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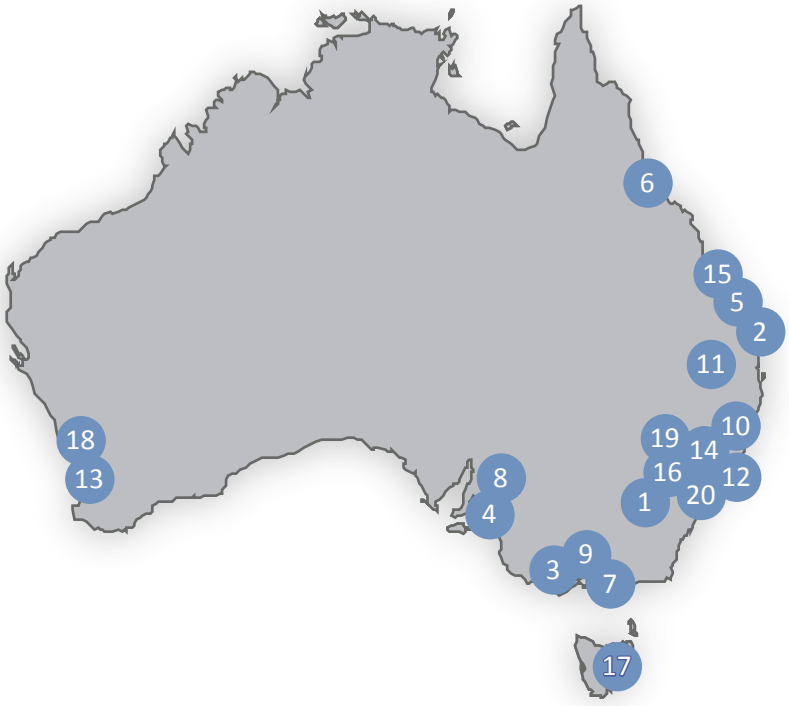

Editor's welcome: Student research in an evolving research landscape

Dr. David Jakabek
Editor-in-Chief, AMSJ

Welcome to Volume 7, Issue 1, of the Australian Medical Student Journal (AMSJ). The hard work of our volunteer staff has come together again for another issue we are all proud to publish.

The AMSJ serves as a fully peer-reviewed national journal for over 14000 medical students to showcase their work. We aim to provide not just a medium for publication, but also to assist as an introduction to scholarly publication and to encourage medical research. For this issue, there is an extensive breadth of topics covered. From contextualising health in both global and rural environments, to disciplines of surgery, anaesthesia, medicine and pediatrics. There is surely something for every interest in this issue of the AMSJ.

Editorially, the focus is on the changing research landscape. As Professor Christine Bennett describes, Australian medical students are increasingly exposed to research practices and will hopefully go on to be leaders in their fields. How this research is communicated is also progressing, and as Dr Virginia Barbour explains, open access and other research developments provide faster and easier dissemination of new findings to all corners of the online world.

Open access is progressively spreading across journals and the AMSJ is proud of continue to make the journal available free of charge. More broadly, open access is important for medical students both as consumers and producers of medical research. Medical students are generally busy establishing a core medical knowledge base, and the broader resources that can be utilised for this purpose, the better. Although traditional journals in open access format are useful, newer developments in Free Open Access Meducation (FOAM, e.g. Life in the fast lane, http://lifeinthefastlane.com/) are invaluable resources. Alternatively, as producers of research, medical students publishing in open access journals allows greater global reach of their work.

Lastly, there has been a changing of the guard within the AMSJ. For all their tireless work in steering the journal we thank the outgoing internal director, Dr Karen Du, and external director, Dr Grace Yeung. We wish them all the best in their future endeavours. Furthermore, the AMSJ team is excited to embrace our incoming internal director, Joanna Mills, and external director, Ashley Antovich, and look forward to their input in growing the AMSJ.

With thanks to the entire AMSJ team that has made this possible, as well as our authors, peer-reviewers, and sponsors, I hope you enjoy this issue.

Correspondence
D Jakabek: d.jakabek@amsj.org

Thank you to AMSJ Peer Reviewers

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Erratum

Yasheer Haripersad, academic convener of the 2015 Australasian Students' Surgical Conference, was incorrectly affiliated with Monash University. He is a sixth year medical student at The University of Western Australia.

Hannah Hartman's (Risk factors for iatrogenic opioid dependence: An Australian perspective, 2015, AMSJ Volume 6, Issue 2) previous degree was incorrectly listed. Her previous degree was a Bachelor in Biomedicine at the University of Melbourne.

Student surgical societies in Australia and New Zealand: Do they play a role in early surgical exposure and streaming?

Dr. Kilian Brown
BBiomed, MBBS
Royal Prince Alfred Hospital
University of Sydney

Kilian is an intern at Royal Prince Alfred Hospital, Sydney, and past president of the Sydney University Surgical Society.

Vincent An
BSc (Adv)
University of Sydney

Vincent An is student currently undertaking an MD/MPhil at the University of Sydney. He is the current Vice-President of the Sydney University Surgical Society.

Nathalie Rasko
BSc (Adv)
University of Sydney

Nathalie Rasko is a third year medical student at the University of Sydney, and current President of the Sydney University Surgical Society (SUSS). She completed a Bachelor of Science (Advanced) in 2013 and is also currently undertaking a Master of Philosophy (MPHIL) in oxidative signalling and cardiovascular disease at the Kolling Institute of Medical Research.

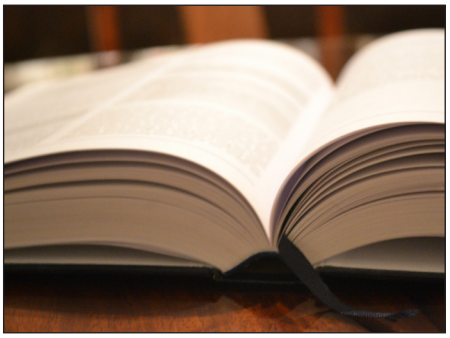
Paul D Morris
MBBS BE(Hons) MEngSci
Royal Prince Alfred Hospital
University of Sydney

Paul Morris completed his MBBS at the University of Sydney in 2015 and started working as a Junior Medical Officer at the Royal Prince Alfred Hospital in January 2016. Prior to undertaking medical school he studied engineering and worked as a software developer and business process engineer in New Zealand and London. His area of interest is general surgery; outside of medicine he enjoys travel and skiing.

In recent years, there has been an increase in the number and activity of student surgical societies and interest groups in Australian and New Zealand medical schools. To remain competitive, the modern medical student seeks out opportunities for additional surgical research and takes on extra-curricular activities, in addition to their medical studies. This has occurred in the context of increasingly busy curricula and concerns about the reduction in time devoted to structured surgical teaching in medical schools. [1] Most recently the introduction of Doctor of Medicine (MD) programs at several Australian universities, where the qualification of the medical graduate no longer includes a Bachelor of Surgery, reflects a transition whereby surgical teaching now takes place largely in expensive postgraduate courses. Medical training in general is lengthening whilst the number of graduates is increasing and the competition for jobs continues to heighten. In this setting, student surgical societies are becoming more active, and will likely play an increasingly important role in facilitating early exposure to surgery during medical school. [2]

Discussion about the length of general medical and specialty training in Australia and New Zealand continues and several authors suggest there is room for reduction. [3,4,5] It has been proposed that early streaming of general practitioners and specialists from the senior medical student level, as seen in the US, should be considered as a way to potentially reduce the length of training without compromising its quality. [3,6,7] Development and implementation of change to training requires coordination and compromise between the various stakeholders, including universities, teaching hospitals, and medical colleges, which makes formal career streaming seem unlikely in the foreseeable future. But does this already happen informally at our medical schools? Throughout Australia, student surgical societies and interest groups help to facilitate early medical student exposure to both academic and clinical surgery. Already, medical students with an interest in surgery enrol in higher degrees by research in surgical areas, develop technical skills from an early level, complete extra professional courses, and take on leadership and advocacy roles in which they liaise with university faculties, Health Education and Training Institute (HETI), Royal Australasian College of Surgeons (RACS), and other professional bodies. Although there are no guarantees for these surgical-hopefuls, our surgical societies do help to facilitate early streaming albeit in an informal way and at the initiative of the student.

