical outcome. [10-12]

A study conducted by Ng *et al.* (2012) examined the post-operative alignment outcome in 569 PSTKA, compared to 155 TKAs performed using intra- and extra-medullary alignment techniques. Of the patients undergoing PSTKA, only 9% had alignment outside of three degrees post-operatively, when compared to 22% using conventional methods ($p=0.02$). [11] While there is evidence in the literature that alignment outcome in PSTKA are comparable to those achieved with computer assisted surgery (CAS), utilisation of CAS in America remains low due to the cost of the technology, with only 3% percent of TKA being performed using CAS alignment systems. [12]

Of particular interest to both surgeons and hospitals is the proposed reduction in surgical time offered by PSTKA. Research conducted by Hamilton *et al.* (2013) compared intra-operative time of 52 patients undergoing PSTKA, and those undergoing conventional methods. [14] That study demonstrated no reduction in surgical time offered by those receiving PSTKA. Of interest, the study noted the fact that the surgeon who performed all 52 of the cases had vast experience using conventional methods prior to the study. This included performing over 1,500 conventional TKAs compared to 20 PSKTA. [14] With this significant limitation in mind, there is clear impetus for further evaluation into the possible time efficacy of PSTKA when performed by surgeons equally skilled in both techniques.

In further research assessing the time efficacy of PSTKA, Nunley *et al.* (2012) reported a positive trend in reducing tourniquet time from 61.0 ± 15.0 minutes in the conventional group, compared to 56.2 ± 15.1 minutes in the PSTKA group ($p=0.09$). Alternately, another recent study



demonstrated a significant reduction in total operating theatre time from 137.2 ± 33.6 in the conventional group, compared to 125.1 ± 22.7 in the PSTKA group ($p=0.028$). [6] While some of these results are not statistically significant, they highlight the need for continued evaluation of PSTKA compared to alternative methods of TKA. Evaluation of the current research reveals an optimistic view of PSTKA in its ability to reduce intra-operative time. [15] With any new approach to surgery, practice is needed to hone the skills essential for efficiency.

Possible drawbacks highlighted in current literature include the additional workload of pre-operative imaging. Specifically, the cost of pre-operative CT or MRI remains a consideration. While the scans do not require interpretation by a radiologist, saving both time and money, the cost of a MRI ranges from A\$500 to A\$1000 depending on the institution. Additionally, in the use of CT imaging there is dosing of ionizing radiation, which must be considered. [4]

In addition to patient outcomes, the cost involved in adopting a new approach to surgery must always be considered. Currently, PSTKA is not cost-effective on a case-by-case basis, when compared to conventional TKA. PSKTA is, however, more cost effective when compared to computer-assisted TKA surgery. [13] Interestingly, the authors noted a reduction of 28 minutes per case of operating room time in PSTKAs, and this was not factored into the costing analysis. At an institutional level, perhaps an increased case turnover in the operating room will prove cost effective when compared to alternative techniques. [13]

At this point in time, further research needs to be conducted into the durability and longevity of PSTKA. While this requires extended follow-up and evaluation of records, survival rates of implants may become particularly important in light of the growing trend toward a younger patient population. [3] Currently, TKAs are being performed at an earlier age due to increasing levels of obesity, active lifestyles and increasing life expectancy. [3] With this younger population group comes the need to provide patients with prostheses that will last, reducing the need for subsequent revision. Importantly, with aseptic loosening of prosthesis being shown as the most common cause of premature failure, perhaps a customised approach to initial surgery may demonstrate improved longevity at follow-up. [9]

As in any new area of research, there is a particular need for larger trials with extended follow-up. The purpose of this article is not to condone the widespread use of PSTKA, but rather to illustrate the importance of technology and the continued search for improvement. As doctors, it is essential to always question current methods of practice and seek to refine technique, finding improvements where possible. PSTKA makes use of some of the most advanced imaging and engineering techniques currently available, and provides an innovative approach to knee surgery. There is no doubt PSTKA offers an exciting alternative to conventional surgical methods, meshing surgical expertise with advanced engineering technologies. In the future, could the 3D printing of patient specific prostheses take this technology to the next level?

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The role of the food industry in tackling Australia's obesity epidemic

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Samantha is a fourth year medical student at the University of New South Wales. She is currently completing an honours year, undertaking research in the field of limbal stem cells. She serves as the undergraduate representative on the UNSW University Council and as the ILP/Honours representative on the UNSW Medical Society. She is a keen traveller, bungy-jumping novice and appreciates the quirky side of life.

Whilst a number of factors contribute to Australia's rapidly rising obesity rates, the role of fast food companies in addressing the epidemic remains controversial. This report discusses the contribution of fast food companies to high obesity rates, explores the notion of corporate social responsibility, and discusses a range of government policies that could be implemented to limit the contribution of fast food chains in promoting obesity.

Introduction

Obesity is a major concern in Australia, with 62.8% of the adult population termed overweight (35.3%) or obese (27.5%). [1] Multiple factors contribute to these rising statistics, and whilst fast food companies undeniably contribute to obesity, defining the exact role that they play and their responsibility remains controversial. Whilst difficult to numerically define, previous studies have offered various definitions of fast food, broadly defining it as food purchased from cafeterias, restaurants and 'big brand' companies (such as McDonalds) that are high-calorie and low in nutritional value. [2-4] Food produced in restaurants, for example, is at least 20% higher in fat-content than the home-cooked equivalent. [5] It has now been over a decade since the infamously termed 'McLawsuit,' in which a group of overweight children in America filed legal action against the McDonalds corporation for their obesity-related health problems, first bringing the issue of corporate responsibility to a head. [6] Increasingly, now, trends are towards increasing regulation of the fast food industry, with recent debate over a fat tax in Australia, [7] and New South Wales enforcing nutrition labelling of fast food products. [8] The obesity epidemic continues to contribute to the morbidity and health expenditure of many developed countries, with minimal resolution on the role that fast food companies should play in tackling it.

Obesity in Australia: The contribution of fast food companies

The complex array of factors contributing to obesity makes the issue of responsibility a difficult one. [9] Australia's obesogenic environment comprises multiple factors, such as increasingly sedentary lifestyles, poor education regarding nutrition and the accessibility of fast food. [10] In this respect, fast food companies, government and the wider community are all stakeholders with differing degrees of responsibility.

Fast food companies are considered a key stakeholder in contributing to Australia's obesogenic environment. This is attributed to factors such as their large portion sizes, and marketing ploys that intensively promote the accessibility of unhealthy snack foods and target vulnerable groups such as low-income earners and children. [11] These factors make it difficult for consumers to make informed choices and resist unhealthy options, ultimately contributing to overeating and excess body weight. [12] Establishing a causal link between fast food companies and obesity is difficult due to the complexity of the relationship. An analysis by Chou, Rashad and Grossman (2005) indicated that a ban on fast food advertising would reduce the number of overweight children by 10% in the 3-11 year age group, and by 12% amongst 12-18 year olds, suggesting a causal component to the relationship in this vulnerable population group. [13] Accessibility of fast food outlets is also a contributing factor, with Maddock and colleagues (2004) showing that there is a significant correlation between proximity to fast food restaurants and obesity. [14] Furthermore, ever-increasing portion



sizes also provide evidence for the influence of fast food companies on obesity; with Young and Nestle (2002) noting that portion sizes have paralleled the increase in average body weight. [15] Whilst some claim that fast food companies simply respond to consumer desires, and that the average consumer is well aware of the obesity epidemic, it can be argued that they are still partly responsible by providing and promoting this supply.

Corporate Social Responsibility

Corporate Social Responsibility (CSR) is a form of self-regulation that corporations integrate into their business model. [16] It involves taking responsibility for the impact of the company's decisions on society and the environment. [17] Guler and Crowther (2010) further describe CSR as honouring the triple bottom line of people, planet and profit rather than solely focusing on profit maximisation. [18]

Proponents of CSR claim that it maximises long-term profits by encouraging firms to operate sustainably, decreasing risks despite initial costs. [19] Wood (2010) argues that 'strategic CSR' rewards business for CSR activities via the positive responses of consumers, employees and shareholders. [20] Ethical business policy may lead to brand differentiation and customer loyalty, increasing purchase intention and willingness to pay. Similarly, employees may be attracted and motivated by strong CSR policies, potentially increasing recruitment, work ethic and employee loyalty. Successful CSR strategies can also improve a firm's reputation, reduce external pressure from non-government organisations (NGOs) and attract shareholders. [21] For example, Becker-Olsen *et al.* (2006) argues that McDonald's funding of programs such as Maths Online, Little Athletics and its Ronald McDonald House Charities acts as subconscious advertising to improve its reputation. [21-23]

However, as well as these incentives, firms also face challenges in establishing CSR policies. Some economists claim that CSR distracts from the role of business, which is to maximise profit. [24] The financial costs of introducing CSR policies may also be barriers for firms, particularly small businesses that lack the required resources. [20] Moreover, CSR does not necessarily equate to positive consumer perceptions, as the credibility of corporations is often doubted. [21] For example, partnerships between KFC and the McGraw foundation, McDonalds and WeightWatchers, and Nestle and Jenny Craig have been criticised as marketing ploys, termed 'weightwashing' by the Obesity Policy Coalition. [25]

In the context of Australia's obesity epidemic, CSR policies in the food industry may have varied impacts. Fast food companies, at a time of increasing obesity rates, may see an opportunity in utilising health policy to establish consumer goodwill and brand value, creating a profit-driven incentive to engage in obesity prevention. Self-motivation in CSR policy construction could, however, be detrimental to health prevention, with, for example, fast food companies shifting blame from 'foods' to 'sedentarism' in their marketing, rather than altering the quality of their products. [20] Additionally, as a defensive response to avoid government regulation, the food industry has created an opening for itself in a health and sports promotion role, which, whilst contributing to preventative health programs in the short-term, may in time detract from the conventional governmental role in public health, devolving government of some responsibility without effectively satisfying community needs.

Despite its challenges, the potential benefits of CSR and the rise of privatisation and globalisation make self-regulation in the food industry an important, and perhaps inevitable, approach to consider in tackling obesity. [25]

Government Regulation

In light of steadily increasing obesity rates in many Western societies, a number of governments have implemented policies to reduce the impact of fast food companies in promoting overeating. [26,27] Outlined below are four categories of legislative change and their implications.

Restricting fast food advertising

Fast food advertising can send misleading messages to consumers, particularly those less informed. [28] Ethically, from a communitarian perspective, restricting advertising may denormalise fast food by making it less ubiquitous, helping change social attitudes, which is key to combating obesity. [29] Conversely, restrictions on advertising limit choice by making consumers less aware of their options, contradicting the principle of autonomy. Whilst it could be said that advertising of healthy foods continues to provide this autonomy, critics argue that fast food is not harmful in moderation and thus consumers should be able to make an informed decision of their purchases. Similarly, in alignment with narrative ethics, individuals have different approaches to eating, which may be compromised by eliminating the information delivered by fast food advertising. [30,31] It is important to note, however, that many of these concerns assume advertising delivers accurate information, which is often not the case. Critics also claim that restricting advertising is ineffective, as there are more important factors contributing to obesity. In addition, there are concerns about how the distinction between healthy and unhealthy foods would be made and the rights of companies to market their goods. [32]

Examples of restrictions on fast food advertising include banning fast food company sponsorship of sporting events and celebrity endorsement of unhealthy foods, as well as banning advertising that targets children, a population group particularly susceptible to marketing ploys. In regards to this, banning advertising to children in prime-time hours has already been successfully achieved in a number of countries. Quebec, for example, has had a 32-year ban on fast food advertising to children, leading to an estimated US\$88 million reduction in fast food expenditure. [33] Australia has been moving towards restricting fast food advertising that targets children, with the Australian Food and Grocery Council resolving to not advertise fast foods in programs where at least 35% of the audience are children. [34] However, analyses of the difficulties of self-regulation in the food industry indicate that its effectiveness depends on the rate of engagement by individual companies and is not sufficient to adequately protect consumers. [35,36]

Cost measures

A 'fat tax' would involve taxing foods or beverages high in fat content

(other 'unhealthy' components such as sugar and salt could also be taxed). It aims to discourage consumers from unhealthy products and offset their health costs with the tax revenue generated. [37] Subsidies for healthy food options are considered less practical with a greater cost-burden for taxpayers. Critics argue that a 'fat tax' would disproportionately affect low socio-economic consumers, unless healthy alternatives are made cheaper. [38] Some argue that obese individuals are also less responsive to increased prices than consumers of average BMI, reducing the effectiveness of a tax. [39] A 'fat tax' could even exacerbate health problems – a tax only on saturated fat, for example, may increase salt intake, which increases cardiovascular risk. [38] Denmark was the first country to introduce a tax on fat in 2011; however, it has since resolved to repeal the legislation, claiming that it increased consumer prices, increased corporate administration costs, and damaged Danish employment prospects without changing Danish eating habits, reducing the likelihood of this approach being trialled by other countries, including Australia. [40] It should be noted, however, that country-specific differences may have contributed to its lack of success. These include the ability of the Danish population to travel to neighbouring countries to maintain their eating habits despite the government tax, which would not be feasible in Australia. Alternatively, the government could consider combining subsidies for healthy food options with a 'fat tax,' as this approach would be more acceptable to the public than a tax alone, and also yield a lower cost-burden for taxpayers than subsidies alone.

