Volume 3, Issue 2 | 2012

Australian Medical Student Journal

Predicting falls in the elderly

A systematic review

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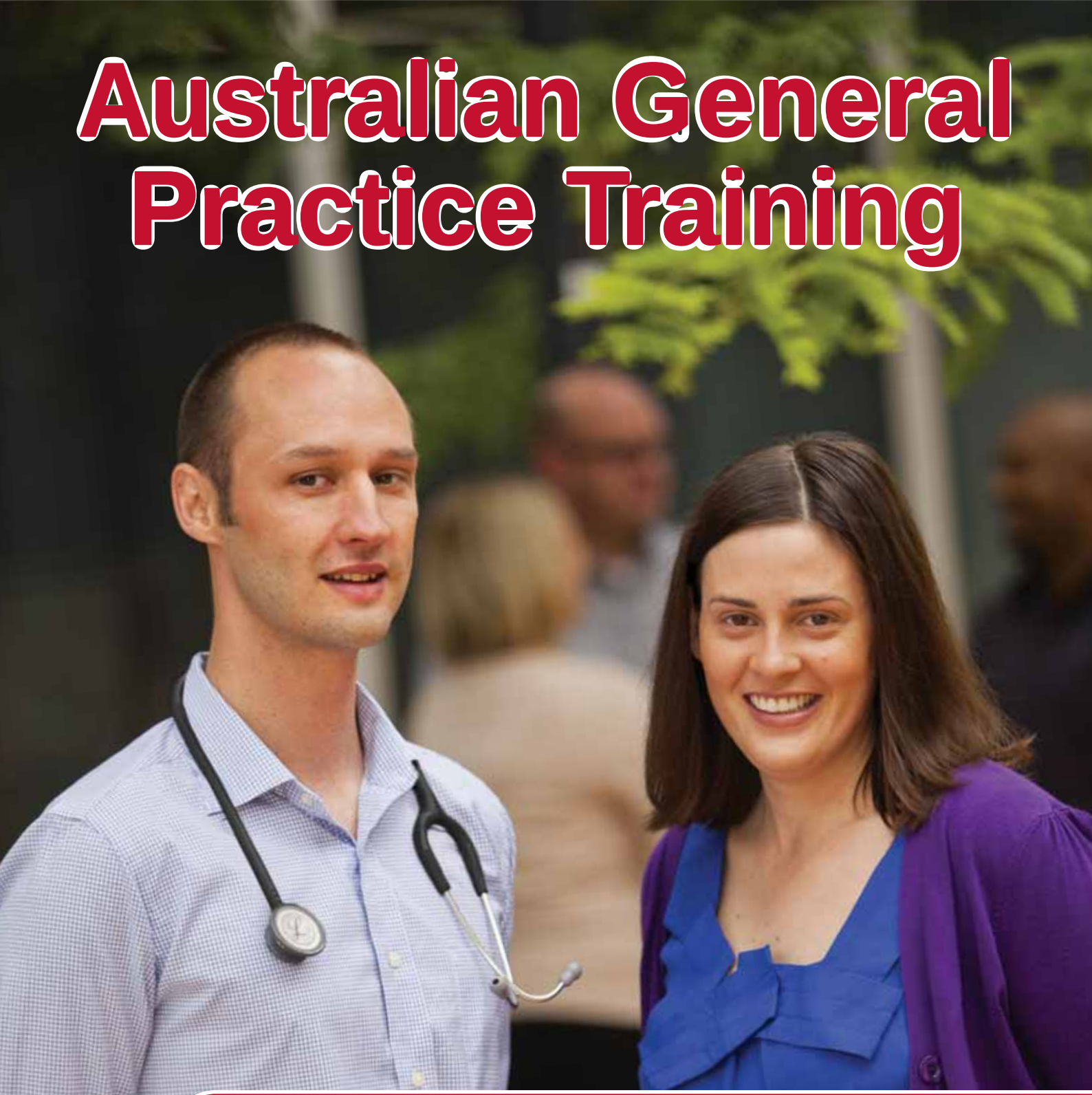

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Australian Medical Student Journal, 330 Anzac Parade, UNSW Sydney, 2052
enquiries@amsj.org
www.amsj.org

ISSN (Print): 1837-171X
ISSN (Online): 1837-1728

Printed and bound in Australia by Ligare Book Printers.

The Australian Medical Student Journal is an independent not-for-profit student organisation.

Australian Medical Student Journal

Volume 3, Issue 2 | 2012

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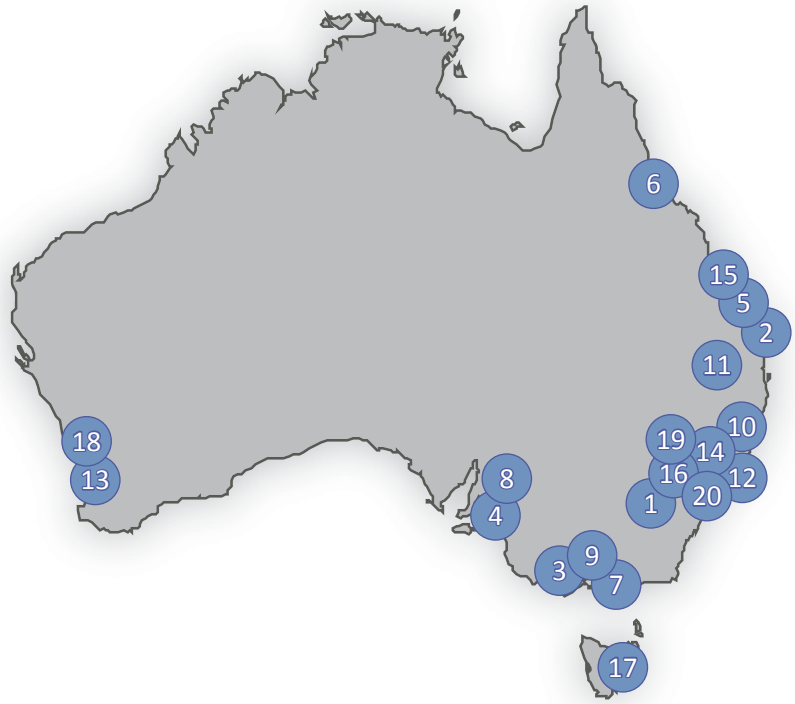

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The AMSJ leading the way in Australian medical student research

Hasib Ahmadzai
Editor-In-Chief, AMSJ

Grace Leo
Internal Director, AMSJ

Alexander Murphy
External Director, AMSJ

Welcome to Volume 3, Issue 2, another successful issue of the Australian Medical Student Journal. The current issue again provides our medical student and junior doctor readership with a broad range of intellectually intriguing topics.

Our medical student authors have continued to submit quality articles, demonstrating their important contribution to research. Publication of medical student research is an important part of the transition from being a medical student to a junior academic clinician and the AMSJ continues to provide this opportunity for Australian medical students.

Some key highlights from this issue include an editorial from our Associate Editor, Foong Yi Chao, who illustrates the important role that medical students have in clinical settings - in addition to their role in medical research. Continuing this theme are submissions that describe an impressive Australian medical student-led project aimed at reducing the incidence of malaria in a Ugandan community as well as a student elective project in India. Other submissions range from an examination of the traditional white coat in clinical medicine, the history and evolution of abdominal aortic aneurysm repair surgery, case reports in paediatric surgery and infectious diseases, a student perspective in palliative care medicine and the future role of direct-to-consumer genetic tests.

We also present a systematic review on "Predicting falls in the elderly" by Mina Sarofim, which has won the award for the best article for Volume 3, Issue 2. This research was identified by our editors and reviewers to be of a significantly high quality, with robust and rigorous methodology. Sarofim's article analyses an important problem and cause of great morbidity in the elderly population.

The Hon. Jillian Skinner MP, New South Wales Minister for Health and Minister for Medical Research provides us with an insightful discussion on the role of e-health and telemedicine programs in improving healthcare. Advances in e-health will be of significant value to the Australian community, especially in rural and regional areas where a lack of appropriate specialist care has been a major problem.

The AMSJ continues to support initiatives to encourage student research. We are pleased to be publishing a supplementary online issue of research abstracts presented at the Australasian Student's Surgical Conference (ASSC) in June this year.

Another new addition to our website will be a database of all peer-reviewers who have contributed in 2012. We are always on the look out for new peer reviewers who are welcome to fill in their details via our website.

The AMSJ Blog is another initiative that we are excited to have been redeveloping and revitalising. From November 2012, readers can look forward to regular fortnightly articles from the AMSJ staff. Topics coming up include conference summaries, tips on professional networking and even a discussion on the coffee habits of medical students!

Since our inaugural issue in 2010, the AMSJ has continued to expand as a student publication. We received over 70 submissions for this issue and have been able to continue to publish approximately 30-50% of submissions. We have also recently completed a new Australia-wide recruitment for staff members. Our nation-wide based staff have continued to successfully work together through the use of teleconference meetings and email.

The production of this journal is a major undertaking, with several staff members completing their final medical school exams during the process of compiling this issue. We would like to extend our thanks to all of our voluntary staff members as well as the invaluable assistance of our external peer-reviewers for donating their time and efforts in ensuring a successful issue of the AMSJ.

In addition, we would like to thank you- our valued readers and authors for your continued support and providing the body of work that has made this publication possible. We hope that you will enjoy the current issue as much as we have in compiling it.

Medical students in the clinical environment

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Introduction

It is common amongst medical students to feel apprehension and uncertainty in the clinical environment. It can be a daunting setting, where medical students can sometimes feel as if they are firmly rooted to the bottom of the pecking order. However, there are many ways medical students can contribute to their respective healthcare teams. Whilst students are not able to formally diagnose patients or prescribe medications, they remain an integral part of the healthcare landscape and culture. The step from being 'just' a medical student to being a confident, capable medical professional is a big step to take, but an important one in our development from the textbook to the bedside. By being proactive and committed, students can be of great help and achieve improved outcomes in a clinical setting. Through this editorial we hope to illustrate several methods one can employ to ease this transition.

Concerns of medical students

When faced with the clinical environment, most medical students will have some form of reservation regarding various aspects of clinical practice. Some of the concerns listed in the literature revolve around being accepted as part of the team, [1] fatigue, [2, 3] potential mental abuse, [4, 5] poor personal performance and lifestyle issues. [6, 7] These points of concern can mostly be split up into three parts: concern regarding senior clinicians, concern regarding the clinical environment, and concern regarding patient interaction. [1] Practicing clinicians hold the key to effective medical education and their acceptance of medical students is often crucial for a memorable learning experience. [1] Given the hierarchical nature of most medical organisations, senior clinicians being the direct 'superiors', are given the responsibility of assessing students. Concerns regarding the clinical environment refer to the demands on students during clinical years, such as on calls, long hours, early starts and the pressure to gain practical knowledge. Anecdotally, it's common to hear of medical students becoming consumed by their study of medicine and rarely having the time to pursue other interests in life.

Patient-student interaction is another common source of anxiety, as medical students are often afraid to cause harm to real-life patients. Medical students are often encouraged to perform invasive practical skills (such as venipuncture, intravenous cannulation, catheterisations, suturing, invasive clinical exams, nasogastric tube insertion, airway management, arterial blood gases) and to take sensitive histories. We have the ability to physically or psychologically hurt our patients, and Rees *et al.* [8] have recently reported the performance of intimate examinations without valid consent by Australian medical students. This has to be balanced against our need to learn as students so that we avoid making errors when we eventually enter clinical practice. These are all pertinent points that have to be addressed to ensure that the average medical student can feel comfortable and contribute to the team in an ethical manner.

Attitudes towards medical students

Despite the concerns of medical students regarding the attitudes of clinicians, allied health professionals and patients towards them, most actually take a positive view on having students in the clinical environment. Most studies have shown that the majority of patients are receptive to medical students and had no issues with disclosing personal information or being examined. [9-11] In particular, patients

who were older and had prior admissions tended to be more accepting of student participation in their care. [9, 12] These findings were consistent across a number of specialties, even those dealing with genitourinary issues. [13] On a cautionary note, students should bear in mind that a sizable minority of patients prefer to avoid medical student participation, and under these circumstances it is important to respect patient autonomy and refrain from being involved with their care. [14] Graber *et al.* [14] have also reported that patients are quite apprehensive regarding having medical students perform procedures on them, particularly more invasive procedures such as central line placement or lumbar puncture. Interestingly, a sizable minority (21%) preferred to never have medical students perform venipuncture, [14] a procedure often considered minor by medical professionals. It is a timely reminder that patient perspectives often differ from ours and that we need to respect their opinions and choices.

Ways we can contribute

As aspiring medical professionals our primary objective is to actively seek ways to learn from experienced colleagues and real-life patients about the various conditions that they face. Being a proactive learner is a crucial aspect of being a student and this in itself can be advantageous to the clinical team by sharing new knowledge, promoting academic discussion or as a source of motivation for senior clinicians. However as medical students we can actively contribute to the healthcare team in a variety of practical ways. These methods include formulating a differential diagnosis, assisting in data collection, preventing medical errors and ensuring the emotional well-being of patients. These are simple yet effective ways of fulfilling one's role as a medical student with potentially meaningful outcomes for patients.

Preventing medical errors

As medical students, we can play an important role in preventing patient harm and picking up medical errors. Medical errors can be caused by a wide variety of reasons, ranging from miscommunication to a loss of documentation to the lack of time on the part of physicians. [15-18] These are all situations where medical students can be as capable as medical professionals in noticing these errors. Seiden *et al.* [19] reports four cases where medical students prevented medical errors and ensured patient safety, ranging from ensuring sterile technique in surgery to correcting a medication error to respecting a do not resuscitate order. These are all cases within the circle of competence of most medical students. Anecdotally, there are many more cases of situations where a medical student has contributed to

reducing medical errors. Another study has shown that up to 76% of second-year medical students at the University of Missouri-Columbia observed a medical error. [17] However, only 56% reported the error to the resident-in-charge. Various factors contribute to this relatively low percentage: inexperience, lack of confidence, hesitancy to voice opinions, being at the bottom of the medical hierarchy and fear of conflict. [17] Whilst medical students should not be relied upon as primary gatekeepers for patient safety, we should be more forthcoming with voicing our opinions and concerns. By being involved and attuned to the fact that medical errors are common, we can make a significant difference to a patient's well-being. In recognition of the need to educate medical students about the significance of medical errors, there have been efforts to integrate this formally into the medical student curriculum. [20, 21]

Assistance with collecting data

Physicians in clinical environments are notoriously limited with time. Average duration of consultations may range from eight to nineteen minutes, [22-24] which is often insufficient to take a comprehensive history. There are also a range of administrative duties that reduce patient interaction time, such as ordering investigations, filling out drug charts, arranging referrals or finding a hospital bed. [25,26] Mache *et al.* [25,26] have reported that pediatricians and surgeons spent up to 27% and 21% of their time on administrative duties and documentation. Medical students tend to have less administrative duties and are thus able to spend more time on individual patients. Medical students can be just as competent at taking medical histories or examining patients, [27,28] and they can uncover crucial pieces of information that had gone unnoticed, such as the presence of a 'Do Not Resuscitate' order in a seriously ill patient. [19] Students are also often encouraged to try their hand at practical skills such as venipuncture, history taking or clinical examination, all of which saves physician time and contribute to the diagnostic process as well.

Emotional well-being of patients

Due to the unique nature of the hospital environment, patients often have a range of negative emotions, ranging from anxiety to apprehension and depression. [29-31] A patient's journey in the hospital can be an unnerving and disorientating experience, where he/she is referred from unit to unit with several different caregivers at each stage of the process. This issue is further compounded by the fact that clinicians simply do not always have sufficient patient contact time to soothe their fears and emotional turmoil; studies have shown that direct patient contact time represented a small proportion of work time, as little as 4% in some cases. [25,26,32,33] Most patients feel comfortable and enjoy their interactions with medical students and some even feel that they benefit from having medical students in the healthcare team. [9,10,12,14,34] By being empathetic and understanding of our patient's conditions, we can often alleviate the isolating and disorientating nature of the hospital environment. [12,35]

International health

Most medical students, particularly earlier in the course are motivated by idealistic notions of making a difference to the welfare of our patients. [36,37] This often extends to the less fortunate in developing countries and students often have a strong interest in global health and overseas electives (38, 39). This can be a win-win situation for both parties. Healthcare systems in developing countries stand to benefit from the additional help and expertise provided by students and students gain educational benefits (recognising tropical conditions, public health, alternative medicine), enhanced skills (clinical examination, performing investigations), cultural exposure and fostering certain values (idealism, community service). [38] However, it is important to identify our limits as medical students and learn how to turn down requests that are beyond our scope of knowledge, training and experience. This is an ethical dilemma that many students face whilst on electives in resource-poor areas, and it is often a fine line to tread between providing help to those in desperate need and inappropriate abuse of one's position. We have the potential to do more harm than good when exceeding our capabilities, and given the lack of clear guidelines it comes down to the student to be aware of these ethical dilemmas and draw the line between right and wrong in these situations. [40,41]

Student-run clinics and health promotion activities

In other countries, such as the United States, student-run medical clinics play a crucial role in the provision of affordable healthcare. [42-45] These clinics number over 120 across the country and have up to 36 000 visits nation-wide. [43] In these clinics, students from a variety of disciplines (such as medicine, nursing, physiotherapy, dentistry, alternative medicine, social work, law and pharmacy) collaborate to manage patients coming from disadvantaged backgrounds. [46] Whilst this concept is still an emerging one in Australia (the first student run clinic was initiated by Doutta Galla Community Health and the University of Melbourne this year, culminating in the REACH clinic – Realising Education, Access and Collaborative Health), [47] there has been a strong tradition of medical students being heavily involved with health promotion projects in their respective local communities. [48] It is not uncommon to hear of students being actively involved in community health promotion clinics, blood donation drives or blood pressure screening, [49] all of which have practical implications on public health. Through modifying our own health behaviours and active participation in local communities, students can have a tangible impact and influence others to lead a healthier lifestyle.

Note of caution

Whilst medical students should actively participate and be an integral part of a medical team, care must be taken to not overstep the professional boundaries of our role. It is always important to remember that our primary aim is to learn how to care for patients, not to be the principle team member responsible for patient care. There have been several ethical issues surrounding the behavior of medical students in clinical settings in recent times. A prominent example of this is the lack of valid consent whilst observing or performing intimate examinations. This report by Rees *et al.* [8] generated widespread controversy and public outrage. [50] The study showed that most medical students complied with the instructions of more senior clinicians and performed sensitive examinations without explicit consent, sometimes whilst patients were under anaesthesia. There were a variety of reasons leading up to the action, ranging from the lack of similar opportunities to the presumed pressure from supervising doctors. This is not a new issue; a previous study by Coldicott *et al.* [51] had also highlighted this as a problem. As emerging medical professionals we must avoid getting carried away by the excitement of clinical practice and ignore the vulnerability of our patients.

Conclusion

The clinical environment offers medical students limitless potential to develop their clinical acumen. As medical students we have the opportunity to participate fully in all stages of patient care, from helping formulate a diagnosis to proposing a management plan. Holistic care for our patients goes beyond the physical aspect of disease and medical students can play an important role in ensuring that the psychosocial wellbeing of patients is not ignored. Our impact is not just restricted to a hospital setting; we are only limited by our imagination and determination. By harnessing the idealism unique to medical students we are able to come up with truly inspirational projects that influence local or overseas communities. Through experiencing a full range of clinical scenarios in different environments we can develop a generation of doctors that are not only clinically astute, but also well-rounded individuals with the ability to connect to patients from all backgrounds. As medical students we have the potential to contribute in a practical manner with tangible outcomes, and we should aspire to that as we make the fifth cup of coffee for the busy registrar on call.

Acknowledgements

Michael Thompson for his feedback and assistance in editing draft manuscripts.

Conflict of interest

None declared.

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Modelling human development and disease: The role of animals, stem cells, and future perspectives.

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Introduction

The 'scientific method' begins with a hypothesis, which is the critical keystone in forming a well-designed study. As important as it is to ask the correct questions to form the hypothesis, it is equally important to be aware of the available tools to derive the answers.

Experimental models provide a crucial platform on which to interrogate cells, tissues, and even whole animals. They broadly serve two important purposes: investigation of biological mechanisms to understand diseases and the opportunity to perform preclinical trials of new therapies.

Here, an overview of experimental models based on animals commonly used in research is provided. Limitations which may impact clinical translation of findings from animal experiments are discussed, along with strategies to overcome this. Additionally, stem cells present a novel human-derived model, with great potential from both scientific and clinical viewpoints. These perspectives should draw attention to the incredible value of model systems in biomedical research, and provide an exciting view of future directions.

Animal models – a palette of choices

Animal models provide a 'whole organism' context in studying biological mechanisms, and are crucial in testing and optimising delivery of new therapies before the commencement of human studies. They may be commonly referred to under the classification of invertebrates (flies, worms) and vertebrates (fish, rodents, swine, primates); or small animal (fish, rodents) and large animal (swine, primates, sheep).

Whilst organisms have their own niche area of research, the most frequently used is the humble mouse. Its prominence is attested by the fact that it was only the second mammalian species after humans to have its genome sequenced, demonstrating that both species share 99% of their genes. [1] Reasons for the popularity of mice as a choice include that mice share many anatomical and physiological similarities with humans. Other advantages include that they are small, hardy, cheap to maintain and easy to breed with a short lifespan (approximately three years), [2] allowing experiments to gather results more quickly. Common human diseases such as diabetes, heart disease, and cancer affect mice, [3] hence complex pathophysiological mechanisms such as angiogenesis and metastasis can be readily demonstrated. [2] Above all, the extraordinary ease with which mice are manipulated has resulted in the widespread availability of inbred, mutant, knockout, transgenic or chimeric mice for almost every purpose conceivable. [3] By blocking or stimulating the overexpression of specific genes, their role in developmental biology and disease can be identified and even demonstrated in specific organs. [4]

Humanised mice are another step closer in representation of what happens in the human body, thereby increasing the clinical value of knowledge gained from experiments. Humanised mice contain either human genes or tissue allowing the investigation of human mechanisms whilst maintaining an *in vivo* context within the animal. Such approaches are also available in other organisms such as rats, but are often adapted from initial advances in mice, and hardly mirror the ease and diversity with which humanised mice are produced.

Aside from the mouse, invertebrates such as the *Drosophila* vinegar fly [5] and *Caenorhabditis elegans* worm [6] are also widely used in

research of genetics or developmental biology studies. They are particularly easy to maintain and breed and therefore large stocks can be kept. Furthermore, there are fewer ethical dilemmas and invertebrates have a genome simple enough to be investigated in its entirety without being cost-prohibitive or requiring an exhaustive set of experiments. Their anatomies are also distinct and simple, allowing developmental changes to be readily visualised.

Another alternative is the Zebrafish, which shares many of the advantages offered by *Drosophila* and *C. elegans*. Additionally, it offers greater scope for investigating more complex diseases like spinal cord injury and cancer, and possesses advanced anatomical structures as a vertebrate. [7] Given the inherent capacity of the Zebrafish for cardiac regeneration, it is also of interest in regenerative medicine as we seek to harness this mechanism for human therapy. [8]

Large animals tend to be prohibitively expensive, time-consuming to manage and difficult to manipulate for use in basic science research. Instead, they have earned their place in preclinical trials. Their relatively large size and physiological similarity to humans provides the opportunity to perform surgical procedures and other interventions on a scale similar to that used clinically. Disease models created in sheep or swine are representative of the complex biological interactions that are present in highly evolved mammals; hence may be suitable for vaccine discovery. [9] Furthermore, transgenic manipulation is now possible in non-human primates, presenting an opportunity to develop humanised models. [10] Despite this, there are obvious limitations confining their use to specialised settings. Large animals need more space, are difficult to transport, require expert veterinary care, and their advanced psychosocial awareness raises ethical concerns. [9]

The clinical context of animal experimentation

A major issue directly relevant to clinicians is the predictive value of animal models. Put simply, how much of research using animals is actually clinically relevant? Although most medical therapies in use today were initially developed using animal models, it is also recognised that many animal experiments fail to reproduce their findings when translated into clinical trials. [11] The reasons for this are numerous, and require careful analysis.

The most obvious is that despite some similarities, animals are still animals and humans are humans. Genetic similarities between species as seemingly disparate as humans and mice may lead to assumptions of conserved function between humans and other animal species that

are not necessarily correct. Whilst comparing genomes can indicate similarities between two species such studies are unable to capture differences in expression or function of a gene across species that may occur at a molecular level. [12]

The effectiveness and clinical relevance of experimental animal trials is further complicated by epigenetics. Epigenetics is the modification of genetic expression due to environmental or other cues without actual change in DNA sequence. [13] These changes are now considered just as central to the pathogenesis of cancer and other conditions as genetic mutations.

It is also important to consider the multi-factorial nature of human diseases. Temporal patterns such as asymptomatic or latent phases of disease can further complicate matters. Patients have co-morbidities, risk factors, and family history, all of which contribute to disease in a way that we may still not completely understand. With such complexity, animal models do not encapsulate the overall pathophysiology of human disease. Animals may be too young, too healthy, or too streamlined in sex or genetics. [14] To obtain animals with specific traits, they are often inbred such that two animals in the same experiment will have identical genetic make-up - like twins, hardly representative of the diversity present in nature. Understandably, it can be an extraordinary challenge to incorporate all these dimensions into one study. This is especially so when the very principles of scientific method dictate that variables except for the one under experimentation should be minimised as much as possible.

A second area of concern is the sub-optimal rigour and research design of animal experiments. Scientists who conduct animal experiments and clinicians who conduct clinical trials often have different goals and perspectives. Due to ethical and cost concerns, the sample size of animal experiments is often kept to a minimum, and studies are prolonged no more than necessary, often with arbitrarily determined end-points. [14] Randomisation, concealed allocation, and blinded outcome of assessment are poorly enforced, leading to concerns of experimental bias. [11] Additionally, scientific experiments are rarely repeated due to an emphasis on originality, whereas clinical trials are often repeated (sometimes as multi-centre trials) in order to assess reproducibility of results. Furthermore, clinical trials are more likely to be published regardless of the nature of results; in contrast, scientific experiments with negative findings or low statistical significance often fail to be reported. These gaps highlight the fact that preclinical trials should be expected to adhere to the same standards and principles of clinical trials in order to improve the translatability of results between the two settings.

Although deficiencies in research conduct is a concern, the fundamental issue that remains is that even the best-designed preclinical study cannot overcome the inherent differences that exist between animal models and 'real' human patients. However, it is reassuring to know that we are becoming better at manipulating animal models and enhancing their compatibility with their human counter-parts. As such, this drive towards increasingly sophisticated animal models will provide more detailed and clinically relevant answers. Additionally, with the recognition that a single animal model is inadequate on its own, experiments may be repeated in multiple models. Each model will provide a different perspective and lead to the formation of a more comprehensive and balanced conclusion. A suggested structure is to start initial proof-of-principle experiments in small, relatively inexpensive and easily manipulated animals, and then scale up to larger animal models.

'Human' experimental models - the revolution of stem cells

Given the intrinsic differences between animals and humans, it is crucial to develop experimental systems that simulate human biology as much as possible. Stem cells are 'master cells' with the potential to differentiate into more mature cells, and are involved in the development and maintenance of organs through all stages of life from an embryo (embryonic stem cells) to adult (tissue-specific stem cells). [15] With the discovery of human embryonic stem cells [16] and other tissue-specific stem cells [17] it is now possible to appreciate the developmental biology of human tissues and organs in the laboratory. Stem cells may be studied under various controlled conditions in a culture dish, or even implanted into an animal to recapitulate *in vivo* conditions. Furthermore, stem cell transplantation has been used in animal models of disease to replace lost or damaged tissue. These methods are now commencing high-profile clinical trials with both embryonic stem cells [18] and tissue-specific stem cells. [19] Although stem cells hold great potential, translating this into the clinical environment has been hindered by several obstacles. Chiefly, tissue-specific stem cells are rare and difficult to isolate, while embryonic stem cells can only be created by destroying an embryo. In order to generate personalised embryonic stem cells for cell therapy or disease modelling, they need to be created via 'therapeutic cloning.' The considerable ethical quandary associated with this resulted in a field mired in controversy and political debate. This led to research coming almost to a standstill. Fortunately, stem cell research was rejuvenated in 2007 with the revolutionary discovery of induced pluripotent stem (iPS) cells - a discovery notable enough to be awarded the 2012 Nobel Prize in Physiology/Medicine.

Induced pluripotent stem (iPS) cells are created by reprograming mature cells (such as skin fibroblasts) back into a pluripotent 'stem cell' state, which can then re-differentiate into cells of any of the three germ layers irrespective of what its original lineage was. [20] Cells from patients with various diseases can be re-programmed into iPS cells, examined and compared to cells from healthy individuals to understand disease mechanisms and identify therapeutic opportunities. Rather than using models created in animals, this approach represents a 'complete' model where all genes contributing to a specific disease are present. Crucially, this enables the previously inconceivable notion of deriving patient-specific 'disease in a dish' models, which could be used to test therapeutic response. [21] It also provides unprecedented insight into conditions such as those affecting the heart [22] or brain, [23] which have been difficult to study due to limitations accessing tissue specimens and conducting experiments in live patients.

However, if a model system rests purely on stem cells alone this would relegate the approach to *in vitro* analysis without the whole organism outlook that animal experiments afford us. Accordingly, by combining this with rapidly evolving cell transplantation techniques it is possible to derive stem-cell based animal models. Although this field is flourishing at an exponential rate it is still in its infancy. It remains to be seen how the actual translation of iPS technology will fit into the pharmacological industry, and whether personalised drug screening assays will become adopted clinically.

Conclusion

Experimental models provide us with insight into human biology in ways that are more detailed and innovative than ever before, with a dazzling array of choices now available. Although the limitations of animal models can be sobering, they remain highly relevant in biomedical research. Their contribution to clinical knowledge can be strengthened by refining models to mimic human biology as closely as possible, and by modifying research methods to include protocols similar to that used in clinical trials. Additionally, the emergence of stem cells has shifted current paradigms by introducing patient-specific models of human development and disease. However, it should not be seen as rendering animal models obsolete, but rather a complementary methodology that should improve the predictive power of preclinical experiments as a whole.

Understanding and awareness of these advances is imperative in becoming an effective researcher. By applying these models and maximising their potential, medical students, clinicians and scientists alike will enter a new frontier of scientific discovery.

Conflict of interest

None declared.

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The hidden value of the Prevocational General Practice Placements Program

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Daniel has a key interest in general surgery. The writing of this article stemmed from his personal experiences in a Prevocational General Practice Placement in Griffith, New South Wales, as part of his internship rotations.

Medical students, prevocational doctors and general practitioners (GPs) may have little knowledge of the Prevocational General Practice Placements Program (PGPPP).

This article seeks to explore the value of such placements and provide an aspiring surgeon's reflection on a PGPPP internship placement in rural New South Wales (NSW).

General practice placements for interns have been available for the past three decades in the United Kingdom, with literature unanimously promoting the educational benefits. [1] The Australian PGPPP experiences in Western Australia and South Australia reinforce the feasibility of such placements, and propose cooperation between universities, postgraduate councils, training networks and specialist training colleges. [2] Semi-structured interviews with interns who had completed the PGPPP indicated experience in communication, counselling and procedural skills, with a range of patient presentations. [3] The uptake of the PGPPP has varied between states, with NSW until recently, having substantially fewer placements, particularly at an intern level. [4]

Prevocational GP placements have the potential to alleviate some of the pressure of sourcing additional postgraduate placements for junior doctors. With the dramatic increase of Australian medical school graduates - by 81% in seven years - overwhelming traditional postgraduate training placements, [5] the growth of PGPPP will continue. Despite available qualitative data, there is currently no published information that adequately describes the range and volume of patient and procedural experiences in PGPPP placements. In response, a prospective study of caseload data is currently underway to better inform medical students, prospective PGPPP doctors, GP supervisors and specialist training colleges of the potential value of such placements.

In April 2012, I undertook an eleven week placement at Your Health Griffith, a medical centre in Griffith, NSW. The practice was staffed by seven GPs and two practice nurses. Two GPs alternated as clinical supervisors and a third GP, separate from the practice, conducted informal weekly tutorials and reviewed patient encounter and procedure logs. Both clinical supervision and teaching exceeded RACGP standards. [6]

Presentations during a single day included complex medical or surgical issues, paediatrics, obstetrics, gynaecology, dermatology, mental health, occupational health, preventative health and more. The workload included booked appointments and consenting patients from the GP supervisors' bookings, thus ensuring a reasonable patient caseload. Patients often attended follow up appointments during this term. The continuity of patient care in PGPPP was in stark contrast to acute medicine and surgery in tertiary hospitals. This allowed establishment of greater rapport, with patients openly discussing intimate social or mental health issues during subsequent consultations.

The majority of tertiary hospitals encompass an established hierarchy of fellows, accredited and unaccredited registrars, residents and enthusiastic medical students vying for procedures. With the possible exception of emergency, most interns complete only a few procedures in hospital rotations. Hence, in PGPPP, junior doctors value the opportunities to practice procedural skills including administration of local anaesthesia, skin lesion excisions and suturing.

The main source of frustration within the placement was administrative red tape. The restrictions placed upon interns with provisional medical registration meant all scripts and referrals had to be counter-signed and conducted under the GP supervisors' provider number and prescription authority. Interns routinely prescribe medications and make referrals in the hospital system. That this authority in a supervised hospital system has not been extended to similarly supervised PGPPP is bewildering. The need to obtain formal consent prior to consults, in contrast to the implied consent in hospital treatment, was reminiscent of medical school.

One of the main purposes for the development of PGPPP was to promote general practice to prevocational junior medical officers. These placements provide junior doctors with valuable exposure to community medicine, develop confidence to deal with the uncertainty of diagnoses, a range of patient presentations, and improve counselling and procedural skills. These skills and experiences are likely to be retained regardless of future specialisation. Perhaps it is just as important for GPs to play a role in educating future tertiary care specialists, so all may better understand both the capabilities and limitations of community medicine. While I still wish to pursue a career in surgery, this placement has provided insight into the world of community medicine. The value of PGPPP truly extends beyond the attraction of prevocational doctors to general practice careers.

Conflict of interest

None declared.

Acknowledgements

Dr Marion Reeves, Dr Jekhsi Musa Othman and Dr Damien Limberger for their supervision and guidance through this clinical rotation.

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Predicting falls in the elderly: do dual-task tests offer any added value? A systematic review

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Mina spent a year working alongside some great researchers at Neuroscience Research Australia. Most of his work focused on falls in the elderly, which is very relevant today thanks to our ageing population.

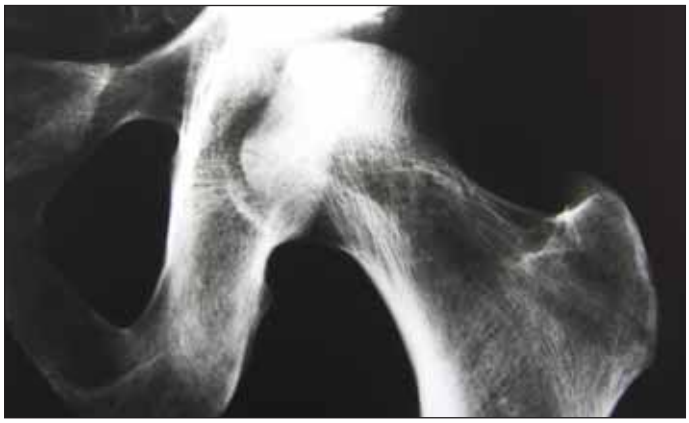
The issue of falls is a significant health concern in geriatric medicine and a major contributor to morbidity and mortality in those over 65 years of age. Gait and balance problems are responsible for up to a quarter of falls in the elderly. It is unclear whether dual-task assessments, which have become increasingly popular in recent years, have any added benefit over single-task assessments in predicting falls. A previous systematic review that included manuscripts published prior to 2006 could not reach a conclusion due to a lack of available data. Therefore, a systematic review was performed on all dual-task material published from 2006 to 2011 with a focus on fall prediction. The review included all studies published between 2006-2011 and available through PubMed, EMBASE, PsycINFO, CINAHL and the Cochrane Central Register of Controlled Trials databases that satisfied inclusion and exclusion criteria utilised by the previous systematic review. A total of sixteen articles met the inclusion criteria and were analysed for qualitative and quantitative results. A majority of the studies demonstrated that poor performance during dual-task assessments was associated with a higher risk of falls in the elderly. Only three of the 16 articles provided statistical data for comparison of single- and dual-task assessments. These studies provided insufficient data to demonstrate whether dual-task tests were superior to single-task tests in predicting falls in the elderly. Further head-to-head studies are required to determine whether dual-task assessments are superior to single-task assessments in their ability to predict future falls in the elderly.

Introduction

Many simple tasks of daily living such as standing, walking or rising from a chair can potentially lead to a fall. Each year one in three people over the age of 65 living at home will experience a fall, with five percent requiring hospitalisation. [1, 2] Gait and balance problems are responsible for 10-25% of falls in the elderly, only surpassed by 'slips and trips,' which account for 30-50%. [2] Appropriate clinical evaluation of identifiable gait and balance disturbances, such as lower limb weakness or gait disorders, has been proposed as an efficient and cost-effective practice which can prevent many of these falls. As such, fall prevention programs have placed a strong emphasis on determining a patient's fall risk by assessing a variety of physiological characteristics. [2, 3]

Dual-task assessments have become increasingly popular in recent years, because they examine the relationship between cognitive function and attentional limitations, that is, a subject's ability to divide their attention. [4] The accepted model for conducting such tests involves a primary gait or balance task (such as walking at normal pace) performed concurrently with a secondary cognitive or manual task (such as counting backwards). [4, 5] Divided attention whilst walking may manifest as subtle changes in posture, balance or gait. [5, 6] It is these changes that provide potentially clinically significant correlations, for example, detecting changes in balance and gait after an exercise intervention. [5, 6] However, it is unclear whether a patient's performance during a dual-task assessment has any added benefit over a single-task assessment in predicting falls.

In 2008, Zijlstra *et al.* [7] produced a systematic review of the literature which attempted to evaluate whether dual-task balance assessments



are more sensitive than single balance tasks in predicting falls. It included all published studies prior to 2006 (inclusive), yet there was a lack of available data for a conclusion to be made. This was followed by a review article by Beauchet *et al.* [8] in 2009 that included additional studies published up to 2008. These authors concluded that changes in performance while dual-tasking were significantly associated with an increased risk of falling in older adults. The purpose of this present study was to determine, using recently published data, whether dual-task tests of balance and/or gait have any added benefit over single-task tests in predicting falls. A related outcome of the study was to gather data to either support or challenge the use of dual-task assessments in fall prevention programs.

A systematic review of all published material from 2006 to 2011 was performed, focusing on dual-task assessments in the elderly. Inclusion criteria were used to ensure only relevant articles reporting on fall predictions were selected. The method and results of included manuscripts were qualitatively and quantitatively analysed and compared.

Methods

Literature Search

A systematic literature search was performed to identify articles which investigated the relationship between falls in older people and balance/gait under single-task and dual-task conditions. The electronic databases searched were PubMed, EMBASE, PsycINFO, CINAHL and Cochrane Central Register of Controlled Trials. The search strategy utilised by Ziljstra *et al.* [7] was carried out. Individual search strategies were tailored to each database, being adapted from the following which was used in PubMed:

1. (**gait** OR **walking** OR **locomotion** OR **musculoskeletal equilibrium** OR **posture**)
2. (**aged** OR **aged, 80 and over** OR **aging**)
3. #1 AND #2
4. (**cognition** OR **attention** OR cognitive task(s) OR attention tasks(s) OR dual task(s) OR double task paradigm OR second task(s) OR secondary task(s))
5. #3 AND #4
6. #5 AND (**humans**)

Bold terms are MeSH (Medical Subjects Headings) key terms.

The search was performed without language restrictions and results

were filtered to produce all publications from 2006 to March 2011 (inclusive). To identify further studies, the author hand-searched reference lists of relevant articles, and searched the Scopus database to identify any newer articles which cited primary articles.

Selection of papers

The process of selecting manuscripts is illustrated in Figure 1. Only articles with publication dates from 2006 onwards were included, as all relevant articles prior to this were already contained in the mini-review by Ziljstra *et al.* [7] Two independent reviewers then screened article titles for studies that employed a dual-task paradigm – specifically, a gait or balance task coupled with a cognitive or manual task – and included falls data as an outcome measure.