The Sydney University Surgical Society (SUSS) was established in 2006 with the aims of promoting the development of the nine surgical competencies outlined by the Royal Australasian College of Surgeons, facilitating communication between students and surgeons, and providing educational opportunities for students. [8] These goals are achieved by organising student grand rounds, surgical skills tutorials, a journal club, advocating at faculty meetings and working with academic surgeons to facilitate student research. SUSS attempts to ensure early exposure for all students by running surgical career events targeted particularly at students in years one and two, such as the annual 'Introduction to Surgery: SET & Beyond' lecture which consistently attracts over 200 students. Many students are enrolled in concurrent honours, masters,



and PhDs programs in surgical areas and the academic output is high. Academic surgery is encouraged through a monthly journal club meeting and our relationship with the new Institute of Academic Surgery at Royal Prince Alfred Hospital, where the SUSS President sits on the advisory board. A RACS-accredited eight week intensive anatomy by whole body dissection course is run in the elective period at Sydney Medical School and has become an important way for surgically-inclined students to identify themselves and develop their skills at an early stage. [9] Most importantly, medical students who have been involved with SUSS and related activities can progress through medical school and graduate with a competitive set of skills, knowledge, and insight into the training that lies ahead.

The Surgical Interest Network (SurgIN) is a subcommittee of the Australian Medical Students' Association that coordinates student surgical societies and interest groups across Australasia. Broadly most of these groups have a similar focus on extra-curricular skills sessions and seminars in clinical surgery, although approaches and philosophies vary. In addition to SUSS, other student surgical groups in New South Wales include the

UNSW Surgical Society, Surgical Society of Notre Dame Sydney, Surgical Association of Western Sydney, University of Wollongong Surgical Interest Group, University of New England Surgical Society, and Newcastle University Surgical Society. There has been increasing cooperation and shared events between these NSW groups, most recently coming together to organise and compete in the Golden Scalpel Games Student Edition (previously the NSW Students' Surgical Skills Competition) with sponsorship from RACS and HETI. [10] Organisational structure or models will necessarily vary, as surgical societies must be run within the confines of their University's bylaws and regulations; particularly regarding whether they are part of their university's student union, a sub-division of their medical society, or a stand-alone entity. However, communication and cooperation between surgical societies across Australasia has allowed them to learn from each other and gain access to innumerable opportunities such as conferences, seminars, skills workshops, and networking events to maximise engagement and exposure.

In the face of reduced surgical teaching at medical schools, surgical societies in Australia and New Zealand will play an increasingly important role in promoting and fostering surgery and it is critical that they are well run. A society must present themselves as a professionally oriented and academically productive group of students to ensure support from their medical faculty and input from surgeons.

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None declared.

Correspondence
K Brown: kilian.brown@sydney.edu.au

References

[1] Truskett P. Surgeons of the future: where will they come from? *ANZ J Surg* 2014; 84: 399–400
[2] Dolan-Evans E, Rogers GD. Barriers for students pursuing a surgical career and where the Surgical Interest Association can intervene. *ANZ J Surg* 2014; 84: 406–11.
[3] Dowton SB. Imperatives in medical education and training in response to demands for a sustainable workforce. *MJA* 2005; 183: 595-598
[4] McNamara S. Does it take too long to become a doctor? Part 1: Medical school and prevocational training. *MJA* 2012; 196: 528-530
[5] McNamara S. Does it take too long to become a doctor? Part 2: Vocational training. *MJA* 2012; 196: 595-597
[6] Taylor TKF. Changes to the University of Sydney medical curriculum. *MJA* 2008; 189: 414-415.
[7] Taylor TKF. Training doctors – too long in the cellar? *MJA*
[8] Sydney University Surgical Society (SUSS). About Us [Internet]. NSW (Australia) 2015. Available from: http://surgsoc.org.au/about-suss/
[9] Ramsey-Stewart G, Burgess A, Hill D. Back to the future. Teaching anatomy by whole body dissection. *MJA* 2010; 193: 668-671
[10] Golden Scalpel Games Student Edition [Internet]. NSW (Australia) 2015. Available from: http://www.ssscomp.org

Why should students write a global health case report?

Manasi Jiwrajka
Final Year Medicine (Graduate)
University of Queensland

Manasi is a student editor for BMJ Case Reports, studying medicine at the University of Queensland. She is also pursuing a concurrent MPhil at the Queensland Institute of Medical Research, studying glioblastoma multiforme. She has a previous degree in neuroscience from Vassar College in the US, and spent a year at University College London pursuing biomedical science and international health. She is interested in gliomas, global health, medical ethics, writing, and travelling.

Dr. Seema Biswas
General surgeon and editor in chief of BMJ Case Reports

Dr Seema Biswas studied medicine in London and trained in surgery in the UK and South Africa. She works as a field surgeon for the International Committee of the Red Cross and teaches surgery and global health. The global health case report was developed by the editorial team at BMJ Case Reports and has been validated as an educational tool in undergraduate medical education.

Introduction

We often see a case report about something absolutely fascinating - that one condition found on that page of Robbins [1] that we vaguely remember - but we don't often hear about a global health case report. In this short piece, we offer a tangible definition of global health, discuss the concept of a global health case report, [2] and make the case for why we, as medical students, should be writing these.

Defining Global Health

Most medical students find global health quite nebulous and so overarching that it does not necessarily fit with our idea of treating the individual patient in front of us. Global health seems to be for health policy makers rather than doctors. It seems far-fetched that as medical students we could have any effect on how patients live and the determinants of health, especially when we hear that global health concerns only low-income countries. There are two main reasons for this perception: one, a single definition of global health is not universally accepted; and two, worldwide, there remain profound differences in global health education. [3,4]

We propose that the 'global' in global health does not refer so much to 'overseas' or 'over there', as it refers to 'over here'; indeed, the real definition of 'global' in global health is 'health everywhere'. Even if a doctor, or any health professional, trains and works in their home town, never travelling beyond the limits of what they see every day, they will inexorably meet and treat someone of a different socioeconomic group, ethnicity, religion, race or language. Dealing at an individual level with patients who have become ill because they do not have a safe and clean environment in which to live, have nowhere to sleep, are exploited at work, or vulnerable at home means that those international problems over there for doctors without borders who travel all over the world, are right here for all doctors whose routine practice is right at home. Global health has much in common with public health in that aspects of global health address populations and changes may be implemented at population levels through local, national, and international governments. However, 'global' also refers to all aspects of health, i.e. a holistic approach essential to exploring and taking on the real causes of disease, the social determinants of health. This focuses our attention and intervention on the patient in front of us and what we need to do to prevent them from becoming ill again. [5] Global health is, therefore, health that affects every patient we treat, and their families, at a very personal and individual level.

The British Medical Journal Case Reports has published several global health case reports. Here we summarise two examples. In one case, a 2 year-old boy with 40% burns to his head and arms presented to an eye clinic in Turkey one month after his injury. By then, he was blind. [6] The author was moved to write because of the severity of the burns, the preventable causes of house fires, the dire need for equitable access to medical care, and the devastating consequences for the child. Perhaps on their own, each of these global health problems is too large to contemplate and tempting to ignore, but no one can ignore the clinical history of this child, and the authors were moved to investigate the lack of health resources and the social circumstances responsible for this lamentable outcome. The authors offer solutions in healthcare that seem very practical. Certainly, they provide the evidence that these changes are necessary.

