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Shaping our future of medicine together

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Editor's welcome

Rachel Park, PhD
Editor-in-Chief, AMSJ

Welcome to Volume 8, Issue 2 of the Australian Medical Student Journal (AMSJ). The AMSJ is a national peer-reviewed journal serving as a publication platform for all medical students in Australia. Our aim is to showcase medical students' perspectives on current issues in medicine. The editorial theme of this issue is shaping our future of medicine together as medical students.

Several original and feature articles in this issue clearly show medical students taking ownership of the future of medicine. This includes proposals for better delivery methods of medical education and policy. Dr Timothy Wittick and colleagues highlight the importance of community engagement activities on medical students' personal and professional development. Dr Nicholas Wilson and colleagues emphasise the significant educational and cultural value for students participating in Aboriginal community placements. In addition, Mr Benjamin Bravery shares his personal experience as a cancer survivor, and discusses potential improvements in delivering oncology education in medical schools. Dr Anna-Kristen Szubert and colleagues address the issue of mistreatment in Australian medical education, and provide recommendations to better shape the future of medical culture and professionalism.

In this issue, we are honoured to feature the voice of influential leaders across the medical field as guest articles. They have generously shared their insights on shaping the future of medicine. Dr Michael Gannon, President of Australian Medical Association (AMA), states that while AMA policy and advocacy address many issues for building a better society, its core lies in the medical education and training for the next generation of medical professionals. A/Prof Stuart Lane defines and explains the core of professionalism and professional behaviour; an essential component in our medical careers as highlighted in many articles in this issue. Prof Michael Besser AM highlights human anatomy as the basis of medicine and states that "human cadaveric dissection represents a profound rite of passage into the medical profession". Furthermore, invaluable advice on making career decisions is given by Prof Catriona McLean and A/Prof Steven Lane from perspectives of a mother-pathologist-scientist and a physician-scientist, respectively.

Also in this issue, we are excited to present the winning abstract by Manon Audigé from the 3-Minute-Thesis Competition at AMSA Convention 2017, in collaboration with Australian Medical Students' Association (AMSA).

The AMSJ is run by medical students in Australia. This issue would not be possible without commitment from many individual medical students, led by executive members, who volunteered their time to work in the editorial teams, and in the roles of publication, publicity, sponsorship, finance and university

representatives. On behalf of the AMSJ, I would like to show my appreciation to all our authors, peer reviewers and sponsors. Their expertise, time and support have largely contributed to the successful publication of this issue. In addition, I would like to gratefully acknowledge the Medical Journal of Australia (MJA) for their invaluable support in the professional development of our editorial team. Finally, on behalf of the AMSJ, I would like to thank our readers and I hope we, as medical students, continue taking ownership of shaping our future of medicine together!

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The wide world of medicine

Dr Michael Gannon
MBBS(WA) MRCPI FRANZCOG
AMA President

Dr Michael Gannon is the President of the Australian Medical Association, the Chairman of the Federal AMA Ethics & Medico-Legal Committee and is a member of both the Cases Committee of MDA National and the AMA's Public Health Committee and Medical Practice Committee. Dr Gannon is also an obstetrician and gynaecologist with an interest in medical problems in pregnancy and perinatal loss, holding the positions of Head of the Department of Obstetrics and Gynaecology at St John of God Subiaco Hospital in Perth, the Lead Obstetrician in the Perinatal Loss Service at King Edward Memorial Hospital and the RANZCOG nominee to the state Perinatal and Infant Mortality Committee.

It is a pleasure to contribute to the *Australian Medical Student Journal*, and to be involved in the work and the thinking of the next generation of medical professionals.

Medical education and training are at the core of Australian Medical Association (AMA) policy and advocacy. Without a quality future medical workforce, the health policies and reforms of government cannot succeed. The AMA keeps reminding governments at all levels of this important fact.

But the concerns of medical students and young doctors extend well beyond the medical and the professional. You want to help build a better society. You want to empower people and communities.

You have strong views on issues like climate change and marriage equality. Like the AMA, you want to make a difference – a real difference.

AMA advocacy is very broad and very deep; it has to be. No other medical or health organisation in the country can even come close to our success in initiating or influencing change across the health system and society.

Single-issue or narrow focus groups, like Doctors for the Environment and Doctors for Refugees, do great work, as do the learned Colleges, Societies, and Associations. The other health professions, the public health groups, consumer representatives, and other groups all do their jobs and also do them well.

But the AMA's mission goes so much further.

If you look at the AMA website, we have around 150 Position Statements, which include:

- Climate Change and Health;
- Workplace Bullying and Harassment;
- Indigenous Health;
- Sexual and Reproductive Health;
- Women's Health;
- Men's Health;
- Obesity;
- Human Cloning;
- End of Life Care;
- Family and Domestic Violence;
- Female Genital Mutilation;
- Concussion in Sport; and
- Firearms.

Dr Michael Gannon

These issues cover many facets of society and many ideologies. Some are regarded as progressive, some are conservative, but most are controversial — and therefore potentially divisive.

We do this on top of our other core business — Medicare, the Pharmaceutical Benefits Scheme (PBS), public hospital funding, the Professional Services Review (PSR), medical workforce, private health, rural health, doctors' health, and a broad range of public health issues.

The AMA has to always tread a fine line, and we do that willingly, as with recent topical issues like climate change, pollution, air quality, and renewable energy.

The AMA believes that climate change poses a significant worldwide threat to health and urgent action is required to reduce this potential harm.

We have been vocal about the need for urgent government action, and have repeatedly called for the development of a National Strategy for Health and Climate Change.

The AMA Position Statement, *Climate Change and Human Health 2015*, is a very strong document. It was developed from the ground up, with input from AMA members at grassroots level around the country.

The AMA wants to see a national strategic approach to climate change and health, and we want health professionals to play an active and leading role in educating the public about the impacts and health issues associated with climate change.

Human health is ultimately dependent on the health of the planet, and the AMA lobbies governments for urgent measures to mitigate the evolving effects of climate change, including the transition to non-combustion energy sources.

The evidence is clear — we cannot sit back and do nothing.

There is considerable evidence to encourage governments around the world to plan for the major impacts of climate change, which include extreme weather events, the spread of diseases, disrupted supplies of food and water, and threats to livelihoods and security.

Our stance is not limited to the Position Statement. We are actively engaged in advocacy on climate change and health. We attended the Health Leaders Roundtable at Parliament House in 2016, where health advocacy bodies met with Members of Parliament to discuss the health impacts of climate change and the need for urgent action.

We make regular submissions to relevant Parliamentary inquiries, where we take every opportunity to highlight the connection between climate change and human health.

We adopt this approach across the broad range of policies we, as the peak medical organisation in the country, embrace. We take this role very seriously.

You are the future of the medical profession. It is my job — and that of all AMA leaders — to pass on to you a strong policy platform, and an even stronger advocacy agenda, to help you achieve your ambitions in medicine and to make the world a better place in which to live. We will not let you down.

Professionalism and professional identity: what are they, and what are they to you?

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A/Prof Stuart Lane is coordinator of Clinical Studies, and chair of the PPD theme for the Sydney Medical Program. He has a decorated record for teaching, and has developed a national and international reputation in researching human experience using qualitative methodologies. His PhD thesis explored the experiences of medical interns who had been involved in open disclosure. He is an examiner for the College of Intensive Care Medicine (CICM), Senior NSW CICM Supervisor of training, and Deputy Chair of the NSW CICM Regional Committee. He is a keen swimmer and successfully swam the English Channel in 2017.

The terms profession, professional, professional identity and professionalism are quoted many times in medical student teaching and are often used interchangeably. This can lead to confusion as to what the concepts really are. We, therefore, need to be careful what we mean when we quote them and, more importantly, what we understand about how they relate to our personal clinical practice. Medical students are constantly being told in lectures, tutorials and workshops that they need to demonstrate professionalism in their future careers, so what is vital in their professional development is that they understand not only how everybody else defines professionalism but, most importantly, what it means to them, that they have got it right and that they keep getting it right throughout their careers.

The American philosopher Mortimer J. Adler defined a professional as "a man or woman who does skilled work to achieve a useful social goal. In other words, the essential characteristic of a profession is the dedication of its members to the service they perform [1]." So, if professionals belong to a profession, what does it take to be part of one? In the early 20th century, E. P. Scarlett defined what he believed were the seven pillars of a profession: (1) technical skill and craftsmanship, renewed by continuing education; (2) a sense of social responsibility; (3) a knowledge of history; (4) a knowledge of literature and the arts; (5) personal integrity; (6) faith in the meaning and value of life; and (7) the grace of humility [2]. This 'list' of attributes defining a person or a concept has become common amongst modern society, and, just as humans have a 'tick-box' of what they may desire in a future partner, healthcare organisations have 'tick-boxes' as to what they expect of their members. For example, the Accreditation Council for Graduate Medical Education (ACGME) in another seven-point list defined the core competencies of a doctor as respect, compassion, integrity, responsiveness to needs, altruism, accountability, commitment to excellence, sound ethics, and sensitivity to culture, age, gender, and disabilities [3]. We can see that professionalism is an expected attribute for a member of the medical profession, aligning with old-fashioned values considered to be core properties of a profession, and the people who define these pillars are not just the profession themselves, but society as well. The profession has a contract with society: that society grants them self-determination and awards them an elevated status in return for civic responsibility, community leadership and this professionalism.

So, what is the connection between professional identity and professionalism? Burke states that "identities are the meanings that individuals hold for themselves, what it means to be who they are. These identities have bases in being members of groups (social identity), having certain roles (role identities) or being the unique biological entities that they are (personal identities) [4]." This is important for medical students as they develop their identity during their time at medical school. Tajfel and Turner [5] proposed that people tend to categorise themselves into one or more in-groups, deriving their identity from the group and forming boundaries with other groups. This group identification promotes self-esteem within the group and leads to greater commitment to the group, even if the group's status is low. They believed the three major components of social identity

A/Prof Stuart Lane

are: (1) categorisation: putting others or ourselves into categories, labelling the person as a way of defining the person; (2) identification: the way in which we define our self-image through association with a group, in-groups being the ones with which we identify and out-groups those which we do not; and (3) comparison: we compare our own groups to others and create favourable biases towards our own. This process is very strong within people's minds and leads to stereotyping. If doctors are stereotyped as being caring, altruistic individuals by one person, they may now be stereotyped in another person's mind as greedy and arrogant. Ultimately, once these stereotypes are formed they can become rigid.

Coulehan [6] distinguishes three types of professional identity in medicine: (1) technical identity: the doctor abandons traditional values, becoming cynical about duty and integrity, and narrows the sphere of responsibility to the technical arena; (2) non-reflective identity: the doctor espouses and consciously adheres to traditional medical values whilst subconsciously basing behaviour, or some of it, on opposing values, thus being self-deluded and detached; and (3) compassionate and responsive identity: the doctor overcomes conflicts between tacit and explicit socialisation, internalises the virtues and values professed, and manifests these in behaviour. What is worrying is that Coulehan [6] demonstrated that a large percentage of medical graduates can be classed as having a non-reflective professional identity, maintaining that this outcome is most likely where there are conflicting values in the learning environment. The inability to reflect appropriately was demonstrated by the participants when there were deficits in their clinical reasoning, and this highlighted the need for expert facilitation and education. With poor supervision and mentorship, new doctors may internalise beliefs that certain 'unvirtuous' behaviours are virtuous, since that is 'the way things are in medicine'; that is to say, it is the

cultural norm. However, the development of a person's professional identity is strongly influenced by another concept, the notion of 'belongingness'. Belongingness is the human emotional need to be an accepted member of a group. Whether it is family, friends, co-workers or a sports team, humans have an inherent desire to belong and be an important part of something greater than themselves. This implies a relationship that is greater than simple acquaintance or familiarity. The need to belong is the need to give and receive affection from others [7]. Without belonging, a person cannot identify oneself as clearly, thus having difficulties communicating with and relating to one's surroundings. This implies that belongingness is related to identity. However, there is a danger with belongingness in that the desire to belong can lead to conformity, which can lead to lack of self-regulation. And this is what brings us back to the notion of professionalism.

When you look at the definitions of medical professionalism, there are numerous differing statements. For example, the University of Ottawa states that professionalism embodies the relationship between medicine and society as it forms the basis of patient-physician trust [8]. It attempts to make tangible certain attitudes, behaviours and characteristics that are desirable among the medical profession [8]. The Medical Protection Society in the UK has a whole page on it, but does not give a definition [9]. The Australian Medical Association (AMA) makes a statement on it: "while the expression medical professionalism is used in different ways, for the purposes of this position statement we are using it to refer to the values and skills that the profession and society expects of doctors, encapsulating both the individual doctor-patient relationship and the wider social 'contract' between the profession and society [10]." Despite this, professionalism remains very vague as a concept.

The previous discussion and statements suggest that professional identity is constructed at the level of the individual, whereas professionalism is constructed by the community and medical profession as a whole. These community and societal ideals are articulated in professional codes, institutional frameworks and formal medical curricula, which may or may not reflect reality. However, professional identity is a reality that might not correspond to the ideal, for reasons that can be valid or not. It is based on one's beliefs about what it means to be professional, and a doctor's beliefs may differ from those of the community or other health professionals. It therefore follows that a responsive and reflective professional identity is more likely to develop where there is alignment between the understandings and expectations of others, self-identity and personal values, the social identity of the professional group, and the cultural milieu of the working environment. Since identity implies values and goals, it will also determine motivation; thus it has important educational implications for self-regulated learning. This means that professionalism must be defined by the individual, and they have to ensure that their personal beliefs and concept of what professionalism means resonates with the organisations and society in which they operate.

Ensuring that you define professionalism to yourself in the correct manner necessitates critical reflection. Reflection can occur at either a superficial, moderate or deep level [11], and it is this deeper level of reflection that makes it critical. Superficial reflection is purely descriptive, and whilst it might make reference to existing knowledge it does not critique it. With moderate reflection, often called dialogic reflection, the person takes a step back and starts to explore thoughts, feeling, assumptions and gaps in knowledge. The reflector makes sense of what has been learnt from the experience, and what future action might need to take place. Deep or critical reflection leads to a change due to the experience. To achieve this, the learner needs to be aware of the relevance of multiple perspectives from contexts beyond the chosen incident, and how the learning from the chosen incident will impact on other situations.

So how does this translate to me, a practicing clinician? After all, if I am to suggest that you should practice in a certain manner, then I should lead by example. Professionalism as defined by myself to myself is based on '3 rights': (1) I know what the patient has a right to; (2) I know what the right thing to do is, and I will do it; and (3) I know the right manner to do it in. This, conveniently for me, encompasses the legal, ethical and moral aspects of my clinical practice, and I believe it is summarised by the concept of integrity: integrity for me is what defines professionalism. To translate this into a clinical concept, consider the delivery of open disclosure. I know the patient has a right to an apology, I am aware of the need to apologise, and I want to apologise. To ensure that I hopefully continue to practice in this way, I reflect with the right people, at the right time, in the right manner, meaning I don't seek out those who will always agree with me, and I ask them for them an opinion before I state my beliefs, whilst I am ready to listen to their suggestions.

Over the next few years of your careers, you will hear it repeated many times from senior clinicians that, as your career progresses, the knowledge becomes fairly straightforward. This is not entirely true as new advances and techniques are continually being developed, however, understanding yourself and those around you to a greater depth is the best piece of armamentarium you can acquire as you begin to forge your medical careers. Your curriculum is extremely busy and you will probably not relish the thought of further background reading, however, this will not change throughout your career, so make time to see medicine beyond the facts. Consider concepts such as intellectual humility, growth mindset, situational awareness and the competency matrix, concepts beyond your basic curriculum, as this will ensure your career is as successful and fulfilling as possible.

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Human anatomy

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Prof Michael Besser was awarded the Order of Australia (AM) in 2001 and was the recipient of the ESR Hughes Medal RACS in 2009. He was former Head of the Department of Neurosurgery at the Royal Prince Alfred Hospital, Chairman of the Institute of Clinical Neurosciences, Chairman of the Neurosurgical Board, President of the Neurosurgical Society of Australasia, and Examiner in Neurosurgery for the Royal Australian College of Surgeons (RACS). He has over 90 publications in peer-reviewed journals. He is the past Chairman of The Greater Metropolitan Clinical Taskforce (Neurosurgery) and RACS representative of the Bicycle Safety Committee of Standards Australia. He is currently Chairman of the National Brain Cancer Biobanking Consortium, and sits on the Medicare Review Taskforce of the Federal Department of Health. He also represented Australia at eight triathlon world championships in standard, long course and Ironman events.

Rembrandt's painting "The Anatomy Lesson of Doctor Nicolaes Tulp" in 1632 makes it clear that human anatomical dissection had become one of the spectacles and symbols of the age. Anatomy had become accepted as a portal into the human condition [1]. In many ways, it can be viewed as part of the cultural movement of the Renaissance, despite human dissection existing primarily as a procedure of medicine [2].

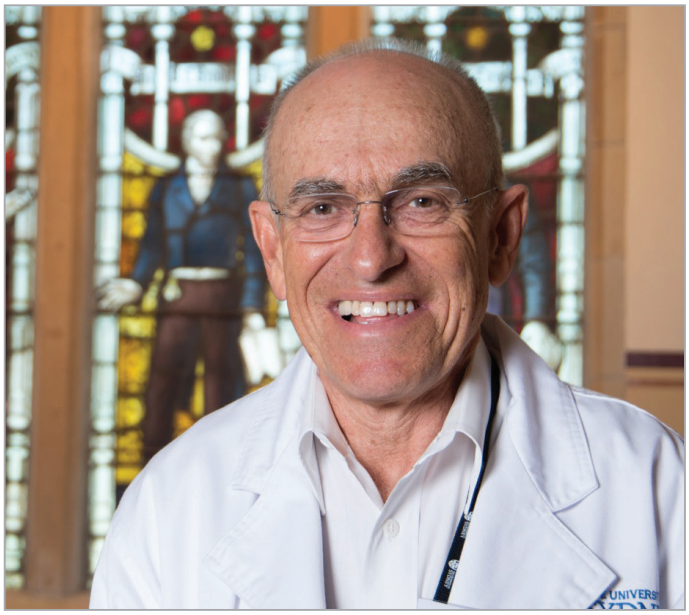
Wide-ranging circumstances influenced the revival and unfolding of human anatomy. Anatomical dissection became the cutting edge of medical investigation and the essence of a doctor's training. This anatomical revolution brought about a paradigm shift away from the traditional thinking of the body and its relationship with the mind and soul, which had so dominated medieval thinking [3].

Human cadaveric dissection was first introduced during the third century BC at the School of Greek Medicine in Alexandria, championed by Herophilus, but this was subsequently not allowed under Roman rule [4]. Galen, in the second century AD, became the anatomical authority; however, all his dissections were on animals, and the extrapolation of his findings to humans resulted in inaccuracies not corrected until the time of Vesalius [5]. His huge collection of work was written in Attic Greek, the contemporaneous language of science, and was largely lost with the fall of Rome [6].

Medieval medical practice [7], carried out mainly in monasteries with small charity hospitals, was dominated by religious values to an extraordinary degree. The declaration of Pope Innocence the Third in 1215 forbade clergy from engaging in any activities likely to cause bloodshed [3]. This prevented clerics from practicing surgery or studying anatomy. Surgery was left to layman practitioners, who were mostly uneducated manual workers, degraded by their contact with blood [2].

With the beginnings of vernacular literature and the founding of the first universities, a more humanistic approach to medicine developed [5]. This coincided with a revival of Greek culture, science, and mathematics, together with advances in industrialisation. The city of Salerno was famous as a health centre since Roman times, and it developed an orientation around Greek medicine when its archbishop, Alphanus, travelled to Constantinople in 1063 [5]. As well as introducing Byzantine and Islamic medicine, a crucial advance came with the re-discovery and translation of Galen's anatomical texts from Arabic into Latin [2]. This allowed the sharing of medical thinking, and a specialised vocabulary was generated which provided a framework for medical teaching [5]. A foundation medical text called The Articella was created, and this was used throughout the newly-established medical schools of Europe by the mid-12th century [2].

Anatomical knowledge was boosted by the discovery of Galen's text On Anatomical Procedures, which was a treatise on how to carry out a dissection [8]. The first public record of a systematic anatomical dissection was in 1315 on a condemned criminal at the Bologna medical school by Mondino de Luzzi [9]. De Luzzi subsequently wrote the standard anatomical text for the time based on the Galenic model [5]. Dissection based on this model soon became part of medical education in universities across Europe, and authorities began supplying condemned criminals to medical faculties for human anatomical dissection [9].



Prof Michael Besser AM

The anatomical basis of medicine paved the way for its foundation as a rational science [10]. However, the idea that dissection might be used to verify, or even correct, established medical thought was still quite alien [9]. A typical dissection scene consisted of the physician, in his academic robes, sitting high on a throne reading from a Galenic text, whilst a surgeon dissected, aided by a teaching assistant pointing out anatomical details [10]. The goal was not to add to knowledge, but to verify the text in which the knowledge was enclosed [5]. Surgical benefits were rarely mentioned, and surgeons still learned their anatomy by practical apprenticeship [11].

By the 16th century, permanent anatomy theatres were built to accommodate a growing audience, including laymen and artists [4]. University anatomy dissections became somewhat theatrical events lasting many days, followed by banquets in an almost carnival-like atmosphere [1]. Enthusiasts of anatomy included Renaissance artists, such as Leonardo da Vinci [12], and a revival of naturalistic art involved them in not only attending dissections, but in performing their own [2]. The new involvement of artists with anatomy resulted in more realistic medical illustrations, which became increasingly available [13].

Andreus Vesalius, at the University of Padua, not only transformed research in human anatomy, but also, equally profoundly, the teaching of anatomy. Vesalius based his research and teaching on the dissections of cadavers he carried out himself, in contrast to his contemporaries [14]. He rapidly exposed Galen's anatomical errors, and published his beautifully illustrated seven-volume book De Humani Corporis Fabrica in 1543. This marked a turning point in the understanding of the human body, and Vesalius' core ideas became the essence of the new anatomy [15].

Over time, cadavers became increasingly difficult to obtain. Clandestine acquisition of bodies, including grave-robbing, together with fear of vivisection in the community, caused increasing public disquiet regarding anatomical practice [11]. A gradual decline in public dissection developed, despite the practice being considered a linchpin of surgical training and an important component of medical education. The dubious morality surrounding the procurement of cadavers was mitigated with the British Anatomy Act of 1832 which allowed for body donations, and excluded the use of executed criminals [9]. This was a paradigm shift in the procurement of human cadavers for anatomical dissection.

The teaching of anatomy by dissection has gradually declined in the modern era, often replaced by virtual and digital imagery to save time and money [16]. Many have reasoned, however, that clarity of understanding regional relational anatomy and construction of a mental three-dimensional representation of the human body cannot occur without anatomical dissection [17]. Some research has shown that decreased use of dissection as a teaching tool is one of the factors that can have a negative influence on the anatomical skills of medical students and, somewhat paradoxically, leads to a decline in anatomical knowledge [18].

The lack of anatomical knowledge in students reaching their clinical years, and by extension surgical trainees, led to a review of the University of Sydney Medical School program and re-introduction of a whole-body dissection course in 2009 [19]. Subsequently, the pass rate in anatomy for the Generic Surgical Sciences Examination (GSSE) went from 57% in 2007 to 92% in 2015 for graduates of the university.

There are also other considerations. The handling of a human cadaver encourages humanistic qualities in medical students, and provides some insight into the meaning of human embodiment and mortality [20]. Indeed, some would argue that human cadaveric dissection represents a profound rite of passage into the medical profession [21].

Vesalius was a pioneer of medical illustration in medical teaching, but he saw this only as an aid to learning [22]. He insisted that anatomy could only be studied and understood by inspection of the human body through dissection [23]. Despite the passage of 500 years since his birth, this principle still remains of enduring relevance today.

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Moments in a mother's medical career in pathology

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I am 20. At a social barbecue I talk with an obstetrician about careers in medicine. She tells me that there is no point becoming an obstetrician if I want to have a family. I remain quiet.

I am 22. I compliment my favourite aunt on her new hairstyle. Her look is blank. It is a wig. I am so naïve. She dies the night of my fourth-year final exam. I forget to go to my exam.

I am 24, an intern in my first term. I am looking after Ian, who is having the first bone marrow transplant in my hospital. I am fascinated by the science. I see Ian remain positive and friendly at all times despite what he is going through. He has a lovely family. I don't want him to die with this brand new treatment. I remain vigilant and work to my capacity; to my great relief, Ian lives.

I am 27, a senior resident medical officer. I have offers to continue training in oncology, cardiology, or neurology. I am unsure which direction I really want to go. I am pregnant. There is no maternity leave in the medical officer award in 1987. I am forced to resign. I let all three physician training offers go. I lose my entitlements. My little boy eclipses medical study.

Choosing what you should do with your medical degree, and balancing this with your personal life may not be clear to you early in your medical career. A single event, person or patient may inspire you in a direction. Your career choice may not evolve as you wish it to. You may need to make compromises. You may face hurdles that you never thought would occur.

After some deliberation about which path I should take I chose to become a pathologist. At the time I also thought it was going to be more practical for me and my young family. I'd always been fascinated by pathology and I remain fascinated by pathology. Whilst there is disease, there is the need to diagnose, understand pathogenesis, and find effective treatments. Even today, I often see something new down the microscope. It could be something I've overlooked every other time or an extremely rare disease. I've learnt to keep my eyes and my mind open.

Often I get questioned by junior doctors about moving into pathology and moving away from the patient. I do not see it that way. I feel that the patient is very central to our role. We want to make sure their diagnosis is correct, that we offer them accurate information about their disease. We are not disconnected from them.

It has not always been plain sailing trying to juggle fellowship exams, consultancy and being a mother. I did, however, create a rule for myself very early on. This rule was to never study once I returned home after work. If I could not keep family and work separate it would not work for me in the long run. So, I learnt to concentrate super hard. If

Prof Catriona McLean

I read something once, it had to stick. If I saw something down the microscope, I had to be able to recognise it the next time. I still abide by this rule today.

Once I'd completed my fellowship, there were very few public hospital jobs around so I started a doctorate and received some sessional work. It was a 56 kilometre round trip to the hospital for one of the sessions. Sometime later I was pregnant again. I chose to resign from the distant workplace, took eight weeks off, and continued to work on my thesis at the university. Fifteen months later I was pregnant with twins. I took annual leave. I'd finished my experimental work so I wrote my final thesis when my twins were three months old. They'd sleep and I'd write. They'd wake and I'd feed them. Don't ask me details about this time of my life.

Following my doctorate, I found a consultant job close to home. I also decided early on that collaboration would offer me more scope for research than trying to juggle full time service work and leading research. Some colleagues choose to become the leaders of research laboratories. I choose to contribute my skills and knowledge to research. Everyone is different.

I am 44. I have four children. I am offered a job as professor and head of anatomical pathology and I take it. The children can all walk to school and I never make or find time to wash my car. Time is of the essence.

I am 57. I am still head of anatomical pathology amongst other new titles and fellowships I've gained. My special interest is in brain and muscle pathology, particularly rare diseases. My world-ranked expertise is shared with medical science via more than 350 research papers in which I am a co-author.

What will the future be for certain specialties in medicine? Will algorithms and robots overtake large aspects of our work? It is important to look to the future but also to remain optimistic and to be prepared to change. One aspect of my field, rare paediatric neuromuscular diseases, has seen a great deal of change in the past five years. Next generation — and now whole exome — sequencing has resulted in many genetic diagnoses being made. What about those children who remain without a genomic resolution? What happens to those in whom a specific mutation has been found? Is there a specific treatment available based on this new information? Not usually. Not yet. What then?

Knowing the gene mutation does not mean that the mechanism of pathogenesis is known. Without a good understanding of pathogenesis, specific treatments remain unknown. It is a group effort to solve these unknowns with input required from multiple specialties. I've been involved in several recent cases looking at new gene mutations and how they affect muscle. There has been much for me to learn from using this new information to help interpret future cases and to aid in understanding the pathogenesis of a disease. This new genomic information adds to the new information provided in the seventies by electron microscopy and in the nineties by immunohistochemistry — each of which was revolutionary in its time.

Making each career decision, each medical decision, requires adaptation and use of your knowledge in new ways. At the same time, it is important to remember that your career should always be fun. It should always be challenging. You will always be learning.

A balancing act: life as a physician-scientist

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Craig is a fourth-year medical student at the University of Queensland. Before starting medicine, he completed a Bachelor of Science (Advanced) at the University of Sydney with majors in Biochemistry and Statistics.

In this issue of the AMSJ, we talk to A/Prof Steven Lane about life as a physician-scientist. A/Prof Lane is a clinical haematologist at Royal Brisbane and Women's Hospital (RBWH) and head of the Gordon and Jessie Gilmour Leukaemia Research Laboratory at the QIMR Berghofer Medical Research Institute. He has recently been awarded a prestigious CSL Centenary Fellowship.

His lab researches myeloid blood cancers such as acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and the myeloproliferative neoplasms (MPN). These are very aggressive and rapidly fatal blood cancers that are among the most common types of cancer affecting Australians.

Q: What is the current focus of your research?

A: We are a cell biology laboratory researching leukaemia and other blood cancers. We try to understand at the cellular level how leukaemia forms from normal blood cells, what are the pathways that turn it from being a normal cell into a leukaemic cell, and how it is that treatments can reverse that process or target the cancer cells.

Q: What drew you to specialise in haematology?

A: I was initially drawn to haematology mostly because of the patients. The patients are often young people. These are very unlucky people who have very severe illnesses but have a possibility for cure. There's a lot at stake, but it's very rewarding because of that.

Additionally, the science and clinical trials are right on the cutting edge of the latest developments.

Craig Coorey

Finally, in any career you look for good examples and mentors. Haematology at RBWH and PA Hospital in Brisbane are very lucky to have some excellent people working there. I guess they were very inspiring to work around and you want to be like those senior doctors. I think those aspects make haematology a very attractive specialty and lead to a lifetime of challenges and rewards.

Q: When did you first become interested in research?

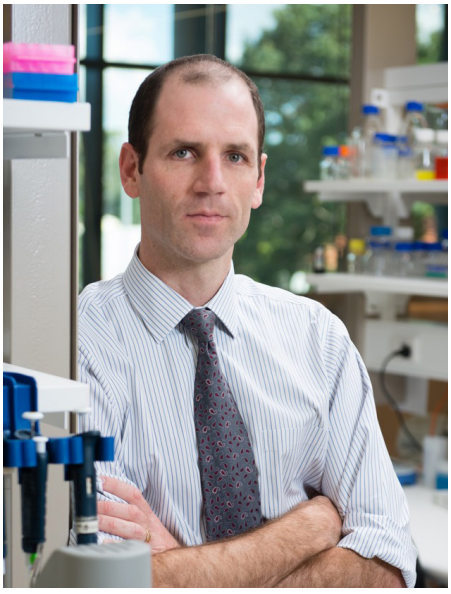
A: Actually, I was never interested in research when I was a medical student. When I started my advanced training in haematology I realised that research was a very necessary part of what we do and I really wanted to get involved in clinical research. I found clinical research at some levels rewarding and some levels frustrating because we are really limited by the fact that we have rare diseases, small numbers of patients and a lot of conflicting priorities with funding, drug companies and investigator-initiated research.

That experience motivated me to look at translational research and understanding the fundamental biology as to why things happen. You realise as you become more exposed to a certain field that the big breakthroughs do not happen at the clinical trial end but happen at the very basic biology end. It is those massive discoveries that change medicine. For example, imatinib (Gleevec) which is used for chronic myeloid leukaemia, comes from the basic laboratory from an understanding of how a disease process works.

I also felt that other people had a strong aptitude for clinical research whereas there was an opportunity for me to get involved in the other preclinical side of it.

Q: Medical students often ask when the best time is to do a PhD in their training. When in your career did you complete your PhD and how did you find it?

A: I did my PhD after I completed my speciality training.



A/Prof Steven Lane

One of the advantages of doing it later is that you have to maintain momentum in a research career. If you do some research, then leave research for few years and try to come back, you have to start back from square one.

Completing a PhD also resets your career so that you are eligible for young investigator funding, so if you do it later it has other advantages as well.

I think what is important is to get exposure to research but not on a full time basis at the early points. You need to get involved in reading journal articles and writing papers.

A downside to research is that it can be more financially challenging to step out of your career later and it can be challenging if you are married with kids. For all the talk from government and hospitals, they still don't know how to appropriately manage and fund clinician researchers, and this is an ongoing challenge for the entire field.

Q: You completed an overseas fellowship in Boston as a part of your haematology training. Do you recommend heading overseas for a fellowship?

A: I don't think it matters if you head overseas or stay locally, what matters is that you give yourself the best opportunity. You may be

lucky enough to be interested in an area of research where there are experts locally and in that case you should absolutely study with them.

If you get the opportunity to go to a great international centre, I think you should take it, but there is a very substantial financial penalty to doing it. In real dollars, it costs an enormous amount of money. In opportunity cost, it costs about three times that because you are not earning money here, but you really shouldn't worry about that now!

Q: When you returned from the overseas research fellowship, how did you find establishing yourself as a physician-scientist in Brisbane?

A: I currently have two separate part-time appointments: 70% as a researcher (QIMR) and 30% as a clinician (RBWH). At the moment in Brisbane they do not have combined physician-scientist positions, so you need to get a clinical job and a laboratory job and put them together to make a full-time position. Some hospitals in other cities such as Melbourne do have combined roles.

For my clinical appointment, I have regular clinic days each week and also do ward service, on call, and other clinical meetings.

Q: Lastly, what advice and tips would you give a medical student interested in a career as a physician-scientist?

A: You have to be self-motivated, proactive and have self-discipline. Do not expect too much too quickly. If you show you are interested and spend time on it, opportunities will present themselves. Keep an open mind and follow those opportunities. If you do the right things and do them for the right reasons, it will work out in the end.

Designing a literature review: critical considerations

Mr Ross Penninkilampi
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Ross is a fifth-year medical student at UNSW who is fascinated by the human brain, and is currently completing his Honours year in Alzheimer's research. His other interests include history, cricket and playing blues guitar.

A comprehensive literature review is one of the first steps in the research process. It is important to contextualise any study in terms of what is currently known, and identify knowledge gaps that need to be filled. A well-conducted literature review, particularly when performed with a systematic methodology, can be an important contribution to a field of research in its own right. This article will summarise the aims and methodological differences between the most common types of review articles. This article does not provide step-by-step instructions for the completion of a literature review. As such, readers are encouraged to review the referenced articles for further information [1,2].

Is this review necessary?

The key aim of a literature review, in terms of the research process, is to orient the researcher to the current scholarship on a certain topic, and to guide the development of research questions. Another key aim is to answer a specific research question or present key findings in a field, based on the entirety of the accumulated evidence. A sufficiently comprehensive search of the literature needs to be performed to develop an integrated answer to this question.

The review may not be necessary if:

1. A previous review article has been published that answers your question, and there is insufficient new evidence to warrant a replication or expansion of the review; or
2. Answering the research question will not expand the current base of knowledge, or help to guide further research.

Types of review articles

There are many types of literature reviews, which can be broadly grouped into three categories based on the rigorousness of the methodology used: systematic reviews, scoping reviews and narrative reviews.

Systematic review

Systematic reviews are designed to comprehensively review all of the available evidence relating to a specific and narrow research question. Systematic reviews are both systematic and comprehensive: they have a detailed methodology and aim to capture all, or the vast majority of, the available literature in answer to a specific question. Meta-analyses are similar to systematic reviews, but also include a quantitative synthesis, by which they synthesise an overall estimate of effect based on all of the accumulated data within individual studies [3].