Nutrition labelling

Nutrition labelling aims to ensure consumers understand the nutritious value of foods. In Australia, all food labels must abide by the national Food Standards Code. [41] Options to simplify food labelling include traffic light food labelling, which codes foods red, yellow or green based on their fat, sugar and salt content. [42] Another option is health warnings on unhealthy foods to deter consumption. [43] Australia-wide, a new star rating system for packaged foods has been developed by a working group which included industry and public health experts; as of June 2013, this has been approved by state and federal governments. [44] The scale will rate foods from half-star to five stars based on nutritional value, despite concerns raised by the Australian Food and Grocery Council over the cost to manufacturers and how nutritional value would be determined. Sacks *et al.* (2009) argues, however, that there is insufficient evidence to suggest that food labelling would reduce obesity. [45] Critics also argue that more restrictive practices, such as health warnings, are excessive and impractical considering the ubiquity of high fat foods. [46]

Limit physical accessibility of fast food

Easy accessibility of unhealthy foods makes them difficult to resist. Making fast food less accessible again denormalises it, helping change social attitudes. This is supported by studies showing that obesity rates are higher in areas with an increased number of fast food outlets. [14] Zoning laws have been suggested as a policy tool to limit the accessibility of fast food, with findings suggesting success in reducing alcohol-related problems. [47] Other approaches to restrict access include removing fast food from high accessibility shelves in supermarkets, banning fast food vending machines and banning fast food from school canteens. Victoria, for example, has imposed strict canteen rules restricting the sale of fast food to twice a term. [48] However, critics argue that restricting the accessibility of fast food may undermine consumer autonomy and choice, impinge on the legal rights of companies to market their goods, and could also be a precedent for government intervention in other areas. [49]

Conclusion

Whilst it is difficult to define the extent of the role that fast food companies play, there is no doubt that they significantly contribute to Australia's obesity epidemic through their large portion sizes, low quality food, extensive fast food advertising and high accessibility.

Ultimately, combating obesity will require a multi-faceted approach that denormalises unhealthy foods – a process that requires both consumers and government to take a role in regulating the quality, marketing practices and accessibility of unhealthy products produced by the food industry.

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Conflict of interest

None declared.

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Improving medication adherence amongst Aboriginal and Torres Strait Islander peoples

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Introduction

Aboriginal and Torres Strait Islander peoples represent a minority population in Australia, comprising approximately 2.5% of the total Australian population in 2011. [1] There are a number of challenges faced by Aboriginal and Torres Strait Islander peoples, due to social, economic and health differentials as a consequence of the history of marginalisation. [3] Despite improvement in detection and management of chronic disease, Aboriginal and Torres Strait Islander peoples continue to have higher incidences of chronic diseases such as cardiovascular disease and diabetes mellitus. [2,4]

A contributing factor to this gap in health statistics is a low rate of adherence to medication amongst Aboriginal and Torres Strait Islander peoples. [5] While this problem is not unique to this population, there is global evidence that the rates of adherence to medication are lower amongst marginalised groups. [6] In order to help reduce the burden of disease amongst this group, it is important to explore some reasons for non-adherence that are unique to Aboriginal and Torres Strait Islander peoples. In particular, this article will focus on the impact of cultural insensitivity and problems with access to healthcare and medications amongst this population. It will suggest how adherence can be improved through improving cultural sensitivity and access to healthcare, in order to reduce the gap in health statistics between Aboriginal and Torres Strait Islander peoples and non-Aboriginal and Torres Strait Islander peoples.

Impact of non-adherence

The World Health Organisation (WHO) estimates that, in developed countries, 50% of patients fail to comply with advice given by medical practitioners, including both medication and lifestyle advice. [6] Non-adherence with medication is a complex problem that is multi-factorial, and can contribute both to the failure of treatment [5] and increased costs to the healthcare system. [7] Often, this lack of adherence is intentional due to side effects, perceived drug effectiveness, and cost. [8] The implications of these barriers to adherence for Aboriginal and Torres Strait Islander peoples will be discussed below, with an emphasis on cultural barriers preventing adherence. [9]

Chronic diseases require adherence to medications and lifestyle modifications, in order to slow disease progression and prevent complications. [10] Therefore, non-adherence to either form of treatment can contribute to the perpetuation of this gap in health statistics. For example, in general, Aboriginal and Torres Strait Islander peoples have higher rates of cardiovascular disease than non-Aboriginal and Torres Strait Islander peoples. [3] Given that medication and lifestyle modifications reduce risk factors of cardiovascular disease and improve mortality, failure to comply with these treatments can result in exacerbation of disease rates. [3] Similarly, diabetes mellitus is a condition that is more prevalent amongst the Aboriginal and Torres Strait Islander population, and its morbidity and mortality are also disproportionately higher amongst this population. [10] Poorly controlled diabetes mellitus, through lack of adequate pharmacological management, can have serious vascular complications. This perpetuation of health inequality would in turn have a negative impact on national health expenditure, leading to increased costs to the health system. [9]



Barriers to adherence

According to the WHO, there are five dimensions that can impair a patient's adherence with medication. [6] These are the healthcare team or system, socioeconomic factors, the nature of the therapy, the patient and the medical condition. [6] The first four dimensions are especially relevant to Aboriginal and Torres Strait Islander peoples in both rural and urban settings, and will be discussed below.

Socioeconomic factors

First, as stated by the WHO, socioeconomic factors play an important role in the low rates of adherence amongst Aboriginal and Torres Strait Islander peoples. Aboriginal and Torres Strait Islander peoples have a lower income status than non-Aboriginal and Torres Strait Islander peoples, and also have a higher unemployment rate. [11] This may therefore affect adherence to long-term, expensive medical treatment. Geographic location has previously been a barrier to accessing medications for some Aboriginal and Torres Strait Islander communities [3] and is within the WHO's healthcare system dimension. However, the Australian Government has, in recent years, initiated national programs and legislated to improve access to prescription medications for Aboriginal and Torres Strait Islander peoples. This will be discussed below.

Cultural insensitivity

Of the Aboriginal and Torres Strait Islander peoples who do live in urban centres, many report cultural insensitivity as being the main barrier to receiving care from services that do not specialise in Aboriginal and Torres Strait Islander health. [12] This in turn can influence medication uptake and adherence. In particular, the non-Aboriginal and Torres Strait Islander healthcare system can be seen as unwelcoming. [11] This is a barrier under WHO's healthcare team dimension. For example, one Aboriginal and Torres Strait Islander patient was unhappy because he was told to go to an Aboriginal and Torres Strait Islander health service, when he presented to a service that does not specialise in Aboriginal and Torres Strait Islander health. [12] This attitude often fosters a poor relationship between the clinician and the individual. [11]

Miscommunication between health practitioner and patient contributes to a lack of adherence to medications. For example, the services outside the Aboriginal and Torres Strait Islander system often do not provide enough support for people who only speak traditional languages within communities. [5] Cass *et al.* (2002) demonstrated that communication by healthcare service providers to Aboriginal

and Torres Strait Islander peoples who preferred to communicate in languages other than English was often poor. [13]

Other causes of miscommunication were the health practitioner failing to share control in the consultation with the patient, failing to overcoming language barriers by not using interpreters, and using too much biomedical language during the consultation. [13] When the patient does not feel involved in decision-making, he or she is less motivated to adhere to treatment advice. [5] Furthermore, miscommunication is often unrecognised by the health practitioner, meaning that concepts are never clarified. [13] While most Aboriginal and Torres Strait Islander peoples are fluent in English, such miscommunication can have a negative impact on adherence to treatment for many people, leading in turn to adverse health outcomes. [13]

Furthermore, services that do not specialise in Aboriginal and Torres Strait Islander health sometimes do not accommodate Aboriginal and Torres Strait Islander cultural practices, which may hinder medication adherence. In some Aboriginal and Torres Strait Islander communities, traditional healers can be the first point of call for health problems. [14] Only when the traditional healers are unable to provide a solution does an individual from such a community approach the Western health system. [14] As a consequence, Aboriginal and Torres Strait Islander peoples may be less likely to comply with prescriptions due to unfamiliarity with Western medicine. [13] Furthermore, the concept of prophylactic medication does not exist in some Aboriginal and Torres Strait Islander cultures, so some community members may be reluctant to take medications that are not for the treatment of acute conditions. [15]

The family plays an important role in many Aboriginal and Torres Strait Islander people's health. [5] Therefore, the family itself can act as a barrier to medication adherence in a number of ways. [5] First, there can be a culture of sharing medications in some communities. [5] This can result in under-treatment of the person who was prescribed the medication. Secondly, some families can influence a person's decision to adhere to medication, by failing to support the person to adhere to medication, or by encouraging the notion that medication adherence is not cultural. [5] Therefore, educating the community and seeking familial support is important to improve adherence rates to therapies amongst some Aboriginal and Torres Strait Islander peoples. [5]

Healthcare practitioners' role

There are a number of issues with adherence due to healthcare practitioner behaviours. First, due to cultural differences, a lack of flexibility when prescribing medication has been identified as contributing to non-adherence amongst some groups. [12] For example, health service providers are not always using long-acting medication preparations where possible, nor appropriate combination medications, to reduce the number of tablets that the patient has to take. [15] This falls under the WHO dimension of the nature of the therapy, and is something that health service providers should be aware of when engaging in culturally sensitive medical practice.

Similarly, medical practitioners themselves can be non-adherent to clinical practice guidelines when providing treatment to some Aboriginal and Torres Strait Islander peoples. [16] The study by Fürthauer *et al.* (2013) showed that medical practitioners may deliberately deviate from a clinical guideline for a particular patient, if they feel that the patient may not adhere to the treatment in the long-term, due to cultural practices or socioeconomic background. [16] This comes under the WHO healthcare team dimension, and is an important cause of non-adherence that needs to be examined closely in the Australian context.

The WHO states that patients should be supported, not blamed, for a lack of adherence. [6] Therefore, practitioners should take an active role to ensure that the healthcare environment supports adherence to medication. [6] For example, practitioners should work with patients to

create a therapy regime that fits the patient's lifestyle. [6] It has been shown that a shift in attitude amongst healthcare practitioners to a more empathetic, collaborative approach with their patients achieves better adherence rates. [6] This includes the practitioner taking the socio-demographic characteristics of the patient into account. [6]

History of marginalisation

In addition, some Aboriginal and Torres Strait Islander peoples feel that health services should recognise the history surrounding racism and discrimination against Aboriginal and Torres Strait Islander peoples, in order to facilitate trust and improve service uptake. [12] This issue is within WHO's patient-specific dimension, and may eliminate any feelings of 'cultural shame' for accessing Western medication due to the history of marginalisation of Aboriginal and Torres Strait Islander peoples. [3] This indicates that more research needs to be undertaken on the psychological impact of marginalisation on Aboriginal and Torres Strait Islander and its link to non-adherence.

Minimising non-adherence

There are two main ways to improve adherence rates amongst Aboriginal and Torres Strait Islander peoples. One is by improving cultural sensitivity amongst health service providers to provide appropriate services to Aboriginal and Torres Strait Islander peoples, and welcome them to services outside the Aboriginal and Torres Strait Islander system. The other way is by subsidising medications so that Aboriginal and Torres Strait Islander peoples can have better access to treatments.

Improving cultural sensitivity

In order to minimise non-adherence, it is imperative that the health system be more culturally sensitive towards Aboriginal and Torres Strait Islander peoples. [3] Service providers outside the Aboriginal and Torres Strait Islander health system need to be trained in the cultural values and healthcare beliefs of Aboriginal and Torres Strait Islander communities, in order to provide culturally sensitive advice and treatment. [3] Service providers should also be trained in communicating concepts to non-English speaking patients. [4] This involves the use of interpreters, which has been found to be beneficial in improving communication between Aboriginal and Torres Strait Islander peoples and health practitioners. [4] If required, these individuals can also be educated about medications through the use of pictures and anatomical models. [14] Similarly, medical practitioners should be encouraged to adhere to clinical guidelines when prescribing medications and to treat this group as they would any other group of patients. [16]

Another way of creating a culturally sensitive environment in healthcare centres is to better engage Aboriginal and Torres Strait Islander peoples in this process. [5] While interpreter services clearly fulfil this objective, [3] their role can be supplemented with other culturally sensitive practices. For example, Aboriginal and Torres Strait Islander peoples may feel more welcome if they see members of their communities in brochures. [5] It has been suggested that pharmacies displaying Aboriginal and Torres Strait Islander paintings and employing more Aboriginal and Torres Strait Islander staff will make Aboriginal and Torres Strait Islander peoples more likely to seek information and participate in screening programs. [5]

Increased engagement of Aboriginal and Torres Strait Islander peoples with health workers can be achieved by employing more Aboriginal and Torres Strait Islander Health Workers (AHWs), who have often lived in the region where they work. [17] AHWs act in a variety of capacities to better liaise with Aboriginal and Torres Strait Islander peoples in healthcare settings and facilitate a more positive experience. [5] They undertake clinical work, such as providing health checks and administering vaccinations, or conduct research and implement community development projects. [17] One study found that AHWs, together with pharmacists, have the potential to improve adherence with appropriate funding and education. [5] However more

research needs to be undertaken to further evaluate the role of AHWs, specifically in reducing non-adherence.

A difficulty, however, in building culturally-sensitive practices, is that there are many Aboriginal and Torres Strait Islander cultures in Australia, not simply one unified culture. Therefore, a strategy that works for one group may not necessarily work for another. [5] Aboriginal and Torres Strait Islander peoples should therefore be involved in the formulation of policy strategies with health services to increase adherence. [3]

Subsidising medications

It is also necessary to consider the fiscal situation of individuals in Aboriginal and Torres Strait Islander communities. Aboriginal and Torres Strait Islander peoples have a lower median weekly household income than non-Aboriginal and Torres Strait Islander peoples. [1] Therefore, access to subsidised medication may be a way to improve adherence to medication. There are a number of initiatives funded by the Australian Government to try to improve adherence to medications.

As part of the Australian National Medicines Policy, a Quality of Use of Medicines (QUM) strategy was introduced in Australia in 1992. [18] This strategy included evaluating and improving Aboriginal and Torres Strait Islander health in remote areas through a number of ways, including the development of guidelines for culturally appropriate pharmaceutical services and evaluating medication use. [18] On the whole, it appears that the program achieved a number of its objectives, including improving Aboriginal and Torres Strait Islander health. [19] It was intended to complement a legislative change made around the same time to the *National Health Act 1953*.