Another case report explores the link between HIV/AIDS and Jogini culture of sexual exploitation. [7] The case is of a 32 year-old woman who, since the age of seven, has worked as a Jogini. It's a powerful story. We read of her first sexual encounter, teenage pregnancy, and total isolation. The global

health issues discussed by the authors include the consequences to health of profound social inequalities, gender inequality, criminal prostitution, and the scourge of HIV/AIDS amongst the most vulnerable of society. The author remains focussed on the patient's life and we read with dismay about her relationship with her son and the likelihood that his life will also be in poverty, without the education or opportunities to change a course that seems bitterly unfair. These global health problems, overwhelming and pervasive, are poignantly real and move us to act. The doctors and medical students submitting global health case reports are describing the lives of patients they see every day, and are moved to write because tackling these problems head-on is essential to making their patients healthy again, keeping them healthy, and helping people just like them. Enormous, ethereal global health problems are now individual and personal; indeed, they are tangible and very much inside our consulting room or hospital ward.

Why are these case reports useful? Why should we write these?

1. To look at the root causes of the illness. Let's think about why our patient is really ill. While a discussion of the social determinants of health may switch off an audience over-

awed by the magnitude of these issues, with a patient in front of them no doctor or medical student can ignore the causes of illness and the factors limiting the effectiveness of medical therapy for that patient.

2. To learn about society, economics, politics, cultures, and how they affect our patients. These help us understand our patients better and facilitate all contact with them. These case reports show how individuals deal with illness, how they seek out medical assistance, and what is available for them. By writing these case reports, we also understand better how healthcare priorities are set and decided.

3. Global health is an in depth analysis of the causes of ill-health, perceptions of health and disease and how healthcare is provided. This is relevant not simply to general practice or public health, but to all medical specialties.

4. To learn global health. Global health case reports help both the students and faculty discover together the global burdens of disease, the social determinants of health, and factors essential to equity in access to healthcare.

5. To publish and share patient cases. Publishing an excellent piece of work that speaks for your patient and society in general, and promotes peer discussion of these issues.

6. To create an evidence base. Every time a global health case is published, we provide more evidence of what our patients need, the reality of their lives, and the care that they received. No one is closer to patients than we are in the medical profession [3]; we have a responsibility to advocate for our patients, and we can do this by writing their stories. It builds evidence that these problems are real and that they cannot be neglected.

7. To create change. We publish and keep publishing in order for the medical community and the public to read and demand change. Change is possible – doctors are responsible for seat belts, helmets, and much legislation that has saved millions of lives. [8,9]

For the audience reading these case reports, global health becomes personal and individual. The case reports are a call to action to work for our patients, and an inspiration to look beyond a pharmacological prescription to the underlying social determinants of health and disease. Ultimately, we must look through the global health lens because, as Virchow famously said:

Medicine is a social science and politics is nothing else but medicine on a large scale. Medicine as a social science, as the science of human beings, has the obligation to point out problems and to attempt their theoretical solution; the politician, the practical anthropologist, must find the means for their actual solution. [10]

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Correspondence
M Jiwrajka: manasi.jiwrajka@uq.net.au

References

[1] Robbins SL, Kumar V, Abbas AK, Fausto N, Cotran RS. Robbins and Cotran pathologic basis of disease. Philadelphia: Elsevier Saunders; 2005.
[2] BMJ case reports; (Journal, Electronic). www.bmjcasereports.com
[3] Liu Y, Zhang Y, Liu Z, Wang J. Gaps in studies of global health education: an empirical literature review. Glob Health Action 2015;8(1):25709.
[4] Rowson M, Willott C, Hughes R, Maini A, Martin S, Miranda JJ, et al. Conceptualising global health: theoretical issues and their relevance for teaching. Global Health. 2012;8(36).
[5] Marmot MG. Status syndrome: a challenge to medicine. JAMA. 2006;295(11):1304-7.
[6] Istek, Ş. The devastating effects a fire burn in a child. BMJ Case Rep. 2015 Jun 8;2015. pii: bcr2014206663. doi: 10.1136/bcr-2014-206663
[7] Borick J. HIV in India: the Jogini culture. BMJ Case Rep. 2014 Jul 11;2014. pii: bcr2014204635. doi: 10.1136/bcr-2014-204635[8] Bike helmets a no-brainer, say surgeons. The Australian Doctor [Internet]. 2015 Aug 13 [cited 2015 Oct 09]; Available from: http://www.australiandoctor.com.au/news/latest-news/bike-helmets-a-no-brainer-say-surgeons.
[9] Children's doctors urge national 20mph limit in built-up areas. The Guardian [Internet]. 2014 Nov 19 [cited 2015 Oct 09]; Available from: http://www.theguardian.com/uk-news/2014/nov/18/children-doctors-20mph-speed-limit.
[10] Virchow R. Die medizinische reform 2. Medicine and Human Welfare. 1949.

Why all medical students need to experience research

Prof. Christine Bennett AO
MBBS, FRACP
Dean, School of Medicine, Sydney,
The University of Notre Dame Australia

Professor Bennett is the Dean of Medicine at the University of Notre Dame Australia (Sydney); Chair of Research Australia – an alliance of over 170 member organisations promoting health and medical research in Australia; The Sydney Children's Hospitals Network in NSW; and the Bupa Health Foundation Steering Committee.

Medical students are very busy. The demands of studying medicine are extraordinary. Why then is it so important, on top of all there is to learn, to bother engaging in health and medical research? It is particularly important to consider this question at a time when, nationally and internationally, medical schools are including a research project as either a requirement of their program or a highly encouraged option. In fact, the Australian government is now supporting research by medical students with a specific category of scholarship funding from the National Health and Medical Research Council (NHMRC) available to students undertaking in a combined MBBS/PhD or MD/PhD program. [1]

As a Dean of Medicine, and passionate advocate of health and medical research (HMR) in Australia, I support the inclusion of research in medical programs. Research training and experience are not just 'nice to have' but a 'must' for our doctors of the future. Increased research training in medical programs is beneficial for a student's professional pathway, their evolving practice and, most importantly, for the health of the patients and communities they serve. [2,3]

Demonstrated research experience at medical school is increasingly important in obtaining positions in training programs post-graduation. [4] Recognition of the importance of HMR in developing and applying the skills and knowledge acquired in their medical studies has seen many of the specialist colleges including research training and productivity (for example publications) in their approach to selection of trainees. Competition for vocational and advanced training places is fierce, and a professional resume that includes research productivity and qualifications is and will continue to be important. Some colleges may even move to requiring a PhD for entry into advanced training.

A research experience may be the first time a student has had to write and record what they do, think, and find coherently, concisely and precisely. This can contribute to developing lasting habits of critical thinking. In a landmark and classic essay, C. Wright Mills commented that there was never a time he was not thinking, reflecting, analysing, and writing – he was always working on an idea. [5] This is the mindset that research can build up, and this is surely the mindset we want in clinical medicine and population health, where continuing critical appraisal of new evidence and engagement with new ideas is vital. In addition to stimulating ongoing interest in learning, this intellectually curious mindset contributes to a sense of personal satisfaction and eagerness to engage in discovery and learning as part of a team. [3,6] Research achievements are rarely made by individuals in isolation. Developing a mindset of critical inquiry in individuals and teams clearly encourages research productivity in grants and publications in the longer term, [3] which can 'future-proof' careers at a time when research performance is important in professional esteem and progression. Even more importantly, involvement in research appears to improve clinical practice. Research-active healthcare providers appear to provide better care and achieve better patient outcomes, [7] making the investment of time in research training for medical students potentially very important to building a healthier society in the long term. Given the potential benefits to early career clinicians and to patients, it is important to expose recent medical graduates to research as well, and successful postgraduate training programs are also taking steps to include research training. [3,8]

So, what is the best way for medical schools and postgraduate training programs to provide research training that maximises these benefits? It is clear from the literature that the most important thing is to have protected time to pursue research. Whether the research is a programmed experience as part of a course (as is increasingly the case), or something pursued independently by the individual student or trainee, giving as much time as possible is key to getting the best quality outcomes. For recent graduates, hospitals need to allow time to do research. [8] For students, time should be set aside within the program. [4] Students and trainees also need to be mentored by experienced researchers to get the best results. [3] Research experiences for students and trainees that combine mentorship and protected time can deliver the biggest benefits to our future clinical leaders and society as they are most likely to result in high quality outputs that are published and improve knowledge and practice. Where possible, trainees without research degrees should try to enrol in these at the same time as pursuing their research experiences, through a university that offers flexible research training and options to

submit theses by publication, as earning a research degree such as a PhD is increasingly becoming a prerequisite for obtaining research funding that can support a clinical research career.