Article abstracts were then appraised to determine whether the dual-task assessment was used appropriately and within the scope of the present study; that is to: (1) predict future falls, or (2) differentiate between fallers and non-fallers based on retrospective data collection of falls. Studies were only considered if subjects' fall status was determined by actual fall events – the fall definitions stated in individual articles were accepted. Studies were included if participants were aged 65 years and older. Articles which focused on adult participants with a specific medical condition were also included. Studies that reported no results for dual-task assessments were included for descriptive purposes only. Interventional studies which used the dual-task paradigm to detect changes after an intervention were excluded, as were case studies, review articles or studies that used subjective

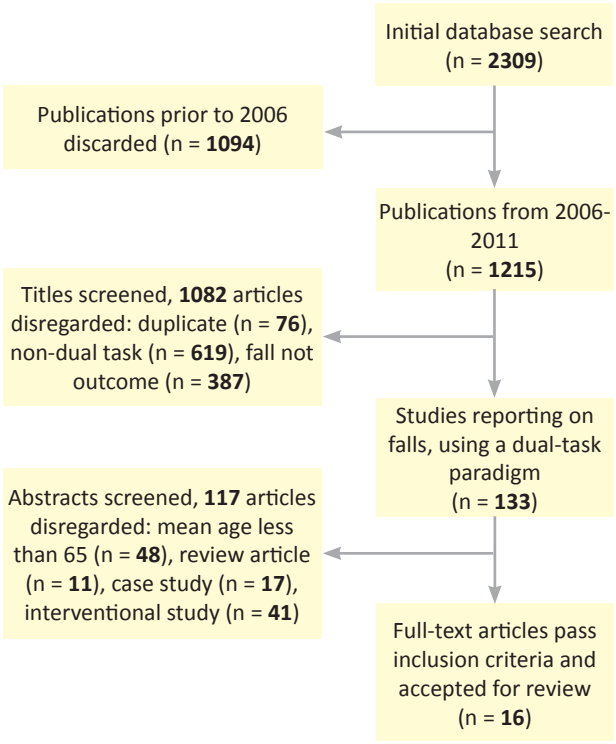


Figure 1. *Flow diagram illustrating study selection.*

Table 1A. *Retrospective studies – summary of main features.*

Study	Population	Sample size (% female)	Mean age (years ± SD)	Classification of fallers	Group sample size	Fall-data collection
Lindemann *et al.*, 2010 [23]	Patients with progressive supranuclear palsy	26 (54%)	67.5	Frequent fallers (>1 fall/month) OR infrequent fallers (≤1 fall/month)	18 frequent fallers & 8 infrequent fallers	Self-reported^
McCulloch *et al.*, 2010 [25]	Patients recovering from acute brain injury	24 (25%)	39.4 ± 13.3	Fallers (≥1 fall in previous 6 months) OR Non-fallers	13 fallers & 11 non-fallers	Self-reported~
Siu *et al.*, 2008 [10]	Community dwelling	24 (70.8%)	74.1 (HOA) & 81.0 (BIOA)	Balance impaired older adults (≥1 fall in previous 12 months) OR Healthy older adults	12 HOA & 12 BIOA	Self-reported^
Faulkner *et al.*, 2007 [12]	Community dwelling	370 (51.7%)	78 ± 3	Recurrent fallers (≥2 falls in previous 12 months) OR Non-recurrent fallers (≤1 fall in previous 12 months)	37 recurrent fallers & 333 non-recurrent fallers	Self-reported^
Melzer *et al.*, 2007 [13]	Self-care, residential facilities	100 (74%)	78.4 ± 5.7	Fallers (≥2 falls in previous 6 months) OR Non-fallers#	11 fallers & 71 non-fallers	Self-reported~
Springer *et al.*, 2006 [22]	Community dwelling	41	76.1 ± 4.8 (fallers) & 71.0 ± 5.9 (non-fallers)	Fallers (≥1 fall in previous 6 months) OR Non-fallers	17 fallers & 24 non-fallers	Self-reported~
Hyndman *et al.*, 2006 [24]	Recently discharged stroke patients	60 (41.7%)	66.5 ± 11.8 (stroke patients) & 62.3 ± 11.61 (control)	Stroke fallers OR Stroke non-fallers OR Control	36 stroke patients & 24 Control	Self-reported^
Toulotte *et al.*, 2006 [19]	Community dwelling	40 (100%)	70.4 ± 6.4 (fallers) & 67.0 ± 4.8 (non-fallers)	Fallers (≥1 fall in previous 24 months) OR Non-fallers	21 fallers & 19 non-fallers	History taken by two separate clinicians
Vaillant *et al.*, 2006 [20]	Community dwelling with osteoporosis	95 (100%)	73.4 ± 1.7	Fallers (≥1 fall in previous 12 months) OR Non-fallers	25 fallers & 70 non-fallers	Self-reported^

*DT = Dual-task, HOA = Healthy Older Adults, BIOA = Balance Impaired Older Adults, MCQ's = Multiple Choice Questions, AP = Anterior-Posterior, ML = Medial-Lateral, TUG = Timed Up & Go, ^ Over previous 12 months, ~ Over previous 6 months, * Only 'fast but safe' used during dual-task assessment, # In this particular study, subjects who fell only once were not included in either group*

scoring systems to assess dual-task performance.

Analysis of relevant papers

Information on the following aspects was extracted from each article: study design (retrospective or prospective collection of falls), number of subjects (including gender proportion), number of falls required to be classified a 'faller', tasks performed and the corresponding measurements used to report outcome, task order and follow up period if appropriate.

Where applicable, each article was also assessed for values and results which allowed comparison between the single and dual-task assessments and their respective falls prediction. The appropriate statistical measures required for such a comparison include sensitivity, specificity, positive and negative predictive values, odds ratios or likelihood ratios. [9] The dual-task cost, or difference in performance between the single and dual-task, was also considered.

Results

The database search of PubMed, EMBASE, PsycINFO, CINAHL and Cochrane produced 1154, 101, 468, 502 and 84 references respectively. As alluded to by Figure 1, filtering results for publications between 2006-2011 almost halved results to a total of 1215 references. A further 1082 studies were omitted as they fell under the category of duplicates, non-dual task studies, or did not report falls as the outcome.

The 133 articles which remained reported on falls using a dual-task approach, that is, a primary gait or balance task paired with a secondary cognitive task. Final screening was performed to ensure that the mean age of subjects was at least 65, as well as to remove case studies, interventional studies and review articles. Sixteen studies met the inclusion criteria, nine retrospective and seven prospective fall studies, summarised by study design in Tables 1A and 1B respectively.

The number of subjects ranged from 24 to 1038, [10, 11] with half the studies having a sample size of 100 subjects or more. [11-18] Females were typically the dominant participants, comprising over 70% of the subject cohort on nine occasions. [10, 13, 14, 16-21] Eight studies

Table 1A (Continued). *Retrospective studies – summary of main features.*

Study	Balance/gait task	Cognitive/secondary task	Task order randomised	Outcome(s) measured	Fall rate (%)	DT performance associated with falls?
Lindemann *et al.*, 2010 [23]	7m walk (3 speeds: slow, normal and fast but safe*)	Serial subtraction by threes, starting from 97	No	Gait parameters (gait speed, stride length and cadence) Time of backward counting	8/26 (30.8%)	Yes
McCulloch *et al.*, 2010 [25]	6m walk, then turn and walk back	Numeric memory task	No	Walking time Recall accuracy	13/24 (54.2%)	No
Siu *et al.*, 2008 [10]	10m walk (normal pace), obstacle avoidance (normal pace)	Auditory stroop task (High or low pitch voices)	Yes	Gait parameters (temporal-distance parameters, range of motion and peak velocity of the centre of mass Verbal reaction time	12/24 (50%)	Yes
Faulkner *et al.*, 2007 [12]	Straight 20m walk (normal pace), turn walk (at 10m on the 20m path)	Push-button task, Visio-spatial decision task (clock face)	Yes	Walking time Reaction time (for push-button and visiospatial decision task)	37/370 (10%)	Yes
Melzer *et al.*, 2007 [13]	Voluntary step execution test	Visual stroop task	No	Step execution times	11/100 (11%)	Yes
Springer *et al.*, 2006 [22]	Continuous walking up and down a 25m path for 2 minutes (normal pace)	10 MCQs after hearing a passage of text (simple or complex), Serial subtraction of sevens	No	Swing time, gait variability and average gait speed	17/41 (41.5%)	Yes
Hyndman *et al.*, 2006 [24]	Balance: quiet standing Gait: straight 5m walk (normal pace)	Recall of 'shopping list'	No	Balance: sway in the AP and ML directions Gait: walking time, stride length and velocity	12/60 (20%)	Yes
Toulotte *et al.*, 2006 [19]	Balance: one-leg balance test (± vision) Gait: straight 10m walk (normal pace)	Holding a glass of water in dominant hand	No	Walking speed, cadence, stride time and step time	21/40 (52.5%)	Yes
Vaillant *et al.*, 2006 [20]	TUG, One-leg balance test	Serial subtraction by two or five, or addition by three	Yes	TUG	25/95 (26.3%)	No

*DT = Dual-task, HOA = Healthy Older Adults, BIOA = Balance Impaired Older Adults, MCQ's = Multiple Choice Questions, AP = Anterior-Posterior, ML = Medial-Lateral, TUG = Timed Up & Go, ^ Over previous 12 months, ˜ Over previous 6 months, * Only 'fast but safe' used during dual-task assessment, # In this particular study, subjects who fell only once were not included in either group*

Table 1B. *Prospective studies – summary of main features.*

Study	Population	Sample size (% female)	Mean age (years ± SD)	Classification of fallers	Fall definition	Fall-data collection
Yamada *et al.*, 2011 [11]	Community dwelling	1038 (61.4%)	77 ± 8	#Fastest (230) OR Faster (258) OR Slower (264) OR Slowest (286)	"Any event that led to unplanned, unexpected contact with a supporting surface during walking"	Incident falls were collected by phone every month
Nordin *et al.*, 2010 [14]	Community dwelling	23 (72.2%)	78.0 (non-fallers) & 80.0 (fallers)	N/A	"An event in which the participant unintentionally came to rest on the floor or ground, regardless of the cause or the consequences of the fall"	Patient journal, mailed to authors monthly
Herman *et al.*, 2010 [15]	Community dwelling	262 (60.3%)	76.3 ± 4.3	Of 262, only 201 formed target cohort*	"Unintentionally coming to rest on a lower surface"	Incident falls were recorded on calendars and mailed monthly
Beauchet *et al.*, 2008 [16]	Senior housing facilities	213 (83.6%)	84.4 ± 5.5	N/A	"Unintentionally coming to rest on the ground, floor, or other lower level"	Incident falls were collected by phone every month
Beauchet *et al.*, 2008 [17]	Senior housing facilities	187 (84.5%)	84.8 ± 5.2	N/A	"Unintentionally coming to rest on the ground, floor, or other lower level"	Incident falls were collected by phone every month
Kressig *et al.*, 2008 [21]	Hospital inpatients	57 (77.2%)	85 ± 6.6	N/A	"Unintentionally coming to rest on the ground, floor, or other lower level"	Incident falls were collected by phone every month
Beauchet *et al.*, 2007 [18]	Senior housing facilities	187 (84.5%)	84.8 ± 5.2	N/A	"Unintentionally coming to rest on the ground, floor, or other lower level"	Incident falls were collected by phone every month

*DT = Dual-task, # Based on results of Timed Up & Go test, ^ Dual-task cost derived from walking speed, ~ Only for the elderly with high functional capacity (i.e. 'faster' and 'fastest' groups), $ Only for two of the five tasks (i.e. serial subtractions and carrying a cup), * Only the 201 non-fallers (at baseline) were included*

Table 1B (continued). *Prospective studies – summary of main features.*

Study	Balance/gait task	Cognitive/secondary task	Task order randomised?	Outcome(s) measured	Follow-up period	Fall rate	DT performance associated with falls?
Yamada *et al.*, 2011 [11]	Straight 15m walk (normal pace)	Cognitive: backward counting aloud from 100 Manual: carrying a ball	No	Incidence of falls & DT cost^	12 months	309/1038 (29.8%)	Yes~
Nordin *et al.*, 2010 [14]	Straight 10m walk (slow, normal and fast)	Carry cup, tray, cup & tray Naming animals Serial subtractions	No	1 or more falls & Gait parameters (step width, step time, step length)	12 months	110/230 (48%)	Yes$
Herman *et al.*, 2010 [15]	Up and down a straight 25m walk, for 2 minutes (normal pace)	Serial subtraction by threes	No	Incidence of falls & Gait variability	24 months	131/262 (50%)	Yes
Beauchet *et al.*, 2008 [16]	Straight 10m walk (normal pace)	Backward counting aloud from 50	Yes	First fall and recurrent falls & Walking speed whilst dual tasking	12 months	57/213 (26.8%)	Yes
Beauchet *et al.*, 2008 [17]	Straight 10m walk (normal pace)	Backward counting aloud from 50	Yes	First fall & Mean walking time during dual task	12 months	54/187 (28.9%)	No
Kressig *et al.*, 2008 [21]	Straight 10m walk (normal pace)	Backward counting aloud from 50	No	First fall & Coefficient variation of stride time variability during DT	12 months	10/57 (21.3%)	Yes
Beauchet *et al.*, 2007 [18]	Straight 10m walk (normal pace)	Backward counting aloud from 50	Yes	First fall & Improved counting performance	12 months	54/187 (28.9%)	Yes

*DT = Dual-task, # Based on results of Timed Up & Go test, ^ Dual-task cost derived from walking speed, ~ Only for the elderly with high functional capacity (i.e. 'faster' and 'fastest' groups), $ Only for two of the five tasks (i.e. serial subtractions and carrying a cup), * Only the 201 non-fallers (at baseline) were included*

Table 2. *Studies reporting on the predictive ability of the single and/or dual-task tests.*

	Sensitivity (%)*	Specificity (%)*	PPV (%)*	NPV (%)*	Odds Ratio: OR (95% CI) p-value	Likelihood Ratio: LR (95% CI)	Notes
Lindemann *et al.*, 2010 [23]	13/18 (72.2)	6/8 (75.0)	13/15 (86.7)	6/11 (54.5)	N/A	N/A	Figures based on number of subjects with 'Altered walking pattern during DT' (i.e. decreased stride length and increased cadence).
Faulkner *et al.*, 2007 [12]	N/A	N/A	N/A	N/A	PUSH-BUTTON TASK [a] straight walk: 1.12 (0.87-1.44) p= 0.37 [b] turn walk: 1.21 (0.97-1.51) p= 0.10 VISIO-SPATIAL TASK [a] straight walk: 1.34 (1.06-1.69) p= 0.01 [b] turn walk: 1.23 (0.99-1.51) p= 0.06	N/A	Odds ratio based on walking-time and history of recurrent falls. Adjusted for randomised task order and cane use.
Melzer *et al.*, 2007 [13]	9/11 (81.8)	N/A	N/A	N/A	N/A	N/A	Foot contact <1,100ms used by authors as cut off.
Yamada *et al.*, 2011 [11]	N/A	N/A	N/A	N/A	FASTEST GROUP MT cost: 1.068 (1.04-1.10) p <.001 FASTER GROUP CT cost: 1.03 (1.01-1.04) p <.001	N/A	MT and CT cost^ used to determine OR of future falls. No other balance/gait data reported.
Nordin *et al.*, 2010 [14]	N/A	N/A	N/A	N/A	SERIAL SUBTRACTION 2.3 (1.02-5.36)$ CARRYING A CUP [a] 0.2 (0.1-0.5)% [b] 0.4 (0.2-0.9)# [c] 0.3 (0.2-0.7)~	SERIAL SUBTRACTION 0.5 (0.3-0.9)@ CARRYING A CUP 2.3 (1.3-3.9)+	Figures based on DT cost^. LR boundaries for prognostic guidance were ≤ 0.5 or ≥ 2.0.
Herman *et al.*, 2010 [15]	N/A	N/A	N/A	133/193 (69.9)	Univariate analysis: 1.47 (1.13-1.92) Multivariate analysis: 1.39 (0.99-1.96)	N/A	OR based on gait variability during DT. Univariate and multivariate analysis reported.
Beauchet *et al.*, 2008 [16]	12/72 (16.7)	133/141 (94.3)	12/20 (60.0)	76/95 (80.0)	Single-task: 0.96 (0.94-0.99) p= 0.002 Dual-task: 0.60 (0.41-0.85) p= 0.005	N/A	OR based on walking speed and recurrent falls (i.e. ≥2). Authors calculated that decreased walking speed corresponds to increased risk of recurrent falls, 1.04 for single-task and 1.67 for DT.
Beauchet *et al.*, 2008 [17]	35/54 (64.8)	76/133 (57.1)	35/92 (38.0)	41/44 (93.2)	Single-task: 1.1 (1.0-1.2) p= 0.037 Dual-task: 1.1 (0.9-1.1) p= 0.012	N/A	OR based on walking time and first fall event.
Kressig *et al.*, 2008 [21]	7/10 (70.0)	41/47 (87.2)	7/13 (53.9)	120/133 (90.2)	Single-task: 13.3 (1.6-113.6) p= 0.018 Dual-task: 8.6 (1.9-39.6), p= 0.006	N/A	OR based on coefficient of variation of stride time and first fall event.
Beauchet *et al.*, 2007 [18]	45/52 (86.5)	117/130 (90.0)	46/54 (85.2)	120/133 (90.2)	N/A	N/A	-

OR = Odds ratio, CI = Confidence intervals, N/A = Data not available, LR = Likelihood ratio, DT = Dual-task, MT = Manual task, CT = Cognitive task
** Predictive value of the dual-task test, ^ The difference in performance between single and dual-tasks, $ If DT cost of mean step-width is ≥ ±3.6mm, % If DT cost in mean step-width is ≥ ±3.7mm, # If DT cost in step-length variability is ≥ ±7.1cm, ~ If DT cost in mean step-time is ≥ ±5.2ms, @ If DT cost in mean step-width ≤ ±3.6mm, + If DT cost in mean step-width ≤ ±3.7mm*

investigated community-dwelling older adults, [10-12, 14, 15, 19, 20, 22] four examined older adults living in senior housing/residential facilities [13, 16-18] and one focused on elderly hospital inpatients. [21] A further three studies exclusively investigated subjects with defined pathologies, specifically progressive supranuclear palsy, [23] stroke [24] and acute brain injury. [25]

Among the nine retrospective studies, the fall rate ranged from 10.0% to 54.2%. [12, 25] Fall rates were determined by actual fall events; five studies required subjects to self-report the number of falls experienced over the preceding twelve months, [10, 12, 20, 23, 24] three studies asked subjects to self-report over the previous six months [13, 22, 25] and one study utilised a history-taking approach, with subjects interviewed independently by two separate clinicians.

[19] Classification of subjects as a 'faller' varied slightly, with five studies reporting on all fallers (i.e. ≥ 1 fall), [10, 19, 20, 22, 25] three reporting only on recurrent fallers (i.e. ≥ 2 falls), [12, 13, 23] and one which did not specify. [24]

The fall rate for the seven prospective studies ranged from 21.3% to 50.0%. [15, 21] The number of falls per subject were collected during the follow-up period, which was quite uniform at twelve months, [11, 14, 16-18, 21] except for one study which continued data collection for 24 months. [15] The primary outcome measure during the follow-up period was fall rate, based on either the first fall [16-18, 21] or incidence of falls. [11, 14, 15]

The nature of the primary balance/gait task varied between studies. Five studies investigated more than one type of balance/gait task. [10, 12, 19, 20, 24] Of the sixteen studies, ten required subjects to walk along a straight walkway, nine at normal pace [10, 11, 14, 16-19, 21, 24] and one at fast pace. [23] Three studies incorporated a turn along the walkway [15, 22, 25] and a further study comprised of both a straight walk and a separate walk-and-turn. [12] The remaining two studies did not employ a walking task of any kind, but rather utilised a voluntary step execution test [13], a Timed Up & Go test and a one-leg balance test. [20]

The type of cognitive/secondary task also varied between studies. All but three studies employed a cognitive task; one used a manual task [19] and two used both a cognitive and a manual task. [11, 14] Cognitive tasks differed greatly to include serial subtractions, [14, 15, 20, 22, 23] backward counting aloud, [11, 16-18, 21] memory tasks, [24, 25] stroop tasks [10, 13] and visuo-spatial tasks. [12] The single and dual-tasks were performed in a random order in six of the sixteen studies. [10, 12, 16-18, 20]

Thirteen studies recorded walking time or gait parameters as a major outcome. [10-12, 14-17, 19, 21-25] Of all studies, eleven reported that dual-task performance was associated with the occurrence of falls. A further two studies came to the same conclusion, but only in the elderly with high functional capacity [11] or during specific secondary tasks. [14] One prospective [17] and two retrospective studies [20, 25] found no significant association between dual-task performance and falls.

As described in Table 2, ten studies reported figures on the predictive ability of the single and/or dual-tasks; [11-18, 21, 23] some data was obtained from the systematic review by Beauchet *et al.* [8] The remaining six studies provided no fall prediction data. In predicting falls, dual-task tests had a sensitivity of 70% or greater, except in two studies which reported values of 64.8% [17] and 16.7%. [16] Specificity ranged from 57.1% to 94.3%. [16, 17] Positive predictive values ranged from to 38.0% to 86.7%, [17, 23] and negative predictive values from 54.5% to 93.2%. [21, 23] Two studies derived predictive ability from the dual-task 'cost', [11, 14] which was defined as the difference in performance between the single and dual-task test.

Only three studies provided statistical measures for the fall prediction of the single task and the dual-task individually. [16, 17, 21] Increased walking time during single and dual-task conditions were similarly associated with risk of falling, OR= 1.1 (95% CI, 1.0-1.2) and OR= 1.1 (95% CI, 0.9-1.1), respectively. [17] Variation in stride time also predicted falls, OR= 13.3 (95% CI, 1.6-113.6) and OR= 8.6 (95% CI, 1.9-39.6) in the single and dual-task conditions respectively. [21] Walking speed predicted recurrent falls during single and dual-tasks, OR = 0.96 (95% CI, 0.94-0.99) and OR= 0.60 (95% CI, 0.41-0.85), respectively. [16] The later study reported that a decrease in walking speed increased risk of recurrent falls by 1.67 in the dual-task test compared to 1.04 during single-task. All values given in these three studies, for both single and dual-task tests, were interpreted as significant in predicting falls by their respective authors.

Discussion

Only three prospective studies directly compared the individual predictive values of the single and dual-task tests. The first such study concluded that the dual-task test was in fact equivalent to the single-task test in predicting falls. [17] This particular study also reported the lowest positive predictive value of all dual-task tests at 38%. The second study [21] also reported similar predictive values for the single and dual-task assessments, as well as a relatively low positive predictive value of 53.9%. Given that all other studies reported higher predictive values, it may be postulated that at the very least, dual-task tests are comparable to single-task tests in predicting falls. Furthermore, the two studies focused on subjects from senior housing facilities and hospital inpatients (187 and 57 participants respectively), and therefore results may not represent all elderly community-dwelling individuals. The third study [16] concluded that subjects who walked slower during the single-task assessment would be 1.04 times more likely to experience recurrent falls than subjects who walked faster. However, after a poor performance in the dual-task assessment, their risk may be increased to 1.67. This suggests that the dual-task assessment can offer a more accurate figure on risk of falling. Again, participants tested in this study were recruited from senior housing facilities, and thus results may not be directly applicable to the community-dwelling older adult.

Eight studies focused on community-dwelling participants, and all but one [20] suggested that dual-task performance was associated with falls. Evidence that dual-task assessments may be more suitable for fall prediction in the elderly who are healthier and/or living in the community as opposed to those with poorer health is provided by Yamada *et al.* [11] Participants were subdivided into groups by results of a Timed Up & Go test, separating the 'frail' from the 'robust'. It was found that the dual-task assessments were associated with falls only in groups with a higher functional capacity. This intra-cohort variability may account for, at least in part, why three studies included in this review concluded that there was no benefit in performing dual-task assessments. [17, 20, 25] These findings conflicted with the remaining thirteen studies and may be justified by one or all of several possible reasons: (1) the heterogeneity of the studies, (2) the non-standardised application of the dual-task paradigm, or (3) the hypothesis that dual-task assessments are more applicable to specific subpopulations within the generalised group of 'older adults', or further, that certain primary and secondary task combinations must be used to produce favourable results.

The heterogeneity among the identified studies played a major role in limiting the scope of analysis and potential conclusions derived from this review. For example, the dichotomisation of the community-dwelling participants in to frail versus robust [11] illustrates the variability within a supposedly homogenous patient population. Another contributor to the heterogeneity of the studies is the broad range of cognitive or secondary tasks used, which varied between manual tasks [19] and simple or complex cognitive tasks. [10-21, 23-25] The purpose of the secondary task is to reduce attention allocated to the primary task. [5] Since the studies varied in secondary task(s) used, each with a slightly different level of complexity, attentional resources redirected away from the primary balance or gait task would also be varied. Hence, the ability of each study to predict falls is expected to be unique, or poorer, in studies employing a secondary task which is not sufficiently challenging. [26] One important outcome from this review has been to highlight the lack of a standardised protocol for performing dual-task assessments. There is currently no identified combination of a primary and secondary task which has proven superiority in predicting falls. Variation in the task combinations, as well as varied participant instructions given prior to the completion of tasks, is a possible explanation for the disparity between results. To improve result consistency and comparability in this emerging area of research, [6] dual-task assessments should be comprised of a standardised primary and secondary task.

Sixteen studies were deemed appropriate for inclusion in this systematic review. Despite a thorough search strategy, it is possible

that some relevant studies may have been overlooked. Based on limited data from 2006 to 2011, the exact benefit of dual-task assessments in predicting falls compared to single-task assessments remains uncertain. For a more comprehensive verdict, further analysis is required to combine previous systematic reviews, [7, 8] which incorporates data prior to 2006. Future dual-task studies should focus on fall prediction and report predictive values for both the single-task and the dual-task individually in order to allow for comparisons to be made. Such studies should also incorporate large sample sizes, and assess living conditions and health status of participants. Emphasis on the predictive value of dual-task assessments requires these studies to be prospective in design, as prospective collection of fall data is considered the gold standard. [27]

Conclusion

Due to the heterogeneous nature of the study population, the limited statistical analysis and a lack of direct comparison between single-task and dual-task assessments, the question of whether dual-task assessments are superior to single-task assessments for fall prediction remains unanswered. This systematic review has highlighted significant variability in study population and design that should be taken into account when conducting further research. Standardisation of dual-task assessment protocols and further investigation and characterisation of sub-populations where dual-task assessments may offer particular benefit are suggested. Future research could focus on different task combinations in order to identify which permutations provide the greatest predictive power. Translation into routine clinical practice will require development of reproducible dual-task assessments that can be performed easily on older individuals and have validated accuracy in predicting future falls. Ultimately, incorporation of dual-task assessments into clinical fall prevention programs should aim to provide a sensitive and specific measure of effectiveness and to reduce the incidence, morbidity and mortality associated with falls.

Acknowledgements

The author would like to thank Professor Stephen Lord and Doctor Jasmine Menant from Neuroscience Research Australia for their expertise and assistance in producing this literature review.

Conflict of interest

None declared.

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Where to from here for Australian childhood obesity?

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Aim: At least one in twenty Australian school children are obese. [1] The causes and consequences of childhood obesity are well documented. This article examines the current literature on obesity management in school-aged, Australian children. **Methods:** A systematic review was undertaken to examine the efficacy of weight management strategies of obese Australian school-aged children. Search strategies were implemented in Medline and Pubmed databases. The inclusion criteria required original data of Australian origin, school-aged children (4 to 18 years), BMI defined populations and publication within the period of January 2005 to July 2011. Reviews, editorials and publications with inappropriate focus were excluded. Thirteen publications were analysed. **Results:** Nine of the thirteen papers reviewed focused on general practice (GP) mediated interventions, with the remainder utilising community, school or tertiary hospital management. Limitations identified by GP-led interventions included difficulties recognising obese children, discussing obesity with families, poor financial reward, time constraints, and a lack of proven management strategies. A school-based program was investigated, but was found to be ineffective in reducing obesity. Successful community-based strategies focused on parent-centred dietary modifications or exercise alterations in children. **Conclusion:** Obesity-specific management programs of children are scarce in Australia. As obesity remains a significant problem in Australia, this topic warrants further focus and investigation.

Introduction

In many countries the level of childhood obesity is rising. [2] Whilst the popular press have painted Australia as being in a similar situation, research has failed to identify significant increases in the level of childhood obesity since 1997, and in fact, recent data suggests a small decrease. [2,3] Nonetheless, an estimated four to nine percent of school-aged children are obese. [1,4] Consequently, the Australian government have pledged to reduce the prevalence of childhood obesity. [5]

In this review, articles defined Body Mass Index (BMI) by dividing weight (in kilograms) by the square of the height (in metres). [1] BMI was then compared to age- and gender-specific international set points. [6] Obesity was defined as children who had a BMI ≥ 95% of children with the same age and gender. [6] The subjects of this review, Australian school-aged children, were defined as those aged 4 to 18 years in order to include most children from preschool to the completion of secondary school throughout Australia. As evidence suggests that obese individuals have significantly worse outcomes than overweight children, this review focused on obesity rather than overweight and obese individuals. [1]

The aim of this article was to examine the recent Australian literature on childhood obesity management strategies.

Background

Causes of obesity

A myriad of causes of childhood obesity are well established in the literature. Family and culture influence a child's eating habits, their level of physical activity and ultimately their weight status. [4,7,8] Parental attributes such as maternal obesity and dismissive or

disengaged fathers also play a role. [9] Notably, maternal depression or inappropriate parenting styles have little effect on obesity. [10] Children from lower socio-economic status (SES) are at a greater risk of being obese. [9,11-13]

Culture and genetic inheritance also influence a child's chance of being obese. [8] Evidence suggests that culture influences an individual's beliefs regarding body size, food and exercise. [7,14] O'Dea (2008) found that Australian children of European and Asian descent had higher rates of obesity when compared with those of Pacific Islander or Middle Eastern heritage. [8] Interestingly, there is conflicting evidence as to whether being an Indigenous Australian is an independent risk factor for childhood obesity. [7,9]

A child's nutritional knowledge has little impact on their weight. Several authors have shown that while obese and non-obese children have different eating styles, they possess a similar level of knowledge about food. [4,13] Children with a higher BMI had lower quality breakfast and were more likely to omit meals in comparison to normal weight children. [4,7,13]

The environment in which a child lives may impact their weight status; existing literature suggests that the built environment has little influence over dietary intake, physical activity and ultimately weight status. [15,16] However, there is limited research presently available.

Consequences of obesity

Obesity significantly impacts a child's health, resulting in poorer physical and social outcomes. [4,17] Obese children are at greater risk of becoming obese in adulthood. [4,18] Venn *et al.* (2008) estimates that obese children are at a four- to nine-fold risk of becoming obese adults. [18] Furthermore, obese children have an increased risk of acquiring type 2 diabetes, sleep apnoea, fatty liver disease, arthritis and cardiovascular disease. [4,19]

An individual's social health is detrimentally affected by childhood obesity. Obese children have significantly lower self worth, body image and perceived level of social acceptance amongst their peers. [7,20,21] Indeed, overall social functioning is reduced in obese children. [17] Interestingly, some studies identify no differing rates of mental illness or emotional functioning between obese and non-obese children. [12,17,22,23]

Method

Using Medline and Pubmed, searches were undertaken with the following MeSH terms: child, obesity and Australia. Review and editorial publication types were excluded, as only original data was sought for analysis. Further limits to the search included literature available in English, focused on school-aged children from 4 to 18 years, articles which defined obesity in their population using BMI, publications which addressed the research question (management of childhood obesity), and recent literature. Recent literature was defined as articles published from 1 January 2005 until 31 July 2011. This restriction was placed in part due to resource constraints, but January 2005 was specifically chosen, as this marked the introduction of several Australian government strategies to reduce childhood obesity. [5]

In total, 280 publications were identified in the Pubmed and Medline searches. The abstracts of these articles were manually assessed by the investigator for relevance to the research question and described inclusion and exclusion criteria. As a result of inappropriate topic focus, population, publication type, publication date and repetition, 265 articles were excluded. Ten articles were identified as pertinent via Pubmed. Medline searches revealed five articles of relevance, all of which were duplicated in the Pubmed search. Hence, ten publications were examined. Additionally, a search of relevant publications' reference lists identified three further articles for analysis. Subsequently, this paper reviews thirteen articles.

Publications included in this study were either randomised controlled trials or cross-sectional analyses. The papers collected data from a variety of sources, including children, parents, clinicians and simulated patients. Consequently, population sizes varied greatly throughout the literature.

Results

Much of the Australian literature on childhood weight management does not specifically focus on the obese; instead, it combines the outcomes of obese and overweight children, sometimes including normal weight children.

Thirteen intervention articles were identified in the literature, nine of which employed GP mediated interventions, with the remainder using a community-based approach, school-based or tertiary hospital mediated obesity management.

General practitioner intervention

The National Health and Medical Research Council (NHMRC) guidelines recommend biannual anthropometric screening for children; however, many studies illustrate that few GPs regularly weigh and measure children. [24,25] Whilst Dettori *et al.* (2009) reported 79% of GPs interviewed measure children's weight and height, only half of their respondents regularly converted these figures to determine if a child was obese. [26] A possible reason for the low rates of BMI calculation may be that many GPs find it difficult to initiate discussions about weight status in children. [24-27] A number of authors have identified that some GPs fear losing business, alienating or offending their clients. [24,25,27]

There was wide variability in the tools GPs used to screen children, which may ultimately have led to incorrect weight classifications. [24] Spurrier *et al.* (2006)investigated this further, identifying that GPs may use visual cues to identify normal weight children; however, using visual cues alone GPs are not always able to recognise an obese from an overweight child or an overweight from a normal weight child. [28] Hence, GPs may fail to identify obese children if appropriate anthropometric testing is not performed.

There is mixed evidence regarding the willingness of GPs to manage obese children. Firstly, McMeniman *et al.* (2007) identified that GPs felt there was a lack of clear management guidelines, with the majority of participants feeling they would not be able to successfully treat an obese child. [27] Some studies identified that GPs see their role as gatekeeper for allied health intervention. [24,25] Another study showed that GPs preferred shared care, providing the primary support for obese children, which involved offering advice on nutrition, weight and exercise, whilst also referring onto other health professionals such as nutritionists, dieticians and physicians. [11]

Other factors impeding GP-managed programs are time and financial constraints. The treatment of childhood obesity in general practice is time consuming. [11,26,27] Similarly, McMeniman *et al.* [27] highlighted that the majority of responders (75%) felt that there was not adequate financial incentive to identify and manage obese children.

Evidence suggests that providing education to GPs on identifying and managing obesity could be useful in building their confidence. [26] One publication found that over half of GPs receiving education were able to better identify obese children. [26] Similarly, Gerner *et al.* (2010) illustrated, by using simulated patients, that GPs felt they had improved their competence in the management of obese children. [29] In the Live, Eat and Play (LEAP) trial, patient outcomes at nine months were compared to GP's self-rated competence, simulated patient ratings and parent ratings on consultations. [29] Interestingly, simulated patient ratings were shown to be a good predictor of real patient outcomes, with higher simulated patient marks correlating to larger drop in a child's BMI. [29]

Unfortunately, no trials illustrated an effective GP-led child obese management strategy. The LEAP trial, a twelve week GP-mediated intervention focused on nutrition, physical exercise and the reduction of sedentary behaviour, failed to show any significant decrease in BMI of the intervention group compared with the control. [30] Notably, the LEAP trial failed to separate the data of obese and non-obese children. [30]

Further analysis of the LEAP trial illustrated that the program was expensive, with the cost to an intervention family being $4094 greater than of that to a control family. [31] This is a significant burden on families, with an additional fiscal burden of $873 per family to the health sector. [31] Whilst these amounts are likely to be elevated due to the small number of children, program delivery is costly for both families and the health care sector. [31]

Community-based programs

Literature describing community-based obesity reduction was sparse. Two publications were identified, both of which pertained to the HICKUP trial. These articles illustrated that parent-centred dietary program and child-focused exercise approaches can be efficacious in weight reduction in a population of children including the obese. [32,33] In this randomised controlled trial, children were divided into three groups: i) parent-focused dietary program, ii) child-centred exercise, and iii) combination of the aforementioned. [32,33] Dietary programs focused on improving parenting skills to provide behavioural change in children, whilst physical activity program involved improving children's fundamental skills and competence. [32,33] A significant limitation of the study was that children were identified through responding to advertising in school newsletters and GP practices, lending this investigation to volunteer bias. Additionally, the outcome data in these studies failed to delineate obese children from overweight or normal weight children.

School-based programs

Evidence suggests that an education and exercise-based program can be implemented into a school system. [34] The Peralta *et al.* (2009) intervention involved a small sample of twelve to thirteen year old boys who were either normal weight, overweight or obese, and were randomised to a control or intervention group. [34] The program's curriculum focused on education as well as increasing physical activity. Education sessions were based on dietary awareness, goal setting and

behavioural modification. [34] This randomised control trial failed to identify any change in the BMI of individuals who participated in the intervention versus those in the control group. [34]

Tertiary hospital interventions

The literature search highlighted a single article describing weight management programs in tertiary hospitals throughout Australia. In 2008, Spilchak *et al.* [35] identified nine dedicated services. Approaches included BMI, exercise and sedentary behaviour assessment, as well as modification of dietary intake and patient review. [35] The study highlights several limitations to these services. Firstly, services are only available in three states. [35] In addition, children were waiting an average of five months for an appointment, and the services were only available to the severely obese. [35] A further issue is that only three services perform in-house appraisals to determine the effectiveness of their treatment regime. [35]

Discussion

This review highlights the poorer physical and social outcomes of obese Australian children. The findings emphasise the need for effective management strategies to reduce the current rates of obesity amongst younger Australians. However, data on the management of obese Australian children is lacking.

Out of the publications discussed, all six articles initiating intervention failed to delineate the outcomes of obese children from non-obese overweight children. This was an unexpected finding for several reasons: childhood obesity is more detrimental than being overweight, obesity is prevalent amongst Australian children and notably, the Australian government's recent commitment to reducing obesity. Additionally, if populations were stratified into obese or non-obese, the efficacy of studies may have been more favourable.

GPs have access to a large proportion of Australian school children each year. Ideally, general practices could be used as a gateway to identify, treat and refer children whom are obese. Studies have illustrated that there are many limitations in the ability of GPs to manage obese children, including identification, practitioner willingness, time and financial constraints. [24-27]

There remains scarce evidence for GP mediated programs, with the only intervention identified failing to be efficacious. More interventions assessing the effectiveness of GPs managing childhood obesity should be undertaken. Additionally, further funding and education should be provided to GPs to encourage them to identify and manage obese children.

Wake *et al.* (2008) illustrated that implementing GP-based programs is expensive for both families and the health care sector. [31] Given that children from lower socioeconomic backgrounds are more likely to be obese than affluent children, this could prove to be an overwhelming barrier to receiving GP-managed obesity therapy.

Programs run in the community focusing on parent-centred dietary changes and children increasing physical exercise can be successful in reducing the weight of obese children. [32,33] Despite being labour intensive and requiring specialised staff, community-based initiatives can have long-term reduction in the level of obese children. Further investigation utilising the HICKUP trial method should be undertaken to determine the specific outcome of obese children.

While it is encouraging that some publications are available on school-based initiatives, data remains rare. Peralta *et al.* (2009) have shown that weight management programs can be operated in schools; however, this intervention did not reduce BMI. [34] Schools have regular access to children and could encourage exercise through a variety of avenues including physical education lessons, lunchtime games, extracurricular activities, as well as provide educational sessions. As a result, school-based programs could be efficacious in reducing the number of obese school children.

Obesity management services at tertiary hospitals are scarce within Australia. These services should evaluate the efficacy of their approaches and make these findings available to the community, so that lessons learnt from these programs can be applied to other intervention strategies.

Limitations

In total, thirteen publications were reviewed for this summary. The literature considered could have been expanded by inclusion of data from other developed countries. This was not undertaken as the Australian community operates under a unique healthcare system. Using a broader range of search engines, such as EMBASE, may have identified further data. This study reviewed several publications that used convenience sampling, leading to the possibility of volunteer bias and the ultimate skewing of data. In addition, many of the publications investigated a subset of the childhood population. None of the 13 publications utilised the 4 to 18 year age range. As a result, some of the evidence may not be able to be applicable to this wider population.

Conclusion

This review has considered the existing Australian literature on childhood obesity interventions. Obese children are at an increased risk of detrimental health outcomes when compared with their peers. It is vitally important that effective interventions are developed to reduce childhood obesity in Australia.

Current evidence on the effectiveness of interventions is lacking. Present intervention trials using GP, community, and school-based management should delineate between overweight and obese children. Further research in each of these areas should be undertaken, to better determine their effectiveness. Similarly, tertiary hospital-based programs should be expanded to cater for a wider population of obese children. Each of these strategies requires further funding as well as commitment from the Australian government, practitioners, and community.

Conflict of interest

None declared.

Acknowledgements

Dr. Jason Abbott, Royal Hospital for Women, Randwick for selection of topic for review.

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A biological explanation for depression: The role of interleukin-6 in the aetiology and pathogenesis of depression and its clinical implications

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Stephy has a special interest in mental health, particularly in rural and remote Australia. She hopes to promote awareness about the importance of mental health in communities by breaking down the negative perception surrounding it. In the near future, she hopes to also conduct research in the field of mental health in Indigenous populations.

Depression is one of the most common health problems addressed by general practitioners in Australia. It is well known that biological, psychosocial and environmental factors play a role in the aetiology of depression. Research into the possible biological mechanisms of depression has identified interleukin-6 (IL-6) as a potential biological correlate of depressive behaviour, with proposed contributions to the aetiology and pathogenesis of depression. Interleukin-6 is a key proinflammatory cytokine involved in the acute phase of the immune response and a potent activator of the hypothalamic-pitutary-adrenal axis. Patients with depression have higher than average concentrations of IL-6 compared to non-depressed controls, and a dose-response correlation may exist between circulating IL-6 concentration and the degree of depressive symptoms. Based on these insights the 'cytokine theory of depression' proposes that proinflammatory cytokines, such as IL-6, act as neuromodulators and may mediate some of the behavioural and neurochemical features of depression. Longitudinal and case-control studies across a wide variety of patient cohorts, disease states and clinical settings provide evidence for a bidirectional relationship between IL-6 and depression. Thus IL-6 represents a potential biological intermediary and therapeutic target for the treatment of depression. Recognition of the strong biological contribution to the aetiology and pathogenesis of depression may help doctors to identify individuals at risk and implement appropriate measures, which could improve the patient's quality of life and reduce disease burden.

Introduction

Our understanding of the immune system has grown exponentially within the last century, and more questions are raised with each new development. Over the past few decades research has emerged to suggest that the immune system may be responsible for more than just fighting everyday pathogens. The term 'psychoneuroimmunology'was first coined by Dr Robert Ader and his colleagues in 1975 as a conceptual framework to encompass the emerging interactions between the immune system, the nervous system, and psychological functioning. Cytokines have since been found to be important mediators of this relationship. [1] There is considerable research that supports the hypothesis of proinflammatory cytokines, in particular interleukin-6 (IL-6), in playing a key role in the aetiology and pathophysiology of depression. [1-5] While both positive and negative results have been reported in individual studies, a recent meta-analysis supports the association between depression and circulating IL-6 concentration. [6] This review will explore the impact of depression in Australia, the role of IL-6 and the proposed links to depression and clinical implications of these findings.