This legislative change was made by the Australian Government to improve Aboriginal and Torres Strait Islander peoples' access to the Pharmaceutical Benefits Scheme (PBS). Section 100 of the *National Health Act 1953* gives the Minister for Health the power to make special arrangements for the supply of pharmaceutical benefits to people who are living in isolated areas, are receiving treatment for which pharmaceutical benefits are inadequate, or for whom pharmaceutical benefits can be more conveniently supplied. [20] If the Minister exercises this power, pharmacies can supply remote Aboriginal and Torres Strait Islander primary healthcare services with PBS-listed drugs in bulk, and Aboriginal and Torres Strait Islander patients can access prescription medication free of charge. [20]

The impact of this scheme on access to medications for Aboriginal and Torres Strait Islander peoples in remote areas has been evaluated. [21] It has been found that access to subsidised medications has significantly improved due to the S100. [21] However, it has been recommended that non-PBS medications commonly used by Aboriginal and Torres Strait Islander peoples should be included under S100, in order to further improve access. [21] In addition, there are limitations for people who live just outside the geographic boundaries and are not able to access the medications. [21] Therefore, it has been recommended that the section's scope be broadened. [21]

More recently, the Australian Government Department of Health and Ageing began funding the Quality Use of Medicines Maximised for Aboriginal and Torres Strait Islander People Program (QUMAX) in 2008. [22] The aim of this program is to improve adherence with, and

access to, medication amongst non-remote Aboriginal and Torres Strait Islander populations specifically. [23] This is achieved by providing financial assistance to Aboriginal and Torres Strait Islander health services to purchase medications, as well as providing patients directly with co-payments. [23] In addition, the Closing the Gap – Copayment Measure Program was introduced in 2010 to improve access to PBS medications for all Aboriginal and Torres Strait Islander peoples who are living with a chronic disease and required treatment. [24] Eligible patients are entitled to receive a waiver on the co-payment for medications under the PBS. [24]

In 2011, the Australian Government undertook an evaluation of the QUMAX and found that there was a 14% increase in PBS utilisation by Aboriginal and Torres Strait Islander peoples, especially for anti-hypertensive, lipid-lowering and asthma medications. [23] Furthermore, there was an 18% increase in utilisation among patients who were not entitled to concessional medications. [23] Some health services combined the QUMAX initiative with Aboriginal and Torres Strait Islander health assessments and care plans, which further incentivised patients to take up subsidised medications. [23]

QUMAX has arguably shown efficacy in reducing the cost barrier to accessing and complying with medications. [23] However, it is not clear whether it has eradicated inequities in PBS expenditure between Aboriginal and Torres Strait Islander and non-Aboriginal and Torres Strait Islander populations. [23] Therefore, it should continue, taking into account the recommendations set out in the evaluation. In particular, measures to address geographical barriers by providing transport for the delivery and the collection of medications should be implemented. [23] Furthermore, the recommendation to improve cultural training amongst pharmacists should be given special attention. [23]

Conclusion

Non-adherence with medication is a significant problem. It leads to negative health outcomes for the individual, and can result in the public health system incurring high costs. Given that the rates of non-adherence and chronic disease are greater amongst the Aboriginal and Torres Strait Islander population, specific measures need to be taken in order to minimise non-adherence. Healthcare workers should be trained to be more culturally sensitive and to provide clear, unambiguous treatment advice. They should also take care when prescribing medications to provide treatments with the lowest number of tablets appropriate. Healthcare services should be made more welcoming to Aboriginal and Torres Strait Islander peoples by including Aboriginal and Torres Strait Islander artwork, employing more Aboriginal and Torres Strait Islander staff, and involving Aboriginal and Torres Strait Islander communities in the policy-making process. Policy-makers need to be aware that there are many distinct Aboriginal and Torres Strait Islander cultures, not just a single homogenous one. Finally, medications should continue to be subsidised to Aboriginal and Torres Strait Islander peoples, to ensure that those most vulnerable to chronic illness are able to access treatment.

Conflict of interest

None declared.

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Evidence based practice; keep it simple stupid

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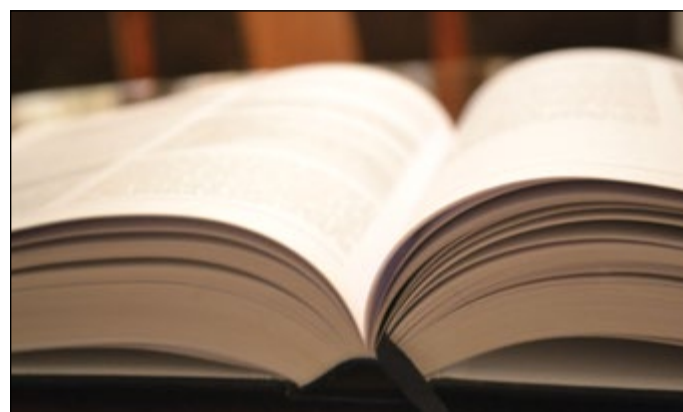
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Learning and implementing evidence based practice is an expected component of good medical practice. Synthesising evidence in an effective and timely manner is a skill that is growing in importance and relevance. Evidence based practice is widely included in medical school curricula, and information literacy skills are known to be difficult to acquire. We provide a fresh look at a streamlined approach to evidence based practice, using a 'real world' case study.



Introduction

The importance of evidence based practice (EBP) is ever increasing. [1,2] However, the complexities of collecting, interpreting and synthesising information may be time consuming and laborious. [3] Information literacy skills are known to be difficult to learn. [4] In an effort to condense the process, a variety of models have been designed for evidence retrieval, including the 4S, [5] the 5S, [6] and more recently the 6S pyramid (Fig. 1). [7] In this article we will focus on the 6S pyramid and its application to a clinical case.

The technology explosion of the last decade has increased access to information for clinicians in almost all settings. The rapid development of handheld electronic devices, paired with the licenses to evidence based databases being held by many universities and institutions,

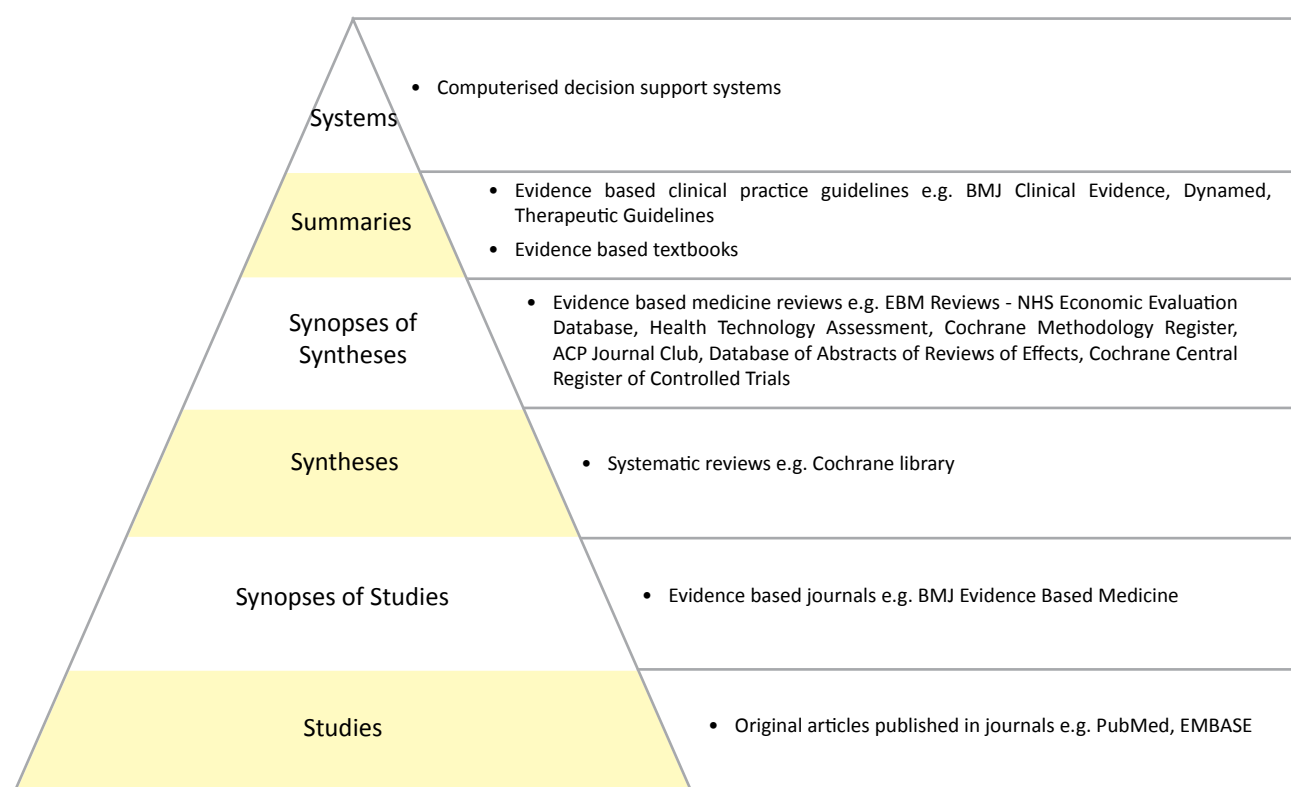


Figure 1. The 6S Model. Modified from DiCenso et al (2009). [7]

results in information being easier to access. The problem then arises of how to find the best information for a clinical scenario in the swiftest manner. The 6S pyramid is useful as it provides a guide showing where to look first; additionally, it tracks the integration of research into clinical practice, with a decision support system at the pinnacle. An example of this is the 'PrimaryCare Sidebar' [8] integrating evidence based guidelines into the clinical data already in the patient record. Although the tip of the pyramid is not always readily available, as we step down the pyramid there are a variety of other evidence based tools available, including Dynamed, [9] BMJ Clinical Evidence, [10] and the Therapeutic Guidelines. [11] Further down the pyramid are reliable resources such as PubMed [12] and the Cochrane Database of Systematic Reviews, [13] which are freely available online.

This article presents a streamlined approach to EBP, demonstrating the multistep process via a clinical case. One of the most difficult aspects of evidence based practice, translating medical jargon and statistics into 'layman's terms' with the goal of empowering the patient to make an informed decision, is demonstrated. Our aim is to demystify EBP and its application for medical students and practitioners, thereby encouraging a wider application in day-to-day clinical work.

Case Details

Mrs SJ is a 62yo Caucasian female who is fairly new to the practice; she presents to discuss the topic of her back pain. SJ reports a three year history of bilateral lumbar radiculopathy; MRI showed degenerative spinal canal stenosis at L5/S1 and nerve conduction studies confirmed neural involvement. Failing a period of conservative measures and continuing to report severe pain, SJ underwent an L5/S1 laminectomy and posterior fusion.

Postoperatively, SJ reported minor relief of her symptoms; she continues to have 6/10 bilateral leg pain on a daily basis. The surgeon advised SJ there was no role for further operative procedures and SJ confirmed she did not want to even consider another procedure. Following the surgery she trialled gabapentin, with minimal effect. Since then she has been attempting to manage her pain with paracetamol, which has only had a partial effect.

Although not under any major financial stress, SJ felt the benefit of the gabapentin did not justify the cost, contributing to cessation of the medication. As an adjunct to pharmacotherapy, SJ had five sessions of physiotherapy addressing postural correction and stretching. She felt there was no benefit from this treatment.

SJ has an otherwise unremarkable medical history, is not on any regular medication and has no allergies. She lives with her husband, who is well. Friends have mentioned other drugs that they found effective for their pain, and she asks why she shouldn't use them.

Determining a specific, targeted question

Before we seek our answers, we need to define the question/s. [14] This will lead us to a more precise, relevant answer, and save time sifting through irrelevant information.

In patients with chronic lumbar neuropathic pain (radiculopathy), what are the pharmacological options? This question is really what the patient has asked; however, our clinical problem is: what are the pain management options (pharmacological and non-pharmacological) in a patient with radiculopathy who has failed surgical therapy. In practice, we may choose to enquire about the pharmacotherapy about which Mrs SJ has asked; however, a holistic approach to the longterm management of this patient would involve a review of all options, including those that are non-pharmacological. In order to stay focused on the purpose of this article, which is the process of EBP and not the best practice treatment for lumbar radiculopathy, we will focus on pharmacotherapy only.

PICO:

- Population: Chronic radiculopathy, unsuccessful lumbar surgery, menopausal women
- Intervention: Medication, not gabapentin
- Comparator: No medication, paracetamol
- Outcome: Pain reduction and quality of life improvement. [15]

Collecting the evidence

In order to approach this therapy question, we started as high up the pyramid as possible. When creating a search we used keywords that were defined during the formulation of our targeted (PICO) question. Boolean operators (AND, OR, NOT) are also useful and function well in most search engines. Dynamed contained a topic entitled 'Lumbar spinal stenosis,' and the treatment section covered some information about medications, but this was not complete. Using BMJ Clinical Evidence (a clinical guideline tool) we searched 'chronic pain.' That search led us to the topic 'chronic pain syndromes,' and, although there wasn't a direct answer to our question, under the treatment section we found an international guideline dated 2007.

Now that we knew guidelines existed on the topic, we searched Medline for a more recent version. This led us to three international guidelines. We used the 2010 paper 'Recommendations for the pharmacological management of neuropathic pain: an overview and literature update' by Dworkin et al as the primary paper. [16] Unfortunately, as is often the case, evidence specific to our patient was not available.

Determining levels of evidence and strength of recommendation in order to deliver appropriate advice

In order to give valid advice we need to know the strength of the evidence it is based upon, and the size of effect in our population of interest. Various guides exist in order to systemise this process and various methods are commonly used in the literature. The Oxford Centre for Evidence-based Medicine [17] is a well established resource. More recently, The Grading of Recommendations Assessment, Development and Evaluation (GRADE) [18] has been developed with the aim of providing a comprehensive system for grading quality of evidence and strength of recommendations. The resources above provide quality instruction on how to perform the vital step of appraising evidence. Fortunately, this has often already been done for us by others who have summarised the literature, in guidelines or systematic reviews, but it is good to be familiar with the process.

Breaking down the evidence in a real world scenario

Evidence comes from a variety of communities worldwide, and as such, a patient's specific situation always needs to be taken into account. [22] Various approaches for communicating evidence [23] and mediums for doing so have been evaluated. [24] The way we communicate with patients about risk and effectiveness of treatments can affect their perception and understanding of illness. Communicating with the aid of numerical data, absolute risk (instead of relative risk), both negative and positive perspectives, and with visual aids, all help to improve understanding. [25] Closed loop communication can be used in order to verify understanding. We need to start by translating the evidence into dialogue that would take place between two human beings. This can be helpful in conceptualising the information retrieved. Let's try...