In summary, more than ever before, being a doctor in the 21st century is a career of lifelong learning. The combination of continued, rapid growth in knowledge and advancing technology bringing that information to your fingertips, have brought both a richness to the practice of medicine as well as a challenge. There is a growing appreciation that researchers make better clinicians. Research exposure increases understanding of clinical medicine; facilitates critical thinking and critical appraisal; improves prospects of successful application for post graduate training, grants, and high impact publications; develops teamwork skills; and increases exposure to the best clinical minds. The government is lifting its investment in health and medical researchers like never before. The establishment of the Medical Research Future Fund by the Australian Government, for example, offers the promise of continued durable investment in HMR and innovation, and the NHMRC's substantial investment in research training scholarships for current students and recent graduates signals the Government's commitment to developing clinician researchers for the future.

I encourage all students to make the most of research opportunities in medical school and beyond, not only for the personal and professional benefits, but in contributing to the health of their patients and to the Australian community.

Correspondence
Assistant to Prof Christine Bennett AO,
S Jones: susan.jones@nd.edu.au

References

[1] NHMRC Funding Rules 2015: Postgraduate Scholarships – 6 Categories of Award – 6.2. Clinical Postgraduate Scholarship. 2015. https://www.nhmrc.gov.au/book/6-categories-award-3 (accessed Nov 2015).

[2] Laidlaw A, Aiton L, Struthers J, Guild S. Developing research skills in medical students: AMEE guide no. 69. *Med Teach*. 2012;34:754–71.

[3] Lawson PJ, Smith S, Mason MJ, Zyzanski SJ, Stange KC, Werner JJ, Flocke SA. Creating a culture of inquiry in family medicine. *Fam Med*. 2014;46(7):515–521.

[4] Collier AC. Medical school hotline: importance of research in medical education. *Hawai'i Journal Med Public Health*. 2012;71(2):53-6.

[5] Mills, CW. On intellectual craftsmanship. In: Seale, C. Editor. Social research methods: A reader. London: Routledge, 2004.

[6] von Strumm S, Hell B, Chamorro-Premuzic T. The hungry mind: intellectual curiosity is the third pillar of academic performance of university. *Perspect Psychol Sci*. 2011;6(6):574-88.

[7] Selby P, Autier P. The impact of the process of clinical research on health service outcomes. *Ann Oncol* 2011;22(Suppl 7):vii5-vii9.

[8] Chen JX, Kozin ED, Sethi RKV, Remenschneider AK, Emerick KS, Gray ST. Increased resident research over an 18-year period - a single institution's experience. *Otolaryngol Head Neck Surg*. 2015;153(3):350-6.

Looking to the future: Students and academics leading the charge in publishing innovation

Dr. Virginia Barbour
MBBS
Professor, Griffith University

Dr Virginia Barbour is the Executive Director of the Australasian Open Access Strategy Group, Chair of the Committee on Publication Ethics (COPE), and a Director of the World Association of Medical Editors (WAME). Dr Barbour was one of the three founding editors of PLOS Medicine and became Medicine and Biology Editorial Director of PLOS in 2014.

As a medical student (a long time ago, admittedly), peering into the far future to wonder what publishing was going to look like when I graduated and practiced was very far down my list of priorities, if it ever crossed it.

But, as the Australian Medical Student Journal's Editor in Chief recently described in the Australian Open Access Support Group (AOASG) blog [1], medical students today are already immersed in a rapidly evolving world of publishing, which is changing the way that they access and publish information, via journals such as the Australian Medical Student Journal. [2]

There is even more profound change going on and unlike for much of the recent history of publishing, which has been led by publishers, many for profit, the next wave is being led by academics, even students.

How has this happened? The underlying technology driving all this is, not surprisingly, the Internet. The Internet is 25 years old [3] and for most university students and younger, it was essentially always there. Even for academics in their 30s and 40s, it was there while they grew up. As well as the technology, the Internet signalled a change in mindset – academics were not just consumers of the scholarly literature, they were generators of it even in ways that could lie outside the scholarly publishing system.

So in my mind, this enabling technology also led to a profound shift in immediate behaviour, such as blogging, but also to changes in behaviour for solving problems.

What has this behaviour change led to in scholarly publishing? Several examples illustrate this well.

First, Open Access (OA) publishers such as Public Library of Science (PLOS) [4] came about as a result of academics seeing a need to make the research literature open – that is, free and shareable [5] - and starting their own publishing houses.

A second example came about when an academic needed to have a place to deposit and share his figures and data, but was not yet ready to incorporate them into a full paper. Hence, Figshare [6] was founded.

Third was when a group of medical students saw the need to get access to papers that were not OA and also to catalogue the extent of this need. Thus, the OA button [7] came into being.

Fourth, two separate groups of academics, one in New Zealand and one in Australia, saw a problem with researchers not getting credit for peer review. Publons [8] and Academic Karma [9] took up this challenge.

Fifth, and even more relevant to medical publishing, innovation has been used to specifically improve the reliability of the medical literature. This move started in the 1990s when editors and trialists began to explore how to better report research with low-tech solutions, such as checklists, to improve trial reporting. [10] Two developments have led on from that. One of these developments is known as a 'threaded publication' and aims to link all parts of a medical study, from protocol to trial report, to post marketing surveillance. [11] The other, following on from the AllTrials [12] initiative to get all trials registered and all results reported, is Open Trials [13], which will have a fully linked and searchable database of all trials, linked to their authors, institutions, and funders.

This growth of innovation – of academics seeing a need, designing a solution, and then building it, is now, I believe, fundamentally woven into the structure of new publishing, so much so that there is now a site that is cataloguing all these innovations [14] (not all of which are researcher-led) and this is a movement that can only grow.

What underpins the successful publishing enterprises now is, I believe, three things. First, they are built on the principle of openness - the data around the innovation itself, as well as the content is openly available, as is, increasingly, the code. Second, is the need for solid principles to build the innovation into something that works – the equivalent of making sure a revolution has functional water systems and drains. The third is the notion of interoperability – of seamless linking of all parts of the innovation with other innovations, for example, people through their ORCiD identifiers [15], trials through their registration numbers, [16] and papers [17] and funders [18] through their own unique identifiers.

In the end, all these innovations are working in one direction – to a more open, transparent and reproducible academic literature. It is not going to be perfect at every step but at least if there are novel ideas, built on transparent infrastructure, we can ensure that what is built will allow the next generation of innovation to be built upon them in turn.

Correspondence
V Barbour: eo@aoasg.org.au

References

[1]http://aoasg.org.au/2015/11/24/open-access-and-why-it-matters-to-medical-students/
[2] http://www.amsj.org/
[3]http://www.ft.com/cms/s/2/f3fe9c4a-4bd1-11da-997b-0000779e2340.html
[4] https://www.plos.org/
[5] http://aoasg.org.au/what-is-open-access/
[6] http://figshare.com/
[7] https://openaccessbutton.org/
[8] https://publons.com/
[9] http://academickarma.org/
[10] http://www.equator-network.org/
[11] http://www.trialsjournal.com/content/15/1/369
[12] http://www.alltrials.net/
[13] http://opentrials.net/
[14] https://innoscholcomm.silk.co/
[15] http://orcid.org/
[16] http://www.anzctr.org.au/
[17] https://www.doi.org/
[18] http://www.crossref.org/fundref/

Mental health in the medical profession: Support for students

Dr. Stuart Dorney
MBBS, FRACP
Medical Director, Medical Council of NSW

Dr. Greg Kesby
MBBS, BSc Hons, PhD, DDU FRANZCOG CMFM
President, Medical Council of NSW

Dr Dorney has extensive experience in clinical practice and medical governance as a former specialist in paediatric gastroenterology and former Director of Clinical Governance with the Sydney Children's Hospitals Network.