Depression in Australia and its diagnosis

Depression belongs to a group of affective disorders and is one of the most prevalent mental illnesses in Australia. [7] It contributes to one of the highest disease burdens in Australia, closely following cancers and cardiovascular diseases. [7] Most of the burden of mental illness, measured as disability adjusted life years (DALYs), is due to years of life lost through disability (YLD) as opposed to years of life lost to death (YLL). This makes mental disorders the leading contributor (23%) to the non-fatal burden of disease in Australia. [7] Specific populations, including patients with chronic disease, such as diabetes, cancer,

cardiovascular disease, and end-stage kidney disease, [1,3,4,10] are particularly vulnerable to this form of mental illness.[8, 9] The accurate diagnosis of depression in these patients can be difficult due to the overlapping of symptoms inherent to the disease or treatment and the diagnostic criteria for major depression. [10-12] Nevertheless, accurate diagnosis and treatment of depression is essential and can result in real gains in quality of life for patients with otherwise incurable and progressive disease. [7] Recognising the high prevalence and potential biological underpinnings of depression in patients with chronic disease is an important step in deciding upon appropriate diagnosis and treatment strategies.

Role of IL-6 in the body

Cytokines are intercellular signalling polypeptides produced by activated cells of the immune system. Their main function is to coordinate immune responses; however, they also play a key role in providing information regarding immune activity to the brain and neuroendocrine system. [13] Interleukin-6 is a proinflammatory cytokine primarily secreted by macrophages in response to pathogens. [14] Along with interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), IL-6 plays a major role in fever induction and initiation of the acute-phase response. [14] The latter response involves a shift in the composition and abundance of proteins synthesised and secreted by the liver, favouring several acute phase proteins that act like broad spectrum antibodies to opsonise pathogens and activate complement cascade. [14] Some examples of these include C-reactive protein (CRP), mannan-binding lectin and serum amyloid protein. [14] Interleukin-6 also regulates T-cell activation and proliferation, B cell growth and differentiation, antibody production and prostaglandin secretion. [15]

Numerous studies in human and animal models have shown that inflammatory cytokines can induce 'sickness behaviour.' Sickness behaviour consists of a group of symptoms including fatigue, anorexia, anhedonia, psychomotor retardation, altered sleep patterns, defects in learning and memory and reduction of personal hygiene and grooming. [16] The signs and symptoms that accompany immunologic responses to infection overlap significantly with the symptoms seen in the development and maintenance of depression. [11,17,18] Of the numerous cytokines secreted in the inflammatory response, IL-6 has shown a particularly robust association with depressive symptoms. [6] Numerous studies have documented higher than normal plasma concentrations of IL-6 in depressed individuals compared to non-

depressed, healthy controls. [1-4,9,11,18] This positive association has been consistently demonstrated in both clinical and community based trials. As a result of this, special attention has been placed on the role of IL-6 in the aetiology and pathogenesis of depression.

Proposed links between IL-6 and depression

The 'cytokine theory of depression' proposes that proinflammatory cytokines such as IL-6 act as neuromodulators and may mediate some of the behavioural and neurochemical features of depression. [4] In addition to depressed individuals possessing higher than average concentrations of IL-6, [6] it has been suggested that a dose-response relationship may exist between IL-6 concentration and the severity of depressive symptoms. [11,18] Higher concentrations of cytokines may therefore induce greater degrees of 'sickness behaviour.' Furthermore, Maes *et al.* [5] reported that plasma concentrations of soluble IL-6 receptor (sIL-6R) were significantly increased in patients with major depression. They proposed that the positive relationship between IL-6 and sIL-6R concentrations may be due to the hyperproduction of IL-6, causing an upregulation of the expression of IL-6 receptor mRNA. This simultaneous upregulation of IL-6 and sIL-6R in the plasma of patients with major depression may have a synergistic effect on the biological activities of IL-6. From these findings, the study hypothesised that IL-6 may elicit a greater biological response in depressed subjects than estimated from the plasma IL-6 values alone. [5]

An early study by Dentino *et al.* [17] postulated that the pathophysiologic mechanism between the observed 'sickness behaviour' and IL-6 levels was due to an immunoendocrine dysregulation. Interleukin-6 is a potent activator of all three of the organs in the hypothalamic-pituitary-adrenal axis and thus may independently stimulate an increased production of cortisol.[10,11,15,19] Sustained elevation in circulating IL-6 eventually leads to chronic pathologic hyperactivity of the HPA axis. [20] Furthermore, inflammation is possibly not the only initiator of IL-6 secretion. [21] Interleukin-6 production can also be stimulated by catecholamines in a time-dose dependent manner. [21] This suggests that strong emotional stress could induce elevated levels of plasma IL-6 independent of any inflammatory process. The hypothesis of HPA axis dysregulation has been supported in more recent studies and remains one of the key explanations for the link between IL-6 and depression. [10,15,17,20] The mechanism by which IL-6 can activate the HPA axis is not fully understood. However, some studies have reported that elevated concentrations of IL-6 induce a state of impaired glucocorticoid-mediated negative feedback on the HPA axis via inhibition of the glucocorticoid receptor. [10,22] This results in HPA hyperactivation.[10,22] In support of this concept, many observational studies have noted a decrease in the relative diurnal variation of plasma cortisol as well as reduced suppression of cortisol values post dexamethasone administration in depressed patients compared with healthy control subjects. [4,10,11,15]

While intriguing and consistent across many studies in a variety of settings, it should be recognised that associations between IL-6 concentrations and depression have not been observed in every published report. Brambilla *et al.* [23] compared IL-6 plasma concentrations in ten elderly women with major depressive disorder with ten age-matched healthy females and found no significant differences. Similar findings were reported in a study conducted by Kagaya *et al.* [24] which compared depressed patients in Japan with control subjects. Furthermore, the relationship and extent of IL-6 involvement in the clinical manifestations of different types of depression is yet to be determined. Therefore a generalised pattern between IL-6 concentrations and depressive symptoms still needs to be fully defined. [6] Alternative explanations for the relationship between IL-6 and depressive symptoms include the potential confounding effect of IL-6 as a generic marker of the acute phase response. Many other inflammatory cytokines, including IL-1, TNF-α, interleukin-2 (IL-2) and interferon-gamma have shown similar associations with depression. [4,15] Müller *et al.* [25] recently reported that IL-2, interferon-gamma and TNF-α activate the tryptophan and serotonin degrading enzyme, indoleamine 2,3-dioxygenase, leading to a reduction in tryptophan and serotonin levels. Decreased serotonin concentrations have been robustly linked to the development of depressive symptoms and pharmacotherapies aimed at enhancing serotonin signalling are the mainstay of current treatment regimes for depression. [26] Although a number of studies have shown that proinflammatory cytokines, such as IL-1, IL-2 and interferon-gamma, may contribute to the development of depressive symptoms, a recent meta-analysis reported that these associations were not significant. [6] However, the consistency and nature of the relationship between IL-6, depression and the severity of depressive symptoms has lead many experts to believe that IL-6 may have a causative role in the aetiology and pathogenesis of depression. [19] Other proinflammatory cytokines have not been shown to have the same potent effect that IL-6 exerts on the HPA axis. [11,15] Given that HPA dysfunction is hypothesised as one of the main drivers of depression symptoms, it can be inferred that IL-6 plays a notable role in the onset and progression of depression. Interestingly, there have also been recent reports that suggest a similar association between circulating IL-6 levels and patients with schizophrenia. [27]

Causal Pathways

The cause-effect relationship between inflammation and depression has been researched extensively. The literature strongly suggests that a complex, bidirectional process exists between depression and inflammation. [28] It is likely that these two processes are part of a complex feedback loop that involves the neuroendocrine and immune systems. A major, long-term prospective cohort study conducted by Stewart *et al.* [29] found that the level of depressive symptoms was a predictor of six year change in IL-6, thus implying that depression may lead to inflammation. In 2001 Musselman *et al.* [3] posed that, if proinflammatory cytokines like IL-6 were to play a direct role in inducing major depression, then patients with diseases associated with immune activation may be at increased risk for depression. [3] It has since been shown that rheumatoid arthritis, Alzheimer's disease, cancer and coronary artery disease are all associated with an increase in the concentration of inflammatory markers and possess a clear association with depression. [30-32] These findings imply that immune activation due to a biological disorder may precipitate, or aggravate, depression-like symptoms. [8, 9] While those longitudinal studies that do exist [9, 29] support the bidirectional nature of the relationship between IL-6 and depression, it should be noted that most of the studies investigating the relationship between IL-6, depression and chronic disease are cross-sectional and thus cause and effect relationships cannot be directly inferred. [11] Further elucidation of the causal pathways between depression and inflammatory cytokines will require more prospective studies to be carried out in community based and clinical samples. [18]

Clinical implications

The association between depression and circulating IL-6 concentration is supported by a large number of longitudinal and case-control studies across a wide range of patient cohorts, disease states, and clinical settings. [1,5,6, 11,17,18] This has many implications for the health of individuals with depression. Interleukin-6 stimulates CRP production, which influences the initiation and progression of atherosclerosis [33] and may also promote growth of certain types of cancer by inhibiting apoptosis and facilitating angiogenesis in solid tumours.[34, 35] Therefore, a plausible link between depression and an increased risk of cardiovascular diseases and cancer must be considered, especially in patients with other comorbidities. Our understanding of the role of IL-6 in depression also opens many avenues for novel antidepressant therapies. Inflammatory cytokine synthesis inhibitors (for example, pyridinyl imidazole compounds), cytokine antagonists and anti-inflammatory cytokines may be incorporated into the management of mood disorders. [16,36,37] One day patients may receive immunotherapy to reduce or eliminate the cytokine-induced 'sickness

behaviours.' [36] Educating the community about these findings may help alleviate the negative stigma that commonly surrounds mental health disorders. [38] This could increase the likelihood for presentation to doctors, which means an earlier diagnosis can be made and appropriate treatment plans implemented to maximise the quality of life for individuals with depression. [38]

Conclusion

The importance of IL-6 in the aetiology and progression of depression has been implied in a number of studies. The level of IL-6 in the blood appears to be correlated with the degree of depressive symptoms. Dysregulation of the HPA axis has been strongly implicated as the major biological mechanism behind this link. A better understanding of IL-6 may lead to the development of innovative anticytokine antidepressant therapies, which could fundamentally change the way depression is perceived and treated.

Conflict of interest

None declared.

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The therapeutic potentials of cannabis in the treatment of neuropathic pain and issues surrounding its dependence

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Cannabis is a promising therapeutic agent, which may be particularly beneficial in providing adequate analgesia to patients with neuropathic pain intractable to typical pharmacotherapy. Cannabinoids are the lipid-soluble compounds that mediate the analgesic effects associated with cannabis by interacting with the endogenous cannabinoid receptors CB_1 and CB_2, which are distributed along neurons associated with pain transmission. From the 60 different cannabinoids that can be found in cannabis plants, delta-9 tetrahydrocannabinol (THC) and cannabidiol are the most important in regards to analgesic properties. Whilst cannabinoids are effective in providing diminished pain responses, their therapeutic use is limited due to psychotropic side effects via interaction with CB_1, which may lead to cannabis dependence. Cannabinoid ligands also interact with glycine receptors, selectively to CB_2 receptors, and act synergistically with opioids and non-steroidal anti-inflammatory drugs (NSAIDs) to attenuate pain signals. This may be of therapeutic potential due to the lack of psychotropic effects produced. Clinical trials of cannabinoids in neuropathic pain have shown efficacy in providing analgesia; however, the small number of participants involved in these trials has greatly limited their significance. Although the medicinal use of cannabis is legal in Canada and some parts of the United States, its use as a therapeutic agent in Australia is not permitted. This paper will review the role cannabinoids play in providing analgesia, the pharmacokinetics associated with various routes of administration and dependence issues that may arise from its use.

Introduction

Compounds in plants have been found to be beneficial, and now contribute to many of the world's modern medicines. Delta-9-tetrahydrocannibinol (THC), the main psychoactive cannabinoid derived from cannabis plants, mediates its analgesic effects by acting at both the central and peripheral cannabinoid receptors.[1] The analgesic properties of cannabis were first observed by Ernest Dixon in 1899, who discovered that dogs failed to react to pin pricks following the inhalation of cannabis smoke.[2] Since that time, there has been extensive research into the analgesic properties of cannabis, including whole plant and synthetic cannabinoid studies. [3-5]

Although the use of medicinal cannabis is legal in Canada and parts of the United States, every Australian jurisdiction currently prohibits its use.[6] Despite this, Australians lead the world in the illegal use of cannabis for both medicinal and recreational reasons. [7]

Although the analgesic properties of cannabis could be beneficial in treating neuropathic pain, the use of cannabis in Australia is a controversial, widely debated subject. The issue of dependence to cannabis arising from medicinal cannabis use is of concern to both medical and legal authorities. This review aims to discuss the pharmacology of cannabinoids as it relates to analgesia, and also the dependence issues that may arise from the use of cannabis.

Medicinal cannabis can be of particular benefit in the treatment of neuropathic pain that is intractable to the typical agents used, such as tricyclic antidepressants, anticonvulsants and opioids. [3,8] Neuropathic pain is a disease affecting the somatosensory nervous system which thereby causes pain that is unrelated to peripheral tissue injury. Treatment options are limited. The prevalence of chronic pain

in Australia has been estimated at 20% of the population, [9] with neuropathic pain estimated to affect up to 7% of the population. [10]

The role of cannabinoids in analgesia

Active compounds found in cannabis

Cannabis contains over 60 cannabinoids, with THC being the quintessential mediator of analgesia and the only psychoactive constituent found in cannabis plants. [11] Another cannabinoid, cannabidiol, also has analgesic properties; however, instead of interacting with cannabinoid receptors, its analgesic properties are attributed to inhibition of anandamide degradation. [11] Anandamide is the most abundant endogenous cannabinoid in the CNS and acts as an agonist at cannabinoid receptors. By inhibiting the breakdown of anandamide, its time in the synapse is prolonged and its analgesic effects are perpetuated.

Cannabinoid and Vanilloid receptors

Distributed throughout the nociceptive pathway, cannabinoid receptors are a potential target for the administration of exogenous cannabinoids to suppress pain. Two known types of cannabinoid receptors, CB_1 and CB_2, are involved in pain transmission. [12] The CB_1 cannabinoid receptor is highly expressed in the CNS as well as in peripheral tissues, and is responsible for the psychotropic effects produced by cannabis. There is debate regarding the location of the CB_2 cannabinoid receptor, previously found to be largely distributed in peripheral immune cells. [12-13] Recent studies, however, suggest that CB_2 receptors may also be found on neurons. [12-13] The CB_2 metabotropic G-protein coupled receptors are negatively coupled to adenylate cyclase and positively coupled to mitogen-activated protein kinase. [14] The cannabinoid receptors are also coupled to pre-synaptic voltage-gated calcium channel inhibition and inward-rectifying potassium channel activation, thus depressing neuronal excitability, eliciting an inhibitory effect on neurotransmitter release and subsequently decreasing pain transmission. [14]

Certain cannabinoids have targets other than cannabinoid receptors through which they mediate their analgesic properties. Cannabidiol can act at vanilloid receptors, where capsacsin is active, to produce analgesia. [15] Recent studies have found that the actions of administered cannabinoids in mice have a synergestic effect to the response of glycine, an inhibitory neurotransmitter that may contribute to its analgesic effects. Analgesia was absent in mice that lacked

glycine receptors, but not in those lacking cannabinoid receptors, thus indicating an important role of glycine in the analgesic affect of cannabis. [16] Throughout this study, modifications were made to the compound to enhance binding to glycine receptors and diminish binding to cannabinoid receptors, which may be of therapeutic potential to achieve analgesia without psychotropic side effects. [16]

Mechanism of action in producing analgesia and side effects

Cannabinoid receptors also play an important role in the descending inhibitory pathways via the midbrain periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM). [17] Pain signals are conveyed via primary afferent nociceptive fibres to the brain via ascending pain pathways that synapse on the dorsal horn of the spinal cord. The descending inhibitory pathway modulates pain transmission in the spinal cord and medullary dorsal horn via the PAG and RVM before noxious stimuli reaches a supraspinal level and is therefore interpreted as pain. [17] Cannabinoids activate the descending inhibitory pathway via gamma-aminobutyric acid (GABA)-mediated disinhibition, thus decreasing GABAergic inhibition and enhancing impulses responsible for the inhibition of pain; this is similar to opioid-mediated analgesia. [17]

Cannabinoid receptors, in particular CB_1, are distributed throughout the cortex, hippocampus, amygdala, basal ganglia outflow tracts and cerebellum, which corresponds to the capacity of cannabis to produce motor and cognitive impairment. [18] These deleterious side effects limit their therapeutic use as an analgesic. Since ligands binding to CB_1 receptors are responsible for mediating the psychotropic effects of cannabis, studies have been undertaken on the effectiveness of CB_2 agonists; they were found to attenuate neuropathic pain without experiencing CB_1-mediated CNS side effects. The discovery of a suitable CB_2 agonist may be of therapeutic potential. [19]

Synergism with commonly used analgesics

Cannabinoids are also important in acting synergistically with non-steroidal anti-inflammatory drugs (NSAIDs) and opioids to produce analgesia; cannabis could thus be of benefit as an adjuvant to typical analgesics. [20] A major central target of NSAIDs and opioids is the descending inhibitory pathway. [20] The analgesia produced by NSAIDs through its action on the descending inhibitory pathway requires simultaneous activation of the CB_1 cannabinoid receptor. In the presence of an opioid antagonist, cannabinoids are still effective analgesics. Whilst cannabinoids do not act via opioid receptors, cannabinoids and opioids show synergistic activity. [20] On the other hand, Telleria-Diaz *et al.* reported that the analgesic effects of non-opioid analgesics, primarily indomethacin, in the spinal cord can be prevented by a CB_1 receptor antagonist, thus highlighting synergism between the two agents. [21] Although no controlled studies in pain management have used cannabinoids with opioids, anecdotal evidence suggest synergistic benefits in analgesia, particularly in patients with neuropathic pain. [20] Whilst the interaction between opioids, NSAIDs and cannabinoids is poorly understood, numerous studies do suggest that they act in a synergistic manner in the PAG and RVM via GABA-mediated disinhibition to enhance descending flow of impulses to inhibit pain transmission. [20]

Route of Administration

Clinical trials of cannabis as an analgesic in neuropathic pain have shown cannabis to reduce the intensity of pain. [5,22] The most common administration of medicinal cannabis is through inhalation via smoking. Two randomised clinical trials assessing smoked cannabis showed that patients with HIV-associated neuropathic pain achieved significantly reduced pain intensity (34% and 46%) compared to placebo (17% and18% respectively). [5,22] One of the studies was composed of participants whose pain was intractable to first-line analgesics used in neuropathic pain, such as tricyclic antidepressants and anticonvulsants. [22] The numbers needed to treat (NNT=3.5) were comparable to agents already in use (gabapentin: NNT=3.8 and lamotrigine: NNT=5.4). [22] All of the studies undertaken on smoked cannabis have been short-term studies and do not address long-term risks of cannabis smoking. An important benefit associated with smoking cannabis is that the pharmacokinetic profile is superior to orally ingested cannabinoids. [23]After smoking one cannabis cigarette, peak plasma levels of THC are reached within 3-10 minutes and due to its lipid solubility, levels quickly decrease as THC is rapidly distributed throughout the tissues. [23] While the bioavailability of THC when inhaled via smoke is much higher than oral preparations, due to first pass metabolism, there are obvious harmful affects associated with smoking which warranted the study of using other means of inhalation such as vapourisation. In medicinal cannabis therapy, vapourisation may be less harmful than smoking as the cannabis is heated below the point of combustion where carcinogens are formed. [24] A recent study found that the transition from smoking to vapourising in cannabis smokers improved lung function measurements and, following the study, participants refused to participate in a reverse design in which they would return to smoking. [24]

Studies undertaken on the efficacy of oro-mucosal cannabinoid preparations (Sativex) showed a 30% reduction in pain as opposed to placebo; the NNT was 8.6.[4] Studies comparing oral cannabinoid preparations (Nabilone) to dihydrocodeine in neuropathic pain found that dihydrocodeine was a more effective analgesic. [25] The effects of THC from ingested cannabinoids lasted for 4-12 hours with a peak plasma concentration at 2-3 hours. [26] The effects of oral cannabinoids was variable due to first pass metabolism where significant amounts of cannabinoids are metabolized by cytochrome P450 mixed-function oxidases, mainly CYP 2C9. [26] First pass metabolism is very high and bioavailability of THC is only 6% for ingested cannabis, as opposed to 20% for inhaled cannabis. [26] The elimination of cannabinoids occurs via the faeces (65%) and urine (25%), with a clinical study showing that after five days 90% of the total dose was excreted. [26]

The issue of cannabis dependence

One of the barriers to the use of medicinal cannabis is the controversy regarding cannabis dependence and the adverse effects associated with chronic use. Cannabis dependence is a highly controversial but important topic, as dependence may increase the risk of adverse effects associated with chronic use. [27] Adverse effects resulting from long-term use of cannabis include short term memory impairment, mental health problems and, if smoked, respiratory diseases. [28] Some authors report that cannabis dependence and subsequent adverse negative effects upon cessation are only observed in non-medical cannabis users, other authors report that dependence is an issue for all cannabis users, whether its use is for medicinal purposes or not. An Australian study assessing cannabis use and dependence found that one in 50 Australians had a DSM-IV cannabis use disorder, predominately cannabis dependence. [27] They also found that cannabis dependence was the third most common life-time substance dependence diagnosis following tobacco and alcohol dependence. [27] Cannabis dependence can develop; however, the risk factors for dependence come predominantly from studies that involve recreational users, as opposed to medicinal users under medical supervision. [29]

A diagnosis of cannabis dependence, according to DSM-IV, is made when three of the following seven criteria are met within the last 12 months: tolerance; withdrawal symptoms; cannabis used in larger amounts or for a longer period than intended; persistent desire or unsuccessful efforts to reduce or cease use; a disproportionate amount of time spent obtaining, using and recovering from use; social, recreational or occupational activities were reduced or given up due to cannabis use; and use continued despite knowledge of physical or psychological problems induced by cannabis. [29] Unfortunately, understanding of cannabis dependence arising from medicinal use is limited due to the lack of studies surrounding cannabis dependence in the context of medicinal use.. Behavioural therapies may be of use;

however, their efficacy is variable. [30] A recent clinical trial indicated that orally-administered THC was effective in alleviating cannabis withdrawals, which is analogous to other well-established agonist therapies including nicotine replacement and methadone. [30]

The pharmacokinetic profiles also affect cannabis dependence. Studies suggest that the risk of dependence seems to be marginally greater with the oral use of isolated THC than with the oral use of combined THC-cannabidiol. [31] This is important because hundreds of cannabinoids can be found in whole cannabis plants, and cannabidiol may counteract some of the adverse effects of THC; however, more studies are required to support this claim. [31]

The risk of cannabis dependence in the context of long term and supervised medical use is not known. [31] However, some authors believe that the pharmacokinetic profiles of preparations used for medicinal purposes differ from those used for recreational reasons, and therefore causalities in terms of dependence and chronic adverse effects between the two differ greatly. [32]

Conclusion

Cannabis appears to be an effective analgesic and provides an alternative to analgesic pharmacotherapies currently in use for the treatment of neuropathic pain. Cannabis may be of particular use in neuropathic pain that is intractable to other pharmacotherapy. The issue of dependence and adverse side effects including short term memory impairment, mental health problems and if smoked, respiratory diseases arising from medicinal cannabis use is a highly debated topic and more research needs to be undertaken. The ability of cannabinoids to modulate pain transmission by enhancing the activity of descending inhibitory pathways and acting as a synergist to opioids and NSAIDs is important as it may decrease the therapeutic doses of opioids and NSAIDs required, thus decreasing the likelihood of side effects. The possibility of a cannabinoid-derived compound with analgesic properties free of psychotropic effects is quite appealing, and its discovery could potentially lead to a less controversial and more suitable analgesic in the future.

Conflict of interest

None declared.

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Spontaneous regression of cancer: A therapeutic role for pyrogenic infections?

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

Spontaneous regression of cancer is a phenomenon that is not well understood. While the mechanisms are unclear, it has been hypothesised that infections, fever and cancer are linked. Studies have shown that infections and fever may be involved in tumour regression and are associated with improved clinical outcomes. This article will examine the history, evidence and future prospects of pyrogenic infections towards explaining spontaneous regression and how they may be applied to future cancer treatments.

Introduction

Spontaneous regression of cancer is a phenomenon that has been observed since antiquity. [1] It can be defined as a reversal or reduction of tumour growth in instances where treatment has been lacking or ineffectual. [2] Little is known about its mechanism but two observations in cancer patients are of particular interest: first, infections have been shown to halt tumour progression while second, development of fever has been associated with improved prognosis.

Until recently, fever and infections have been regarded as detrimental states that should be minimized or prevented. However, in the era preceding the use of antibiotics and antipyretics, the prior observations were prevalent and were used as the basis of crude yet stunningly effective immunological-based treatments. The promise of translating that success to modern cancer treatment is a tempting one and should be examined further.

History: Spontaneous Regression & Coley's Toxins

Spontaneous regression of cancers was noted as early as the 13th century. The Italian Peregrine Lazoisi was afflicted with painful leg ulcers which later developed into a massive cancerous growth. [3]The growth broke through the skin and became badly infected. Miraculously, the infection induced a complete regression of the tumour and surgery was no longer required. He later became the patron saint of cancer sufferers.

Reports that associated infections and tumour regression continued to grow. In the 18th century, Trnka and Le Dran reported cases of breast cancer regressions which occurred after tumour site infection. [4, 5] These cases are often accompanied by signs of inflammation and fever and gangrene are common. [3]

In the 19th century, such observations became the basis of early clinical trials by physicians such as Tanchou and Cruveillhier. Although highly risky, they attempted to replicate the same conditions artificially by applying a septic dressing to the wound or injecting patients with pathogens such as malaria. [1] The results were often spectacular and suddenly, this rudimentary form of 'immunotherapy' seemed to offer a genuine alternative to surgery.

Until then, the only option for cancer was surgery and outcomes were at times very disappointing. Dr. William Coley (a 19th century New York surgeon) related his anguish after his patient died despite radical surgery to remove a sarcoma of the right hand. [3] Frustrated by the limitations of surgery, he sought an alternative form of treatment and came across the work of the medical pioneers Busch and Fehleisen. They had earlier experimented with erysipleas, injecting or physically

applying the causative pathogen, *Streptococcus pyogenes*, onto the tumour site. [6] This was often followed by a high fever which correlated with a concomitant decrease in tumour size in a number of patients. [3] Coley realized that using live pathogens was very risky and he eventually modified the approach using a mixture of killed *S. pyogenes* and *Serratia marescens*. [7] The latter potentiated the effects of *S. pyogenes* such that a febrile response can be induced safely without an 'infection', and this mixture became known as Coley's toxins. [1]

A retrospective study in 1999 showed that there was no significant difference in cancer death risk between patients treated using Coley's toxins and those treated with conventional therapies (i.e. chemotherapy, radiotherapy and surgery). [8] Data from the second group was obtained from the Surveillance Epidemiology End Result (SEER) registry in the 1980s. [3] This observation is remarkable given that Coley's toxins were developed at a fraction of the cost and resources afforded to current conventional therapies.

Researchers also realized that Coley's toxins have broad applicability and are effective across cancers of mesodermal embryonic origin such as sarcomas, lymphomas and carcinomas. [7] One study comparing the five-year survival rate of patients with either inoperable sarcomas or carcinomas found that those treated with Coley's toxin showed had a survival rate as high as 70-80%. [9]

Induction of a high grade fever proved crucial to the success of this method. Patients with inoperable sarcoma who were treated with Coley's toxins and developed a fever between 38-40 °C had a five-year survival rate three times higher than that of afebrile patients. [10] As cancer pain can be excruciating, pain relief is usually required. Upon administration of Coley's toxins, an immediate and profound analgesic effect was often observed; allowing the discontinuation of narcotics. [9]

Successes related to 'infection' based therapies are not isolated. In the early 20th century, Nobel laureate Dr. Julius Wagner-Jauregg used tertian malaria injections in the treatment of neurosyphilis-induced dementia paralytica. [3]This approach relied on the induction of prolonged and high grade fevers. Considering the high mortality rate of untreated patients in the pre-penicillin era, he was able to achieve an impressive remission rate of approximately one in two patients. [11]

More recently, Bacillus Calmette-Guérin (BCG) vaccine has been used in the treatment of superficial bladder cancers. [12] BCG consists of live attenuated *Mycobacterium bovis* and is commonly used in tuberculosis vaccinations. [12,13] Its anti-tumour effects are thought to involve a localized immune response stimulating production of inflammatory cytokines such as tumour necrosis factor α (TNF-α) and interferon *γ* (IFN-*γ*). [13] Similar to Coley's toxins, it uses a bacterial formulation and requires regular localized administration over a prolonged period. BCG is shown to reduce bladder cancer recurrence rates in nearly 70% of cases and recent clinical trials suggest a possible role in colorectal cancer treatment. [14] From these examples, we see that infections or immunizations can have broad and effective therapeutic profiles.

Opportunities Lost: The End of Coley's Toxins

After the early success of Coley's toxins, momentum was lost when Coley died in 1936. Emergence of chemotherapy and radiotherapy overshadowed its development while aseptic techniques gradually gained acceptance. After World War II, large-scale production of antibiotics and antipyretics also allowed better suppression of infections and fevers. [1] Opportunities for further clinical studies using Coley's toxins were lost when despite decades of use, it was classified as a new drug by the US Food and Drug Administration (FDA). [15] Tightening of regulations regarding clinical trials of new drugs after the thalidomide incidents in the 1960s meant that Coley's toxins were highly unlikely to pass the stringent safety requirements. [3]

With fewer infections, spontaneous regressions became less common. An estimated yearly average of over twenty cases in the 1960-80s decreased to less than ten cases in the 1990s. [16] It was gradually believed that the body's immune system had a negligible role in tumour regression and focus was placed on chemotherapy and radiotherapy. Despite initial promise, these therapies have not fulfilled their full potential and the treatment for certain cancers remains out of reach.

In a curious turn of events, advances in molecular engineering have now provided us with the tools to transform immunotherapy into a viable alternative. Coley's toxins have provided the foundations for early immunotherapeutic approaches and may potentially contribute significantly to the success of future immunotherapy.

Immunological Basis of Pyrogenic Infections

The most successful cases treated by Coley's toxins are attributed to: successful infection of the tumour, induction of a febrile response and daily intra-tumoural injections over a prolonged period.

Successful infection of tumour

Infection of tumour cells results in infiltration of lymphocytes and antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs). Binding of pathogen-associated molecular patterns (PAMPs) (e.g. lipopolysaccharides) to toll-like receptors (TLRs) on APCs induces activation and antigen presentation. The induction process also leads to the expression of important co-stimulatory molecules such as B7 and interleukin-12 (IL-12) required for optimal activation of B and T cells. [17] In some cases, pathogens such as the zoonotic vesicular stomatitis virus (VSV) have oncolytic properties and selectively lyse tumour cells to release antigens. [18]

Tumour regression or progression depends on the state of the immune system. A model of duality in which the immune system performs either a defensive or reparative role has been proposed. [1, 3] During the defensive mode, tumour regression occurs and immune cells are produced, activated and mobilized against the tumour. In the reparative model, tumour progression is favoured and invasiveness is promoted via immunosuppressive cytokines, growth factors, matrix metalloproteinases and angiogenesis factors. [1, 3]

The defensive mode may be activated by external stimuli during infections; this principle can be illustrated by the example of M1/M2 macrophages. M1 macrophages are involved in resistance against infections and tumours and produce pro-inflammatory cytokines such as IL-6, IL-12 and IL-23. [19, 20] M2 macrophages promote tumour progression and produce anti-inflammatory cytokines such as IL-10 and IL-13. [19, 20] M1 and M2 macrophage polarization is dependent on transcription factors such as interferon response factor 5 (IRF5). [21] Inflammatory stimuli such as bacterial lipopolysaccharides induce high levels of IRF5 and this commits macrophages to the M1 lineage while also inhibiting expression of M2 macrophage marker expression. [21] This two-fold effect may be instrumental in facilitating a defensive mode.

Induction of febrile response

In Matzinger's 'danger' hypothesis, the immune system responds to signals produced during distress known as danger signals, including inflammatory factors released from dying cells. [22] T cells remain anergic unless both danger signals and tumour antigens are provided. [23] A febrile response is advantageous as fever is thought to facilitate inflammatory factor production. Cancer cells are also more vulnerable to heat changes and elevated body temperature during fever may promote cell death and the massive release of tumour antigens. [24]

Besides a physical increase in temperature, fever encompasses profound physiological effects. An example of this is the induction of heat-shock protein (HSP) expression on tumour cells. [16] Studies have shown that Hsp70 expression on carcinoma cells promotes lysis by natural killer T (NKT) cells *in vitro*, while tumour expression of Hsp90 may play a key role in DC maturation. [25, 26] Interestingly, HSPs also associate with tumour peptides to form immunogenic complexes involved in NK cell activation. [25] This is important since NK cells help overcome subversive strategies by cancer cells to avoid T cell recognition. [27] Down regulation of major histocompatibility complex (MHC) expression on cancer cells results in increased susceptibility to NK cell attacks. [28] These observations show that fever is equally adept at stimulating innate and adaptive responses.

Route and duration of administration

The systemic circulation poses a number of obstacles for successful delivery of infectious agents to the tumour site. Neutralization by pre-immune Immunoglobulin M (IgM) antibodies and complement activation impede pathogens. [18] Infectious agents may bind non-specifically to red blood cells and undergo sequestration by the reticuloendothelial system. [29] In the liver, specialized macrophages called, Kupffer cells, can also be activated by pathogen-induced TLR binding and cause inflammatory liver damage. [29] An intratumoural route therefore has the advantage of circumventing most of these obstacles to increase the probability of successful infection. [18]

It is currently unclear if innate or adaptive immunity is predominantly responsible for tumour regression. Coley observed that shrinkage often occurred hours after administration whereas if daily injections were stopped, even for brief periods, the tumour continued to progress. [30] Innate immunity may therefore be important and this is consistent with insights from vaccine development, in which adjuvants enhance vaccine effectiveness by targeting innate immune cells via TLR activation. [1]

Although T cell numbers in tumour infiltrates are substantial, tolerance is pervasive and attempts to target specific antigens have been difficult due to antigenic drift and heterogeneity of the tumour microenvironment. [31] A possible explanation for the disproportionality between T cell numbers and the anti-tumour response is that the predominant adaptive immune responses are humoral rather than cell-mediated. [32] Clinical and animal studies have shown that spontaneous regressions in response to pathogens like malaria and *Aspergillus* are mainly antibody mediated. [3] Further research will be required to determine if this is the case for most infections.

Both innate and adaptive immunity are probably important at specific stages with sequential induction holding the key to tumour regression. In acute inflammation, innate immunity is usually activated optimally

and this in turn induces efficient adaptive responses. [33] Conversely, chronic inflammation involves a detrimental positive feedback loop that acts reversibly and over-activates innate immune cells. [34] Instability of these immune responses can result in suboptimal anti-tumour responses.

Non-immune considerations and constructing the full picture

Non-immune mechanisms may be partly responsible for tumour regression. Oestrogen is required for tumour progression in certain breast cancers and attempts to block its receptors by tamoxifen have proved successful. [35] It is likely that natural disturbances in hormone production may inhibit cancerous growth and promote regression in hormone dependent malignancies. [36]

Genetic instability has also been mentioned as a possible mechanism. In neuroblastoma patients, telomere shortening and low levels of telomerase have been associated with tumour regression. [37]This may be due to the fact that telomerase activity is required for cell immortality. Other potential considerations may include stress, hypoxia and apoptosis but these are not within the scope of this review. [38]

As non-immune factors tend to relate to specific subsets of cancers, they are unlikely to explain tumour regression as a whole. They may instead serve as secondary mechanisms which support a primary immunological system. During tumour progression, these non-immune factors may either malfunction or become the target of subversive strategies.

A simplified outline of the possible role of pyrogenic infections in tumour kinetics is illustrated below (Figure 1).

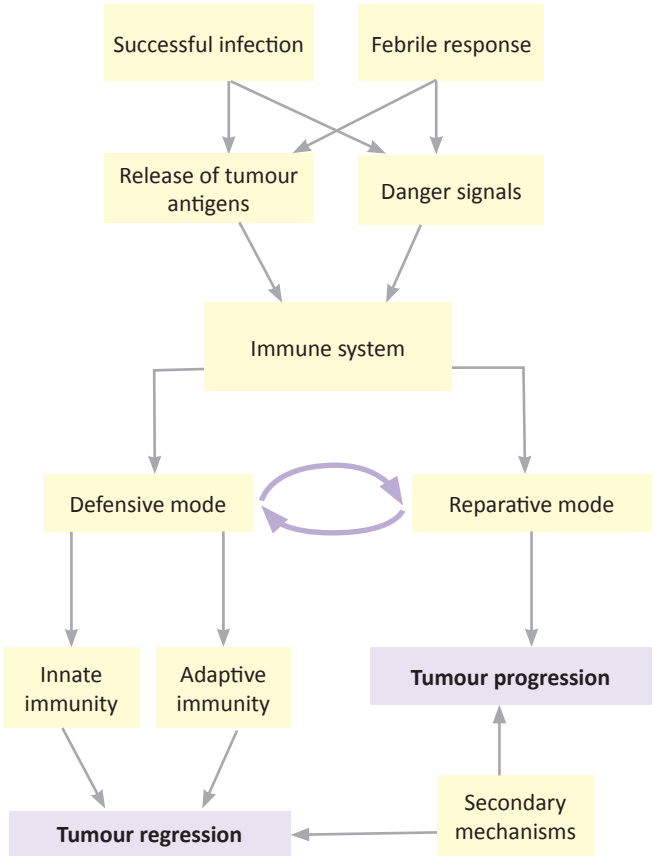

Figure 1. *Hypothetical role of pyrogenic infections in waxing and waning of tumours. Successful infection and febrile response promote release of tumour antigens and danger signals, tilting the immune system to a defensive mode where innate and adaptive responses favour tumour regression. Lack of these stimuli triggers the reparative mode and results in tumour progression. Secondary mechanisms may influence regression or progression in specific cancers.*

Discussion

The intimate link between infections, fever and spontaneous regression is slowly being recognized. While the incidence of spontaneous regression is steadily decreasing due to circumstances in the modern clinical setting, Coley's toxins are a timely reminder that lessons from the past can shape the future of cancer therapy.

Limitations to be addressed

Immunotherapy in its present form has been limited in efficacy primarily due to several reasons. Firstly, single cytokines or PAMPs have been used in trials in the hope of achieving an immediate effect. [39] This 'magic bullet' approach fails to recognize that a typical immune response involves a complex cascade of events, and that PAMPs may be involved in triggering several TLRs simultaneously. This is difficult to replicate given our incomplete understanding of intricate multi-faceted immune processes. Realistically, this may currently only be achieved by natural challenges such as infections.

Furthermore, the use of single cytokines and their related inhibitors remains a dilemma. This is best illustrated by the incorporation of recombinant TNF-α and anti-TNF-α agents into cancer treatment. TNF-α is produced physiologically by cancers to maintain a tumour-promoting chronic inflammatory state. [40, 41] A pronounced anti-tumour effect is observed when high therapeutic dosages of exogenous TNF-α are administered and transition to acute inflammation occurs. [41] However, this beneficial effect is often achieved at a risk of severe toxicities like organ failure. [40] Similarly, anti-TNF-α agents like infliximab (anti-TNF-α antibody) and etanercept (soluble TNF-α receptor) may reduce pathological levels of TNF-α but there is a trade-off between impeding tumour progression and higher risk of opportunistic infections (e.g. listeriosis) and possibly secondary malignancies (e.g. lymphoma) due to suppression of TNF-α protective effects. [41] These paradoxical observations suggest that the present form of cytokine-based immunotherapy is still fraught with difficulties.

Secondly, fever immunology has been largely neglected. Febrile responses are pushed aside as detrimental side effects; the potential benefits have been ignored. [6] Fever is important in potentiating immune responses, but the use of antipyretics alongside immunotherapy appears to defeat the purpose of stimulating the body's immune system.

Recent studies have started to demonstrate the prophylactic potential of pyrogenic infections. Koelmel *et al.* analyzed the melanoma risk in a group of more than six hundred patients and found that the lifetime risk is lowered to two in five patients if the frequency of infections and severity of fever are both increased. [42] This brings about an interesting dilemma, where we are caught between resolving current infections at a greater risk of developing cancer later in life. A change in treatment approach can be justified if this is proved for other cancers. It is foreseeable that such a change ultimately depends on our ability to discern between cancer-causing and beneficial infections and their associated inflammatory patterns (i.e. chronic or acute).

Some of Coley's techniques (i.e. intra-tumoural and prolonged administration) are currently favoured in immunotherapy, illustrating that some key principles remain useful over time. Nonetheless, certain technical difficulties will need to be resolved. An intra-tumoural route sometimes requires multiple injections to achieve a desired level of infection while prolonged administration and its long term discomfort may reduce treatment compliance and in turn, affect the clinical outcome.

Incorporating Coley's principles into current treatment regimes

In the near future, Coley's principles will need to coexist alongside current treatment modalities. This is because immunotherapy has yet to produce consistent clinical results to justify a mainstream role in cancer therapy and realistically, there is still some way to go before we

can fully comprehend and harness the potential of the immune system.