Systematic reviews are performed according to the Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [4]. Important components of a systematic review include:

1. A comprehensive literature search using broad, relevant search terms across multiple databases, such as PubMed and Embase.
2. Pre-specified inclusion and exclusion criteria for studies, and a study selection process conforming to these criteria.
3. Synthesis of evidence to answer narrow research questions.
4. An assessment of study quality, usually using validated quality assessment scales such as the Jadad scale for randomised controlled trials and the Newcastle-Ottawa scale for observational studies [5,6]. It is worth noting that there have been some concerns raised about the validity of the Newcastle-Ottawa scale, despite its relatively frequent use [7].

Systematic reviews typically require significant effort on the behalf of the authors to execute, but, along with meta-analyses, provide the highest level of evidence available in answer to a research question [8,9]. This is particularly the case when the included studies are randomised controlled trials. It is important to note that poorly-conducted systematic reviews and meta-analyses of low quality studies may result in biased conclusions [9]. The editorial staff at the *AMSJ* strongly encourage medical students to attempt systematic reviews to both learn about methodological processes in research and to elevate the quality of their review.

Scoping review

Scoping reviews have been labelled in a variety of ways in the past: rapid review, mini-review, scoping study and literature mapping. A scoping review is less strictly defined than a systematic review because it does not have its own set of standardised guidelines. Instead, the general guidelines proposed by Arksey and O'Malley [10], and further developed by Levac *et al.* [11], can be used for guidance on how to complete reviews of this type.

In brief, a scoping review differs from a systematic review in that:

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1. It is typically addressing a *broad* rather than a narrow research question, in order to map knowledge in a particular field.
2. It is usually, but not always, performed in a shorter time span and hence may utilise fewer databases or a more limited search.
3. It does not typically include extensive bias and quality assessments required in systematic reviews.

A scoping review is usually still "systematic" in that it is performed according to a pre-defined methodology, but this methodology is often less prescriptive and may capture fewer articles. Hence it may be labelled semi-systematic or systematic but not comprehensive. While scoping studies can be limited in terms of the level of evidence they provide, it is often a more practical method by which the literature can be reviewed before completing a research study. See the referenced studies by Arksey and O'Malley [10] and Levac *et al.* [11] for a description of methodologies for completing a scoping review.

Narrative review

A narrative review is a non-systematic exploration of the literature performed to explore the key findings in a field [1]. The word "narrative" in the name is telling because these types of reviews are normally written in an eminently readable narrative style, which

makes them suitable for communicating the key points on a particular topic. If readability is a major strength of narrative reviews, then a lack of comprehensiveness is their fundamental weakness. It is typical for reviewers conforming to this methodology to select studies at their own discretion for inclusion, leaving out any they believe to be non-vital.

This approach is particularly suitable when the writer is an expert in the field who is very familiar with the literature and can use their knowledge to select only the most pertinent studies for their time-pressed readers. Students employing this review style should take caution to avoid omission of important studies and ideas by first reading widely on the topic area to be reviewed.

Review articles at *AMSJ*

At the *AMSJ*, we take a more flexible approach as we aim to be a platform by which students can get their first experiences at publishing good quality research, and also to be a source of articles containing information that a typical medical student would find useful and engaging. Aligning with these values, we will accept submissions of any of the review types mentioned above.

We strongly encourage students to attempt to use the framework for a scoping review. This type of review is particularly suitable for medical students and submissions to the *AMSJ* as it involves a more rigorous methodology than a narrative review but is far quicker and more practical to complete than a full systematic review. It is often possible to convert a narrative review completed for an essay or assignment to a scoping review by performing a systematic search of at least one comprehensive database such as PubMed, MEDLINE or Embase and ensuring all relevant articles are included.

A narrative review should not simply be a rehashed assignment. These assignments are typically not written in the style and to the level of rigour necessary for a peer-reviewed publication. A well-composed narrative review should be detailed and well-referenced with primary studies (rather than just other review articles), and the information contained should be current. Please ensure that the research question or topic to be addressed is well defined.

Conclusion

Writing a literature review is a vital part of the early research process, in both orienting an individual to the current state of knowledge in a particular field and aiding with the development of research questions for investigation. It is hence a particularly important skill for medical students to develop early in their careers, and, at the *AMSJ,* we strongly encourage students to prepare and submit these types of articles. The use of systematic methodology enhances articles of this type, and can be a valuable experience in learning about the critical evaluation of evidence.

Conflict of interest

None declared.

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Symbiotic, medical student initiated community engagement on a rural longitudinal integrated clerkship

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Abstract

Background: Community engagement is an important aspect of a successful rural placement.

Materials and Methods: In this study, medical students undertaking longitudinal integrated clerkships at a rural clinical school instigated community engagement activities with a special school. Six health education sessions were delivered to eight adolescent special school students. This paper describes the perceptions of medical students and special school teachers in relation to the effect of this program on medical student personal and professional development, its acceptability by special school teachers, and the factors which contributed to the program outcomes. Two separate focus groups were conducted with seven medical students and two special school teachers.

Results: Theme 1: Symbiotic nature of the program. There was perceived improvement in the medical students' communication, leadership and teaching skills, and their understanding of working with people with disabilities. Special school teachers noted benefits to their students from the health expertise and role modelling provided. The university experienced enhanced links with the community. Theme 2: Factors that contributed to the success of this community engagement activity. All parties wanted to engage in the program. Valuable time was spent developing relationships and preparing with all stakeholders. Constructive teamwork was paramount.

Discussion: Involvement in this program gave students a unique opportunity to develop skills in professionalism that are essential to working as health practitioners but difficult for universities to teach. The voluntary nature of the initiative was novel, promoting this skill development and enhancing the effectiveness of the program. The factors that contributed to the success of this program are potentially applicable to other settings.

Conclusion: This initiative was highly acceptable to the special school teachers involved and was perceived to have positive effects on medical student personal and professional development.

Introduction

Medical student rural clinical rotations are well established in Australia and internationally [1-7]. Typically, longitudinal rotations involve students being placed into a rural community where they undertake their year's university curriculum. These placements provide unique educational opportunities and are an important way to attract future doctors to address increasing rural workforce shortages [8].

The symbiotic clinical education model developed from research conducted on medical students completing longitudinal integrated clerkships (LICs) [9,10]. This model proposes that clinical education is underpinned by relationships between key stakeholders and that a symbiotic curriculum can be achieved if these relationships lead to mutual benefit. One of these key stakeholders is the community in which medical students are placed. Community engagement by medical students can therefore be seen as an important aspect of a successful rural placement.

Community engagement is also important for the future of our rural medical workforce. Studies indicate it is a predictor of longer duration of stay for rural doctors and that positive community engagement experiences encourage students and doctors to undertake similar activities in the future [11,12].

Monash University's East Gippsland Rural Clinical School (RCS) was established in 2001 [13]. One of their sites is in Bairnsdale (East Gippsland, Victoria, Australia). Bairnsdale and its surrounds are classified as RA3 on the Australian Standard Geographical Classification – Remoteness Area (ASGC-RA), defined as 'Outer Regional' [14]. At the time of this study an integrated, community-based curriculum was provided for a group of eight fourth-year medical students during their five-year Bachelor of Medicine, Bachelor of Surgery (MBBS) undergraduate degree. Students lived and studied in East Gippsland for the entire academic year while studying the disciplines of paediatrics, obstetrics and gynaecology, psychiatry and general practice.

Materials and Methods

Intervention

Seven fourth-year medical students from the East Gippsland RCS developed a community engagement program which involved the delivery of six health education sessions to students at the East Gippsland Specialist School. This initiative developed after two special school teachers approached one medical student who had been volunteering at the school for assistance with health education, which they were required to deliver as part of the school curriculum. This medical student subsequently facilitated the development of links between the RCS and the special school, which led to the initiative growing and more medical students becoming involved.

The sessions were presented to one class of eight students, between 14 and 18 years of age, with autism, attention deficit hyperactivity disorder, and learning disabilities. Various topics, content and pedagogical approaches were used (Table 1). Each session was conducted by two to four medical students with the support of the two special school teachers. The sessions were developed by the medical students in consultation with the special school teachers. Resources were utilised from the local community health centre, East Gippsland RCS and the local general practices where the medical students were completing their clinical placements.

This paper describes the perceptions of the medical students and special school teachers in relation to the effects of the program on the personal and professional development of the medical students involved, the acceptability of the program to the special school teachers involved, and the factors which contributed to the program outcomes.

Evaluation

Data was collected at the conclusion of the program via two semi-structured focus groups; one with the seven medical students and another with the two special school teachers who had been involved in the program delivery. Informed consent was obtained from all participants. The focus groups were conducted by three of the authors (DGC, DCF, MAC), each of whom was employed by Monash University's RCS in East Gippsland. These three researchers had existing relationships with the medical students whom they interviewed but had not previously met the special school teachers.

The focus group questions centred on three areas:

1. Perceptions of the program content and delivery methods
2. Perceived impact of the program on the special school students, medical students, institutions, and other groups or individuals
3. Challenges and future improvements

All information was audio recorded and transcribed. A mixed deductive and inductive analysis was completed. We hypothesised that the program impacted on the medical students, special school teachers, school students and, potentially, other stakeholders, and so used this as a framework to guide our analysis. Data coding was completed by hand. The initial data analysis was completed by AD, a staff member working with the East Gippsland RCS who was not involved in the program delivery. Three other authors (TAW, DCF, and DGC), one of whom (TAW) was a medical student involved in the program, coded sections of the data independently. The four authors (AD, TAW, DCF, and DGC) then cross-checked codes and subsequently came to a consensus on the themes.

Ethics approval

Ethics approval was obtained from the Monash University Human Research Ethics Committee (Approval Number: A8/2009 2009001726). Consent was obtained from study participants for publication.

Results

Two main themes were identified: the symbiotic nature of the program, and the factors that contributed to the success of this community engagement activity.

Symbiotic nature of the program

The program was perceived to have mutual benefits for all involved. Its symbiotic nature was reflected by one student stating "... it was a real reciprocal thing. It felt like you were really giving... [the special school students] an opportunity to learn, but at the same time it was a personal experience of growth and learning."

1. Benefits to the medical students and university:

Development of communication, organisation, leadership and teaching skills

The medical students reflected that "[community engagement] really helped us grow as people and as future doctors." They felt that they improved their communication, organisation, leadership and teaching skills, with another medical student commenting, "It gave me the opportunity to teach... It was a challenge at times to keep [the special school students']... attention... and you had to learn techniques to hold the audience."

Table 1. Descriptions of the six topics covered in the health education sessions.

Session topic	Contents and pedagogical approach
The human body: what does what?	• Information delivery through discussions • Animal organs (liver, heart, brain, kidney) — dissections and discussions • Poster of the body and pictures of different organs — special school students had to match the organ picture with a written description of its function and then place it in the appropriate place on the poster of the body
Exercise and nutrition	• Discussion about healthy eating • Discussion about exercise — why it's important and ways to exercise • Played basketball
Alcohol	• Discussion about the types of alcohol • Discussion about the concept of a standard drink — students had to arrange different cans/bottles from most to least amounts of alcohol content • Small group (2-3 specialist school students) discussion — provided special school students with a written scenario involving alcohol use • Safe and unsafe drinking — group discussion with options written out on whiteboard • Discussions on the health effects — use of pictures illustrating the immediate and long term effects • Use of beer goggles to see the effects of alcohol — played games with beer goggles on • Discussion about how to get help
Smoking and illicit substance use	• Guest speaker — individual with emphysema on home oxygen, discussion with students afterwards • Discussion about cannabis and other illicit substances — types of drugs, consequences of substance use, and what to do if offered drugs
Sexual health	• Discussed the anatomy — use of an anatomy magnet kit • Why people have sex • Discussion about the female menstrual cycle • Discussion about STIs — pictures used as adjuncts • Discussion about contraception — used condoms on bananas • Provided the special school students with a written scenario relating to legal issues
First aid	• Visited the simulation suite at the East Gippsland Rural Clinical School • A guest speaker discussed Basic Life Support concepts • The students rotated through 5 stations: - Asthma - Seizures and choking Table 1. Descriptions of the six topics covered in the health education sessions. - Snake bite and fractures - Bee stings, anaphylaxis and burns - Laceration and haemorrhage

Insight into interacting with and caring for a person with a disability

The program encouraged the medical students to develop their understanding of developmental disability, as "...it was an opportunity for... [medical students] to appreciate what it was like to interact with these... children." One medical student reflected on parallels with the medical curriculum by stating, "...the range of issues these... [special school students] face might not be as wide as the whole developmental disability curriculum encompasses... but the teaching gave us a much deeper insight than I think we would have got reading text or listening perhaps to a lecture, because you meet these kids one-on-one..." The medical students felt that they would be more comfortable in the future when seeing patients with a disability. One student commented: "...when we are interns... and someone with a disability comes in we might change the way we interact with them."

A desire for future community engagement

Medical students were enthusiastic to continue their involvement in community engagement activities. They felt that the experience had opened their eyes to the possibilities to help in their community, with comments such as "it was a good example for me of how you can become engaged in a community [as a doctor]." Another stated, "the difference you can make as a clinician and as a teacher is really inspiring."

2. Benefits to the special school teachers and students:

It was perceived that this program benefited the special school students and its teachers. The teachers were positive in their reflections, stating "...it has been very impressive..."

Table 2. Themes and sub-themes identified from the focus groups.

Theme 1	**Symbiotic nature of the program**
Sub-themes	Benefits to the medical students and university • Developed communication, organisation, leadership and teaching skills • Insight into interacting with and caring for a person with a disability • A desire for future community engagement
	Benefits to the specialist school teachers and students • Intra-generational education • Health expertise and behaviour change • Breaking down barriers • Links within the community
Theme 2	**Factors which contributed to the success of this community engagement activity**
Sub-themes	• All parties wanted to engage • Taking time to develop relationships • Collaborative development of the program and activities • Leadership • Facilitators worked as a team • Preparation of teaching sessions • Non-didactic facilitation techniques

Health expertise and behaviour change

The teachers at the special school were positive about the impact on their students, saying "...I really do believe that they have got a lot out of it. It has been hugely beneficial." It was not compulsory for special school students to attend these sessions, however "...[special school students] kept turning up and staying in the sessions... if they didn't like it, they wouldn't have stayed there." The teachers were impressed by the focus shown by special school students during the sessions, which they believed indicated their level of engagement with the medical students.

This was reiterated in the reflections of the medical students, who also thought they had provided the special school students with a foundation to influence future decision-making. One medical student expressed, "They were actually responding and getting engaged in these issues. I hope that is a step in the right direction." Another added, "It is not going to change massive things but it plants a seed, I think."

The teachers felt they too gained a greater knowledge of the topics: "There were different terminologies and things that I learnt as well." They believed an important factor was that the information presented was tailored to their students, acknowledging "...[the medical students] targeted everything very well in relation to the issues that... [special school students] are going through at the moment."

Breaking down barriers

It was suggested that the program helped in breaking down barriers between the special school students and health professionals, making it more likely that these students would seek medical help when needed. One medical student reflected "... maybe it will make doctors seem less intimidating later if they need to see one."

Links within the community

Overall, the medical students and special school teachers believed that the program had enhanced relationships between the East Gippsland Clinical School, the medical students and the local community.

Factors that contributed to the success of this community engagement activity.

1. All parties wanted to engage:

It was suggested that the program would not be as successful if it was compulsory for the medical students. One student stated, "if anyone went there and didn't really want to, it could be destructive both from our point of view and for the kids."

Support from both organisations was essential for this engagement. In addition to permitting medical students to take time out of scheduled activities, the RCS gave them access to equipment and facilities. One student said, "We contacted people at the community health centre or we used equipment from ... [East Gippsland RCS] ..." The special school was equally supportive and accommodative of the program, providing staff, a workplace, equipment, and remaining very flexible with teaching times.

2. Taking time to develop relationships:

The trust and rapport established between the medical students, special school students and teachers was perceived to be paramount to the program's success. A special school teacher commented, "A big part with these kids is trust… They did so well to attend these sessions and ask questions and I think they felt comfortable enough to be able to ask questions." The medical students also believed their relationship with the special school students grew over the course of the program. One student commented, "I was involved in three sessions... and definitely by the third one [engagement improved]. ...I felt like I got to know... [the special school students] reasonably well ...and the sessions got better."

Teachers felt that the medical students' contact with the specific special school class prior to beginning the program assisted in tailoring the sessions appropriately. They stated that the "... [medical students] knew what type of kids they were going to deal with, so that prior knowledge... definitely helped to make these sessions a success… If you were just sending medical students into a classroom you would really be running blind because you don't know the personalities of the students..."

The medical students also stated that the prior knowledge of the school, students and staff helped them feel comfortable and was integral to the success of the program. It was suggested that if the program were to be repeated in the future, "...you would need one or two people... to go into the school for a few months and just... get to know how things work."

3. Collaborative input into the development of the program and activities:

Both medical students and the teachers agreed that cross-checking the content of each individual session helped both parties prepare for the sessions. One teacher stated, "...[the medical students] rang me before the sessions... [and] went over everything." A medical student concurred, "...the teachers appreciated... the process of going back to them before a session and checking [the content] with them."

4. Leadership:

Having one person dedicated to liaising with all the stakeholders and to delegating the planning and implementation of each session was seen to be important. A medical student stated, "[One of the medical students] ...has put in a huge amount of work and unless someone is prepared to be that person then I don't think it will work as well [in the future]."

5. Facilitators worked as a team:

Knowing each other was perceived to help the medical students facilitate the sessions effectively as a team. One medical student observed, "...we really tried to look at the strengths of different people in the group… As a group of students running the sessions we need to be comfortable with each other as well." The teachers reiterated that "...[medical students] worked as a team" and "...were well organised."

6. Preparation of teaching sessions:

Both the teachers and medical students frequently mentioned the need for well-prepared sessions. There were however difficulties for the medical students, with one stating that "...one of the downsides is the time it takes to prepare for it, on top of everything else we are doing."

Special school teachers felt it would be helpful to have a set schedule, noting "There were a couple of times where the sessions had to be changed… That is the only drawback… [some special school students] don't take change very well."

The medical students reflected that the best way to run the sessions was to plan activities and refresh their knowledge of the topic, but to also be flexible and to adjust the sessions as they proceeded. One medical student commented, "...for me it was about having as much information in my mind ready for the session and just sort of letting the group go with it a bit and still bringing it back on track... it was really quite fluid." The teachers were impressed by this approach, stating that "... [medical students] prepared the lessons but they would also get a feel for what ...[the special school students] knew."

7. Non-didactic facilitation techniques:

Hands-on activities and discussions were reportedly preferable to didactic lessons. One special school teacher recalled, "There was only one session... that didn't really have a lot of visuals. You could tell when they didn't have the hands-on activities and visuals that... [special school students] weren't as attentive." Special school teachers went on to say that more hands-on activities would make sessions even more effective at engaging the special school students. They also suggested that having the key session content in writing would be beneficial.

One important aspect of the medical students' approach to teaching was said to be a focus on informing special school students about consequences of their behaviour, rather than simply telling them that it is wrong. One student said, "The sessions… [were about] educating and saying 'look, these are the risks and these are the issues'…rather than saying… 'you shouldn't do this because it is wrong.' That helped with the engagement."

8. Intra-generational education

The teachers thought that having medical students conduct the sessions was particularly beneficial, as their ages and experiences were more identifiable to their students. It was noted, "... [special school students] connect with that ... [medical students are] not old, they're still cool!"

Discussion

The results reflect our hypothesis that the program impacted stakeholders in positive ways, as well as presenting challenges for those involved. Of particular note was the perceived importance of the symbiotic nature of the program in contributing to its success. We had not foreseen the enhanced relationship that was thought to develop between the East Gippsland RCS and the local community. This was an important institutional benefit, as relationships of this nature are essential for the success of the LIC model in East Gippsland. Furthermore, universities have community engagement responsibilities and need to remain 'socially accountable' [15].

We also noted the responses of the medical students in relation to the perceived impact of the program on their personal and professional development. The skills in communication, teamwork, leadership, and organisation that the medical students were reported to have developed were important outcomes of the program. These are key skills highlighted in the Australian Curriculum Framework for Junior Doctors [16], and are difficult skills for a university to teach.

Determining the impact of this program on the special school students is beyond the nature of this research. Our paper does, however, highlight how this program provided an innovative and engaging way for the special school teachers to deliver areas of their health education curriculum.

A number of potential limitations must be considered when interpreting the results. Pre-existing relationships existed between the researchers conducting the focus groups and the medical student participants. This, along with a lack of anonymity within a focus group format, may have prevented participants from discussing concerns they had with the program. The results are also potentially limited by small participant numbers. Including additional stakeholders in the focus group discussions, most particularly the special school students, would have been beneficial but was difficult due to ethical considerations around interviewing a potentially vulnerable group.

We consider the East Gippsland RCS' role and the fact that this was a voluntary, student-driven initiative to be of key importance. This is highlighted through the comparison of our program with a similar program where medical students based at a RCS (in NSW, Australia) were placed at a special school as part of their paediatric studies [17]. The main difference between both initiatives was that the program in NSW was designed and implemented by the university whereas our program was student initiated and directed. In both cases, benefits were experienced by all stakeholders. There were, however, drawbacks to the NSW program. Its compulsory nature may have forced some medical students to engage against their will, which, as highlighted by one of the respondents in our focus groups, could have negative ramifications. Furthermore, the medical students in our study had far greater opportunities to develop their leadership, teamwork, communication, and organisation skills as they were the drivers of the initiative. There were also drawbacks to our program. The medical students found it challenging at times to balance their existing curricular commitments with this extra activity. Furthermore, the non-compulsory nature of our program means that its future is uncertain and depends on the motivation of subsequent medical student groups. Overall, we consider the positive aspects of this voluntary, student-driven model to outweigh the negative aspects.

Conclusion

This voluntary, medical student-initiated community engagement activity which took place during LICs was perceived to impact positively on the personal and professional development of the medical students

involved, as well as being acceptable to the special school teachers. The factors that contributed to the perceived success of this program could be applied to other settings where students have the opportunity to engage with their local community. We encourage universities to play a supportive role by linking students with the local community and fostering any constructive opportunities that arise.

Conflict of interest

None declared.

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Medical students in Aboriginal Community Controlled Health Services: identifying the factors involved in successful placements for staff and students

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Abstract

Background: To identify the facilitators and barriers to positive medical student placements at Aboriginal Community Controlled Health Services (ACCHSs).

Materials and Methods: A total of 15 focused interviews were conducted with medical students from Victorian universities and staff from two Victorian ACCHSs. Staff and students were asked about their expectations of students' placements; the learning outcomes for students; the structural elements that have an influence on student placements; and the overall benefits and challenges of placements within these settings. This data was then thematically analysed.

Results: The study found that student placements in ACCHSs were of benefit to both the student and the organisation. However, areas for improvement were identified, including avenues for administrative assistance from universities in managing placements and clarifying expectations with regard to learning objectives. Overall, it was the opinion of participants that placements in this setting should be encouraged as a means of medical and cultural education.

Conclusion: The study contributes to building an understanding of the elements that lead to good practice in student placement design, and developing relationships between medical schools and ACCHSs. The study provides grounding for further research into the development of a framework for assisting successful student placements in the ACCHS setting.

Introduction

Medical education can be a powerful tool for social reform [1]. The teaching that occurs within medical schools, and the manner and context in which it is delivered, has the potential to influence the practice of future doctors and have an effect on addressing social inequities. One of the greatest heath inequities in Australia is between Indigenous and non-Indigenous Australians [2].

In an effort to address this health disparity, there has been increasing emphasis on the teaching and learning of Indigenous health issues in medical schools within Australia, with a range of initiatives guiding the development and improvement of the medical curriculum and associated activities [3,4]. One of the most significant is the inclusion in 2006 of Indigenous health in the Australian Medical Council's guidelines for Assessment and Accreditation of Medical Schools [5]. An important element of the Standards for Accreditation is the emphasis on offering student placements in Aboriginal Community Controlled settings and the development of relationships between medical schools and Aboriginal Community Controlled Health Services (ACCHSs) to facilitate this (see Standards 1.6.2 (regarding effective community partnerships) and 8.3.3 (regarding exposure to culturally competent healthcare) [6].

Student placements in such a setting offer an opportunity for students to develop cultural competency in the area of Indigenous health. This was outlined in the National Best Practice Framework for Indigenous Cultural Competency in Australian Universities as a critical area of need, and defined as:

"Student and staff knowledge and understanding of Indigenous Australian cultures, histories and contemporary realities and awareness of Indigenous protocols, combined with the proficiency to engage and work effectively in Indigenous contexts congruent to the expectations of Indigenous Australian peoples [7]".

Standard 1.6.2 *"The medical education provider has effective partnerships with relevant local communities' organisations and individuals in the Indigenous health sector to promote the education and training of medical graduates. These partnerships recognise the unique challenges faced by this sector."*

Standard 8.3.3 *"The medical education provider ensures the clinical learning environment provides students with experience in the provision of culturally competent health care to Aboriginal and Torres Strait Islander peoples and/or Maori."* [6].

Figure 1

While ACCHSs have played host to medical students for some time, there has been little formal research regarding ACCHS as a setting for student placements, locally or at other universities across Australia [8-11]. The purpose of this study is to investigate the key facilitators and barriers to positive medical student placements in this sector.

Materials and Methods

Participants for this research included Victorian medical students who had completed a placement at an ACCHS and staff members of Victorians ACCHSs who had been involved in medical student placements. Students were recruited on a voluntary basis by responding to an electronic noticeboard announcement. 'Snowball' sampling was also employed. A total of seven student interviews were recorded. Of these, six had been involved in placements in ACCHSs, and one in a remote Aboriginal community government-run health service. The duration of placements ranged from one to six weeks, and were conducted in ACCHSs located across Australia in Queensland, Victoria, New South Wales, Western Australia and the Northern Territory.

The ACCHSs involved in this study were all located in Victoria and selected on the basis of having a pre-existing relationship with the University of Melbourne. Each organisation provided approval for involvement in the research following internal protocols, and staff members were nominated by the ACCHSs on the basis of their direct involvement in medical student placements. A total of eight interviews were conducted with the staff members from Victorian ACCHSs.

Data for this project was collected through a series of one-on-one semi-structured inter-views with participants, conducted by the first author, either in workplaces of participants or university campus interview rooms. Interviewees understood the context and purpose of the research, as explained prior to interviews. Interview questions focused on the benefits and challenges both groups experienced during student placements at the services. Transcripts were returned to participants for comment and correction.

The data gathered from the transcribed interviews was arranged according to questions asked, and then further under thematic headings. Shared themes were derived from the data, without use of supportive software.

This project was conducted as part of the Scholarly Selective program of the University of Melbourne Doctor of Medicine. The first author at time of writing was a fourth-year postgraduate medical student, supervised by two experienced researchers. Ethics approval for this project was obtained through School of Population and Global Health Human Ethics Advisory Group of the University of Melbourne (approval no. 1443395).

Results

In total, 15 interviews were recorded for this research. All students were studying medicine at universities in Victoria. The ACCHS placements were undertaken as either GP placements or electives. Staff from the ACCHSs had a variety of roles including general practitioner, nurse, Aboriginal health worker, medical director, clinical director, and executive director of health services. Points of discussion arising from the data fell largely under six major themes:

- Student exposure
- Burden on health services
- Interpersonal value
- Community benefits
- Educational value
- Student engagement

All participants, on direct questioning, agreed that medical student placements in ACCHSs are important. The data was, therefore, considered on the basis that there is strong support from both students and staff to make these placements a positive and constructive experience for all.

Student exposure

A strong theme that emerged from the responses of both groups was that these placements offered medical students practical exposure to Indigenous health, culture and community, with several students stating that they offered an important insight into Indigenous health that was not possible through theoretical teachings delivered elsewhere in the curriculum:

> *"I mean, you hear it, you read it, and so you know it superficially, but when you're sitting in front of multiple people who can tell you the details of their story, you get a much better understanding as to why these families have had opportunities denied to them"* (Student 6).

Students and staff also recognised that placements provided an opportunity to teach students about the ACCHS model of healthcare, which involves not only the delivery of medical services, but also health prevention, social outreach and advocacy programs that address the social determinants of health [12-15]. For one Aboriginal health worker, the value lies in teaching the principles of self-determination upon which ACCHS are founded [15]:

> *"I just like the fact that they're in our setting, our community, and learning from us, not being told by someone else that this is how it is"* (Staff member 6).

Community benefits

Staff and students cited the potential benefits for Indigenous communities, such as recruiting medical staff and strengthening ties between the medical profession and Indigenous communities, as a primary benefit of student placements:

> *"... we see it as an opportunity to expose people to what it's like working in Ab-original health, and that helps us with recruitment"* (Staff member 8).

Several staff and students commented on the role of placements to promote awareness of ACCHSs amongst the medical community, thereby increasing the likelihood of referrals and support for the services:

> *"... it's very good for the organisation and the community to see that students come here to learn because it gives them the message that this is a place of excellence … I think that builds confidence on their part in the service"* (Staff member 8).

In addition, placements provided ACCHSs and their patients the opportunity to engage in the medical education process:

> *"... it makes medical education more transparent for Aboriginal people … and in turn I think that has the potential to create more trust between the patient and the doctor in Aboriginal health centres"* (Student 6).

Participants also saw that placements could have a broader impact on the healthcare system outside of the ACCHS setting, in that the students who have had this experience would go on to work in practices and hospitals across the country in a more culturally appropriate way. As such, these placements are *"... seeding the medical workforce with people who have some understanding and experience in Aboriginal health"* (Staff member 4).

Burden on health services

Participants recognised that the administrative and organisational duties required for placements were very time-consuming, and that supervising students put pressure on practitioners' time,

increasing delays for patients and overall demand on the practice. The administrative duties for ACCHS staff include scheduling time for teaching, coordinating the student's timetable to allow them to spend time in various parts of the organisation, and working through requests for placements from different universities and faculties.

Many of the challenges that students experienced in their placements related to how well the organisation was able to handle these tasks. This was, as several students noted, a feature of clinical placements that is not unique to the ACCHS setting. Challenges for some students included an apparent lack of structure to the placement, staff being una-ware in advance of the student's arrival, finding the clinic to be underprepared for the student or understaffed, or doctors simply not having the time available to teach the student. As one student commented, the service was, *"… definitely very welcoming … but they were very space-limited and time-limited in terms of how much attention they can pay to students"* (Student 6).

Several students mentioned the value of a careful introduction and orientation to the practice as a way of helping students to feel comfortable in the new environment and, as a result, improving student engagement and relieving some of the administrative stress on the organisation:

> *"If the host organisation gives a good introduction to the student, it will be easier for them right the way through the placement because the student will know what they're doing and where they fit, so they won't be constantly having to direct them"* (Student 6).

Educational value

Responses in regards to the education value of the placement varied both between and within the two groups. Most staff at the ACCHSs were generally very happy with the educational experience they provided, not only in terms of general practice knowledge but also holistic care, community medicine and Aboriginal culture. Several staff, however, recognised that the emphasis placed on cultural and holistic care may not have been in line with what students expected from placements:

> *"... I don't know if they come with that same perspective of the holistic model of care … yes, the clinical side is important, but that's not the whole reason why they're coming to [ACCHS]s"* (Staff member 2).

Conversely, some of the staff interviewed said that some students were surprised by the degree of emphasis placed on the general practice aspect of the placement.

While all students reported that the placement had been a valuable learning experience, more than half of those interviewed commented that in terms of examinable material for a general practice rotation, the ACCHS placement was perhaps not as rewarding as a placement in a 'mainstream' practice:

> *"I don't think I learned a lot of examinable material"* (Student 3).

One student noted the fact that the longer consultations, which staff regarded as a virtue, meant fewer patients were seen, and the opportunity for learning through repetition was diminished on a purely quantitative basis.

In contrast to the opinions of some of their peers, several students stated explicitly that they believed the educational experience was better for being in an ACCHS setting, and many said that the cultural and community teachings had enriched their learning.

> *"I can only say that I think if anything it was an advantage because not only did I get the clinical experience I also got the community, social aspect of it as well which might be harder to grasp if you hadn't done that"* (Student 1).

This discrepancy in opinions to some extent reflects a differing of expectations both within the student group and between the students and staff.

Student engagement

Participants were asked what they defined as a 'successful' placement. Responses from students varied and largely focused on basic principles of medical education such as patient contact and fulfilling the curriculum requirements, but also included having clear expectations and an orientation to the ACCHS.

While staff responses also varied, the majority of comments related to student engagement—with the staff, the service as a whole, and with the community:

> *"If … I get a sense that they're starting to integrate with the broader team … that sort of marrying in with the team well, I think, is a very good sign"* (Staff member 8).

Several staff commented that students who were confident in the ACCHS and able to seek out their own learning opportunities were 'easier', more engaged and more likely to be active learners:

> *"Some of them are much easier and more outgoing. Whereas some of them you have to spend a bit of time engaging and making them feel confident...that's not a bad thing but it's harder work"* (Staff member 5).

Interpersonal value

The value of the human interactions that arose from placements emerged as a common theme in the interviews. Several students spoke of their relationships with staff and the trust that they developed with community members returning to the clinic as particularly rewarding experiences:

> *"I got to see a number of patients quite a few times so that made it a very good learning experience, and a lot of the patients were very trusting, and so I got to do a lot in terms of their care. That ... was really rewarding"* (Student 6).

Staff from the ACCHSs spoke enthusiastically of having engaged students around the clinics and the organisations more broadly:

> *"It's enjoyable, honestly, to see someone who wants to come here and work with Aboriginal people"* (Staff member 7).

They cited the benefits of a fresh perspective on health, a new skill set, at times a helping hand and, importantly, a sense of goodwill toward the Indigenous community and the health organisation in the form of a demonstration of interest in Indigenous people and their health.

Discussion

Major benefits and challenges

This study highlights strong support for student placements in ACCHSs. The most commonly cited reasons for this support centre is the ability to offer students first-hand experience in an Aboriginal community health setting, and the reciprocal benefit to the community in creating a more culturally educated workforce.

The challenges reported by staff and students emphasise areas in need of improvement in the placement process, and provide a foundation for refinement. The foremost of these is the administrative and organisational burden on the health services, how the co-ordination of placements can be improved, and what the implications are for the relationships between universities and ACCHS in this process. Nelson et al [10] suggest that there is a role to be played by university-appointed administrators to assist ACCHSs in the processes required to ensure students and the ACCHSs themselves are adequately prepared for placements. Their study highlights the positive feedback received when such appointments have been made, and the interviews here reinforce the message that good preparation and coordination improves the experience of both staff and students [10].

Orientation

Ensuring that students feel both socially and culturally oriented in the placement environment is an important element of a successful experience for both staff and students. Students who feel at ease, or more confident in the environment, tend to be more proactive with their learning and less demanding on the organisation. An important way of fostering this is through a formal orientation.

At the sites where an orientation was undertaken and involved specific cultural awareness training, students felt more confident and engaged. While this responsibility sat with the ACCHS, several participants noted that cultural awareness training should be a core part of medical education in the university environment. Preliminary training would then be the basis for, and be complementary to, the localised and more specific learning provided once students are in the ACCHS setting. Improved coordination between the universities and the ACCHSs is therefore important to ensure that appropriate training and orientation is completed before the student begins their work in the clinical environment.