Dr Kesby is a subspecialist in maternal fetal medicine. He is currently a senior visiting medical officer in the Department of High Risk Obstetrics and Fetal Medicine at the Royal Prince Alfred Hospital in Sydney, a Director of the Australian Medical Council, and the immediate past Chair of the New South Wales Medical Board of Australia.

Much has been reported about the prevalence of mental health concerns amongst medical students and doctors, both internationally and in Australia.

In 2013, beyondblue released the results from its national survey of Australian medical students and doctors. Among the survey's key objectives was to better understand the issues associated with the mental health of Australian medical students and doctors, and to increase awareness of these issues across the profession and the wider community. [1]

The survey included questions about general mental health status, substance use, suicidal ideation and self-harm, workplace and life stressors, levels of burnout, impact of mental health symptoms, treatment and coping strategies employed to address mental health symptoms, barriers to seeking treatment and support, and attitudes regarding doctors with mental health conditions. The survey was completed by 1,811 (27%) of the 6,658 students and 12,252 (28.5%) of 42,942 doctors sampled. [2] Most of the students who participated were aged 22-25 years old (45.1%), female (62.6%), non-Indigenous (98.8%), located in a metropolitan region (66.5%), and worked part-time on average 12 hours per week (50%). [2] The responses from the survey were compared with the responses from the National Survey of Mental Health and Wellbeing, conducted by the Australian Bureau of Statistics in 1997. [2]

Bqeyondblue found that very high levels of psychological distress was three times higher in medical students than in the general population (9.2% and 3.1% respectively), and two times higher than levels reported by interns (9.2% and 4.4% respectively). [2] Students also reported higher rates of burnout and emotional exhaustion, with the highest rates being reported by females. [2]

When it came to perceptions about mental health within the medical profession, a high proportion of respondents held the view that doctors who had a mental health issue were stigmatised as a consequence, a finding particularly prevalent amongst those respondents who had been diagnosed with a mental illness themselves. Students with a current mental health diagnosis, compared with those not currently diagnosed, were more likely to report they felt doctors with with a history of mental illness were less competent (52.4% and 38.2% respectively). Furthermore, 42% of students with a current mental health diagnosis felt that doctors tended to advise colleagues not to divulge their history of depression or anxiety disorders, compared to 22.6% of students who were not currently diagnosed with depression or anxiety. [2] This finding is particularly disturbing and probably explains the considerable reluctance of some medical students and members of the medical profession to seek independent help for mental health issues, and instead pursue a pathway of self-diagnosis and self-treatment with its associated risks. Too often we see students and medical practitioners only first presenting for appropriate independent care when they are acutely unwell or in crisis. This is unnecessary and needs to change.

The Medical Council of New South Wales has published a guideline for self-treatment and treating family members, which encourages all medical practitioners (and students) to have their own, independent general practitioner and advises practitioners against self-diagnosis or initiating treatment for themselves or their family members. [3] The Medical Board of Australia's Good medical practice: a code of conduct for doctors in Australia also advises medical practitioners who know or suspect they have a health condition or impairment that could adversely affect their judgement, performance, or patients' health not to rely on their own assessment of the risk they pose to patients and to instead consult their doctor about whether, and in what ways, they may need to modify their practice. [4]

Just as we would recommend to patients, it is important for medical students and doctors to adopt a healthy lifestyle through a balanced diet and regular exercise. It is also vital to ensure that immunisations are kept up to date, alcohol is consumed within the National Health and Medical Research Council guidelines, and that illicit drug use and prescription drug misuse is avoided. It is also helpful to have a strong personal support network and develop interests outside of medicine.

Dr. Stuart Dorney

Dr. Greg Kesby

Key to addressing health issues, including mental illness, is early intervention. Medical students should feel comfortable and be encouraged to seek independent, objective advice from a general practitioner as early as possible when mental health issues arise, and in providing care medical practitioners must endeavour to provide a non-judgemental and supportive environment that good medical practice dictates for all patients. In addition to seeking advice and treatment from a general practitioner, psychologist, or psychiatrist, there are a range of early intervention services and supports available to promote optimal care, including the various university health services, university medical facilities, beyondblue, Headspace, Lifeline, and the Doctor's Health Advisory Service, available in each state and territory.

Under the Health Practitioner Regulation National Law (NSW) (the National Law), impairment is one of the grounds under which a complaint or notification can be made about a student or practitioner. This often generates fear amongst students as to whether their mental health issues will exclude them from graduating and practising as a medical practitioner. However, it needs to be appreciated that the term "impairment" has a specific meaning under the National Law. It refers to a physical or mental impairment, disability, condition, or disorder (including substance abuse or dependence) that is linked to a student's capacity to undertake clinical training, or a doctor's capacity to practise medicine. [5] In some instances notification is mandatory.

While recent media reports and editorial columns have suggested that mandatory reporting laws in all states and territories excluding Western Australia may be a barrier to medical students and doctors accessing support and treatment for mental health problems, there is no reliable evidence to support such claims and no reason that this should be the case. The purpose of mandatory reporting is to act as a safeguard when medical students and doctors are unwilling or unable to seek help and manage any risk to public safety by compelling practitioners to raise serious concerns with the regulatory authorities. The threshold for making a mandatory notification about an impaired colleague is high. A practitioner treating a medical student or doctor is not automatically required to make a mandatory notification simply because they have a mental health issue. The National Law states it is only when a practitioner has formed a reasonable belief that a fellow practitioner has placed the public at risk of substantial harm in the practice of the profession because of their impairment that they are required to make a mandatory notification. [6]

Education providers also have an obligation to make a mandatory notification if they have formed a reasonable belief that a student undertaking clinical training has a health issue that may place the public at substantial risk of harm. The formation of a reasonable belief may well be influenced by factors such as whether the medical student is receiving appropriate treatment and advice or has made a voluntary notification. [6]

Medical students and doctors who believe they may have an impairment are encouraged to make a voluntary notification to the Australian Health Practitioner Regulation Agency (AHPRA). [6] For individuals with mental health issues who self-notify or who are the subject of a notification to AHPRA, there are remedial, non-disciplinary programs, which differ from state to state, that are designed to support students to remain in study and doctors to remain in practice whilst receiving appropriate treatment, provided it is safe for them to do so.

In NSW, the Medical Council's Health Program aims to protect the public while at the same time supporting medical students and doctors affected by health issues, including mental illness. Not everyone with a mental health issue who self-notifies or is the subject of a notification to AHPRA enters into the Health Program. Many are assessed as having a psychiatric illness that is under appropriate management, with the student/doctor having appropriate insight and support networks, and are therefore not considered to place the public at a significant risk of harm. That is, they are not considered "impaired" as defined in the National Law. Most of those who do enter the Health Program remain in practice or study, subject to conditions on their registration tailored to address their particular circumstances and designed to ensure public safety while they undertake treatment and rehabilitation. Participants remain under the care of their own treating practitioners, but also undergo independent reassessment by Council-nominated practitioners from time to time. Participants in the Health Program meet with Council delegates, usually at six to 12 monthly intervals, and as they progress in their rehabilitation and recovery, the conditions on their registration are gradually eased, until the Medical Council considers that they no longer require being under the Council's surveillance and consequently exit the Health Program. Whilst return to unconditional practice is a goal of the Program, some participants, for example those with a recurring psychiatric illness, may remain on the Program indefinitely, albeit with low level conditions and occasional review by the Council.