Theoretically, immunotherapy is based on stimulating the immune system while existing modalities such as chemotherapy and radiotherapy tend to suppress it. This explains why early clinical trials involving bacterial extracts called mixed bacterial vaccine (MBV) have not been as successful as predicted. [14] Selected patients have usually undergone conventional treatment previously and MBV is only given at a late stage of cancer development as a last resort. [43] Conditions then would have been predominantly immunosuppressive, severely affecting the ability of MBV to stimulate immunity.

However, recent clinical trials involving oncolytic viruses seem to suggest a role for immunosuppression in mediating an effective virus-mediated anti-tumour response. Chemotherapeutic drugs like cyclophosphamide can suppress antibody neutralization of viruses and facilitate delivery to tumour sites. [44] Similarly, a radiotherapy-reovirus combination has shown promising results in promoting T-cell trafficking and recognition of tumour cells. [16] It appears that the main determinant is not the theoretical nature of each treatment modality but rather, how they can be integrated to provide a synergistic effect. Furthermore, this also suggests that viruses may be more suitable for combinatorial treatments. If so, incorporating infection-based immunotherapy into cancer treatment is highly feasible once the correct combinations and infectious agents are identified.

Conclusion

As we grapple with the challenges and limitations of cancer treatment, it may prove beneficial to revisit the work of early experimenters such as William Coley. His contributions have been neglected for decades but as we begin to recognize the significance of his work, his status as a pioneer of cancer immunotherapy appears to be well justified.

Conflict of interest

None declared.

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Seasonal influenza vaccination in antenatal women: Views of health care workers and barriers in the delivery of the vaccine

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Surabhi undertook this research project as part of the General Practice Student Network First Wave Academic Scholarship. She has a growing interest in maternal health research and infectious disease, and has been involved in a couple of research projects in the fields of Primary Health Care and Vascular Biology. In second year, she received the Norway Bursary and did a four week rural placement in Northern Norway. Other than research, she enjoys working as the President of the Rural Health Club - RHINO and attending conferences around Australia.

Background: Pregnant women are at an increased risk of developing influenza. The National Health and Medical Research Council recommends seasonal influenza vaccination for all pregnant women who will be in their second or third trimester during the influenza season. The aim of this review is to explore the views of health care workers regarding seasonal influenza vaccination in antenatal women and describe the barriers in the delivery of the vaccine. **Methods:** A literature search was conducted using MEDLINE for the terms: "influenza," "pregnancy," "antenatal," "vaccinations," "recommendations," "attitudes," "knowledge" and "opinions". The review describes findings of publications concerning the inactivated influenza vaccination only, which has been proven safe and is widely recommended. **Results:** No studies have addressed the knowledge and attitudes of Australian primary health care providers towards influenza vaccination despite their essential role in immunisations in Australia. Overseas studies indicate that factors that contribute to the low vaccination rates are 1) the lack of general knowledge of influenza and its prevention amongst health care workers (HCWs) 2) variable opinions and attitude regarding the vaccine 3) lack of awareness of the national guidelines 4) and lack of discussion of the vaccine by the HCW. Lack of maternal knowledge regarding the safety of the vaccine and the cost-burden of the vaccine are significant barriers in the uptake of the vaccination. **Conclusion:** Insufficient attention has been given to the topic of influenza vaccinations in pregnancy. Significant efforts are required in Australia to obtain data about the rates of influenza vaccination of pregnant women.

Introduction

Seasonal influenza results in annual epidemics of respiratory diseases. Influenza epidemics and pandemics increase hospitalisation rates and mortality, particularly among the elderly and high risk patients with underlying conditions. [1-3] All pregnant women are at an increased risk of developing influenza due to progressive suppression of Th1-cell-mediated immunity and other physiological changes that cause culmination of morbidity towards the end of pregnancy. [4-7]

Annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications [8] Trivalent inactivated influenza vaccine (TIV) has been proven safe and is recommended for person aged ≥6 months, including those with high-risk conditions such as pregnancy. [8-10] A randomised controlled study in Bangladesh demonstrated that TIV administered in the third trimester of pregnancy resulted in reduced maternal respiratory illness and reduced infant influenza infection. [11, 12] Another randomised controlled trial has shown that influenza immunisation of pregnant women reduced influenza-like illness by more than 30% in both the mothers and the infants, and reduced laboratory-proven influenza infections in 0- to 6-month-old infants by 63%. [13]

The current Australian Immunisation Guidelines recommend routine administration of influenza vaccination for all pregnant women who will be in the second or third trimester during the influenza season, including those in the first trimester at the time of vaccination. [4,14,15] The seasonal influenza vaccination has been made available

for free to all pregnant women in Australia since 2010. [4] However, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZOG) statement for 'Pre-pregnancy Counselling and routine Antenatal Assessment in the absence of pregnancy Complications' does not explicitly mention routine delivery of influenza vaccination to healthy pregnant women. [16] RANZCOG recently published the college statement on swine flu vaccination during pregnancy; advising that pregnant women without complications and recent travel history must weigh the risk-benefit ratio before deciding to uptake the H1N1 influenza immunisation. [17] Therefore, it is evident that there is conflicting advice in Australia about the routine delivery of influenza vaccination to healthy pregnant women. In contrast, firm recommendation for routine influenza vaccination for pregnant women was established in 2007, by the National Advisory Committee on Immunisations (NACI) in Canada, with minimal conflict from The Society of Obstetricians and Gynaecologists of Canada (SOGC). [6] Succeeding the 1957 influenza pandemic, the rate of influenza immunisations increased significantly with greater than 100,000 women receiving the vaccination annually between 1959-1965 in the United States. [8] Since 2004 the American Advisory Committee on Immunisation Practice (ACIP) has recommended influenza vaccination for all pregnant women, at any stage of gestation. [9] This is supported by The American College of Obstetricians and Gynaecologists' Committee on Obstetric Practice. [18]

A recent literature review performed by Skowronski *et al.* (2009) found that TIV is warranted to protect women against influenza-related hospitalisation during the second half of normal pregnancy, but evidence is otherwise insufficient to recommend routine TIV as the standard of practice for all healthy women beginning in early pregnancy. [6] Similarly, another review looked at the evidence for the risks of influenza and the risks and benefits of seasonal influenza vaccination in pregnancy and concluded that data on influenza vaccine safety in pregnancy is inadequate. [19] However, based on the available literature, there was no evidence of serious side effects in women or their infants, including no indication of harm from vaccination in the first trimester. [19]

We aim to review the literature published on the delivery and uptake of

influenza vaccination during pregnancy and identify the reasons for low adherence to guidelines. The review will increase our understanding of how the use of the influenza vaccination is perceived by health care providers and the pregnant women.

Evidence of health care provider's attitude, knowledge and opinions

Several published studies have revealed data supporting deficits in the knowledge of health care providers regarding the significance of the vaccine and the national guidelines, hence suggesting a low rate of vaccine recommendation and uptake by pregnant women. [20] A research project in 2006 performed a cross-sectional study of the knowledge and attitudes towards the influenza vaccination in pregnancy amongst all levels of health care workers (HCW's) working at the Department for Health of Women and Children at University of Milan, Italy. [20] The strength of this study was that it included 740 HCWs representing 48.4% working in obstetrics/gynaecology, 17.6% in neonatology and 34% in paediatrics, of whom 282 (38.1%) were physicians, 319 (43.1%) nurses, and 139 (18.8%) paramedics (health aides/healthcare assistants). The respondents were given a pilot-tested questionnaire about their perception of the seriousness of influenza, their general knowledge of influenza recommendations and preventive measures, and their personal use of influenza vaccination; which was to be self-completed in 20 mins in an isolated room. Descriptive analysis of the 707 (95.6%) HCWs that completed the questionnaire revealed that the majority (83.6%) of HCW's in obstetrics/gynaecology never recommended the influenza vaccination to healthy pregnant women. Esposito *et al.* (2007) highlighted that only a small number of nurses and paramedics, from each speciality, regarded influenza as serious in comparison to the physicians. [20] Another study investigating practices of the Midwives found that only 37% believed that influenza vaccine is effective and 22% believed that the vaccine was a greater risk than influenza. [21] The results from these studies clearly indicate deficiencies in the general knowledge of influenza and its prevention amongst health care staff.

In contrast, a study by Wu *et al.* (2006) suggested unusually high vaccination uptake rate of the fellows from the American College of Obstetricians and Gynaecologists (ACOG) who live and practice in Nashville, Tennessee. [22] The survey focussed on physician knowledge, practices, and opinions regarding influenza vaccination of pregnant women. Results revealed that 89% of practitioners responded that they routinely recommend the vaccine to pregnant women and 73% actually administered the vaccination to pregnant and postpartum women. [21] Sixty-two percent responded that the earliest administration of the vaccine should be the second trimester, while 32% reported that it should be offered in the first trimester. Interestingly, 6% believed that it should not be delivered at all during the pregnancy. Despite the national recommendation to administer the vaccination routinely to all pregnant women, [4] more than half of the obstetricians preferred to withhold it until second trimester due to concerns regarding vaccine safety, association with spontaneous abortion and possibility of disruption in embryogenesis. [22] Despite the high uptake rate identified by the respondents, there are a few major limitations in this study. First, the researchers excluded the family physicians and midwives practicing obstetrics in their survey, which prevents a true representation of the sample population. Second, the vaccination rates were identified by the practitioners and not validated, which increases the likelihood of personal bias by the practitioners.

It is evident that HCWs attending to pregnant women and children have limited and frequently incorrect beliefs concerning influenza and its prevention. [20,23] A recent study by Tong *et al.* (2008) demonstrated that only 40% of the health care providers at the three hospitals studied in Toronto were aware of the high-risk status of pregnant women and only 65% were aware of the NACI recommendations. [23] Furthermore, obstetricians were less likely than family physicians to indicate that it was their responsibility to discuss, recommend, or provide influenza vaccination. [23] Tong *et al.* (2008) also demonstrated that high levels of provider knowledge about influenza and maternal vaccination, positive attitudes towards influenza vaccination, increased age, being a family physician, and having been vaccinated against influenza, were associated with recommending influenza vaccine to pregnant women. [23] This data is also supported by Wu *et al.* and Espostio *et al.*

In 2001, Silverman *et al.* (2001) concluded that physicians were more likely to recommend vaccine if they were aware of current 'Centers for Disease Prevention and Control' guidelines, gave vaccinations in their offices and had been vaccinated against influenza themselves. [24] Similarly, Lee *et al.* (2005) showed that midwives who received the immunisation themselves and firmly believed in its benefits, were more likely to offer it to pregnant women. [21] Wallis *et al.* (2006) conducted a multisite interventional study involving educational sessions with the physicians and the use of "Think Flu Vaccine" notes on active obstetric charts, to illustrate a fifteen fold increase in the rate of influenza vaccinations in pregnancy. [25] This study also demonstrated that increase in uptake was greater in family practices versus obstetric practices, and furthermore increased in small practices as opposed to large practices.

Overall, the literature here is derived mostly from American and Canadian studies as there is no data available for Australia. Existing data suggest that there is a significant lack of understanding regarding influenza vaccine safety, benefits and recommendations amongst the HCW's. [20-27] These factors may lead to wrong assumptions and infrequent vaccine delivery.

Barriers in delivering the influenza vaccinations to pregnant women

Aside from the gaps in the health care provider's understanding of vaccine safety and national guidelines, several other barriers in delivering the influenza vaccine to pregnant women have been identified. A study published in 2009, based on CDC analysis of data from the Pregnancy Risk Assessment and Monitoring System from Georgia and Rhode Island over the period of 2004-2007, showed that the most common reasons for not receiving the vaccination were, "I don't normally get the flu vaccination" (69.4%), and "my physician did not mention anything about a flu vaccine during my pregnancy" (44.5%). [28] Lack of maternal knowledge about the benefits of the influenza vaccination has also been demonstrated by Yudin *et al.* (2009), who conducted a cross-sectional in hospital survey of 100 postpartum women during the influenza season in downtown Toronto. [29] This study concluded that 90% of women incorrectly believed that pregnant women have the same risk of complications as non-pregnant women and 80% incorrectly believed that the vaccine may cause birth defects. [29]. Another study highlighted that 48% of physician listed patient refusal as a barrier for administering the vaccine. [22] These results were supported by Wallis *et al.* (2006), which focused on using simple interventions such as chart reminders to surmount the gaps in knowledge of women. [25] 'Missed opportunities' by obstetricians and family physicians to offer the vaccination have been suggested as a major obstacle in the delivery of the influenza vaccination during pregnancy. [14,23,25,28]

During influenza season, hospitalized pregnant women with respiratory illness had significantly longer lengths of stay and higher odds of delivery complications than hospitalized pregnant women without respiratory illness. [5] In some countries cost-burden of the vaccine to women is another major barrier that contributes to lower vaccination rates among pregnant women. [22] This is not an issue in Australia where the vaccination is free for all pregnant women. Provision of free vaccination to all pregnant women is likely to have a significant advantage when considering the cost-burden of influenza on the health-care sector. However, the cost-burden on the patient can be viewed as lack of access, as reported by Shavell *et al.* (2012) As such

patients that lacked insurance and transportation were less likely to receive the vaccine. [30]

This is supported by several studies that have shown that the vaccine is comparatively cost-effective when considering the financial burden of influenza related morbidity. [31] A 2006 study based on decision analysis modelling revealed that vaccination rate of 100% in pregnant women would save approximately 50 dollars per woman, resulting in a net gain of approximately 45 quality-adjusted hours relative to providing supportive care alone in the pregnant population. [32] Beigi *et al.* (2009) demonstrated that maternal influenza vaccination using either the single- or 2-dose strategy is a cost-effective approach when influenza prevalence is 7.5% and influenza-attributable mortality is 1.05%. [32] As the prevalence of influenza and/or the severity of the outbreak increases the incremental value of vaccination also increases. [32] Moreover, a study in 2006 has proven the cost-effectiveness to the health sector of the single dose influenza vaccination for influenza like illness. [31] Therefore, patient education about the relative cost-effectiveness of the vaccine and adequate reimbursement by the government is required to alleviate this barrier in other nations but not in Australia where the vaccination is free for all pregnant women.

Lack of vaccine storage facilities in physician offices is an important barrier preventing the recommendation and uptake of the vaccine by pregnant women. [23,33] A recent study monitoring the immunisation practices amongst practicing obstetricians found that less than 30% store influenza vaccine in their office. [18] One study showed acceptance rates of influenza vaccine of 71% of 448 eligible pregnant women who were offered the influenza vaccine at routine prenatal visit due to the availability of storage facilities at the practice, suggesting that the uptake of vaccination can be increased by simply overcoming the logistical and organisational barriers such as vaccine storage, inadequate reimbursement and patient education. [34]

Conclusion

From the limited data available, it is clear that there are is a variable level of knowledge of influenza and its prevention amongst HCWs. There is also and a general lack of awareness of the national guidelines in their countries. However, there is no literature for Australia to compare with other nations. There is some debate regarding the trimester in which the vaccine should be administered. There is further lack of clarity in terms of who is responsible for the discussion and delivery of the vaccine – the general practitioner or the obstetrician. These factors contribute to a lack of discussion of vaccine use and amplify the amount of 'missed opportunities.'

Lack of maternal knowledge about the safety of the vaccine and its benefits is also a barrier that must be overcome by the HCW through facilitating an effective discussion about the vaccine. Since the vaccine has been rendered free in Australia, cost should not prevent vaccination. Regular supply and storage of vaccines especially in remote towns of Australia is likely to be a logistical challenge.

There is limited Australian literature exploring the uptake of influenza vaccine in pregnancy and the contributing factors such as the knowledge, attitude and opinion of HCWs, maternal knowledge of the vaccine and logistical barriers. A reasonable first step would be to determine the rates of uptake and prevalence of influenza vaccination in antenatal women in Australia.

Conflict of interest

None declared.

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Treatment of persistent diabetic macular oedema - intravitreal bevacizumab versus laser photocoagulation: A critical appraisal of BOLT Study for an evidence based medicine clinical practice guideline

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Laser photocoagulation has remained the standard of treatment for diabetic macular oedema (DME) for the past three decades. However, it has been shown to be unbeneficial in chronic diffuse DME. Intravitreal bevacizumab (ivB) has been proposed as an alternate and effective treatment of DME. This review evaluates the evidence behind comparing bevacizumab to laser photocoagulation in treating persisting DME. A structured systematic search of literature, with critical appraisal of retrieved trials, was performed. Four randomised controlled trials (RCTs) supported beneficial effects of ivB over laser photocoagulation. Only one RCT, the BOLT study, compared laser to ivB effect in persistent DME. The results from the study showed significant improvement in mean best corrected visual acuity (BCVA) and greater reduction in mean central macular thickness (CMT) in the ivB group, with no significant difference in safety outcome measures.

Introduction

Diabetic macular oedema is a frequent manifestation of diabetic retinopathy and is one of the leading causes of blindness and visual acuity loss worldwide. [1] The presence of DME varies directly in proportion with the duration and stage of diabetic retinopathy, with a prevalence of three percent in mild non-proliferating retinopathy, 38% in moderate-to-severe non-proliferating retinopathy and 71% with proliferative retinopathy. [2]

Diabetic macular oedema (DME) is a consequence of micro-vascular changes in the retina that lead to fluid/plasma constituent accumulation in the intra-retinal layers of the macula thereby increasing macular thickness. Clinically significant macular oedema (CSME) is present when there is thickening within or close to the central macula with hard exudates within 500µm of the centre of the macula and with retinal thickening of at least one disc area in size. [3,4] As measured in optical coherence tomography, central macular thickness (CMT) corresponds approximately to retinal thickness at the foveal region and can quantitatively reflect the amount of CSME a patient has. [5] Two different types of DME exist: focal DME (due to fluid accumulation from leaking micro-aneurysms) and diffuse DME (due to capillary incompetence and inner-retinal barrier breakdown).

Diabetic macular oedema pathogenesis is multi-factorial; influenced by diabetes duration, insulin dependence, HbA1C levels and hypertension. [6] Macular laser photocoagulation has remained the standard treatment for both focal and diffuse DME, based on the recommendations of the Early Treatment Diabetic Retinopathy Study (ETDRS) since 1985. This study showed the risk of CSME decreases by approximately 50% (from 24% to 12%) at three years with the use of macular laser photocoagulation. However, the improvement in visual acuity is modest, observed in less than three percent of patients. [3]

Recent research indicates that macular laser therapy is not always beneficial and has limited results, especially for chronic diffuse DME, [3,7] with visual acuity improving in only 14.5% of patients. [8] Following laser treatment, scars may develop and reduce the

likelihood of vision improvement [3] hence alternate treatments for DME such as intravitreal triamcinolone (ivT), have been investigated. Intravitreal triamcinolone (ivT) works via a number of mechanisms including reducing vascular permeability and down regulating VEGF (vascular endothelial growth factor). Anti-VEGF therapies have been the focus of recent research, and those modalities have been shown to potently suppress angiogenesis and to decrease vascular permeability in ocular disease such as DME, leading to improvement in visual acuity. [9] The results of treating DME with anti-VEGFs are controversial and are in need of larger prospective RCTs. [10]

Currently used anti-VEGFs include bevacizumab, ranibizumab and pegatanib. Ranibizumab has been shown to be superior in treating DME, both in safety and efficacy, compared to laser therapy, in several studies that include RESTORE, RESOLVE, RISE and RIDE studies. [11-13] It has been recently approved by the Food and Drug Administration (FDA) for treating DME in the United States of America. [14] Bevacizumab (Avastin®) is a full length monoclonal antibody against VEGF, binding to all subtypes of VEGF. [10] In addition to treating metastatic colon cancer, bevacizumab is also used extensively off-label for many ocular conditions that include age related macular degeneration (AMD), DME, retinopathy of prematurity and macular oedema secondary to retinal vein occlusion. [15] Documented adverse effects of ivB include transiently elevated intraocular pressure (IOP) and endopthalmitis. [16] Systemic effects associated with ivB injection include rise in blood pressure, thrombo-embolic events, myocardial infarction (MI), transient ischemic attack and stroke. [16,17] Other significant adverse events of bevacizumab when given systemically include delayed wound healing, impaired female fertility, gastrointestinal perforations, haemorrhage, proteinuria, congestive heart failure and hypersensitivity reactions. [17] Although not currently approved, a 1.25-2.5mg infusion of ivB is used for treating DME without significant ocular/systemic toxicity. [15]

The DRCR.net study (2007) has shown that ivB can reduce DME. [18] In addition, several studies, which have been carried out on diabetic retinopathy patients with CSME evaluating the efficacy of ivB ± ivT versus laser, demonstrated better visual outcomes with BCVA. [6,19-21] Meta-analysis of those studies indicated ivB to be an effective

short-term treatment for DME, with efficacy waning after six weeks. [6] This review evaluates the evidence behind the effect of ivB, compared to laser, in treating persisting DME despite standard treatment.

Clinical question

Our clinical question for this focused evidence based medicine article has been constructed to address the four elements of the problem, the intervention, the comparison and the outcomes as recommended by Strauss *et al.* (2005) [22]. "In diabetic patients with persistent clinically significant macular oedema (CSME) is intravitreal Bevacizumab (Avastin®) injection better than focal/grid laser photocoagulation in preserving the best-corrected visual acuity (BCVA)?"

Methodology

Comprehensive electronic searches in the British Medical Journal, Medical Journal of Australia, Cochrane Central Register of Controlled Trials, MEDLINE and PUBMED were performed for relevant literature, using the search terms diabetic retinopathy, CSME, CMT, bevacizumab and laser photocoagulation. Additional information from the online search engine, Google, was also incorporated. Reference lists of studies were then hand-searched for relevant studies/trials.

Selection

Results were restricted to systematic reviews, meta-analysis and randomised clinical trials (RCTs). Overall six RCTs were identified, which evaluated the efficacy of ivB compared to lasers in treating DME. [18-21,23,24] There was also one meta-analysis comparing ivB to non-drug control treatment (lasers or sham) in DME. [7] One study was published showing pilot study results of the main trial, so the final version was selected for consideration to avoid duplication of results. [20,23]

Table 1. *Table showing the individual study characteristics of relevant RCTs to the current topic of analysis.*

Name Year Place	Study duration	Total number of eyes	Mean age (years)	Inclusion criteria	Exclusion criteria
BOLT Study [24] 2012 UK	24 months	80 eyes (80 patients)	64.2 ± 8.8	Age 18 ≥ years with diabetes mellitus (type 1 or 2); Snellen BCVA in the study eye ≥6/60 or ≤6/12; centre-involving CSME with CMT on OCT of 270 µm; at least one prior MLT; media clarity, pupillary dilation and subject co-operation; IOP < 30 mmHg; fellow eye BCVA ≥ 3/60 and has received no anti-VEGF treatment within the past three months and no expectation of such treatment during the study.	Macular ischaemia; macular oedema due to a cause other than DME; co-existent ocular disease; any treatment for DME in the preceding three months; panretinal photocoagulation after enrolment; HbA1c >11.0%; medical history of chronic renal failure; BP>170/100 mmHg; thrombo-embolic event within six months; acute coronary syndrome characteristics on ECG; major surgery during study; participation in an investigational drug trial; systemic anti-VEGF or pro-VEGF treatment within three months of enrolment; pregnancy, breast feeding or intention to become pregnant; intraocular surgery; aphakia; uncontrolled glaucoma; significant external ocular disease.
Soheilian *et al.* [20] 2009 Iran	9 months	150 eyes (129 patients)	61.2 ± 6.1	Clinically significant DME based on ETDRS criteria with Snellen BCVA of ≥6/90 or ≤6/12.	Previous panretinal or focal laser photocoagulation; prior intraocular surgery or injection; history of glaucoma or ocular hypertension; BCVA of 20/40 or better or worse than 20/300; presence of iris neovascularisation; high-risk proliferative diabetic retinopathy; significant media opacity; monocularity; pregnancy; serum creatinine ≥ 3 mg/dl; uncontrolled diabetes mellitus.
Faghihi *et al.* [21] 2008 Iran	4 months	130 eyes (110 patients)	57 ± 7	BCVA equal to or less than 20/40 (ETDRS chart) (≤0.3 logMAR); Central macular thickness (CMT) ≥250 µm.	Macular oedema related to recent intraocular surgery or other procedures; Vitreous traction (based on OCT); History of any treatment for diabetic retinopathy at any time or anticipating the need for panretinal laser photocoagulation (PRP) in the six months following randomisation; uncontrolled glaucoma; recent history of arterial thrombo-embolic event; poorly controlled hypertension.
DRCR Study [18] 2007 USA	6 months	109 eyes (121 patients)	65 (median age)	Type I or type II DM; BCVA ≥20/320 and ≤20/32; definite central macular thickening clinically; CMT ≥275 µm.; no previous treatment for DME within last three months.	Macular oedema due to other causes, inflammatory ocular disease; any treatment for DME in the previous three months; PRP in the previous four months; Major ocular surgery in the previous six months, history of PPV; aphakia, uncontrolled glaucoma, hypertension.

UK = United Kingdom, USA = United States of America

One study was excluded because it excluded focal DME patients. [19] The DRCR study (2007) was excluded because it was not designed to evaluate if treatment with ivB was beneficial in DME patients. [18] A meta-analysis by Goyal *et al.* was also excluded because it evaluated bevacizumab with sham treatment and not laser therapy. [7]

Thus, three relevant RCTs were narrowed down for analysis (Table 1) in this evidence based medicine review. [20,21,24] However, only the BOLT study (2012) evaluated the above treatment modalities in persistent CSME. The other two RCTs evaluated the treatment efficacies in patients with no prior laser therapies for CSME/diabetic retinopathy. Hence, only the BOLT study (2012) has been critically appraised in this report. The study characteristics of the other relevant RCTs evaluating ivB versus lasers are represented in Table 1, and where possible will be included in the discussion.

Outcomes

The primary outcomes of interest are changes in BCVA and CMT, when treated with ivB or lasers for DME, whilst the secondary outcomes are any associated adverse events. All three studies were prospective RCTs with NHMRC level-II evidence. Table 1 summarises the overall characteristics of the studies.

Critical appraisal

The BOLT Study (2010) is a twelve month report of a two year long single centre, two arm, randomised, controlled, masked clinical trial from the United Kingdom (UK). As such, it qualifies for NHMRC [25] level-II quality of evidence. It is the only RCT that compared the efficacy of ivB with laser in patients with persistent CSME (both diffuse and focal DME) who had undergone at least one laser therapy for CSME previously. Comparison of study characteristics of the three RCTs chosen are presented in Table 2.

Major strengths of the BOLT Study compared to Soheilian *et al.* and Faghihi *et al.* studies include the duration of study and increased frequency of review of patients in ivB groups. The BOLT Study was a

Table 2. *Summary of the major aspects of the three RCT designs for evaluating the validity of the studies.*

Study characteristic	BOLT Study [24]	Soheilian *et al.* [20]	Faghihi *et al.* [21]	Comments
Randomised?	Yes	Yes	Yes	
Randomisation concealed?	Yes	Yes	Yes	
Blinding?	Yes	Yes	Yes	
Clinically similar patient population in intervention groups?	Yes	Yes	Yes	Characteristics assessed include demographics, BCVA, CMT, IOP, mean duration of diabetes, severity of retinopathy
Groups treated equally apart from experimental therapy?	No	Yes	Yes	
All patients in the groups analysed?	Yes	No	Yes	
Sufficient treatment/ follow up?	Maybe	Perhaps not	No	

Table 1 (Continued). *Table showing the individual study characteristics of relevant RCTs to the current topic of analysis.*

Name Year Place	Intervention's nature and groups	Follow up visits (weeks)	Primary outcomes	Trial quality (NHMRC)
BOLT Study [24] 2012 UK	1) ivB - given at baseline visit, 6 and 12 weeks, prn with every 6 weeks review, thereafter (n=42) 2) Laser - given at baseline, prn at 16, 32, 48, 64, 80 and 96 weeks (n=38)	ivB - 6, 12, 18, 24, 30, 36, 42, 48, 52 Laser -16, 32, 48, 52	BCVA, CMT	Level II (RCT)
Soheilian *et al.* [20] 2009 Iran	1) ivB (1.25mg) given at baseline (n=50) 2) ivB (1.25mg) + IVT (2mg) given at baseline (n=50) 3) Laser (n=50) Re-treatments were performed at 12-week intervals as required	6, 12, 24, 36	BCVA	Level II (RCT)
Faghihi *et al.* [21] 2008 Iran	1) ivB (1.25mg) (n=42) 2) ivB (1.25mg) + IVT (2mg) (n=41) 3) Laser (n=47) No re-treatment were given to any of the groups	6, 16	BCVA, CMT	Level II (RCT)
DRCR Study [18] 2007 USA	1) MPC at baseline (n=19) 2) ivB (1.25mg) - baseline, week 6 (n=22) 3) ivB (2.5mg) - baseline, week 6 (n=24) 4) ivB (1.25mg) - baseline, sham at week 6 (n=22) 5) ivB (1.25mg) - baseline & week 6, MPC at week 3 (n=22)	3, 6, 9, 12, 18, 24	BCVA, CMT	Level II (RCT)

UK = United Kingdom, USA = United States of America

two year study, whereas the other two studies' duration was limited to less than a year (Table 1). Because of its lengthy duration, it was possible to evaluate the safety outcome profile of ivB in the BOLT Study, unlike in the other two studies.

Research has indicated that the effects of ivB could last between two to six weeks, [6] and the effects of lasers could last until three to six months. [3] In BOLT, the ivB group was assessed every six weeks, and re-treatment provided with ivB as required, while the laser group were followed up every four months ensuring the preservation of efficacy profile and its reflection in the results. Whereas, in Sohelian *et al.*, [20] follow up visits were scheduled every twelve weeks after the first visit, and in Faghihi *et al.*, [21] follow up was at six and sixteen weeks. Therefore, there may have been a bias against the efficacy profile of ivB, given the insufficiency in the nature of follow up/treatment. Apart from the follow up and therapy modalities, the groups were treated equally in BOLT, preserving the analysis against treatment bias.

Weaknesses of the BOLT Study [24] include limited number of patients: 80 eyes in total, with 42 patients allocated to ivB and 38 patients to laser therapy. Of them, in the ivB group, six patients discontinued intervention; only 37 patients were included in the analysis at 24 months and five were excluded as the data was not available. Similarly, of the 38 patients allocated to the laser group, 13 patients discontinued the intervention; 28 patients were analysed overall where ten were excluded from analysis. However, the BOLT Study performed intention to treat analysis minimizing dropout effects. Given these, we feel the BOLT Study fulfills the criteria for a valid RCT with significant strengths.

Magnitude and precision of treatment effect from BOLT Study

Best corrected visual acuity outcomes

Significant difference existed between mean ETDRS BCVA at 24 months in the ivB group (64.4±13.3) compared to the laser group (54.8±12.6) with p=0.005 (Any p-value <0.05 indicates statistical significance between the groups under comparison). Furthermore, the study reports of the ivB group gaining a median of 9 ETDRS letters whereas the laser group gaining a median of 2.5 letters (p=0.005). Since there was a significant difference between the duration of CSME between the two groups, the authors of the study performed analysis after adjusting for this variable. They also adjusted for the baseline BCVA and for patients who had cataract surgery during the study. The mean BCVA still remained significantly higher in the ivB group compared to laser.

Marked difference has also been shown in the proportion of people who gained or lost vision between the two treatment groups. Approximately, 49% of patients in the ivB group gained more than or equal to ten ETDRS letters compared to seven percent of patients in laser group (p-value = 0.01). Similarly, none of the patients in the ivB group, compared to 86% in the laser group (p=0.002), lost fewer than 15 ETDRS letters. In addition, the study also implied that BCVA and CMT can be maintained long term with reduced injection frequency of six to twelve months. However, the authors also suggest that increasing the frequency of injections to every four weeks (rather than the six week frequency opted in the study) may provide better visual acuity gains as reported in RISE and RIDE studies. [13]

Central macular thickness outcomes

The mean change in the CMT over the 24 month period was -146±171µm in ivB group compared to -118±112µm in the laser group (p=0.62), showing statistically no significant difference in ivB/laser effectively reducing the CMT. This differed from the twelve month report of the same study that indicated improvement in CMT in the ivB group compared to the laser group.

Retinopathy

Results of the BOLT Study indicated a trend of reducing retinopathy severity level in the ivB group, while the laser group showed stabilised grading. However, the Mann-Whitney test indicated no significant difference between the groups (p=0.13). [24]

We summarised the results of the author's analysis of the step-wise changes in retinopathy grading levels, for further analysis, into three categories: deteriorating, stable and improving (Table 3). As shown in the table, we calculated the p-values using the chi-square test between both groups for each category.

Table 3. *Summary of change in ETDRS retinopathy severity level in the two groups between baseline and twelve months.*

Retinopathy severity	ivB group (No. of patients)	Laser group (No. of patients)	Chi-square	Two-tailed p-value
Deteriorated	1	3	0.214	0.64
Stable	23	17	0.038	0.84
Improved	11	5	0.753	0.38
TOTAL	35	25		

We attempted to further quantify the magnitude of ivB treatment compared to lasers on the retinopathy severity level by calculating the number needed to treat (NNT) using the data in Table 3. The results showed an absolute risk reduction of nine percent with an NNT of 10.9 (95% CI indicating harm in 21.6 harm to benefit in 3.6 patients treated). Since the confidence interval indicates an uncertainty between benefit and harm, this trial does not give sufficient information to inform clinical decision making regarding change in retinopathy severity levels with ivB treatment.

Safety outcome measures

As mentioned, one of the strengths of the BOLT Study is evaluating the safety profile of ivB given its two year duration. The study analysed the safety outcomes of macular perfusion and retinal nerve fibre layer (RNFL) thickness in detail. The results indicated no significant difference in the mean greatest linear diameter of foveal avascular zone between the laser and the ivB group, from baseline or in the worsening of severity grades. Similarly, no significant changes in median RNFL thickness have been reported between ivB and laser groups.

At 24 months, the number of observed adverse events, ocular and systemic, in the study was low. We have analysed the odds ratio (Table 4) as per the published results in the study. Statistically significant higher chances of having eye pain and irritation (eighteen times greater risk) during or after intervention, sustaining sub-conjunctiva haemorrhage and of having a red eye (eighteen times greater risk) was found in the ivB group compared to lasers. As can be further inferred from the table, no significant differences in sustaining other non-ocular adverse events, ocular serious adverse events or non-ocular serious adverse events including stroke/MI/other thrombo-embolic events were found between both the groups.

Clinical applicability of results

The BOLT Study participants were from Moorfields Eye Hospital (UK) and had comparable demographics and healthcare standards to Australia. In the study, both patient (BCVA, retinopathy severity level changes, adverse events) and disease-oriented outcomes (CMT) were considered, making the study both theoretically and practically relevant, informing both clinicians and researchers of the outcomes. Given this, clinical applicability of the results to the Australian population appears reasonable. All other personnel involved in the study (outcome assessors) and imaging technology are available as well, making the treatment feasible in our setting.

In Australia, the overall diabetic retinopathy prevalence is 24.5%, [6] the statistics associated with it rise every year due to the progressing obesity/diabetes epidemic. Bevacizumab is currently approved under the pharmaceutical benefits scheme for metastatic colon cancer.

Table 4: *Individual adverse/serious adverse event rates along with analysed odds ratio between ivB and laser groups*

	IvB (n=42)	Laser (n=38)	Odds ratio	p -Value
Ocular adverse events				
Eye pain/irritation/watering during or after injection	8	0	18.97	0.046
Red eye after injection (including sub-conjunctival haemorrhage)	8	0	18.97	0.046
Loss of ≥15 or <30 ETDRS letters (transient/ permanent)	4	4	0.89	0.881
Transient increased IOP >30mmHg	4	0	9	0.14
Floaters after injection	2	0	4.75	0.319
Corneal epithelial deficit	1	0	2.78	0.534
Non-ocular adverse events				
Uncontrolled hypertension	1	0	2.78	0.534
Polymyalgia rheumatica	1	0	2.78	0.534
Gastroenteritis	1	1	0.902	0.942
Anemia	0	1	0.294	0.457
Fall and wrist fractures	0	2	0.171	0.260
Headache, dizziness, tiredness	0	1	0.294	0.457
Ocular serious adverse events				
Increased IOP ≥ 45 mmHg	1	0	2.78	0.534
Vitreous haemorrhage (non-study eye)	0	1	0.294	0.457
Vitreomacular traction with macular oedema	0	1	0.294	0.457
Loss of ≥30 ETDRS letters	0	1	0.294	0.457
Non-ocular serious adverse events				
Admission for fall/loss of consiousness	0	1	0.294	0.457
Worsening angina	0	1	0.294	0.457
MI	2	0	4.753	0.319
Coronary artery bypass graft	1	0	2.78	0.534
Dyspnoea/chest pain - hospital admission for observation	1	0	2.78	0.534
Cerebrovascular accident	0	1	0.294	0.457
Total events	**40**	**17**		

It is being successfully used 'off-label' for the treatment of ocular conditions including age related macular degeneration and diabetic macular oedema. It costs about 1/40th the cost of ranibizumab, another anti-VEGF drug that has current approval for AMD treatment in Australia and FDA approval for DME treatment in America. [26] Since recent studies indicate no superior effect of ranibizumab versus bevacizumab in safety and efficacy profile in preserving visual acuity, [27,28] and since recent NICE guidelines also recommend not using ranibizumab for diabetic macular oedema due to high costs involved with the administration of that drug, [29] bevacizumab must be further considered and evaluated for cost effectiveness in routine usage in clinical practice.

Given the benefits with ivB, that is, improved BCVA, no significant adverse events and no risk of permanent laser scarring of the retina, and the aforementioned discussion, using ivB in treatment for persisting DME appears to be evidence based, and relatively safe practice.

Conclusion

The BOLT Study assessed the safety and efficacy of ivB in persistent DME despite previous laser therapy. The power of the study was 0.8 enabling it to detect BCVA differences between two groups. In line with many other previous studies evaluating ivB's efficacy, the results indicate significant improvement in the mean ETDRS BCVA, and no significant differences in severe systemic/ocular adverse events compared to the laser group. This study supports the use of ivB in patients with CSME, with adequate precision. However the magnitude of the effect on changes in the severity of diabetic retinopathy, in CMT changes and other adverse events, needs to be evaluated further through large prospective RCTs.

Conflict of interest

None declared.

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Dengue fever in a rural hospital: Issues concerning transmission

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Ross received a certificate of commendation for this report from the Centre for Healthcare Related Infection Surveillance and Prevention (CHRISP). He is passionate about surgery and medical education.

Introduction: Dengue is either endemic or epidemic in almost every country located in the tropics. Within northern Australia, dengue occurs in epidemics; however, the *Aedes aegypti* vector is widespread in the area and thus there is a threat that dengue may become endemic in future years. **Case presentation:** An 18 year old male was admitted to a rural north Queensland hospital with the provisional diagnosis of dengue fever. No specific consideration was given to the risk that this patient posed to other patients, including a 56 year old male with chronic myeloid leukaemia and prior exposure to dengue. **Discussion:** Much media and public attention has been given to dengue transmission in the scope of vector control in the community. Hospital-based dengue transmission from patient-to-patient requires consideration so as to minimise unnecessary morbidity and mortality. Vector control within the hospital setting appears to be an appropriate preventative measure in the context of the presented case. Transfusion and transplantation-related transmission of dengue between patients are important considerations. Vertical dengue infection is also noted to be possible. **Conclusion:** Numerous changes in the management of dengue-infected patients can be made that are economically feasible. Education of healthcare workers is essential to ensure the safety of all patients admitted to hospitals in dengue-affected areas. Bed management in particular is one area that may benefit from increased attention.

Introduction

Dengue is diagnosed annually in more than 50 million people worldwide and represents one of the most important arthropod-borne viral infections. [1-4] Estimates suggest that the potentially lethal complication of dengue haemorrhagic fever occurs in 500 000 people and an alarming 24 000 deaths result from infection annually. [1,2,4] Coupled with the increasing frequency and severity of outbreaks in recent years, dengue has been identified as a major and escalating public health concern. [2,4,5]

Whilst most of the burden of dengue occurs in developing countries, northern Australia is known to have epidemics. Suggestions have been made that dengue may become endemic in this region in future years based on increasing migration, international travel, population growth, climate change and widespread presence of vectors. [6-12] The vast majority of studies have focused on vector control in the community setting. [2,4,5,9] The purpose of this report is to discuss the risks of transmission of dengue in a hospital setting and in particular, patient-to-patient transmission. Transmission of dengue in a hospital is important to consider as immunological responses and health status of hospitalised patients can be poor. Inadequate management of dengue-infected patients may ultimately threaten the lives and complicate treatment of other patients, creating unnecessary economic costs and demands on healthcare. [12-14]

This case report highlights the difficulties of handling a suspected dengue-infected patient from the perspective of an Australian rural hospital. Recommendations are made to improve management of such patients, in particular, embracing technological advancements including digital medical records that are likely to become available in future years.

Case report

An 18 year old male, patient 1, presented to a rural north Queensland hospital emergency department with a four day history of fever, generalised myalgia and headache. He resided in an area that was known to be in the midst of a dengue outbreak. He had no past medical or surgical history and had never travelled. On examination, the patient's tympanic temperature was 38.9°C and he had dry mucous membranes. No rash was observed and no other abnormal findings were noted. Laboratory investigations, which included dengue PCR and dengue serology, were taken. He was admitted for observation and given intravenous fluids. A provisional diagnosis of dengue fever was made.

The patient was subsequently placed in a room with four beds. Whilst two of the beds in the room did not have patients in them, the remaining bed was occupied by patient 2, a 56 year old male with chronic myeloid leukaemia (CML), who had been hospitalised the previous day with a lower respiratory tract infection. The patient's medical history was notable for a past episode of dengue fever five years previously following an overseas holiday.

The patient with presumed dengue fever remained febrile for two days. He walked around the ward and went outside for cigarettes. He also opened the room window, which was unscreened. Tests subsequently confirmed that he had a dengue viral infection.