Educational value of placements in ACCHSs

A successful placement requires that all parties have a clear understanding of the nature and purpose of the placement, with shared expectations of learning objectives. Most placements are either part of general practice rotations or student-initiated electives. While the interviews included positive accounts of both types of placements, the flexibility of student-initiated electives was noted as an advantage in the ACCHS context. Electives, as distinct from other in-semester rotations, are not intended to fulfil precise curriculum requirements, and allow students to engage more freely in learning about Indigenous health and culture and the broader healthcare delivery services provided by ACCHS. However, participants also noted the importance of ACCHSs being included in general practice rotations. It must also be recognised that the medical curriculum is not limited to clinical decision-making, and the educational value of these placements should not be restricted to these domains.

Selection of students

The administrative burden and over-demand for student placements in ACCHSs raises the issue of whether students should be required to demonstrate an interest in Indigenous health to be granted a placement, a requirement that already exists in some ACCHSs. The interview data clearly identified that the burden on the heath service was greater if students were unenthusiastic, disinterested and unable to self-manage. Approximately half the respondents agreed that an expression of interest should be requisite. The remainder of respondents suggested that those students who do not express an interest in Indigenous health placements might have the most to gain from the experience. Adequate orientation may provide a solution in terms of familiarising the student, managing expectations, and facilitating a positive experience for the student and health service.

Limitations

This study was limited in its breadth by the nature of the research as a University of Melbourne Scholarly Selective project. The study therefore had limited scope and a small sample size, and, while strongly-shared themes arose from the data, the interviews did not reach saturation. The authors also acknowledge that students interviewed had all voluntarily selected Aboriginal health placements, and therefore a selection bias may exist with regard to their views of the value of these placements. The authors further acknowledge that while students interviewed were placed in ACCHSs across Australia, the ACCHS staff were from Victorian ACCHSs only, and therefore the placements they describe are not necessarily shared experiences. No community members visiting the ACCHSs were interviewed. Their opinions on the presence of students in the organisations may form a basis for further research.

For ACCHSs to continue to be an active part of medical education, as mandated by the AMC, it is important to ensure that they have the resources to provide a good learning environment, and that the presence of students is not an impediment to the organisations. Placements should contribute to cultivating trust between Indigenous communities and the medical profession, and this is more likely with careful planning and coordination of placements. It is hoped that the findings of this research will help guide student placements into the future and contribute to ensuring a mutually beneficial system. Further research and larger trials in this area may include investigation of the perspectives of community members on the presence and engagement of students in ACCHSs, as well as a deeper exploration of the effects of student placements in other settings, including remote areas.

Conflict of interest

None declared.

Abbreviations and notes

ACCHS- Aboriginal Community Controlled Health Service

* Note: the term ‘Indigenous’ is used in this article to refer to the Aboriginal and Torres Strait Islander peoples of Australia.

St *x*- student no. *x*

Sf *x*- staff member no *x*

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Mistreatment in Australian medical education: a student-led scoping of experiences

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Abstract

Background: Evidence of bullying and harassment of medical students and junior doctors has existed for over 30 years. However, there has been little attempt to explore the dimensions of this issue in Australia to date. Given the evidence which indicates that experiencing abusive behaviour has a detrimental effect on professional identity formation and on mental health, the Australian Medical Students' Association (AMSA) undertook a national scoping study to better understand the experiences of Australian medical students.

Materials and Methods: We conducted a mixed methods survey of the 16,959 students enrolled in a medical degree at an Australian university in 2015. An anonymous, voluntary online questionnaire was distributed through AMSA's social media, email newsletter and website, and medical students' societies.

Results: We received 519 responses, including 194 (37%) detailing at least one incident of bullying or harassment. 335 (65%) survey respondents were women and 345 (67%) were in the clinical years of their training. 60% of all respondents reported experiencing or witnessing mistreatment during their medical education. The most common theme in the free text was belittlement of the student's competence and capacity to be a good doctor. Some gave details about how universities failed to prevent or appropriately respond to students' experiences of bullying and harassment.

Conclusion: In line with international data, this study shows that many Australian medical students perceive mistreatment as an important problem that is not always managed well by faculties. Multi-pronged policy and practice responses are needed to instigate cultural change in Australian medical education.

Introduction

"How can we care for our patients, man, if nobody cares for us?" — Chuck the Intern, The House of God, Samuel Shem [1].

Evidence of bullying of medical students and junior doctors has existed for over 30 years in the United States and the United Kingdom [2-7]. In Australia over the past two years, the topics of bullying, teaching by humiliation, and sexual harassment in Australian medical training have attracted attention both from the mainstream news media and within the profession. There is also some formal evidence about the extent of this problem nationally. A recent local study of "teaching by humiliation" found 74% of medical students reported experiencing this practice and 84% witnessed it [5].

Worldwide, similar studies have shown that any student can be affected, regardless of gender or race [8-10]. The most common form of mistreatment reported is covert, mostly in the form of belittling, exclusion or humiliation, rather than overt yelling or violence [4-6,11]. Sexual harassment is the most common form of documented incident [12-14]. The perpetrators of bullying are most commonly senior male clinicians [4,15]. Under-reporting is the norm, especially when the

perpetrator of mistreatment is the student's clinical supervisor, due to fears about the possible impact on career progression [4,10].

There is evidence that experiencing abusive behaviour causes harm both to the student and, later, potentially to their patients (and colleagues). Other research has demonstrated how a student's developing identity affects their subsequent career progress, employability and performance [17-19].

Mistreatment may be a contributor to the high levels of psychological distress found among medical students. Studies have shown that rates of such distress are three times higher among medical students than the general population (9.2% and 3.1% respectively), and that female medical students were more likely than male students to have considered suicide in the past twelve months, with 4.5% having attempted suicide. In particular, Indigenous students found bullying to be a substantial source of stress [16].

The exact nature of bullying and discrimination can be difficult to define. Through this research, we determined which incidents students found distressing, and what they considered to be bullying or discriminatory behaviour.

Prompted by an increase in reports of mistreatment from Australian medical students following media attention to the issue, the Australian Medical Students' Association (AMSA), in association with the Sydney School of Public Health (SSPH), undertook scoping research to better understand the experiences of Australian medical students.

Rather than confirm the prevalence of abuse, demonstrated by previous research and by the Report of the Senate Inquiry into Medical Complaints Processes [20], we aimed to explore aspects of students' experiences and their responses.

Materials and Methods

Study design and sample

As the only other previous survey of this issue in Australia was distributed to students from two medical schools only [5], our study aimed to reach a wide variety of students from all Australian medical schools and to confirm that previously published findings were generalisable nationally. For this reason, a survey was chosen as the medium for this research as it could be easily disseminated nationally online.

Medical students aged 18 and older who were enrolled in an Australian University between the 25th of August and the 5th of November 2015 were surveyed. The survey was an anonymous voluntary online questionnaire using REDCap survey software (Vanderbilt University, Tennessee, USA) (see Supplementary Materials online).

The survey link and description were distributed through AMSA's official Facebook page, Twitter account, website and email newsletter ("Embolus"). Some medical schools' student societies, as well as individual participants, also shared the survey link.

The questionnaire contained four parts. Part one collected demographic information. In part two, respondents rated their perception of the extent of five categories of mistreatment — "general bullying", "sexism", "disability discrimination" (including mental illness), "racism", and "homophobia" — in Australian medical education, by moving a pointer on a scale from 0 to 100. In part three, respondents rated the attributes of incidents they had witnessed or experienced and were then invited to use free text boxes to describe these incidents. They were also asked about their response to these incidents. In part four, students could describe what actions they felt AMSA could take in response.

The project received ethics approval from the Human Research Ethics Committee (HREC) of the University of Sydney [Protocol number 2015/642].

Data and statistical analysis

Basic demographic information about the respondents was reported, along with the proportions who reported experiencing or witnessing mistreatment. We tested whether experiencing or witnessing mistreatment was associated with gender, age, enrolment, sexuality, and training stage using Fisher's exact test and Pearson's chi-squared test. Boxplots were created based on the levels of agreement scales in part two. Differences in levels of agreement between subgroups of respondents were tested using two-sided exact Wilcoxon rank sum tests (gender, enrolment and sexuality) and Kruskal-Wallis test (age), as the data were negatively skewed (Figure 2). These analyses were performed in R version 3.2.4 [21]. No adjustment has been made for multiple statistical comparisons.

Authors A-KS, EB and KI independently conducted an initial close coding of the open text responses with advice from CH. The taxonomies and categories developed in this process were then reviewed by the research team for comparison and reliability, and a primarily taxonomic thematic coding structure was agreed upon [22,23]. This was then applied to the free text data.

Results

We received 531 completed surveys. Twelve surveys (2%) were excluded as they contained demonstrably unreliable answers or answers unrelated to medical education, leaving a sample of 519 surveys (Figure 1). The respondents were predominantly female (65%), young (median age of 24 years), local students (90%), and at the clinical stage of their training (67%) (Table 1). Each Australian medical school was represented.

It was reported by 60% of all respondents that they had witnessed or experienced adverse treatment (Table 1). Adverse treatment was more likely to be reported by: female than male students (64% vs 53%), older than younger students (79% for 35 years and older vs 55% for 20-24 years), non-heterosexual than heterosexual students (75% vs 58%), and clinical than pre-clinical students (70% vs 40%).

For the five categories of mistreatment (general bullying, sexism, disability discrimination including mental illness, racism, and homophobia), females reported greater problems in medical education than males ($p \leq 0.004$) (Figure 2). Non-heterosexuals tended to report greater problems than heterosexuals, particularly regarding homophobia ($p < 0.001$). International students believed mistreatment was less of an issue in medical education than local students for all categories, except racism, though differences were small ($p > 0.05$), and there were no consistent patterns with age (data not presented).

Information about 301 incidents involving mistreatment was given by 194 students (Figure 1). In 92% of incidents, the victim was a student (Table 2). The respondents nominated consultants as the primary instigator in 46% of the incidents. Belittlement, condescension or humiliation were present in 65% of the incidents. Most students (68%) reported they did not react (that is, take action in response) to the event. Two major reasons for not reacting were not knowing what to do, and fear of repercussions. Most students were bothered by the incident, with only 4% moving the slider scale from "a little" bothered to "not at all". Over a third moved the slider to the lowest tenth of the scale, described as "very much".

Of the 519 respondents, 168 submitted text descriptions of individual events (Figure 1). Of these, 41 described two events, 14 described three events, and ten described four events. In total, 267 events were

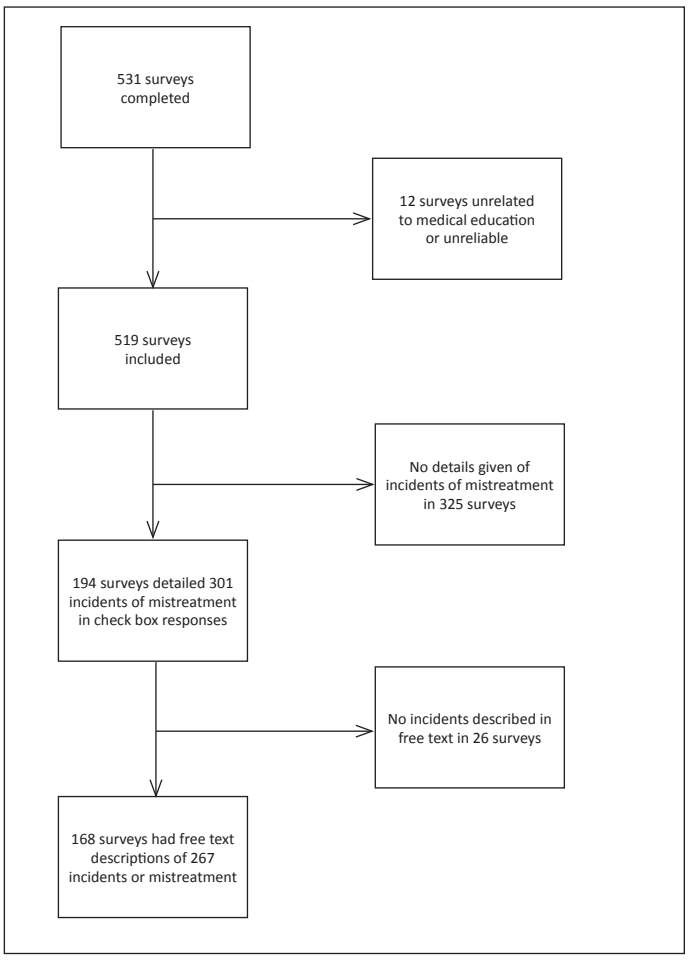

Figure 1. Number of surveys included and number of incidents of mistreatment described in check box responses or free text.

described. Themes captured by coding the text responses included the type of event, the perpetrator, the situation and context, aspects that compounded the situation, and any potential outcomes of the event.

The most common theme was the denigration of the student's competence and capacity to be a good doctor.

"The senior registrar in this instance verbally abused the student regularly, claiming that it was inconceivable that she would one day be a doctor and would cause great harm to potentially anyone she would treat."

A commonly used framing motif was that the recipient was unworthy, should not have been allowed entry into medical school, or should make way for those who are actually fit to be doctors. The stories included examples of discrimination in all the social categories we investigated. One of the most common was the perceived incompetence or unworthiness of women.

"When we got it wrong, he would tell us we were stupid, we should drop out of medicine because we'd never make a good doctor, or there was no point trying, because we'd quit later to have babies like women should."

"I was a new mother… and was told by another student I should be at home looking after my child instead of wasting a place at medical school that would have been better off given to someone else."

A minority of the comments were on non-medical themes such as attractiveness, racial stereotypes, or perceived promiscuousness of the student.

"I would hear jibes about 'Indians taking over the healthcare system of Australia' and how 'No one could understand their curry accent so they shouldn't be able to work in this country."

"All the women in our class [were] being scaled on 'crazy versus hot.' [The respondent was] followed into a women's toilet and told to get down on my knees and 'suck my dick' while [a male medical student] grabbed his crotch."

The more the abuse was related to medical practice or competence, the more respondents constructed it as acceptable or understandable.

"The taunts were often unrelated to medicine which made it even more unprofessional."

Harm and suffering

Implicitly or explicitly, almost all of the 267 free text stories indicated that the recipient(s) of mistreatment were negatively affected as a result. Some accounts directly indicated that teaching by humiliation inhibited rather than enhanced medical learning, decreasing confidence and stopping the student from seeking out further educational opportunities from medical staff.

"Instead of attempting to teach the student in any way, she would harangue the student with increasingly difficult questions — lambasting her further with every question she answered incorrectly… this destroyed the confidence of the student in question quite quickly, to the point where she was afraid and unwilling to go to her clinical placement and learn for fear of the treatment she would receive the next day."

"I understand that his motivation is to encourage us to be thorough, safe doctors. However, I was so scared at being yelled at for getting an answer wrong in his tutorials that I didn't learn anything."

Perpetrators

Students

Of the 38 responses indicating students as perpetrators, the same frame of medical incompetence and unworthiness was common.

"A fellow student kept on telling me that I was stupid and inept and kept saying things like if you don't know this that (sic) you [don't] belong in medicine … he threatened to hit me if I continue (sic) doing idiotic things."

Faculty

We did not include the faculty as perpetrators in our questionnaire. Nevertheless, we received 22 responses citing medical school faculty (including both non-clinical staff and clinical staff in non-clinical roles) as reported perpetrators. These most often related to mishandling of reports of bullying, refusal or inability to make reasonable allowances for mental illness or disability, and instances of discrimination against students.

"I was told that I was at risk of failing, had my depression called 'your condition' the whole time, making me think it was dirty or bad since it couldn't even be addressed … They said to ask them any questions and the school of medicine would do everything it could to support me, but when I directly asked what they could offer they had nothing."

Some respondents expressed disappointment and frustration at feeling unsupported by staff.

"The direct inaction by my university nearly led to my suicide … For me the only way I thought the Uni would notice my problem would be

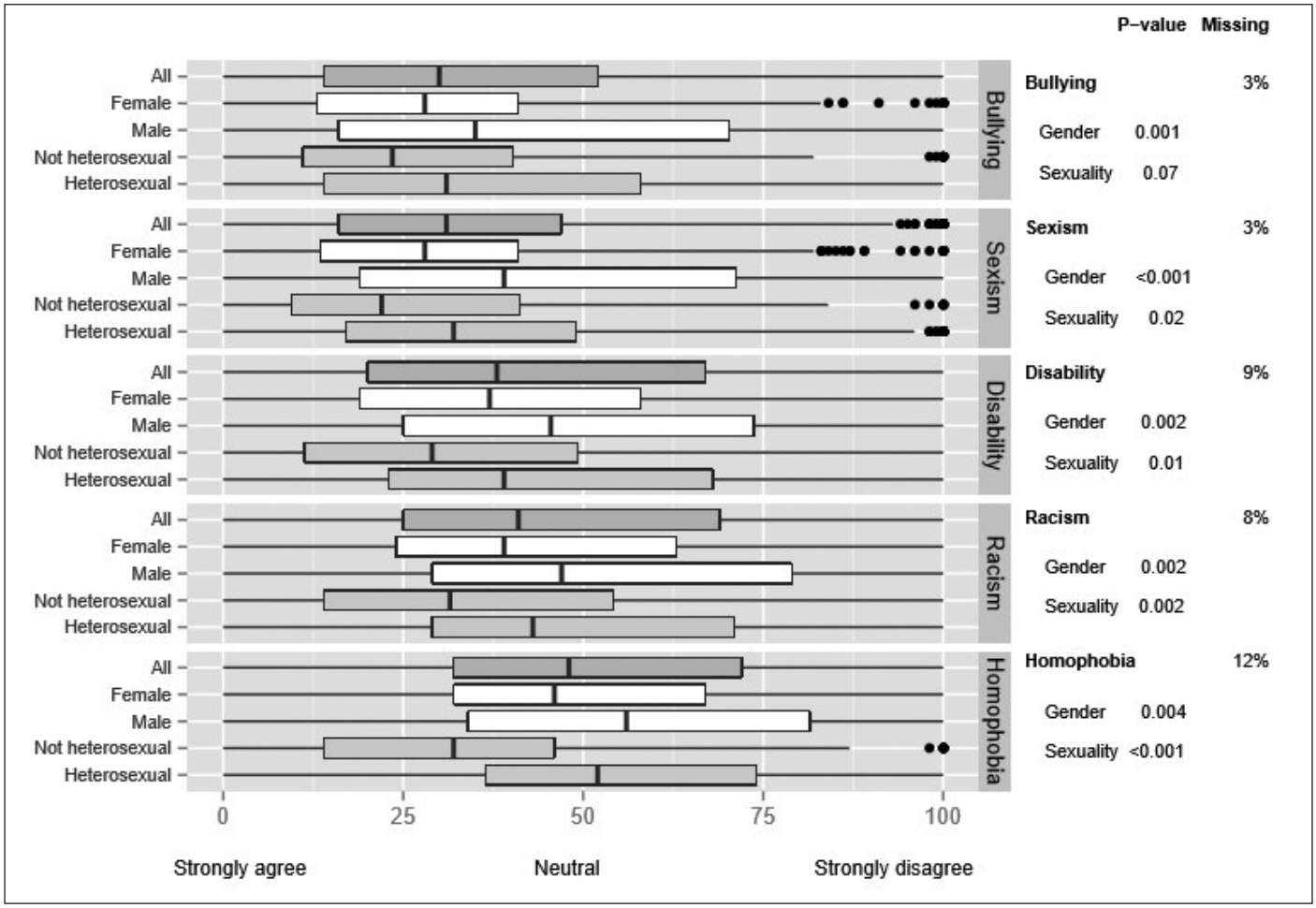

Figure 2. Boxplots of responses of 519 medical students to statements that general bullying, sexism, disability discrimination, racism and homophobia are a problem in medical education.

if I was to kill myself. Thankfully I pulled myself out of it and am still fighting week in week out to keep myself going."

Often, students reported faculty promising support to the student, but providing no support or enacting no change. Other responses cited direct bullying or discriminatory action from the faculty towards the student.

"We get mistreated by the very people that are in control of our assessment/progression. How can you complain against the very person that controls your future? It's just easier to endure it."

Discussion

Our study indicates that a significant proportion of medical students across the country experience or witness mistreatment, extending existing evidence of this issue which had been previously confined to only two Australian medical schools. In line with other studies [4,11,24], our study shows that bullying and discrimination are commonly "medically themed", in ways that belittle a student's core identity and competency. This fits with sociologies of medicine that have shown that surviving humiliating treatment is often a ritual of socialisation into the profession [25]. Our study also extends our understanding of which students are affected and identifies a wider range of perpetrators than had earlier studies [5,14], including professional and support staff in their clinical schools and other students.

A limitation of our study was the sliding response scale for which the default setting was in the middle of the scale. If the respondent did not touch the slider, we could not be sure if they had elected to forego answering the question entirely (because they did not have an opinion or they did not want to answer) or if they were agreeing with the default mid-range answer.

While our low response rate and methods of recruitment mean that our results cannot be regarded as necessarily representative of the whole Australian medical student population, our data strengthen worldwide trends and provides confirmation that Australian medical students often experience serious mistreatment. It also reflects the findings of the Inquiry into Medical Complaints Processes, released in December 2016 [20,26].

Our study underscored that these behaviours can be damaging to students' mental health. Our data also confirmed the widespread reluctance to disclose, report or confront mistreatment as students fear direct educational and professional disadvantage as a result.

This research demonstrates that mistreatment is justified by the idea of upholding professional competence in medical students. It has also shown that, for some students, the mistreatment has a negative effect on their mental health and their willingness to perform. While there will be no single intervention or solution for this problem, the authors suggest that clinical teaching staff may find an evidence-based short course on adult education and effective and constructive criticism

useful training for teaching medical students. This could include clear guidelines for both staff and students on the difference between effective teaching and bullying. Indeed, as teaching is often considered an integral part of clinical medicine, targeted preparation for this could commence in medical school. This should be paired with effective policies ensuring that staff who have been reported repeatedly for bullying behaviours are removed from teaching positions and receive appropriate training to improve their skills before resuming work.

We also saw that under-reporting is often due to fear of educational and professional disadvantage. We can address this by encouraging the production of university and hospital policies ensuring anonymity and protection for those who report, and providing alternatives such as switching the student to a different rotation.

Another finding was how some students felt that universities were failing to take action to support them. This was particularly linked to students with a disability or mental health conditions. The reports detail either a perceived choice by the university to not support the student or the admission that university staff did not have the ability or resources to support the student.

The authors suggest that universities enact stronger policies with safety nets available for struggling students (such as changing rotations, alternate exam arrangements, or taking time off) and ensure they have the necessary resources to do so. We also suggest the creation of policies that monitor how many students are struggling, detailing the issues, and taking steps to ensure the problem does not continue. The authors suggest that medical school accreditation processes should include a more rigorous examination of institutional performance on this issue.

These recommendations run alongside those handed down by the Inquiry into Medical Complaints Processes, which specifically identified the government, hospitals, colleges and universities as parties with responsibility for addressing bullying and harassment in the medical profession [26].

Changes in policy and training educators on effective criticism would be strengthened by slowly incorporating cultural change through encouraging positive professionalism training. Such programs use creative techniques such as acting skills to build core professional values and behaviours. They can also reveal the impact of bullying on others without directly shaming perpetrators or exposing victims [27-29].

Table 1. Demographics of 519 survey respondents and the proportion who witnessed or experienced mistreatment in medical education. *Reported p values are for tests of independence between experiencing/witnessing mistreatment and gender, age, enrolment, sexuality and training. Fisher's exact test was used for gender and training, and Pearson's chi-squared test for enrolment, sexuality and training.*

	N (% of total)	Experienced/witnessed mistreatment (n (% of category))	Did not experience/witness mistreatment (n (% of category))	p-value
All respondents	519 (100)	313 (60)	206 (40)	
Gender				0.02
Male	177 (34)	93 (53)	84 (47)	
Female	335 (65)	216 (64)	119 (36)	
Other	7 (1)	4 (57)	3 (43)	
Age (years)				<0.001
18-19	22 (4)	6 (27)	16 (73)	
20-24	291 (56)	159 (55)	132 (45)	
25-29	143 (28)	102 (71)	41 (29)	
30-34	34 (7)	23 (68)	11 (32)	
35 and over	29 (6)	23 (79)	6 (21)	
Enrolment*				0.92
Local student	466 (90)	281 (60)	185 (40)	
International student	52 (10)	31 (60)	21 (40)	
Sexuality*				0.004
Heterosexual	439 (85)	253 (58)	186 (42)	
Non-heterosexual	79 (15)	59 (75)	20 (25)	
Training				<0.001
Pre-clinical	163 (31)	65 (40)	98 (60)	
Clinical	345 (67)	240 (70)	105 (30)	
Other	11 (2)	8 (73)	3 (27)	

*There is 1 missing value.

Table 2. Details of 301 incidents of mistreatment reported by 194 medical students.

	n (%)
Victim (n=299)*	
Student	275 (92)
Doctor/nurse/resident/intern/patient	20 (7)
Both	4 (1)
Primary instigator (n=297)	
Consultant	138 (46)
Other or unspecified doctor	48 (16)
Clinical tutor/lecturer/faculty staff	43 (14)
Student	42 (14)
Other instigator or combination of instigators	26 (9)
What was involved? (n=301)**	
Bullying	197 (65)
Sexism	120 (40)
Disability discrimination	29 (10)
Racism	34 (11)
Homophobia	7 (2)
Other	4 (1)
What occurred? (n=294)**	
Belittlement / condescension / humiliation	190 (65)
Lack of courtesy	151 (51)
Stereotyping	116 (39)
Intimidation / threatening	98 (33)
Name-calling / slurs / taunts	77 (26)
Singling out for difficult treatment	76 (26)
Neglecting / ignoring	75 (26)
Denying opportunities or rewards	54 (18)
Unwanted sexual advances / questions / comments	51 (17)
Other[3]	133 (44)
Did you respond? (n=301)	
No	191 (63)
Why didn't you respond?** (n=191)	
Didn't know what to do	103 (54)
Afraid of the repercussions	95 (50)
Happened too quickly	42 (22)
Other****	107 (56)
Yes	95 (32)
How did you respond?** (n=95)	
Reported incident	55 (58)
Confronted the instigator	39 (41)
Defused the situation	24 (25)
Other	18 (19)
Missing	15 (5)
How much did this situation bother you (scale 0 to 100)? (n=284)	
0-9 (very much)	106 (37)
10-49	166 (58)
>50 (a little to not at all)	12 (4)

**The number of incidents with this question answered.*

***More than one response could be selected therefore the percentages do not sum to 100.*

**** "Other" includes (from most to least frequently reported) intrusive/unwanted questions, refusal to make reasonable allowance for the needs of others, threatening failure/low grade, receiving lower evaluations/grades, asking to perform personal/inappropriate tasks, spreading malicious rumours, being coerced into unprofessional behaviour, other, and actual/threatened physical punishment.*

***** "Other" includes (from most to least frequently reported) not there at the time, other, chalked it up to experience, told not to respond, it wasn't that bad, didn't have the time, my fault, didn't care, not intentional, not important, and the data field not being filled in.*

Further research is required to determine the effectiveness of these approaches to change. It is as yet unknown whether a pre-emptive educational approach or more capacity to remove perpetrators from teaching roles would be most effective in reducing mistreatment. Further qualitative research would better capture the dimensions and effects of mistreatment, which may be experienced differently by male and female students, on the basis of mental health status, or with respect to sexuality or ethnicity. Such research could assist in identifying institutional barriers to managing poor behaviour among teaching and non-clinical staff, and identify the best strategies by which the effects of mistreatment in medical education can be ameliorated.

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Conflict of interest

None declared.

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Knowledge needs and coping with atopic dermatitis: perspectives of patients and healthcare professionals in Singapore

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Abstract

Background: Atopic dermatitis (AD) is a common chronic skin condition which has significant disease burden. Hence, it is important to understand the knowledge needs and coping of patients with AD.

Materials and Methods: This study was conducted in a dermatology outpatient clinic in Singapore. Qualitative, semi-structured interviews were conducted with patients, dermatologists, dermatology nurses and a medical social worker (MSW). A sample of patients with AD was recruited. Dermatologists and dermatology nurses who regularly worked with patients with AD were selected. Interviews were recorded and transcribed verbatim. The framework method was employed for data analysis.

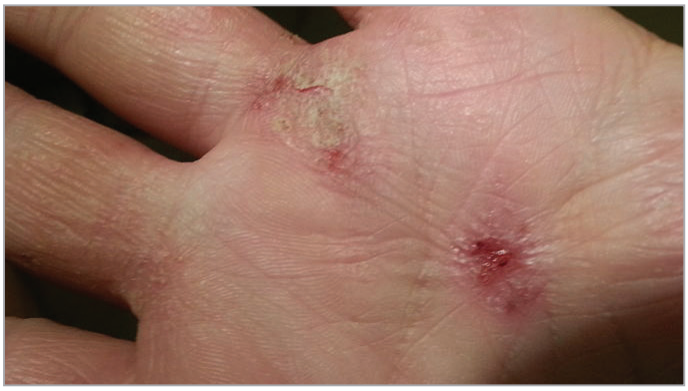
Results: A total of 22 participants were recruited, comprising of eight patients with AD, eight dermatologists, five dermatology nurses, and one MSW. The main needs of patients that were identified were: knowledge about AD and coping with psychosocial aspects of the disease. Regarding knowledge about AD, patients wanted to know more about the underlying causes and management of AD. On coping with psychosocial aspects, patients expressed their appreciation for both the concern shown by their healthcare professionals and the opportunity to share their experiences. Some patients had difficulties coping with the rashes on the visible areas of their body.

Conclusion: It is essential to include education surrounding AD pathophysiology and the psychosocial aspects of coping with AD during counselling of these patients. Itch management, knowledge of possible triggers, and discussion on complementary and alternative medicine should be included as components of counselling. With respect to psychosocial counselling, patients could be given strategies to cope with both the changes in appearance and the frustration associated with undesired outcomes.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a common chronic skin condition prevalent in people who have a family history of atopy, including asthma, eczema or allergic rhinitis [1]. In the United States, the prevalence of AD has been reported to be 10.7% in children and 10.2% in adults [2]. AD is also the most common skin disease in the Asian population [3,4]. In Singapore alone, 20.8% of children between the ages of seven and 16 have been diagnosed with AD [4].

AD is characterised by intermittent periods of exacerbation and remission. Patients with AD have pruritic rashes, erythema, lichenified patches and excoriations due to scratching of the skin. These symptoms often affect the patient's sleep and mood, resulting in a decreased overall quality of life [5,6].



Due to its significant disease burden, understanding the education needs of patients is important for developing a holistic program to help patients manage their condition. From a review of the literature, the education needs of AD patients and their caregivers include disease pathophysiology, awareness of trigger factors, skin care (including application of topical creams such as steroids, moisturisers, and wet wraps), a range of treatment modalities, management of symptoms such as itch and sleep disturbances, nutritional aspects and coping strategies [7,8]. A good education program has been found to result in a significantly lower dermatitis severity index, increased use of emollients and wet wraps, decreased use of steroids, reduced itching and irritability, and improved sleep [7,9].

It is important to understand the knowledge needs and coping mechanisms from both the patient's and healthcare professional's perspectives. Studies to understand the education needs of AD patients were mainly conducted in Western countries. Conducting such a study in an Asian context will enable us to tailor AD education programmes for these populations [10]. This study aims to achieve an understanding of these issues through group interviews with patients and their multidisciplinary healthcare team.

Materials and Methods

Design

This study was conducted in a tertiary dermatological centre in Singapore between June and December 2015 after obtaining ethical approval from the Domain Specific Review Board (DSRB) by the National Healthcare Group (NHG), study reference 2015/00236. Qualitative semi-structured interviews were conducted with AD patients and healthcare professionals. Both patients and healthcare professionals were included to obtain the perspectives from both groups, and to identify any conflicts. In a semi-structured interview, an interview guide with broad questions was used to focus the discussion

Table 1. The guide used to focus the group discussions on atopic dermatitis for patients and healthcare professionals.

Participant group	Question
For patients	1. What are your needs relating to your eczema in the initial encounter (first six months)/middle encounter (six months to one year)/late encounter (more than one year) with a specialist dermatologist? Specifically, what are your needs with respect to: a. Disease b. Treatment c. Psychosocial aspects 2. How can healthcare professionals address these needs?
For healthcare professionals	1. What are the education needs of patients with eczema? 2. Do your education needs change depending on the severity or duration of disease? 3. Do you feel that all of this information is important from the outset, or should the education come when the patient needs it? 4. What are the psychosocial needs of patients with eczema, and how do you help them address these? 5. When do you think counselling should be provided? For example, the first time they come to the national skin centre, or based on disease severity? 6. If you were to have a counselling programme for these patients, what do you feel should be included in the content?

(Table 1). Patients and nurses were interviewed in groups of three to five participants, while dermatologists and a medical social worker (MSW) were interviewed individually. All interviews were conducted in English, by the same primary investigator to ensure consistency.

Participants

A purposive sample of patients with AD was recruited for the focus group interviews. Recruited patients had AD for at least twelve months and were all older than 21. Dermatologists and dermatology nurses, who regularly worked with patients with AD, were selected for the interviews.

Data collection

Patients who met the inclusion criteria and had clinic visits during the study period were recruited and written consent was obtained. Demographic data obtained from the patients included age, gender, race, level of education, occupation, smoking and drinking status, areas of skin affected by AD, age of onset, disease duration, previous treatments and history of inpatient admission due to their skin condition.

The demographic data obtained for dermatologists and nurses included age, position, number of years practicing and academic qualifications. The focus group interviews lasted around 60 minutes, and the individual interviews lasted 20-45 minutes. Data was collected until saturation was achieved, which meant that no new information was obtained from subsequent interviews.

Data analysis

Recorded interviews were transcribed verbatim. The framework method was employed for data analysis. Briefly, this included the analysers familiarising themselves with the interview content, coding of transcripts, and categorising the data into themes [11]. Trustworthiness was achieved using strategies suggested by Lincoln and Guba [12], which included credibility, transferability, dependability and confirmability. Credibility was achieved through triangulation and critical self-reflection. Triangulation, which was used to ensure validity through exploring multiple perspectives, was achieved through interviewing both patients and their healthcare professionals [13]. Critical self-reflection (the reflection of one's viewpoints) was used in data collection and analysis to reduce bias from self-imposed viewpoints [14]. Transferability (generalisability of results) was achieved through transcription of the entire interview to provide context and meaning [15]. Dependability (the reliability of the results) was ensured by developing an audit trail which consisted of raw data, audio recordings, products of data analysis and synthesis, and interview guides, to increase overall transparency of the research process [14]. Finally, confirmability was achieved when the criteria of credibility, transferability and dependability were established [12]. The preliminary analysis was completed by a single researcher, who then presented the selected pre-codes and themes to the other team members.

Results

A total of 22 participants were recruited: eight patients with AD, eight doctors, five nurses and one MSW. Two focus groups were conducted for the patients, and one for the nurses. There were nine face-to-face interviews with the doctors and MSW.

Patient demographics and clinical data

The mean age of the patients was 30.9±7.8 years, and there was equal gender distribution (11 (50%) males, 11 (50%) females). AD affected numerous body regions, including the scalp (n=4, 18%), face (n=4, 18%), trunk (n=5, 23%), upper limbs (n=6, 27%) and lower limbs (n=8, 36%). The mean age of onset of AD was 13.9±12.1 years and the mean duration since AD diagnosis was 17.0±9.1 years. Topical steroids (n=8), prednisolone (n=6) and phototherapy (n=7) were common treatments received.