Doctor: Let's start by talking about the type of pain you have.

The pain you have is a nerve pain, often called neuropathic pain. This can be due to a lesion or disease. In your case, structures in your lower back are directly irritating nerves. In a simple world you remove the 'lesion or disease' and the pain would go away.

Unfortunately, after chronic stimulation the pain message continues to be 'switched on' even without a stimulus. This pain can be treated with medications but is often more difficult to manage.

Patient: I totally agree, this pain has been really difficult to manage, and has been getting on top of me for a long time.

Doctor: So your friends have mentioned medications?

Patient: Yes, they have mentioned a few different ones. I'm not sure of the names.

Doctor: There's a lot of research about medications for the treatment of neuropathic pain, [16] but not a lot have looked at your particular scenario. [26] Of the few medications that have been tested, the evidence suggests only a small amount of benefit. There are some medications that have a lack of efficacy and we should avoid these.

Patient: I am really interested in trying another medication, even if the improvement is only small. Anything that would help me get through the day would be positive.

Doctor: Studies have shown that there are a few main groups of medications that are considered first choice; gabapentin (the one you tried) was one of them. Alternatives include opioids and some antidepressants. We use the antidepressants not because we think you are depressed, but because they have good pain relieving properties for this type of pain. You should know that research found these medications gave meaningful pain relief to around 50 percent of the patients. [23] So, effectively one in two patients. Although this gives us an idea of what to expect, it doesn't mean it will work for you.

Because of the unclear nature of the evidence, we need to approach the choice of medication carefully, considering your situation. [16]

Patient: So...what are the side effects and how much do these medications cost?

Doctor: Antidepressants, particularly an older group called 'TCAs' (tricyclic antidepressants) have been shown to be effective. We don't fully understand how they work for pain, but do know they provide pain relief in patients who aren't depressed. [28] On the positive side, they are cheap, are taken once a day and can help with sleep. On the negative side, there are some side effects including dry mouth and constipation. These are not harmful, but annoying, and often resolve with a change in dosage. Rarely, these drugs can cause disturbance to the heart rhythm, and an overdose of these medications is very dangerous to children, so they need to be kept out of reach at all times. Newer antidepressants called SNRIs have shown fewer side effects, but haven't been studied as thoroughly. [16]

Patient: Besides the heart thing these sound pretty good. I don't have children at home so that shouldn't be an issue. Is there anything else on offer?

Doctor: Another group of medications work by slowing down pain impulses; gabapentin is one of these. Although they have proven effectiveness, side effects include dizziness and sedation. As you have mentioned, this is an expensive choice and hasn't worked for you, so it's probably not the best option for us at the moment.

Patient: Agreed!

Doctor: Finally, the opioid-like medications are an option. However, I would prefer if we could avoid these. Generally, individuals build tolerance to them and they can be addictive.

Patient: I don't want to have to rely on it all the time, or have to keep using more of the medication. It sounds like the first option, the antidepressants, is the best, particularly if they are going to help me sleep.

Doctor: Yes, assisting with sleep is a great attribute of TCAs, but

Table 1. Levels of Evidence and strength of recommendation.

Pharmacological Intervention	Levels of Evidence (CEBM)*
Neuropathic pain (general)	
Secondary amine TCAs (nortriptyline, desipramine)	Efficacious (Level 1-2) [16]
SSNRIs (duloxetine and venlafaxine)	Efficacious (Level 1-2) [16]
Calcium channel α_2 -d ligands (gabapentin or pregabalin)	Efficacious (Level 1-2) [16]
Opioid agonists (morphine, oxycodone, methadone, levorphanol, tramadol)	Efficacious (Level 1-2) [16]
Neuropathic pain (chronic radiculopathy)	
Effective pharmacotherapy	No high level evidence available (Level 5)
Gabapentin	Efficacious (Level 3) [19]
Pregabalin	Inefficacious (Level 2) [20]
Morphine	Inefficacious/poor efficacy or discrepant results (Level 1-2) [21]
Nortriptyline	Inefficacious/poor efficacy or discrepant results (Level 1-2) [21]
Nortriptyline-morphine	Inefficacious/poor efficacy or discrepant results (Level 1-2) [21]
Topiramate	Inefficacious/poor efficacy or discrepant results (Level 1-2) [21]

*Levels of Evidence from Oxford Centre for Evidence-Based Medicine. [17]

it takes a while for full effect, so let's trial a medication called amitriptyline for six weeks and reassess after that. The medication will cost around A\$30 a month. I would like to do an ECG to get an idea of your baseline heart rhythm, and for you to complete two questionnaires in order for us to keep track of your progress: the McGill pain questionnaire [29] and the Short form 36. [30]

Please come back and see me sooner if you have any concerns or develop the side effects we talked about. Also, I would like you to consider other ways this pain can be managed. There are many alternative approaches we should explore, most of which do not include medications.

Conclusion

So, that wasn't too hard, was it? We defined the question, used a top down approach to the evidence pyramid, and accessed a synthesis of the best literature to answer our question. We made an assessment of the quality of the information available, and attempted to translate 'doctor speak' into lay terms. Implementation of the evidence will inevitably lead to further questions. The ongoing process of EBP is illustrated as a cycle (Fig. 2).

Gathering evidence based information should no longer be a chore. Using evidence at any level of the pyramid needs thoughtful consideration, requiring close scrutiny of the methods of evidence generation and the method of appraisal. Due to the increasing amount of evidence being published, synthesis and weighing of existing

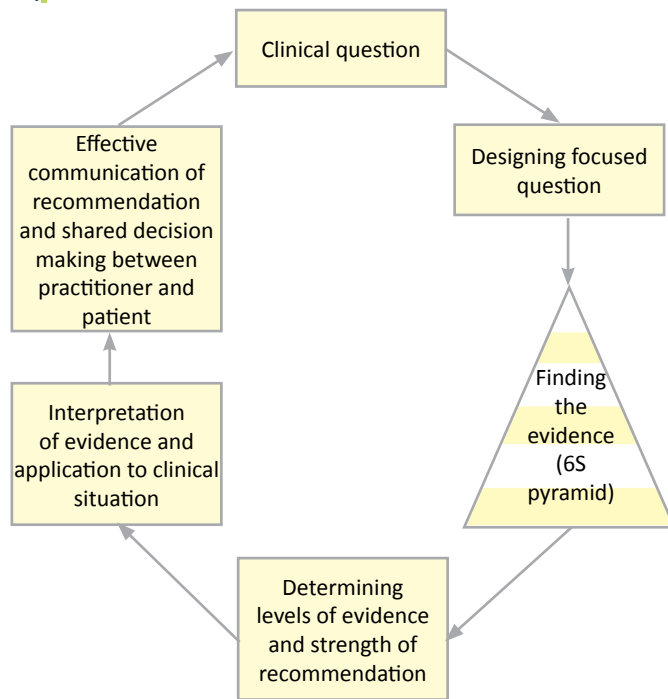


Figure 2. Approach to gathering, synthesizing and delivering evidence.

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evidence can serve to provide a more comprehensive and relevant source of evidence based recommendations. The streamlined pyramid approach can be skimmed during consultations or scrutinised for assignments.

So the next time a patient (or an examiner!) throws you a curveball, use EBP to find the comprehensive answer they deserve.

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Conflict of interest

None declared.

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Probiotics: A New Recommendation with Proton Pump Inhibitors?

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Introduction

Clostridium difficile-Associated Diarrhoea (CDAD) is becoming a worldwide epidemic with significant patient morbidity and mortality, as well as increasing the costs to health care systems. Although CDAD is generally associated with antibiotic use, there are multiple studies demonstrating that proton pump inhibitors (PPIs) may also be linked with CDAD. This is particularly worrisome for physicians in general practice, where PPIs are among the most frequently prescribed drugs. [1]

Clostridium difficile is a gram-positive, spore-forming, anaerobic bacillus that may cause gastrointestinal infections with poor patient outcomes and significant medical costs. [2,3] In one study, 3% of *C. difficile* infections resulted in death or admission to an Intensive Care Unit. [4] In 2002, another study demonstrated a mortality rate of 15.7% due to *C. difficile* colitis. [5] Although there is no complete cost analysis done in Australia, the figures emerging from the United States are staggering, with the average *C. difficile* infection cost ranging between \$10,970-\$29,000 per patient [6,7] and the estimated annual cost of \$55 million in the state of New York alone. [7]

The mechanism of infestation and standard treatment

C. difficile enters the human body by spores which are ingested orally. Five percent of the population carries *C. difficile* asymptomatically due to growth-regulation by gastrointestinal flora. [8] In the presence of antibiotics, normal flora may be reduced, allowing an over-colonization of *C. difficile*. Typically, *C. difficile* is treated with a 10-day course of metronidazole for less severe infections, or with vancomycin for severe infections, with recurrence rates as high as 25%. [9]

PPIs and the link with *C. difficile*

PPIs are a class of drugs frequently prescribed in the general practice setting for Gastro-Oesophageal-Reflux-Disease (GORD), [10] peptic ulcer disease [11] and related conditions. [12] PPIs inhibit the hydrogen-potassium ATPase of parietal cells in the stomach, decreasing gastric acid production, thereby settling acid-related gastric symptoms. General practitioners are prescribing PPIs with increasing frequency. This is not surprising, as between 3% and 7% of the population suffer from GORD. [13] The mechanism by which PPIs may lead to *C. difficile* colitis is unclear; it may be that reduced stomach acidity allows more of the bacterial spores to survive, thereby increasing bacterial load in the gastrointestinal system. [14]

There are multiple studies demonstrating a link between *C. difficile* and PPIs. [15-18] In one meta-analysis of case-control and cohort studies, it was shown that PPIs imparted a relative risk of 1.69 for the development of *C. difficile* infection. [19] Another meta-analysis published by Kwok *et al.* (2012) suggested a 70% increase in risk of this infection. [20] Given the considerable risk of developing CDAD in association with PPIs, and the morbidity and mortality associated with CDAD, it is recommended that general practitioners use caution when prescribing these medications, observe patients for secondary diarrhoea and investigate with *C. difficile* cytotoxin assays.

A multi-center case control trial from the Netherlands identified that the greatest risk for development of *C. difficile* infection was within the first three months after initiation of antibiotics, with the risk peaking at one month and declining between one and three months. [21] According



to this study, third-generation cephalosporins and carbapenems were associated with the greatest risk of CDAD.[21] Other risk factors for CDAD include living in long term care facilities, major bowel diseases such as Inflammatory Bowel Disease (IBD), colorectal cancer, radiation and chemotherapy, and age, with highest risk beyond the age of 65 years. [22] It is yet to be determined if similar risk factors are involved in the development of PPI-associated diarrhoea.

It should be noted that the meta-analytic link between PPIs and CDAD is criticized, as there are multiple methodological problems with many of the studies involved. [23] One criticism is that duration and dose of PPI exposure were not variables considered in the meta-analyses; therefore, the exposure-dependent and dose-dependent relationship cannot be established. [23] Further research is required to determine whether there is a causal relationship between PPI use and CDAD.

What can physicians do in the meantime while the link is investigated?

There may be a role for probiotics in the prevention of PPI related CDAD. Probiotics are broadly defined as live microorganisms that exert beneficial effect on the host. [24-26] The mechanism for this is unclear, but may involve the suppression of pathogenic bacteria and/or suppression of inflammation in the gut. [27] There are a wide range of probiotics marketed today to improve immune function including *Bifidobacterium lactis*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus* and others for diarrhoea including *Saccharomyces boulardii*, *Lactobacillus casei*, *Lactobacillus acidophilus* and others. *Lactobacillus*, *bifidobacteria* and certain yeasts (eg: *Saccharomyces*) are the most common microbes used in commercial probiotics. These can be consumed as part of fermented foods, such as yogurt, or directly as supplements. Recommendation of the probiotic *S. boulardii* with antibiotics has shown a significant reduction in the incidence of antibiotic-associated-diarrhoea in two separate double-blind placebo controlled studies. [28,29] A meta-analysis reveals nine studies have shown use for both *S. boulardii* and *lactobacilli* in the prevention but not the treatment of CDAD. [30]

At this point there is no research examining the effects of probiotics regarding the prevention of PPI associated CDAD; however, it is reasonable to presume there may be a role for *S. boulardii* and *lactobacilli* in balancing the gastrointestinal tract flora whether the disruption of its microenvironment is secondary to antibiotics or PPIs. If future research demonstrates a similar reduction in PPI-related

CDAD, as has been documented with antibiotic-related CDAD, there may be grounds for adjustment of future clinical recommendations to include probiotics with PPIs in the general practice setting.

In general practice, deciding whether to prescribe any medication requires evaluation of risks and benefits to the patient. As minimal risks have been reported in healthy individuals with probiotic use, [31] and given the potential benefit to reduce the incidence of CDAD, research needs to be done to determine whether there is benefit to prophylactically recommending *S. boulardii* with PPIs. It would be logistically difficult to ensure compliance and no use of alternate anti-acid medication in a randomly controlled longitudinal trial in the development of *C. difficile* infection. However, a well controlled prospective cohort study may minimize confounding factors and suggest causality by examining patients with limited comorbidities.

The risks of recommending probiotics

There are no systematic reviews demonstrating risk of probiotics; however, general practitioners should be aware that multiple case studies indicate there may be a risk of recommending probiotics in immunocompromised patients. These include cases of hepatic

abscesses and pneumonia, [32] probiotic sepsis [33,34] and *S. boulardii* fungaemia. [35,36] There are no cases of such probiotic sepsis or fungaemia in healthy individuals.

Conclusion

Probiotics have been recommended in the prevention but not the treatment of *C. difficile* infection associated with antibiotics. While the pathogenesis of PPI-related CDAD is unknown, it presumably involves the disruption of gastrointestinal flora, which is potentially amenable to probiotic supplementation. Given minimal documented risks of probiotics in immunocompetent individuals, research needs to determine whether there are direct benefits of the use of probiotics in the prevention of PPI-related CDAD. Such recommendation on the part of the general practitioner may reduce morbidity and mortality associated with CDAD and reduce costs to the health care system.