Whilst no dengue transmission occurred, the incident raised a number of issues for consideration, as no concerns regarding transmission was raised by staff or either patients.

Discussion

The dengue viruses are single positive-stranded RNA viruses belonging to the *Flaviviridae* family, with four distinct serotypes described. [4,12] Infection can range from asymptomatic, to a mild viral syndrome associated with fever, malaise, headache, myalgia and rash, or an eventual severe presentation characterised by haemorrhage and shock. [3,9] Currently the immunopathogenesis of severe dengue infection, which occurs in less than 5 percent of infections and includes dengue haemorrhagic fever and shock syndromes, is poorly defined. [2,3]

Whilst primary infection in the young and well nourished has been associated with the development of severe infection, the major

aetiology of severe infection is thought to be secondary infection with a different serotype. [3,9] This has been hypothesised to be as a result of an antibody-mediated enhancement reaction, although authors also suggest that other factors are likely to contribute. [3,4,9] Untreated dengue haemorrhagic fever is characterised by increased capillary permeability and haemostatic changes and has a mortality rate of 10-20 percent. [2,3,5] This complication can further deteriorate into dengue shock syndrome. [3] Whilst research shows that the serious complications of dengue infection occurs mainly in children, adults with asthma, diabetes and other chronic diseases may be at increased risk and secondary dengue infections could be life threatening in these groups. [4,5,15]

The most commonly reported route of infection is via the bite of an infected *Aedes* mosquito, primarily *Aedes aegypti.* [2-14] This vector feeds during the day, prefers human blood and breeds in close proximity to humans. [5,12,13] The transmission of dengue has been widely reported in the urban setting and has a geographical distribution including more than 100 countries. [3,13] However, only one study has reported dengue vector transmission from within a hospital. [16] Kularatne *et al.* (2007) recently described a dengue outbreak that started within a hospital in Sri Lanka and was unique such that a building site next to the hospital provided breeding sites for mosquitoes. [16] Dengue infection was noted to cause significant cardiac dysfunction, and of particular note was that medical students, nurses, doctors and other hospital employees were the main targets. [16] The authors report that at the initial outbreak one medical student died due to shock and severe pulmonary oedema as a result of acute viral myocarditis. [16] This case highlights the risk of dengue transmission within a hospital setting.

In addition to the vector-borne transmission, dengue can be also be transmitted by other routes, including transfusion. [17,18] The incidence of blood transfusion-associated dengue infection has been one area of investigation that has primarily been reported in endemic countries. In one study conducted in Hong Kong by Chuang *et al.* (2008) the prevalence of this mode of transmission was 1 in 126. [17] Whilst rare in Australia, an investigation undertaken during the 2004 outbreak in Cairns, Queensland calculated the risk of transfusion-related dengue infection by mathematical modelling and reported the risk of collecting a viraemic donation as 1 in 1028 persons during the course of the epidemic. [18] Donations from the affected areas were not used for transfusion. [18]

Case reports have also been published demonstrating that transplantation can represent a route of dengue infection between hospitalised patients. [19,20] Rigau-Pérez and Laufer (2006) described a six year old child who developed fever four days post-bone marrow transplantation and subsequently died. [19] Dengue virus was isolated from the blood and tissues of the child and the donor was subsequently known to have become febrile with tests for dengue being found to be positive. [19] Dengue infection resulting from solid organ transplantation has also been described in a 23 year old male with end-stage renal failure. [20] The donor of the transplanted kidney had dengue fever six months prior to the transplant and the recipient of the organ had dengue fever five days postoperatively. [20] The recipient had a complicated recovery and required an emergency laparotomy and blood products to ensure survival. [20] The authors of this case report further discuss the fact that the patient in question had resided in a dengue-endemic region and therefore could not exclude the usual mode of infection. [20]

Whilst not applicable to the presented case, vertical transmission of dengue has also been noted to be an important consideration in hospitalised patients. Reports from endemic countries have suggested that transmission can occur if infection of the mother occurs within eight days of delivery. [9,21] One neonatal death has been reported as a result of dengue infection and a number of studies have reported peripartum complications requiring medical treatment in other neonates. [21,22] Interpretation of this result should be viewed with caution due to difficulties cited in the clinical diagnosis of dengue in neonates, as it is possible that vertical transmission may be underreported. [22]

Taking into account the reported case study and presented evidence, it is clear that patient 1 presented a risk to patient 2. It is essential to acknowledge that dengue transmission can occur within a hospital setting. Whilst only one study has reported vector transmission of dengue within a hospital, it does define the real possibility of transmission associated with close contact and a competent vector. [16] There is also a need to emphasise the fact that patient 1 walked outside the hospital on numerous occasions and that unscreened windows were open within the hospital ward room. Consequently, it can be stated that patient-to-patient dengue infection would have been possible not only for patient 2, but also other admitted patients. Additionally, healthcare workers and community members that lived within the area surrounding the hospital were also at risk.

In acknowledging that vector transmission within a hospital is the most important hazard in regards to transmission of dengue from patient-to-patient, numerous control measures can be implemented to decrease the risk of transmission. Infrastructure plans within hospitals are important, as screened windows would decrease the ability of mosquitoes to enter hospitals. In those hospitals where such changes may not be economically feasible, studies have reported that having patients spend as much time as possible under insecticide treated mosquito nets, limiting outdoor time for infected patients, wearing protective clothing and applying insecticide numerous times throughout the day may decrease the possibility of dengue infection within hospitals. [23-25]

Educational programs for healthcare professionals and patients also warrant consideration. Numerous programs have been established primarily in the developing world and have proven to be beneficial. [26,27] It is important to create innovative education programs aimed at educating those healthcare workers that care for suspected dengue-infected patients as well as members of the public. This is one area that needs to be explored in future years.

Additionally, this case study demonstrates that current protocols in bed management do not consider a past medical history of dengue infection when assigning patients to beds. This report draws attention to the importance of identifying those patients at risk of secondary infection with dengue. As electronic patient records are implemented in many countries throughout the world, a past history of confirmed dengue infection needs to be considered. This may mean when resources are available, that patients are not placed in the same room thereby avoiding unnecessarily placing patients at risk. Whilst this would not completely exclude the possibility of dengue transmission in a hospital, it may set the trend for improved protocols in infection control particularly when secondary infection is associated with poorer outcomes. [2-5,9]

Conclusion

Infection control is often targeted in tertiary referral centres. This report clearly highlights the importance of appreciating infection control within a rural setting. Dengue infection between patients is a possibility with available evidence suggesting that this is most likely to be from exposure of an infected individual to a competent vector. Numerous changes have the potential to decrease the likelihood of dengue infection. Healthcare worker education is a critical component of these changes so that suspected dengue infected patients may also be educated regarding the risk that they represent to members of the public. The utilisation of screened windows, insecticide treated mosquito nets, and patient measures such as wearing protective clothing and applying insect repellents are all preventative measures that need to be considered. Future research is likely to develop technological aides for appropriate bed assignment. This will ensure that unnecessary morbidity and mortality associated with dengue infection are avoided.

Consent declaration

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

Conflict of interest

None declared.

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An unusual case of bowel perforation in a 9 month old infant

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In Australia, between 2009 and 2010 almost 290 000 cases of suspected child abuse and neglect were reported to Australian state and territory authorities. Child maltreatment may present insidiously, not allowing signs of the maltreatment to be elicited until after a culmination of events. Ms. LW, a 9-month-old Indigenous female, presented to the Alice Springs Hospital emergency department (ED) with complaints of bloody diarrhea. A provisional diagnosis of viral gastroenteritis was suggested and she was managed with fluids to which her vitals responded positively. She was discharged six hours post presentation but presented three days later in a worsened condition with a grossly distended abdomen. Exploratory laparotomy found a perforated jejunum, which was deemed as a non-accidental injury. This case outlines the pitfalls in collateral communication in which we discuss the lack of use of an interpreter or Aboriginal health worker. We also emphasise the onus on junior doctors to practice in a reflective manner with the burdens of ED, so that they do not miss key diagnostic clues. Early detection of chronic maltreatment is important in the prevention of toxic stress to the child, which has been shown to contribute to a greater burden on society in the form of chronic manifestations later in life.

Introduction

Maltreatment, especially that of children can be insidious in nature, whose signs may not be evident until a culmination of unfortunate events. In Australia, during 2010-2011, there were 286,437 [1] reports of suspected child abuse and neglect made to state and territory authorities with a total of 40,466 substantiations (Figure 1). These notifications include four maltreatment types: physical abuse, sexual abuse, emotional abuse and neglect (Figure 2). As of 30 June 2010, there were 11,468 Aboriginal and Torres Strait Islander children in out-of-home care as a result of this. The national rate of Indigenous children in out-of-home care was almost ten times higher than for non-Indigenous children. [1]

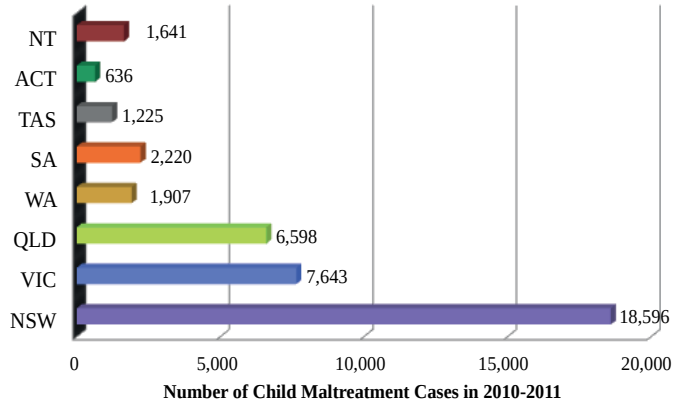

Figure 1. *Number of substantiations of child maltreatment recorded within Australian states and territories in 2011.*

Child protection statistics shown above tells us how many children have come into contact with child protection services; however, they do not take in to account the silent statistics of those who suffer without seeking aid. In all jurisdictions in 2010-11, girls were much more likely than boys to be the subject of a substantiation of sexual abuse. In contrast, boys were more likely to be subject to physical abuse than girls in all jurisdictions except Tasmania and the Northern Territory. [1]

Unfortunately it is difficult to obtain accurate statistics regarding the number of children who die from child abuse or neglect in Australia, as currently comprehensive information is not collected in every jurisdiction. Taking this into account however latest data recorded indicated that in 2006, assault was the third most common type of injury causing death for Australian children aged 0-14 years, [2] and totaled 27 children mortalities in 2006-07. Medical practitioners must be aware of the signs of child maltreatment and their long-term consequences, as they possess the opportunity to intervene and change the consequences of this terrible burden on afflicted children.

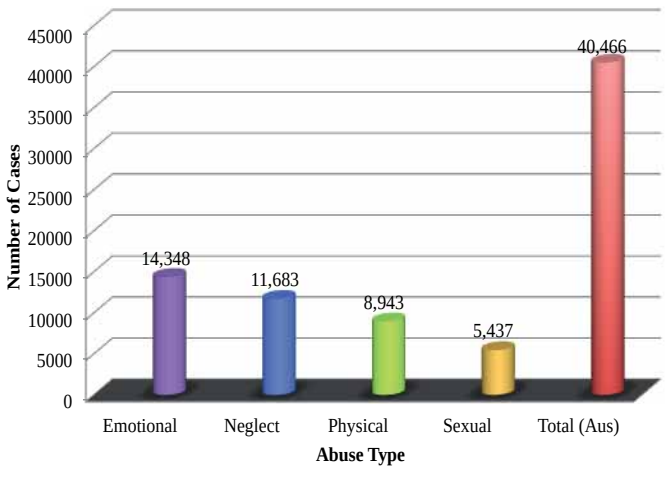

Figure 2. *Notifications of maltreatment types made in 2011 (From Australian Institute of Health and Welfare and Australian Bureau of Statistics, 2011).*

Case Presentation

Ms. LW, a nine month old Indigenous female and her mother presented to the Alice Springs ED at 2100, with complaints of bloody diarrhea. Emergency department staff noted that on presentation the infant was notably uncomfortable and tearful. She was afebrile, with mild tachypnoea (50 respirations per min) all other vitals were normal. Examination of the infant revealed discomfort in the epigastric region with no other significant findings including no organomegaly or distention. No other abdominal signs in particular signs such as guarding or rigidity were noted on admission. Systemic review did not show any significant findings. Past medical history included recurrent chest infections with the last episode two months prior. No immunisation history was available. The staff had difficulty examining the child because she was highly irritable. It was also difficult to elicit a comprehensive history from the mother as she spoke minimal English and was relatively dismissive of questions. No interpreter was used in this setting.

The patient was diagnosed with viral gastroenteritis and treated conservatively by the administration of intravenous fluids to maintain hydration. After six hours of observation and a slight improvement in Ms. LW's vitals she was sent home in the early morning hours after intense pressure from the family. No other treatments and investigations were done and the staff discharged her with the recommendation of returning if the symptoms worsened over the next day.

The patient returned three days later to ED with symptoms clearly of a different nature and not that of the previous diagnosis of gastroenteritis. On general observation the patient appeared unwell, irritable and was crying weakly. On examination she was found to be febrile (40°C) and toxic with tachycardia (168 bpm) tachypnoea (60 respirations per minute), and gross distention of her abdomen (Figure 3).

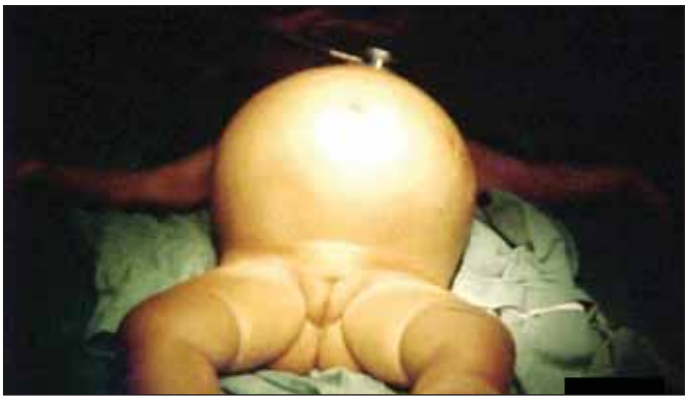

Figure 3. *Image showing the gross distention of the bowel of Ms. LW taken at the time of presentation.*

An emergency chest x-ray was taken which revealed pneumoperitoneum (Figure 4).

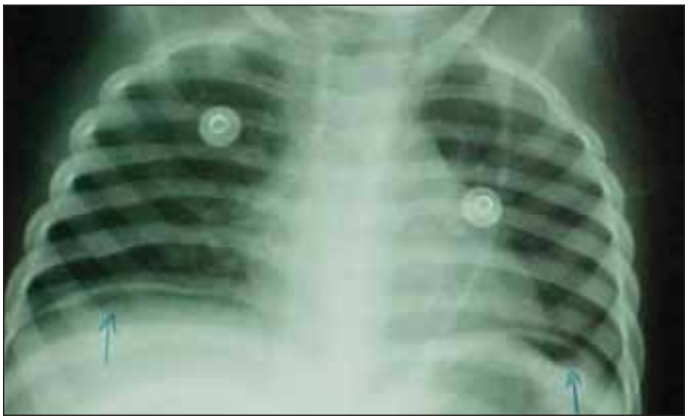

Figure 4. *Anterior/posterior CXR indicateing bilateral free gas under the diaphragm (arrows) confirming perforated viscus.*

The case was referred to the on-call surgeon, who gave a provisional diagnosis of perforated bowel and decided to perform a laparotomy. She was immediately started on intravenous broad-spectrum antibiotics, ampicillin (200mg /6hourly), metronidazole (30mg /12 hourly) and gentamicin (20 mg/daily) before surgery.

Emergency laparotomy was performed, and on initial exploration it was found that the peritoneum contained foul smelling serous fluid with a mixture of blood and faecal matter. Further exploration found perforation of the jejunum with the mesentery torn from the fixed end of the jejunum (Figure 5). The surgeons resected the gangrenous portion of the jejunum and performed an end-to-end anastomosis of small bowel.

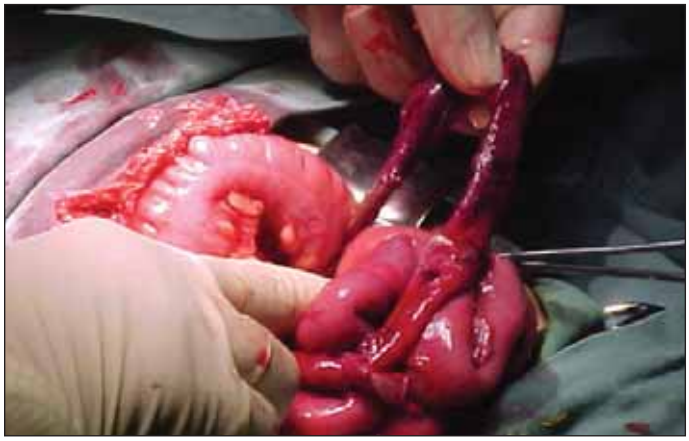

Figure 5. *Devitalised upper jejunum with torn mesentery, with small perforation at the distal portion of the jejunum.*

The abdomen was lavaged with copious amounts of warm saline and the abdominal wall was closed in interrupted layers. Post surgery the child remained intubated, ventilated and was admitted to the ICU. After 24 hours post surgery the infant was extubated successfully and oral feeding was commenced after 48 hours post surgery. The patient made an uneventful recovery and was later transferred to the paediatric ward.

The surgeons commented that the initial perforation to the jejunum fixed to the mesentery caused de-vascularisation of this portion, leading to the further degradation and gangrenous state of the intestine and thus worsening the child's condition.

As the surgeons had indicated that this injury was of a non-accidental nature the parents of the infant were brought in to be interviewed by the consultant, with the aid of an interpreter. The parents denied any falls or injuries sustained in the events leading to the presentation, which the surgical team had already exclude, due to the absence of associated injuries and symptoms. The consultant noted that both parents were not forthcoming with information even with the aid of an interpreter. Further questioning from the allied health team finally led to an answer. The father admitted that on the morning of the initial presentation while he was sitting on the ground his daughter pulled his hair from behind him to which he responded by elbowing her in the mid-region of her abdomen. Upon obtaining this information a skeletal survey was undertaken, in which a hairline fracture of the shaft of the left humerus and minor bruising in this region was found.

Case resolution

The infant was assumed into care under the basis of neglect and the case was mandatorily reported to Child Protective Services. The parents were then reported to the police for further questioning and probable court hearings. Once the patient was stable, she was discharged into the care of her grandmother, with a further review to be made by Child Protective Services at a later date.

Discussion

Child abuse is still a cause for concern in Australia although there

has been a decrease in substantiations since 2007. [3] Although the total substantiations have decreased, on a state level, Victoria, South Australia, Western Australia, Tasmania and the Northern Territory have recorded an increase in the number of abuse substantiations. The most common abuse type reported in the 2010-2011 was of emotional abuse (36%) followed by neglect (29%), physical abuse (22%) and sexual abuse (13%).

Children who suffer through maltreatment not only have physical burdens placed on them, they often have many associated long-term problems. [4] The term recently coined is 'toxic stress', which results from sustained neglect or abuse. Children are unable to cope and hence activate the body's stress response (elevated cortisol levels). When this occurs over a prolonged period of time it can lead to permanent changes in the development of the immune and central nervous systems (e.g. hippocampus). [5] This combination results in cognitive deficits that result in unwanted manifestations during adult life including poor academic performance, substance abuse, smoking, depression, eating disorders, risky sexual behaviors, adult criminality and suicide. [6] These health issues contribute to a significant proportion of society's health burden.

Medical practitioners and especially those working in ED, are in an advantageous position to be able to intervene in child toxic stress. It is important to be aware of signs or 'red flags' that may point to maltreatment including: failure to thrive, burn marks (cigarette), unusual bruising and injuries, symptoms that do not match the history, recurrent presentation to health services, recurrent vague symptoms, child being cold and withdrawn, lethargic appearance, immunodeficiency without specific pathology and less commonly Munchausen syndrome by proxy. [7]

Previously we alluded to the fact that the child protection data only reflects those reported to the child protective services. Economically disadvantaged families are more likely to come into contact with and be under the scrutiny of public authorities. This means that it is more likely that abuse and neglect will be identified in the economically disadvantaged, [4] however child abuse may occur in all socioeconomic demographics.

This case illustrates the common pitfalls in the clinical setting, one of these being the lack of a clear history obtained at initial presentation. It was mentioned that there was poor communication between the patient's mother and the attending to gain any meaningful information, yet there was no use of an interpreting service or Aboriginal health workers. As Aboriginal health workers have usually lived in the community they work in and most have developed lasting relationships with the community and with the various government agencies. [8] This makes them experts at bridging the communication gap between the patient and the doctor.

Another clinical pitfall demonstrated by this case was the poor examination of this infant, and the failure to recognise important signs such as guarding and rigidity - highly suggestive of insidious pathology. These finding would lead a clinician to perform further investigations such as a CXR or CT-scan which would have determined the underlying pathology. Additionally, no systemic examination was conducted in the haste to discharge the patient from ED. However, this meant, another important sign of abuse - the bruising on the infant's left arm, was missed. Additionally, no investigations were performed when the infant initially presented to ED and hence, the diagnosis of viral gastroenteritis was not confirmed. Furthermore, bacterial gastroenteritis was not properly excluded although it is highly likely in the context of bloody diarrhoea.

Emergency department physicians have many stressors and constant interruptions during their shifts and this combination is known to cause breaks in routine tasks. [9] In 2008, the Australian Medical Association conducted a survey of 914 junior doctors and found that the majority of individuals met well established criteria for low job satisfaction (71%), burnout (69%) and compassion fatigue (54%). [10] These factors indirectly affect patient outcomes and in particular, can lead to overlooking key diagnostic clues. With the recent introduction of the National Emergency Access Target (NEAT), also know as the '4 hour rule', statistics have shown that there has been no change in mortality. [11,12] However, this is a recent implementation and there is a possibility that with junior doctors and nursing staff pushed for a high turnover of patients, that child maltreatment may be missed.

Recommendations

1. Early recognition of child abuse requires a high index of suspicion.
2. Be familiar with mandatory reporting legislation as it varies between state/territories.
3. As junior doctors it is imperative that we use all hospital services such as the interpreting services and the Aboriginal health workers. We can thus enhance optimum history taking.
4. It is important to practice in a reflective manner to prevent inexperience, external pressures and job dissatisfaction from affecting patient quality of care.
5. Services should be encouraged to have Indigenous social/case workers available for consultation.

Conclusion

Paediatric presentations within a hospital can be very challenging, and as junior doctors have the most contact with these patients, they must be aware of important signs of abuse and neglect. We have outlined the importance in communicating with Indigenous patients and the related pitfalls if this is done incorrectly. Doctors are in a position to detect child abuse and to intervene before the long-term consequences manifest.

Conflict of interest

None declared.

Consent declaration

Informed consent was obtained from the next-of-kin for publication of this case report and all accompanying figures.

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Metastatic melanoma: a series of novel therapeutic approaches

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The following report documents the case of a 63 year old male with metastatic melanoma following a primary cutaneous lesion. Investigation into the molecular basis of melanoma has identified crucial regulators in melanoma cell proliferation and survival, leading to the inception of targeted treatment and a shift toward personalised cancer therapy. Recently, the human monoclonal antibody ipilimumab and the targeted BRAF inhibitor vemurafenib have demonstrated promising results in improving both progression-free and overall survival.

Introduction

A diagnosis of metastatic melanoma confers a poor prognosis, with a median overall survival of six to ten months. [1-3] This aggressive disease process is of particular relevance in Australia, owing to a range of adverse risk factors including a predominantly fair-skinned Caucasian population and high levels of ultra-violet radiation. [4-6] While improved awareness and detection have helped to stabilise melanoma incidence rates, Australia and New Zealand continue to display the highest incidence of melanoma worldwide. [4-7] Clinical trials have led to two breakthroughs in the treatment of melanoma: ipilimumab, a fully human monoclonal antibody, and vemurafenib, a targeted inhibitor of BRAF V600E.

Case Presentation

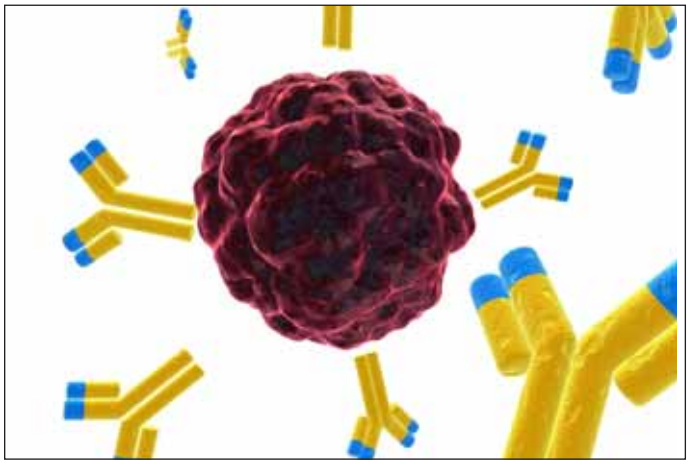
The patient, a 63 year old male, initially presented to his general practitioner ten years ago with an enlarging pigmented lesion in the centre of his back. Subsequent biopsy revealed a grade IV cutaneous melanoma with a Breslow thickness of 5mm. A wide local excision was performed, with primary closure of the wound site. Sentinel node biopsy was not carried out, and a follow-up scan six months later found no evidence of melanoma metastasis.

In mid-2010, the patient noticed a large swelling in his left axilla. A CT/PET scan demonstrated increased fluorodeoxyglucose avidity in this area, and an axillary dissection was performed to remove a tennis ball-sized mass that was histopathologically identified wholly as melanoma. A four week course of radiotherapy was commenced, followed by six weeks of interferon therapy. However, treatment was discontinued when he developed acute abdominal pain caused by pancreatitis.

CT/PET scans were implemented every three months; in early 2011 pancreatic metastases were detected.

The tumour was tested for a mutation in BRAF, a protein in the mitogen activating protein kinase (MAPK) signaling pathway. BRAF mutations are found in approximately half of all cutaneous melanoma, and this is a target for a recently developed inhibitor, vemurafenib. [8-11] The patient's test was negative, and he was commenced on a clinical trial of nanoparticle albumin bound (nab) paclitaxel. He completed a nine month course of nab-paclitaxel, and experienced many adverse side effects including extreme fatigue, nausea, and arthralgia. A CT/PET scan demonstrated almost complete remission of his pancreatic lesions. Despite this progress, three months after completing treatment, a follow-up CT/PET scan revealed liver metastases that were confirmed by biopsy.

In 2012 he was commenced on the novel immunotherapy agent ipilimumab, which involved a series of four infusions of 10mg/kg



three weeks apart. One week after his second dose, he was admitted to hospital with a two day history of maintained high fevers reaching above 40°C, rigors, sweats, and diffuse abdominal pain. These symptoms were preceded by a week long mild coryzal illness. On investigation he had elevated liver enzymes, more than double the reference range, and his blood cultures were negative. His symptoms settled within eight days, and he was discharged after an admission of two weeks in total.

The patient remains hopeful about his future, and is optimistic about the 'fighting chance' that this novel therapy has presented.

Discussion

The complexity of the melanoma pathogenome poses a major obstacle in developing efficacious treatments; however, the identification of novel signaling pathways and oncogenic mutations is challenging this paradigm. [12,13] The resultant development of targeted treatment strategies has clinical importance, with a number of new molecules targeting melanoma mutations and anomalies specifically. The promise of targeted treatments is evident for a number of other cancers, with agents such as trastuzumab in HER-2 positive breast cancer and

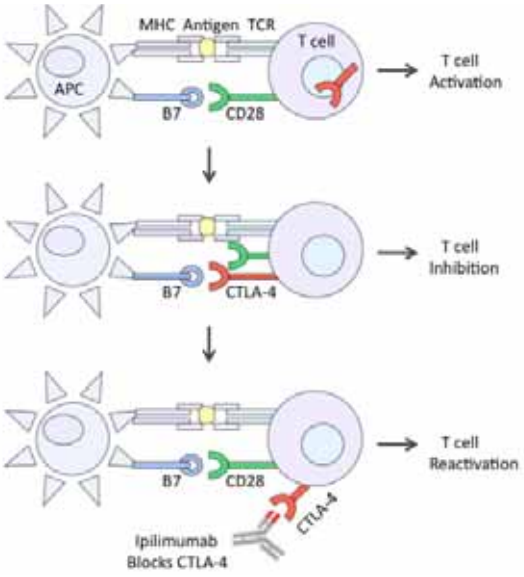


Figure 1. *Ipilimumab mechanism of action.*

imatinib in chronic myelogenous leukaemia now successfully employed as first-line options. [14,15]

This patient's initial treatment with interferon alpha aimed to eradicate remaining micro-metastatic disease following tumour resection. While interferon-alpha has shown disease-free survival benefit, studies have failed to consistently demonstrate significant improvement in overall survival. [16-18]

Favourable outcomes in progression-free and median survival have been indicated for the taxane-based chemotherapy nab-paclitaxel that he next received; however, it has also been associated with concerning toxicity and side effect profiles. [19]

Ipilimumab is a promising development in immunotherapy for metastatic melanoma, with significant improvement in overall survival reported in two recent phase III randomised clinical trials. [20,21] This novel monoclonal antibody modulates the immune response by blocking cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), which competitively binds with B7 on antigen presenting cells to prevent secondary signaling. When ipilimumab occupies CTLA-4, the immune response is upregulated and host versus tumour activity is improved. Native and tumour-specific immune response modification has led to a profile of adverse events associated with ipilimumab that is different from those seen with conventional chemotherapy. Immune-related dermatologic, gastrointestinal, and endocrine side effects have been observed, with the most common immune specific adverse events being diarrhoea, rash, and pruritis (see Table 1). [20,21] The resulting patterns of clinical response to ipilimumab also differ from conventional therapy. Clinical improvement and favourable outcomes may manifest as disease progression prior to response, durable stable disease, development of new lesions while the original tumours abate, or a reduction of baseline tumour burden without new lesions. [22]

Table 1. *Common adverse effects with ipilimumab (percentage of patients).*

Side effect	Ipilimumab alone [20] (%)	Ipilimumab + gp100 [20] (%)	Ipilimumab + dacarbazine [21] (%)	Placebo + dacarbazine [21] (%)
Any immune-related event	61.1	58.2	77.7	38.2
Diarrhoea	32.8	38.4	36.4	24.7
Fatigue	42.0	36.1	41.7	39.0
Nausea	35.1	33.9	48.6	48.6
Pyrexia	12.2	20.5	36.8	9.2

Recently discovered clinical markers may offer predictive insight into ipilimumab benefit and toxicity, and are a key goal in the development of personalised medicine. Pharmacodynamic effects on gene expression have been demonstrated, with baseline and post-treatment alterations in CD4+ and CD8+ T cells implicated in both likelihood of relapse and occurrence of adverse events. [23] Novel biomarkers that may be associated with a positive clinical response include immune-related tumour biomarkers at baseline and a post-therapy increase in tumour-infiltrating lymphocytes. [24]

Overall survival was reported as 10 and 11.2 months for the two phase III studies compared with 6.4 and 9.1 months in the control arms. [20,21] Furthermore, recently published data on the durability of response to ipilimumab has indicated five year survival rates of 13%, 23%, and 25% for three separate earlier trials. [25]

Somatic genetic alterations in the MAPK signaling cascade have been identified as key oncogenic mutations in melanoma, and research into independent BRAF driver mutations has resulted in the development of highly selective molecules such as vemurafenib. Vemurafenib inhibits constitutive activation of mutated BRAF V600E, thereby preventing upregulated downstream effects that lead to melanoma proliferation and survival. [26,27] A multicentre phase II trial demonstrated a median overall survival of 15.9 months, and a subsequent phase III randomised clinical trial was ended prematurely after pre-specified statistical significance criteria was attained at interim analysis. [8,9] Crossover from the control arm to vemurafenib was recommended by an independent board for all surviving patients. [8] Conversely, in patients with mutated upstream RAS and wild-type BRAF mutation status, the use of vemurafenib is unadvisable on the basis of preclinical models. For these mutations, BRAF inhibition may lead to paradoxical gain-of-function mutations within the MAPK pathway, and drive tumourigenesis rather than promoting downregulation. [13] The complexity of BRAF signaling and reactivation of the MAPK pathway is highly relevant in the development of intrinsic and acquired drug resistance to vemurafenib. Although the presence of the V600E mutation generally predicts response, acquisition of secondary mutations has resulted in short-lived treatment duration. [28]

Ipilimumab and vemurafenib, when used individually, clearly demonstrate improvements in overall survival. Following the success of these two agents, a study examining combination therapy in patients testing positive to the BRAF V600E mutation is currently underway. [29]

With the availability of new treatments for melanoma, the associated health care economics of niche market therapies need to be acknowledged. It is likely that the cost of these drugs will be high, making it difficult to subsidise in countries such as Australia where public pharmaceutical subsidies exist. Decisions about public subsidy of drugs are often made on cost-benefit analyses, which may be inadequate in expressing the real life benefits of prolonging a patient's lifespan in the face of a disease with a dismal prognosis. Non-subsidy may lead to the availability of these medicines to only those who can afford it, and it is concerning when treatment becomes a commodity stratified by individual wealth rather than need. This problem surrounding novel treatments is only expected to increase across many fields of medicine with the torrent of medical advances to come.

Conclusion

This case illustrates the shift in cancer therapy for melanoma towards a model of personalised medicine, where results of genomic investigations influence treatment choices by potentially targeting specific oncogenes driving the cancer.

Conflict of interest

None declared.

Consent declaration

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

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Blood culture negative endocarditis – a suggested diagnostic approach

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Sadid is a final year medical student at Monash University. He has a variety of interests, with particular passion for infectious diseases, public health and medical education.

This case report describes a previously healthy male patient with a subacute presentation of severe constitutional symptoms, progressing to acute pulmonary oedema, and a subsequent diagnosis of blood culture negative endocarditis with severe aortic regurgitation. Blood culture negative endocarditis represents an epidemiologically varying subset of endocarditis patients, as well as a unique diagnostic dilemma. The cornerstones of diagnosis lay in careful clinical assessment and exposure history, as well as knowledge of common aetiologies and appropriate investigations. The issues of clinically informed judgement and having a systematic approach to the diagnosis of these patients, especially within an Australian context, are discussed. Aetiological diagnosis of these patients modifies and directs treatment, which is fundamental in minimising the high morbidity and mortality associated with endocarditis.

Case

Mr NP was a previously healthy, 47 year old Caucasian male who presented to a small metropolitan emergency department with two days of severe, progressive dyspnoea which was subsequently diagnosed as acute pulmonary oedema (APO). This occurred on a three month background of dry cough, malaise, lethargy and an unintentional weight loss of 10 kilograms.

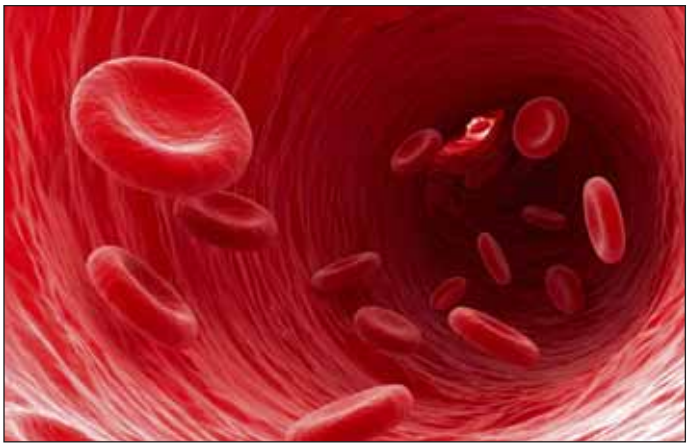
History

Apart from the aforementioned, Mr NP's history of the presenting complaint was unremarkable. In the preceding three months Mr NP was previously treated in the community for pertussis and atypical pneumonia, resulting in no significant improvement. Notably, this therapy included two courses of antibiotics (the specifics unable to be remembered by the patient), with the latest course completed the week prior to admission. He had no relevant past medical or family history, specifically denying a history of tuberculosis, malignancy, and heart and lung disease. There were no current medications or known allergies; he denied intravenous or other recreational drug use, reported minimal alcohol use, and had never smoked.

Mr NP lived in suburban Melbourne with his wife and children. He kept two healthy dogs at home. There had been no sick contacts and no obvious animal or occupational exposures, although he noted that he occasionally stopped cattle trucks on the highway as part of his occupation, but had no direct contact with the cattle. He recently travelled to Auckland, New Zealand for two weeks, two months prior. There were no stopovers, notable exposures or travel throughout the country.

Table 1. *A suggested schema for assessing exposures to infectious diseases during the clinical history, illustrated using the commonly used CHOCOLATES mnemonic.*

Exposure Assessment Schemata: CHOCOLATES mnemonic
Country of origin
Household environment
Occupation
Contacts
Other: Immunisations, intravenous drug user, immunosuppression, splenectomy, etc.
Leisure activities/hobbies
Animal exposures
Travel and prophylaxis prior
Eating and drinking
Sexual contact



During the initial assessment of Mr NP's acute pulmonary oedema, blood cultures were drawn with a note made of oral antibiotics during the preceding week. A transthoracic echocardiogram (TTE) found moderate aortic regurgitation with left ventricular dilatation. A subsequent transoesophageal echocardiogram (TOE) noted severe aortic regurgitation, a one centimetre vegetation on the aortic valve with destruction of the coronary leaflet, LV dilation with preserved ejection fraction greater than 50%. Blood cultures, held for 21 days, revealed no growth.

Empirical antibiotics were started and Mr NP was transferred to a large quaternary hospital for further assessment and aortic valve replacement surgery.

Examination

Examination of Mr NP, after transfer and admission, showed an alert man, pale but with warm extremities, with no signs of shock or sepsis. Vital signs revealed a temperature of 36.2°C, heart rate of 88 beats per minute, blood pressure of 152/50 mmHg (wide pulse pressure of 102 mmHg) and respiratory rate of 18 breaths per minute, saturating at 99% on room air.

No peripheral stigmata of endocarditis were noted, and there was no lymphadenopathy. Examination of the heart and lungs noted a loud diastolic murmur through the entire precordium, which increased with full expiration, but was otherwise normal with no signs of pulmonary oedema. His abdomen was soft and non-tender with no organomegaly noted.

Workup and Progress

Table 2 shows relevant investigations and results from Mr NP.

Empirical antibiotics for culture negative endocarditis were initiated during the initial presentation and were continued after transfer and admission:

- Benzylpenicillin for streptococci and enterococci
- Doxycycline for atypical organisms and zoonoses
- Ceftriaxone for HACEK organisms
- Vancomycin for staphylococcus and resistant gram positive bacteria.

Table 2. *Table outlining the relevant investigation results for Mr NP performed for further assessment of blood culture negative endocarditis.*

Investigation		Result
Blood Cultures	Repeat Blood Cultures x 3 (on antibiotics)	No growth until date; held for 21 days
Autoimmune	Rheumatoid Factor	Weak Positive – 16 [N <11]
	ANA	Negative
	ENA	Negative
Serology	Q Fever	Phase I Negative Phase II Negative
	Bartonella	Negative
	Atypical Organisms; (*Legionella, Mycoplasma*)	Negative
Valve Tissue (post AVR)	Histopathology	Non-specific chronic inflammation and fibrosis
	Tissue Microscopy and Culture	Gram positive cocci seen. No growth until date.
	16S rRNA	*Streptococcus mitis*
	18S rRNA	Negative

AVR – Aortic valve replacement; ANA – Antinuclear antibodies; ENA – Extractable nuclear antigens

During his admission, doxycycline was ceased after negative serology testing and microscopy identifying gram positive cocci. Benzylpenicillin was changed to ampicillin after a possible allergic rash. Ceftriaxone, ampicillin and vancomycin were continued until the final 16S rRNA result from valvular tissue identifying *Streptococcus mitis*, a viridians group Streptococci.

The patient underwent a successful aortic valve replacement (AVR) and was routinely admitted to the intensive care unit (ICU) post cardiac surgery. He developed acute renal failure, most likely due to acute tubular necrosis from a combination of bacteraemia, angiogram contrast, vancomycin, and the stresses of surgery and bypass. Renal functional gradually returned after resolution of contributing factors without the need for removal of vancomycin, and Mr NP was discharged to the ward on day six ICU.

Clinical improvement was seen in Mr NP, as well as through a declining white cell count and a return to normal renal function. He was discharged successfully with Hospital in the Home for continued outpatient IV vancomycin for a combined total duration of four weeks and for follow up review in clinic.

Discussion

There is an old medical adage, that "persistent bacteraemia is the *sine qua non* of endovascular infection." The corollary is that persistently positive blood cultures is a sign of an infection within the vascular system. In most clinical situations this is either primary bacteraemia or infective endocarditis, although other interesting, but less common differentials, exist (e.g. septic thrombophlebitis/Lemierre's Syndrome, septic aneurysms, aortitis, etc.). Consequently, blood culture negative endocarditis (BCNE) becomes both an oxymoron, and a unique clinical scenario.