Healthcare professional demographics

The mean age of the healthcare professionals was 42.1±12.2 years. The mean duration of specialisation in dermatology was 12.1±10.4 years.

Themes

The main needs of patients could be broadly divided into two themes: knowledge about AD and coping with the psychosocial aspects of the disease (Table 2).

Knowledge about AD

This theme includes the knowledge needs of patients with AD comprising the underlying pathophysiology of AD and management of the disease.

Table 2. Themes, sub-themes and codes arising from the patient and healthcare professional interviews on atopic dermatitis.

Theme	Subtheme	Codes
Knowledge on atopic dermatitis	Nature of atopic dermatitis	Basic information Types of eczema Severity of eczema
	Management of atopic dermatitis	Importance of topical therapies Management of itch Role of complementary and alternative medicine Identification of triggers Food related
Coping with the psychosocial aspects of atopic dermatitis		Lack of empathy from friends and family Focus on physical appearance Importance of support groups

Pathophysiology of AD

Most healthcare professionals believed that most patients required only the most basic information on the nature of AD so as not to overwhelm them with too much information. However, some patients were interested to know the various subtypes of eczema, and important tips to help them identify the severity and status of their condition.

"They just need to know two or three key points of information. Otherwise they forget everything which is said. Firstly, I tell them the genetic causes. The gene makes good skin that's why they have poor skin. Because of the poor skin, they have poor skin barrier. Water is lost and a lot of allergens or infectious agents can come in. [This is] good enough." (Healthcare professional 3)

"Personally I will like (sic) to have more information. But I can see how sometimes more information gets you more worried especially if they tell you some eczema are more dangerous and it can last forever (sic), for example. It would have been nice if I knew 'here are different severities of eczema' for example. Not just types, but more serious, less serious and some kind of sense of where you are along the spectrum. That will be useful." (Focus group 2)

Management of AD

Healthcare professionals felt that the importance of the use of moisturisers and topical steroids could not be overemphasised among patients with AD. Patients were often very concerned with their itch, and wanted better strategies to alleviate their symptoms. They were also very keen to discuss the role of complementary and alternative medicines (CAMs) as part of their overall management, however, these options were often not addressed or quickly dismissed.

"I think they need to know the importance of moisturiser. I think when you ask the patients if they put (sic) moisturiser, most of them will say, 'maybe once' or sometimes, 'forget'. They always think that steroid is the main thing. So moisturiser is very important for eczema because you want to resolve the barrier function. So most of the time I spend quite a long time telling them how important the moisturiser is as a maintenance." (Healthcare professional 6)

"Maybe for them [healthcare professionals] to be more open to alternative treatment. You [another participant] mentioned is (sic) gut health and all that. Things like having more holistic treatment options instead of just dismissing it as, 'Ah, doesn't work'. They need to be able to discuss with you." (Focus group 1)

Patients had variable preferences with respect to the amount and types of treatment related information they received. Some preferred to know all the possible types of treatment options, while others believed that the doctors would make the best decision for them.

"[The doctors can] outline the different treatment methods and what are the pros and cons of each." (Focus group 1)

"I think I will put myself in the hands of the doctor. Because they know our condition better. They have seen a lot of patients with similar conditions. So maybe they know what is the best for us." (Focus group 1)

Coping with the psychosocial aspects of AD

Patients expressed feeling frustrated and stressed by the supposedly well-intended opinions of relatives, friends and strangers who did not understand that there was no cure for their eczema, yet still continued to provide advice. Patients also expressed that they appreciated the concern shown by their healthcare professionals, and also the opportunity to talk about their eczema exacerbations and how to prevent them. Some patients had difficulties coping with the unsightly rashes on visible areas of the body, such as the face, arms and legs.

"Some uncles and aunties will say, 'you must do this, do that'. But I think sometimes these kind (sic) of things make us feel a bit down. As I mentioned, my friend's son has severe eczema on his face. So she also has people coming up to her and telling her things. She feels very upset about it. So I feel that, it's a kind of a stress in a way." (Focus group 1)

"I think it's showing concern for you. Because when you come up for your routine check-ups, it is good that they give you a chance to share about any flare ups that you experienced, and discuss what might have caused it, and what you can do to prevent it." (Focus group 1)

Both patients and healthcare professionals agreed that having support groups for AD patients is essential for enabling them to share their challenges and provide support for one another.

"I do think such support groups are good for patients to come together and share. Because they [patients] do trial and errors for different kind of remedies (sic). So sharing experience will help different patients to spot each other needs (sic)." (Focus group 2)

"Showing them support groups. So it's just not the nurses [only], but you organising a good support group. I think that is very critical for them." (Healthcare professional 7)

Discussion

Due to the chronic nature and impact of AD on patients' physical and psychosocial health, education is critical to ensure successful long-term management of the disease and adherence to treatment. Barbarot and colleagues [10] emphasised the importance of tailoring AD education programmes to the sociocultural context of the patient. In this study, we have explored the education needs of patients with AD in an Asian context. Both patients and healthcare professionals expressed two main components pertinent in AD counselling, which were knowledge about AD, and coping with the psychosocial aspects of the disease.

Knowledge about AD

Although both patients and healthcare professionals agreed that providing knowledge on the pathophysiology of AD was important, patients wanted to know more about the different subtypes of AD and severities, which contrasted with healthcare professionals believing that providing only basic information relating to AD was sufficient. Patients felt that this knowledge could help them manage an impending exacerbation when, for example, they noticed subtle changes in their

skin condition. Although the majority of patients in this study felt that they wanted more information on their disease, one patient also acknowledged that having more knowledge might generate unnecessary worry and could therefore have a negative impact. Hence, it is important to tailor the amount and type of information provided to the needs of the patient.

Healthcare professionals tend to emphasise the use of moisturisers and topical steroids in the management of AD, which plays a large role in nurse-led eczema counselling programmes [7,9]. However, patients did not feel that they needed more information on the use of topical treatments, possibly indicating that sufficient information is already being provided in this respect.

Regarding medical treatments, patients expressed that they wanted healthcare professionals to be more open to discussions surrounding CAMs, and not simply discount them as unscientific or ineffective. A recent study also described that the majority of patients rated it as being important that healthcare professionals know about CAMs for the treatment of AD [16]. Education and counselling regarding CAMs may prove to be an important part of patient counselling, particularly when considering the chronic nature of AD and the limitations of current therapies [17]. It has also been found that, in addition to their prescribed therapies, patients who were more familiar with the Internet were likely to search for alternative complementary therapies online, including homoeopathy, ingestion of essential fatty acids, Chinese herbal therapy, phytotherapy, acupuncture, autologous blood therapy and bioresonance [18]. Small trials have shown that these therapies may have some positive effects, but the evidence is not yet sufficient to support their use [19]. Despite the lack of scientific and clinical evidence supporting the effectiveness of CAMs, healthcare professionals need to be able to address these issues with their patients.

Symptomatic itch was a major concern for all patients included in this study, and they expressed a desire for more information relating to its management. Although patients knew that they should not scratch their skin as it would worsen their AD, many found this hard to avoid. This highlights the importance of including itch management as an important component in AD counselling. Besides antihistamines, the current first-line therapy for controlling itch (which is often unsuccessful), patients could be taught to use distraction and habit reversal techniques [20].

Coping with the psychosocial aspects of AD

Both healthcare professionals and patients agreed that having a support group could be a platform for patients to share their AD coping methods. Weber and colleagues [21] found that support groups helped improve patients' quality of life, personal relationships, and participation in leisure activities. The impact of AD on body image has been documented in the literature [6]. As a result of impaired socialisation secondary to changes in body image, support groups could provide a platform for overcoming these issues.

Participants also found it stressful and frustrating to receive advice from relatives and friends who did not have much knowledge relating to AD. It was reported by the study participants that most people believed that the rashes were caused by a food allergy, and told them to avoid certain foods, or tried to provide suggestions to cure their AD which did not have any effect. The participants in this study were all adults above 21 years of age, which meant that they were now unlikely to outgrow their disease. On a community level, there could be more education on the various types of skin rashes and the possibility of AD continuing into adulthood.

Study limitations

A cross-sectional study was conducted, therefore we do not know the changes in the needs and coping of patients over time. Also, the experiences of the participants relating to their initial diagnosis was based on recall, which may be inaccurate or subject to bias.

Practical implications

Itch management and management of exacerbations are essential for helping AD patients cope with their disease. AD is a chronic skin condition with no cure. Hence, it is common for patients to seek alternate methods of treatment, and therefore CAMs are widely used. Furthermore, people who are more familiar with the Internet could search for information on these therapies online [18]. Healthcare professionals need to be able to discuss the use of these therapies with patients, including explaining that, while there may not be any evidence to support their use, CAMs may be used if the components of the therapy are identified and not known to cause any serious adverse effects.

Support groups could be used to help patients cope with the psychosocial aspects of their disease. Patients may also benefit from support in managing the stress and frustration arising from well-intentioned but unhelpful comments from family members and friends.

Potential future directions

This study highlighted some conflicts in the perceived information requirements of AD patients and healthcare professionals. Most patients wanted more information on the nature of AD, which healthcare professionals believed was unnecessary. For treatments, besides the use of topical steroids and moisturisers, patients wanted more information on CAMs, which healthcare professionals did not believe were beneficial or useful. Despite the lack of scientific and clinical evidence to support the effectiveness of CAMs, healthcare professionals need to have a basic knowledge on these therapies as the discussion of such therapies was important to patients. With respect to psychosocial issues, patients could be taught how to cope with the changes in appearance associated with AD, and the stress and frustration arising from the advice given by their family and friends. A counselling programme should be developed to address these patient needs.

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Conflict of interest

None declared.

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Routine blood tests in hospital patients: a survey of junior doctors' cost awareness and appropriate ordering

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Abstract

Background: Excessive and redundant ordering of pathology tests contributes to increasing healthcare costs. Common blood tests, such as full blood counts, liver function tests, serum electrolytes, and C-reactive protein are frequently ordered with little consideration of purpose or intent. Most commonly the ordering of 'routine' blood tests is the responsibility of the most junior member of the medical team (the intern). We hypothesise that overutilisation of pathology tests exists due to an under-appreciation of the costs of testing.

Materials and Methods: We surveyed 50 interns regarding their comprehension of the cost of four commonly ordered pathology tests. We also identified the proportion of participants that had ordered an investigation inappropriately.

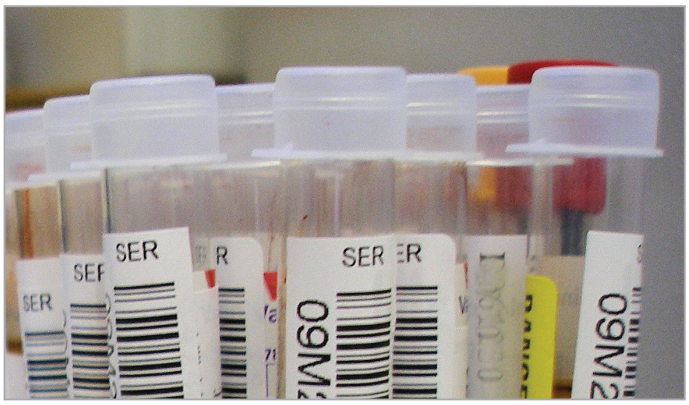
Results: Full blood counts, serum electrolytes, liver function tests and C-reactive protein were, on average, overestimated in cost by 9%, 32%, 36%, and 71% respectively. Costs for each test were underestimated in only a minority of cases, 32% for full blood counts, 14% for serum electrolytes, 16% for liver function tests, and 18% for C-reactive protein. All participants recall circumstances in which they inappropriately ordered an investigation.

Conclusion: Junior doctors did, on the whole, not underestimate the cost of pathology tests. Junior doctors are poorly informed about the cost of tests, however, this does not appear to influence their ordering. 100% of participants reported that they had inappropriately ordered investigations.

Introduction

The use of diagnostic testing is essential in the accurate diagnosis, monitoring and screening of various diseases [1], with an estimated 70% of clinical decisions being substantially based on the results of such investigations [2]. Over the past 20 years, the number of laboratory tests available to clinicians has more than doubled [3], with most clinical laboratories in Australia reporting a 5-10% increase in their annual workload [4]. Similar to biochemical investigations, the uptake of imaging based diagnostics has growth at a rate of 9% annually [5]. Laboratory medicine is the single highest volume activity in healthcare, with demand increasing disproportionally to other medical activities [6].

Unfortunately, these increased volumes of testing have not always resulted in clinically relevant or useful patient interventions. Indeed, numerous studies [3,7-9] have attempted to investigate the impact of inappropriate pathology testing. While definitions of inappropriate use



vary, it can generally be understood as pathology findings that do not have any impact on the clinical decision-making pathway. Estimating the size of this issue is difficult, but has been explored in numerous studies. Miyakis et al [10] found that 68% of a panel of 25 investigations failed to contribute to a patient's clinical management. Sarkar et al [11] reviewed the cases of 200 patients with haemostatic disorders, and found that 78% of investigations ordered did not influence patient management. This represented an avoidable cost of $200,000. Rogg et al [12] found that repeat investigations are redundantly ordered in 40% of patients transferred from the emergency department to inpatient wards.

Rates of overuse reported in other studies ranged from 40-65%, depending on how 'appropriate use' was defined [13-17]. Walraven et al [19] reported, in a systematic review of laboratory clinical audits, pervasive overuse ranging from 4.5-95%. A more recent meta-analysis by Zhi et al [20] estimates the general prevalence of overuse as 20.6%. In Canada, redundant test ordering is expected to represent an annual cost of $36 million (CAD) [21], finances that could have otherwise been redistributed to other essential areas of healthcare.

The impact of inappropriate testing cannot, however, be qualified simply in terms of monetary cost. Even high-value and high-quality investigations can have limitations. False positive results can lead to unnecessary, anxiety provoking and costly follow-up investigations [22-24]. Appropriate ordering decreases the likelihood of false positive results, thereby reducing the associated physical and emotional stress associated with these false positive values.

Improving the practice of ordering laboratory diagnostics is a challenging issue, the solution of which has been widely studied with variable levels of success. Consensus between these studies seems to suggest that education, audit and feedback regarding appropriate investigations can limit the demand for diagnostic investigations. Miyakis et al [10] observed a 20% reduction in avoidable testing after

education was provided to clinicians regarding their test ordering behaviours, the costs of ordering, and the factors that contributed to overuse. Feldman et al [25] found that attaching fee data to routinely ordered pathology investigations reported an 8.6% reduction in the number of tests ordered. A similar study by Tierney et al [26] reported a 7.7% reduction in the number of tests ordered. Hampers et al [27] found that listing the individual charges of diagnostic tests at the time of ordering resulted in a 27% reduction in the total ordering of diagnostic tests.

Miyakis et al [10] found that junior medical staff are 20% more likely to order unnecessary investigations when compared to senior staff. This observation is vitally important as, in public teaching hospitals, junior medical staff are generally responsible for the ordering of relevant investigations, often under a degree of self-direction. It is in this group where education regarding cost awareness would be most impactful in reducing inappropriate ordering. Limited numbers of past studies suggest there is a knowledge gap regarding cost comprehension in junior medical staff. Khromona et al [28] found that 82 (70%) respondents at a single institution felt they needed further education into the ordering of appropriate tests. Stanfliet et al [29] found that all interns interviewed (n=61) across two South African Hospitals reported that they would benefit from further education into the appropriate ordering of investigations.

The aim of this pilot study was to evaluate the awareness that junior medical staff (interns) at the Gold Coast University Hospital have of the costs of various commonly requested blood tests. It was hypothesised that systematic over-ordering may be accounted for by underestimation of cost. If this was confirmed, it would be possible to devise educational interventions designed to manage these deficiencies, which may subsequently promote more cost-effective and appropriate investigation. The efficacy of this process has been suggested in previous studies [10,25-27].

Materials and Methods

Study design

The study utilised an observational design, with the development of a questionnaire aimed at assessing cost compression of interns at the Gold Coast University Hospital (Table 1). The questionnaire included questions relating to some of the most commonly ordered investigations at the hospital: full blood count (FBC), liver function tests (LFTs), serum electrolytes (UES), and C-reactive protein (CRP). Additionally, we requested that participants report if they had ever requested a pathology test that they felt was not clinically indicated, or was inappropriate.

Table 1. Example of questions asked of survey participants to gauge their understanding of the costs associated with pathology testing in hospitals

Questions relating to the cost of common pathology tests
How much do you think a single Urea and Electrolyte (UES) screen costs to process within the pathology lab of the Gold Coast University Hospital?
How much do you think a single full blood count (FBC) costs to process within the pathology lab of the Gold Coast University Hospital?
How much do you think a single Liver Function Test (LFT) screen costs to process within the pathology lab of the Gold Coast University Hospital?
How much do you think a single C-reactive protein (CRP) test costs to process within the pathology lab of the Gold Coast University Hospital?
Have you ever ordered a pathology test that you felt was clinically inappropriate?

Ethics approval to perform this survey was granted by the Human Research and Ethics Committee of the Gold Coast University Hospital (HREC//16/QGC/320).

Participant selection and setting

Medical staff of the classification of intern (first year medical graduates) were approached for inclusion. These staff represented the most junior element of their respective medical/surgical teams. The centre in which this project was conducted is the largest facility of the Gold Coast Health district, which, across its Southport and Robina campuses, serves over 750 beds, with over 100,000 emergency presentations annually. Both campuses are major teaching hospitals, and the majority of interns were graduates of Queensland universities.

The questionnaires were completed during mandatory teaching sessions, which all interns were required to attend. Each participant from the study population had an equal likelihood of being involved in the study. A total of 88 interns were present at these education sessions. Participants were approached randomly with requests for their participation until a sample of 50 participants was reached.

To enhance the response rate and ensure reliability, all surveys were completed during face-to-face meetings with the principal investigator, thus ensuring responders could not have advance understanding of the nature of the specific questions and, therefore, could not prepare accordingly by accessing reference materials.

Data collection

The actual cost of the four commonly ordered pathology tests (FBC, CRP, UES, LFTs) according to hospital financial records was used as a comparison with participant estimates. These values are represented as a total dollar value without a breakdown of individual costs, and represent the cost of labour, consumables, processing and reporting.

Questionnaire responses were de-identified, and no personal or identifying information was retained. Participation and completion of the questionnaire was completely voluntary. This process was repeated until a minimum of 50 completed questionnaires had been collected. It was thought that this number would allow for an equal distribution of uncontrolled variables amongst the study sample.

Statistical analysis

Data was collated using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and statistical analysis was performed using SPSS version 23 (SPSS Inc, Chicago, Ill, USA). Continuous data were analysed for normality using the Kolmogorov-Smirnov method. The mean estimated cost provided by participants was compared to the true cost of the relevant test and was analysed using a one-sample T-test, where $p<0.05$ was considered statistically significant. Simple graphical representations were used to visualise the number of participants that had overestimated or underestimated the cost of the test. Responses within 25% of the actual cost were regarded as accurate, with estimates more than 25% above the true cost being considered an overestimate, and, likewise, estimates more than 25% below the true cost being considered underestimates. These thresholds were suggested by a previous systemic review which examined physician cost awareness of pathology testing [29].

Results

A total of 50 interns at the Gold Coast University Hospital were included in this study. The mean assumed cost of pathology testing was, for all tests, higher than that of the true cost.

For almost all tests (with the exception of FBC), costs were routinely overestimated. Costs were overestimated by 50% of participants with respect to UES, 56% of participants with respect to LFTs, and 68% of participants with respect to CRP testing (Figure 1, Table 2). The FBC was the most accurately predicted test, with 40% of respondents accurately estimating the true cost.

Comparing the mean estimated cost and true value directly, we observed that for LFTs, UES and CRP testing, there was a statistically significant overestimation of cost. LFTs, UES, and CRP were overestimated by 35.5% ($20.87±10.53, p<0.001), 31.5% ($19.76±12.55, p=0.001) and 70.6% ($39.97±38.20, p<0.001), respectively, when compared to the true costs. FBC testing was overestimated by only 9% ($17.25±13.43, p=0.442).

Of note is that 100% of responders reported ordering an inappropriate pathology test during their clinical practice. We hypothesised this inappropriate ordering would be explained by an assumption that tests were cheaper than their true value; however, this was not the case as the majority of participants were found to overestimate costs for most investigations (Figure 2, Table 3).

100% of participants reported that they had previously ordered tests inappropriately.

Discussion

The results of this study seem to suggest that the understanding of the cost of common pathology tests is highly variable between individuals, with a clear lack of consensus amongst the study group a whole. Surprisingly, on average, the estimated cost of pathology testing was generally more than the true cost of testing. In this study, 100% of individuals report having ordered a pathology test inappropriately, and various previous studies [7-11] explore the prevalence of test overordering. This would suggest that factors other than underappreciation of cost are driving excessive ordering amongst medical staff.

It was not surprising that the majority of interns would admit to ordering unnecessary blood tests. This could be because it is often easier to perform the tests with onsite phlebotomy services. Due to the high workload of interns, ordering "routine blood tests" is convenient, time-efficient and often an expectation of senior staff.

In agreement with previous studies [29,30], interns at the Gold Coast University Hospital demonstrate a poor understanding of the cost of pathology investigations. They also report knowingly ordering

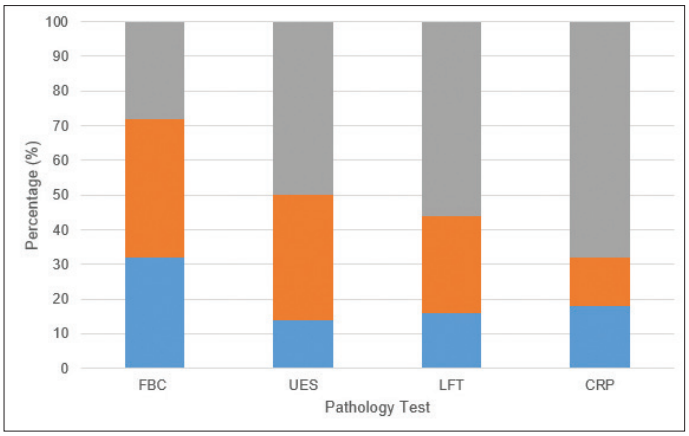


Figure 1. Proportion of candidates to overestimate (grey), accurately estimate (orange) or underestimate (blue) the true cost of pathology tests. *Estimates within 25% of the true cost were regarded as accurate. Estimates more than 25% above the true cost were regarded as overestimates. Estimates more than 25% below the true cost were regarded as underestimates*

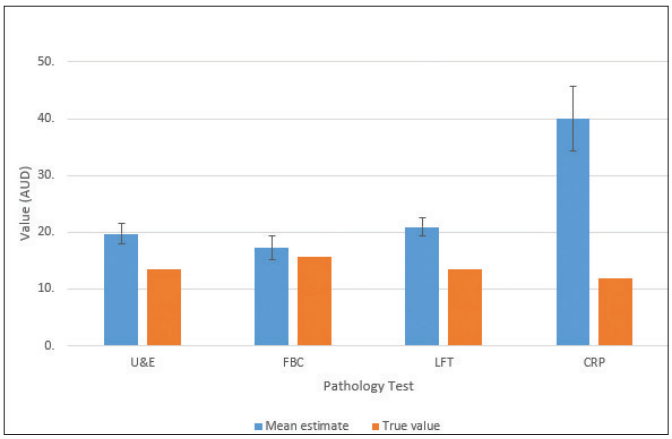


Figure 2. Comparison of the mean estimates of pathology test costs amongst interns (blue), compared with the actual cost of the test (orange).

Table 2. Proportion of respondents who underestimated costs, accurately predicted costs and overestimated costs of commonly ordered blood tests. *Estimates within 25% of the true cost were regarded as accurate. Estimates more than 25% above the true cost were regarded as overestimates. Estimates more than 25% below the true cost were regarded as underestimates.*

Biochemical test	No (and %) underestimating value >25%	No (and %) accurately predicting value (within 25%)	No (and %) overestimating costs >25%
FBC	16 (32)	20 (40)	14 (28)
UES	7 (14)	18 (36)	25 (50)
LFT	8 (16)	14 (28)	28 (56)
CRP	9 (18)	7 (14)	34 (68)

Table 3. Actual and estimated cost of pathology tests.

Pathology test	True cost ($)	Estimated mean cost ($)	Standard deviation	p-value (CI 96%)	IQR
FBC	15.70	17.25	13.43	0.442	10.00
LFT	13.48	20.87	10.53	<0.001	11.00
UES	13.48	19.76	12.55	0.001	18.00
CRP	11.75	39.97	38.20	<0.001	48.50

inappropriate or unnecessary investigations. We propose three potential explanations for this. First, some participants may have had prior experience with or knowledge of commercial pathology testing, which tends to carry higher costs than in-house hospital pathology tests. Second, due to clinical inexperience, the perceived clinical value of the unnecessary tests was thought to be greater than the monetary costs of performing the investigation. Finally, it is possible that cost reduction is not perceived to be the responsibility of the most junior member of the management team. One study by Tiburt et al [29] in 2013 found that only 36% of physicians considered themselves responsible for reducing healthcare costs. Simply put, many clinicians do not acknowledge or accept their own role in rationalising healthcare costs.

Miyakis et al [10] found that junior staff will order inappropriate investigations 20% more frequently than senior staff (across a single Australian emergency department). However, the same study did not suggest cost-comprehension as a driving force for this difference. Schilling [31] found that only 28% of Swedish emergency department physicians correctly predicted the cost of investigations used to investigate pulmonary emboli, concluding that level of experience did not imply a better knowledge of the costs of investigation. A systematic review by Allan et al [32] of 14 studies of diagnostic and non-drug therapy cost estimates reported that clinicians of various nationalities estimated costs to within 25% of the tests correct value 33% of the time, and that the year of study, level of training, and specialty did not appear to impact this accuracy. These studies were represented by mixed specialties in various European and American based institutions. Broadwater-Hollifeild et al [33] found that only 20% of emergency physicians correctly predicted the costs of common medical tests (within 25% of true cost) across eleven emergency departments in Utah, USA. For comparison, interns in our study were, as an aggregate, able to correctly predict costs (within 25% of true value) in 29.5% of proposed tests. The individual populations and settings varied in these studies and the resounding consensus is that clinicians, in general, will poorly predict the cost of investigations.

While experienced clinicians may have a limited knowledge of the costs of the investigations they order, they may request more relevant investigations, likely to be a consequence of experience and a better understanding of the specific indications and limitations of particular tests [33]. However, in some scenarios, seniority does not always correlate with a reduced volume of testing. For example, a recent study by Magin et al [34] found that in Australian GPs, for every 6 months of cumulative training, the number of investigations ordered increased by 11%. This indicates the relationship between ordering and experience may be more complex. This may be because, with greater comprehension of potential pathology, registrars in later stages of training have greater concern for potential missed diagnoses, or, in general, have a lower acceptance of ambiguity.

Although unnecessary testing is often associated with a net detrimental effect, examples do exist where excessive ordering of low yield investigations can result in the capture of significant pathology, allowing for the early management of conditions that may have otherwise led to significant mortality and morbidity. These screening programs usually undergo rigorous cost-benefits analyses, ensuring the net benefits outweigh any risks and costs associated with implementing such a program. Some examples of which include routine screening for breast cancer [35] and colorectal cancer [36,37]. These are examples of tests where, despite low pretest probability of disease, the impact of a positive value can significantly alter patient mortality and morbidity to the level that routine testing is justifiable for relevant parties. Another example is routine screening for inborn errors of metabolism, which is performed for every child born in Australia. Although these illnesses are rare, these routine tests have high sensitivity and specificity, allowing for early intervention and leading to substantially better outcomes for affected patients [38]. While we acknowledge that this 'shotgun' approach can occasionally have positive outcomes, clinicians face an ethical conundrum. Maximising the use of resources in every patient runs the risk of eroding and diluting the overall effectiveness of the healthcare system, and each investigation ordered for a patient increases the risk of a false positive result or adverse event. We do not advocate compromising patient safety in favour of retaining finances, but, as 100% of the junior doctors surveyed in this study have ordered inappropriate tests, some degree of cost containment must be considered.

Targeted interventions to curtail unnecessary investigations may assist in this regard. Given the overestimation of costs found in this study, it is unlikely that providing fee data for investigations would impact ordering behaviours significantly. A better approach would be to try and understand what factors are taken into consideration when ordering tests by more senior clinicians, given their tendency to order less inappropriate investigations than interns. Further studies would benefit from comparisons between interns and more senior medical staff, to establish what behaviours in senior staff result in more appropriate test ordering. Targeted education of these concepts may produce a reduction in inappropriate test ordering.

Study limitations and future directions

Our study analysed only awareness of costs, but did not demonstrate or attempt to ascertain the degree of inappropriate usage. Based on our current results, we could not provide an opportunity for a cost reduction through education of true cost, as participants generally overestimate rather than underestimate test values.

In future studies, it may be beneficial to include additional questions incorporating a Likert scale in which participants rank the factors most important to them when ordering a blood test (for example, including factors such the cost of the test, expectations from a superior, desire for completeness, and expectations from patients). This would allow for identification of the traits most likely to lead to excessive ordering. Consequently, future interventions could be developed to address factors most likely to contribute to these behaviours. As discussed, it may be beneficial to compare groups of interns to more senior clinicians to establish the behaviours that most strongly correlate with rational test ordering.

Another limitation of this study was that we did not ascertain the degree of previous education regarding pathology testing costs that each participant had received. Previous studies [26,27] suggest that this may be a widespread phenomenon. It would also be valuable to ascertain how many tests participants are ordering to establish if participants who routinely underestimate the cost of tests tend to order more frequently, or vice versa. Such data could be linked to administrative data to assess for clustering and to determine if ordering behaviours vary between departments.

Conclusion

Junior doctors frequently report ordering inappropriate tests and, in general, overestimate the costs of these pathology tests. This has a financial impact on the health system. We advocate that pathology services develop educational strategies for reducing inappropriate testing. Cost awareness does not appear to be a highly relevant factor in test ordering. Further study is needed to recognise the specific factors that contribute to systematic over-ordering.

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Conflict of interest

None declared.

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Combined epiretinal membrane and cataract surgery: visual outcomes

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Abstract

Introduction: This study compares visual outcomes between patients undergoing a single surgery combining cataract and epiretinal membrane (ERM) peel versus cataract surgery preceding ERM surgery as separate procedures.

Materials and Methods: A retrospective review was undertaken of electronic medical records for patients undergoing ERM surgery by vitrectomy, performed by a single surgeon. Peri-operative, three month and twelve month follow-up visual data were collected. Three groups were identified: 1) Cataract surgery prior to ERM peel; 2) Combined ERM and cataract surgery; and 3) Cataract surgery post-ERM peel. Post-operative complications and mean change in visual acuity (VA) were investigated in the cataract surgery prior to ERM group compared to the combined surgery group.

Results: A total of 271 eyes underwent ERM peel either before or after cataract surgery, or combined with cataract surgery. 62 eyes were excluded as they did not have follow-up data available. Of the 209 included eyes, 62 had cataract surgery prior to ERM peel, 105 had combined ERM peel and cataract surgery, and 28 had cataract surgery post-ERM peel. Analysis of outcomes in the cataract surgery pre-ERM versus combined surgery group found improvements in both groups' VA at three months (mean logMAR (logarithm of minimum angle of resolution) improvement -0.10 vs. -0.08, p=0.87) and twelve months post-operative follow-up (mean -0.18 vs. -0.22 p=0.54), with no significant difference between the groups. There was no difference in the proportion of eyes in either group that had peri-operative (9.5% vs. 4.8%, p=0.28) or post-operative complications (5.9% vs.1.8%, p=0.42).

Conclusion: Combined cataract and ERM vitrectomy is as effective as consecutive operations for improving VA, whilst reducing patient exposure to the risks associated with two separate procedures.

Introduction

The epiretinal membrane (ERM), also referred to as macular pucker or cellophane maculopathy, is a sheet of fibrous cells on the surface of the retina. Proliferation of the fibrous cells and the subsequent contraction of the membrane lead to defective visual symptoms, in particular distortion and blurred vision. ERM is a relatively common occurrence with ageing, with the prevalence of ERM ranging from 8.6% to 12.1% amongst various ethnic groups and countries [1-3], and typically affecting patients over 60 years old [3]. Often symptoms are only minimal and ERM requires no intervention unless progression occurs. In some instances, however, ERM adversely affects vision and requires treatment through surgical intervention with vitrectomy and an ERM peel procedure. Patients requiring treatment for ERM may have other comorbid eye conditions, such as cataract, which also need to be addressed. Therefore, the question arises if these two problems are best addressed simultaneously or sequentially. The current literature provides only small case series in answering this question and results have been mixed, although most papers have found no significant differences [5-7]. There is also a paucity of literature that compares combined surgery and cataract surgery prior to ERM peel.

Aim

In this study, we sought to identify the number of patients who underwent ERM vitrectomy before or after cataract surgery and the number of patients who received ERM phacovitrectomy combined with cataract surgery at a single site. Secondly, we sought to determine complication rates and visual outcomes in patients who had combined ERM cataract surgery compared to cataract surgery prior to or after ERM vitrectomy.

Materials and Methods

Following approval from the University of Tasmania Human Research Ethics Committee (H0015009), we conducted a retrospective review of the medical records of patients who were diagnosed with ERM and underwent an ERM peel vitrectomy by a single surgeon. The surgeries were conducted in an Australian regional town (Launceston) between July 1, 2005 and May 12, 2014. Inclusion criteria were patients with pre-operative visual data and twelve month post-surgery follow-up visual data.

Information retrieved from patient medical records consisted of:

- Baseline demographics
- Medical comorbidities (pre-operative and post-operative)
- Lens status (phakic or pseudophakic)
- Date of cataract surgery (cataract surgery pre-ERM, combined, or cataract surgery post-ERM)
- Surgical complications during ERM removal
- Best corrected visual acuity (VA) pre-operatively as well as at three months and twelve months post-operatively
- Central macular thickness (CMT) (pre-operatively and twelve months post-operatively)

Patients were classified according to the date of cataract surgery in relation to their ERM vitrectomy: cataract surgery before ERM vitrectomy, combined phacovitrectomy, or cataract surgery after ERM vitrectomy. Patients who did not return for twelve month follow-up were excluded.

Snellen acuity measurement of best-corrected visual acuity (BCVA) was performed and the results were converted into a logarithm of the minimal angle of resolution (logMAR) before analysis. To utilise a stable BCVA, the twelve month post-operative follow-up BCVA was used in the final analysis. The surgeries were performed by one surgeon. Details on posterior vitreous detachment (PVD) and peri-operative complications were also collected.

Data from patient records were extracted into an Excel 2010 (Microsoft, Redmond, WA, USA) spreadsheet and imported into Stata 14.1 (StataCorp, College Station, TX, USA) for analysis. Continuous data distributions were investigated and one-way analyses of variance (ANOVA) were used to investigate baseline differences between the three groups (cataract surgery pre-ERM, combined, or cataract surgery post-ERM) with Tukey-Kramer post-hoc tests. For categorical data, crosstabs with Chi-square and Fisher's exact tests were utilised to investigate differences among the three groups at baseline. These were also used to investigate complications and the proportion of eyes with VA improvements of one chart line or greater at three month and twelve month follow-ups for the cataract surgery pre-ERM group versus the combined surgery group. Independent t-tests were used for the investigation of mean change in VA (logMAR) and mean change in CMT from baseline to three month follow-up, and twelve month follow-up between the pre-ERM group versus the combined surgery group. All tests were two-sided and differences were accepted as significant at $p<0.05$.