Conflict of interest

None declared.

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Reproductive Healthcare in Latin America: Perspectives from a Guatemalan Elective

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Cate recently graduated with an MBBS/BA (Eng/Poli.Sci) from UWA and is now studying towards an MPH. She split her final year elective between a community health placement in the highlands of Guatemala and Paediatric Infectious Disease in New York, in order to explore the globally disparities in healthcare. More recently she was been working on setting up a Global Health Summer School with a group of students at UWA and a health organization in Timor-Leste. The summer school will provide opportunities for medical students to learn about key issues in global health in a group environment, while giving students some exposure to regional health disparities earlier in their medical education than the current final year elective system allows.

If medicine is to fulfill her great task, then she must enter the political and social life.

—Rudolf Virchow, founder of modern pathology

An overseas elective is a time to experience medicine in another setting, and it is as much about the setting as it is about the medicine. While gunshot wounds in Johannesburg, and tropical diseases in East Timor, are the often the draw cards when we are planning an elective, it is witnessing the social conditions that lead to those health problems that really change our outlook. Rudolph Virchow was right about many things, but this dictum seems to go unheeded in much of our medical education. Perhaps that is best; there doesn't seem to be much space in the curriculum for a quick course on East Asian history, Latin American politics or economic development. It does mean, however, that for many of us, our elective becomes a crash course on the political and social life we aren't taught about in medical school.

After some deliberation, I decided on a women's health elective in Guatemala. It seemed like a good chance to spend some time learning about a single public health issue in more depth, and at the time I was interested in how cervical cancer, a disease so preventable in our own country, could be such a significant killer of women in the developing world. Some quick research led me to believe Guatemala was no different. Once I arrived, however, I discovered that most of the women in that area of Guatemala, Antigua, a wealthy area popular with tourists, were already engaged by cervical cancer screening programs. While the hospital I was working at openly encouraged women to be screened for cervical cancer, there was an issue that no one seemed to be talking about. An issue that inextricably links medicine to the political and social lives of women. Contraception.

In the first week I went out on a few visits with the social worker to the villages surrounding Antigua where most of the patients lived. As we walked farther from the edge of town the roads diminished to dirt tracks, the cinder block houses became tin shacks. We spoke mostly to women and many of their stories were similar; they worried when their husbands would next get regular work, whether there would be enough money for food, whether they could continue to afford to send their children to school. It also seemed as if every family had upwards of five or six children, many of them only a year or two apart. The doctors at the hospital had said they did not discuss family planning with the women because it was a cultural issue, and they did not want to alienate the community. Although the hospital was run by a Christian non-profit based in the United States (US), the director stated the practices at the hospital were not guided by religious belief. The doctors and health workers at the hospital would not raise the issue of contraception with patients. If women requested contraception the hospital would refer them to another US-based non-governmental organization (NGO), WINGS, that dealt with family planning amongst other reproductive health issues, and had limited funding and scope. Walking through those tin shacks and dirt lanes family planning seemed much more than a cultural issue, it seemed to be about gender, politics, economics, education, religion and history too.



Mayan ceremony at Temple 1 in Tikal on Winter Solstice.

Guatemala has one of the highest fertility rates in Latin America of four children per woman. [1] Amongst Indigenous women that rate is 6.8, and in some rural areas is reported to be as high as 10 per woman. Indeed the Indigenous population, mostly Maya, make up approximately 50% of Guatemala's population, of which 80% live rurally. [2] As is true almost universally for Indigenous populations, they suffer from significantly poorer health parameters, which can be traced back to a brutal colonial history followed by a 36-year civil war, and the ongoing economic and educational disparities related to this.

On a quest to find out more about contraceptive use, I decided to spend the remainder of my elective with another NGO, Maya Gift, doing village clinics in the Lago de Atitlan region of the Guatemalan highlands, where the population is largely Indigenous and the fertility rates are highest. Maternal mortality rate (MMR) in this region is up to 534 per 100 000, compared to 120 per 100 000 in Guatemala as a whole, or 7 per 100 000 in Australia. [3] Most births are not attended by a skilled midwife, but by a *comadrona*, a traditional birth attendant. In Guatemala, 59% of births are attended by a traditional birth attendant only, in rural areas this percentage is thought to be much higher. [4] The high fertility rates, combined with high maternal mortality rates, result in a 1 in 20 lifetime chance of dying in childbirth in the highlands surrounding Atitlan. [5] That is significantly higher than the 1 in 190 lifetime risk in Guatemala as a whole, or the 1 in 8100 lifetime risk of dying in childbirth in Australia. [3]

Given the incredible impact of pregnancy on women's lives in this part of the world it seemed strange for health organizations to not actively discuss the issue, or to consider it as purely cultural. It seemed like these women were missing out on a basic element of healthcare, but were they really? What does contraceptive use mean to the individual and the society they live in.

A revolutionary pill

Family planning may date back to the fertility goddesses of ancient Egypt, but modern family planning methods started in the 1960s with the contraceptive pill. The availability of effective contraception had far reaching consequences for role of women in society, particularly in

terms of marriage and the workforce. [6]

It was not long before family planning entered the domain of public health. Amid concerns about rapid population growth, international family planning programs in the 1960s and 70s were framed with population policies, with the focus on reaching demographic and fertility targets. In this context some nations adopted coercive population control policies that violated human rights and often targeted sections of the population based on race and socioeconomic status. [7] This sort of practice is completely at odds with the family planning efforts of the majority of governments and public health organizations today.

Family planning in 2012

The marked shift in the basis of family planning policy from population control to human rights was clearly demarcated in 1994 by the Program of Action of International Conference on Population and Development in Cairo. [8] Here, 179 countries signed on to a Program of Action that framed family planning as a women's health issue rather than a purely demographic issue. For the first time, universal access to contraceptives was set as the goal, rather than the population targets set in the past. From this conference onwards the focus has been on autonomy, choice and improving access.

With this approach in mind, the benefits of family planning programs in developing countries have been marked. In development terms family planning provides one of the best returns for investment of any public health measure. [9] When women are given access to modern family planning methods they have fewer children and those children go on to be better educated and healthier, suffering significantly less from malnutrition. The most well known cases are perhaps in South East Asia, where countries like Thailand dropped their fertility rate from 6.3 in 1967 to 1.7 in 2003. [10] In this setting the decrease in fertility was associated with an explosion in economic growth, leading to a phenomenon known as the 'demographic dividend'. [11] This phenomenon occurs in countries with high fertility rates, where an increased investment in family planning results in a significant fertility drop across one generation. [12] As a greater proportion of the population are at working age relative to dependants, there may be more funds to spend on health and education. This raises the 'human capital' of the population, as those children who have grown up in an environment with increased access to health and education become more economically productive than their predecessors.

Despite the knowledge of the profound effect of family planning on economic development, funding for programs was slowly eroded from the 1980s onwards. [13] This was in part due to the redirection of funds to fight the AIDS epidemic, and in part due to the political rise of the Christian right in US politics. The Christian right lobbied to block US funding to the United Nations Population Fund (UNFPA), a key reproductive health body, and prevented the United States Agency for International Development (USAID) funding any organisations that were linked with abortion. Many of those organisations were also key providers of less controversial aspects of family planning, including the contraceptive pill and injectable contraceptives. [14]

In 2012, however, family planning was placed back on top of the development agenda, when Melinda Gates, of the Bill and Melinda Gates Foundation, the largest philanthropic organization in the world, decided to make family planning her signature issue, investing several billion dollars in the cause. Gates highlighted the key issues in her first public speech on the topic: accessibility, education and above all, removing the taboo surrounding contraception. [15] At the landmark London Summit on Family Planning in July 2012, organized by the Gates Foundation, world leaders gathered to orchestrate a plan to address the enormous unmet need for contraceptives. It is estimated that 222 million women who would like to use contraception do not have access to it. Of the 210 million pregnancies each year, 80 million are estimated to be unintended. Furthermore, there are 22 million unsafe abortions

occurring each year, resulting in 47,000 deaths. [13]

There is, of course, another reason family planning has been put back on the agenda: climate change. Uncontrolled population growth has been touted as one of the most significant contributors to carbon emissions. [16] A 2011 UN report on the predicted population of the world in 2050 outlined the variability in our global future. [17] The report released three variants of estimated population, a smaller, medium and large variant, 8.1 billion, 9.3 billion and 10.6 billion, respectively. The medium variant, largely held to be the most likely, relies on fertility rates in high fertility countries dropping from an average of 4.9 children per woman to 2.8. Family planning services in high fertility countries in Africa and Asia will need to be expanded if they are to meet this need. Alarming, Africa, which struggles to provide food and water to its inhabitants today, could see its population more than triple, from 1 billion today to 3.6 billion by 2100. [18]

The global, the local

For the women of the Lago de Atitlan region of Guatemala these global issues are largely esoteric. The inaccessibility of contraception at the local level is made up of a different set of factors, albeit related to these global issues. After talking with these women for a few weeks it seemed that the barriers to contraceptive use could be broadly broken down into economic, educational, cultural, historical and geographical obstacles.

In this area of Guatemala, generally only the males worked for a paid wage, which for a *campesino* (rural labourer) was US\$150 per month. [19] Speaking with the *campesinos* who came to the clinic, it seemed this wage would often need to support families with six or more children and dependant grandparents. An average workday involved 12 hours of backbreaking labour, carrying 60kg sacks of coffee back and forth. Speaking with the women it was clear they worked just as hard: labouring, preparing meals and selling food in the bigger towns. In this environment it seemed there was rarely a free morning, or spare funds, to go and get an injection of depot contraceptive at the clinic in the next town. Contraception would have to be cheaper, or free, and more accessible if they were to use it consistently.

Inextricably linked to the economic disadvantage of rural Guatemala was the educational disadvantage. Many families could not afford to send their children to school, which although free, required purchasing shoes, uniforms, books and supplies. The average amount of schooling is 4.28 years per person. [20] Illiteracy rates are amongst the highest in Latin America; 21.8% for men and 39.8% for women. [21] It is estimated that two million children of school age are not attending school. The majority of these are Indigenous girls living in rural areas, the very demographic that go on to experience poor reproductive health and the highest fertility rates. [22] These educational disparities are apparent in every aspect of health and particularly in reproductive health. Myths of contraceptive side effects abound in such an environment. Some I commonly heard were that contraceptives can give you cancer, can cause irreversible infertility, or can cause menstrual blood to collect in the uterus and make a woman sick.

Perhaps the most commonly referred to barriers to contraception are culture and religion. In fact, it was the reason the doctors in Antigua gave me for not discussing contraception with their patients. Certainly the Guatemalans are very religious people, 55-60% are Catholic and 40% are Evangelical Christian. [23] There is also a strong machismo culture, as in much of Latin America, and virility is associated with manhood. Culture, however, has proven to be exquisitely sensitive to change when it comes to contraception. In historically strong Catholic countries like Ireland and Italy contraceptive use rates have grown to mirror other developed countries. In 2010, 94% of sexually active adults trying to avoid pregnancy in Ireland had used contraception in the previous year. [24] Similarly, 85% of Catholics in the United States no longer believe that the use of contraception is immoral. I think this signifies that when people are educated and have access

to contraception, they are willing to integrate different forms of knowledge into their own belief systems and practices. Attributing the low rate of contraceptive use as religious in origin seems overly simplistic, given members of the same religion in another cultural and economic environment make different decisions.

Lastly, nothing can be discussed in relation to Guatemala without mentioning history and geography. The Indigenous Guatemalans bore the brunt of a brutal 36-year civil war, which only ended in 1996. Assumed to have sided with the left wing guerrillas, who supported more populist policies, the Indigenous were targeted by the right wing military government. [25] Some of the towns in the Lago de Atitlan region were the sites of acts of genocide by the government. It goes without saying that public health, and family planning, for these people was not a priority for the Government. Aside from small NGOs that carried out work in the Atitlan region throughout the violence, the health system of the region has been developed from scratch since 1996 and remains grossly underfunded. The Atitlan region remains one of the poorest in a country with one of the most unequal distributions of wealth in the world. Contributing further to the disadvantaged health status of these people is the difficulty of accessing services in larger towns. Seemingly regular natural disasters have severely damaged what little infrastructure there was connecting small mountain villages. Even the shortest of distances can take hours to travel, and poor roads and lack of transport are yet another barrier to delivering effective healthcare.

Xocomil: wind of change

Despite all these barriers to accessing contraception, it seems there is real hope. Many of the Guatemalans I met believed the end of the

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- Mayan calendar on winter solstice 2012 would bring change, a new world, and an end to the old world of inequality and injustice. Thinking of the immense change contraception brought to many countries, and the very real possibility that this will soon be available to women in developing countries, I found myself sharing in the optimism.
- But optimism should never breed complacency, and the struggle to make contraception universally available to women continues. Continued progress towards this goal raises new obstacles. After all, it was only recently in the United States, where contraception has been available since the 1960s, that there was a push to remove the requirement for health insurers to cover contraception from the Affordable Care Act. We cannot afford to forget Virchow's words now. In order to fulfil our tasks as future medical professionals, we must not forget the political and social life of the world we live in.
- The Xocomil is the midday wind that crosses Lake Atitlan. The local Mayan people believe the wind carries away sin and the souls of lives lost in the lake. It is famous in the region and is a symbol of change and vitality.*

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See no evil, hear no evil, speak no evil: Tanzania's struggles with the HIV epidemic

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Nestled on the south-eastern slopes of Mt Kilimanjaro in Northern Tanzania, the sprawling village of Machame emerges from the surrounding rainforest. This village is home to the Machame Hospital, where I was fortunate enough to undertake a month-long elective before commencing my final year of medical school. This elective was a challenging, yet enriching experience, and helped me gain a glimpse into some of the major public health issues affecting the country.