BCNE can be strictly defined as endocarditis (as per Duke criteria) without known aetiology after three separate blood cultures with no growth after at least seven days, [1] although less rigid definitions have been used throughout the literature. The incidence is approximately 2-7% of endocarditis cases, although it can be as much as 31%, due to multiple factors such as regional epidemiology, the administration of prior antibiotics and the definition of BCNE used. [1-3] Importantly, the morbidity and mortality associated with endocarditis remains high despite multiple advances, and early diagnosis and treatment remains fundamental. [1,4,5]

The most common reason for BCNE is prior antibiotic treatment before blood culture collection, [1-3] as was the case with Mr NP. Additional associated factors for BCNE include exposure to zoonotic agents, underlying valvular disease, right-sided endocarditis and presence of a pacemaker. [1,3]

Figure 1 shows the aetiology of BCNE; Table 3 lists clinical associations and epidemiology of common organisms which may be identified during assessment. Notably, there is a high prevalence of zoonotic infections, as well as a large portion remaining unidentified. [2] Additionally, the

Table 3. *Common aetiologies in BCNE and associated clinical features and epidemiology. [1,2,5-9]*

Aetiology	Clinical Associations and Epidemiology
Q Fever *(Coxiella burnetii)*	Zoonosis: contact with farm animals (commonly cattle, sheep, and goats). Farmers, abattoir workers, veterinarians, etc. Check for vaccination in aforementioned high risk groups.
Bartonella spp.	Zoonosis: contact with cats (*B henselae*); transmitted by lice, poor hygiene, homelessness (*B quintana*).
Mycoplasma spp.	Ubiquitous. Droplet spread from person to person, increased with crowding. Usually causes asymptomatic or respiratory illness, rarely endocarditis.
Legionella spp.	Usually *L pneumophila; L longbeachae* common in Australia. Environmental exposures through drinking/inhalation. Colonises warm water, and soil sediments. Cooling towers, air conditioners, etc. help aerosolise bacteria. Urinary antigen only for *L pneumophila* serogroup 1. Usually respiratory illness, rarely endocarditis.
Tropheryma whipplei	Associations with soil, animal and sewerage exposures. Wide spectrum of clinical manifestations. Causative organism of Whipple's Disease (malabsorptive diarrhoeal illness).
Fungi	Usually with *Candida spp*. Normal GIT flora. Associated with candidaemia, HIV/immunosuppression, intravascular device infections, IVDU, prosthetic valves, ICU admission, parenteral feeding, broad spectrum antibiotic use. Associated with larger valvular vegetations.
HACEK organisms*	*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella spp*. Fastidious Gram negative rods. Normal flora of mouth and upper GI. Associated with poor dentition and dental work. Associated with larger valvular vegetations.
Streptococcus viridans group*	Umbrella term for alpha haemolytic streptococci commonly found as mouth flora. Associated with poor dentition and dental work.
*Streptococcus bovis**	Associated with breaches of colonic mucosa: colorectal carcinoma, inflammatory bowel disease and colonoscopies.
*Staphylococcus aureus**	Normal skin flora. IVDU, intravascular device infections, post-operative valve infections.

IVDU – Intravenous drug user; GIT – Gastrointestinal tract.
** Traditional IE organisms. Most BCNE cases with usual IE bacteria isolated where antibiotics given before culture. [1-3]*

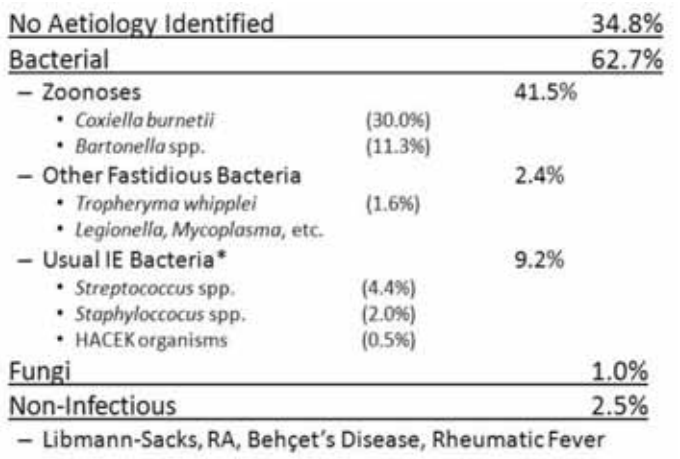


Figure 1. *The percentage incidence of BCNE aetiologies. [2]*
IE: Infective endocarditis; RA: Rheumatoid Arthritis; HACEK (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella): See Table 4
** Most BCNE cases with usual IE bacteria isolated where antibiotics given before culture. [1-3]*

incidence of normal endocarditis organisms is comparatively high, which in most cases have been suppressed through prior antibiotic use. [2]

The HACEK organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella*) are fastidious (i.e. difficult to grow), gram negative oral flora. Consequently (and as a general principle for other fastidious organisms), these slow growing organisms tend to produce both more subacute presentations as well as larger vegetations at presentation. They have been traditionally associated with causing culture negative endocarditis, but advancements in microbiological techniques have resulted in the majority of these organisms being able to be cultured within five days, and now have a low incidence in true BCNE. [1]

Q Fever is of particular importance as it is both the most common identified aetiology of BCNE, as well as an important offender in Australia, given the large presence of primary industry and the consequent potential for exposure. [1-3,6] Q Fever is caused by the Gram negative obligate intracellular bacteria *Coxiella burnetii,* (named after Australian Nobel laureate Sir Frank Macfarlane Burnet), and is associated in particular with various farm animal exposures (see Table 4). The manifestations of this condition are variable and nonspecific, and the key to diagnosis often lies in an appropriate index of suspicion and an exposure history. [6] In addition, Q fever is a very uncommon cause of BCNE in Northern Europe and UK, and patient exposures in this region may be less significant. [1,2,6]

The clinical syndrome is separated into acute and chronic Q Fever. This differentiation is important to note for two reasons: firstly, Q fever endocarditis is a manifestation of chronic, not acute, Q fever, and secondly because of the implication on serological testing. [6] Q fever serology is the most common diagnostic method used, and is separated into Phase II (Acute Q Fever) and Phase I (Chronic Q Fever) serologies. Accordingly, to investigate Q fever endocarditis, Phase I serology must be performed. [6]

Given the large incidence of zoonotic aetiologies, the modified Duke criteria suggests that positive blood culture or serology for Q fever be classed as a major criterion for diagnosis of endocarditis. [10] However, Lamas and Eykyn [3] found that even with the modifications to the traditional Duke criteria this is still a poor predictor for BCNE, identifying only 32% of their pathologically proven endocarditis patients. Consequently, they suggest the addition of minor criteria to improve sensitivity, making particular note of rapid onset splenomegaly or clubbing which can occur especially in patients with zoonotic BCNE. [3]

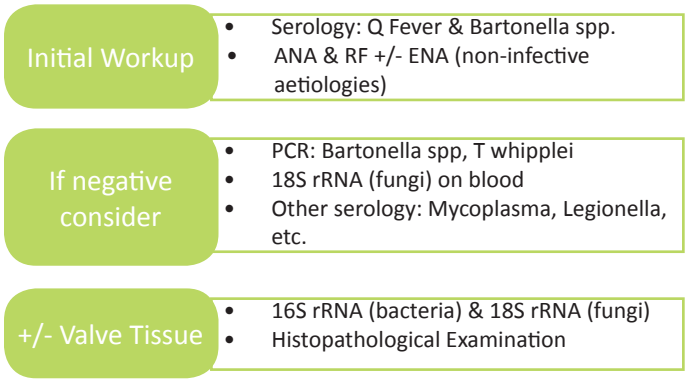


Figure 2. *The suggested diagnostic approach to BCNE, shown in a stepwise fashion.*
ANA – Antinuclear antibodies; ENA – Extractable nuclear antigens; RF – Rheumatoid Factor.

Figure 2 outlines the suggested diagnostic approach, modified from the original detailed by Fournier *et al.* [2] The initial steps are aimed at high incidence aetiologies and to rule out non-infectious causes, with stepwise progression to less common causes. Additionally, testing of valvular tissue plays a valuable role in aiding diagnosis in situations where this is available. [1,2,11,12]

16S ribosomal RNA (rRNA) gene sequence analysis and 18S rRNA gene sequence analysis are broad range PCR tests, which can be used to amplify genetic material that may be present inside a sample. Specifically, it identifies sections of rRNA which are highly preserved against mutation, and are specific to a species of organism. When a genetic sequence has been identified, it is compared against a library of known genetic codes to identify the organism if listed. 16S identify prokaryotic bacteria, and 18S is the eukaryotic fungal equivalent. These tests can play a fundamental role in the identification of aetiology where cultures are unsuccessful, although they must be interpreted with caution and clinical judgement, as they are highly susceptible to contamination and false positives due to their high sensitivity. [11-13] Importantly, antibiotic sensitivity testing is unable to be performed on these results, as there is no living microorganism isolated. This may necessitate broader spectrum antibiotics to allow for potential unknown resistance – as was demonstrated by the choice of vancomycin in the case of Mr NP.

The best use of 16S and 18S rRNA testing in the diagnosis of BCNE is upon valvular tissue; testing of blood is not very effective and not widely performed. [2,11,13] Notwithstanding, 18S rRNA testing on blood may be appropriate in certain situations where first line BCNE investigations are negative, and fungal aetiologies become much more likely. [2] This can be prudent given that most empirical treatment regimes do not include fungal cover.

Fournier *et al.* [2] suggested the use of a *Septifast©* multiplex PCR (F Hoffmann-La Roche Ltd, Switzerland) – a PCR kit designed to identify 25 common bacteria often implicated in sepsis – in patients who have had prior antibiotic administration. Although studies have shown its usefulness in this context, it has been excluded from Figure 2 because, to the best of the author's knowledge, this is not a commonly used test in Australia. The original diagnostic approach from Fournier *et al.* [2] identified aetiology in 64.6% of cases, with the remainder being of unknown aetiology.

Conclusion

BCNE represents a unique and interesting, although uncommon, clinical scenario. Knowledge of the common aetiologies and appropriate testing underpins the timely and effective diagnosis of this condition, which in turn modifies and directs treatment. This is especially important due to the high morbidity and mortality rate of endocarditis and the unique spectrum of aetiological organisms which may not be covered by empirical treatment.

Acknowledgements

The author would like to thank Dr Adam Jenney and Dr Iain Abbott for their advice regarding this case.

Consent declaration

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

Conflict of interest

None declared.

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Health care to meet the future needs of New South Wales

Jillian Skinner MP
Minister for Health
Minister for Medical Research

When thinking about innovation and ways to transform how health care is delivered to the patients of today and tomorrow, the importance and growing potential of e-Health springs to mind.

In Opposition and now as Minister for Health and Minister for Medical Research I am absolutely convinced of the enormous gains to be made using e-Health technology, whether electronic patient records, telehealth connecting clinicians in remote settings, managing assets and other important clinical information and governance arrangements.

My years in Opposition did much to foster my knowledge, understanding and passion for the health system and I had the rewarding opportunity to meet with leaders in health care to discuss both challenges and future possibilities.

In 2007, as NSW Shadow Minister for Health, I was humbled to be invited to speak at Hewlett Packard's Health and Life Sciences Symposium. Hosted at San Diego, the conference connected specialists in the e-Health field from across the globe to discuss its impacts and contribution to the wider health agenda.

The conference was incredibly inspiring for an aspiring health minister. While many there were caught up in the gadgetry, I found myself thinking a lot of about the experiences of patients back home and how they needed to be improved by advancements in technology.

Now, the NSW health system boasts one of the largest information and communication technology (ICT) portfolios of any government agency or corporate organisation in this country.

ICT has an important role to play in the delivery of health services; whether in acute hospital care, preventative health, patient self-care and those treatments provided in a range of health care settings – in a patient's home, in the community, a private or not-for-profit facility or through the public health system.

And these services will be delivered by a range of health professionals, including those of you reading who hope to enter these fields.

For many years, I have been committed to enhancing e-Health services in this state as it is these very services that put the patient at the forefront while boosting contemporary methods of care.

NSW Health will spend more than $1.5 billion over the next 10 years on ICT to improve both care and patient outcomes across the state.

Jillian Skinner

We've achieved a lot in this space in the past 12-18 months and are setting the foundations to do great things for the benefit of patients in the future.

We have developed numerous innovative e-Health programs across the health system including:

- The use of telehealth to link patients in rural and regional NSW with face-to-face specialist care in tertiary hospitals, making services available anywhere, anytime.
- We are collaborating with clinicians by activating voice recognition software in emergency departments to free-up precious time for patient care.
- We have established real-time emergency department waiting time data for the community, published online and updated every fifteen minutes.
- We have technology that now provides instant digital images, which can be reviewed and reported by specialist doctors even before the patient is back in the ward. This slashes waiting times for results and is seeing treatments delivered earlier than ever before.
- We are developing and introducing apps and tablet technology to provide instant access to clinical research and digital medical libraries for better information sharing between clinicians and their colleagues.
- We are supporting trials where electronic health records have revolutionised the speed and accuracy of medical information between hospital wards and between patients and their General practitioners.
- We are using technology to better track financial and performance management, not only in clinical incident monitoring, but in preparations for an Activity Based Funding model and to ensure value for money for every tax-payer dollar spent.

These are not future ambitions. These are services being utilised today to ensure our patients are not just well-cared for but well-informed and connected to health services.

As the Minister for Health, I want to see these initiatives driving better performance in our state's hospitals – leading to better outcomes for patients and their families.

Telehealth remains a particular passion of mine. From what I am seeing utilised by clinicians on the ground, it is an impressive tool and one that sees patients receiving the best possible care with treatment transcending geographical barriers.

Recently, I was in Canberra to launch the Improving Critical Care Outreach and Training in the ACT and South East NSW project.

This pilot telehealth system will connect Canberra Hospital emergency department and helicopter base with hospitals at Queanbeyan, Moruya, Batemans Bay and Cooma.

It utilises overbed cameras, microphones and speakers and has viewing monitors positioned in the resuscitation area of the Emergency Department in the NSW spoke sites. The system uses the ACT and NSW videoconferencing networks to transmit images and vital signs to the referral or hub site in the ACT.

Telehealth initiatives have become a key component of clinical care and improving access to services in NSW.

We currently have more than 600 videoconferencing locations across the state which are used for a range of services in the areas of mental health; critical and emergency care; oncology; radiology; diabetic foot care; genetic services; and, chronic disease management.

The NSW Government is committed to supporting innovative projects such as this for the benefit of patients across NSW. We currently oversee the provision of telehealth technology in a variety of health facilities across regional NSW including Goulburn, Queanbeyan, Yass, Braidwood, Crookwell, Moruya, Bega, Batemans Bay, Cooma, Pambula and Bombala.

Telehealth affords local patients the opportunity to be treated locally with the support, guidance and expertise of clinicians at tertiary teaching hospitals..

Do medical students have a role to play in the state's e-Health agenda? Absolutely.

Starting out in politics almost two decades ago, e-Health was considered the stuff of science fiction. Now, we're seeing its use move from the bench to the bedside for the benefit of patients.

As our tech-savvy workforce increases, we will get smarter and more innovative.

I want a resilient system but one that is flexible and able to innovate to achieve greater efficiencies.

Above all, I want a health system that can deliver the highest quality care to patients.

Health often gets lost in statistics but technology does not substitute for the high quality care provided by clinicians, rather it enhances it.

By providing both current and future clinicians with the modern tools and information they need, we are going a long way to empowering them to achieve much more for their patients.

Dealing with futile treatment: A medical student's perspective

Michael Li
Third Year Medicine (Undergraduate)
Australian National University

Michael is a 3rd year Rural Stream student placed in Cooma. He is thoroughly enjoying the hands on work in ED and anaesthetics after slogging through 2 years of pre-clinical study.

A 76 year old man with metastatic liver cancer lies feebly in his hospital bed surrounded by family. He's in cardiac and respiratory failure. Attached to him are multiple lines, cannulas and monitors. There are more machines present than people. Despite this, his breathing is laboured, he's gaunt, and he is clearly suffering. In a rare moment of lucidity, he gestures for his son to come closer and whispers: "No more." An obviously grief stricken man turns to the rest of the family, gestures, and heads outside to make one of the most difficult decisions he will ever make.

Confused and anxious, a fifteen year old boy sits and listens to the pros and cons of stopping his grandfather's treatment being discussed by the doctors and the family. Questions keep popping up in his head "Why is he giving up? How could they consider withdrawing treatment, the same treatment that was obviously keeping this man alive? How could anyone live with that decision?"

How do I know this? Because I was that fifteen year old boy.

It is, perhaps, ironic that modern advances in medicine have made it feasible to sustain life and sometimes suffering, for an indefinite period. [1] The dramatic improvement in technology for life preservation has created ambiguity and has dehumanised the dying process. The result of this is that very difficult legal and moral decisions must now be made about transitions from aggressive treatment to palliative care. [2] At times, the existence of this technology creates a moral obligation to use it, especially when societal belief is that to treat is to care. [3]

It was all too much back then for a teenage boy, but now ten years down the line, is it still too much for a medical student? After all, what can we as mere fledgling trainees do to help ease those heavy burdens? Reflecting on these experiences helps address the powerlessness we experience in these morally and ethically challenging cases and serves as a reminder to everyone that even as mere 'students', we are capable of playing a vital therapeutic role in the care of patients whose treatments have been deemed futile.

Defining futility

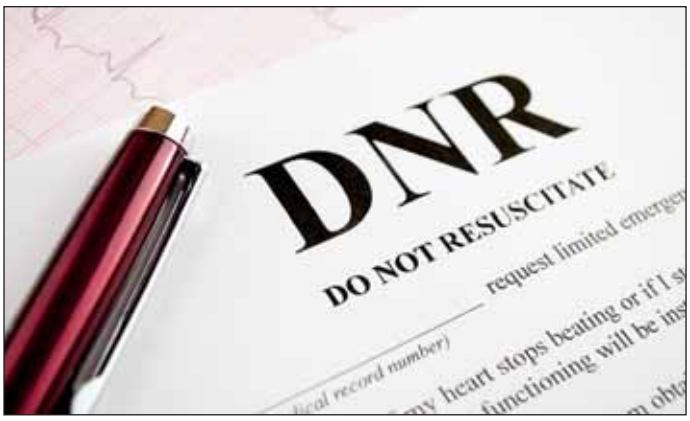
Looking back at that period of time now, it is difficult to justify the last few weeks of futile treatment that my grandfather received.

How does one decide when treatment is futile? Some have defined it quantitatively as treatments that have less than a 10% chance of success, [4] while others have tried to express it qualitatively as "treatment which provides no chance of meaningful prolongation of survival or may only briefly delay the inevitable death of the patient." [5] The majority of physicians will deem this poor outcome unsatisfactory and thus the treatment futile; however, most families will not. [6] Whatever the definition, futile treatment is not a black and white concept, but must be considered as a complex composite of quality of life issues that need to be discussed either with the patient early in their diagnosis, or with their legal next of kin. [5]

Ethical decisions

This choice is difficult enough for clinicians with years of health-care experience, let alone medically untrained families under stress, grieving for the imminent loss of a loved one.

How are these decisions made? There are no protocols or parameters



set out which suggest treatment should be withdrawn. While students are often taught to use the four principles of bioethics: beneficience, non-maleficience, autonomy and justice to guide them through ethically challenging cases, [7] the general public often places a special emphasis on beneficence, and thus consider continuing treatment as the only option. This was demonstrated in a questionnaire study by Rydvall and Lynoe (2008), asking both physicians and the general public when they believed treatments should be withdrawn from terminally ill patients. While the majority of physicians chose to withdraw treatment early on to prevent further suffering, the majority of the general public chose to continue aggressive treatment until the very end, stating that the first task of health care professionals is to save lives. [8]

This highlights the higher expectations that the general public may have of what the health care system should achieve, [8] which can lead to points of contention and miscommunication when it comes to making critical care decisions. The role of the medical student in these cases is often as a moderator; to listen, discuss and bridge the gap of communication between the two understandably apprehensive parties.

The therapeutic use of self

The feeling of helplessness was overwhelming, none of the doctors paid me any attention; I was just a child after all, not worthy of their attention or time. But he was my grandfather, not just their patient.

The concept of 'therapeutic use of self' is the use of oneself as a therapeutic agent by integrating and empathising with the patient and their family. This can be to alleviate fear or anxiety, provide reassurance and obtain or provide necessary information in an attempt to relieve suffering. [9] This is particularly relevant in circumstances where treatments have a limited effect on the disease process, where suffering is prolonged rather than prevented.

Medical school does not always formally teach the importance of connecting with patients and the therapeutic role that students play. [10] Many young aspiring doctors seek to emulate the 'professional' and sometimes detached demeanour of their more senior counterparts; often getting too close to the patients is seen to be a one way street towards emotional burnout. However, therapeutically, the importance of being physically near patients and their families during their personal illness and distress cannot be over stated. [9]

While many students may claim to never have enough time in their schedules, they are often the most time-rich personnel. For this reason they are often the only ones who have the opportunity to sit down with the family and the patient. This is not to take away, explain or understand the pain, but rather as a symbol of support, so that they know we are witnesses to their suffering and that they have not been abandoned. [10]

Withdrawing versus withholding

The debate went on throughout the night: "We're abandoning him?"

"No, it's for the best, he doesn't need to go through any more of this, the doctor said there's no way he's going to get better."

"You want to stop all treatments? We should be trying new things not stopping old treatments!"

Traditional medical training places an emphasis on the acquisition of skills and expertise to help 'fix' the patients or their diseases. Interestingly, many clinicians are more comfortable withholding treatment – that is, not beginning new aggressive treatments – than stopping currently initiated treatments. [1,11,12] This may be because withdrawing attaches a feeling of responsibility and culpability for the death. [3,13] To avoid this, clinicians will often only withdraw support when it becomes clear that death will occur regardless of further treatment. In this way, a "causative link between non-treatment and death is avoided." [14]

Increasingly in today's medical system, a simple 'fix' does not exist for many patients and their diseases. For these patients, success is judged not on the amelioration of the pathological process, but instead, on whether a good quality of life can be achieved in spite of the presence of chronic disease. Various religions and cultures have differing views on quality of life arguments adding a further layer of complexity to the decision making process. Therefore it is important to take the background of the patient and their relatives into consideration. [3]

Similarly, individual variations exist between physicians, because although each will use the most current evidence available to decide plans for the best outcome, each person is influenced by their own ethical, social, moral and religious views. [3] This perhaps, is the reason why the modern curriculum has incorporated elements of personal reflection, professionalism and social foundations of medicine to guide students into thinking more reflectively and sensitively, allowing for a more holistic patient-centered approach.

Moral decisions

"He's not going to get better," I was told, "The doctors said we should stop the treatments because all they're doing is causing him to suffer." Even I could understand that decision when it was justified to me like that. Unfortunately others don't necessarily see it that way.

Moral situations often arise when clinicians tell relatives that they believe treatment will not help the patient recover, and the option is given to withdraw aggressive treatment in favour of palliative care. Many perceive continued treatment to not only be life sustaining, but also potentially curative, and thus moving onto palliative care is often interpreted as a choice to end their loved one's life. [5] Some feel it is better to watch their relative die while undergoing treatment rather than live with the belief that they consented to death. [3, 5] Unsurprisingly, relatives will often demand that "everything be done" to preserve life. [5, 15, 16]

It is important to remind family that withdrawing futile treatment does not mean withdrawing all treatment. Palliative management including analgesia, respect for dignity, and support will always be provided throughout the ordeal. [2] We must be mindful that in this day of medical advancements, it is quite common that caring for a chronically ill loved one becomes the sole purpose in the carer's life. The health care system has generated a 'patient support system' in which the carer has one role, and is deprived of energy and time for anything else, forgoing careers, friends and hobbies. It is perhaps unsurprising, that towards the end of a patient's life, the carer maybe unwilling to let go of the only remaining source of meaning in their life. [6]

These difficult decisions often don't need to be made if adequate preparation has been made beforehand, by having advanced care directives documented and a durable power of attorney arranged before the condition of the patient declines. These items can make a world of difference for both the family and the health care staff. [13]

Final thoughts

Would I have done anything differently if I had the maturity and the training that I have now?

Medical students in general feel that completing a full history and examination is the extent of what they can offer to patients; [16] however, this is often not the case. Their support and knowledge base is invaluable to patients and their family. Students play a vital therapeutic role in assisting the patient and family to come to terms with the limitations of modern medicine, and to recognise that extension of the dying process undermines what both the medical team and the family ultimately want – a dignified and peaceful death.

It is easy to objectively look at a patient with whom we've had no past relationship and decide what the right choice is. But for families, it will never be that straight forward when a decision has to be made about a loved one. During these times, as medical students, we need more than the ability to communicate effectively, we need the mental fortitude to be able to step into that dark and difficult place with the patient and their family to truly connect, and be there for them not only with our book smarts, but as figures of support and strength.

Never underestimate the therapeutic potential of who we are. While we may lack the mountains of factual knowledge of our senior colleagues, we have the potential to excel in the more humanistic aspects of patient care. By learning to approach these cases with compassion and humility, we can hope that our presence and understanding will render healing in situations that cannot be cured by our medical knowledge. [10]

As he requested, treatment was withdrawn and palliative care started, the 76 year old grandfather, father, and husband returned home and passed away in a dignified and peaceful way surrounded by family.

Acknowledgements

The author would like to thank his grandfather who gave him the world by teaching him to how to learn.

The author would also like to acknowledge the fantastic feedback provided by both reviewers which allowed him to gain a greater understanding into this fascinating topic.

Conflict of interest

None declared.

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The history of abdominal aortic repair: from Egypt to EVAR

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Introduction

An arterial aneurysm is defined as a localised dilation of an artery to greater than 50% of its normal diameter. [1] Abdominal aortic aneurysm (AAA) is common with an incidence five times greater in men than women. [2] In Australia the prevalence of AAAs is 4.8% in men aged 65-69 years rising to 10.8% in those aged 80 years and over. [3] The mortality from ruptured AAA is very high, approximately 80%, [4] whilst the aneurysm-related mortality of surgically treated, asymptomatic AAA is around five percent. [5] In Australia AAAs make up 2.4% of the burden of cardiovascular disease, contributing 14,375 disability adjusted life years (DALYs), ahead of hypertension (14,324) and valvular heart disease (13,995). [6] Risk factors for AAA of greater than four centimetres include smoking (RR=3-5), family history (OR=1.94), coronary artery disease (OR= 1.52), hypercholesterolaemia (OR= 1.44) and cerebrovascular disease (OR= 1.28). [7] Currently, the approach to AAA management involves active surveillance, risk factor reduction and surgical intervention. [8]

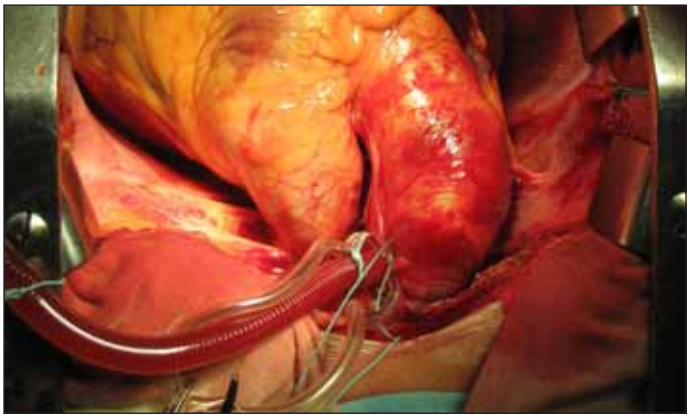
The surgical management of AAAs dates back over 3000 years and has evolved greatly since its conception. Over the course of surgical history arose three landmark developments in aortic surgery: crude ligation, open repair and endovascular AAA repair (EVAR). This paper aims to examine the development of surgical interventions for AAA, from its experimental beginnings in ancient Egypt to current evidence based practice defining EVAR therapy, and to pay homage to the surgical and anatomical masters who made significant advances in this field.

Early definition

The word aneurysm is derived from the Greek aneurysma, for 'widening'. The first written evidence of AAA is recorded in the 'Book of Hearts' from the Eber Scolls of ancient Egypt, dating back to 1550 BC. [9] It stated that "only magic can cure tumours of the arteries." India's Sushruta (800 ~ 600 BC) mentions aneurysm, or 'Granthi', in chapter 17 of his great medical text 'Sushruta Samhita'. [10] Although undistinguished from painful varicose veins in his text, Sushruta shared a similar sentiment to the Egyptians when he wrote "[Granthi] can be cured only with the greatest difficulty". Galen (126-c216 AD), a surgeon of ancient Rome, first formally described these 'tumours' as localised pulsatile swellings that disappear with pressure. [11] He was also first to draw anatomical diagrams of the heart and great vessels. His work with wounded gladiators and that of the Greek surgeon Antyllus in the same period helped to define traumatic false aneurysms as morphologically rounded, distinct from true, cylindrical aneurysms caused by degenerative dilatation. [12] This work formed the basis of the modern definition.

Early ligation

Antyllus is also credited with performing the first recorded surgical interventions for the treatment of AAA. His method involved midline laparotomy, proximal and distal ligation of the aorta, central incision of the aneurysm sac and evacuation of thrombotic material. [13] Remarkably, a few patients treated without aseptic technique or anaesthetic managed to survive for some period. Antyllus' method was further described in the seventh century by Aetius, whose detailed paper 'On the Dilation of Blood Vessels,' described the development and repair of AAA. [14] His approach involved stuffing the evacuated



sac with incense and spices to promote pus formation in the belief that this would aid wound healing. Although this belief would wane as knowledge of the process of wound healing improved, Antyllus's method would remain largely unchanged until the late nineteenth century.

Anatomy

The Renaissance saw the birth of modern anatomy, and with it a proper understanding of aortic morphology. In 1554 Vesalius (1514-1564) produced the first true anatomical plates based on cadaveric dissection, in 'De Humani Corporis Fabrica.' [15] A year later he provided the first accurate diagnosis and illustrations of AAA pathology. In total, Vesalius corrected over 200 of Galen's anatomical mistakes and is regarded as the father of modern anatomy. [16] His discoveries began almost 300 years of medical progress characterised by the 'surgeon-anatomist', paving the way for the anatomical greats of the sixteenth, seventeenth and eighteenth centuries. It was during this period that the great developments in the anatomical and pathological understanding of aneurysms took place.

Pathogenesis

Ambroise Pare (1510-1590) noted that aneurysms seemed to manifest following syphilis, however he attributed the arterial disease to syphilis treatment rather than the illness itself. [17] Stress on the arteries from hard work, shouting, trumpet playing and childbirth were considered other possible causes. Morgagni (1682-1771) described in detail the luetic pathology of ruptured sacular aortic aneurysms in syphilitic prostitutes, [18] whilst Monro (1697-1767) described the intima, media and adventitia of arterial walls. [19] These key advances in arterial pathology paved the way for the Hunter Brothers of London (William Hunter [1718-1783] and John Hunter [1728-1793]) to develop the modern definitions of true, false and mixed aneurysms. Aneurysms were now accepted to be caused by 'a disproportion between the force of the blood and the strength of the artery', with syphilis as a risk factor rather than a sole aetiology. [12] As life expectancy rose dramatically in the twentieth century, it became clear that syphilis was not the only cause of arterial aneurysms, as the great vascular surgeon Rudolf Matas (1860-1957) stated: "The sins, vices, luxuries and worries of civilisation clog the arteries with the rust of premature senility, known as arteriosclerosis or atheroma, which is the chief factor in the production of aneurysm." [20]

Modern ligation

The modern period of AAA surgery began in 1817 when Cooper first ligated the aortic bifurcation for a ruptured left external iliac aneurysm in a 38 year old man. The patient died four hours later; however, this did not discourage others from attempting similar procedures. [21]

Ten further unsuccessful cases were recorded prior to the turn of the twentieth century. It was not until a century later, in 1923, that Matas performed the first successful complete ligation of the aorta for aneurysm, with the patient surviving seventeen months and dying from tuberculosis. [22] Described by Osler as the 'modern father of vascular surgery', Matas also developed the technique of endoaneurysmorrhaphy, which involved ligating the aneurysmal sac upon itself to restore normal luminal flow. This was the first recorded technique aiming to spare blood flow to the lower limbs, an early prelude to the homograft, synthetic graft and EVAR.

Early Alternatives to Ligation

Despite Matas' landmark success, the majority of surgeons of the era shared Suchruta's millennia-old fear of aortic surgery. The American Surgical Association wrote in 1940, "the results obtained by surgical intervention have been discouraging." Such fear prompted a resurgence of techniques introducing foreign material into the aneurismal lumen with the hope of promoting thrombosis. First attempted by Velpeau [23] with sewing needles in 1831, this technique was modified by Moore [24] in 1965 using 26 yards of iron wire. Failure of aneurysm thrombosis was blamed on 'under packing' the aneurysm. Corradi used a similar technique, passing electric current through the wire to introduce thrombosis. This technique became known as fili-galvanopuncture or the 'Moore-Corradi method'. Although this technique lost popularity for aortic procedures, it marked the beginning of electrothrombosis and coiling of intracranial aneurysms in the latter half of the twentieth century. [25]

Another alternative was wrapping the aneurysm with material in an attempt to induce fibrosis and contain the aneurysm sac. AAA wrapping with cellophane was investigated by Pearse in 1940 [26] and Harrison in 1943. [27] Most notably, Nissen, the pioneer of Nissen fundoplication for hiatus hernia, famously wrapped Albert Einstein's AAA with cellophane in 1948. [28] The aneurysm finally ruptured in 1955, with Einstein refusing surgery: "I want to go when I want. It is tasteless to prolong life artificially." [28]

Anastomosis

Many would argue that the true father of modern vascular techniques is Alexis Carrel. He conducted the first saphenous vein bypass in 1948, the first successful kidney transplant in 1955 and the first human limb re-implantation in 1962. [13,29] Friedman states that "there are few innovations in cardiac and vascular surgery today that do not have roots in his work." [13] Perhaps of greatest note was Carrel's development of the triangulation technique for vessel anastomosis.

This technique was utilised by Crafoord in Sweden in 1944, in the first correction of aortic coarctation, and by Shumacker [30] in 1947 to correct a four centimetre thoracic aortic aneurysm secondary to coarctation. Prior to this time, coarctation was treated in a similar fashion to AAA, with ligation proximal and distal to the defect. [31] These developments would prove to be great milestones in AAA surgery as the first successful aortic aneurysm resection with restoration of arterial continuity.

Biological grafts

Despite this success, restoration of arterial continuity was limited to the thoracic aorta. Abdominal aneurysms remained too large to be anastomosed directly and a different technique was needed. Carrel played a key role in the development of arterial grafting, used when end-to-end anastomosis was unfeasible. The original work was performed by Carrel and Guthrie (1880-1963) with experiments transplanting human and canine vessels. [32,33] Their 1907 paper 'Heterotransplantation of blood vessels' [34] began with:

"It has been shown that segments of blood vessels removed from animals may be caused to regain and indefinitely retain their function."

This discovery led to the first replacement of a thrombosed aortic bifurcation by Jacques Oudot (1913-1953) with an arterial homograft in 1950. The patient recovered well, and Oudot went on to perform four similar procedures. The landmark first AAA resection with restoration of arterial continuity can be credited to Charles Dubost (1914-1991) in 1951. [35] His patient, a 51 year old man, received the aorta of a young girl harvested three weeks previously. This brief period of excitement quickly subsided when it was realised that the long-term patency of aortic homografts was poor. It did, however, lay the foundations for the age of synthetic aortic grafts.

Synthetic grafts

Arthur Voorhees (1921-1992) can be credited with the invention of synthetic arterial prosthetics. In 1948, during experimental mitral valve replacement in dogs, Voorhees noticed that a misplaced suture had later become enveloped in endocardium. He postulated that, "a cloth tube, acting as a lattice work of threads, might indeed serve as an arterial prosthesis." [36] Voorhees went on to test a wide variety of materials as possible candidates from synthetic tube grafts, resulting in the use of vinyon-N, the material used in parachutes. [37] His work with animal models would lead to a list of essential structural properties of arterial prostheses. [38]

Vinyon-N proved robust, and was introduced by Voorhees, Jaretski and Blakemore. In 1952 Voorhees inserted the first synthetic graft into a ruptured AAA. Although the vinyon-N graft was successfully implanted, the patient died shortly afterwards from a myocardial infarction. [39] By 1954, Voorhees had successfully implanted 17 AAAs with similar grafts. Schumacker and Muhm would simultaneously conduct similar procedures with nylon grafts. [40] Vinyon-N and nylon were quickly supplanted by Orlon. Similar materials with improved tensile strength are used in open AAA repair today, including Teflon, Dacron and expanded Polytetrafluoroethylene (PTFE). [41]

Modern open surgery

With the development of suitable graft material began the golden age of open AAA repair. The focus would now be largely on the Americans, particularly with surgeons DeBakey (1908-2008) and Cooley (1920) leading the way in Houston, Texas. In the early 1950s, DeBakey and Cooley developed and refined an astounding number of aortic surgical techniques. Debakey would also classify aortic dissection into different types depending on their site. In 1952, a year after Dubost's first success in France, the pair would perform the first repair of thoracic aneurysm, [42] and a year later, the first aortic arch aneurysm repair. [43] It was around this time that the risks of spinal cord ischaemia during aortic surgery became apparent. Moderate hypothermia was first used and then enhanced in 1957, with Gerbode's development of extracorporeal circulation, coined 'left heart bypass'. In 1963, Gott expanded on this idea with a heparin-treated polyvinyl shunt from ascending to descending aorta. By 1970, centrifuge-powered, left-heart bypass with selective visceral perfusion had been developed. [44] In 1973, Crawford simplified DeBakey and Cooley's technique by introducing sequential clamping of the aorta. By moving clamps distally, Crawford allowed for reperfusion of segments following the anastomoses of what had now become increasingly more complex grafts. [45] The work of DeBakey, Cooley and Crawford paved the way for the remarkable outcomes available to modern patients undergoing open AAA repair. Where once feared by surgeons and patients alike, in-hospital mortality following elective, open AAA now has a 30-day all-cause mortality of around five percent. [58]

Imaging

It must not be overlooked that significant advances in medical imaging have played a major role in reducing the incidence of ruptured AAAs

and the morbidity and mortality associated with AAAs in general. The development of diagnostic ultrasound began in the late 1940s and 50s, with simultaneous research by John Wild in the United States, Inge Elder and Carl Hertz in Sweden and Ian Donald in Scotland. [46] It was the latter who published 'Investigation of Abdominal Masses by Pulsed Ultrasound,' regarded as one of the most important papers in diagnostic imaging. [47] By the 1960s, Doppler ultrasound would provide clinicians with both a structural and functional view of vessels, with colour flow Doppler in the 1980s allowing images to represent the direction of blood flow. The Multicentre Aneurysm Study showed that ultrasound screening resulted in a 42% reduction in mortality from ruptured AAAs over four years to 2002. [48] Ultrasound screening has resulted in an overall increase in hospital admissions for asymptomatic aneurysms; however, increases in recent years cannot be attributed to improved diagnosis alone, as it is known that the true incidence of AAA is also increasing in concordance with Western vascular pathology trends. [49]

In addition to the investigative power of ultrasound imaging, computed tomography (CT) scanners became available in the early 1970s. As faster, higher-resolution spiral CT scanners became more accessible in the 1980s, the diagnosis and management of AAAs became significantly more refined. [50] CT angiography has emerged as the gold standard for defining aneurysm morphology and planning surgical intervention. It is crucial in determining when emergent treatment is necessary, when calcification and soft tissue may be unstable, when the aortic wall is thickened or adhered to surrounding structures, and when rupture is imminent. [51] Overall operative mortality from ruptured AAA fell by 3.5% per decade from 1954-1997. [52] This was due to both a significant leap forward in surgical techniques in combination with drastically improved imaging modalities.

EVAR

The advent of successful open surgical repair of AAAs using synthetic grafts in the 1950s proved to be the first definitive treatment for AAA. However, the procedure remained highly invasive and many patients were excluded due to medical and anatomical contraindications. [53] Juan Parodi's work with Julio Palmaz and Héctor Barone in the late 1980s aimed to rectify this issue. Parodi developed the first catheter-based arterial approach to AAA intervention. The first successful EVAR operation was completed by Parodi in Argentina on seventh September 1990. [54] The aneurysm was approached intravascularly via a femoral cutdown. Restoration of normal luminal blood flow was achieved with the deployment of a Dacron graft mounted on a Palmaz stent. [55] There was no need for aortic cross-clamping or major abdominal surgery. Similar non-invasive strategies were explored independently and concurrently by Volodos, [56] Lazarus [57] and Balko. [58]

During this early period of development there was significant Australian involvement. The work of Michael Lawrence-Brown and David Hartley at the Royal Perth Hospital led to the manufacture of the Zenith endovascular graft in 1993, a key milestone in the development of modern-day endovascular aortic stent-grafts. [59] The first bifurcated graft was successfully implanted one year later. [60] Prof James May and his team at the Royal Prince Alfred Hospital in Sydney conducted further key research, investigating the causes of aortic stent failure and complications. [61] This group went on to pioneer the modular design of present day aortic prostheses. [62]

The FDA approved the first two AAA stent grafts for widespread use in 1999. Since then, technical improvements in device design have resulted in improved surgical outcomes and increased ability to treat patients with difficult aneurysmal morphology. Slimmer device profiles have allowed easier device insertion through tortuous iliac vessels. [63] Furthermore, fenestrated and branched grafts have made possible the stent-grafting of juxtarenal AAA, where suboptimal proximal neck anatomy once meant traditional stenting would lead to renal failure and mesenteric ischaemia. [64]

AAA intervention now and beyond

Today, surgical intervention is generally reserved for AAAs greater than 5.5cm diameter and may be achieved by either open or endoluminal access. The UK small aneurysm trial determined that there is no survival benefit to elective open repair of aneurysms of less than 5.5cm. [8] The EVAR-1 trial (2005) found EVAR to reduce aneurysm related mortality by three percent at four years when compared to open repair; however, EVAR remains significantly more expensive and requires more re-interventions. Furthermore, it offers no advantage with respect to all cause mortality or health related quality of life. [5] These findings raised significant debate over the role of EVAR in patients fit for open repair. This controversy was furthered by the findings of the EVAR-2 trial (2005), which saw risk factor modification (fitness and lifestyle) as a better alternative to EVAR in patients unfit for open repair. [65] Many would argue that these figures are obsolete, with Criado stating, "it would not be unreasonable to postulate that endovascular experts today can achieve far better results than those produced by the EVAR-1 trial." [53] It is undisputed that EVAR has dramatically changed the landscape of surgical intervention for AAA. By 2005, EVAR accounted for 56% of all non-ruptured AAA repairs but only 27% of operative mortality. Since 1993, deaths related to AAA have decreased dramatically, by 42%. [53] EVAR's shortcomings of high long-term rates of complications and re-interventions, as well as questions of device performance beyond ten years, appear balanced by the procedure's improved operative mortality and minimally invasive approach. [54]

Conclusion

The journey towards truly effective surgical intervention for AAA has been a long and experimental one. Once regarded as one of the most deadly pathologies, with little chance of a favourable surgical outcome, AAAs can now be successfully treated with minimally invasive procedures. Sushruta's millennia-old fear of abdominal aortic surgery appears well and truly overcome.