Many participants have had great success on the Health Program and have found the experience of significant benefit. For example, one participant, who had suffered from depression since his teenage years, found the Program's impact on his work and personal life to be "only positive". He said the Program encouraged him to set realistic work schedules, engage in activities outside the workplace, develop insight into the demands that he had previously placed on himself, and establish strong networks of support, both personally and professionally. Upon exiting, he said the Program had assisted him to successfully return to practice and engage in a "full and meaningful life". Another, who had been self-prescribing and suffering from depression, and by his own assessment entered the Health Program "at a time when I was out of control and rapidly heading towards disaster", found the Program forced him to confront his problems, encouraged him to maintain engagement with a treating psychiatrist, and enabled him to stop his prescription drug misuse and eventually return to full time work. He attributes his professional survival to his involvement in the Health Program and, at the time of exiting the Program, was receiving consistent feedback that he was excelling in his practice of medicine.

We are a caring profession, and we need to care for ourselves as well as each other. The Medical Council and other regulatory authorities encourage everyone with mental health issues, including medical students and doctors, to seek appropriate care – and seek it early. We recognise that some will be reluctant or unable to do so – through fear, or a lack of insight, or simply due to the lack of energy and initiative that may accompany their illness. You are therefore all encouraged to reach out to your colleagues if you suspect they may be suffering in silence. Offer those who appear to be troubled with life assistance in accessing appropriate support. Help them frame their thinking around whether they should self-notify to AHPRA. You can start by simply asking "are you okay?"

Correspondence

Medical council of NSW:
mcnsw@mcnsw.org.au

References

[1] beyondblue. Doctors' mental health program. https://www.beyondblue.org.au/about-us/programs/workplace-and-workforce-program/programs-resources-and-tools/doctors-mental-health-program (accessed Nov 2015).
[2] beyondblue. National mental health survey of doctors and medical students. 2013. http://www.beyondblue.org.au/docs/default-source/default-document-library/bl1148-report---nmhdmss-exec-summary_web (accessed Nov 2015).
[3] Medical Council of NSW. Guideline for self-treatment and treating family members. 2014. http://www.mcnsw.org.au/resources/1460/Guideline%20for%20self-treatment%20and%20treating%20family%20members%20PDF.pdf (accessed Nov 2015).
[4] Medical Board of Australia. Good medical practice: a code of conduct for doctors in Australia. http://www.medicalboard.gov.au/Codes-Guidelines-Policies/Code-of-conduct.aspx (accessed Nov 2015).
[5] Medical Board of Australia, Information on the management of impaired practitioners and students. 2012. http://www.medicalboard.gov.au/documents/default.aspx?record=WD12%2F7049&dbid=AP&chksum=Pzr054PF7tcB6ZQnesHKvA%3D%3D (accessed Nov 2015).
[6] Medical Board of Australia, Guidelines for mandatory notifications, http://www.medicalboard.gov.au/Codes-Guidelines-Policies/Guidelines-for-mandatory-notifications.aspx (accessed Nov 2015).

Systematic review article: Evidence for interventions to reduce the incidence of abusive infant head trauma

Hannah Royster
Fifth Year MBBS
James Cook University

Hannah Royster is a 5th year medical student at James Cook University in Australia. She is interested in paediatric health and particularly child injuries. Hannah is supported by a Remote Area Medical Undergraduate Scholarship. Upon graduating, she plans to work in rural north Queensland.

Background: Abusive Infant Head Trauma (AIHT) is preventable, but there are few reviews of interventions to prevent AIHT. In the Australian health system context, only one review of AIHT was found. Its primary focus was to raise awareness of AIHT, detailing AIHT incidence and outcomes, but only briefly touching on prevention. [1] This literature review attempts to fill this gap by providing the findings of a systematic search of available studies of AIHT prevention programs and approaches at the primary, secondary, and tertiary level, which may be applicable in Australian settings.
Methods: International peer-reviewed journal articles were systematically searched via MEDLINE-Ovid and PubMed databases. All papers that were not original research and were not published after the year 2000 were excluded from this review. Original research was further classified into intervention research, descriptive, and measurement research. The quality of intervention research studies was assessed using two assessment tools: EPHPP (quantitative studies) and CASP (qualitative studies).
Results: The search found 50 papers. Thirty-two did not meet inclusion criteria, leaving a total of 18 original research papers. Eight were intervention research (three strong, one moderate, and four weak), ten were descriptive research, and there were no measurement studies.
Conclusion: The key to AIHT prevention is through universal primary prevention, with education increasing knowledge in parents and healthcare practitioners. Of the studied programs, the Period of PURPLE Crying Program© has been shown to be the most effective. However, further studies are required to assess the relevance of this program in Australian settings.

Background

Abusive Infant Head Trauma (AIHT) has significant morbidity and mortality outcomes. [2,3] Violent, manual shaking of an infant causes rapid and repetitive acceleration-deceleration and rotation of the head, leading to vascular and neural injuries. [2] Neurologic disability occurring in survivors can include cognitive, motor, visual, and behavioural disturbances. [2,4-6] Infants may also present with variable fractures including fractures of long bones, ribs, or vertebrae. [5] Identifying injuries of AIHT can result in children being removed from parents, loss of parental rights, and imprisonment. [4] In Australia, AIHT incidence has been estimated as 29.6 cases per 100,000 infants; this is based on hospitalised cases only. [3]

The peak incidence of AIHT occurs in the second month of life and corresponds to the normal development of increased crying in the infant. [7,8] Prolonged and inconsolable crying is reported as the most common trigger. Parents are the most common agents of infant shaking. [4,5,7,9] Therefore, AIHT is a good candidate for the development of a prevention strategy, with parents being the risk group and crying being the stimulus.

Evidence indicates that AIHT is preventable. [2,9-14] Efforts to find effective prevention strategies have increased with the growing recognition of AIHT's clinical symptoms, its prevalence, and devastating consequences. [4] AIHT prevention strategies include primary, secondary, and tertiary methods. [9] By systematically searching and providing a summary of available research, this literature review aims

to highlight what we do and do not know about AIHT prevention thereby increasing the awareness of AIHT in medical professionals and encouraging implementation of prevention programs in Australian healthcare settings.

Methods

International peer-reviewed journal articles were systematically searched via MEDLINE-Ovid and PubMed databases using the search terms: "shaken baby syndrome", "shaken baby syndrome prevention", "infant abusive head trauma", and "period of purple crying program". Article titles and abstracts were searched for AIHT prevention interventions. This search resulted in 50 articles, which were further analysed and classified. All review articles, program descriptions, discussion papers, commentaries, case reports, and literature published prior to the year 2000 were excluded from the search results. Original research published from 2000 was included in the review. The start date designated for the search was determined by the timeframe when prevention strategies were developed and researched (in the early 2000s). [9]

The quality of intervention research was then analysed using the Effective Public Health Practice Project assessment tool (EPHPP) for quantitative research, [16] and the Critical Appraisal Skills Programme tool (CASP) for qualitative research. [17] Consistent with the purpose of the appraisal tools to assess the effectiveness of public health programs and interventions, the quality of only intervention research studies that evaluate what works was assessed. The EPHPP Quality Assessment Tool sections A to F (A. selection bias; B. study design; C. confounders; D. blinding; E. data collection methods; F. withdrawal and drop-outs) were coded strong, moderate, or weak according to the rating scale of the EPHPP dictionary. For qualitative studies, the CASP quality assessment tool was used to assess the clarity of study objectives, methodological quality, research design, data collection and analyses, ethical considerations, clarity of the statement of findings, and the value of the research. To assess the study quality of those using mixed-methods study design, the qualitative and quantitative components were assessed separately using both of the aforementioned tools.

Results

The search resulted in 50 articles. Of these, 32 were excluded as not being original research published after the year 2000, leaving a total of 18 original research papers. Of these, only 8 were intervention research studies, 10 were program descriptions, and there were no measurement research studies (Figure 1).