Results

A total of 271 eyes underwent ERM peel either before or after cataract surgery, or combined with cataract surgery. There were 62 eyes excluded as they did not have follow-up data available. Twelve month follow-up data was available for 209 eyes from 199 patients (93 women and 106 men) and these were selected for analysis. There were 108 (51.7%) right eyes and 101 (48.3%) left eyes (Table 1). There were 62 (29.7%) eyes with cataract surgery prior to ERM peel, 28 (13.4%) eyes proceeding to cataract surgery post-ERM peel, 105 (50.2%) eyes with combined ERM peel and cataract surgery, and 14 (6.7%) eyes with solely ERM peel that have not yet required cataract surgery (Table 1).

Table 1. Baseline characteristics of all eyes.

	Total n=209
	Mean ± SD or n (%)
Group	
Cataract surgery prior to ERM peel	62 (29.7)
Combined ERM peel and cataract surgery	105 (50.2)
Cataract surgery post-ERM peel	28 (13.4)
Only ERM peel (no cataract surgery)	14 (6.7)
Mean age (years)	72.5±7.5
Sex (total patients = 199)	
Female	93 (44.5)
Male	106 (50.7)
Eye	
Left	101 (48.3)
Right	108 (51.7)
Pre-operative VA	
6/12 or better	32 (15.3)
6/15 to 6/24	100 (47.8)
6/30 to 6/48	49 (23.4)
6/60 or worse	28 (13.4)
Pre-operative VA as logMAR	0.65±0.40
Pre-operative CMT	433.6±115.1
Pre-operative CMO	40 (19.1)

There was no significant difference between the groups for pre-operative CMT or cystoid macular oedema (CMO). There was a significant difference in mean age between the groups ($F_{2,192}$=7.8, p=0.001) with the Tukey-Kramer post-hoc test indicating a significant difference between the cataract surgery prior to ERM peel group and the cataract surgery post-ERM peel group ($p<0.0001$) and the combined group and the post-ERM peel group (p=0.02), but not between the cataract surgery prior to ERM peel group and the combined group (p=0.13). The combined surgery group had better mean VA (logMAR) pre-operatively compared to the cataract surgery prior to ERM or post-ERM groups (p=0.04). In the cataract surgery pre-ERM group, there was a mean of 1347±1179 days between cataract surgery and ERM peel.

Overall, there were 18 peri-operative complications: 17 retinal tears or breaks (8.1%) and one lens touch (0.48%) There was no difference in the proportion of eyes that had peri-operative complications in the cataract surgery pre-ERM group compared to the combined group (4.8% vs. 9.5%, p=0.38) or in the proportion of eyes with postoperative complications (1.8% vs. 5.9%, p=0.42).

In the post-operative period, CMO developed in five eyes that had combined surgery and three eyes that had cataract surgery after ERM peel. No eyes that had cataract surgery pre-ERM developed CMO post-operatively (Table 3). Comparing the cataract surgery after ERM peel versus combined surgery group, there was a trend for a larger proportion of eyes receiving cataract surgery after ERM to have CMO post-operatively, although this was not statistically significant (11.1% vs. 4.8%, p=0.36).

Table 2. Baseline characteristics of cataract surgery pre-ERM, combined surgery and cataract surgery post-ERM groups.

	Cataract surgery prior to ERM peel (n=62) Mean±SD or n (%)	**Combined surgery group (n=105)** Mean±SD or n (%)	**Cataract surgery post ERM peel (n=28)** Mean±SD or n (%)	**p-value**
Mean age (years)	74 ±7.7	72±6.7	68±7.6	<0.05
Sex				
Female	33 (53.2)	42 (40.0)	16 (57.1)	ns
Male	29 (46.8)	63 (60.0)	12 (42.9)	
Eye				
Left	29 (46.8)	51 (48.6)	13 (46.4)	ns
Right	33 (53.2)	54 (51.4)	15 (53.6)	
Pre-operative CMT	406±97.2	436±129.6	470±77.0	ns
Pre-operative VA 6/12 or better	10 (16.1)	19 (18.1)	2 (7.1)	ns
Pre-operative VA 6/24 or better	34 (54.8)	75 (71.4)	15 (53.6)	ns
Pre-operative VA as logMAR (Snellen equivalent)	0.73±0.48 (6/30)	0.58±0.35 (6/24)	0.70±0.35 (6/30)	<0.05
Pre-operative VA				
6/12 or better	10 (16.1)	19 (18.1)	2 (7.1)	*
6/15 to 6/24	24 (38.7)	56 (53.3)	9 (32.1)	
6/30 to 6/48	16 (25.8)	23 (21.9)	11 (39.3)	
6/60 or worse	12 (19.4)	7 (6.7)	6 (21.4)	
Pre-operative CMO	14 (22.6)	17 (16.2)	6 (21.4)	ns

**Unable to calculate due to small expected cell sizes.*
ns: not significant.

There were improvements in both the cataract surgery pre-ERM group and the combined group at three month and twelve month post-operative follow-up appointments (Table 3). There was no difference between the groups for mean change in VA (logMAR) from baseline to three month (p=0.87) or twelve month follow-ups (p=0.54). There was also no significant difference in mean change in CMT from baseline to three month follow-up (p=0.07) or twelve month follow-up (p=0.20) between the groups.

Discussion

BCVA is our main tool for predicting visual outcomes in ERM vitrectomy. It is a widely used and reliable prognostic factor to measure visual outcomes [4]. Our study utilised results from a single vitreoretinal surgeon and one centre, which provided consistency for this study, and reduced variation. We investigated outcomes in the combined surgery and the cataract surgery prior to ERM peel groups, due to the limited published research comparing these groups. For these outcome analyses, we excluded the cataract surgery post-ERM group.

Dawson et al [10] found pre-operative VA may predict visual improvements at follow-up. Our results confirm Dawson et al's [10] research for both groups, with the strongest prediction being for the consecutive surgery group (pre-surgery VA is a stronger predictor of follow-up VA in consecutive versus combined surgery). In our study, the combined surgery group had better mean (logMAR) pre-operative BCVA, due to a greater proportion of eyes within the 6/15 to 6/24 range. To control for greater baseline visual acuity in the combined group, we analysed change in BCVA (logMAR) at follow-up between the two groups.

Our finding of no significant difference in mean VA improvement between the cataract surgery pre-ERM group and the combined group is similar to previous research. In a 2010 study by Dugas et al [5], 174 eyes were compared for surgical outcomes between combined and consecutive cataract extraction and ERM vitrectomy. At twelve months follow-up, the groups did not demonstrate a statistically significant difference in VA improvements [5]. In another similar study conducted by Yiu et al [6] in 2013, 81 eyes from 79 patients were grouped into combined cataract and ERM vitrectomy, and ERM vitrectomy alone. Yiu et al [6] found no statistically significant differences between the groups on VA improvements at six month and twelve month follow-up. We also found no significant difference in mean improvement in CMT between the cataract surgery pre-ERM group and the combined group. This finding is also consistent with both Dugas et al [5] and Yiu et al [6].

Eyes that had cataract surgery after ERM peel had approximately double the incidence of post-operative CMO compared to the combined surgery group. While this finding was not statistically significant, this may be explained by the small number of eyes that developed CMO in each group, resulting in a lack of power to detect a significant difference between the groups. Among the combined group in our study, 5.0% developed CMO. This concurs with previous studies that reported incidences of 3.6% to 8.1% in combined surgical cases [7,8]. A separate study also concluded no difference in the incidence of CMO between combined surgery and pre-ERM groups [9]. Due to the small sample size, and no eyes in the cataract surgery pre-ERM group developing CMO post-operatively, we were unable to determine if the incidence of CMO would have improved if consecutive surgery (either cataract surgery before or after ERM peel) was conducted. Perhaps a further study with larger population sizes would allow for a clearer understanding of this.

Table 3. Visual acuity at three month and twelve month follow-up in pre-ERM versus combined surgery group.

Three month follow-up	Mean±SD or n (%) Cataract surgery pre-ERM (n=57)*	Mean±SD or n (%) Combined surgery group (n=95)*	p-value
Follow-up VA as logMAR (Snellen equivalent)	0.62 ±0.54 (6/24)	0.50±0.37 (6/19)	ns
Improvement in VA as logMAR from baseline	-0.10±0.56	-0.08±0.38	ns
VA improved by one line or greater	36 (63.2)	53 (55.8)	ns
Difference in CMT from baseline	-63.8±97.9	-40.3±118.6	ns
Twelve month follow-up	**Cataract surgery pre-ERM (n=62)†**	**Combined surgery group (n=105)**	**p-value**
Follow-up VA (logMAR) (Snellen equivalent)	0.54±0.52 (6/21±6/19)	0.36±0.33 (6/15-2±6/12)	<0.05
Improvement in VA (logMAR) from baseline	-0.18±0.52	-0.22±0.38	ns
VA improved by one line or greater	46 (74.2)	81 (77.1)	ns
Difference in CMT from baseline	-104.8±137.6	-73.7±146.9	ns
PVD‡			
PVD present	24 (38.7)	39 (37.1)	ns
PVD induced	33 (53.2)	59 (56.2)	
PVD n/a	5 (8.1)	7 (6.7)	
Post-operative complications	1 (1.8)	6 (5.9)	ns
Post-operative CMO	0 (-)	5 (5.0)	ns

**Note: Five pre-ERM eyes and ten combined eyes did not have three month follow-up data available.*

†Three eyes with missing twelve month follow-up VA excluded.

‡There were 41 eyes with twelve month follow-up PVD information not available.

ns: not significant.

ERM peel is known to be a safe and effective procedure. Our study indicated that there was no statistically significant difference in the proportion of patients in the combined or sequential groups who had peri-operative or post-operative complications. Peri-operative complications included retinal tears and lens touch. Post-operative complications included CMO and posterior capsule opacification. The rate of complications we observed was also consistent with similar studies. As such, we would conclude that there was no evidence to demonstrate that combined surgery would be safer in terms of complications. The benefits of a combined operation include the reduced risks of two separate operations, reduced costs, and increased convenience for the patient. Furthermore, a cataract operation after an ERM peel might be more challenging for the surgeon, due to the lack of vitreous support and increased difficulty of intraocular lens placement, thus increasing peri-operative complications [11]. Both ERM and cataract affect vision, so conducting a cataract operation alone might not provide optimal VA improvement, as there may be progression of ERM. Considerations against combined surgery include an increased post-operative inflammatory response, CMO, and increased rates of posterior capsule opacification and posterior synaechiae formation [12].

Limitations of this study include its retrospective design. Unfortunately, this was necessary to identify a substantial number of patients for inclusion (this required an eight year study inclusion period), as the study recruited patients from the only cataract and vitreoretinal surgeon in the region. A prospective study including patients from several surgeons would have less bias and the results would have greater generalisability. We excluded patients from the study if they did not return for post-surgery follow-up. This resulted in 29 combined surgery eyes and 33 pre-ERM eyes being excluded. If these eyes were included in the study, 21.6% of the combined surgery group and 34.7% of the pre-ERM would have been categorised as lost to follow-up. It is probable that patients lost to follow-up may have had better improvements in their VA. However, it is unknown to what extent the exclusion of these eyes may have introduced bias to the study results, particularly when comparing the two groups. The patients who underwent combined phacovitrectomy had a better mean (logMAR) VA and a greater proportion had a pre-operative VA of 6/24 or better. Given the presence of both pathologies, these patients underwent combined surgical procedures. However, some of these patients with both pathologies (ERM and cataract) may have had an acceptable VA improvement from cataract surgery alone, such that they would not have ordinarily proceeded to epiretinal surgery. In contrast, the patients in the cataract surgery prior to ERM peel group had already selected themselves into that group requiring ERM surgery as they were sufficiently affected by ERM. Thus, the patients in the consecutive surgery group potentially would not present for surgery unless already having a worse pre-operative VA than the combined surgery cohort.

We acknowledge that an analysis of a twelve month follow-up BCVA would include various confounders, such as new ophthalmic pathologies or worsening of pre-existing pathologies. Those factors were not taken into account during our analysis. As post-operative conditions tend to stabilise by three months following operation, we also analysed our patients at the three month follow-up period. The results were similar at three and twelve month follow-up intervals. Whilst we made an assumption that the patients were stable at three months, they appeared to continue improving after this time, as demonstrated by the twelve month follow-up results. Additionally, our comparison did not include patients who were diagnosed with ERM but only underwent cataract surgery, as they might not present for ERM

peel secondary to acceptable visual improvements. Our consecutive group involved patients who underwent cataract operation then ERM peel. Some of these patients might have developed ERM only after the cataract surgery. Finally, our study is limited by the absence of baseline comorbidity data. As such, we were unable to assess the impact, if any, of comorbidities on VA improvements.

Conclusion

This study has shown that combined cataract and ERM vitrectomy is at least as effective as consecutive operations, if not better, for improving VA. As such, it may be prudent to conduct combined surgery, as it reduces patient exposure to the risks of two separate operations, as well as being more convenient for the patient.

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Conflict of interest

None declared.

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Multilevel approaches to optimising antenatal care: its delivery, uptake and the subsequent health outcomes

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Abstract

Introduction: The World Health Organisation recommends that all pregnant women receive at least four antenatal visits. However, nearly half of all women worldwide, particularly in less developed countries, do not receive this care. Antenatal care (ANC) provides an opportunity to improve the outcome of pregnancy and reduce maternal and fetal mortality rates, particularly in low- and middle-income countries.

Summary: There is a critical need for evidence-based studies surrounding ANC and its provision and uptake, both in Australia and on an international level. This is to ensure that the care provided is specific to the needs of every woman the medical community serves. In this article, we examine a Cochrane review of a variety of community-based and health systems-related approaches that target determinants of reduced ANC coverage. The review aims to address the issues affecting ANC coverage, highlight the gaps in the care we currently provide, and discusses its implications for the current healthcare policies regarding ANC provision. While transport and cost remain the basic barriers to accessing ANC, woman-doctor partnerships, contextual care, women's satisfaction, and cultural safety are also of paramount importance if ANC is to reach more women. The part clinicians play, particularly in delivering holistic and woman-centered care, must also be realised in order to restructure care to be more coordinated and effective.

Introduction

Michelle Obama once said, "Communities and countries and ultimately the world are only as strong as the health of their women [1]."

Antenatal care (ANC) plays an important role in assisting and preparing pregnant women mentally, emotionally and physically for childbirth. ANC ensures that the well-being of both the mother and child is well monitored to ensure an ongoing pregnancy with an increased likelihood of a successful birth and a healthy baby. Despite the importance of ANC for both mother and child, globally, only 82% of pregnant women have access to at least one ANC visit during their entire gestation period, and only 54% receive the recommended minimum of at least four antenatal visits [2,3]. It is important to discern and address the causes of this disparity. A 2015 systematic review by Mbuagbaw and colleagues analysed a variety of community-based and health systems-related interventions that targeted determinants of reduced ANC coverage in order to ascertain their effectiveness in increasing the number of women who received ANC [4]. This article analyses and interprets the findings of the review, exploring its implications for women, clinicians and the broader medical community.

Summary of the systematic review by Mbuagbaw et al. [4]

The review evaluated results from up to 400,000 women across 34 randomised controlled trials assessing different methods of optimising antenatal care. Of these trials, 29 used a cluster-randomised design. The trials tested two main types of interventions, both aimed at improving the uptake of ANC: health system interventions that included home visits for pregnant women and provision of adequate equipment for clinics; and community-based interventions, such as media campaigns, provision of education, or financial incentives for pregnant women.

Using one intervention, as opposed to none, was found to be effective, as demonstrated by an increase in the number of women who received four or more antenatal visits, an increase in the number of women who received at least one antenatal visit, and the number of births carried out in a health facility. There was no evidence of any change in the number of pregnancy-related deaths or any impact on the rates of low birth weight babies [4].

Using a combination of interventions in comparison to no intervention resulted in an increase in the proportion of pregnant women who obtained at least one antenatal visit. Combined interventions also resulted in a reduction in perinatal deaths and a reduction in underweight babies, compared with no intervention. There were no differences between single interventions and combined interventions for any outcome measured [4].

The findings revealed that, regardless of the number of interventions used, the implementation of at least one intervention led to a positive outcome. In view of this, it is important to evaluate the methods used and to understand and appreciate why the interventions were successful.

Interpretation of the findings

Two main categories of interventions were used in the systematic review, as detailed above. The first targeted the health system and involved the reorganisation of health services and patient-centred care. This proved effective as it addressed the woman's sociocultural context and agenda, serving as an example of patient-centred care as defined by the Institute of Medicine [5]. Both personal and social environments play a role in influencing the experience of pregnancy. It is, therefore, essential to consider these factors when administrating health services to ensure that the best care is provided and the needs and expectations of the woman are met [6].

The majority of the trials were implemented in low and middle income countries. Most pregnant women in these populations are still unable to gain access to healthcare and thus experience poorer health outcomes [7]. In a similar study that evaluated the factors affecting ANC attendance across four sub-Saharan regions, the results showed that the way women described ANC was often vague: many of the women had very generalised descriptions about care during pregnancy, what it comprised of, what transpired when one was administered ANC, and the necessity of at least four visits [8].

Moreover, the women often only sought ANC when they faced problems or uncertainties with their pregnancies. How the ANC services responded to these uncertainties, together with their general interactions with the pregnant women, affected women's ANC attendance [8]. The attitudes and behaviours of healthcare workers has long been recognised to influence patient care. Poor interpersonal relationships may act as a barrier to the successful conveyance and interpretation of information, a key component of a successful patient-centred interview [9].

In view of these results, the second intervention that targeted the community proved to be highly effective. The methods used were aimed at helping women, particularly pregnant women, gain a greater understanding of the purpose of ANC. A study carried out in Pakistan's Punjab province showed that women's lack of awareness of ANC was also responsible for low ANC coverage [10]. With limited knowledge, the use of ANC services is reduced. As health professionals, it is important that we never assume a woman has any previous health knowledge. Provision of information regarding the services rendered and their usefulness can prompt more women to use the available services while, ideally, improving patient satisfaction [11]. In addition, the provision of education about health in pregnancy should be culturally appropriate, including supplying a local adaptation of the written materials, making them culturally and linguistically applicable to the target population [6].

The second intervention additionally offered financial incentives, which increased access to ANC for women who were previously deterred due to its cost. It also addressed social mobilisation, which consequentially actuated community initiatives and creativity in addressing the problem at hand. This intervention also included changes in behaviour, such as birth preparedness, aimed at modifying behaviour patterns that can cause low ANC uptake.

Implication of the systematic review findings

A woman-centred healthcare system involves the meaningful engagement of women and the formation of partnerships with the woman and their families. The trust that arises as a result of a strengthened woman-provider relationships has the power to drive change in healthcare delivery. Taking time to build rapport helps improve women's experience of ANC. It requires effective communication, as women who understand their healthcare providers are more likely to understand their treatment and adhere to follow-up recommendations [12].

"Put patients first" declared Harvey Fineberg, President of the Institute of Medicine. "When one has truly understood what the patient needs, they have truly put the patient first [13]." Both interventions used in this study involved reaching out to individual women. Findings revealed that the usage of ANC was considerably lower in women who lived far from the place ANC was delivered, as the long distances reduced access. This was largely the case for women living in rural and remote areas [14]. The use of mobile clinics and greater involvement of the healthcare system, such as requiring skilled attendants to make home visits to pregnant women in remote communities, would greatly reduce such problems. Mobile clinics in particular, as an integral part of the healthcare system, have proven to be highly beneficial in the provision of high-quality, low-cost care to vulnerable isolated populations. They offer a wide scope of services tailored to the community's needs, thus removing the logistical constraints (transport and financial issues, long waiting periods, and complex and often tedious administrative practices) faced by many [15].

Adequate improvements in the utilisation of ANC and thus its coverage require much more than an increase in the health workforce or an increase in the number of health centres established. It demands a greater focus on a woman's overall social, political and economic determinants of health. When ANC provision is both theoretically and contextually opposed to local beliefs and experiences, its usage is diminished, especially when women experience any form of abuse in their care setting or when their attendance puts them at risk from their immediate family or community [16].

Implications within an Australian context

In 2002, Hunt published research aimed at improving ANC and its protocols and practice in the Northern Territory in Australia [17]. He suggested that antenatal visits be prolonged in time, but less in number, thus making them more likely to be comprehensive and delivered in a more flexible woman-centred manner that makes no generalisations or assumptions about its patients. Likewise, the Daruk Aboriginal Community Controlled Medical Service in New South Wales succeeded in achieving earlier ANC attendance and increasing the number of ANC visits through a comprehensive primary healthcare program. This program incorporated a wide range of ANC services, including home visits and transport provision: both examples of strategies which could be extended to many other Aboriginal communities [18,19]. Conversely, a large proportion of Aboriginal and Torres Strait Islander people live in urban or inner regional areas and have their healthcare channelled through mainstream services. Therefore, it is imperative that we optimise the care we provide to these groups by applying the same principles of cultural competence in all healthcare services, in order to heighten the authentic involvement of women in decision-making. Such measures have the potential to see a greater proportion of this population gain access to the services available to them [19].

These interventions could prove to be very useful in many rural and remote regions, specifically in the Aboriginal community, through the engagement of the wider community. The assistance from Aboriginal health workers facilitates communication and understanding between the woman and the healthcare provider, which may consequentially engender trust and responsiveness to ANC [20].

Recommendations

When providing care as health professionals, we need to consider the woman's context and establish a holistic approach that addresses the needs and concerns of that specific woman [17]. This is pertinent in places where culture plays a pivotal role. 'Shame' in Australian Aboriginal communities is a culturally-held belief that introduces behaviours and attitudes, evident in patient-doctor encounters, that can be easily misconstrued, resented and/or disregarded by care providers who fail to appreciate its role in a woman's life and family [18]. A basic yet appreciative understanding of the history and policies that have moulded the lives of Aboriginal women and their families may assist in the comprehension of some of their health behaviours. For example, the systematic removal of Aboriginal children from their families, the Stolen Generation, has been suggested as a prevailing source of distrust in the Aboriginal mothers' community [19,20]. Provision of a healthcare service that is culturally equipped to provide holistic ANC is essential if we are to successfully reach out to all communities, including the Aboriginal community.

Conclusion

Based on the findings of this systematic review, it is evident that several interventions were effective in increasing ANC coverage and improving other pregnancy-related outcomes. Reported interventions addressed the common problems that affected the utilisation of ANC, which included maternal knowledge, accessibility to healthcare facilities, and financial difficulties. Accordingly, as doctors and future practitioners, it is imperative that when we provide maternal and antenatal care, we structure the healthcare services around the woman and cater to their individual preferences, needs and concerns. We are advised to accommodate the woman as much as we can, which means providing them with care that is specific to them and care that addresses the whole person [15-17]. The evidence obtained in Mbuagbaw's review should be applied effectively in all areas, especially in those places with low ANC coverage [4]. This also serves as an indicator of the gaps in the current evidence that still require further research.

Therefore, instead of asking "Why do women not accept the service that we offer?", the important question should be "Why do we not offer a service that women will accept [22]?"

Conflict of interest

None declared.

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Oncology teaching in Australian medical schools: opportunities for patient-centred change

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Abstract

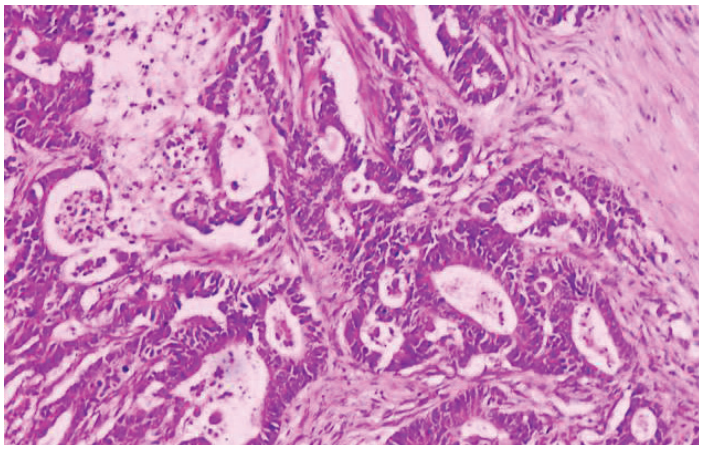
Introduction: Given the prevalence of cancer and its multidisciplinary and increasingly personalised treatments, this group of diseases is an ideal vehicle for teaching medicine and medical care. The teaching of oncology in medical school environments is of paramount importance to the skill sets and efficacy of future doctors. But do we do it well, and could we do it better?

Summary: Oncology education in medical schools in Australia and abroad is explored through a personal lens, a qualitative survey, and a literature review in this article. First, the author reflects on his own experience of oncology education as a cancer survivor and third-year medical student. Qualitative data from a survey of medical students at one institution provide insight into the potential benefit of increased exposure to people living with cancer while in medical school. Australia's andragogic oncological landscape is critically evaluated, and opportunities for change are proposed.

Introduction

As a cancer survivor, the frightening experience of a cancer diagnosis is something I intimately understand. Cancer remains the major cause of mortality in Australia and many cancers still have very high mortality rates [1]. One in two Australians will be diagnosed with a cancer before the age of 85. In 2016, it was estimated that 130,466 people were diagnosed with cancer [2] and 46,880 people died from cancer. In this same year, 384,593 Australians reported living with cancer [2].

Despite large volumes of research, it is a disease that continues to kill indiscriminately and its treatment inflicts harsh side effects during therapy and late toxicities in survivorship. The contradictory way that the causes of cancer are communicated and the complexity of the disease all contribute to a fear of cancer. Medical students are not immune to this fear and many develop additional anxiety about cancer throughout their university training. Cancer, for medical students, is a complex disease process, often of unfamiliar and unknown aetiology. It challenges our understanding of genetics, anatomy, physiology, therapeutics, psychology and public health. As a major health burden, all doctors and medical students should possess a foundational understanding of cancer screening, the pathophysiology underpinning its signs and symptoms, principles of diagnosis and cancer treatment, and appreciate the importance of multidisciplinary care. Simultaneously, doctors require the confidence to effectively and empathetically facilitate conversations with patients and their families about the diagnosis of cancer, fear and grief, prognosis, side-effects, palliative care, and end-of-life planning [3-5].



Reflections from a cancer survivor and their learning community

During my first two years of medical school, I was surprised to not once encounter a cancer advocate or patient as part of my learning. This was surprising because patient narratives and engagement are regarded as central to medical education. Early exposure in preclinical years to cancer patients and oncology content has been shown to improve communication confidence and increase empathy towards cancer patients [6].

I am open about my stage-three colorectal cancer journey [7] and it felt natural to share my lived experience with my problem-based learning team of seven other students during first year. Learning about cancer within this context I believe benefited me and my colleagues. Their questions and knowledge allowed me to conceptualise my own experience in new ways, and helped me retain a greater amount of the material encountered during oncology cases. The prevalence of cancer and growing incidence of certain cancers in young adults means medical students will be increasingly confronted by cancer in some way during their learning. This should be embraced by medical curricula and extracurricular structures as a strategy to create more rewarding oncology learning environments that draw on lived experience within medical cohorts (when appropriate) and cancer groups in the wider community.

When in second year, I asked members of my first-year problem-based learning group to reflect on their experience of learning about cancer alongside me. At my medical school, we have traditional lectures, occasional workshops, and frequent tutorials with a problem-based learning group. Its membership remains the same for the academic year. Oncology is not taught as a block, but is weaved throughout the curriculum. There were no specific tutorials or workshops on oncology, but from time to time discussion in my tutorial group would turn to oncology and my experience and we would have involved discussions together.

An eight-item survey was distributed via SurveyMonkey to the seven other members (average age 24 years old; five females and two males) of the learning unit in April 2016 and data was anonymously collected from five respondents (two colleagues did not provide data for reasons I did not ascertain to protect anonymity). Closed questions concerned the quality of oncology teaching (for example: *Do you believe the amount of oncology education provided by the school's current curriculum is ideal?* and *Would you have liked more contact with cancer survivors last year?*) and learning about cancer alongside a cancer survivor (for example: *Was your cancer learning experience advantaged, disadvantaged or unaltered by the presence of someone in your problem-based learning group with direct lived experience with cancer?*). Two questions asked students to list the topics they believed they would be most comfortable with when entering hospital and which format for learning about oncology was the most appreciated (for example: lectures, workshops, or tutorials). Two open questions asked for opinions on the role of cancer consumers in education and any other reflections related to oncology education.

Overall, students reported that contact with a colleague living with cancer was transformative, broadened their understanding of oncology, and helped form connections between the biological and humanistic aspects of cancer (Table 1). All five respondents indicated that their cancer learning experience had been positively influenced by the presence of a cancer survivor, and four of the five respondents indicated they would have preferred more contact with cancer survivors in their first year of medicine.

This small sample is neither robust nor generalisable, but these qualitative impressions demonstrate that early exposure to cancer survivors in a medical education environment was a transformative experience for these preclinical students. Given the nature of this survey, sources of bias are numerous and include the sample size, familiarity between myself and the subjects, that the benefits are self-reported only, and that the survey was done several months after the problem-based group was dissolved. However, learning alongside me and hearing about my disease informally throughout the year created patterns of change seen in more robust assessments of oncology educational experiences discussed below.

Table 1. Responses from five members of the same problem-based learning group reflecting on their cancer education experience learning alongside a cancer survivor.

"I felt so fortunate to be studying cancer alongside someone who had lived the experience, it made the discussions incredibly real and considered in our approach. It resulted in me retaining so much more information… It was an irreplaceable learning experience."
"I enjoyed learning about the humanity aspect; that is associating the mechanistic and physiological dysregulation with the human and his/her lived experiences."
"Best way to learn about cancer survivorship and cancer management… Also, early exposure is ideal."
"I never truly understood the impact or the importance of a personal attachment to learning. How much more learning there is to be done besides the core information that you can read in a textbook. It was an incredible addition that I feel very fortunate to have been a part of."
"Having cancer advocates actively involved in the tutorial sessions, or even sharing their recorded experiences whether that be at time of diagnosis, their journey, or events after would be fascinating and having more exposure to the journey would be enlightening to medical students."

Given the benefits of early patient contact, why is contact with cancer patients not standard practice in medical schools? To address this question, this article evaluates the historical development and current status of oncology teaching more broadly.

The evolution of oncology teaching

The education of medical students must change over time in response to the changing needs of patients, society and governments. Cancer education for Australian medical students has a history of responding and adapting to external drivers of change. In 1988, Cancer Council Australia released guidelines for core competencies for medical graduates and called for compulsory oncology education in all medical schools [3]. These guidelines were reviewed and amended as the Ideal Oncology Curriculum for Medical Schools in 1999 and in 2007 by the Oncology Education Committee [3]. Over the same period, a call for a foundation oncology curriculum in Europe was made in 1989. The independent International Union Against Cancer released a paper on oncology curricula in 1994 and an Australian Government inquiry into breast cancer in 1995 concluded that medical schools should urgently develop curricula enabling students to better acquire knowledge about the diagnosis and management of cancer [3].

Medical schools have undergone significant changes in the last decade, including growth in graduate-entry medical degrees, problem-based curricula, student-directed learning, and integrated content. Despite the increasing agility of medical schools to adopt improved teaching and learning models for oncology [5,8-10], assessments of medical students' understanding of oncology have consistently found knowledge and skill deficits [5,10-16]. The curriculum is crowded, medicine grows more complex, and the volume of information available about a given topic is now unmanageable. This is on a background of a general fear of cancer that many students likely possess. The disjunction between students' knowledge of cancer and the knowledge they are expected to have remains an active and rich research space in Australia and globally.

What should medical students know about cancer?

While the diagnosis of cancer is usually confirmed by oncologists, the responsibility for facilitating screening and detection remains primarily in the domain of general practitioners (GPs). GPs also provide the majority of general health care for cancer-diagnosed patients [17]. The role of the GP in cancer care and long-term follow-up is growing due to increasing cancer incidence and survivorship, the shift towards defining cancer as a chronic disease, and proposed policy changes aimed at restoring GPs as the keystone of chronic disease management [17-19]. Although approximately half of Australian medical graduates go on to train as GPs, access to oncology training is limited outside of specialist oncologist training programs. Thus, effective oncology training during medical school is of paramount importance in establishing an appropriate skill set for internship and beyond. Further, as the numbers of cancer survivors and people living with cancer grow, cancer care and support issues will impact an increasing number of specialists outside of oncology.

The role of medical curricula is to prepare students for their first year after university as interns. However, what students *should* know by this point will differ depending on the views of various stakeholders. From a patient perspective, medical graduates need to be able to recognise and identify cancer, understand treatments, engage in discussion around the psychosocial implications of cancer, and appreciate the roles of different health professionals involved in cancer journeys. From

a senior doctor perspective, medical graduates should understand history-taking and examination, red flag symptoms, screening and diagnosis, treatment modalities and goals, chronic care needs, communication and ethics [5,20]. From a public health perspective, medical graduates should understand the principles and guidelines for cancer prevention, screening and detection, and the relationships between cancer prevalence, demography and geography [5,20]. Last but not least, medical graduates have expectations of their own cancer knowledge: they expect to know about cancer prevention, patterns of cancer prevalence, and the signs and symptoms of cancer. They also strive to effectively communicate with cancer patients, and be up-to-date on the principles of surgery, chemotherapy, immunotherapy and radiotherapy.

Trends in the cancer knowledge of medical graduates

Two major surveys of Australian medical graduates' attitudes and understanding of cancer were conducted in 1990 and 2001 [4,13]. According to these samples, students in 2001 had more exposure to palliative care and radiation oncology and better knowledge about breast cancer over other cancer types [4]. Procedural-based skills such as performing a Papanicolaou smear and analysing a pigmented skin lesion worsened, but breast examination competency and an understanding of screening guidelines for cervical cancer improved [4]. In the eleven years between surveys, the number of students who felt dissatisfied with the teaching of curable versus non-curable cancer management grew, while the number of students reporting little or no skills in discussing death with dying patients fell [4].

Overseas, a survey of medical graduates in the UK in 2005 found that only 61% of students completed a clinical attachment or special module in oncology, three-quarters would have liked more teaching on oncology, namely radiotherapy, chemotherapy and symptom management, and only 40% felt prepared to care for cancer patients [14]. Evaluation of American medical graduates found that many lacked knowledge on cancer prevention and history-taking, alongside an unpreparedness to care for cancer patients [5]. In Canada, a 2011 survey found that only half of medical schools taught oncology as a separate topic [11]. It also found that 67% of final-year students felt that oncology education was inadequate and the most poorly taught subject at medical school, a sentiment shared by curriculum committees, residents and training program managers alike [11].

How can we better teach and learn about cancer?

Medical school oncology education has suffered, and in many places continues to suffer, from neglect, fragmentation, a narrow scope, under-resourcing and inconsistency between curricula and schools [5,21]. Despite acknowledgement almost 30 years ago of the need for common oncology teaching based on shared principles and standardised learning objectives, disparity in oncology education remains the norm [21,22]. Debate persists around the role of oncologists as educators within medical schools, and how much focus there should be on oncology at medical school. The degree to which oncology should be integrated into curricula [22] or taught as blocks of content is also disputed [23]. Despite a lack of congruence amongst medical oncology teaching, methods to improve oncology teaching have emerged from medical schools around the world.