Conflict of interest

None declared.

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Eye protection in the operating theatre: Why prescription glasses don't cut it

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Introduction

Needle-stick injury represents a serious occupational hazard for medical professionals, and much time is spent on educating students and practitioners on its prevention. Acquiring a blood-borne viral infection such as Human Immunodeficiency Virus (HIV), Hepatitis B or C from a patient is a rare yet devastating event. While most often associated with 'sharps' injuries, viral transmission is possible across any mucocutaneous membrane – including the eye. Infection via the transconjunctival route is a particularly relevant occupational hazard for operating room personnel, where bodily fluids are commonly encountered. Published cases of HIV seroconversion after ocular blood splash reinforce the importance of eye protection. [1]

Surgical operations carry an inherent risk of blood splash injury - masks with visors are provided in operating theatres for this reason. However, many surgeons and operating personnel rely solely upon prescription glasses for eye protection, despite spectacles being shown to offer an ineffective safeguard against blood splash injury. [2]

Incidence of blood splash injury

The incidence of blood splash is understandably more prevalent in some surgical specialties, such as orthopaedics, where power tools and other instruments increase the likelihood of blood spray. [3] Within these specialties, the risk is acknowledged and the use of more comprehensive eye protection is usually routine.

Laparoscopic and endoscopic procedures may particularly be viewed as low-risk, despite the rates of positive blood splash evident on post-operative examination of eye protection in one prospective study approaching 50%. [4] These results imply that even minimally invasive procedures need to be treated with a high level of vigilance.

The prevalence of blood splash during general surgical operations is highlighted by a study that followed one surgeon over a 12 month period and recorded all bodily fluids evident on protective eyewear following each procedure. [5] Overall, 45% of surgeries performed resulted in blood splash and an even higher incidence (79%) was found in vascular procedures. In addition, half of the laparoscopic cases were associated with blood recorded on the protective eyewear postoperatively.

A similar prospective trial undertaken in Australia found that protective eye shields tested positive for blood in 44% of operations, yet the surgeon was only aware of the incident in 18% of these cases. [6] Much blood spray during surgery does not occur at a visually perceivable level, with this study demonstrating that the incidence of blood splash during a procedure may be considerably higher than is realised.

Despite the predominance of blood splash occurring within the operating theatre, the risks of these injuries are not limited to surgeons and theatre staff - even minor surgery carries a considerable risk of blood splash. A review of 500 simple skin lesion excisions in a procedural dermatology unit revealed positive blood splash on facemask or visor in 66% of cases, which highlights the need for protective eyewear in all surgical settings. [7]

Risk of blood splash injury

Although a rare occurrence, even a basic procedure such as venepuncture can result in ocular blood splash injury. Several cases

of confirmed HCV transmission via the conjunctival route have been reported. [8-10]

Although the rates of blood-borne infectious disease are reasonably low within Australia, and likewise the rates of conversion from a blood splash injury are low at around 2%, [9] the consequences of contracting HIV, HBV or HCV from a seropositive patient are potentially serious and require strict adherence to post exposure prophylaxis protocols. [11] Exposure to bodily fluids, particularly blood, is an unavoidable occupational risk for most health care professionals, but personal risk can be minimised by using appropriate universal precautions.

For those operating theatre personnel who wear prescription glasses, there exists a common belief that no additional eye protection is necessary. The 2007 Waikato Eye Protection Study [2] surveyed 71 practicing surgeons, of which 45.1% required prescription glasses while operating. Of the respondents, 84.5% had experienced prior periorbital blood splash during their operating careers, and 2.8% had gone on to contract an illness from such an event. While nearly 80% of the participants routinely used eye protection, amongst those who wore prescription glasses, 68% used them as sole eye protection.

A 2009 *in vitro* study examining the effectiveness of various forms of eye protection in orthopaedic surgery [12] employed a simulation model, with a mannequin head placed in a typical position in the operating field, with femoral osteotomy performed on a cadaveric thigh. The resulting blood splash on six different types of protective eyewear was measured, and found that prescription glasses offered no benefit over control (no protection). While none of the eye protection methods tested offered complete protection, significantly lower rates of conjunctival contamination were recorded for recommended eyewear, including facemask and eyeshield, hard plastic glasses and disposable plastic glasses.

Prevention and management of blood splash injury

Given that blood splash is an occupational hazard, the onus is on the hospital and clinical administration to ensure that there are adequate supplies of protective eye equipment available. Disposable surgical masks with full-face visors have been shown to offer the highest level of protection from blood splash injury [12] and ought to be readily accessible for all staff involved in procedures or settings where contact with bodily fluids is possible. The use of masks and visors should be standard practice for all theatre staff, including assistants, scrub nurses

and observers, regardless of the use of prescription spectacles.

Should an incident occur, a procedure similar to that used for needle-stick injury may be followed to minimise the risk of infection. The eye should first be rinsed thoroughly to remove as much of the fluid as possible and serology should be ordered promptly to obtain a baseline for future comparisons. An HIV screen and acute hepatitis panel (HAV IgM, HB core IgM, HBsAg, HCV and HB surface antibody for immunised individuals) are indicated. Post-exposure prophylaxis (PEP) should be initiated as soon as practicable unless the patient is known to be HIV, HBV and HCV negative. [13]

Conclusion

Universal precautions are recommended in all instances where there is the potential for exposure to patient bodily fluids, with an emphasis on appropriate eye protection. Prescription glasses are unsuitable for use as the sole source of eye protection from blood splash injury. In light of the fact that a blood splash injury can occur without knowledge of the event, regular blood tests for health care workers involved in regular procedural activity may allow for early detection and intervention of workplace acquired infection.

Conflict of interest

None declared.

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The risks and rewards of direct-to-consumer genetic tests: A primer for Australian medical students

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Introduction

Over the last five years, a number of overseas companies, such as 23andMe, have begun to offer direct-to-consumer (DTC) genetic tests to estimate the probability of an individual developing various diseases. Although no Australian DTC companies exist due to regulations mandating the involvement of a health practitioner, Australian consumers are free to access overseas mail-order services. In theory, DTC testing carries huge potential for preventing the onset of disease by lifestyle modification and targeted surveillance programs. However, the current system of mail-order genetic testing raises serious concerns related to test quality, psychological impacts on users, and integration with the health system. There are also issues with protecting genetic privacy, and ethical concerns about making medical decisions based on pre-emptive knowledge. This paper presents an overview of the ethical, legal and practical issues of DTC testing in an Australian context. The paper concludes by proposing five conditions that will be key for harnessing the potential of DTC testing technology. These include improved clinical utility, updated anti-discrimination legislation, accessible genetic counselling, Therapeutic Goods Administration (TGA) monitoring, and mechanisms for identity verification. Based on these conditions, the current system of mail-order testing is unviable as a scalable medical model. For the long term, the most sustainable solution is integration of pre-symptomatic genetic testing with the healthcare system.

The rise of direct-to-consumer testing

"Be on the lookout now." This is the slogan of 23andMe.com, a Californian biotechnology company that has been offering personal genetic testing since late 2007. Clients mail a in a sample of their saliva and, for the humble fee of US$299, 23andMe will isolate their DNA and scan across key regions to estimate that individual's risk of developing different diseases. [1] Over 200 different diseases in fact – everything from widespread, life-threatening conditions including breast cancer and coronary artery disease, to the comparatively obscure such as restless legs syndrome. Table 1 gives an example of the risk profile with which an individual may be faced.

Table 1. *Simulated excerpt from a disease risk analysis provided by a direct-to-consumer genetic testing company. [1]*

		Your risk	Average risk
Elevated Risks	Diagnostic Type 2 Diabetes	65.0%	25.7%
	Melanoma	3.5%	2.9%
Decreased Risks	Macular Degeneration	4.2%	6.5%
	Psoriasis	5.7%	11.4%

Genetic testing has existed for decades as a diagnostic modality. Since the 1980s, clinicians have used genetic data to detect monogenic conditions such as cystic fibrosis and thalassaemia. [2] These studies were conducted in patients already showing symptoms of the disease in order to confirm a suspected diagnosis. 23andMe does something quite different: it takes asymptomatic people and calculates the risk of diseases emerging in the long term. It is a pre-emptive test rather than a diagnostic one.

23andMe is not the only service of its kind. There is a growing family of these direct-to-consumer (DTC) genetic tests: Navigenics (US), deCODEme (Iceland) and Genetic Health (UK) all offer a comprehensive disease screen for under $1000 AUD. There are currently no Australian companies that offer DTC disease scans due to regulations that require the involvement of a health professional. [3] However, Australian consumers are still free to access overseas services. Although no Australian retail figures exist, the global market for pre-symptomatic genetic testing is growing rapidly: 23andMe reported that 150,000 customers worldwide have used their test, [4] and in a recent European survey 64% of respondents said they would use a genetic test to detect possible future disease. [5] The Australian market for DTC testing, buoyed by increasing public awareness and decreasing product costs, is also set to grow.

Australian stakeholders have so far been divided on the issue of DTC testing. Certain parties have embraced it. In 2010 the Australian insurance company NIB offered 5000 of its customers a half-price genetic test through the US company Navigenics. [6] However, controversy arose over the fine-print at the end of NIB's offer letter: "You may be required to disclose genetic test results, including any underlying health risks and conditions which the tests reveal, to life insurance or superannuation providers." [6]

Most professional and regulatory bodies have expressed concern over the risks of DTC testing in an Australian context. In a 2012 paper, the Australian Medical Association argued that health-related genetic testing "should only be undertaken with a referral from a medical practitioner." [7] It also highlighted issues surrounding the accreditation of overseas laboratories and the accuracy of the test results. Meanwhile, the Human Genetics Society of Australasia has stressed the importance of educating the public about the risks of DTC tests: "The best way to get rid of the market for DTC genetic testing may be to eliminate consumer demand through education … rather than driving the market underground or overseas." [8]

Despite the deficiencies in the current model of mail-order services, personal genetic testing carries huge potential benefits from a healthcare perspective. The 2011 National Health and Medical Research Council (NHMRC) publication entitled *The Clinical Utility of Personalised Medicine* highlights some of the potential applications of genetic tests: targeting clinical screening programs based on disease risk, predicting drug susceptibility and adverse reactions and initiating

preventative therapy before disease onset. [9] Genetic risk analysis has the potential to revolutionise preventative medicine in the 21st century.

The question is whether free-market DTC testing is a positive step towards an era of genetically-derived preventative therapy. Perhaps it creates more problems than it solves. What is the clinical utility of these tests? Is it responsible to give untrained individuals this kind of risk information? Could test results get into the wrong hands? These are the practical issues that will directly impact Australian medical professionals as genetic data infiltrates further into daily practice. This paper aims to grapple with some of these issues in an attempt to tease out how we as a healthcare community can best adapt to this new technology.

What is the clinical utility of these tests?

In 2010, a Cambridge University professor sent his own DNA off for analysis by two different DTC testing companies - 23andMe and deCODEme. He found that for approximately one third of the tested diseases, he was classed in a different risk category by the two companies. [10] A similar experiment carried out by a British journalist also revealed some major discrepancies. In one test, his risk of a myocardial infarction was 6% above average, while on another it was 18% below. [11]

This variability is a reflection of the current level of uncertainty about precisely how genes contribute to many diseases. Most diseases are polygenic, with an array of contributing environmental and lifestyle factors also playing a role in disease onset. [12] Hence, in all but a handful of diseases where robust genetic markers have been identified (such as the BRCA mutations for breast and ovarian cancers), these DTC test results are of questionable validity. An individual's risk of Type 2 Diabetes Mellitus cannot simply be distilled down into a single numerical value.

Even for those diseases where isolated genetic markers have been identified in the literature, the findings are specific to the population studied. The majority of linkage analyses are performed in North American or European populations and may not be directly applicable to an Australasian context. Population bias aside, there is also a high level of ambiguity in how various genetic markers interact. As an example, consider two alleles that have each been shown to increase the risk of macular degeneration by 10%. It is not valid to say that the presence of both alleles signifies a 20% risk increase. This relates to the concept of *epistasis* in statistical genetics – the combined phenotypic effect of two alleles may differ from the sum of the individual effects. The algorithms currently used by DTC testing companies do not account for the complexity of gene-phenotype relationships.

For these reasons, the NHMRC states in its guide to the public about DTC testing: "At this time, studies have yet to prove that such susceptibility tests give accurate results to consumers." [12] At best, current DTC testing is only valid as a rough guide to identify any risks that are particularly high or low. At worst, it is a blatantly misleading risk estimate based on insufficient molecular and clinical data. However, as our understanding of genetic markers improves, so too will the utility of these tests.

Can customers handle the results?

Assuming test quality improves, the next question is whether average individuals can deal with this type of risk information. What may the psychological consequences be if a healthy 25-year-old discovered that they had a 35% chance of developing ischaemic heart disease at some time during their life?

One risk is that people with an unfavourable prognosis may become discouraged from caring about their health at all, because they feel imprisoned within an immutable 'genetic destiny.' [13] As disease is written into their genes, they may as well surrender and accept it. Even someone with an average disease risk may feel an impending sense of doom when confronted with the vast array of diseases that may one day debilitate them. Could endless accounting of genetic risks overshadow the joy of living?

It is fair to say that DTC testing will only be useful if individuals have the right attitude – if they use this foreknowledge to take preventative measures. But do genetic test results really cause behaviour modification? A fascinating study in the New England Journal of Medicine in 2011 analysed the behavioural patterns of 2037 patients before and after a DTC genetic test. [14] They found no difference in exercise behaviour or dietary fat intake, suggesting that the genetic risk analysis did not translate into measurable lifestyle modification.

In order for individuals to interpret and use this genetic information effectively, they will need advice from healthcare professionals. Many of the DTC testing companies offer their own genetic counselling services; however, only 10% of clients reported accessing these. [15] The current position of the Australian Medical Association is that patients should consult a general practitioner when interpreting the results of a DTC genetic test. [7] However, a forced marriage between commercial sequencing companies and the healthcare system threatens to create problems of its own.

How should the health system adapt?

A 2011 study in North Carolina found that one in five family physicians had already been asked a question about pre-symptomatic genetic tests, yet 85% of the surveyed doctors reported that they were not sufficiently prepared to interpret test data [16]. In Australia, the healthcare system needs to adapt to this emerging trend. The question is - to what extent?

One controversial issue is whether it should be mandatory for doctors to be consulted when an individual orders a genetic test. Australia currently requires the involvement of a health practitioner to perform a disease-related genetic test. [3] Many countries, with the notable exception of the United States, share this stance. The German government ruled in early 2010 that pre-symptomatic testing could only be ordered by doctors trained in genetic counselling. [11] However, critics argue that mandatory doctor involvement would add medical legitimacy to a technology still in its infancy. [17] There is also an ethical argument that individuals should have the right to know about their own genes independent of the health system. [18]

Then there is the issue of how DTC genetic data should influence treatment. For example, should someone genetically predisposed to Type 2 Diabetes Mellitus be screened more regularly than others? Or, in a more extreme scenario: should those with more favourable genetic outlooks be prioritised for high-demand procedures such as transplant surgery?

These are serious ethical dilemmas; however, the medical community has had to deal with such issues before, whenever a new technology has arisen. With appropriate consultation from ethics committees (such as the NHMRC-affiliated Human Genetics Society of Australasia) and improved genetic literacy among healthcare professionals, it is possible to imagine a symbiotic partnership between the health system and free-market genetic testing.

How do we safeguard genetic privacy?

If DTC testing is indeed here to stay, a further concern is raised: how do we protect genetic privacy? Suppose a potential employer were to gain access to genetic data – the consequences could be disastrous for those with a poor prognosis. The outcome may be even worse if these data were made available to their insurance company.

In Australia, the disclosure of an individual's genetic data by third parties (such as a genetic testing company) is tightly regulated under the *Privacy Act 1988,* which forbids its use for any purpose beyond that for which it was collected. [19] The only exception, based on the P*rivacy Legislation Amendment Act 2006*, is for genetic data to be released to 'genetic relatives' in situations where disclosure could

significantly benefit their health. [19]

In spite of the *Privacy Act*, individuals may still be forced to disclose their own test results to a third party such as an insurer or employer. There have been numerous reports of discrimination on the basis of genetic data in an Australian context. [20-22] The Australian Genetic Discrimination Project has been surveying the experiences of clients visiting clinical geneticists for 'predictive or pre-symptomatic' genetic testing since 1998. The pilot data, published in 2008, showed that 10% of the 951 subjects reported some negative treatment as a result of their genetic results. [23] Of the alleged incidents of discrimination, 42% were related to insurance and 5% to employment.

The use of genetic data by insurance companies is a complex issue. Although private health insurance in Australia is priced purely on basic demographic data, life and disability insurance is contingent on an individual's prior medical record. This means that customers must disclose the results of any genetic testing (DTC or otherwise) they may have undergone. This presents a serious disincentive for purchasing a DTC test. The Australian Law Reform Commission, in its landmark report *Essentially Yours: the Protection of Human Genetic Information in Australia*, discusses the possibility of a two-tier system where insurance below a specific value would not require disclosure of any genetic information. [22] Sweden and the United Kingdom have both implemented such systems in the past; however insurers have argued that the Australian insurance market is not sufficiently large to accommodate a two-tiered model. [22]

As genetic testing becomes increasingly widespread, a significant issue will be whether insurance companies should be allowed to request genetic data as a standard component of insurance applications. Currently, the Investment and Financial Services Association of Australia, which represents all major insurance companies, has stated that no individual will be forced to have a genetic test. [24] But how long will this moratorium last?

Suffice to say that the privacy and anti-discrimination legislature needs to adapt to the times. There needs to be careful regulation of how these genomics companies use and protect sensitive data, and robust legislation against genetic discrimination. Organisations such as the Australian Law Reform Commission and the Human Genetics Society of Australasia will continue to play an integral role in this process.

However, there are some fundamental issues that even legislation cannot fix. For example, with the current system of mail-order genetic testing, there is no way of verifying the identity of the person ordering the test. This means that someone could easily send in DNA that is not their own. In addition, an individual's genetic results reveal a great deal about their close family members. Consequently, someone who does not wish to know their genetic risks might be forcibly confronted with this information through a relative's results. We somehow need to construct a system that preserves an individual's right of autonomy over their own genetic data.

What does the future hold?

DTC genetic testing is clearly a technology still in its infancy, with many problems yet to be overcome. There are issues regarding test quality, psychological ramifications, integration with the health system and genetic privacy. On closer inspection, this risk-detection tool turns out to be a significant risk in itself. So does pre-symptomatic genetic testing have a future?

The current business platform, wherein clients mail their DNA to overseas companies, is unviable as a scalable medical model. This paper proposes that the following five conditions are necessary (although not sufficient) for pre-symptomatic genetic testing to persist into the future in an acceptable form:

i. Improved clinical utility
ii. Updated anti-discrimination legislation pertaining to genetic test data
iii. Accessible genetic counselling facilities and community education about interpreting genetic results
iv. Monitoring of DTC companies by regulatory bodies such as the Therapeutic Goods Administration (TGA)
v. Mechanism for identity verification to prevent fraudulent DNA analysis

Let us analyse each of these propositions. Condition (i) will be gradually fulfilled as our understanding of genetic markers and bioinformatics develops. A wealth of new data is emerging from large-scale sequencing studies spanning diverse populations, with advanced modeling for gene-gene interactions. [25,26] Condition (ii) is also a likely future prospect - the report by the Australian Law Reform Commission is evidence of a responsive legislative landscape. [22] Condition (iii) is feasible, contingent on adequate funding for publicly accessible genetic counselling services and education programs. However, given that the clinical utility of DTC risk analysis is currently low, it would be difficult in the short term to justify any public expenditure on counselling services targeted at test users.

Conditions (iv) and (v) are more difficult to satisfy. Since DTC companies are all located overseas, they fall outside the jurisdiction of the Australian TGA. Given that consumers may make important healthcare choices based on DTC results, it is imperative that this industry be regulated. We have three options. First, we could rely on appropriate monitoring by foreign regulatory bodies. In the US, DTC genetic tests are classed as an '*in vitro* diagnostic device' (IVD), meaning they fall subject to FDA regulation. However, in a testimony before the US government's Subcommittee on Oversight and Investigations in July 2010, the FDA stated that it has "generally exercised enforcement discretion" in regulating IVDs. [27] It went on to admit that "none of the genetic tests now offered directly to consumers has undergone premarket review by the FDA to ensure that the test results being provided to patients are accurate, reliable, and clinically meaningful." This is an area of active reform in the US; however, it seems unwise for Australia to blindly accept the standards of overseas regulators.

The second option is to sanction overseas DTC testing for Australian consumers. Many prescription medicines are subject to import controls if they are shipped into Australia. In theory, the same regulations could be applied to genetic test kits. However, it is not difficult to imagine ways around this ban, e.g. simply posting an oral swab and receiving the results online.

A third option is to open the market for Australian DTC testing companies, which could compete with overseas services while remaining under TGA surveillance. In other words, we could cultivate a domestic industry. However, it may not be possible for fledgling Australian companies to compete on price with the large-scale US operations. It would also be hard to justify the change in policy before conditions (i) to (iii) are fulfilled. That said, of the three options discussed, this appears to be the most viable in the long term.

Finally, condition (v) presents one of the fundamental flaws with DTC testing. If the health system was formally involved in the testing process, the medical practitioner would be responsible for identity verification. However, it is simply not possible to reliably check identity in a mail-order system. The only way DTC testing can verify identity is to have customers come in person to a DTC facility and provide proof when their DNA is collected. However, such a regulation would make it even more difficult for any Australian company to compete against online services.

Conclusion

In summary, it is very difficult to construct a practical model that addresses conditions (iv) and (v) in an Australian context. Hence, for the short term, DTC testing will likely remain a controversial, unregulated market run through overseas websites. It is the duty of the TGA to inform the public about the risks of these products, and the duty of

the health system to support those who do choose to purchase a test.

For the longer term, it seems that the only sustainable solution is to move towards an Australian-based testing infrastructure linked into the healthcare system (for referrals and post-test counselling). There are many hurdles to overcome; however, one might envisage a situation, twenty years from now, where a genetic risk analysis is a standard medical procedure offered to all adults and subsidised by the health system, and where individuals particularly susceptible to certain conditions can maximise their quality of life by making educated lifestyle changes and choosing medications that best suit their genetic profiles. [28]

As a medical community, therefore, we should be wary of the current range of DTC tests, but also open-minded about the possibilities for a future partnership. If we get it right, the potential payoff for preventative medicine is huge.

Conflict of interest

None declared.

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Student-led malaria projects - can they be effective?

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Introduction

In this article we give an account of establishing a sustainable project in Uganda. We describe our experiences, both positive and negative, and discuss how such endeavours are beneficial to both students and universities. The substantial work contributed by an increasing group of students at our university and around Australia demonstrates an increasing push towards a greater national contribution to global health. Undoubtedly, student bodies have the potential to become major players in global health initiatives, but first we must see increased financial and academic investment by universities in this particular area of medicine.

Background

There are an estimated three billion people at risk of infection from malaria, with an estimated one million deaths annually. The greatest burden of malaria exists in Sub-Saharan Africa. [1,2] Amongst the Ugandan population of 26.9 million, malaria is the leading cause of morbidity and mortality, with 8 to 13 million episodes reported. [3] The World Malaria Report estimated that there were 43 490 malaria-related deaths in Uganda in 2008, ranking it third in the world behind Nigeria and the Democratic Republic of Congo. [4] In 2011, the situation remained alarming, with 90% of the population living in areas of high malaria transmission. [5]

The focus of this report is the Biharwe region of south-west Uganda. Due to a lack of reliable epidemiological data regarding the south-west of Uganda, it is difficult to evaluate the effectiveness of current malaria intervention strategies. However, Uganda is a country with relatively stable political and economic factors, [6] making it a strong candidate for the creation of sustainable intervention programs.

Insecticide Treated Nets (ITN)

Insecticide treated nets are a core method of malaria prevention and reduce disease-related mortality. [5] The World Health Organisation (WHO) Global Malaria Programme report states that an insecticide-treated net is a mosquito net that repels, disables and/or kills mosquitoes that come into contact with the insecticide. There are two categories of ITNs: conventionally treated nets, and long-lasting insecticidal nets (LLINs). The WHO recommends the distribution of LLINs rather than conventionally treated nets as LLINs are designed to maintain their biological efficacy against vector mosquitoes for at least three years in the field under recommended conditions of use, removing the need for regular insecticide treatment. [7]

Long-lasting insecticide nets have been reported to reduce all-cause child mortality by an average of eighteen percent in Sub-Saharan Africa (with a range of 14-29%). This implies that 5.5 lives could be saved per 1000 children under five years of age per year. [8] Use of LLINs in Africa increased mean birth weight by 55 g, reduced low birth weight by 23%, and reduced miscarriages/stillbirths by 33% in the first few pregnancies when compared with a control arm in which there were no mosquito nets. [9]

Use of LLINs is one of the most cost-effective interventions against malaria. In high-transmission areas where most of the malaria burden occurs in children under the age of five years, the use of LLINs is four to five times cheaper than the alternate strategy of indoor residual spraying. [10] Systematic delivery of LLINs through distribution projects can be a cost-effective way to make a significant impact on a local community. This makes the distribution of LLINs an ideal project for student-led groups with limited budgets.

Our experience implementing a sustainable intervention project in Uganda

This article comments on student-led research performed in Biharwe, which aimed to evaluate the Biharwe community's current knowledge of malaria prevention techniques; to assess how people used their ITNs and to investigate from where they sourced their ITNs. We also aimed to alleviate the high malaria burden in Biharwe through the distribution of ITNs. We fundraised in Tasmania, with financial support being garnered from local Rotarian groups and student societies. Approximately five thousand dollars was raised which we used to purchase ITNs. Simultaneously we began contacting a local non-governmental organisation (NGO) and a student body from Mbarara University, the largest university in south-west Uganda. We felt we had laid the foundation for a successful overseas trip.

Our endeavours suffered initial setbacks due to the observation of a local organisation we were working with misusing the funds of other projects. We felt that in order to avoid a similar fate we would need to cut ties, and decided to seek out other local groups. We made contact with the Mbarara University students and they pointed us towards the Biharwe sub-county as a region of particular neglect with regards to previous government and NGO ITN distribution programs. At their recommendation we travelled to villages in the area. Access to these villages was obtained through respectfully approaching the village representatives and their councils, and asking their permission to engage with the local community.

Despite all our preparations before heading to Uganda, we were still not fully prepared for the stark realities of everyday life in East Africa. One problem we encountered was the misuse and misunderstanding of the ITN distribution program by locals. We also encountered local 'gangs' who would collect free ITNs from our distribution programs and then sell them at the market place for a profit; people who used their ITNs as materials to build their chicken coups; and widespread myths about the effects of ITNs. To combat this we sought the advice of a local priest who requested that the village heads put together a list of households as a means of minimising the fraudulent distribution of our nets. While not ideal, this approach did give us greater confidence when distributing the ITNs. As Uganda is a religious nation the support of a well-respected local priest made local leaders more receptive to our program.

It became apparent that we had to strengthen our understanding of local attitudes towards and usage of ITNs if we were to create a long-term, meaningful relationship with people in the area. At the suggestion of Mbarara University students, we commissioned DEKA Consult Limited, a local research group, to conduct qualitative epidemiological research in villages in these communities. Data collected was useful in identifying the scope of the problem. It identified that community members already had a significant amount of knowledge on the use of ITNs and that those who owned mosquito nets had purchased them from local suppliers. Local ethics approval and permission for access to local community members was gained by DEKA Consult Limited.

Evaluating local knowledge on malaria prevention

The study commissioned addressed community attitudes towards malaria prevention by surveying two distinct groups living in the Biharwe sub-county of south-west Uganda. Through questionnaires and focus group discussions, local researchers gathered information concerning attitudes towards and usage of mosquito nets in the area. One of the key findings was that ITNs were nominated as the main preventative technique by the respondents (33.3%). This is congruent with previous data indicating an increase in awareness of ITNs in Uganda following the Roll Back Malaria Abuja Summit. [11] A majority of respondents indicated some knowledge of the appropriate use of these mosquito nets (83.3%), meaning though that one in six of the Biharwe community members were unsure of how to correctly use ITNs. The research also explored common reasons why people neglected to sleep under ITNs in the Biharwe sub-county. Common misperceptions such as ITNs causing impotence and leading to burns were identified as barriers to people using their mosquito nets, and were issues that would need to be addressed in future education seminars. The findings indicate that assessment of existing knowledge and perceptions of a community are crucial in identifying obstacles that must be overcome during the implementation of an effective intervention project. Activities promoting education can then be moulded around the particular culture and social dynamic of a community, which will lead to maximal project impact. [12, 13] We believe this data indicates that the distribution of ITNs would be improved if it was accompanied by robust educational initiates that are tailored to local community needs.

Our way forward

In the summer of 2011-2012 another group of students from UTAS implemented an LLIN distribution project in the south-west of Uganda. They furthered the work outlined in this report. Our experiences and connections provided an excellent foundation for them to implement expanded projects. A further group of UTAS students has been assembled and is planning to travel to Uganda this coming summer, once again with the aim of building on the previous two visits. With the generous assistance of the Menzies Institute and UTAS School of Medicine, plans for a more robust epidemiology project have been formulated in order to measure the efficacy of future projects in Uganda. We believe the sustainability and effectiveness of these programs relies on both the development of a long-term relationship between our student organisation and the local community, as well as appropriate evaluation of all our projects.

Free distribution or subsidised LLINs

The majority of the malaria burden exists in the poorest, most rural communities, yet it is these regions that are often neglected in widespread ITN distribution programs. [14]

Our data indicates that only a minority of the households in the rural Biharwe sub-county own ITNs (11.1%), and that all of these ITNs have been purchased through the commercial sector. Again methodological disparities need to be addressed in order to confirm the validity of these results. However it does raise the important question of whether the commercial sector, rather than the public/non-governmental organisation (NGO) sector, would be better placed to serve their local communities.

Our dilemma serves as a microcosm for a much larger debate that has been occurring over the last decade regarding the most effective means of delivering ITNs in order to achieve the greatest national coverage.[15] Free distribution of ITNs is far more equitable and effective at reaching the poor. [16] However, utilisation of the commercial sector through subsidies, vouchers or a stratification model [17] is more sustainable, because a portion of the losses may be recovered. Populations, including those in the rural Biharwe sub-region, that have been neglected from ITN schemes such as Roll Back Malaria, [5] may stand to benefit from free targeted distribution of nets. Collaborations with both local and international students are well placed to combine local knowledge and financial support to best implement such initiatives.

The role of students in malaria prevention and international development projects

Organisations such as the World Health Organisation, when involved in widespread ITN distribution, [5] have far greater capabilities than any student-led project. However, due to shortfalls in funding and co-ordination, these schemes will not be able to reach all at-risk populations, particularly the poorest rural areas. [5] Small scale and independently funded student-led projects can fill a void in this neglected population. In order to achieve the maximal impact with a malaria intervention project, students should identify areas with a low rate of household ITN ownership, as well as areas with a low percentage of the owned ITNs being donated. It is these areas that ultimately stand to make the greatest progress in terms of ITN coverage amongst vulnerable individuals, resulting in a decrease in morbidity and mortality from malaria. [18] With locally-specific research, strong relationships with the community and the community leaders, and appropriate evaluation processes in place, students can make the maximal impact on reducing morbidity and mortality from malaria with limited funds. [19]

The aim should always be for a long-term partnership between the community [19] and student-led organisations who are willing to promote sustainability. This has the greatest opportunity to provide long-term benefits for both parties. Our experience is that medical students provide a continuous stream of like-minded youth who have been able to rise to the challenge and continue the work of previous students. Through bilateral exchanges between students and overseas partners, trust and friendship are able to be fostered, which further encourages participation in the project upon returning. Important information regarding the social hierarchy is also gained, which greatly helps with gaining access to the local decision makers. In turn, this creates greater understanding of the health problems, culture and reasons why particular communities have been left behind. Student-led organisations are perfectly placed to deliver these educational programs, as they constitute a long-term pool of motivated, altruistic skilled workers who are able to learn from their predecessors. Individual students also stand to benefit through increased cultural understanding, application of learned skill sets and an opportunity which can enhance their career paths. [19] Through appropriate

long-term trial, error and proper evaluation, systems of program implementation can be formulated which may then be applied to similar communities elsewhere.

The Role of Universities

Preparing students for a leadership role in global health and its related fields is critical. University curricula should reflect today's problems and those that are likely to be present in the coming decades. [20] It is our opinion that students are increasingly becoming aware and more willing to be involved in providing solutions, no matter how small, to current international issues, thanks mainly to a surge in the exposure to social media. When universities do not explore such issues deeply in their curricula, and do not provide the support for active student involvement, it may lead students to perceive that universities are about something other than the realities of the world. [21] Encouraging participation in international health projects has been reported to encourage students to better examine cross cultural issues, to improve their problem solving skills and to help improve the delivery of healthcare for under-privileged people. [22] These are transferable skills that are vital in the Australian health care system.

North American and European universities continue to lead the way; however, Australian universities are starting to become more involved with global health issues. The Australian Medical Students Association's Global Health Committee aims to link and empower groups of students from each Australian medical school. [23] The Melbourne University Health Initiative, which oversees the Victorian Student's Aid Program, aims to help students make a difference in health issues on a local and international level by running events on campus to promote awareness about several health issues, and by organising public health lectures to promote awareness in the community. [24] The Training for Health Equity Network (THEnet) is a composition of ten schools from around the world, including James Cook and Flinders Universities, who have committed to ensure that teaching, research and service activities address priority health needs, using a focus on underserved communities. [25] A focus of THEnet is on social accountability, with a framework to assess whether the schools are contributing to the improvement of health conditions within their local communities. [26]

In our view, there is no doubt that there needs to be more penetration of such initiatives into each of the universities' curriculum. Should this occur, Australia may be able to produce a generation of graduates who will be well placed to address the numerous complex global health issues we are facing today, and that we will inevitably face in the future.

Conflict of interest

None declared.

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Doctors' health and wellbeing: Where do we stand?

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Doctors continue to record significant rates of burn out, stress-related illness, substance abuse and suicide, despite greater awareness of these issues in the profession. [1,2] Whilst improved support services have been a positive move, there are underlying systemic issues that must be addressed within the profession.

Physician distress results from a complex interplay of several factors that include a challenging work environment, specific physician characteristics and other contextual factors such as stigma (Figure 1). [3] Specific physician characteristics that may make us prone to stress-related illness include the motivated and driven personality types that many of us possess; these are useful in meeting heavy workloads, but can be detrimental in times of distress. When combined with a great sense of professional obligation to patients, an "admirable but unhealthy tradition of self-sacrifice" can ensue. [4]

Stigma is also a contributing factor, with many doctors concerned about how they will be perceived by others. Common stigmatised attitudes include the fear of being considered weak, concern about registration status and career impact, and the need to appear healthy to patients. [1] These individuals are less likely to seek help for their illness or to take time off, which can be compounded by the pressure of 'letting the team down' when they do. Attitudes such as this develop early on as a medical student, and are often reinforced later in professional practice by colleagues and supervisors. [5,6]

These factors contribute to a culture within medicine of the frequent

neglect of preventive health issues. [7] Commonly, there is a reliance on informal care from colleagues ('corridor consultations'), and many doctors may self-diagnose and self-treat. [8] While this might suffice for minor illnesses, during times of serious distress or mental illness, this approach may lead to late or suboptimal treatment and a poor prognosis or to relapse. [6]

In the past, little effort has been made to promote prevention, wellbeing and appropriate self-care, particularly in the early stages of the profession such as during medical school. Current undergraduate medical curricula focus almost exclusively on the acquisition of clinical knowledge, with a clear deficit in the development of self-care skills

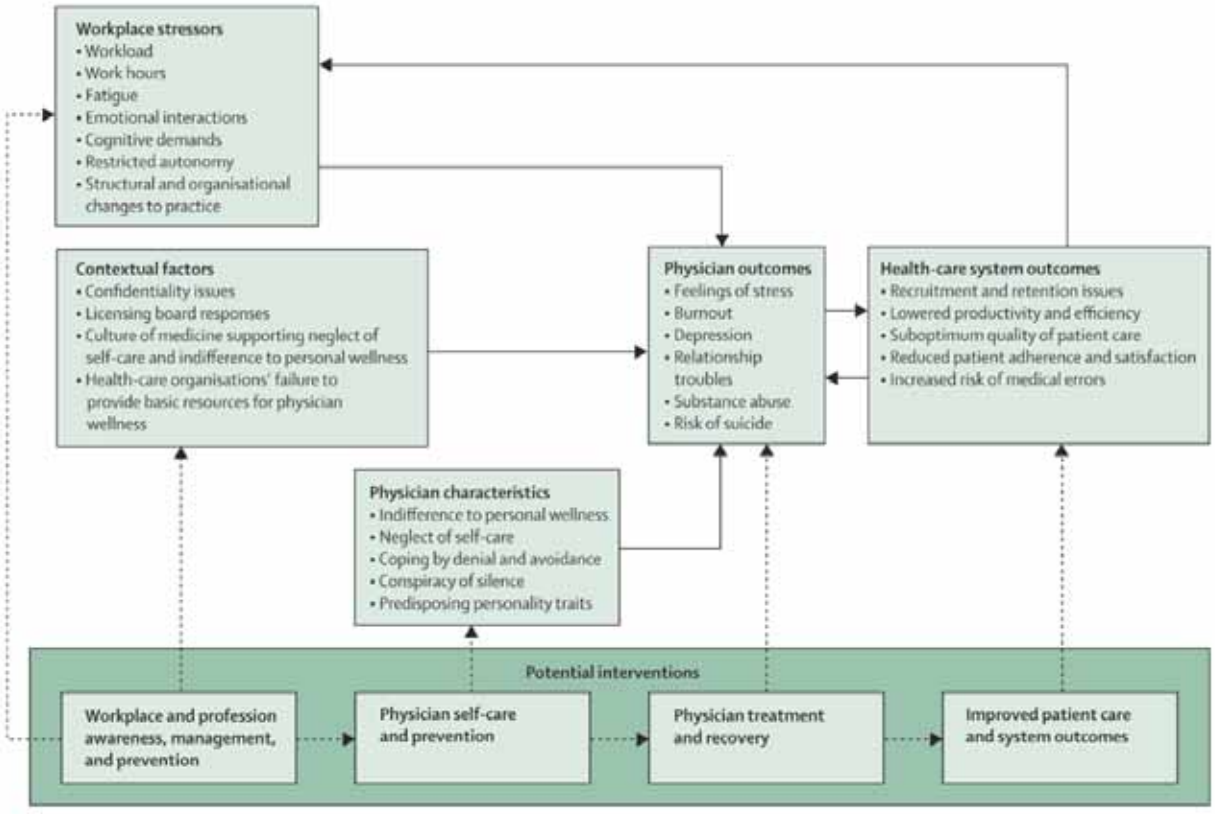

Figure 1. *A model of physician ill health and the links with health-care system outcomes, and potential interventions to improve physician and system outcomes. Solid lines are empirically supported; broken lines are potential links. [3]*

Table 1. Summary of interventions to improve medical student wellbeing and health seeking behavior.

Intervention/Setting	Aims	Intervention	Evaluation	Results
Health Enhancement Program (Monash University School of Medicine) Australia Evidence level: III-1* [15]	Foster behaviours, skills, attitudes and knowledge of self-care strategies for managing stress and maintaining healthy lifestyle, and understanding of the mind-body relationship.	Eight lectures on mental and physical health, mind-body medicine, behaviour change strategies, mindfulness therapies, and the ESSENCE lifestyle program, supported by six two-hour tutorials.	Depression, anxiety and hostility scales of the Symptom Checklist-90-R incorporating the Global Severity Index (GSI) and WHO Quality of Life (WHOQOL) questionnaire to measure effects on wellbeing.	Improved student well-being was noted for depression and hostility subscales but not the anxiety subscale.
Mental Health in Medicine Seminar (Flinders University Medical Students Society) Australia Evidence level: III-3*	Foster behaviours, skills, attitudes and knowledge of self-care strategies or managing stress and maintaining healthy lifestyle, and understanding of the mind-body relationship.	Half-day didactic seminar discussing epidemiology, stigmatising attitudes, causes, risk factors, signs and symptoms of depression, stress management, and support avenues as a student and physician.	Pre/post intervention survey to assess changes in mental health literacy (knowledge/attitudes towards depression and helpseeking behaviour). Based on International Depression Literacy Survey.	Results pending at time of publication.
Student Well-Being Program (SWBP) (West Virginia Uni. School of Medicine) United States Evidence level: III-3* [16]	Prevention and treatment of medical student impairment	Voluntary lunch hour lectures (six lectures over six month period) for first and second year students addressing various aspects of wellbeing.	Post-intervention questionairre distributed to 94 students assessing erceptions of depression, academic difficulties, substance abuse, health-seeking behaviour.	Participants who had one or more symptoms of impairment were more likely to feel a need for counselling and to seek help
Physician Life-style Management Elective (Wright State Uni. School of Medicine) United States Evidence level: III-3* [17]	Enhance the quality of medical student life-planning as a future physician and prevent physician disability.	Voluntary two week elective (lectures) for first year students focusing on physician health, practice management, relationships, and physician disability.	Ratings of each didactic session were collected from seventeen first year medical students.	Students rated sessions on the residency experience highest followed by assertiveness training, then by emotional health management.
Wellness Elective (Case Western Reserve University School of Medicine) United States Evidence level: III-3* [19]	Provide students with information on wellness, stress reduction, and coping strategies.	Series of six, weekly lectures from medical and allied health professionals on wellness, coping strategies and stress reduction.	Evaluated via essay review and a questionnaire administered after the elective concluded.	Participants reported that the elective helped them realise the importance of personal wellbeing, self-care, and provided a variety of coping strategies.
Self-care intervention (Indiana University School of Medicine) United States Evidence level: III-3* [18]	Promote positive health habits and emotional adjustment during students' first semester via selfawareness and self-care interventions.	Lecture, written information, and group discussions on emotional adjustments, sleep hygiene, substance use and recognition/ management of depression and anxiety.	Survey assessing patterns of sleep, alcohol consumption, depression, exercise, caffeine use, satisfaction with teaching, social life, physical health, emotional health, finances, time management.	Promising effects on patterns of alcohol consumption, exercise and socialisation. Influenced some sleep and exercise behaviours, but not overall emotional or academic adjustment.