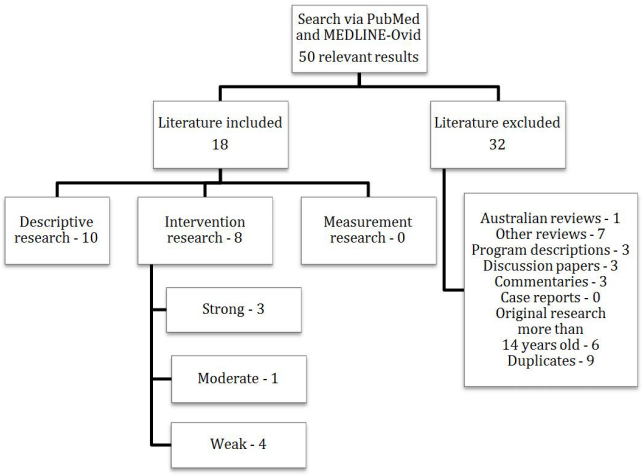

Figure 1. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of search results. This diagram shows the flow of information through the different phases of the systematic search. It depicts the number of articles found, included, and excluded, and the reasons for exclusions.*

Applying the quality appraisal criteria resulted in assessments of the eight intervention studies. Three were rated strong, one moderate, and four weak (Table 1).

Discussion

The review of the available literature indicates that there is little evidence about what works to prevent or treat AIHT, and more than half of the intervention studies were of poor quality.

Primary prevention studies

Two of the strong intervention studies were randomised controlled trials conducted by Barr et al. (2009a, 2009b). They were studies of a universal primary prevention program of AIHT that targeted parents of infants and newborns, and sought to prevent shaking from occurring through education. [10,11] The prevention program was called the Period of PURPLE Crying program (PURPLE©) produced by the National Center of Shaken Baby Syndrome (Utah, USA). [4,5,8-12,14] PURPLE© stands for Peak of crying, Unpredictable crying that has no apparent reason, Resists soothing, Pain-like face, Long-lasting crying for 30 to 40 minutes or longer, and Evening crying. [10,14] The program included a ten-minute DVD and an eleven-page coloured booklet, targeting all parents of newborns. It was an evidence-based program delivered in three instalments that used 25 years of research on normal infant crying to educate parents on crying characteristics, coping strategies, and the dangers of shaking. [14]

The two studies by Barr et al. found that administration of the PURPLE© materials had led to statistically significant improvements in maternal knowledge and behaviour relevant to shaking, compared to control material. Compared to mothers that received the control materials, for mothers who received the PURPLE© program, knowledge about normal infant crying was 5% higher in the first study and 6% higher in

Table 1. *AIHT intervention quantitative studies assessed using EPHPP.*

Study	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawal and drop-outs	Results
Barr et al. 2009a	Strong	Strong	Strong	Strong	Moderate	NA	Strong
Barr et al. 2009b	Strong	Strong	Strong	Strong	Strong	NA	Strong
Altman et al 2011	Moderate	Moderate	Weak	Weak	Moderate	Weak	Weak
Dias et al 2005	Strong	Strong	Strong	Strong	Moderate	N/A	Strong
Shephard et al. 2000	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Stewart et al. 2011	Moderate	Weak	Weak	Weak	Moderate	Weak	Weak
Goulet et al. 2009 (quantitative component)	Moderate	Weak	Weak	Weak	Weak	Weak	Weak
Russell et al 2008	Weak	Moderate	Weak	Moderate	Weak	Strong	Moderate

Table 2. *Qualitative studies assessed using CASP.*

Study	Study objectives	Methodological quality	Research design	Data collection and analyses	Ethical considerations	Statement of findings	Value of the research
Goulet et al. 2008 (qualitative component)	Clearly stated	Appropriate	Appropriate	Poor	Ethically approved	Clearly stated	Valuable

the second study. [10,11] Sharing information was shown to be higher in mothers who received the PURPLE© program than those who received the controls; there was an 8% increase in sharing descriptions of crying, 13% increase in advice about walking away when frustrated, and 13% increase in warnings about the dangers of shaking. [10,11]

The strong intervention study by Dias et al. indicated that a universal hospital-based parent education program regarding the dangers of violent infant shaking, delivered prior to an infant's discharge, significantly reduced the incidence of AIHT. All hospitals that provided maternity care in an eight-county region of western New York State were asked to provide parents with information describing the dangers of violent infant shaking and alternative responses to persistent infant crying. Program compliance was assessed by documenting the number of voluntary commitment statements signed by parents affirming their receipt and understanding of the materials, and returned by participating hospitals. Parents' recall of the information was assessed by follow-up telephone interviews conducted with 10% of parents, seven months after the child's birth. Finally, the regional incidence of AIHT was contrasted with the incidence during the six preceding years, and with statewide incidence rates during the study period. The study found a high voluntary compliance with the program, high recall of the information, and a decrease in AIHT by 47% amongst participating families during the six-year study, with no comparable decrease in the state. [9]

A weak retrospective descriptive study by Stewart et al., found that the three instalments of the PURPLE© program were crucial to AIHT prevention. Stewart et al. compared patients presenting with cases of AIHT that presented to the London Children's hospital (London, UK) from 1991 to 2010. Pre-trained maternity nurses delivered the program to parents. Stewart et al. found a 47% increase in the knowledge of nurses on crying, post-PURPLE© training, and 78% said it would be easy to incorporate into their daily work schedule. Instalment one involved the DVD and booklet. Stewart et al. (2011) stated only 6.3% of families did not receive the program in the hospital, and needed to be educated during their home visits. [14] Instalment two was a reinforcement of the message delivered by a health nurse home visitor, paediatrician, family doctor, or other health practitioner at a public health clinic. It involved simply discussing with the parents the concepts taught in the program and giving parents a copy of the program if they had not collected one at the hospital. Instalment three was a public education campaign. It provided information to the general public in an attempt to educate people in society more generally about inconsolable infant crying and the dangers of shaking. [10,11] Altman et al. conducted a weak intervention study showing that hospital-based parent education, delivered to all those with newborns, could significantly reduce the risk of sustaining an abusive head injury induced by shaking. [12] Further studies are required to gain evidence of the PURPLE© program's effects on reducing the incidence of AIHT in Australia.

Literature available on AIHT prevention programs other than PURPLE© was extremely limited. A moderate-strength study conducted by Russell et al. (2008), compared types of AIHT prevention material. [13] The results showed that material delivered digitally via DVD, particularly material demonstrating alternative behaviours, was more successful in transferring awareness than interventions that involved only a brochure. DVDs significantly increased the potential for improving the population's awareness of AIHT. This study was not specific for the period of PURPLE© crying program DVD, and suggests that digital footage that is Australian-focused may be utilised equally as effectively. [13] Parents watched the DVD in the hospital before taking it home with their newborn. The nurse recommended to parents that they review the materials at home, and share the information with other caregivers of their baby. [10,11]

In a weak intervention study, Shephard et al. found the "Don't Shake the Baby" education package was helpful to the majority of mothers; 49% said that they were less inclined to shake their babies after reading it, and 91% said they thought other parents should receive the same information. [18] The package involved brochures and cards with suggested coping strategies during inconsolable, frustrating crying, and information on the dangers of shaking; as well as television and radio public service announcements and posters containing information about AIHT. [18] These materials could be adapted to suit different language and cultural groups.