Standardisation of objectives and curricula

Guidelines for cancer education by medical schools have existed in Australia since 1999 [3]. While these are criticised for not presenting specific learning objectives according for each stage of a medical degree [5], the guidelines are an excellent summary of cancer education objectives that are both patient-centred and skills-oriented. Indeed, Australia should be proud of its national oncology education framework for medical school teaching, as this has yet to be achieved in the United Kingdom [20], Canada [11] or the United States [24].

Teaching methods and resources

Active learning techniques such as problem-based and team-based learning [9] and information technologies are now a common feature of many medical schools. A recent assessment of oncology education across 130 medical schools in the United States found widespread use of case-based learning, online resources, and virtual laboratories; lectures continued to be the dominant form of teaching in all schools [12]. This and other studies demonstrate that medical schools are modernising the methods they use to teach oncology, albeit slowly and despite the predominately online learning styles of medical students [25,26]. Whether newer teaching methods result in improved learning outcomes for medical graduates remains under-evaluated. However, examples of high-yield oncology education strategies are growing and include e-learning oncology modules [27], short clinical oncology modules [28], cancer centre-hosted research programs [8], and summer schools [21].

Use of an oncology textbook remains variable across medical schools. In a Canadian survey of the oncology learning needs of final-year medical students, 89% would have preferred a textbook or web book dedicated to oncology learning objectives [11]. A standard oncology textbook is not recommended across Australian medical schools. However, *Clinical Oncology for Medical Students*, an e-book produced by faculty representatives across Australian and New Zealand medical schools, is recommended by some institutions and accessible for all medical students to download online [29].

While most Australian medical schools have adopted the concept of learning communities [9], Brazil has expanded student-led and team-focused learning and developed a system of academic leagues with implications for oncology education [30]. The oncology leagues are designed to instil broad knowledge and foster leadership, entrepreneurialism and learning by engaging in research days, outreach, fundraising and charitable work [30].

Contact with people living with cancer

Contact with cancer patients is defined as a core clinical experience in the *Ideal Oncology Curriculum* [3]. However, in Australia, medical student exposure to cancer patients declined from 1990 to 2001 [13]. This is concerning because the need for greater engagement with cancer patients consistently emerges as a theme in surveys of medical graduates, and exposure to cancer patients and hospices is correlated with self-assessments of preparedness for internship [14]. Further, from my small sample of fellow students in my problem-based learning group, contact with me while learning about cancer was beneficial and transformative.

Exposure to patients and advocates is essential to medical school education, and this is particularly the case with oncology because of its complexity, interdisciplinary nature, chronicity and psychosocial impacts. Solid preclinical and clinical exposure to cancer patients directly assists in the acquisition of skills such as communication, and indirectly via contextualisation and personalisation of the disease [6]. While consumer engagement can be formal and didactic, other models like learning leagues provide the freedom to focus on patient-centred activities such as outreach, education and support [30]. Since many of the skills needed to understand cancer and communicate with people living with cancer are transferable to other diseases and contexts, investing in better oncology teaching would likely yield benefits across the board for our junior doctors.

Conclusion

The growth in cancer incidence, treatment complexity, and survivorship has resulted in a large amount of discussion about the cancer education of medical students. Calls for medical curricula to remain agile to the shifting needs of cancer patients and communities have echoed widespread concern about the knowledge gaps and unpreparedness of medical graduates to examine, communicate with, and manage cancer patients. Early efforts to standardise oncology learning objectives have largely been resolved in Australia, and medical curricula are slowly adopting newer teaching and learning strategies. However, the exposure of medical students to cancer patients remains unsatisfactory in medical schools in Australia and around the world. In addition, data about what medical graduates understand about cancer should be updated nationally. Building on the existing case-based approach and role of narrative in medical education by drawing upon the well-developed networks of cancer consumers is one way of enhancing the learning outcomes of medical students, but it cannot take place in isolation. Any assessment of oncology education needs to occur alongside a larger discussion about curriculum inclusion, streamlining, and factors accounting for underperforming disciplines such as oncology. For example, there does not appear to be a good rationale for, say, the emphasis on cardiovascular diseases and interventions over cancer at medical school, when heart disease and cancer are both leading causes of mortality and morbidity. Future work will need to identify and then explain differences between subject domains for true medical curriculum reform to begin.

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Conflict of interest

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Oncology teaching in Australian medical schools: opportunities for patient-centred change

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Within a poignant reflection and critical analysis of Australian medical school curricula, Bravery's article 'Oncology teaching in Australian medical schools: opportunities for patient-centred change' brings to light the growing importance of cancer education for medical trainees and the need for meaningful integration with the existing curricula.

It has been nearly a decade since the publication of the *Ideal Oncology Curriculum for Medical Students* by the Oncology Education Committee (OEC), originally as part of the Cancer Council Australia (CCA) [1]. To date, multidisciplinary members of the OEC remain active and dedicated to improving oncology education across Australia and New Zealand with advocacy, collaboration with medical schools, and development of resources such as the free e-book "*Clinical Oncology for Medical Students*" [2].

Australia has been one of the first countries internationally to present a national framework for the standard of oncology education. The CCA discontinued its affiliation with the OEC in late 2016, and the Clinical Oncology Society of Australia has not taken responsibility of the OEC. Within this changing landscape of medical education, increasing medical schools and work-force shortages, a growing proportion of paediatric and adult populations continue to be affected and at-risk of cancer. It becomes even more important for students, medical schools, clinicians and bodies such as the Australian Medical Council alike to be cognisant and proactive in promoting a high standard of oncology education in foundational years of training.

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A review of the resistance mechanisms under-lying dabrafenib/trametinib combined therapy in the treatment of BRAF mutant metastatic melanoma

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Abstract

Background: BRAF mutant metastatic melanoma treatment is most effective when it targets the changes induced within the mitogen-activated protein kinase (MAPK) cascade. However, due to the cancer's heterogeneous nature, drug resistance predictably develops within 9-10 months, reducing treatment efficacy and producing poor patient outcomes. Understanding the mechanisms behind this acquired resistance is vital in devising optimal therapeutic regimens and ultimately improving the survival rate of this widespread disease.

Methods: This review examines the different resistance mechanisms that develop in BRAF mutant metastatic melanoma to prevent the durable efficacy of combined BRAF and MEK inhibitors as a treatment method. Subsequently, it evaluates possible changes that can be made to ensure therapy is made more effective in future disease management.

Results: Currently recognised resistance mechanisms include: alterations to BRAF (commonly through gene amplification), eIF4F complex mutations, changes activating the upstream regulator N-RAS or downstream effectors MEK1/2, and non-genomic alterations. Together, these factors reactivate the MAPK cascade, despite dual MAPK inhibition, and allow the tumour to continue to grow and metastasise unimpeded by intervention.

Conclusion: The ease at which contemporary treatment is being made redundant highlights the requirement for further research into the underlying molecular aberrations, and, from this, the development of new, more effective therapies into the future.

Introduction

Despite representing only 4% of all possible skin cancers, cutaneous melanoma has shown to be the most aggressive type, contributing to approximately 80% of all skin cancer related deaths (65,000 per year) [1]. It is the most common form of cancer diagnosed in Australians aged 15-29 years, and its incidence in Caucasian populations has been increasing faster than any other malignancy over the last 30 years [2]. Five-year survival is poor for disseminated disease, from 15% to 60% in patients with either distant or local metastases respectively [1,2]. Until 2011, treatment for patients with metastatic melanoma was largely ineffective, with chemotherapy having no effect on either median progression-free or overall survival [3,4]. However, an improved understanding of the underlying molecular aberrations in melanoma tumour cells led to the development of new targeted therapies, which have fortunately shown a significant clinical effect [2,5].

The genetic analysis of melanomas has revealed the clinical importance of BRAF, a protein kinase that plays an essential role in activating the mitogen-actived protein kinase (MAPK)/extracellular signal related kinase (ERK)-signalling pathway [6]. Approximately 40-50% of all cutaneous melanomas harbour activating BRAF mutations, although this aberration is rare in mucosal melanomas and non-existent in the uveal form [7]. The mutation most commonly occurs in valine at codon 600, causing an increase in enzyme activity, which leads to angiogenesis, unchecked replication of cells and an ability to metastasise — all essential factors in tumour growth and spread [8,9]. As such, it is a vital target for drugs in reducing melanoma progression (and thus morbidity and mortality) when the diagnosis is made too late for simple excision. However, whilst treatments targeting a single aspect in the MAPK pathway were previously employed as a first-line defence, resistance to these therapies nearly invariably developed within 5-7 months of commencement [2,9-11].

Combined MAPK inhibition using both selective BRAF and allosteric MEK inhibitors as a method of circumventing these resistance mechanisms was subsequently considered, and in 2014 met the approval of the Australian Therapeutic Goods Administration for disease treatment [3,10,12]. Initial clinical trials merging the BRAF inhibitor dabrafenib with MEK inhibitor trametinib demonstrated an increased durability against drug resistance, thereby improving response rate, and enhancing progression-free and overall survival compared to single agent BRAF inhibition [7]. Following therapy initiation, 50% of patients experienced disease progression after 9-10 months, and long-term clinical outcomes were again impeded by the development of resistance [13,14].

Understanding of these resistance mechanisms is currently improving; however, complete comprehension is vital if a significant reduction in melanoma mortality rates is to be achieved [5,15]. This review aims to provide readers with a thorough understanding of the resistance mechanisms that develop to the combined therapy of dabrafenib/trametinib, and what improvements can be made to make treatment more effective in the future.

Discussion

Mechanism of action of dabrafenib/trametinib combined therapy in BRAF mutant metastatic melanoma

Normal MAPK function

The MAPK pathway (Figure 1) is a highly-conserved signalling cascade, essential for various cellular functions such as proliferation, differentiation and migration of cells [16-18]. Its activation is a complex process which ensures pathway regulation, and is often initiated via RAS (a guanosine triposphate (GTP)-hydrolysing enzyme) binding to a GTP molecule, and leading to phosphorylation and activation of the RAF kinases [2]. These in turn phosphorylate the MEK1/2 kinases, which consequently enable ERK 1 and 2 activation [6,19,20]. ERK then proceeds to phosphorylate a plethora of cytoplasmic and nuclear substrates, which subsequently mediate the pathway's pleiotropic effects. These include: cell cycle protein expression, proapoptotic and antiapoptotic regulation and function, and nuclear transcription factor activation [6,19-21].

BRAF mutation in melanomas

The RAF protein has three isoforms: ARAF, BRAF and CRAF [6,20,21]. As discussed earlier, BRAF mutations occur at the highest frequency within most cutaneous melanomas (commonly as a V600E point

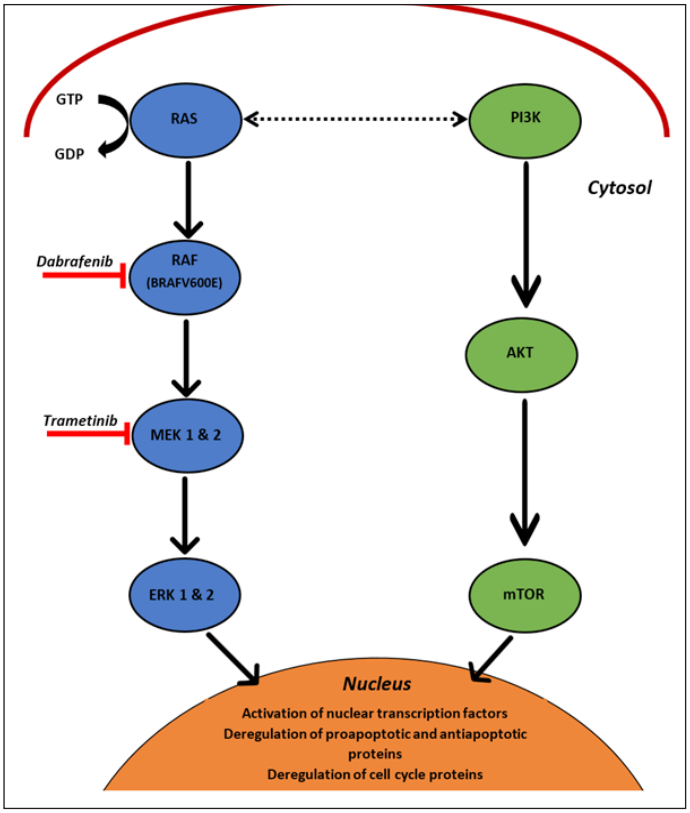

Figure 1. The effect deregulation of the MAPK signalling pathway (left) and PI3K/AKT/mTOR pathway (right) has on melanoma tumourigenesis, and the various sites of intervention that occur with dabrafenib/trametinib dual therapy [21].

mutation) and create a constitutively active BRAF molecule [23]. This subsequently leads to increased MEK and ERK function, which not only completely deregulates the cell cycle, but also increases transcription and inhibits apoptosis, thus inducing the cancer phenotype [23].

Mechanism of action of dabrafenib and trametinib

Dabrafenib is a highly potent, reversible adenosine triphosphate (ATP) competitive inhibitor that selectively inhibits the kinase domain of mutant BRAF (Figure 1) [5,20,21]. This leads to reduced proliferation through subsequent reductions in phosphorylated ERK, and thus increased expression of apoptotic proteins and G1-phase cell cycle arrest [21]. Alternatively, trametinib is an allosteric inhibitor of MEK 1 and 2 that selectively binds and stabilises the closed, inactive conformation of the MEK enzymes, thereby reducing phospho-ERK concentrations and the downstream effects it has on cell proliferation, growth and senescence (Figure 1) [18,24,25]. Ultimately, the combination of these two inhibitors significantly improved progression-free survival and response duration for metastatic melanoma patients when compared to monotherapy [12,14].

Mechanisms behind combined therapy resistance

The mechanisms involved in MAPK inhibitor resistance still largely require further investigation. However, given the nature of combination therapy and the fact it was developed to address many of the mechanisms causing acquired resistance in single target treatment, the culpable genetic aberrations are not as diverse as those seen in monotherapy [10,13,26].

There are currently several categories of mutations consistently identified as the source of MEK/ERK signalling reactivation: BRAF gene amplification, MEK1/2 mutation, and NRAS alteration [10,18,27]. There have also been a number of melanoma phenotypes recognised as possessing innate resistance, the mechanics of which are still under heavy investigation and only briefly covered within this report.

Resistance mechanism of BRAF gene amplification

BRAF copy number gains were most common, affecting 36% of all melanomas treated with combined therapy [10]. Notably, the extent of this amplification was significantly higher than seen in monotherapy resistance. Not only is this reflective of the upsurge in MAPK signalling required to overcome dual treatment, it is also indicative of increased tumour reliance on this resistance mechanism due to inhibition of other avenues [10,11,14]. Ultimately, gene amplification leads to augmented BRAF kinase concentration within the cell, drastically elevating MAPK signalling by creating an excess of activated MEK [8,14]. This has two vital consequences:

1. An increase in the basal level of phosho-ERK, and thus increased activation of nuclear transcription factors, anti-apoptotic and cell cycle regulation proteins to cause proliferation, metastasis, and apoptosis resistance in melanoma cells [21,24].

2. An increase in the IC50 (the concentration of drug required to inhibit a biological process by half) of both trametinib and dabrafenib for inhibition of ERK phosphorylation [6].

The latter point is explained by the mechanism of action of trametinib [14]. The drug has a significantly lower affinity for activated, phosphorylated MEK than it does for inactive MEK [10,14]. The presence of BRAF amplification and the resulting MEK hyperactivation induces an excess of phosphorylated MEK, with little remaining in the drug's favoured inactive conformation [10,24,25]. Overcoming this decreased affinity and adequately inhibiting MEK hence requires higher concentrations of trametinib [14]. Furthermore, because of the increased BRAF kinase concentration, therapeutic levels of dabrafenib cannot compete, and thus have an insufficient effect in inhibition [10].

Resistance mechanism of MEK1/2 mutation

Further implicated in resistance development were de novo mutations in MEK1/2, with an incidence of 26% in treatment-insensitive tumours [10,13]. The majority of MEK mutations employ a similar mechanism of action, with the alterations tending to occur within, or proximal to, a negative regulatory region of MEK: helix A/C sub structure [9,10,13,17]. The helix sits against the area of the kinase that binds both ATP and allosteric inhibitors (such as trametinib). Whilst the mutations are usually located too far from the ligand to directly interact with it, they are close enough to alter the ATP binding site in a way that allosterically increases the intrinsic kinase activity of MEK [14,27]. As a result, ERK levels can be up to 20-fold higher compared to wild type MEK, increasing proliferation and apoptotic inhibition and ultimately creating an environment conducive to tumour growth [10,14]. Furthermore, over-expression of MEK causes a greater than ten-fold decrease in sensitivity to trametinib (due to mechanisms explained above), thereby increasing the concentrations required for MAPK inhibition and abrogating the effects of dabrafenib (which acts immediately upstream), and thus conferring acquired resistance to the combination therapy [10,13,27].

Coexisting NRAS mutation development

The emergence of coexisting BRAF and NRAS de novo mutations are also a possible cause for dual therapy resistance [28]. The NRAS gene encodes for the protein N-Ras, whose primary function involves regulating cell division. Its relatively high mutation rate means it contributes to the development of 15-20% of all non-uveal melanomas, and is subsequently the second most common oncogenic stimulus for cutaneous metastatic melanomas [7,28]. In around 80% of cases, these genetic aberrations involve a gain-of-function

point mutation occurring at codon 61 of the NRAS gene, with the remaining alterations either affecting codons 12 or 13 [28]. This leads to a subsequent hyperactivation of the RAS-RAF-MAPK and P13KT-AKT cascades, thereby increasing pro-survival protein expression, cellular proliferation and cell cycle dysregulation [29]. The resulting synergistic effect of having two gain-of-function mutations within both NRAS and BRAF means a tumourigenic environment that supports metastasis quickly develops, and the efficacy of trametinib/dabrafenib therapy is limited by the need to increase their required levels above what is therapeutically appropriate [28].

eIF4F eukaryotic translation initiation complex hyperactivation

Finally, it is important to consider downstream pathways and their influence on dual therapy drug resistance. MAPK and PI3K/AKT/mTOR signalling converge to influence the eIF4F eukaryotic translation initiation complex, a molecule nexus consisting of the eIF4G scaffolding protein, the eIF4E cap-binding protein and the eIF4A ribonucleic acid (RNA) helicase [30,31]. Its normal function involves modulating specific mitochondrial RNA translation to produce a plethora of proteins that potently regulate cell growth, proliferation, migration, and survival [31]. As such, excessive stimulation of the complex can alter the proteome, and ultimately give rise to the phenotypic heterogeneity of cells essential for drug resistance development, as well as tumour progression and metastasis [31,32]. There are three main mechanisms that have been identified in producing this augmented state, the first of which involves MAPK signalling reactivation through mechanisms described earlier [30]. Persistent phosphorylation of 4EBP1 (a protein that normally inhibits eIF4E binding) to permit increased translation initiation can also instigate hyperactivity, as can increased degradation of eIF4G through raised levels of pro-apoptotic BMF [30]. Ultimately, it is unsurprising that the enhanced formation and activation of the eIF4F complex has been associated with dual therapy resistance in BRAF mutant metastatic melanoma, due to its propensity to produce the intratumoural heterogeneity that helps enable drug resistance development [30-32].

Non-genomic resistance mechanisms

However, clinically acquired resistance to MAPK inhibition therapies cannot be fully explained through acquired genomic mechanisms, given that up to 10-20% of BRAF mutant metastatic melanoma patients never achieve a meaningful treatment response [7,27,33]. Rather, divergent transcriptional profiles exist between drug responsive cell lines and those which are intrinsically resistant, indicating that certain transcription factors are innately present which can modulate melanoma response to MAPK inhibitors [7,29,33].

Differing tumour cell phenotypes and MITF

The significance of the microphthalmia-associated transcription factor (MITF) and its expression levels in treatment outcomes was one such identified transcription factor [34-36]. MITF plays a key role in the survival and differentiation of melanocytes by regulating the expression of a variety of crucial melanogenic genes [35]. Whilst the majority of drug sensitive cells show high levels of MITF, both its expression and function were notably reduced within resistance lines. These cells instead tended to display elevated Nuclear Factor-κB (NF-κB) transcriptional activity, which in itself promotes melanoma progression and metastasis through pro-survival signalling [35,36]. The synergistic effect of these phenotype factors creates a global transcriptional state that induces intrinsic indifference to intervention throughout all three levels of the RAF/MEK/ERK cascade. This was evidenced by the fact that, subsequent to dabrafenib/trametinib therapy, progression-free survival of MITF-low/NF-κB-high melanomas was significantly shorter than the MITF-high/NF-κB-low group (median 5.0 months versus 14.5 months respectively) [35,36]. It should be noted however, that although this transcriptional state is certainly associated with innate resistance, it can also be induced through MAPK hyperactivation, NF-κB induction and MITF dysregulation, thus becoming a mechanism of acquired resistance [36]. Ultimately, this transcriptional class distinction between BRAF mutant metastatic melanomas will aid future efforts in predicting treatment outcome and subsequently developing new therapeutic approaches for those patients unresponsive to RAF/MEK inhibition.

Further transcriptional alterations

There are a plethora of other transcriptional alterations that develop in treatment resistant tumours, frequently as the result of differential methylation of tumour cell-intrinsic cytosine-phosphate-guanine sites [7,28,37]. However, only the most recurrent molecular aberrations will be discussed within this article: *c-MET* up expression, infra-physiologic *LEF1* down expression, and *YAPI* signature enrichment [7,28]. Of the three, up expression of *c-MET* not only remains the most consistently altered gene throughout treatment resistant melanomas, its degree of expression also greatly predicts patient outcomes via the mediation of MAPK-redundant survival signalling [37]. It is a receptor tyrosine kinase that reacts with its hepatocyte growth factor (HGF) ligand and stimulates an array of signalling pathways, ranging from proliferation to migration and invasion through activation of RAS and PI3K [37]. Evidently, its resultant hyperactivation of these path-ways ensures the level of BRAF and MEK inhibitors required to adequately control such a situation are too high to be within safe administration limits, thereby ensuring that melanoma cells carrying this mutation never respond to dual therapy [7,28].

Recurrent β-catenin-LEF1 down regulation has also shown to promote dual therapy in-sensitivity as its normally pro-apoptotic induction to MAPK inhibition is subsequently decreased [7]. Whilst this feature is essential for survival of metastatic cells, primary benign melanoma cells do not depend on this signalling cascade for survival. YAP1, a pro-survival factor that alters cell function through post transitional regulation, was also noticed to be harboured in increased quantities within MAPK inhibitor resistant tumours [7]. Given the history of known interactions between these two pathways in other biological contexts, simultaneous deregulation of both β-catenin-LEF1 and YAP1 signal-ling is common, thereby resulting in an increased apoptotic threshold within melanomic cells, and thus reduced sensitivity to dual MAPK inhibition [7,28]. Given that the high-lighted transcriptional mutations are only a few of many in inducing therapy resistance, it is evident that current genomic diversity is severely limiting the long-term efficacy of dual medication.

Potential mechanisms to overcome acquired resistance in dabrafenib/trametinib combined therapy

Further MAPK pathway inhibition

MAPK-independent mechanisms of resistance were not conferred at a higher frequency in combined therapy compared to single-agent BRAF inhibitors [4,10,13]. This insinuates that BRAF mutant metastatic melanomas remain highly dependent on MEK/ERK signalling for tumour growth and survival, highlighting a potential avenue to increase combined treatment durability in the future and thus improve patient outcomes [10,14]. To elaborate, if other aspects of the pathway can be targeted along with BRAF and MEK inhibition, and thus the potency of MAPK inhibition further increased, it may help circumvent the acquired resistance mechanisms which otherwise increase the concentration of activated MEK to levels dabrafenib/trametinib can no longer inhibit [10,12,13]. Example therapies include those targeting ERK through inhibition [4,26,27]. A preclinical study investigating this phenomenon found that BRAF/MEK/ERK inhibitor combinations not only delayed the emergence of acquired resistance, but they could

also be used to overcome it in desensitised BRAF mutant tumours [27]. Whilst the exact reason for this is not yet clear, it is hypothesised that the ATP-competitive ERK inhibitors are less sensitive to altered conformation dynamics of activated ERK in the context of up-stream oncogene amplification, and thus remain effective in inhibiting its downstream tumourigenic effects on the cell [27]. Evidently, further refined investigation is needed into the area before more conclusive implications can be drawn, but current results allude to a hopeful future for a disease with such a poor survival rate.

Dual pathway inhibition

Furthermore, new studies have recently been released examining dual pathway inhibition [29,33]. The PI3K/AKT/mTOR pathway is an important cascade involved in signalling cellular growth, metabolism and translation initiation (Figure 1). Along with MAPK, it is one of the most commonly altered signalling pathways in solid malignancy [33]. In melanoma cells, PI3K/AKT/mTOR has been shown to interact extensively with the MAPK pathway and potentially lead to its activation via phosphoionsitide 3-kinase (PI3K)-RAS interaction [29]. Whilst alone it is not sufficient to completely confer resistance to combined therapy, PI3K has shown to contribute to earlier resistance development by modulating tumour responses to MAPK inhibitors [26,28]. Current evidence suggests that PI3K/mTOR pathway inhibition via ATP – and, to a lesser extent, non-ATP competitive inhibitors – can have a modest impact on both primary melanoma tumours and metastasis, diminishing the growth and proliferation of cells [29]. Therefore, the efficacy of PI3K and MAPK is being trialled in the hope it will ultimately improve patient outcomes [26,27]. Dual PI3K and MEK inhibition, the most common combination under-going investigation, currently results in only modest success and a number of relatively frequent adverse effects that include diarrhoea, nausea, pyrexia, rash and fatigue. However, this does not discount the feasibility of this dual pathway approach, but merely highlights the requirement for further investigation to improve tolerability [29]. This involves discerning the most optimal dosing schedule, perhaps targeting other members of the P13K/AKT/mTOR pathway, or augmenting patients with predictive factors [29].

Furthermore, the eIF4F complex (discussed earlier) sits at the junction of multiple oncogenic pathways and plays an essential role in producing the intratumoural heterogeneity that ultimately assists drug resistance development [32]. As such, its combined inhibition with the MAPK pathway may provide a formidable effect in improving treatment efficacy [30]. There is currently work being done to target all three components of the complex, including: blocking eIF4E-cap interaction, interfering with eIF4E-eIF4G interaction, inhibiting eIF4A helicase activity, and suppressing eIF4E levels — all with varying degrees of success [31,32]. For example, eIF4A inhibitions (such as silvestrol) have a more potent effect compared to eIF4E in reducing global protein synthesis and thus the capability of tumour cells in developing treatment resistance, largely because cellular translation requires persistently high eIF4A concentrations, but not eIF4E, to be maintained [30,31]. Whilst silvestrol appears an advantageous agent to combine with MAPK inhibitors, it too is vulnerable to drug resistance due to overexpression of ABCB1/P-glycoprotein, thereby hampering its use in *in vivo* studies [30]. Ultimately, the introduction of eIF4F complex and MAPK doublet inhibitors as a possible treatment avenue is only a recent occurrence, and significantly more research is required before any definite conclusion can be established [31]. However, it theoretically can provide a potent influence in the seemingly insurmountable barrier of resistance in metastatic melanoma treatment, and thus provides hope for future patient outcomes [30].

Incorporation of immunomodulation in treatment

The potential of immunotherapy in treatment of metastatic melanoma has also been recognised. Metastatic melanoma patients commonly display tumour-mediated immune suppression and, in the past, treatment with immunomodulatory therapies such as interferon alpha and high dose interleukin-2 has shown positive results [38]. With greater understanding of the immune system and its interaction with tumour cells, further interventional therapies have now been developed with varying degrees of efficacy. These include monoclonal antibodies that inhibit essential immune checkpoints, such as ipilimumab (an anti-cytotoxic T-lymphocyte-associated protein 4 inhibitor) and pembrolizumab (an anti-programmed cell death 1 inhibitor), as well as other methods involving adoptive cell transfer [38]. Whilst it is hoped that a combination between these immunomodulatory therapies with MAPK inhibition will improve clinical outcomes in metastatic melanoma patients, the toxic effects of such combinations currently remain unpredictable [38]. This only indicates the need for further, careful study into the dosing and timing of these dual treatments, as their potent anti-tumour activity and synergistic properties have high potential for improving patient outcomes.

Conclusion

Melanoma remains one of three cancers with an increasing mortality rate, despite extensive clinical investigation and the recent introduction of various novel and specific drugs into its treatment regimen [12]. This is primarily because long-term efficacy of these pharmaceuticals has been limited by the emergence of resistance in targeted cancer cells [3,5,6]. Given that the presence of BRAF mutations in metastatic melanoma has been associated with reduced survival in the absence of specific treatment, it is essential that these mechanisms are overcome to increase drug durability and thus improve patient outcomes [11]. It has been found that dabrafenib/trametinib associated resistance was primarily the result of BRAF gene amplification, MEK1/2 changes, the development of co-existing NRAS mutations, and eIF4F complex hyperactivation, as well as non-genomic alterations [10,13,14]. Together, they abrogate the effects of both drugs and cause resistance within 9-10 months of treatment commencement [21]. Possible solutions to overcome this include further inhibition of kinases downstream of RAF and MEK in the MAPK cascade such as ERK, as well as targeted inhibition of the heavily associated PI3K/ATK/mTOR cascade or eIF4F complex [10,26,28]. Incorporating immunomodulatory therapies into current regimes is also a major point of consideration [36]. Ultimately, full comprehension of the factors influencing combination therapy resistance is fundamental, for only with understanding can solutions be developed, and the currently pitiable patient outcomes for BRAF mutant metastatic melanoma be improved.

As medical students enter the workforce, combination therapies will likely be the forefront of metastatic melanoma treatment and only the beginning of the trend towards mutation-specific cancer management. As such, is it essential to have not only a strong understanding of the basic pathways affected by these cancers, but the clinical relevance the short-term efficacy of these drugs have for patients. This need to be informed is only further augmented by the increasingly high incidence of melanoma in Australia.

Limitations of review

The major limitation of this literature review relates to the contemporary nature of the topic. With primary journal and review articles assessing the efficacy of dabrafenib/ trametinib still being released, investigations into the resistance mechanisms behind these results, and methods

to overcome them, have only recently commenced. Consequently, there were a restricted number of articles available to examine which may affect the validity of conclusions within this review when further information is made available. Furthermore, the sample sizes within the available primary journal articles were small [10]. Whilst the overlap in implicated mutations and possible solutions suggests valid results, it is possible that further vital mechanisms were missed because of the small sample size. Finally, it should be noted that whilst this review only focuses on dabrafenib/trametinib dual therapy, in actuality there are three BRAF/MEK doublets that have shown clinical benefit (dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib) [39].

Conflict of interest

None declared.

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Sickle cell disease and hydroxyurea treatment

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Abstract

Introduction: Sickle cell disease (SCD) is a genetic disorder impacting the patient's haemoglobin. This condition is accompanied by many dangerous phenotypes, which are the result of pathological haemoglobin polymerisation within the red blood cell (RBC). The primary aim of this piece is to review the accepted literature on the SCD pathophysiology and its pharmacological treatment option, hydroxyurea.

Summary: Hydroxyurea has multiple posited mechanisms of action but, most importantly, it is the only SCD treatment that targets the underlying pathology. It was found that hydroxyurea significantly decreases the frequency of hospitalisations, vaso-occlusive events and blood transfusions required. In summary, SCD is a complex hereditary disorder which, for a medical practitioner to effectively manage, requires a comprehensive understanding of both normal haemoglobin physiology and its pathophysiology.

Introduction

Sickle cell disease (SCD) is a common monogenic autosomal recessive disorder of haemoglobin, occurring in approximately 1-2% of Europeans and Americans of African descent and having a prevalence of 4% or higher in West Africa [1]. The primary role of haemoglobin is the transport of oxygen from highly oxygenated areas, such as the lungs, to the comparatively poorly oxygenated tissues. However, in SCD, low oxygen conditions result in the polymerisation of the pathological haemoglobin which, downstream, leads to the SCD signs and symptoms, including vaso-occlusive events, chronic haemolytic anaemia, organ dysfunction, and increased infections.

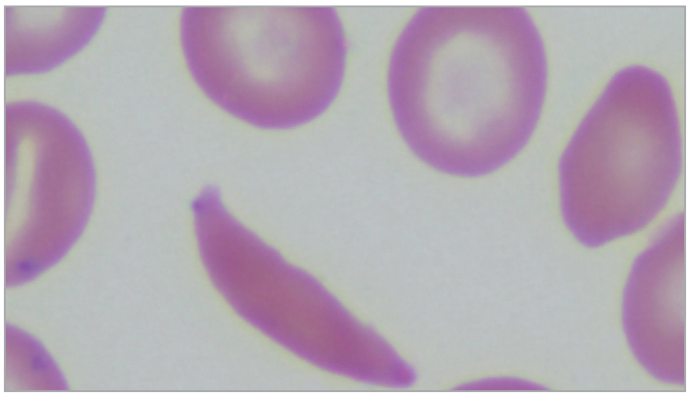
To extensively investigate SCD, this review will first address normal RBC physiology, the SCD pathophysiological models, and, finally, a treatment option for the condition. Regarding SCD treatment, this review will examine the pharmacological use of hydroxyurea, an antineoplastic agent. Finally, this topic is relevant and of considerable importance as it frequently leads to patient hospitalisations, life-threatening characteristics and significant global prevalence.

Materials and Methods

A comprehensive review of literature was conducted using the computerised search databases, PubMed and Ovid MEDLINE. The obtained articles were then filtered and case reports and articles written in languages other than English were excluded. The review was conducted during September of 2016, with the most recent literature used where appropriate.

Normal physiology

The primary function of the RBC is O2 delivery from the lungs to the body's tissues, mainly to allow oxidative phosphorylation in the mitochondria [2]. Within the RBC, it is the chromo-protein haemoglobin that allows for the loading and unloading of O2. Haemoglobin contains four globin chains, with a corresponding haem molecule for which each has the ability to reversibly bind oxygen [3]. As haemoglobin



binds O2 to its haem groups, its affinity for oxygen increases due to the alteration of the haemoglobin molecular structure. However, haemoglobin has more functions, those being: CO2 transport to the lungs from tissues as carbaminohaemoglobin, buffering of H+ via the carbamoyl anhydrase reaction within the RBC, and nitric oxide (NO) metabolism [3,4].

There are two types of adult haemoglobin, those being the major haemoglobin HbA and minor haemoglobin HbA2, comprising of two α-globin and two β-globin chains and two α-globin and two δ-chains, respectively [3]. These differing globin chains make HbA2 a considerably poorer oxygen carrier. Each of the α-chains are made of 141 amino acids, and β-chains of 146 amino acids. Chromosome 16 contains the genes for the α-chain and chromosome 11 has those for the β-chain [3].

The other type of haemoglobin is foetal haemoglobin (HbF) and is clinically and therapeutically significant in SCD, as discussed below. Structurally, HbF comprises of two α-globin and two γ-globin chains. Studies have shown that after 6 months, HbF begins to disappear from infant RBCs, however, the signalling mechanism of this is not known [5,6].

Pathophysiology

SCD is defined by the presence of sickle haemoglobin (HbS) in the RBCs, which causes the distinctive sickle RBC shape. SCD is an inherited disease done so in an autosomal recessive fashion. The carriers for the disease are heterozygous for the mutation and are said to have the sickle cell trait [7]. Patients that are disease compound heterozygous or homozygous have SCD and will exhibit some level of symptoms. In the U.S., the common SCD genotypes include: sickle cell anaemia (HbSS), HbS/β° thalassaemia, and HbS/β+ thalassaemia [7]. There are, however, many more compound heterozygous sickle cell genotypes, though most are rare.