The century-old Machame Hospital is a 120-bed facility that provides essential healthcare to over 150,000 people from the surrounding area. Although severely under-resourced, the hospital was a bustling hive of activity that provided me with a taste of Tanzanian medical, surgical and obstetric services. The locals were exceptionally friendly and welcoming and I was able to get involved in all aspects of hospital functioning including attending clinics, contributing to ward rounds, assisting in surgery and conducting outreach clinics in the community.

Throughout my time there it quickly became apparent that the gravest problem facing the community of Machame, as with much of Tanzania, is that of HIV/AIDS. Indeed, the most recent epidemiological data estimate the national adult prevalence to be 5.7%. [1] This figure, however, is likely to be an underestimation given the prevailing social stigma associated with being HIV-positive and the resultant reluctance of people to come forward for testing.

In Tanzania, HIV is a dirty word. Many of the doctors and health workers were loath to refer to it by name (*virusi vya ukimwi* or *VVU* in Swahili), especially around patients. It was often alluded to by euphemisms, becoming the great unspoken problem. Many Tanzanians have a very poor understanding of its natural history or transmission and this engenders great fear, especially as many have witnessed the devastating effects of the disease firsthand. [2,3] When it comes to HIV, unfortunately many Tanzanians really do 'see no evil, hear no evil, and speak no evil.'

Machame Hospital's HIV clinic was housed in a little hut ten metres from the main hospital complex itself – an apt demonstration of the social segregation of AIDS sufferers. Accommodating patients with HIV within the main facility may discourage others from presenting for fear of contracting the condition while in hospital. The locals were also worried about being sighted at known HIV treatment or testing locations for fear of social repercussions. The building was instead known as the Centre for Disease Control, a deliberately ambiguous name that enabled patients to attend appointments without fear of being stigmatised as a carrier.

During my elective I also had the opportunity to assist with HIV screening using finger-prick antibody testing. Under the auspices of a general clinic, we would travel to different locations around the village and set up a consulting area. It almost seemed that an unspoken agreement existed between the patients and medical staff to ensure HIV testing was conducted surreptitiously, with the testing area tucked away up the back and never mentioned by name. This made the process all very secretive, ensuring that full, informed consent was often overlooked. Despite this, many seemed to know what was going on and, fortunately, people from the village willingly came forward to be tested.

I met numerous patients during my elective but the most confronting case I saw was that of a two-year-old boy infected with HIV. The child's mother had already died from complications of AIDS and the



The main entrance to the Machame Hospital, Tanzania.

grandmother, distraught and surfeited, had brought him in asking for an 'injection to kill her baby' because she could no longer bear to see him so sick. He had already lost 30% of his 10kg body weight within the last month and cried throughout the whole consultation. Apart from being deeply tragic on a human level, seeing patients such as this made me frustrated as this situation might have been prevented. Perhaps the greatest tragedy of medicine in the developing world is when medical knowledge exists to provide a solution, but is not implemented due to a lack of financial or educational resources.

Fortunately, there were also many uplifting cases that did highlight the tangible benefits of effective medical therapy. One 38-year-old presented to the hospital with a paltry CD4 count of 1 (the normal adult range being between 500 and 1,300 cells per microlitre [4]). He was commenced on anti-retroviral therapy and is now doing well, able to again provide for his wife and son.

There are certainly many challenges that Tanzanian health authorities continue to face in the fight against HIV/AIDS.

Firstly, the lack of health resources in the country limits the capacity for investigations. For example, in Machame it was not possible to measure HIV viral loads, a test routinely performed in Australia to monitor disease progress. CD4 counts alone stand as the only available measure of treatment efficacy. Secondly, patients perceive little incentive to continue taking anti-retroviral medication if they do not feel that it is improving their well-being, as the notions of prevention and maintenance therapy are generally poorly understood. This generates significant compliance challenges that undermine the delivery of treatment.

For its part, the government provides all HIV medication free of charge. Although this is an excellent initiative, it makes the reluctance of people to get tested and treated harder to fathom, especially considering the effectiveness of pharmacotherapy. For example, the rate of vertical transmission from untreated mother to child is 25-35%, but this can be reduced by up to two-thirds with Highly Active Anti-Retroviral Therapy during pregnancy and six months of breastfeeding. [5]

Thirdly, the considerable social stigma and widespread reluctance to discuss HIV act as a significant barrier to primary and secondary prevention strategies. Public education about HIV/AIDS is severely limited and it is difficult to counsel patients about preventing transmission of the illness when sex remains a taboo subject. Many people are tragically unaware of the role of unprotected heterosexual

intercourse in spreading infection, in spite of it being the most common mode of transmission. [1]

There is also an issue of protection for health care workers. I noticed a marked contrast in attitudes towards personal safety and infection control between my time in both the Australian and Tanzanian systems. In Australia, additional precautions are taken for patients with diseases like HIV. Such measures include isolating infectious or immunodeficient patients, collection and incineration of contaminated medical waste, use of personal protective equipment and safe handling of sharps. None of these methods were routinely observed to be practiced during my time in Tanzania and it raised concerns about the rate of potentially preventable transmission amongst hospital staff. Indeed, a recent study of two other Tanzanian hospitals found that nearly half of all healthcare workers experienced at least one occupational injury, such as a needle-stick injury, over a twelve-month period. [6] Clearly, efforts need to be made to improve safety procedures and staff awareness.

Overall, reducing the impact of HIV will depend on multiple approaches with a focus on adherence to treatment, early testing and mitigation of high-risk behaviours. Such improvement can only be achieved through education and good public health initiatives.

My time in Tanzania as an elective medical student proved to be a humbling and eye-opening exposure to global health, with a particular focus on HIV/AIDS. By far the most incredible words I have ever learnt to say are *hakuna shida*, as this was the Swahili phrase I used to inform patients that their HIV test was negative. People were so pleased to hear this that several patients cried with joy or hugged me upon learning the good news. In a beautiful moment of symmetry to my previous HIV clinic, I saw another lady accompanying her grandchild who had lost his mother to AIDS. This time the boy was negative and, upon hearing this, the grandmother burst into joyous tears. These experiences have helped change my perspective on medicine and what



Dispensing medications on an outreach clinic in the village of Machame.

I take for granted in Australia. I look forward to potentially returning in the future and to help get people talking about HIV.

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Conflict of interest

None declared.

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Oral Health - An important target for public policy?

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Introduction

A healthy mouth is something we take for granted. We use our mouths to speak, to eat and to socialise without pain or significant embarrassment. Yet when oral disorders develop the impacts can extend well beyond the domains of speech, chewing, and swallowing to sleep, productivity, self-esteem and consequently quality of life. Despite the significant improvements made in oral health on a national scale over the last 20 years, there are still persistently high levels of oral disease and disability among Australians. This is most evident among Aboriginal and Torres Strait Islander peoples. This paper aims to review current medical literature concerning the overlap between oral health and Indigenous health outcomes and whether it may represent an important target for public health policy.

Methodology

A literature review was performed through a search of The Cochrane Library, Google Scholar and Ovid Medline as well as government databases such as the Australian Institute of Health and Welfare. The terms used in the searches included: 'Indigenous health', 'Aboriginal and Torres Strait Islanders', 'oral health', 'dental caries', 'cardiovascular disease' and 'education'. Limits were also set to include only studies published in the English Language and to papers published between 1995 and 2013.

Results

Searches using combinations of the above keywords yielded more than 100 results. Article titles and abstracts were analysed for relevance to the research question and in particular any reference to Indigenous health. Specific key word limits such as 'education' and 'Indigenous health' were used to restrict the yield. Relevant articles were collated from the individual searches and bibliographies were searched for any additional points of interest. This process yielded the 17 papers reviewed for this paper.

Discussion

Indigenous Health

In 2004-2008 the age-standardised death rate for Indigenous people was 1.8 times that of the non-Indigenous population; a representation of just one aspect of the ongoing issue of Indigenous disadvantage in Australia. [1] In terms of the domain of oral health there is also a wide discrepancy between both population groups. However, current literature suggests that, in the past, Indigenous Australians actually enjoyed better oral health than those who were non-Indigenous. [2] Historically, throughout the 19th and 20th centuries caries was considered to be a "disease of affluence" [3] whereas today it could potentially be a better "indicator of deprivation." [4] Foods rich in fermentable carbohydrates are plentiful in Indigenous communities today and so is dental decay. [3] The current Indigenous health situation provides the perfect example of how a non-Western society can be detrimentally impacted upon by the introduction of Western lifestyle [5] and whilst it is not possible to discuss every aspect of this complex issue, the importance of oral health in these communities is something that requires further consideration.

The risk factors for poor oral health are the same whether someone is Indigenous or not, yet there is a disparity between the standard of oral health of both groups. According to the World Health Organisation (WHO) oral health is "being free of chronic mouth and facial pain...and



disorders that affect the mouth and oral cavity." [6] The 'Oral health of Aboriginal and Torres Strait Islander children' report, published by the Australian Institute of Health and Welfare, found that a higher percentage of Aboriginal and Torres Strait Islanders had experienced dental caries than other Australian children aged between four and 14 years. [7] The report further stated that children aged less than five years had almost one and a half times the rate of hospitalization for dental care when compared to their non-Indigenous counterparts. [7] A rising trend was also demonstrated in the prevalence of caries among Indigenous children, particularly in the deciduous dentition. [7] In extrapolating the causes of these inequalities it is important to consider current structural and social circumstances. These social determinants of health include aspects like socioeconomic status, transport and access, racism and housing and with the recognition of these inequalities being embedded in "a history of conflict and dispossession, loss of traditional roles...and passive welfare" a more accurate snapshot of the complicated Indigenous situation can be established. [8]

In order to best understand the issues of Indigenous health it is also important to understand how Indigenous people themselves conceptualise health. The traditional Indigenous notion of health is holistic and encompasses everything from a person's life, body and environment to relationships, community and law; [3] a significant overlap with the social determinants model mentioned above. Whilst following a reductionist approach to medical care may be helpful in treating and managing disease, alone it is inadequate in addressing health disadvantage at a population level where a more holistic method of interpretation is required. The relationship between oral health and one's systemic health illustrates an important area where population-focused medicine could potentially cause a reduction in rates of morbidity and mortality across multiple medical domains. Current medical research has, for example, confirmed an association exists between cardiovascular disease and periodontal disease. [9] A large retrospective cohort study performed by Morrison and colleagues (1999) reported an association between poor dental health and an increase in the incidence of fatal coronary heart disease. [10] The relationship was assessed using Poisson regression and results were adjusted for age, sex, diabetes status, serum total cholesterol, smoking and hypertensive status. [10] Rate ratios of 2.15 (95% confidence interval (CI): 1.25-3.72) and 1.90 (95% CI: 1.17-3.10) were observed in the gingivitis and edentulous status groups respectively and supported a positive association with fatal coronary heart disease. [10] A study by Joshipura and colleagues (2003), looking at 41,380 men who were free

of cardiovascular disease and diabetes mellitus at baseline, suggested that periodontal disease and fewer teeth may also be associated with an increased risk of stroke. [11] During the follow up period, 349 cases of ischaemic stroke were reported, and men who had 24 or less teeth at baseline were at a higher risk of stroke than those with at least 25 teeth (hazard ratio: 1.57; 95% CI: 1.24-1.98). Furthermore, the addition of dietary factors to the model only changed the hazard ratios slightly. [11] Similar relationships have been established in linking oral infection to diabetes mellitus, low birth weight babies and disorders like otitis media and delayed growth. [3] The fact that the area of oral health has been identified as a potential risk factor for so many medical conditions highlights its importance as a target in population health.

The role of education

WHO defines health as “a state of complete physical, mental and social well being and not merely the absence of disease or infirmity.” [6] Whilst “population” is the “total number of people or things in a given place.” [12] So essentially, putting these two terms together there is an orientation towards “preventing disease, prolonging life and promoting health through organised efforts and informed choices” among whole groups rather than individuals. [12] Many of the oral health problems faced by these communities have overlapping risk factors with wider general health conditions [3] and whilst this may be a reflection of the huge amount of work that is to be done it may also be viewed as a golden opportunity, to bring positive change through the many domains of health. Improving oral health through a campaign against alcohol and tobacco will not only have positive ramifications for oral health but its effects may also be seen in the areas of general health and wellbeing. The promotion of better oral hygiene through healthier eating may also have positive developments in the rates of obesity and type two diabetes mellitus.

It is also important to mention the role of education in achieving these goals, as this tool is often the key to someone gaining the power

and knowledge to change their life. Education to create awareness on how dental hygiene can improve all domains of life is important in empowering people from a population perspective. Previous studies looking at the oral health of Indigenous Australians in Port Augusta, South Australia, have revealed associations between low oral health literacy scores and self-reported oral health outcomes. [13-15] It is studies like these that have prompted the need for targeted interventions that use tailored communication and training techniques to improve oral health literacy; however, there remain few interventions actually targeting oral health literacy in Indigenous populations. [16]

Conclusion

Indigenous health is a complex and often controversial topic and there is much debate as to what actually needs to be done to address the huge gap. Oral health is an important field of health care that has associations with many systemic conditions and thus may provide an appropriate target for effective public health policy. Perhaps a fault in our current health care system is that the dental and medical care fields have evolved quite separately and thus many people may habitually fail to understand how a simple cavity can be linked to the rest of their being. [17] Even in the Medicare system today there are no provisions for any preventative oral health services; with the exception for low income earners being entitled to concessions for public dental treatment through the public hospital system. [3] Oral health is an integral aspect of general health and thus should be an important public health goal; especially in Indigenous communities where the high prevalence of oral disease could be prevented through population-level interventions.

Conflict of interest

None declared.

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The B Positive Program as a model to reduce hepatitis B health disparities in high-risk communities in Australia

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As the epicentre for the highest incidence of liver cancer diagnosis in New South Wales, southwest Sydney is simultaneously home to a large number of first generation migrants from Southeast Asia. Alarming, these individuals are six to twelve times more likely to be diagnosed with liver cancer than Australian born individuals. This article aims to explore some of the challenges in diagnosing and managing hepatitis B in culturally and linguistically diverse (CALD) communities as well as to introduce the B Positive Program, a health initiative by the Cancer Council of New South Wales, as a model to address chronic hepatitis B related health issues.