**National Health and Medical Research Council levels of evidence. I: Systematic review of randomised controlled trials. II: One properly designed randomised controlled trial. III-1: One well designed pseudo-randomised controlled trial. III-2: Non-randomised trials, case–control and cohort studies. III-3: Studies with historical controls, single-arm studies, or interrupted time series. IV: Case-series evidence*

and an understanding of the personal challenges of the profession. [5] This is increasingly evident in new graduates, with 38% of Australian junior doctors recently reporting that they were unprepared for life as a doctor and 17% who would not choose medicine as a career again, if given the choice. [8]

With a suicide rate up to two and a half times greater than the general population, a culture of self-care and wellbeing in the profession needs to be nurtured to ensure a more resilient medical workforce. [1,5]

So where do we stand?

The doctors' wellbeing movement has had strong leadership through individual doctors and small groups such as Doctors' Health Services. [7] In South Australia, 'Doctors' Health SA' has developed into a fully independent, profession-controlled organisation that acts as a focal point for doctors' health and provides clinical services in the central business district for doctors and medical students. The program offers comprehensive after-hours check-ups and easier access to a state-wide network of general practitioners and health professionals associated

Tips for those who are struggling

- Don't be afraid to tell someone; struggling in medicine is more common than you think.
- Don't rely on alcohol or other drugs to cope. This can have a brief mood-lifting effect but can later cause feelings of depression or anxiety.
- Try to eat a healthy diet and stay active.
- Keep connected with other people, including a support network outside of medicine.
- Seek help early from a friend, teacher, doctor, or counsellor. All states and territories now have specific health services for doctors and medical students.

with the program. Similar programs are in development in other states. [8]

Medical student groups have also played important roles in health promotion and advocacy for student welfare needs. The Australian Medical Students' Association has focussed heavily on medical student health and wellbeing in recent years, developing policy and resources to support student wellbeing. [9] Student-run wellbeing events are also now common place at most medical schools around Australia. It is essential that medical educators also play a role in promoting student wellbeing; Monash University has been a leader in this area, with the incorporation of a 'Health Enhancement Program' into its core medical curriculum, which aims to teach students about the relevance of mental and physical health in medicine. Further examples of initiatives aimed at students are listed in Table 1. [5]

Sadly, the doctors' health agenda is still lacking within our hospitals, particularly for junior medical staff. Hospitals remain challenging places to work for interns and residents, with variable levels of support from the institutions. Administrative or support staff such as medical education officers may be asked to consider doctors' health issues, but usually as an add-on to their daily roles, rather than as a core component of it. This has led to a sporadic approach towards junior doctor health, with the level of support dependent on individual clinical training staff. The Queen Elizabeth Hospital (SA) has a unique support program for interns, which incorporates five wellbeing sessions throughout the year as part of the weekly education schedule; however, this remains the exception rather than the rule.

For doctors' health to move forward, it needs to become a mainstream workforce issue within medical education, training and practice. Leadership across each of these areas is important so that we can begin to implement systemic initiatives to facilitate resilience in doctors. One key area of focus should be greater mentoring and peer support, particularly within hospitals. [10,11] Whilst junior medical staff currently work fewer hours than in the past, this has also resulted in less 'living in', and reduced opportunities for peer support. Doctors' common spaces, once typical places for medical staff to debrief with colleagues, are also the first areas to be expended within hospitals looking for more administrative space.

Health promotion also needs to occur across the learning and professional continuum of medical practice. It is essential that medical students and junior doctors are targeted, as this seems to be the time when an acceptance of self-treatment and stigmatised attitudes become entrenched.[6] With a greater awareness of these issues amongst the next generation of doctors, we can gradually shift the culture within the profession. Whilst this is difficult and many of us are set in our ways, it is incumbent upon all of us to have a vision of a medical profession that is strong, vibrant and resilient.

Conflict of interest

None declared.

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Putting awareness to bed: improving depth of anaesthesia monitoring

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Intraoperative awareness and subsequent explicit recall can lead to prolonged psychological damage in patients. There are many methods currently in place to prevent this potentially traumatic phenomenon from occurring. Such methods include identifying haemodynamic changes in the patient, monitoring volatile anaesthetic concentration, and various electroencephalographic algorithms that correlate with a particular level of consciousness. Unfortunately none of these methods are without limitations.

Introduction

Intraoperative awareness is defined by both consciousness and explicit memory of surgical events. [1] There are a number of risk factors that predispose patients to such a phenomenon, both surgical and patient-related. Procedures where the anaesthetic dose is low, such as in caesarean sections, trauma and cardiac surgery, have been associated with a higher incidence. Likewise patients with low cardiac reserve or resistance to some agents are prominent attributable factors. [2] A small number of cases are also due to a lack of anaesthetist vigilance with administration of incorrect drugs or failure to recognize equipment malfunction. [2] Ultimately it is largely an iatrogenic complication due to administration of inadequate levels of anaesthetic drugs. Most cases of awareness are inconsequential, with patients not experiencing pain but rather having auditory recall of the experience, which is usually not distressing. [3] In some cases, however, patients experience and recall pain, which can have disastrous, long-term consequences. Awareness has a high association with post-operative psychosomatic dysfunction, including depression and post-traumatic stress disorder, [4] and is a major medico-legal liability. Though the incidence of awareness is infrequent, estimated to occur in 1-2 cases per 1000 patients having general anaesthesia in developed countries, [1] the sequelae of experiencing such an event necessitates the development and implementation of a highly sensitive monitoring system to prevent it from occurring.

Measuring depth of anaesthesia:

1. Monitoring clinical signs

Adequate depth of anaesthesia occurs when the administration of anaesthetic agents are sufficient to allow conduct of the surgery whilst ensuring the patient is unconscious. There are both subjective and objective methods of monitoring this depth. [5] Subjective methods rely primarily on the patient's autonomic response to a nociceptive stimulus. [5] Signs such as hypertension, tachycardia, sweating, lacrimation and mydriasis indicate a possible lightening of anaesthesia. [5] Such signs however are not specific as they can be the result of other factors that cause haemodynamic changes, such as haemorrhage. Additionally, patient body habitus, autonomic tone and medications (in particular beta-adrenergic blockers and calcium channel antagonists) can also haemodynamically affect the patient. [5] Consequently the patient's autonomic response is a poor indicator of depth of anaesthesia, [6] and the presence of haemodynamic change in response to a surgical incision does not indicate awareness, nor does the absence of autonomic response exclude it. [5]

Patient movement remains an important sign of inadequate depth of anaesthesia, however is often suppressed by administration of neuromuscular blocking drugs. [1] This consequent paralysis can be

overcome with the 'isolated forearm technique'. In this technique, a tourniquet is placed on an arm of the patient prior to administration of a muscle relaxant and inflated above systolic pressure to exclude the effect of the relaxant and retain neuromuscular function. The patient is then instructed to move their arm during the surgery if they begin to feel pain. [5] Though this technique is effective in monitoring depth of anaesthesia, it has not been adopted into clinical practice. [7] Furthermore, patient movement and autonomic signs may reflect the analgesic rather than hypnotic component of anaesthesia and thus are not an accurate measure of consciousness. [8]

2. Minimum Alveolar Concentration (MAC)

The unreliable nature of subjective methods for assessing depth of anaesthesia has seen the development and implementation of various objective methods which rely on the sensitivity of monitors. The measurement of end-tidal volatile anaesthetic agent concentration to determine the MAC has become a standard component of modern anaesthetic regimens. MAC is defined as the concentration of inhaled anaesthetic required to prevent 50% of subjects from responding to noxious stimuli. [9] It is recommended that administration of at least 0.5 MAC of volatile anaesthetic should reliably prevent intra-operative awareness. [10]

Unfortunately the MAC is affected by a number of factors and thus it is difficult to determine an accurate concentration that will reliably prevent awareness. Patient age is the major determinate of the amount of inhalation anaesthesia required, as are altered physiological states such as pregnancy, anaemia, alcoholism, hypoxaemia and temperature of the patient. [11] Most importantly, the administration of opioids and ketamine, both commonly included in the anaesthetic regimen, severely curtail the ability of the gas analyser to determine the MAC. [12] Further, the MAC is a reflection of inhalational anaesthetic concentration, not effect. The suppression of response to noxious stimuli whilst under volatile anaesthesia is mediated largely through the spinal cord, and thus does not accurately reflect cortical function and the penetration of the anaesthetic into the brain. [13] Another major limitation to using gas analysers is that they have limited reliability when intravenous anaesthesia is used. Simultaneous administration of intravenous anaesthetic agents is extremely common and in many cases total intravenous anaesthesia is used; in such cases the use of the MAC is not applicable.

3. Electroencephalogram (EEG) and derived indices

Bispectral Index (BIS)

Advances in technology have lead to the concomitant development of processed encephalographic modalities and their use as parameters to assess depth of anaesthesia; the most widely used being the BIS monitor. The BIS monitor uses algorithmic analysis of a patient's EEG to produce a single number from 1 to 100, which correlates with a particular level of consciousness. [5,14] For general anaesthesia, 40-60 is recommended. [14] The establishment of this monitor at first seemed promising with the publication of several studies advocating its use in preventing awareness. The first of these was conducted by Ekman et al, [15] and indeed found that there was a substantial decrease in incidence of awareness when the BIS monitor was used. In this study, however, the patients were not randomly allocated to the control group and the BIS monitoring group, and thus the results are subject to a high degree of bias and cannot be reliably interpreted. The second study, the B-Aware trial, [16] also found that BIS-guided anaesthesia resulted in a reduction in awareness in high risk patients, however despite having a sound study design, subsequent studies failed to reproduce this result. One prominent study, the B-Unaware trial, [17] compared BIS monitoring to more traditional analysis of end-tidal concentrations of anaesthetic gases to assess depth of anaesthesia during surgeries on high risk patients. This study failed to show a significant reduction in the incidence of awareness using BIS monitoring, however a major criticism of this study is that the criteria used to classify the patients in the trial as 'high-risk' was less stringent than those used in the B-Aware trial which likely biased the results. Also, given the low incidence of awareness, a larger number of study subjects would be required to demonstrate any significant reduction.

The BIS monitor also has several practical issues that further question its efficacy in monitoring consciousness. It is subject to electrical interference from the theatre environment, particularly from electromyography, diathermy and direct vibration. [14] This is more likely in cases where the surgical field is near the BIS electrode (such as facial muscle surgery) which will falsely elevate BIS values, leading to possible excess administration of anaesthesia. [14] Similar to the MAC, standard BIS scores are not applicable to all patient populations, particularly in patients with abnormal EEGs – those with dementia, head injuries, cardiac arrest and have hypo- or hyperthermia. [1] In such cases, the BIS value may underestimate the depth of anaesthesia, leading to the administration of excess anaesthetic and a deeper level of anaesthesia than required. Further, as the molecular action of various anaesthetic agents differs, the consequent EEG changes are not uniform. Specifically, the BIS monitor cannot accurately assess changes in consciousness when the patient is administered ketamine [18] and nitrous oxide, [19] both commonly used agents.

Despite these practical downfalls, however, there are substantial benefits to the BIS monitor which should be incorporated into future depth of anaesthesia monitors. The BIS monitor helps anaesthetists to titrate the correct dosage of anaesthetic for the patient, [5] and to adjust this accordingly throughout the surgery to keep the patient within the recommended range for general anaesthesia without administering excess agent. This results in decreased haemodynamic disturbance, faster recovery times and reduced post-operative side effects. [20] A meta-analysis found that use of BIS monitoring significantly reduced anaesthetic consumption by 10%, reduced the incidence of nausea/vomiting by 23% and reduced time in the recovery room by four minutes. [21] This may offer a cost-benefit as less anaesthetic will be required during surgeries.

Despite the aforesaid advantages of using the MAC and BIS monitor to assess consciousness during surgery, the major inadequacy to both of these methods is that they only measure the hypnotic element of anaesthesia. [8] Anaesthetic depth is in fact a complex construct of several components including hypnosis, analgesia, amnesia and reflex suppression. [8] Different anaesthetic agents have varying effects across these areas; some are able to be administered independently, and others only have properties in one area, and thus must be used in conjunction with other pharmacologic agents to achieve anaesthesia. [8] If only the hypnotic component of anaesthesia is monitored, optimal drug delivery is difficult and there is a risk that insufficient analgesia may go unnoticed. Thus the MAC and BIS monitors can be used to monitor hypnosis and sedation, but have little role in predicting the quality of analgesia or patient movement mediated by spinal reflexes.

Entropy

Entropy monitoring is based on the acquisition and processing of EEG and electromyelogram (EMG) signals by using the entropy algorithm. [22] It relies on the concept that the irregularity within an EEG signal decreases as the anaesthetic concentration in the brain rises. Similar to the BIS, the signal is captured via a sensor that is mounted on the patient's forehead, and the monitor produces two numbers between 0 and 100 – the response entropy (RE) and the state entropy (SE). The RE incorporates higher frequency components (including EMG activity) thus allowing a faster response from the monitor in relation to clinical state. [22] Numbers close to 100 suggest consciousness whereas numbers close to 0 indicate a very deep level of anaesthesia. The ideal values for general anaesthesia lie between 40 and 60. [22] Studies have shown that entropy monitoring measures the level of consciousness just as reliably as the BIS, and is subject to less electrical interference during the intraoperative period. [23]

Evoked potentials

Alternative mechanisms such as evoked potentials, which monitor the electrical potential of nerves following a stimulus, have also demonstrated a clear dose-response relationship with increasing anaesthetic administration [14,24]. In particular, auditory evoked potentials (in which the response to auditory canal stimulation is recorded) have lead to the development of the auditory evoked potential index. This index was proven to have greater sensitivity than the BIS monitor in detecting unconsciousness. [24] Unfortunately, using evoked potentials to monitor depth of anaesthesia is a complex process, and as with BIS many artifacts can interfere with the EEG reading. [14,24]

Brain Anaesthesia Response (BAR) Monitor

New electroencephalographically derived algorithms have been developed which define both the patient's hypnotic and analgesic states individually. [25,26] This is essential in cases where combinations of anaesthetic agents that have separate sedative and analgesic properties are used. Dr David Liley, Associate Professor of the Brain Sciences Institute at Swinburne University of Technology, began a research project a decade ago with the aim of producing such a means of assessing consciousness, and subsequently pioneered the Brain Anaesthesia Response (BAR) monitor. [25] Liley initially analyzed EEG data from 45 patients in Belgium who were administered both propofol (a hypnotic agent) and remifentanil (an analgesic agent) as part of their anaesthetic regimen. Two measures were derived from the EEG to measure the brain response to the anaesthetic agents – cortical state (which measures brain responsiveness to stimuli) and cortical input (which quantifies the strength of each stimuli that reaches the brain). He was able to detect the effects of the drugs separately; cortical state reflected changes for hypnotic agents, and cortical input reactions reflected change in levels of analgesia; from this, the BAR algorithm was developed. [25] Its use will allow anaesthetists to determine which class of drug needs adjustment, and to titrate it accordingly. It is suggested that the BAR monitor will narrow the range of the exclusion criteria that limit previously mentioned indexes such as the BIS and Entropy. [25,26] This innovative monitor has an improved ability to detect a number of drugs that are not effectively measured using the BIS monitor, for example ketamine and nitrous oxide. [25] The capacity to titrate anaesthetics specifically and accurately would increase optimal drug delivery, not only reducing the likelihood of intra-operative awareness but also avoiding issues of over or under

sedation. This in turn might reduce side effects associated with excess anaesthetic administration and improve post-operative recovery. The BAR monitor is currently undergoing trial at the Royal Melbourne Hospital under Professor Kate Leslie, and at St. Vincent's Hospital in Melbourne under Dr. Desmond McGlade. [25,26]

Though advancements have undoubtedly been made in regards to depth of anaesthesia monitors, it cannot be emphasized enough that the most important monitor of all is the anaesthetist themselves. A significant percentage of awareness cases are caused by drug error or equipment malfunction. [2,27] These cases can easily be prevented by adhering to strict practice guidelines, such as those published by the Australian and New Zealand College of Anaesthetists. [28]

Conclusion

Measuring depth of anaesthesia to prevent intra-operative awareness remains a highly contentious aspect of modern anaesthesia. Current parameters for monitoring consciousness include the observation of clinical signs, the MAC and BIS indices, as well as less commonly used methods such as evoked potentials and entropy. These instruments allow clinicians to accurately titrate anaesthetic agents leading to a subsequent decrease in post-operative side effects and a reduction in awareness among patients at increased risk of this complication. Despite these benefits, all of the current monitors have limitations and there is still no completely reliable method of preventing this potentially traumatising event. What is required now is a parameter or measure that shows minimal inter-patient variability and the capacity to respond consistently to an array of anaesthetic drugs with different molecular formulations. It is important to remember, however, that no monitor can replace the role of the anaesthetist in preventing awareness.

Conflict of interest

None declared.

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Bring back the white coats?

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Should we bring back the white coat? Is it time for this once-venerated symbol of medicine to re-establish itself amongst a new generation of fledgling practitioners? Or, is this icon of medical apparel nothing more than a potentially dangerous relic of a bygone era?

Introduction

The white coat has long been a symbol of the medical profession, dating back to the late-1800s. [1] It was adopted as medical thought became more scientific. [2] Doctors wore coats aligning themselves with the scientists of the day, who commonly wore beige coats, but instead chose white - the colour lacking both hue and shade - as representation of purity and cleanliness. [3] Nowadays, the white coat is rarely seen in hospitals, possibly due to suspicions that it may function as a vector for transmission of nosocomial infections. [4] This article addresses the validity of such concerns, by reviewing the available literature.

The vanishing white coat

Twenty years ago in the United Kingdom (UK) white coats were commonly worn by junior doctors while consultants wore suits. [5] The choice to not wear a white coat was seen as a display of autonomous, high-ranking professionalism. [6] Many older Australian nurses now recall when doctors commonly wore white coats in the hospital. Over the last decade, white coats have become a rarity in Australian hospitals. [7,8] There are many reasons why this change occurred. Table 1 outlines some common thoughts of doctors on the matter. Paediatricians and psychiatrists stopped using white coats as they thought that it created communication barriers in the doctor-patient relationship. [3] Society viewed white coats as a status symbol, [7] evoking an omnipotent disposition, which was deemed inappropriate. [6,7] In addition, it was thought white coats might be a vector for nosocomial infection. [6,9-13] With these pertinent issues, and no official policy requiring white coats, doctors gradually hung them up.

Table 1. *Reasons for why doctors choose to wear or not wear white coats*

Reasons why doctors wear white coats	Reasons why doctors do not wear white coats
For identification purposes [8]	No one else does [8]
To carry things [14]	Infection risk [5,8,14]
Hygiene [7,8]	Hot or uncomfortable [5,8,14]
To protect clothes [8]	Interferes with the doctor-patient relationship [6,14]
To create a psychological barrier [3]	Lack of seniority [5]
Patients prefer doctors in white coats [14]	
Looks professional [8,14]	

Hospital policies and white coats

In 2007 the British Department of Health published guidelines for healthcare worker uniforms, that banned the white coat from hospitals in England, [15] thereby producing a passionate controversy. [4] The primary reason for the ban was to decrease health-care acquired

infections, [9,12,16] which was supposedly supported by one of two Thames Valley University literature reviews. [6,13] Interestingly, these reviews stated there was no evidence to support the notion that clothing or specific uniforms, could be a noteworthy medium for the spread of infections. [6,13] On closer inspection of the British policy, however, they state: "it seems unlikely that uniforms are a significant source of cross-infection." [15] The text goes on to support the new uniform guidelines, including the abolition of the white coat, because "the general public's perception is that uniforms pose an infection risk when worn inside and outside clinical settings." [6] This statement lacks evidence, as many studies show patients prefer their doctors to wear white coats [7,14,17] and the notion of patients being concerned about infection risk are uncommon. [7] It would appear that the British Department of Health made this decision for some reason other than compulsion by evidence.

Despite significant discussion and debate, the United States (US) has chosen not to follow England in banning the white coat. [3,12,18] The US has a strong tradition associated with the white coat, which may influence their reluctance to abandon them so quickly. In 1993, the 'white coat ceremony' was launched in the US, where graduating medical students were robed in a white coat, as the senior doctors 'demonstrate their belief in the student's ability to carry on the noble tradition of doctoring.' [1] Only five years later, 93 US medical schools had adopted this practice. [1] This indicates that the white coat is a real source of pride for doctors in the US, however, tradition alone cannot dictate hospital policies. In 2009, the American Medical Association (AMA) passed a resolution to encourage the "adoption of hospital guidelines for dress codes that minimise transmission of nosocomial infections." [19] Rather than banning white coats, [16] the AMA proposed the need for more research, noting that there was insufficient evidence to support that there was an increased risk of nosocomial infection directly related to their use. [18]

The Australian Government National Health and Medical Research Council (NHMRC) published the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* in 2010, outlining recommendations for the implementation of infection control in all Australian hospitals, and other areas of healthcare, based on current literature. [20] It states that uniforms should be laundered daily, whether at home or at the hospital, and that the literature has not shown a necessity to ban white coats or other uniforms, as there is no evidence that they increase transmission of nosocomial infections. [20]

These guidelines, also contained the article that the British Department of Health used in support of banning white coats. [6]

The evidence of white coats and nosocomial infection

There are minimal studies done trying to assess whether white coats are potential sources of infection or not. [9-12] Analysis of the limited data paints a uniform picture of the minimal possibility for white coats to spread infection.

In 1991 a study of 100 UK doctors demonstrated that no pathogenic organisms were cultured from the white coats. [10] Notably, this study also found that the level of bacterial contamination of white coats did not vary with the amount of time the coat was worn, but varied with the amount of use. [10] The definition of usage was not included in the article, although doctor-patient time is the most likely interpretation. Similarly, a study in 2000 isolated no *Methicillin-resistant Staphylococcus aureus* (MRSA), or other infective organisms, but still concluded that the white coat was a possible cause of infection. [11] This study stated white coats were not to be used as a substitute for personal protective equipment (PPE) and it was recommended that they should be removed before putting on plastic aprons. [11]

A recent study swabbed MRSA on 4% of the white coats of medical participants, even though it was the biggest study of its kind, there was no statistically significant difference between colonised and uncolonised coats due to the population size. [9] This study has limitations in that it did not compare contamination with clinical dress, which could potentially show there is no difference. There appeared to be a correlation with the MRSA contaminated coats and hospital-laundered coats with four out of the six coats being hospital-laundered. [9] A potential major contributing factor to the contamination of white coats could be the frequency of washing white coats. A survey in the 2009 study showed that 81% of participants had not washed their coats for more than seven days and 17% in more than 28 days. [9] Even though the 1991 study showed that usage, not time, was the determinate for bacterial load, this does not negate a high amount of usage over a long period of time. [10] Interestingly, there may be a correlation with the MRSA contaminated coats and hospital-laundered coats. [9]

In response to the British hospital uniform guidelines, a Colorado study, published in April 2011, compared the degree and rate of bacterial contamination of a traditional, infrequently-washed, long-sleeved white coat, to a newly-cleaned, short-sleeved uniform. [12] Their conclusions were unexpected, such that after eight hours of wear, there was no difference in the degree of contamination of the two. Additionally, the study concluded that there was also no difference in the extent of bacterial or MRSA contamination of the cuffs of the physicians. Consequently, the study does not discourage the wearing of long-sleeved white coats [12] and concludes that there is no evidence for their abolition due to infection control concerns.

While, all these studies indicate the potential for organisms that cause nosocomial infections to be present on white coats, [10-12] the common conclusion is there is no higher infection risk from daily-washed, white coats, than any other clinical attire. [12] It needs to be recognised there are many confounding factors in all of these studies that compare attire and nosocomial infection, hence more studies are needed to clearly establish guidelines for evidence-based practice regarding this issue. Gaining an understanding of the difference in transmission rates between specialities could assist in implementing specific infection control practices. Studies that clearly establish transmission of organism from uniform to patient, and clinical data on the frequency of such transmissions, would be beneficial in developing policy. Additionally, nationwide hospital reviews on rates of nosocomial infections, comparing the dress of the doctors and nurses would contribute to gaining a more complete understanding of the role that uniforms play in transmission of disease.

Australian hospitals and white coats

Queensland State Infection Control Guidelines published by the Centre for Healthcare Related Infection Surveillance and Prevention (CHRISP), surprisingly had no details of recommended dress of doctors that could be found. [21] State guidelines like these, in combination with federal guidelines, influence the policies that each individual hospital in Australia creates and implements.

A small sample of hospitals across all the states and territories of Australia were canvassed to assess what the general attitudes were towards the wearing of white coats during patient contact and whether these beliefs were evidence-based. The infection control officers of each of the hospitals were contacted, by myself and the specifics of their policies attained, along with an inquiry regarding the wearing of white coats by students or staff. This data was collected verbally. Obviously there are limitations to this crude data collection it is the result of attempting to attain data not recorded.

On the whole, individual hospital policies emulated National Guidelines almost exactly, by not expelling white coats; instead encouraging them to be washed daily, like normal dress. Some hospitals had mandatory 'bare-below-the-elbows' and 'no lanyard' policies, while many hospitals did not. White coats were worn in a significant amount of Australian hospitals, usually by senior consultants and medical students (see Table 2). The general response from infection control officers regarding the wearing of white coats was negative, presumably due to the long sleeves and the knowledge that they are probably not being washed daily. [10,12]

Table 2. *Relevant policies in place regarding white coats and if white coats are worn within hospitals in major Australian centres.*

Hospital	Policy regarding white coats	White coat worn
Townsville Hospital	No policy	An Emergency Department doctor and surgeon
Mater Hospital – Townsville	No policy	Nil known
Royal Brisbane and Prince Charles – Metro North*	No policy	Medical students
Brisbane Princess Alexandra and Queen Elizabeth 2 – Metro South*	No policy	Medical students One consultant who requires his medical students to wear white coats
Royal Darwin Hospital	Sleeves to be rolled up	Nil known
Royal Melbourne Hospital	No policy	Nil known
Royal Prince Alfred Hospital – Sydney	No policy	Senior doctors, occasionally
Royal Hobart Hospital	No policy	Nil known
Royal Adelaide Hospital	No policy	Orthopaedics, gynaecologists and medical students
Royal Perth Hospital	Sleeves to be rolled up	Only known to be worn by one doctor
Canberra Hospital	Sleeves to be rolled up	-

All the hospitals in the northern metropolitan region of Brisbane are governed by the same policy, likewise for Metro South.

This table shows white coats are not extinct in Australian hospitals and the policies in place pertaining to white coats reflect the Federal Guidelines. Policies regarding lanyards, ties and long-sleeves differed between hospitals. It is encouraging to note that Australia has not followed in the footsteps of England, regarding the abolition of white coats, as there is limited scientific evidence to support such a decision. The policies in Australia regarding white coats require daily laundering, although current literature even queries the necessity for this. [12] The negative image of white coats in Australian hospitals by the infection control officers is probably influenced by the literature that shows that white coats become contaminated. [9] The real discussion, however, is the difference in contamination of white coats and other clinical wear.

Meditations of a medical student…

My own views…

I have worn a white coat on numerous occasions, during dissections and lab experiments, but never when I am in contact with patients. According to the James Cook University School of Medicine dress policy, all medical students are to wear 'clean, tidy and appropriate' clinical dress. [22] No detail is included regarding sleeve length, colour or style, although social norm is a very powerful force, and the main reason that my colleagues and myself would not wear white coats is simply because no one else is wearing them. This practice is concurrent with a study on what Australian junior doctors think of white coats. [8]

Personally, I think that a white coat would be quite useful. It may even decrease nosocomial infection, as it has big pockets and could carry books and instruments, negating the need for a shoulder bag or putting items down in patient's rooms, thus becoming a potential cross-infection risk. In regards to the effects on patients, I think the psychological impact may have some effect, but this would be different for each individual. White coats are not the cause of nosocomial infections that are rampant in our hospitals, it is the compliance of health professionals washing their hands and adhering to the evidence-based guidelines provided by infection control organisations. In Australia these guidelines give freedom to wear the white coats, so why not?

Conclusion

White coats are a symbol of the medical profession and date back to the beginnings of evidence-based medicine. Suitably, it is appropriate to let the evidence shape the policies regarding the wearing and laundering of white coats in hospitals and medical practice. There has been much debate regarding white coats as an increased risk for nosocomial infection, [3,4,12,16,18] as many studies have shown that white coats carry infectious bacteria. [9-12] But, more notably, a study published in April 2011, showed that the bacterial loads on infrequently washed white coats did not differ from newly cleaned short-sleeve shirts. [12] The reason why Britain decided to ban white coats in 2007 is a mystery. Australia has not banned white coats, although there are some practitioners who choose to wear them, but is it far from the norm. [8] A nation-wide, formal re-introduction of white coats into Australian medical schools has no opposition from infection control according to the current evidence. "…Might not the time be right to rediscover the white coats as a symbol of our purpose and pride as a profession?" [1]

Conflict of interest

None declared.

Acknowledgements

Thank you to Sonya Stopar for her assistance in editing this article.

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Burdens lifted, hopes restored

Tiffany Foo
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University of Tasmania

Born and raised in Malaysia, Tiffany has an immense interest in medicine in developing countries and rural areas. Her interests include reading, writing, baking and travelling. She has special interests in infectious diseases, rheumatology and emergency medicine but is keeping her options open. She wants to make a difference in the lives of the people around her.

Amanda Lim
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University of Tasmania

Amanda loves to spend time with children and volunteers with Variety Tasmania. She is passionate about charity work and aspires to volunteer with Médecins Sans Frontières one day. She also enjoys travelling and badminton outside of medicine. She is active in promoting Malaysian students' welfare in Australia and is proud of her Malaysian heritage.

During the summer break of our third year of medicine at the University of Tasmania, we decided to embark on an elective at Padhar in India. The country of India fascinated us as an opportunity to experience a very different health care system and to learn more about the Indian culture.

Padhar is a small town located in Madhya Pradesh in the central highlands of India. It appealed to us because of its rural location. This tiny town boasts a 200 bed multispecialty missionary hospital, which initially started out in 1958 as a clinic. The hospital is often the first point of contact for many patients from surrounding states, including the Gond and the Korku tribals, and some patients travel for days to seek medical help here.

After fifteen hours of flying and an eventful 26 hour train ride, we arrived at Itarsi Junction, a two hour bumpy drive away from Padhar.

Padhar is declared endemic for malaria so we came 'armed' with insect repellents and mosquito coils. Despite our best efforts, we were not spared the wrath of the mosquitoes. We couldn't help but feel paranoid when we got our first mosquito bites even though we took our doxycycline regularly.

Tuberculosis (TB) is a serious and common health problem in Padhar. We had not expected such a high prevalence to the extent that, for doctors in Padhar, the first differential diagnosis for a cough and a cold was often TB until proven otherwise. It was not uncommon to see the sorts of chest X-rays with cavitating lesions that we had previously only seen in textbooks.

Another difference we observed during our elective was the vastly differing attitudes to hygiene. In Australia we are well familiarised with the hand hygiene posters plastered all over hospital walls. In Padhar, in place of our '5 moments of hand hygiene' signs are signs that read, 'Gloves are useful but not necessary.' The sanitation practices were also very rudimentary as basins of water and lemon replaced the sinks and chlorhexidine we had previously taken for granted.

Textbook photographs of patients with late presentations of cancer came to life in Padhar. Geographical barriers, as well as the habit of

betel nut and tobacco chewing, often result in patients presenting with large tumours of the oral cavity. One of the cases we saw was that of a 45 year old man who presented for a surgical resection of a large squamous cell carcinoma on the left side of his tongue. The skilled surgeons at Padhar performed a COMMANDO Procedure (COMbined MANDibulectomy and Neck Dissection Operation). The surgeons are particularly skilled at this procedure as it is commonly performed. This is because late presentations of cancer are common here due to the lack of preventative screening, as well as geographical barriers and poverty. It saddened us to see that there is a huge health disparity between a developed and developing country.

However, despite disparities in health care systems, we found that generosity knew no boundaries. There were many charming patients and helpful medical staff whom we encountered during our time in Padhar. In particular, we met a pair of omphalophagus conjoined twins, who were four months old at the time of our visit. Their parents were poor farmers who were devastated when their twins were born, as they did not have the means to care for them. Therefore, they did what they thought was best for the twins, by returning home without them and leaving them in the hospital. Won over by the twins' infectious smiles, the hospital staff decided to take them into their care. The current plan is to wait for the twins to reach ten kilograms before separating them. However, the amount needed to separate the twins is more than US$150,000, much more than the hospital can afford. In addition, the hospital would need to cover the cost of raising the twins. However, they are determined to raise the twins and provide them with the best life that they can have. The twins were constantly surrounded by nurses, doctors and other hospital staff. The care and love shown by the team in Padhar certainly tugged at our heartstrings.

We also saw other cases that taught us some fundamental rules about diagnosis and history taking. One was a sixteen year old girl who presented to the emergency department complaining of a five day history of progressively worsening generalised abdominal pain.. She had a background of trauma after a fall whilst collecting water from a well. Although injury to the jejunum is common after blunt force trauma, [1] the medical team had ruled it out as it would be expected

to cause very significant pain, usually leading to immediate hospital presentation. Thus it came as a surprise when a perforated jejunum was found on X-Ray. This case reminded us that clinical presentations, though incredibly useful, can still be deceiving.

One of the highlights of the trip was being a part of the team involved in the Mobile Clinic under the Rural Outreach Program, which was an initiative of Padhar Hospital. The Mobile Clinic services the surrounding villages that have limited access to healthcare due to geographical barriers. More often than not, it would have been months or even years since the villagers engaged with the healthcare system.

The makeshift clinic attracted many people from the village and surrounding villages as people of all ages with a myriad of diseases lined up patiently to seek medical help. The most common presentation was scabies and we quickly ran out of Permethrin cream. As Padhar Hospital has always been passionate about contributing towards the fight against human immunodeficiency virus (HIV) we also took bloods from patients to test for HIV and educated them about the disease and the importance of safe sexual practices.

On the last few days of our trip, we were very lucky to be a part of Padhar's celebration of World Aids Day. The prevalence of HIV/AIDS in India in 2009 was 2.4 million out of a population of 1.2 billion. [2] It was the aim of Padhar Hospital to raise awareness of HIV and AIDS in conjunction with this day. In the morning church service conducted in the hospital compound, testimonials were shared from HIV patients as well as doctors who had clinical contact with them. During the lunch break, the hospital invited school children from nearby primary schools as part of the awareness program. One of the interesting things they had in store for them was a parody of the stereotypes against HIV patients. It is good to see that, unlike for many in the older generations, these young minds were receptive to the idea that HIV is not a deadly infectious disease that spreads through touch. The children were educated about safe sex practices as well as informed about the availability of free needles.

Whilst seeing plenty of patients and medical staff gave us opportunities and insights into medicine, our elective was also a culturally enriching experience. Generally, people were curious about our backgrounds and it was good to be able to share our culture with them and learn about theirs too. It gave us a glimpse into a very different way of life to our own. We experienced firsthand the gracious hospitality of the locals; we were invited to be a part of one of the doctors' daughter's wedding, despite the fact that we have never met the bride before.

We also loved seeing the sights and sounds of the town and outskirts, from people bathing and doing their laundry in rivers to women in

bright coloured sarees carrying urns twice the size of their heads. We also saw families of five piled onto motorcycles. We were touched by the hospitality that was shown by the villagers, despite the fact that we were foreigners who did not speak their language. Many villagers opened their homes to us and we had a chance to see how they live their life, which contrasted immensely to what we were used to. They cooked with firewood and had to walk a fair distance to collect water from wells. What touched our hearts was the fact that everyone seemed satisfied with what they had. Their voices and faces seemed to echo the old adage, "Happiness is not having what you want, but appreciating what you have."

It was a humbling experience, and reminded us to be grateful for everything around us. It is sad to think that in this day and age, there are many people who are still living in poverty and unable to access healthcare. Hospitals like Padhar Hospital have certainly made a difference in terms of rural healthcare provision. When it was time for us to go, we left with a heavy heart but knowing that we will always do our best to uphold the hospital's motto, 'Burdens lifted, hopes restored.'

Acknowledgements

Sharene Chong and Niyanta D'souza for making the trip memorable. Dr Choudrie and the amazing team in Padhar for their hospitality. Pictures taken by Tiffany Foo.

Conflict of interest

None declared.

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Starlight stars bright

Chee Kong Teo
Fourth Year Medicine (Undergraduate)
University of New South Wales

Chee Kong served two years in the Singapore Armed Forces as an artillery specialist prior to commencing medicine at UNSW. His qualitative research on antibiotic stewardship won Best Student Abstract in the National Medicines Symposium 2012. He also recently retired from his post as Print Publications Officer for the AMSJ.

White T. *Starlight: An Australian Army doctor in Vietnam*. Brisbane: CopyRight Publishing; 2011.

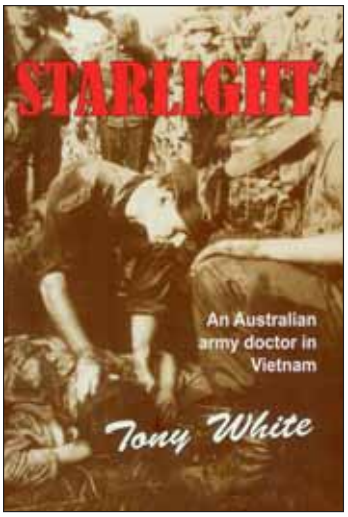
RRP: $33.00

Not many of us dream of serving as a medical doctor in the frontlines of war. War is after all the antithesis of everything the medical profession stands for. [1] In Starlight, Dr Tony White AM vividly recounts his tour of duty in South Vietnam between 1966 and 1967 through correspondence exchanged with his family. STARLIGHT was the radio call sign for the medical officer and it bore the essence of what was expected of young White as a Regimental Medical Officer (RMO) in the 5th Battalion of the Royal Australian Regiment (5 RAR).

White was born in Perth, grew up in Kenya and read medicine in Clare College, Cambridge University. After completing the first half of the six-year degree, he moved back with his family to Sydney where the pivotal decision to join military service was made. White accepted a scholarship from the Australian government to continue at the University of Sydney in exchange for four years of service in the Australian Defence Force after a year of residency.

In May 1966, White's wartime duties commenced with 5 RAR in Vung Tau, southeast of Saigon, dubbed "Sufferer's Paradise". After a brief settling-in, the battalion moved to Nui Dat, their operational base for the year. The initial excitement of the 25-year-old's first visit to Asia quickly faded as the realities of war – the mud, the sweat and the blood – set in. Footnotes and explanation of military jargon and organisation were immensely helpful in acquainting the reader to the battalion's environment. As an RMO, White worked round-the-clock performing General Practice duties such as sick parades and preventive medicine, emergency duties attending to acute trauma, and public health duties monitoring for disease outbreaks and maintaining hygiene. The stark difference from being a civilian doctor is candidly described, "You live, eat, dig, and [defecate] with your patients and, like them, get every bit as uncomfortable and frightened. There is no retreat or privacy."

From the early "friendly fires" and booby traps to the horror of landmines, White's affecting letters offer a very raw view of war's savagery. It was a war fought against guerrillas, much like the present war in Afghanistan, where the enemy is unknown and threat may erupt into danger at any time. During the numerous operations 5 RAR conducted, White attended to and comforted many wounded. With every digger killed in action, a palpable sense of loss accompanies the narration. White clearly laments the "senseless killing of war" as he explained, "You spend all that time – 20 years or so – making a man, preserving his health, educating and training him, to have him shot to death." White himself had close brushes with death. He was pinned down by sniper fire on one occasion and even found himself in the middle of a minefield in the worst of tragedies encountered. The chapter "Going troppo" ruminates on the enduring psychological effects of these events as the year unfolded.



The insanity of war is balanced by many heartening acts. First and foremost is the remarkable resilience of the diggers whose tireless disposition to work inspired White profoundly. White also voluntarily set up regular clinics in surrounding villages to provide care for civilians despite the threat of enemy contact. In an encouraging twist, both friendly and enemy (Viet Cong) casualties were rendered the same standards of care. Even more ironic was the congenial interactions between the two factions within the confines of the hospital. Perhaps the most moving of all was White's heartfelt words of appreciation to his family who supported his spirits through sending letters and homemade goodies like fruitcakes, biscuits and smoked oysters.

So why should you read this book? Textbooks do not teach us empathy. White shares in these 184 pages experiences that we all hope never to encounter ourselves. Yet countless veterans, refugees, abuse victims, etcetera have faced such terror and our understanding of their narratives is essential in providing care and comfort. In the final chapters of this book White gives a rare physician perspective on post-traumatic stress disorder and how he reconciled with the profound impact of war to achieve success in the field of dermatology. These invaluable lessons shine through this book.

Conflicts of Interest

None declared.

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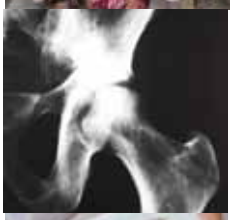


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