HbS occurs due to a single nucleotide β-globin gene mutation, causing the 6th amino acid to be changed from glutamic acid to valine [8]. The mutation results in the binding of β1 and β2 chains of two deoxygenated HbS tetramers. This crystallisation process continues within the RBC, growing until the flexibility and structure is disturbed. Disease severity is dependent upon the degree of HbS polymerisation, which relies on

the degree of haemoglobin deoxygenation and the concentration of intracellular HbS. For HbS, this deoxygenation results in the exposure of the mutated valine residue on the molecule surface, causing hydrophobic interactions with surrounding chains. The consequently formed polymers develop into bundles, causing RBC distortion into its distinguishing sickle appearance. This reduces flexibility which impairs the flow of sickled RBCs through narrow vasculature.

The signs and symptoms of SCD can be understood via the three mechanisms: vascular occlusion, haemolytic anaemia and increased infection tendency (Figure 1).

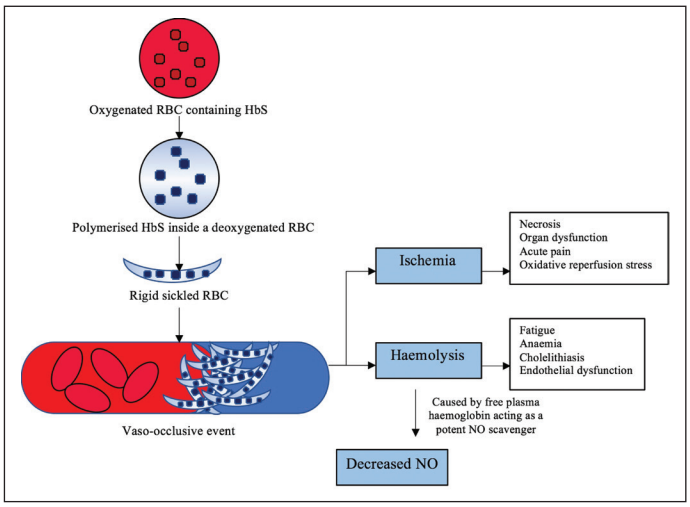


Figure 1. Sickle cell disease pathophysiology. *The pathophysiological effects of sickled haemoglobin (HbS) polymerisation can be seen, being; vaso-occlusion, ischemia, haemolysis and decreased nitric oxide (NO) bioavailability. HbS polymerisation develops following RBC deoxygenation which consequently gives the RBC the characteristic sickle shape. Vaso-occlusion is the effect of interactions between the rigid sickled RBCs and the endothelial surface, causing downstream necrosis, organ dysfunction, acute pain and oxidative reperfusion stress. Haemolysis results in the release of haemoglobin into the plasma which removes bioavailable NO.*

Vaso-occlusion most frequently occurs in the bones – but can occur anywhere – and is the result of sickled cells blocking blood vessels. The physiological requirement for haemoglobin deoxygenation at the tissues precipitates the formation of the pathological sickled RBC shape, resulting in venous blockage. Subsequent systemic disturbances and pain can be felt downstream from the blockage, and are caused by ischaemia, necrosis and organ dysfunction. Fat embolisms can occur secondary to a bone marrow infarct which can exacerbate the vascular occlusion, especially if affecting the respiratory or neurological systems [9].

Initially, it was thought that only the less soluble deoxygenated polymerised HbS caused the sickled RBCs to be ridge and dense, resulting in vaso-occlusion [10,11]. However, the process is multifaceted and dynamic, incorporating stimulatory interactions of the vascular endothelium to increase numerous adhesion molecules, such as integrin. This produces an inflammatory response, RBC and leukocyte adhesion to vessel walls, as well as tissue damage predisposing the patient to vaso-occlusion [12-14]. Such vaso-occlusion causes interrupted blood flow, oxidative reperfusion stress, thrombus formation, stroke and, potentially, severe ischemia [15-18]. The latter mentioned endothelial dysfunction, which occurs due to decreased NO levels causing vasoconstriction, also contributes to this dangerous vaso-occlusive state [19].

Haemolytic anaemia is another marked pathology in sickle-cell disease, which too is promoted by HbS polymerisation. It is accepted that such haemolysis results in fatigue, anaemia and cholelithiasis, and now is also being linked to the advancement of progressive vasculopathy. As patients with SCD age, their vasculopathy risk increases, primarily distinguished by pulmonary and systemic hypertension, as well as vascular intimal and smooth muscle proliferative modifications [20-22]. Clinically, the severity of intravascular haemolysis in SCD patients is determined by measuring the serum levels of lactate dehydrogenase [23].

Epidemiological studies have proposed a positive correlation to both low levels of non-polymerised haemoglobin and significant intravascular haemolysis with increased rates of the SCD manifestations, some of which include; cholelithiasis, cutaneous leg ulceration, priapism and pulmonary hypertension [24,25]. Furthermore, two prospective cohort studies have reported a relationship between pulmonary hypertension and haemolytic anaemia severity [24,26].

One pathophysiological basis for pulmonary hypertension in SCD is through the effect of haemolysed cells on NO and arginase. NO regulates vasodilation via the stimulation of cGMP dependent protein kinases, decreases platelet aggregation and inhibits the release of endothelin-1, a powerful vasoconstrictor [27,28]. RBC haemolysis causes haemoglobin and the arginase enzyme to enter plasma circulation. This free haemoglobin is a potent NO scavenger, hence acting to impede the vaso-protective qualities of NO. Additionally, arginase catabolises arginine which is required for NO synthesis, hence perpetuating the decreased NO bioavailability [29]. Downstream arginase metabolites further increases vascular proliferation, inflammatory stress, and overall endothelial dysfunction [30]. These homeostatic changes will produce pulmonary vascular endothelial remodelling and constriction, hence resulting in pulmonary hypertension.

Another danger to SCD patients is their increased susceptibility to many encapsulated bacterial infections, which is a major cause of mortality and morbidity [31,32]. The primary factors allowing this predisposition to encapsulated bacteria are: post-infarct hypo- or asplenia, abnormal opsonin phagocytosis due to potential defects in the alternative complement pathway, and deficiencies of particular circulating antibodies [33]. Common SCD infections are from *Haemophilus influenza*, non-typhi *Salmonella*, and *Streptococcus pneumoniae* [31,34,35]. The polysaccharide capsule of these bacteria acts to prevent the binding of complement or inhibits complement communication with macrophage receptors [36].

Treatment

As previously described, the underlying mechanism in SCD pathology is the polymerising of deoxygenated HbS, all stemming from the single nucleotide mutation of the β-globin gene.

Numerous management and treatment options are described in medical literature such as RBC exchange transfusions, however, hydroxyurea – an antineoplastic agent – is the only approved pharmacological intervention that treats the underlying SCD pathology and will be discussed at length for the remainder of this paper [37]. Hydroxyurea was approved for therapeutic use in 1998 by the US Food and Drug Administration in SCD patients suffering from frequent painful crises [38]. Despite much evidence supporting the clinical efficacy for SCD hydroxyurea treatment, its HbF induction mechanism of action continues to be largely unknown [39].

Hydroxyurea is a short-acting cytotoxic ribonucleotide reductase inhibitor which acts to arrest S-phase cells by impairing their DNA replication [40]. It may therefore enhance HbF production indirectly, by killing rapidly proliferating late erythroid cells [41,42]. The recurrent

pharmacological injury to the erythropoietic marrow from repeated drug administration results in enhanced erythropoiesis. This increases primitive erythroid precursor recruitment, consequently raising HbF levels [43]. Most of the beneficial effects of hydroxyurea are attributed to the HbF induction, however, clinical improvement has been observed before a marked increase in circulating HbF, which has led to the postulation of additional mechanisms of action including decreased intercellular adhesion enhancing blood flow and increased NO bioavailability. Hydroxyurea metabolism is the cause of this increase in NO levels [41].

It has been known for some time that the primary effect of hydroxyurea, increased HbF levels, can ameliorate SCD [8]. This works by its reduction of RBC sickling because HbF replaces the mutated β-globin with a γ-globin chain which is non-pathological, hence decreasing the number of vaso-occlusive events and infarction. Even if an infarct occurs, the decreased circulating neutrophils from hydroxyurea administration may regulate the degree of tissue damage and pain felt [44]. There is also evidence that hydroxyurea generates NO and increased cGMP levels which causes the induction of foetal γ-globin mRNA and HbF protein [45].

Hydroxyurea has been shown to downregulate the expression of specific adhesion molecules on vascular endothelium [46]. This phenomenon is evidently independent of any of the SCD β-globin gene effects. Considering the importance that exposure to hypoxic capillary bed venules has on sickling, and consequently vaso-occlusive events, any reduction in endothelial-sickled RBC adhesion would have salutary effects.

Pregnancy is contraindicated with the use of hydroxyurea because it is known to have mutagenic, carcinogenic and teratogenic effects in animals [47]. However, this relationship was not observed in 94 pregnancy outcomes of the human SCD patients that participated in hydroxyurea drug trials that, despite precautions, became pregnant mid-trial [47]. This suggests the foetal exposure to therapeutic hydroxyurea may not be teratogenic. Conversely, another study indicated abnormal sperm parameters in males taking hydroxyurea that possibly could have teratogenic effects or cause infertility [48]. It is important to note, however, that most individuals in this study had abnormal sperm prior to commencing hydroxyurea treatment, thus it was difficult to establish the precise contribution of hydroxyurea. Therefore, considerably more research and follow up time should be allocated to pregnant SCD subjects exposed to hydroxyurea to determine definitive results.

At present, there have only been 5 randomised control trials conducted regarding the efficacy of hydroxyurea treatment in patients with sickle cell anaemia. Of these, all except the Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial indicated benefit for hydroxyurea treatment over the standard of care [49-53]. Study sizes range between 44 and 299 participants. The results from these studies described reduced vaso-occlusive crises, pulmonary pathologies, and blood transfusion frequencies in those receiving hydroxyurea treatment (Table 1) [49,50,52,53].

The Belgian paediatric randomised control trial showed that hydroxyurea treatment resulted in statistically significant increases in levels of HbF and decreased both hospitalisations and vaso-occlusive events when compared to the placebo [49]. Wang and associates found that, although changes in renal and splenic function were insignificant, there were statistically relevant decreases in vaso-occlusive events, hospitalisations and the number of blood transfusions required [52]. A small Indian based study also reported that children treated with hydroxyurea experienced decreased numbers of vaso-occlusive events, hospitalisations and blood transfusions required, despite the low doses of drug administered [50]. The findings from the Multicentre Study of Hydroxyurea, conducted by Charache et al [53], too demonstrated decreased incidents of vaso-occlusion, hospitalisations and required transfusions compared to the placebo. However, in Charache et al [53], results were compromised by the substantial loss to follow up, with only 134 of the initial 299 participants completing the full 2-year trial.

At present, no phase 3 randomised control trials are enrolling individuals with different genotypes to HbSS and HbS/β° thalassaemia [38]. However, two cohort studies from Italy and Greece have shown that hydroxyurea efficacy observed in HbSS individuals also extends to those with HbS/β+ thalassaemia [54,55]. However, this hydroxyurea recommendation is weak due to the limited sample population when likened to the size of HbSS data.

Table 1. SCD hydroxyurea randomised control trials.

Author	Patient eligibility	Treatment intervention	Treatment outcome
Ferster et al [49]	SCA, >3 VOC/y	2 groups: HU then placebo, placebo then HU HU: daily 20 mg/kg, some patients escalated to 25 mg/kg.	HU therapy increased HbF levels 15% (p< 0.001). Decreased VOC. HU Patients avoided hospitalisation vs placebo (73% v 14%) (p= 0.0016)
Jain et al [50]	SCA, >3 transfusions or hospitalisation/y	HU vs placebo HU: fixed daily 10 mg/kg	HU increased HbF levels (p< 0.001). 95.0%, 94.6, 93.1% VOC, blood transfusion, hospitalisations, respectively (p< 0.001)
Ware et al [51] (SWiTCH trial)	SCA	HU and phlebotomy vs transfusion and chelation HU: daily 20 mg/kg, some patients escalated to MTD	HU rate of stroke increased but within non-inferiority margin. HbF levels increased 17.9% (p< 0.001)
Wang et al [52]	SCA, 9-18 mo old	HU vs placebo HU: daily 20 mg/kg	Decreased VOC (p< 0.002). Decreased hospitalisations (p< 0.05). Decreased transfusions (p< 0.03). No renal and splenic function change (p> 0.05)
Charache et al [53]	SCA, 18+y old, ≥3 VOC/y	HU vs placebo HU: daily 15 mg/kg which is increased to MTD	Decreased VOC (p< 0.001). Decreased hospitalisations (p< 0.001). Decreased transfusions (p= 0.001)

Abbreviations: HU = hydroxyurea, y = year, SCA = sickle cell anaemia, VOC = vaso-occlusive crisis, ACS = acute chest syndrome, Hx = history, mo = months, MTD = maximum tolerated dose.

Conclusion

To conclude, this literature review has discussed the normal physiology of haemoglobin, pathogenesis of sickle cell disease as well as its course of treatment. It was found this haemoglobinopathy is responsible for vaso-occlusive crises, pulmonary pathologies and increased susceptibility to infection. Nonetheless, hydroxyurea was reviewed as a potential treatment option. Hydroxyurea has multiple posited mechanisms of action but, more importantly, is the only SCD treatment that targets the underlying pathology. There is opportunity for future research into both the exact hydroxyurea mechanism of action in SCD patients and hydroxyurea efficacy and dangers when used to treat SCD patients expressing one of the rare genotypes. Thus, to summarise, SCD is a complex hereditary disorder which, for a medical practitioner to effectively manage, requires a comprehensive understanding of both normal haemoglobin physiology and its pathophysiology.

Conflict of interest

None declared.

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Novel neuroprotective pathways of remote ischaemic post-conditioning in models of cerebral ischemia reperfusion injury

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Domenico has a keen interest in research around vascular surgery, stroke and peripheral arterial disease. This article incorporates components of these three topics.

Abstract

Introduction: This article aims to provide a narrative review of the most recent primary literature on the pathways associated with the neuroprotective effects of remote ischaemic post-conditioning (RIPC) in stroke and discuss the prospect for application in the clinical setting.

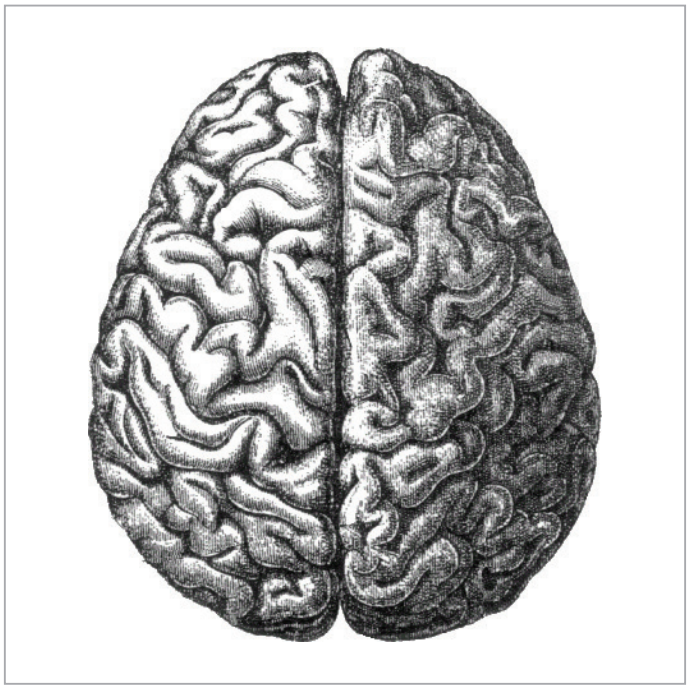
Summary: This narrative review identified multiple pre-clinical in-vivo studies. These studies found that RIPC modulates a wide variety of pathways within the brain, including those associated with inflammation, reactive oxygen species (ROS) production, antioxidant regulation and oedema development. Modulation of these pathways was associated with a significant reduction in the neuronal damage, a finding supported by measured reductions in cerebral infarct volume and apoptotic neuronal populations. Clinical research was limited; only one trial on RIPC in stroke was discovered. Whilst the results were positive, the small sample size of the study does not make them definitive.

RIPC as an intervention for ischaemia reperfusion injury (IRI) in stroke has been found to be considerably effective in animal models, stimulating a wide variety of neuroprotective pathways. The limited clinical research has not yet been able to confirm RIPC efficacy in human stroke models but should be a catalyst for further research.

Introduction

Cerebrovascular disease constitutes the third greatest cause of mortality in the Australian population, with 23 people dying from a stroke every day [1]. Ischaemic stroke occurs when an artery, supplying a particular area of the brain, is blocked by an embolus, starving neuronal tissue of oxygen and resulting in permanent damage of the local area [2]. Treatment for ischaemic stroke usually involves thrombolysis which dissolves the embolus and restores blood supply to the ischaemic area [1]. Although reperfusion is a critical intervention, it is also associated with a spike in neuronal cell damage, in a phenomena known as ischaemia reperfusion injury (IRI) [2,3]. In recent years, considerable effort has gone into developing ways to limit the impact of IRI. One promising therapy is remote ischaemic conditioning (RIC) [4].

The principle of RIC is to expose the brain to a series of sub-lethal cycles of ischaemia and reperfusion through intermittent vascular occlusion of another distant and accessible organ such as the upper or lower limb [5]. Transient ischaemia performed in this manner is known to activate several endogenous neuroprotective pathways which reduce the damage associated with an IRI [5,6]. RIC can be performed before the onset of ischaemia ("pre-conditioning"), during the ischaemic event ("per-conditioning"), and after reperfusion ("post-conditioning") [5]. By their very nature, both pre- and per-conditioning require pre-emptive action which is simply not practical in the health care setting. As such, this review focuses on remote ischaemic post-conditioning (RIPC) performed on the femoral artery in the time immediately following a stroke [7]. This review will explore and integrate the pre-clinical literature surrounding the neuroprotective pathways of RIPC and, thus, produce a narrative on how this novel intervention acts on a molecular level and how it may translate to clinical medicine.



Ischaemia reperfusion injury

IRI is a multi-faceted process in which reperfusion is associated with cellular death rather than the restoration of normal function. This abnormal response is a consequence of the ischaemia induced dysregulation of cellular function [8]. One such example is the dysfunction of the Na+/K+ ATPase which triggers the accumulation of intracellular sodium. Sodium accumulation is an initiator for a series of events including calcium overload, excitotoxicity, acidosis, cellular swelling, and the initiation of apoptosis [4].

Another event which occurs during prolonged ischaemia is damage and dysregulation of the mitochondrial electron transport chain (ETC). Once a cell undergoes reperfusion, the ETC will again utilise oxygen to try to produce ATP. However, due to extensive damage, a high proportion of this oxygen will instead be metabolised to form reactive oxygen species (ROS) [9]. The excessive ROS production overwhelms the brain's anti-oxidant system, resulting in lipid peroxidation, dysregulation of proteins, DNA damage, and alterations in transcription [8].

Ischaemia also has the effect of priming the endothelium for leukocyte recruitment through increasing adhesion molecules and the transcription of pro-inflammatory factors, such as NFκB. Upon reperfusion, these adaptations will stimulate the recruitment of neutrophils to the ischaemic area, where they will release ROS and further exacerbate oxidative damage and cell death [10].

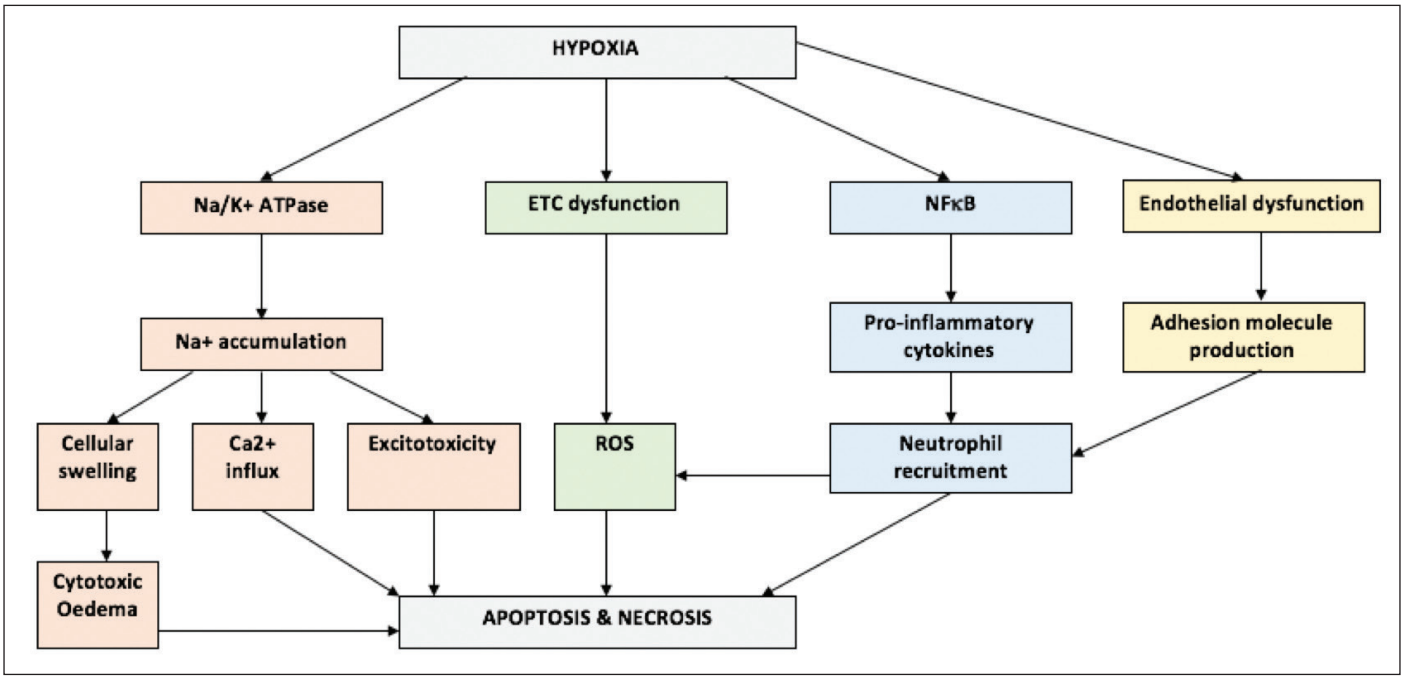


Figure 1. Basic inflammatory pathways resulting in apoptosis and necrosis of neuronal tissue in IRI *[2-8]. ETC, Electron transport chain; ROS, Reactive oxygen species; NFκB, Nuclear factor κB.*

Collectively, these effects of cellular dysfunction, ROS production and inflammation result in the death and destruction of neurons even after blood supply has been restored (Figure 1). Whilst little can be done about the tissue destroyed by the initial ischaemic event, a reduction in IRI may have the potential to prevent the death of otherwise salvageable neurons [2,3].

Discussion

HIF1 α/TIM3 axis in the initiation of inflammation

Inflammation is a key contributor to the damage associated with IRI, with the recruitment of leukocytes responsible for the substantial production of ROS and cytokines [10]. The inflammatory response of cerebral IRI is thought to be mediated in part by Hypoxia Inducible Factor 1α (HIF1α), which is activated and up-regulated during and after cerebral ischaemia [11]. Zong et al [11] investigated the effects of RIPC on HIF1α, discovering that RIPC significantly reduced the expression of HIF1α when compared to the control group one day post reperfusion.

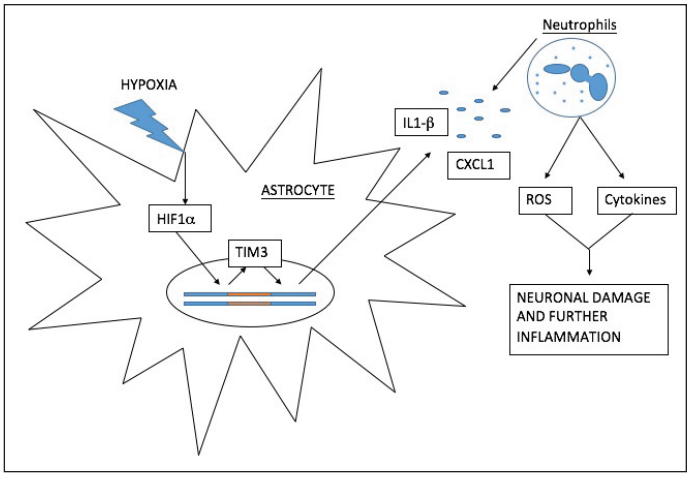


Figure 2. Activation of the HIF1α/TIM3 axis producing inflammatory cytokines and neutrophil recruitment *[11-13]. HIF1α, Hypoxia inducible factor 1α; TIM3, T-cell immunoglobulin and mucin domain protein 3; IL1-β, Interleukin 1β; CXCL1, Chemokine CXC ligand 1; ROS, Reactive oxygen species.*

These results correlated with a 10.3% reduction in cerebral infarct volume [11], suggesting that HIF1α is an important target in the neuro-protective effects of RIPC [11,12].

The mechanism in which HIF1α mediates its downstream effects is still a topic of some speculation [11,12]. Recent research by Koh et al [13] investigated how HIF1α interacts with another downstream signalling molecule, TIM3. It was found that in response to hypoxia, HIF1α binds to the TIM3 prompter region to increase its expression. Increased TIM3 up-regulates the inflammatory cytokines IL1β and CXCL1 (Figure 2) [13]. Blockage of TIM3 activity by monoclonal antibodies showed a significant reduction in the expression of both these cytokines as well as a substantial reduction in cerebral infarct volume. The findings of Zong et al [11] and Koh et al [13] suggest that RIPC exerts its neuro-protective effect via inhibition of HIF1α; subsequently resulting in down-regulation of TIM3 and reduction in cytokine and ROS production [10-13].

PKCδ, JAK2/STAT 3 and P38 MAPK apoptotic pathways

Apoptosis is a process of organised cell death, triggered by an extensive number of signalling cascades. One well known example involves PKCδ, an intracellular enzyme, activated by cell stress to initiate apoptosis [14]. It has been extensively reported that RIPC exerts an anti-apoptotic effect via reduction of PKCδ expression [3,5,14]. However, recent research has investigated several additional pathways which may be involved in the anti-apoptotic effects of RIPC. One such pathway is the JAK2/STAT3 axis which has been found to attenuate apoptosis in multiple models of IRI [15,16]. Cheng et al [17] recently investigated the potential effects of RIPC on JAK2/STAT3, finding that it was associated with a significant increase in both JAK2 activity and STAT3 protein expression. The increase in STAT3 expression results in the transcription of anti-apoptotic Bcl2 family proteins, which inhibit the formation of Bax channels and the initiation of apoptosis [15-17].

As well as its effect on anti-apoptotic signalling, Cheng et al [17] also demonstrated that RIPC was potentially involved in the JAK2/STAT3 mediated inhibition of NFκB. The inhibition of NFκB results in the reduction of pro-inflammatory cytokines such as IL1β and TNFα; subsequently reducing recruitment of neutrophils and other

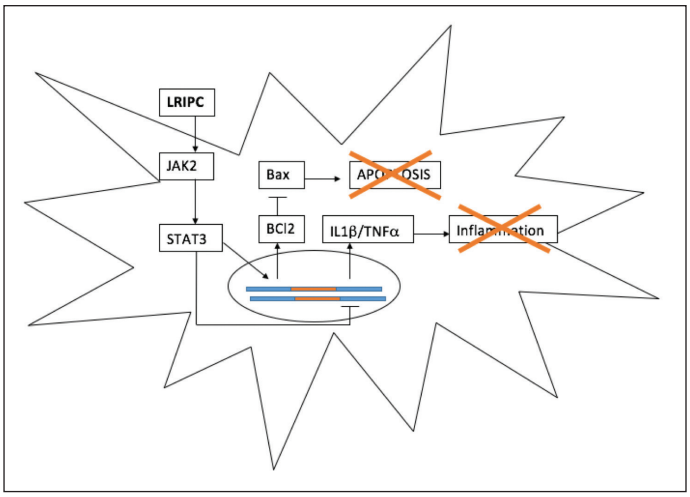


Figure 3. RIPC mediated activation of the JAK2/STAT3 pathway causing inhibition of pro-apoptotic and pro-inflammatory pathways *[15-17]. LRIPC, Limb remote ischaemic post-conditioning; JAK2, Janus kinase 2; STAT3, Signal transducer and activator of transcription 3; IL1β, Interleukin 1β; TNFα, Tissue necrosis factor α.*

leukocytes to the brain [3,17]. The collective effects of RIPC on JAK2/STAT3 mediated reduction of inflammation and apoptosis resulted in a 13.2% reduction in rodent cerebral infarct volume when compared to the IRI control group (Figure 3) [17].

Another recently investigated apoptotic pathway involves the p38MAPK enzyme, responsible for phosphorylation of downstream signalling molecules in response to cellular stress [18]. Li et al [19] investigated the effects of RIPC on p38MAPK on in vivo rodent models. They found that the RIPC intervention was associated with down-regulation of this enzyme as well as a reduction in IRI induced apoptotic neuron populations. Li et al [19] proposed that the attenuation of apoptosis occurred through the RIPC/p38 MAPK mediated reduction of the transcription factor ATF2. How this reduction in ATF2 results in an anti-apoptotic effect is, however, unclear. Other conflicting literature has found that it is the up-regulation of ATF2 which is associated with Bcl2 production, and, hence, a reduction in apoptosis [20,21]. Although the exact mechanism remains a topic of speculation, many studies do support this study's conclusion that P38 MAPK down-regulation is associated with a reduction in apoptosis [18-21].

PI3k/Akt and eNOS uncoupling

Endothelial nitric oxide synthase (eNOS) is responsible for the physiological production of nitric oxide (NO), a key regulator of normal endothelial cell function. During IRI, eNOS can become uncoupled and, as a result, transfer its electrons to an oxygen molecule to produce superoxide free radicals [22]. These superoxide radicals can cause direct cellular damage but can also combine with NO to produce peroxynitrite, a highly destructive reactive nitrogen species (RNS) which suppresses protein function in the same way as ROS [8,22].

The process of eNOS uncoupling is thought to result from both ROS mediated damage and the depletion of the eNOS substrate BH4 [22,23]. Chen et al [22] investigated the capacity of RIPC to attenuate these effects; finding that it was associated with both an increase in BH4 availability as well as a reduction in ROS (through inhibiting transcription of NADPH oxidase and xanthine oxidase). The RIPC mediated inhibition of eNOS uncoupling resulted in a significant reduction in peroxynitrite levels as well as a 15.1% reduction in cerebral infarct volume when compared to the control group [22].

RIPC has also been found to directly increase the synthesis of the eNOS enzyme, leading to higher levels of NO during reperfusion. [22,24,25]. It is thought that this effect may be associated with the RIPC induced up-regulation of the PI3k enzyme, which triggers phosphorylation of the protein kinase B (Akt) transcription factor. Akt is an important anti-apoptotic signalling factor, which is also thought to upregulate eNOS transcription [24,25]. The increased production of eNOS increases the quantity of NO produced within the ischaemic brain; this promotes vasodilation and reduces inflammation and thrombosis [22,24]. Furthermore, the reduction in eNOS uncoupling increases the proportion of NO to superoxide radicals produced [22]. Hence, it appears that RIPC works synergistically to upregulate eNOS transcription whilst reducing uncoupling, resulting in an increase in NO and reduction in ROS and RNS [8,22-25].

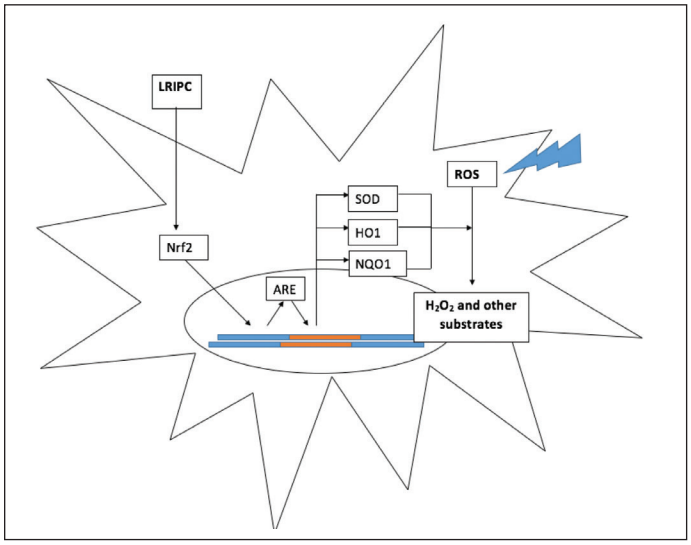


Figure 4. RIPC mediated activation of Nrf2/ARE axis producing anti-oxidising agents to neutralise reactive oxygen species *[26]. LRIPC, Limb remote ischaemic post-conditioning; SOD, Superoxide dismutase; HO1, Heme oxygenase 1; NQO1, NAD(P)H quinone dehydrogenase; Nrf2, Nuclear factor erythroid 2-related factor 2; ARE, Antioxidant response element.*

Nrf-Antioxidant response element (ARE) pathway

Small amounts of ROS are produced in normal physiological processes, but cause no damage because they are rapidly neutralised by cellular antioxidants. The excessive ROS production in IRI overwhelms the antioxidant system and leads to extensive cellular damage [8,26]. Li et al [26] investigated the effects of RIPC on the Nrf2-ARE pathway. It was found that RIPC increased the activity of Nrf2 which subsequently increased ARE transcription [26]. ARE increases the production of the antioxidant molecules SOD, HO1 and NQO1 which, through a range of different cellular processes, neutralise oxygen free radicals into less reactive substrates (Figure 4) [27,28]. RIPC mediated neutralisation of ROS correlated with a significant reduction in MDA (a lipid peroxidation marker) as well as a 16.9% reduction in cerebral infarct volume compared to the control group [26].

AQP4 and ROS in formation of cerebral oedema

ATP deficiency during the period of ischaemic stroke triggers dysfunction of the Na+/K+ ATPase, accumulation of intracellular sodium, and influx of water into the astrocytes. Fluid accumulation within the astrocyte produces cytotoxic oedema, an event which results in death and destruction of nearby tissue [3,4]. Recent research has shown that this influx of water during IRI is likely mediated by the aquaporin 4 (AQP4) channels [29]. Li et al [30] has found that RIPC can reduce the expression of AQP4 channels in the brain following reperfusion, thus reducing the influx of water into the astrocytes. Reduction in astrocyte swelling was found to attenuate cytotoxic oedema formation, resulting in a 15.0% reduction in rodent cerebral infarct volume compared to the control group [30].

Cytotoxic oedema usually occurs in the earlier stages of IRI, when the blood-brain barrier (BBB) is still intact [3,4]. Later in disease progression, there is an increased production of ROS through the mechanisms which have previously been discussed [22,24,26,31]. ROS have been found to mediate BBB damage through oxidative damage, tight junction modification, and activation of matrix metalloproteinases (MMP) [32]. As a result of these events, BBB permeability increases, leading to influx of fluid into the neuronal extracellular space in an event called vasogenic oedema [31,32]. Li et al [30] demonstrated that RIPC may reduce BBB permeability and, hence, reduce vasogenic oedema; a finding supported by another study investigating RIPC in carotid stenosis [33]. RIPC most likely reduces BBB permeability through a variety of pathways targeting inflammation, ROS and antioxidant production that may all impact the integrity of the vascular endothelium or initiate endothelial dysfunction [29-33].