Challenges in Diagnosing and Managing Hepatitis B Infection in High Risk Communities in Australia

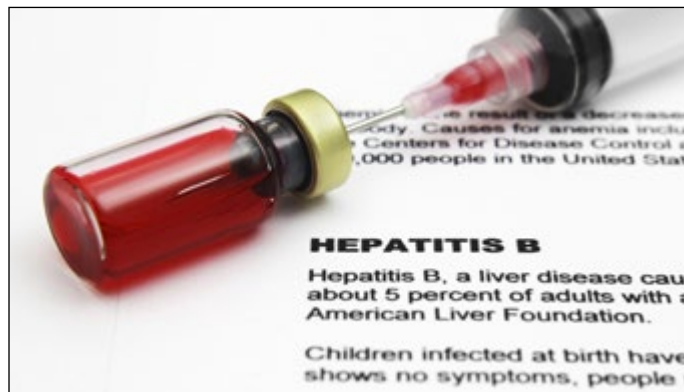
While hepatitis B vaccination is part of the immunisation program for infants and school-aged children in Australia, the incidence of hepatitis B induced hepatocellular carcinoma (HCC), the most common form of liver cancer, continues to be on the rise. This surge is largely attributed to chronic hepatitis B (CHB) infection amongst the migrant population from endemic areas such as Southeast Asia. [1] Alarming, these migrants are six to twelve times more likely to be diagnosed with liver cancer than Australian born individuals. [2] It is estimated that 90% of individuals acquire CHB at birth through mother-to-infant transmission. [3] Thus, most individuals suffering from CHB are unaware of their status due to the insidious nature of the disease in which individuals are asymptomatic until late adulthood. By the time CHB sufferers present for medical attention, a significant proportion of individuals have developed advanced HCC and treatment options are limited and survival rates are poor. In order to reduce the morbidity and mortality related to CHB related liver cancer, early screening, surveillance and treatment of high risk populations while in the asymptomatic phase are strongly indicated.

The National Cancer Prevention Policy for Liver Cancer recommend that hepatocellular carcinoma surveillance be based on abdominal ultrasound in high-risk groups at 6-month intervals. Blood tests screening for hepatitis B antigen and antibodies are used to diagnose CHB and individuals who are at high risk of hepatocellular carcinoma. If diagnosed early, antiviral agents and regular monitoring are extremely effective in preventing progression of CHB to HCC. As well, low grade HCC can be treated curatively by surgical resection, liver transplantation and percutaneous ablation.

Despite these guidelines and treatment options, it is well established that the culturally and linguistically diverse (CALD) communities in Australia remain undiagnosed or improperly managed due to difficulties in seeking equitable medical services. The following article aims to explore some of the challenges in diagnosing and managing hepatitis B in CALD communities as well as to introduce the B Positive Program, an ongoing health initiative by the Cancer Council of New South Wales, as a model to address chronic hepatitis B related health issues.

Language Barrier and Cultural Differences

Language barrier and cultural differences are often cited as two main challenges that adversely affect the diagnosis and management of hepatitis B infections in at-risk communities. [2,4] Due to language barriers, it is often difficult for patients to communicate with their healthcare providers unless the latter is well versed in the language. In



these circumstances, an interpreter, often the patient's family or friend, assumes the role of facilitating communication unless professional medical interpreters are available. This can be problematic because these novice interpreters might be unfamiliar with medical jargon and may misconstrue or censor physician messages. [4] In addition, the patient's confidentiality and autonomy can be compromised when family or friends are involved. A systematic review study showed that patients benefit from professional interpreters instead of their family or friends. [5] At present, the prevailing solution for balancing patient confidentiality and autonomy while preserving cultural traditions for patients with limited English abilities is to consult language concordant healthcare providers. [6]

Stigmatization

Fear of stigmatization is a legitimate concern that individuals in CALD communities may experience. For example, a Chinese study conducted by Chao *et al.* showed that in China, healthcare professionals reported positive hepatitis B surface antigen (HBsAg) results to 38% and 25% of patients' employers and schools respectively. [7] Although this sort of disclosure practice is considered a breach of patient confidentiality in Australia, migrants coming from hepatitis B endemic countries may be reluctant to seek testing because of the aforementioned practices in their home countries. As a consequence, failure to screen and intervene promptly may result in chronic hepatitis B sufferers seeking health professionals as a last resort and possibly present at more advanced disease states. Presentation at these late stages would confer a worse prognosis to the patient and also increase the burden and cost to the healthcare system.

Knowledge Gaps amongst Healthcare Professionals

Avoiding disease progression is largely dependent on early recognition, monitoring and intervention. Unfortunately, some health professionals have unsatisfactory levels of knowledge. A study conducted by Stanford University in collaboration with the Asian Liver Centre showed that 34% (n=250) healthcare professionals in China who attended the 'China National Conference on the Prevention and Control of Viral Hepatitis' failed to recognize the natural history of hepatitis B infection or that a vaccine can be used as a prophylaxis for individuals who are seronegative. [7]

Not surprisingly, within Australia, similar surveys have shown similar gaps in knowledge amongst general practitioners. [8] Due to lack of knowledge, general practitioners may neglect treatment for individuals suffering from chronic hepatitis B or make inappropriate referrals to specialists for patients who are seronegative. In a system

that is already overstretched with long waiting periods, this can be highly problematic. In addition, a major concern is that healthcare professionals fail to recognise that effective therapies are available for chronic hepatitis B and that hepatocellular carcinoma diagnosed at an early stage can be effectively treated especially with timely diagnosis, surveillance and treatment using antiviral agents and Fibroscan. Fibroscan is an accurate noninvasive investigation that is used regularly to assess the degree of liver scarring based on ultrasound technology. All healthcare professionals should be aware that recent developments in hepatitis B management, like antiviral therapy and FibroScan, have been extremely effective in preventing, monitoring and controlling the disease to progress to cirrhosis, liver failure and liver cancer amongst chronically infected individuals. The concept of “healthy carriers” no longer holds true. Yet, if healthcare practitioners are not imparted with this important knowledge, the wellbeing and health of many individuals suffering from chronic HBV will continue to be in jeopardy.

An added layer of complexity lies in the frequent use of complementary and alternative medical therapies within CALD communities. A 2012 study conducted by Guirgis *et al.* indicated conflicting advice about hepatitis B management given by conventional and complementary medical practitioners within Sydney. [9] The contradictory information patients receive can negatively affect their screening or management intentions. Hence, it is important to reconcile any conflicting management strategies by not only educating conventional medicine practitioners but also complementary medicine practitioners about hepatitis B screening and management so as to allow the two systems to co-exist and complement one another.

B Positive Program - A Program to Reduce Health Disparities in Hepatitis B Care

Given the increased incidence of hepatocellular cancer is clustered within specific geographical and ethnic regions within Sydney, the B Positive program is a good model in reaching a vulnerable Southeast Asian audience within New South Wales. The program, spearheaded by the Cancer Council of New South Wales, employs various strategies to address access issues at the patient, community and health professional levels.

At the patient level, the program initiates numerous educational campaigns and materials to educate the at-risk population and to remove the stigmatization of hepatitis B. One of the strengths of the program is the use of educational materials that are culturally and language concordant. For example, one of the campaign posters features Andy Lau, a prominent Chinese entertainer within the Asian community, as an individual with hepatitis B. Placing a public figure in the spotlight helps to demystify the condition for the CALD community and can demonstrate to carriers that medical therapy is effective given proper management and timely diagnosis. This campaign was highly effective and recently garnered the NSW Multicultural Health Communication Award 2013.



Figure 1. Hepatitis B and liver cancer community event hosted by the B Positive Program in collaboration with the ACMA and CanRevive on 3/11/2012 in downtown Sydney.

sharing food won't give you hepatitis B



Hepatitis B is only passed through blood and body fluids—not saliva.



B Positive Program
PH: 9334 1708
www.cancercouncil.com.au/bpositive
Fight liver cancer!



Figure 2. B Positive campaign poster, winner of NSW Multicultural Health Communication Award 2013.

Another educational strategy employed by the program was the distribution of chopsticks engraved with the phrase “one cannot spread hepatitis B by sharing food” in Vietnamese and Chinese to shed light on the mode of transmission for the virus. A further strategy that the Cancer Council NSW employed was to collaborate and engage with Asian community-based health organizations like CanRevive and Australian Chinese Medical Association during outreach programs to enhance their cultural authenticity and receptivity within the CALD community.

At the community level, the program has recently developed a pilot project in May 2013 to engage high-risk migrant communities by creating a high school certificate course for south-west Sydney students called “Animating Hepatitis B”. This course involves ten weeks of lessons on hepatitis B and animation production before the high school students create short animations to deliver hepatitis B health facts to their community.

At the health professional level, the program also assists general practitioners to better identify and screen patients belonging to high-risk groups. Community nurses visit medical clinics to remind general practitioners about enrolling at-risk patients into screening programs. The program also encourages regular monitoring programs of chronic hepatitis B patients for surveillance of hepatocellular carcinoma. General practitioners are also offered Hepatitis B seminars through the Continuing Medical Education Program, so that their knowledge is up to date.

Conclusion

With the appropriate use of cultural and language concordant educational campaigns and outreach programs for at-risk individuals, community healthcare workers to deliver these programs, community engagement and continuing medical education opportunities for healthcare professionals, the prospect of reducing the disparities in hepatitis B care within the CALD communities in Australia is highly positive.

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Conflict of interest

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Approaching autism

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Autism Spectrum Disorder is a social communication disorder in someone displaying repetitive and restrictive interests. Diagnosed in early childhood, children struggle to develop social relationships required for further learning and independent living. This article discusses changes to the diagnosis, how the diagnosis is made, the prevalence, causes and interventions. Importantly, this review guides medical students towards an understanding of what to expect in individuals with autism spectrum disorder and how to interact with them.



What is autism?

Autism is diagnosed according to the American Psychiatric Association (APA) guidelines in the Diagnostic and Statistical Manual of Mental Disorders (DSM), [1] or alternatively, according to the International Classification of Diseases (ICD) published by the World Health Organization. [2] Mostly because of convention, the DSM is more often used in the diagnosis of autism in Australia.

From 2013, 'autism' would be a short form of the term Autism Spectrum Disorder (ASD). A diagnosis of ASD applies where there is evidence of functional impairment caused by:

- Problems reciprocating social or emotional interaction, including difficulty establishing or maintaining back-and-forth conversations and interactions, inability to initiate an interaction, and problems with shared attention or sharing of emotions and interests with others.
- Severe problems maintaining relationships, ranging from a lack of interest in other people to difficulties in pretend play and engaging in age-appropriate social activities, and problems adjusting to different social expectations.
- Nonverbal communication problems such as abnormal eye contact, posture, facial expressions, tone of voice and gestures, as well as an inability to understand these. [1]

Additionally, two of the four symptoms related to restricted and repetitive behaviour need to be present:

- Stereotyped or repetitive speech, motor movements or use of objects.
- Excessive adherence to routines, ritualised patterns of verbal or nonverbal behaviour, or excessive resistance to change.
- Highly restricted interests that are abnormal in intensity or focus.
- Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment.

Symptoms must be present in early childhood, but may not become fully manifest until social demands exceed limited capacities. There must be an absence of general developmental delay. Finally, symptoms

should not be better described by another DSM-5 diagnosis.

From the criteria it is important to note that there are many combinations of symptoms that can lead to a diagnosis of ASD. Therefore, not only do individuals with ASD share the same degree of uniqueness as the rest of the general population, but even the type of ASD they experience can be unique.

Confusion can arise in the use of the terms 'autism' and 'autism spectrum disorders.' Part of the reason for this emerges from the subtypes of Pervasive Developmental Disorders (PDD) previously recognised by the APA. PDD previously contained the subtypes Asperger's Disorder, Childhood Disintegrative Disorder, Autistic Disorder and PDD-Not otherwise specified (NOS). While the ICD also recognizes Atypical Autism, recent changes to the DSM should simplify the nosology. [2]

The current ASD diagnosis criteria came into effect from May 2013 and is expected to identify approximately 90% of children with a clinical diagnosis from the previous DSM-IV. [3] A new diagnosis called Social Communication Disorder (SCD) has been created. Simply put, SCD is ASD, without the restrictive and repetitive interests. It is not yet clear how many children will receive a diagnosis of SCD, nor how many children previously identified with a DSM-IV diagnosis of PDD would meet the criteria for SCD only.

Diagnoses made under DSM-IV guidelines are still valid. A new diagnosis is not required simply because of the change in criteria. However, individuals being assessed for ASD now, and in the future, will be diagnosed under the new criteria.

Features of ASD

Social communication, interaction and motivation

ASD is principally characterized by social communication and interaction deficits. Individuals often experience difficulty with interpreting facial expressions, tone of voice, jokes, sarcasm, gestures and idioms. Imagine the literal meanings of "Fit as a fiddle," "Bitter pill to swallow" and "Catch a cold." Some people with ASD may have only limited speech or may be completely non-verbal. [4,5] Echolalia, pronoun

reversal, unusual vocalisations and unusual accents are common. [4,5] Alternative, augmentative and visually based communication techniques may help when a child is unable to consistently follow verbal instructions. In this regard, touch-screen portable devices may appeal to their visual and pattern-orientated learning strengths (see Figure 1). [6]



Figure 1. Touch-screen electronic devices help develop communication skills in children with ASD. Where indicated, service providers (e.g. speech therapists) are able to purchase such devices for their clients using funds from the Australian Government Helping Children with Autism program. Photo credit: Lauren Swan.

Difficulties with social interactions mean that affected individuals often grow up without a social circle, and as a consequence, miss out on peer-initiated learning opportunities. [7] Such challenges include difficulty with understanding unwritten social rules such as personal space and initiating conversation. [7] They can appear to be insensitive, because they are unable to perceive how someone else is feeling. Turn taking and sharing is not intuitive or learned, and individuals need to be trained how to do this. An inability to express feelings, emotions or needs results in inappropriate behaviour such as unintentionally aggressive actions. [8] This can lead to isolation, a failure to seek comfort from others and signs of low self-esteem. [7] Individuals can also suffer from hypersensitivity to sensory stimuli, which may lead them to prefer limited social contact. Individuals do feel enjoyment and excitement; however, this tends to be a personal experience and often goes unshared, which may be due to a failure to need the reward of another's attention and praise. [9]

Imagination

Individuals with ASD may experience challenges with social imagination. [10] Individuals are less likely to engage in make-believe play and activities. They are less likely to determine and interpret other's thoughts, feelings and actions, and as a consequence unable to appreciate that other people may not be interested in their topic of interest.