Integrating the pathways

RIPC is an expanding field with more pathways being discovered each year. As this occurs, it is important to know how each pathway relates to another (Figure 5).

RIPC in the clinical setting

The application of RIPC in animal cerebral ischaemia models has been demonstrated to be safe and efficacious, reducing cerebral infarct volume and apoptotic neuronal populations substantially (Table 1) [5,7,34].

Whilst the preclinical evidence for RIPC is convincing, there is still a large gap in the translation to clinical trials. In May of 2017, the results of the RECAST trial were published. This phase I pilot blinded placebo controlled trial involved 26 patients with ischaemic stroke, 13 of whom were given the RIPC intervention within 24 hours of ischaemic stroke. Whilst small, this pilot study found that RIPC was very well tolerated, safe and feasible in the clinical setting. Furthermore, RIPC was found to provide significant improvements in neurological function when compared to the control group [35]. As the only study published of

Table 1. Results from pre-clinical trials.

Summary of pre-clinical results	
Study	**Measurements of efficacy** ***Infarct volume (IV) reduction between RIPC/ IRI groups***
Zong et al [11]	IV: 10.0%
Cheng et al [17]	IV: 13.2%
Li et al [19]	Significant reduction in apoptotic neurons in RIPC group- detected by microscope via TUNEL-staining
Chen et al [22]	IV: 15.1%
Li et al [26]	IV: 16.9%
Li et al [30]	IV: 15.0%

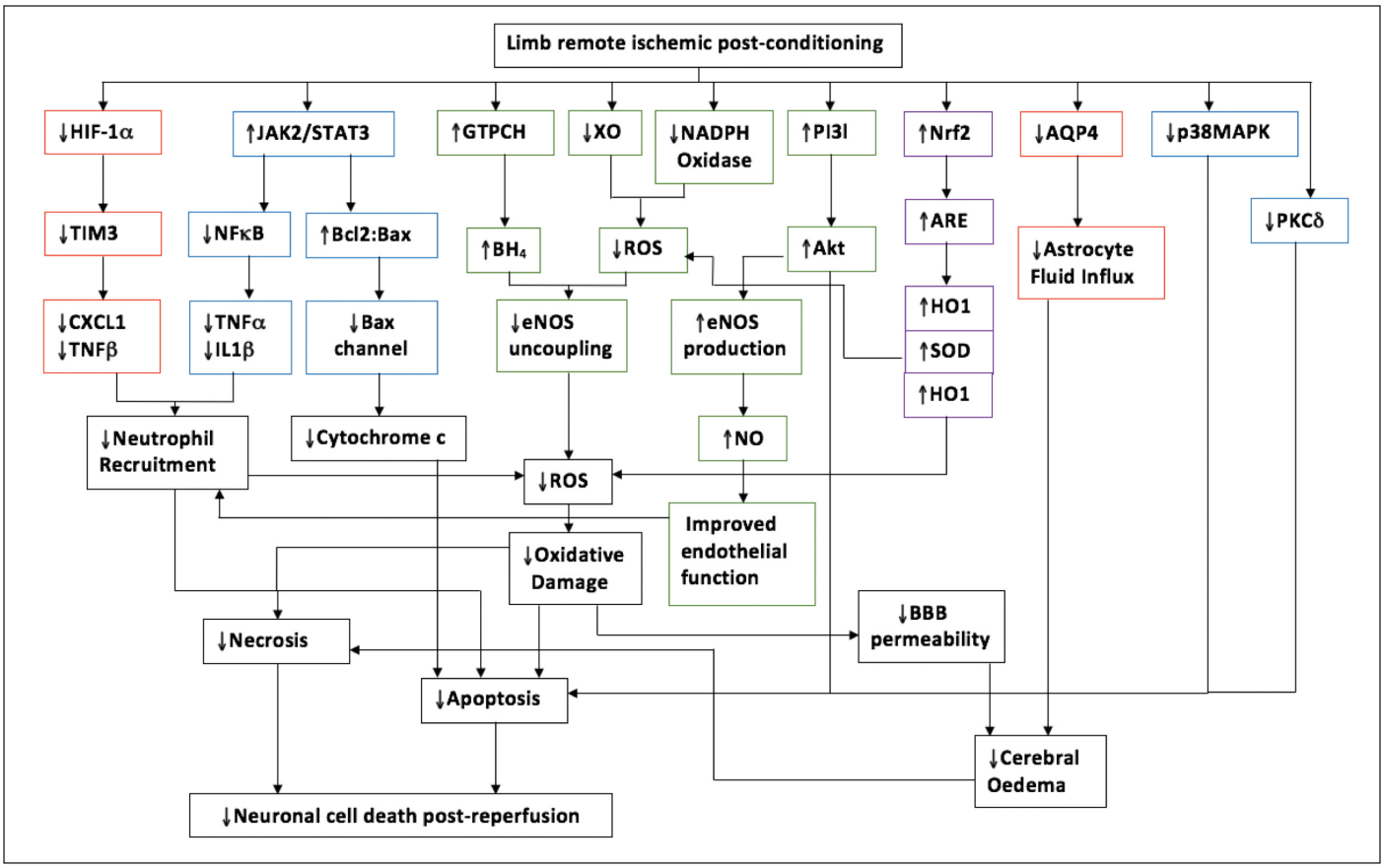


Figure 5. Interconnection of the neuroprotective pathways proposed for RIPC, ultimately leading to reductions in apoptosis, necrosis and neuronal cell death, post reperfusion *[11-33]. LRIPC, Limb remote ischaemic post-conditioning; SOD, Superoxide dismutase; HO1, Heme oxygenase 1; NQO1, NAD(P)H quinone dehydrogenase; Nrf2, Nuclear factor erythroid 2-related factor 2; ARE, Antioxidant response element; JAK2, Janus kinase 2; STAT3, Signal transducer and activator of transcription 3; IL1β, Interleukin 1β; TNFα, Tissue necrosis factor α; HIF 1α, Hypoxia inducible factor 1α; TIM3, T-cell immunoglobulin and mucin domain protein 3; CXCL1, Chemokine CXC ligand 1; ROS, Reactive oxygen species; ETC, Electron transport chain; NFκB, Nuclear factor κB; GTPCH, GTP cyclohydrolase I; BH4, tetrahydrobiopterin; AQP4, aquaporin 4; P38MAPK, p38 mitogen-activated protein kinase; PI3K, phosphoinositide 3 kinase; Akt, Protein kinase B; PKCδ, Protein kinase C δ; eNOS, Endothelial nitric oxide synthase.*

its kind, the evidence for RIPC in stroke is still tentative, however, a recent meta-analysis on the use of RIPC in acute coronary syndrome has provided some more firm results. The analysis of 13 clinical trials demonstrated that RIPC was effective in reducing infarct size, reperfusion injury, and improving patient outcomes post myocardial infarction [36]. These recent publications provide a convincing argument for the further clinical exploration of how RIPC can be utilised in patients who suffer from ischaemic stroke.

Current gaps

Confusion surrounding the molecular mechanism of RIPC primarily pertain to a gap in understanding how an episode of ischaemia in the lower limb can result in an increased expression of neuro-protective factors within the brain [6]. Current research, predominantly conducted on cardiac models, suggests that this effect is likely achieved through multiple neurological, humoral and immune events. How these mechanisms relate to ischaemic stroke and how they result in such diverse effects is still unknown [6,37-39]. Further research must be conducted, particularly in cerebral ischaemia models, before links can be made regarding the initiation of the RIPC neuroprotective pathways.

Conclusion

IRI is a major contributor to the death and destruction of the neuronal tissue after ischaemic stroke. The RIPC intervention aims to attenuate this damage through stimulation of neuroprotective pathways within the brain. Although clinical trials remain limited, RIPC has shown substantial efficacy in the pre-clinical setting: reducing cerebral infarct volume and apoptotic neuron populations. Research should continue to be conducted regarding the pathways involved in RIPC, however, a shift must also take place in translating this pre-clinical knowledge into clinical trials. The limited clinical data is positive thus far, but more must be done to determine whether this intervention is appropriate for the clinical setting.

Conflict of interest

None declared.

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The rare case of a pelvic abscess following caesarean section in a Sri Lankan woman: an argument for medical student electives

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I am currently a final year medical student with a background in nutrition and dietetics. I have participated in several public health nutrition research projects, recently completing a research project on chronic pelvic pain at the Mercy Hospital for Women. I hope to use my academic background and experiences to pursue a career in public health medicine, working on issues affecting women.

Abstract

Introduction: A pelvic abscess is a rare complication that can occur following gynaecological and obstetric procedures. Whilst the condition is not confined geographically, women in less developed countries are at an increased risk of developing this complication, due in part to low resource settings, socioeconomic status, and educational attainment.

Case: A 36 year old primigravid woman in rural Sri Lanka undergoing a non-emergency caesarean section delivery developed clinical signs of puerperal sepsis two days postpartum. Following transfer to a tertiary hospital, imaging and laparotomy confirmed the presence of a pelvic abscess associated with the caesarean section wound. Surgical drainage was performed and IV antibiotics were administered, ultimately resulting in the full recovery of the patient. The infant did not demonstrate clinical signs of sepsis at birth.

Discussion: Numerous factors contributed to the development of this serious complication in this patient, including increased maternal age at first pregnancy, caesarean section management, and the low resource setting of the patient's care. This case also highlights the difficulties and barriers facing patients and doctors in less developed countries, including that of patient transfers from a rural setting and the availability of specific antibiotics recommended in clinical guidelines. The barriers to optimal care faced by this woman are largely disconnected from the experiences of patients that Australian medical students see in their day-to-day training. Overseas electives to low resource areas should be required and supported amongst all Australian medical students to facilitate greater appreciation for such barriers and to foster their skills in resourcefulness and empathy.

Introduction

As a demonstration of the public health issues and associated complications that arise in less developed countries, the following presents a rare case of pelvic abscess formation following caesarean section delivery. This is written from the perspective of an Australian medical student on an obstetrics and gynaecology elective in rural Sri Lanka.

Pelvic abscess is considered a rare complication of pelvic surgery, affecting less than 1% of women undergoing any obstetric or gynaecological procedure [1]. The implications of such a complication are more significant when they occur in a low resource setting, such as Sri Lanka [2]. Data suggest puerperal sepsis accounts for 11.6% of maternal mortality in such settings, compared with 2.1% in developed countries [3]. A range of factors contribute to the risk of puerperal sepsis and pelvic abscess, including increasing maternal age at first pregnancy, high caeserean section rates, and low socioeconomic and educational status, all well-documented factors present in this patient and their demographic [2,4,5]. Whilst pelvic abscess is a complication that has no geographical boundaries, women in less developed countries are at increased risk of dying from this complication [3]. This is likely compounded by sub-optimal infection control and limited access to resources, including trained midwifery and obstetric care [2]. This is reflected in the high rate of hospital-acquired infections, up to 50%, resulting from surgical site wounds [3]. Despite the high morbidity and mortality of pelvic abscesses and puerperal sepsis, the actual incidence of both conditions is poorly defined [3]. The following case exemplifies some of these challenges.

Case

A 36 year old primigravid woman underwent a caesarean section with no immediate surgical complications, in the setting of a reportedly uneventful pregnancy. Surgery was performed at a local rural hospital in Sri Lanka, approximately three to four hours by road transfer from the capital, Colombo. The reason for caesarean section was unclear; however, it was understood that the caesarean section was performed in a non-emergency setting. Two days postpartum, the woman developed fever (temperature not specified) and complained of a triad of foul-smelling and purulent lochia, abdominal distension, and dyspnoea, according to the patient and her family. The patient was denied transfer by the treating hospital, and so the family arranged private transportation to a tertiary centre in Colombo. She arrived in a state of septic shock: mildly hypothermic (36.0˚C), tachypnoeic (45 breaths/min), hypertensive (150/100 mmHg), tachycardic (150 beats/min), and cyanotic with significant generalised oedema. Computerised tomography of the abdomen and pelvis identified abscess formation anterior to the uterine sutures and significant fluid in the peritoneal cavity. An emergency laparotomy was performed. A dehiscence of her uterine scar was repaired and two litres of pus was drained. The fluid cultured positive for Group B beta-haemolytic *Streptococcus*, sensitive to vancomycin. The patient was subsequently commenced on intravenous antibiotics (vancomycin, metronidazole and meropenem) post-operatively.

Following surgery, hyperglycaemia (180-250 mg/dL) and hypertension (160/110 mmHg) persisted for some weeks, with recovery complicated by a secondary wound infection requiring additional antibiotics (flucloxacillin and metronidazole) and a second laparotomy. Mother and baby ultimately recovered completely, with no clinical signs of postnatal sepsis reported in the child. Clinical guidelines for puerperal sepsis recommend a combination of broad-spectrum antibiotics, targeting the common polymicrobial sources, including anaerobic organisms (*E. coli* and *S. pyogenes*), and surgical abscess drainage [5,6]. This case failed to utilise the recommended first-line empirical antibiotics. Poor antibiotic practices, unreliable antibiotic supplies, and a lack of adequate medication delivery protocols are cited as common reasons for increasing rates of puerperal sepsis in the developing world, with one or more of these factors potentially influencing antibiotic choice in this case [2,4].

Discussion

Although the woman had a full recovery, this case serves as a reminder of the seriousness of obstetric complications, and how they may be compounded by geographical factors and a paucity of adequate medical resources. This case offered significant opportunity for learning and personal reflection. Primarily, I was able to recognise that the outcomes of childbirth and postnatal care in less developed countries may be vastly different to such events occurring in Australia. Some of the difficulties I observed included inadequate systems for medical documentation and communication of results and information for clinical handover. The disparity in access to such basic resources is alarming, and I believe all medical professionals should be angry about such injustices. To fully understand this degree of inequality, however, it required the immersive experience of an elective term in Sri Lanka. Based on my own experience, I would strongly recommend an overseas elective as a mandatory component of any Australian medical degree. This could be a useful step in helping Australian graduates to become more resourceful. In addition, it will help our graduates recognise the importance of an effective and well-resourced, high-quality health system in achieving the best health outcomes for our patients.

Consent declaration

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

Acknowledgements

Dr Roshan Zaid (consultant obstetrician and gynaecologist, Nawaloka Hospital, Colombo, Sri Lanka), a senior consultant involved in the above patient's care, who provided clinical advice and support in compiling this report.

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Conflict of interest

None declared.

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Book Review - Balanda: My Year in Arnhem Land

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Lily Aboud is a fourth-year medical student at James Cook University, Townsville. She has a keen interest in tropical health and Indigenous service delivery both in Australia and internationally

In a nation often eager to present a whitewashed version of Australian history, Mary Ellen Jordan gives us an uncomfortable, yet refreshingly honest account of her experiences living in a remote Indigenous community for 14 months. *Balanda: My Year in Arnhem Land* [1] follows her experience, highlighting the stark social and cultural divisions between Indigenous and non-Indigenous Australians. This book recounts Jordan's time at the Community Art Centre in Maningrida, a 2,300 strong coastal Aboriginal community in the heart of Arnhem Land in the Northern Territory [2]. Having previously lived and worked as an editor in Melbourne, Jordan's role in Maningrida is to organise the community art centre and work on a bilingual dictionary including English and the local Indigenous language.

One can only learn so much about Aboriginal culture in a medical school lecture theatre. Guest lecturers, workshops in Australia's history, and explanations of Aboriginal culture as 'deeply spiritual' reward us with only a broad, generalised view of what is, in reality, a diverse collection of tribes, languages and individuals. The impact of these diverse cultures on diagnosis and treatment is often only touched upon, or otherwise described only in general terms.

Despite accounting for 3.7% of total health expenditure, the Close The Gap initiative of 2008 is failing [3,4]. There is an average life expectancy gap of ten years between Indigenous and non-Indigenous Australians, a 2.5 times greater disease burden, and disproportionate incidences of preventable diseases such as rheumatic heart disease and trachoma in Aboriginal and Torres Strait Islander populations [5]. Furthermore, the ultimate goal of Closing the Gap between Aboriginal and non-Aboriginal Australia in terms of culture is not always clear. Is it a covert attempt to achieve Western assimilation? Or an endeavour to preserve a culture already re-shaped by the influences of a dominant white culture?

In remote Maningrida, a sense of cultural alienation results in a type of split community, where "there is very little crossover between the two cultures, although [they] live side-by-side [1]." *Balanda* aims to investigate the involvement of white Australians in Aboriginal communities as 'modern day missionaries', a resonant phrase for medical students considering placements or working in an Aboriginal community. While Jordan's inability to offer a solution to the social determinants of health may frustrate readers, it reinforces her sense of helplessness regarding the complexity of the current situation for Indigenous people and cross-cultural communication.

Confronting and critical, Jordan's recount lingers in the reader's mind long after the covers are closed. Questions regarding what it means to be non-Indigenous in a country built on dispossession are raised and not always answered clearly. For medical students inexperienced with Indigenous cultures, these questions are unsettling. Jordan describes the healthcare system as an imposition of one culture onto another, in which health practices are taught based on the Western model of medicine rather than Aboriginal tradition. To her, the "unspoken… unintentional assimilation [1]" of healthcare delivery is often administered in a paternalistic fashion, in which Aboriginal people are prevented from taking responsibility for themselves and their community.

Integration and success have been noted, however, in the example of Aboriginal Community Controlled Health Services (ACCHS) [6]. These services, offering general practice, allied health, antenatal care and support programs, deliver holistic and culturally appropriate primary healthcare. ACCHS exist as autonomous organisations initiated by Indigenous communities and governed by a locally elected board. These services overcome trends of non-participation and tokenism by engaging the community through partnership, self-determination and community ownership. For these services to succeed, building community capacity, addressing risk factors, and implementing evidence-based strategies to address social determinants is necessary.

Health practitioners and medical students may well feel intimidated by the candid accounts of the communication challenges faced by Jordan, such as differences in verbal and non-verbal language, and social organisation. Jordan's recognition of her difficulties in cross-cultural communication highlights how bridging two disparate cultures can pose a major impediment to clinical practice.

Practitioners and students, however, should not to be dismayed or dissuaded by Jordan's cynicism. Rather, this book encourages us to reflect on how our own beliefs and social milieu shape how we act towards others and, in turn, form partnerships that celebrate diversity. The author's insights and experiences can be used to formulate inventive and novel approaches to addressing health disparities, and help prepare for both the inevitable frustrations and rewards experienced when working with such a unique and ancient culture.

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Conflict of interest

None declared.

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Death in a paediatric hospital: who, where, and how?

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Manon is a French-Australian student with interests in critical care and teaching. When not studying, Manon enjoys travelling, skiing and hiking. She also loves crafting well-balanced wine and cheese platters for friends.

Manon Audigé

Background

In the developed world, most paediatric deaths follow withdrawal or withholding of medical treatment (WWMT), and previous studies have largely focused on an intensive care setting perspective.

Materials and Methods

A retrospective review of medical records was conducted for all paediatric inpatient deaths at the Royal Children's Hospital (RCH) from April 2015 to April 2016. Results were compared with data from January to June 2007. Chi-squared tests were used for comparisons.

Results

A total of 101 deaths in 2015-2016 were reviewed, and compared to 50 deaths in 2007. In both periods, most deaths followed WWMT (84% vs. 87% of deaths) and occurred in children with pre-existing chronic conditions (84% vs. 85% of deaths). From 2007 to 2015-2016, there was a shift to earlier discussions with parents around WWMT. Cases where discussions began prior to the last admission increased from 4% to 19% (p=0.004). There was also increased palliative care involvement (10% vs. 37%, p<0.001), and more children dying outside of intensive care (16% vs. 22%, p=0.253). In 2015-2016, subgroup analysis revealed that children dying on the wards were 76% more likely to have palliative care involved than those dying in intensive care (p<0.001), and 51% more likely to have discussed WWMT with families before the last admission (p<0.001).

Conclusion

The last decade has seen an increase at RCH in paediatric palliative care involvement and advance discussions around WWMT. These are both associated with death outside of intensive care — a world-first finding that warrants further study.

Conflict of interest

None declared.

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Undertaking a medical elective in Peru: a student's perspective

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Kate Van Berkel is a fifth-year medical student (in 2017) at Monash University, Australia. In early 2017 she undertook a six week medical placement in Arequipa, Peru, with Work the World.

I chose to undertake a Work the World placement as I wanted to get a feel for how healthcare operates in countries that have less funding and fewer resources than Australia. Like many students, I had also been bitten by the travel bug. I wanted to get out and see the world. A Work the World placement allowed me to experience Peruvian medicine in a supported way, and meant I could observe and interact with healthcare delivery without feeling like I was stepping outside my role or acting above my qualifications, which was very important to me.

I had already organised to travel to the USA from Australia with family over Christmas and the New Year, so I decided it would be a good time to visit South America. I've always been interested in history, so I was attracted to Peru's Incan and pre-Incan ruins, like Machu Picchu. I also liked the idea of gaining some new language skills while overseas.

I'm also interested in women's health as a career path, and I think part of what makes care in Australia so effective is that we are very secular in our healthcare delivery. Latin America is predominantly Catholic, and their healthcare is very much influenced by their religion, especially when it comes to women's health interventions like contraception and termination. I wanted to discover how these beliefs affect health outcomes for women.

When I arrived in Peru, I was both excited and nervous. My previous travels around South America had introduced me to new people and places, but my actual time in these countries was limited. This time, I was spending six weeks in one place!

The first 24 hours in Arequipa were great. Raul, part of the local Work the World team, met me at the airport and we took a taxi back to the house. Another student had also flown in that day and was waiting at the house when we arrived. A further five people from the US were due to arrive an hour later. All the students who had started their placements earlier were away on weekend trips, as our placements were from Monday to Friday. I was then taken on a tour of the house, shown our rooms, a map of the city, and how to get to our local shopping centre. After a while, the additional new students arrived, and we met Mama Julia and Angelo, our in-house chefs. We all had a quiet night getting to know each other.

As I had booked to do the Work the World intensive Spanish course, the following morning Raul caught the bus to Spanish school with us. There we met Maria, the wonderful, patient and friendly language teacher. We spent the morning getting to grips with Spanish before Raul returned to take us into the centre of Arequipa on our city orientation. He took us out for lunch and on a walking tour to help us get to know the beautiful 'White City'.

The house was fantastic; it had all the amenities you could want. I always felt safe, as there was always a Work the World staff member onsite. But, most importantly, the friends I made at the house were the highlight of my trip. I can now say I have friends on almost every continent! Everyone got along very well, and we enjoyed doing lots of different activities together, from cooking classes and white water rafting, to weekend hiking trips, late-night karaoke, and dancing in the town square. Some friends left the house sooner than others, as we didn't all stay for the same amount of time, but I'm so glad to have met all my former housemates, even the ones I only lived with for a week.

When arriving at the hospital for the first time, my immediate reaction was, "it looks like a convent!" The hospital was old, and there weren't any segregated rooms. All the patients in the obstetrics and gynaecology ward were in beds next to each other, without separating walls, or even dividing curtains for privacy.

I spent a week in oncology and cancer prevention, where I learnt about cervical cancer screening methods from the midwives, as well as seeing cases of cervical cancer. Screening in Peru involves pap smears, but also regular screening with acetic acid under colposcopy, which is not standard practice in my state in Australia. They also do a lot of 'freezing' of cervical lesions, whereas in Australia we're more likely to favour lower loop excision of the transformation zone (LLETZ) procedures for recurrent or high-grade lesions. Screening techniques and the Gardasil vaccine (also available in Peru) have largely decreased cervical cancer morbidity and mortality in Australia, and cases are detected early.

In Peru, many women never undergo screening, as they do not have the means to attend clinics for preventative care. As such, women commonly present late in the disease process. Unfortunately, I saw multiple cases of cervical cancer so advanced that the cervical

appearance would not feature on a grading scale in Australia, because it would never go so long undetected. This was fascinating as a scholar, but hard to observe on a personal level.

In some situations I'd help with things like moving the light for the midwife during a birth, or passing equipment. Under supervision in oncology, I was able to palpate some lumps, discuss X-rays with the consultant, and assist with a cervical biopsy. The more enthusiasm you show, the more you'll be able to do.

Being in the hospital in Peru made me realise how lucky Australia is to have things we consider disposable, like shoe covers and hair nets. Shoe covers are reused until they are falling apart in Arequipa. Everything is re-purposed there. In Arequipa, patients are required to pay for everything, right down to the sterile gloves the surgeon wears in the theatre, the needles required to cannulate and administer medicines and analgesia, even the saline drip!

We travelled almost every weekend, taking trips to Colca Canyon, Cuzco, Machu Picchu, Lake Titicaca and the Nazca lines. Most things are just an overnight bus ride away. Colca Canyon was only three hours from the accommodation, and Lake Titicaca only six. The Work the World staff also gave us tips on how to organise cooking classes, chocolate-making sessions, and many other wonderful activities. What I loved most about Peru was the dancing and the music! Some of the food, like lomo saltado, was amazing. Other cuisine, such as Cuy (guinea pig), was not for me!

It's too difficult to pick my favourite memory, but special mention has to go to our regular Taco Tuesday whole-house lunches at a restaurant near our house. And I will always remember the first time someone didn't reply to me in English after I tried to order in Spanish — the ultimate 'gringa' compliment!

If you're considering doing a Work the World placement in Peru, I say: do it! Prepare to have the time of your life. Everyone is so friendly and so happy to have you visiting their country. Oh, and make sure you haggle with the taxi drivers!

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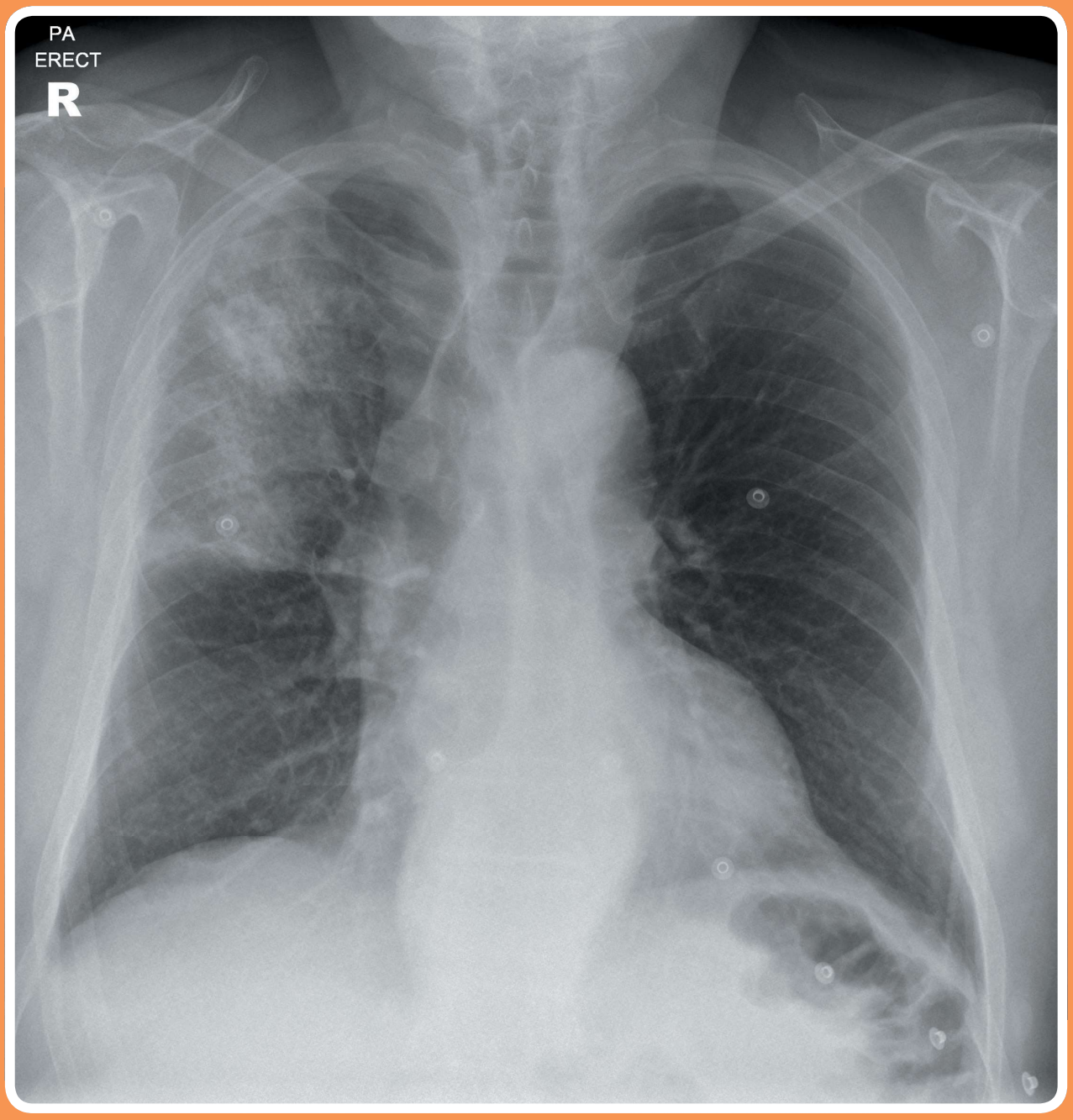
The Unofficial Guide to Radiology: 100 Practice Chest X-Rays

Dr Zeshan Qureshi
BM MRCPCH MSc BSc (Hons)

CASE 1

A 70 year old male who lives in a residential home presents to ED with increasing confusion. He has a productive cough and a fever. He has a past medical history of hypertension, angina and mild cognitive impairment. He has a 25 pack year smoking history. On examination, he has saturations of 89% in air, and is febrile with a temperature of 38.8°C. There is dullness to percussion and coarse crackles in the right upper zone. A chest X-ray is requested to assess for possible pneumonia or collapse.



REPORT – RIGHT UPPER LOBE CONSOLIDATION

Patient ID: Anonymous
Projection: PA
Penetration: Adequate – vertebral bodies just visible behind heart
Inspiration: Adequate – 8 anterior ribs visible
Rotation: Not rotated

AIRWAY
The upper trachea is central. The lower trachea is displaced to the right by the aortic arch.

BREATHING
There is heterogeneous air space opacification in the right upper zone. This has a relatively well defined inferior margin, which is likely to represent the horizontal fissure. There is a focal area of increased opacification in the right upper zone, which may represent focal consolidation or an underlying mass. The remainder of the lungs are clear. The lungs are not hyperinflated.

The pleural spaces are clear.

Normal pulmonary vascularity.

CIRCULATION
The heart is not enlarged.

The heart borders are clear.

There is unfolding of the thoracic aorta, which displaces the lower trachea to the right.

The mediastinum is central, not widened, with clear borders. There is a well-defined density projected over the lower mediastinum, which is in keeping with a hiatus hernia.

Normal size, shape, and position of both hila.

DIAPHRAGM + DELICATES
Normal appearance and position of hemidiaphragms.

No pneumoperitoneum.

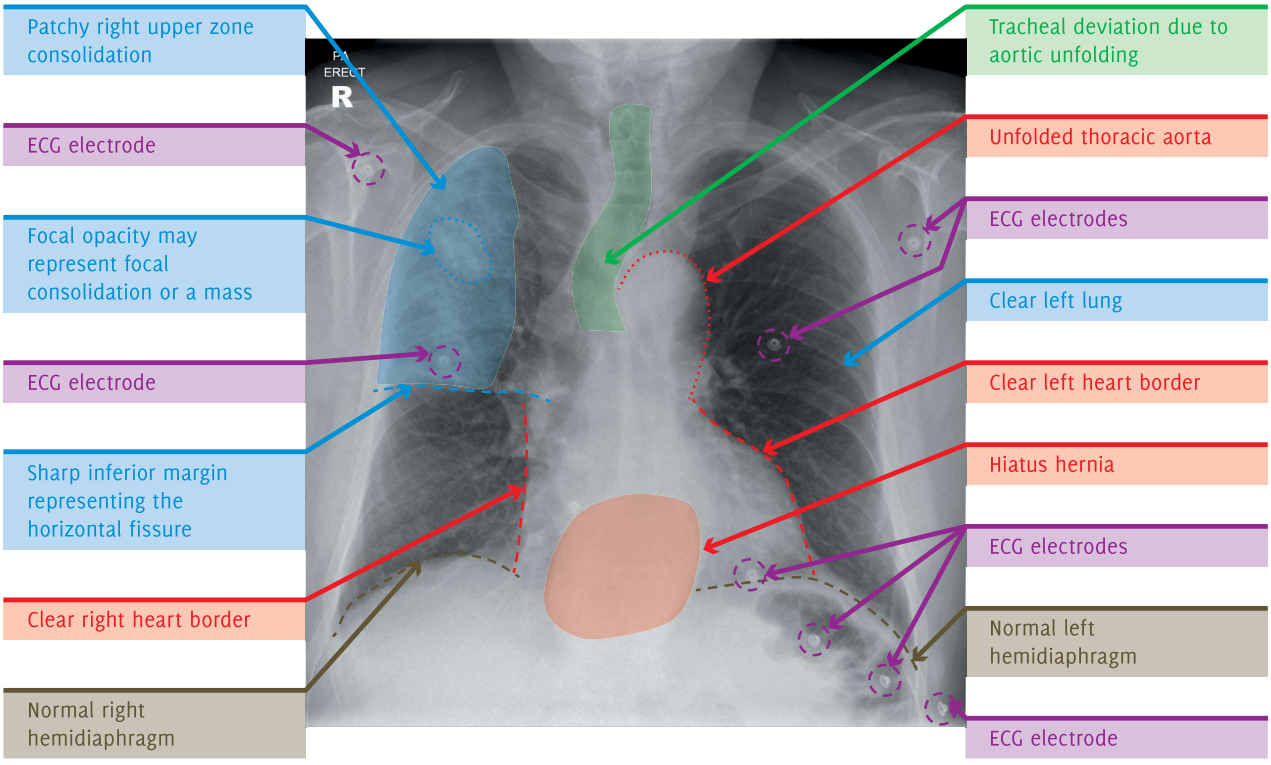
The imaged skeleton is intact with no fractures or destructive bony lesions visible.

The visible soft tissues are unremarkable.

EXTRAS + REVIEW AREAS
ECG electrodes in situ.

No vascular lines, tubes or surgical clips.

Lung Apices: Heterogeneous right apical consolidation. Normal left apex
Hila: Normal
Behind Heart: There is a retrocardiac density, which represents a hiatus hernia
Costophrenic Angles: Normal
Below the Diaphragm: Normal



SUMMARY, INVESTIGATIONS & MANAGEMENT
This X-ray demonstrates heterogeneous right upper zone consolidation in keeping with pneumonia. The consolidation has a relatively abrupt inferior margin in keeping with the horizontal fissure, indicating this is right upper lobe pneumonia. A focal opacity in this region may represent focal consolidation or a mass. Incidentally, there is also a hiatus hernia.

Initial blood tests may include FBC, U/Es, blood cultures, and CRP. A sputum culture may also be taken.

The patient should be treated with appropriate antibiotics for community-acquired pneumonia, and a follow-up chest X-ray performed in 4-6 weeks to ensure resolution. The antibiotics may be oral or intravenous depending on the severity of pneumonia (CURB-65).

If the focal opacity in the right upper zone does not resolve then a CT of the chest and abdomen with IV contrast would be appropriate to assess for a lung tumour. It would also be useful to review previous imaging and case notes to see if there was an abnormality at this site before.

Staff (Volume 8, Issue 2)

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