Individuals with ASD are often unable to predict outcomes, or foresee what might occur next, including hazards. [11] This leads to a difficulty in coping in new or unfamiliar situations, or making plans for the future. Parents, carers and health professionals often need to stick to routines to avoid unpredicted events that could cause distress.

Sensory and motor processing

Sensory information processing is heightened for tactile input, but reduced for social input, in individuals with ASD. [12] Changes in these inputs are understood to contribute to the repetitive and restrictive interest criteria of the diagnosis. Hence, the state of the tactile environment is important to the wellbeing of individuals with ASD, potentially serving as an aggravation by, or as a refuge from,

incomprehensible cues. Changes in sensory information processing may present as an inability to distinguish context-relevant stimuli, and varying capabilities and capacity to respond to a stimulus (e.g. ignoring some sounds but over-reactive to others). They may also experience difficulty with proprioception and responding to pain, including temperature extremes. [12,13] Individuals may explore their environment by smelling or mouthing objects, people and surfaces, and as a consequence, develop eating behaviours that relate to smell, texture or flavor, including inedible objects. Participating in repetitive movements such as rocking, bouncing, flapping arms and hands, or spinning with no apparent dizziness is sometimes as a means of coping with stress, or alternatively, could be used as a means of self-stimulus, providing pleasure. [12] Contrary to popular perception, savant skills are uncommon in individuals with ASD. [14]

What causes ASD?

ASD is a multi-factorial disorder. There is no one cause of ASD. The most prominent risk factor is genetics, both familial and *de novo*. [15] Studies have shown that among monozygotic twins, if one child has ASD, then the other will be affected about 36–95% of the time. [16] In dizygotic twins, if one child has an ASD, then the other is affected up to about 31% of the time. [16] Parents who already have a child with an ASD have a 2%–18% chance of having a second child who is also affected. [17]

In addition to the well-documented increase in chromosomal abnormalities associated with advanced maternal age, the risk of ASD is also associated with advanced paternal age. [18] The current hypothesis to explain this observation is that small, *de novo* genetic mutations and rearrangements accumulate in the sperm, which are then incorporated into the DNA of the child. [19,20] Other risk factors include premature birth or low birth weight, preeclampsia [21] and *in utero* exposure to medications, particularly sodium valproate. [22] There is no evidence to support the theory that the measles, mumps and rubella vaccine causes autism. [23]

Three cognitive theories have evolved to explain the behavioural challenges of ASD: the theory of mind deficit, executive dysfunction, and weak central coherence. The first posits that individuals with ASD are unable to recognize mental states in others, leading to social behaviour discordance. [24,25] The second attempts to explain a lack of goal directed behaviour, and lack of behavioural flexibility. [26] Both these cognitive explanations may be underpinned by an early deficit in social motivation, whereby underdevelopment of the brain regions involved in social recognition and response leads to a failure to learn social cues and their contexts. [27] This has been traditionally thought to impact on imitation learning from which social and food reward by infants is derived and goal-directed behaviour emerges, although research in the area is equivocal. [28] Whether this same underdevelopment also delays acquisition of receptive and expressive language is unclear. [29] Finally, the weak central coherence theory is a means of understanding why individuals focus on details and neglect the context. [30] Yet, it could be argued that a neglect of the context emerges from a deficit in social motivation.

Epidemiology

In the community there is considerable concern of an ASD epidemic. Parental reports indicate ASD prevalence may have increased from 1 in 88 in 2007 to 1 in 50 children in 2012. [31] Currently, the prevalence of ASD in Australia is about 1 in 165 children aged 6–12 years. [32] In the USA this prevalence is slightly higher with 1 in 50–88 eight-year olds receiving a diagnosis; [31,33] this breaks down to 1 in 31–54 boys and 1 in 143–252 girls. [31,33]

A true appreciation of the changes in ASD prevalence can only come from understanding the historical basis of the diagnosis. [34,35] In this regard, marked changes in prevalence have been caused by nosology changes (e.g. autism was once called childhood schizophrenia) and a number of changes to the APA PDD criteria in the DSM over the past 30

years. [36] Other contributing factors include demographic variables (e.g. where older individuals may have missed receiving a diagnosis, but receive one now with the help of a retrospective investigation such as archival home video), increased awareness of normal childhood development and developmental disorders, changes in testing and protocols, and the sampling of data, such as parents versus clinicians, or state schools versus all children. Other factors that often go unreported include socioeconomic factors (e.g. those with sufficient knowledge and resources are able to seek out professional assistance and are more likely to receive a diagnosis than those without) and pressure on clinicians to provide a diagnosis, thereby assisting struggling parents access services and financial support. Trying to account for all these factors in an epidemiological study is very difficult. Hence, the true historical prevalence of ASD is difficult to establish. Studies that have tried show no, or a slight, increase in ASD. [35]

How is a diagnosis made?

While parents often suspect developmental delay or ASD, the variability in child development during the first four years can lead to variability in the age of first diagnosis – typically around three years of age. [34] Reliability of the diagnosis also suffers as a consequence. [37] Restrictive and repetitive interests can be difficult to identify before the age of four because even typically developing two- and three-year-olds can show repetitive behaviours. Since the new diagnosis also requires behaviours to be demonstrably incompetent (such as during a child's interaction at day care), a lag between symptoms and diagnosis is likely to continue.

In Australia, paediatricians, clinical psychologists, psychiatrists and speech pathologists specialising in the field of paediatrics or adolescence make a formal diagnosis of ASD. Further, within these specialisations, diagnoses are likely to be made by practitioners with experience in testing and diagnosing ASD.

A typical diagnostic evaluation involves a multi-disciplinary team including pediatricians, psychologists, speech and language pathologists. Testing takes a number of hours and can be exhausting for subjects, parents and clinicians. Because of this and other factors, waiting times for diagnosis can be up to 24 months across the country, with particular difficulties in rural and remote areas. [38]

In initial consultations, screening tools may be used such as the Autism Behavior Checklist (ABC), Checklist for Autism in Toddlers (CHAT), Modified Checklist for Autism in Toddlers (M-CHAT), Childhood Autism Rating Scale (CARS) and Gilliam Autism Rating Scale (GARS). However, for a diagnosis, the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Schedule (ADOS) are used. [39,40]

Differential diagnoses and comorbidities

There is no single test for ASD and there are no unique physical attributes. For this reason differential diagnoses such as hearing and specific language impairments, mutism, environmental conditions such as neglect and abuse, and attachment and conduct disorders need to be excluded. Disorders similar to ASD include Social Communication Disorder and Social Anxiety Disorder. In the latter, communication is preserved but a degree of social phobia persists.

Since ASD diagnoses are made according to a description of a set of behaviours rather than a developmental abnormality or genetic condition, it is not uncommon to find a diagnosis of ASD comorbid with another pre-existing condition. For example, approximately 20% of children with Down syndrome meet the diagnosis for ASD. [41] Theoretically, all children with genetic abnormalities such as Angelman syndrome or Rett syndrome would also meet criteria for a diagnosis for ASD. In the event of an existing condition, a diagnosis of ASD may also be warranted in order to guide the child's behavioural management and education.

ASD often co-occurs with another developmental, psychiatric, neurologic, or medical diagnosis. [42] The co-occurrence of one or

more non-ASD developmental diagnoses with ASD is approximately 80%. Co-morbidities often occur with attention deficit hyperactivity disorder, Tourette syndrome, anxiety disorders and dyspraxia. Although common, the majority (~60%) of children with ASD do not have an intellectual disability (ID; intelligent quotient ≤ 70). [33] Some individuals with an intellectual disability are likely to always remain dependent on health care services.

There is an increased risk of epilepsy in individuals with ASD. However, the increased co-morbidity of epilepsy is strongly linked to ID – 24% in those with ASD and ID, and 2% with ASD only. [43] There is no evidence that a particular epileptic disorder can be attributed to ASD (or vice versa). [44] The more common presentations include late infantile spasms, partial complex epilepsies and forms of Landau-Kleffner syndrome. Mutations in the tuberous sclerosis genes are particularly associated with ASD and epilepsy. [45]

Gastrointestinal disorders (GID) are a common complication in ASD. [46] Given that some “cognitive” genes of the brain are also expressed in the enteric nervous system, decreased visceral sensitivity, myogenic reflexes or even CNS integration of visceral input may be exacerbated in genetically susceptible individuals. Language impairments may be associated with toilet training difficulties, which can lead to constipation with overflow incontinence and soiling. However, medications and diet are not significantly associated with GID in individuals with ASD. [47]

What treatments are available?

At this point in time, it is thought that biological changes affect the function or structure of the brain over time, leading to different developmental, psychological and behavioural trajectories. There is no cure for ASD, but early intensive behavioural intervention (based on Advanced Behavioural Analysis) is somewhat successful towards promoting learning and independent living. [48] This intervention aims to addressing the core deficits of ASD in a structured, predictable setting with a low student-teacher ratio (initially 1:1). It promotes behavioural systems for generalization and maintenance, promotes family involvement and monitors progress over time. There is some evidence to suggest that participation in social skills groups also improves social interaction. [49] Other intervention strategies are pedagogical approaches to matching faces and actions to meanings.

The Australian Government has made available a support package called Helping Children with Autism. The package includes information, workshops and financial assistance for early intervention services.

At present, pharmacological intervention targets some symptoms associated with ASD. These include serotonin reuptake inhibitors, anti-psychotics, anti-epileptics, mood stabilisers and other medications to treat hyperactivity, aggression and sleep disruption. Given the degree of notable side effects in these pharmacotherapeutics, new generation compounds continue to be tested. There are high rates of complementary and alternative diet use in children with ASD, but a lack of rigorous studies means that the evidence for efficacy is poor. [50,51]

Guidelines on dealing with children with ASD

As medical students and interns, there may be opportunities to participate in a diagnostic clinic or therapy session. Community placements also provide insight into understanding special education interventions, respite and support. However, most interactions would occur during resident training or paediatric rotations. In these situations students will be observing or assisting specialists.

Children with ASD are only likely to be admitted into hospital with a medical problem distinct from their behavioural features. Nevertheless, children with ASD are twice as likely to become inpatients. [52] The more common reasons for hospital admission and general practice visits are seizures, sleep disturbances and constipation. [53]

Parents may describe their child as high-functioning, which tends to

imply an IQ >70. This doesn't usually reflect the social capacity of the child. Ultimately, as with other children, it is important to know the child's strengths and weaknesses; for example, whether they respond more to visual or verbal communication. Most considerations when working generally with typically developing children also apply to children with ASD and developmental disorders. Suggestions for interacting with individuals with ASD can be found in the Table.

Ultimately, by engaging the parents and working with the child's strengths, most issues can be resolved. Even for experienced clinicians, interactions can present challenges. It helps to be patient and adaptable. In some cases it may be pointless performing some examinations if doing them would be disruptive and not provide critical medical information. In such cases, working from the collaborative history will have to suffice.

ASD workshops and training opportunities

Workshops and training opportunities for community members range from one-hour presentations to nationally certified training programs. There are currently two nationally accredited training programs: CHCCS413B 'Support individuals with ASD,' and CHCEDS434A 'Provide support to students with ASD.' Associations around Australia and New Zealand also deliver community education programs and recognized training. The Autism Centre of Excellence (Griffith University, Queensland) provides tertiary training in ASD studies. The Olga Tennison Autism Research Centre (La Trobe University, Victoria) provides behavioural intervention strategy (Early Start Denver Model) training to qualified professionals.

Conferences of note include the annual International Meeting for Autism Research, the biennial Asia Pacific Autism Conference and the Australian Society for Autism Research conferences.

Concluding remarks

Autism is a spectrum disorder. As such, each child is unique. For this reason it is best not to get caught up with the 'label', but to focus on the individual's abilities or disabilities, with an understanding that simplicity, patience and adaptability may be needed. Work with the parents or the carer to achieve the desired outcomes.

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Disclosures

Dr. Moldrich is Adjunct Research Fellow of The University of Queensland investigating biological causes of autism. Together with Drs. Hill-Yardin and Bishop, he is co-organiser of autism research conferences. Dr. Moldrich is on the scientific advisory board of the Foundation for

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Table 1.

Pearls for interacting with individuals with ASD in the health care setting

- Make plenty of time available.
- Children may be averse to doctors and resentful of clinic settings because of their history of doctor visits.
- Speak in a clear, consistent manner, allowing time for processing.
- Work in a team whenever possible, although too many people can also be a problem.
- Parents, carers and next-of-kin are happy to share knowledge of the child's condition, habits and idiosyncrasies, strengths and weaknesses. Ignoring their advice is guaranteed to make the interaction very difficult. You will also relieve parental stress by consulting them first.
- Draw on the expertise of childcare workers, nurses or behavioural specialists. Even tasks such as taking a temperature can be impossible without the right support.
- The fewer surprises, the better. Explain everything that needs to happen beforehand.
- Use communications systems appropriate for the child to explain actions or concepts; keeping in mind that social concepts and feelings may not be understood.
- Even with consent, touching or restraining can be difficult. Children with ASD can lash out, rather than tell you not to touch them.
- They generally like privacy and may not interact with others.
- They may not appear to be paying attention. Eye gaze is no indication of attention.
- Often have disruptive sleep patterns and can wake in the middle of the night.
- Are more relaxed and engaging when they are in familiar surroundings and follow routines.
- Whether in the hospital or general practice, a trivial presenting complaint should be treated quickly to allow the child to return home as soon as possible.
- May not eat hospital food for a plethora of reasons. Parents are usually wise to this and food from home may be a better option.
- May find obsessive compulsions or interests around them, which could be of help or hindrance.

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