Goulet et al. analysed the adequacy and relevance of the Perinatal Shaken Baby Syndrome Prevention Program (PAIHTPP) based on parental and nurse feedback in another weak intervention study. [2] The PAIHTPP used educational cue-cards to increase knowledge about infant crying, triggering of caregiver frustration, and its potential progression to shaking, while suggesting coping strategies for frustration. [2] Findings indicated PAIHTPP to be relevant in all birthing institutions involved in the study. [2] The majority of birthing institutions reported increased knowledge about infant crying, anger, coping strategies, and AIHT. [2]

Other AIHT prevention programs that are available, which have not been evaluated, include programs specific for fathers, especially fathers in the military, prison and youth halfway houses, and programs specific for high school students. The programs are educational and contain appropriate language and imagery for the target audience. [19]

Secondary prevention studies

Secondary prevention programs target specific subsets of the population considered to be at higher risk for child maltreatment. [8] It has been found that an increase in parental or caregiver stress correlates with an increase in AIHT incidence. [2,14,20] Therefore, parents and carers categorised as being under stress can be targeted for secondary prevention programs. Parents who may be under increased stress include single parents, young parents, those that are drug-dependent, alcohol-dependent, have impulse disorders, control problems, low socioeconomic status, or isolated parents. [14,20] Stewart et al. indicated that geographical areas that may be at higher risk for AIHT should be targeted for extra advertising campaigns, specifically those delivered in instalment three of the PURPLE© program. [14] However, studies indicate that the focus of prevention should be primary and universal [10-13]; studies about secondary prevention programs were approximately 20 years old, and as such have not been included in this review. [21,22]

Tertiary prevention studies

Children who have been shaken and diagnosed with AIHT are targeted by tertiary prevention programs, which aim to prevent progression of injury and recurrence in the child affected and or other siblings. Diagnosis of AIHT is required before tertiary prevention can be implemented. Diagnosing AIHT is difficult due to its non-specific presenting symptoms and vague explanations made by perpetrators. [6] Reporting suspicion of shaking to departments of child protection can prevent further abuse to the child. [4,6]

According to research by King et al., the common clinical manifestations of AIHT are subdural effusion, retinal hemorrhages and cerebral oedema. [6] Cerebral oedema can be reduced through pharmacotherapy such as glucocorticoids, hyperosmotic agents, diuretics, and sedative-anesthetic agents to prevent progression of neurological damage. [15,23-25] Tertiary prevention through child protection case management is not specific to AIHT, but rather is managed like all traumatic brain injuries in children, through rehabilitation.

Conclusion

Literature on AIHT prevention is limited. Quality research in this area is needed because of the limited number of articles available, more than half of which are of limited quality. This review identified three qualitatively strong intervention studies, one moderate, and four weak, as well as ten program-description studies. These studies indicate that AIHT can be prevented through universal primary prevention techniques. These must be educational and ideally involve the use of a DVD in addition to written materials. Of the studied programs, the Period of PURPLE Crying Program© has been shown to be the most effective. Tertiary prevention programs through case management by child protection agencies aim to restore child function and prevent progression of neural damage through rehabilitation, and to prevent reoccurrence by legal investigation of the perpetrator. However, further studies are required to assess its impact on AIHT incidence. In particular, evaluation is needed of the relevance of the American-developed Period of PURPLE Crying program© in Australian settings.

This article is dedicated to Baby Joseph. Joseph did not receive any benefit from primary prevention efforts, and the effects of secondary and tertiary efforts to ameliorate the harm from his allegedly repeated shaking experiences have been limited and are ongoing. His prognosis is guarded, and a return to his premorbid level of function is unlikely. His case illustrates a great gulf between what is known about primary prevention and what is currently **practised as primary prevention** in most of Australia. Joseph's situation is sadly and predictably, not unique. Primary prevention programs may lead to better baby outcomes into the future.

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Conflicts of interest

None declared.

Correspondence

H Royster: hannah.royster@my.jcu.edu.au

References

[1] Liley W, Stephens A, Kaltner M, Larkins S, Franklin RC, Tsey K et al Infant abusive head trauma: incidence, outcomes and awareness. Aust Fam Physician. 2012;41(10):823.

[2] Goulet C, Frappier JY, Fortin S, Déziel L, Lampron A, Boulanger M. Development and evaluation of a shaken baby syndrome prevention program. JOGNN. 2009;38(1):7-21.

[3] Kaltner M. Abusive head trauma: incidence and associated factors in Queensland [PhD thesis]. Brisbane, Qld: University of Queensland; 2010.

[4] Christian CW, Block R. Abusive head trauma in infants and children. Pediatrics. 2009;123(5):1409-11.

[5] American Academy of Paediatrics: Committee on Child Abuse and Neglect. Shaken baby syndrome: rotational cranial injuries—technical report. Pediatrics. 2001;108:206–10.

[6] King WJ, MacKay M, Sirnick A. Shaken baby syndrome in Canada: clinical characteristics and outcomes of hospital cases. Can Med Assoc J. 2003;168(2):155-9.

[7] Talvik I, Alexander RC, Talvik T. Shaken baby syndrome and a baby's cry. Acta Paediatr. 2008 June;97(6):782–5.

[8] Barr RG, Trent RB, Cross J. Age-related incidence curve of hospitalized shaken baby syndrome cases: convergent evidence for crying as a trigger to shaking. Child Abuse Neglect. 2006;30(1):7-16.

[9] Dias MS, Smith K, Mazur P, deGuehery K, Li V, Shaffer M. Preventing abusive head trauma among infants and young children: a hospital-based, parent education program. Pediatrics. 2005;115(4):470-7.

[10] Barr R, Rivara F, Barr M, Cummings B, Taylor J, Lengua L et al. Effectiveness of educational materials designed to change knowledge and behaviors regarding crying and shaken-baby syndrome of newborns: a randomized, controlled trial. Pediatrics. 2009;123(3):972-80.

[11] Barr RG, Barr M, Fujiwara T, Conway J, Catherine N, Brant R. Do educational materials change knowledge and behavior about crying and shaken baby syndrome? A randomized controlled trial. CMAJ. 2009;180(7):727-33.

[12] Altman RL, Canter J, Patrick PA, Daley N, Butt N, Brand D. Parent education by maternity nurses and prevention of abusive head trauma. Pediatrics. 2011;128(5):1164-72.

[13] Russell BS, Trudeau J, Britner PA. Intervention type matters in primary prevention of abusive head injury: event history analysis results. Child Abuse Neglect. 2008;32(10):949-57.

[14] Stewart TC, Polgar D, Gilliland J, Tanner D, Murray G, Parry N et al. Shaken baby syndrome and a triple-dose strategy for its prevention. J Trauma Acute Care Surg. 2011;73(6):1801-7.

[15] Papangelou A, Lewin III JJ, Mirski MA, Stevens R. Pharmacologic management of brain edema. Current Treat Option N. 2009;11(1):64-73.

[16] McMaster University. Effective public health practice quality assessment tool for quantitative studies, 2008, McMaster University School of Nursing: Canada.

[17] Network, C.I. Critical Appraisal Skills Programme: Making sense of evidence about clinical effectiveness: qualitative research studies. 2010.

[18] Shepherd J, Sampson A. Don't shake the baby': towards a prevention strategy. Brit J Soc Work. 2000;30(6): 721-35.

[19] Bechtel K, Le K, Martin, KD. Impact of an educational intervention on caregivers' beliefs about infant crying and knowledge of shaken baby syndrome. Acad Pediatr. 2011;11(6):481–6.

[20] Keenan HT, Runyan DK, Marshall SW, Nocera MA, Merten DF, Sinal SH. A population-based study of inflicted traumatic brain injury in young children. JAMA. 2003;290(5):621-6.

[21] Olds D, Henderson CR, Chamberlin R, Tatelbaum R. Preventing child abuse and neglect: a randomized trial of nurse home visitation. Pediatrics. 1986;78(1):65–78.

[22] Olds D, Eckenrode J, Henderson CR, Kitzman H, Powers J, Cole R. Long-term effects of home visitation on maternal life course and child abuse and neglect: 15year follow-up of a randomized trial. JAMA.1997;278(8):637–43.

[23] Galicich JH, French LA, Melby JC. Use of dexamethasone in treatment of cerebral edema associated with brain tumors. Lancet, 1961;81:46-53.

[24] Knapp JM. Hyperosmolar therapy in the treatment of severe head injury in children: mannitol and hypertonic saline. AACN .Clin Issues. 2005;16(2):199-211.

[25] Rhoney DH, Parker D. Use of sedative and analgesic agents in neurotrauma patients: effects on cerebral physiology. Neurol Res. 2001 Mar-Apr;23(2-3):237-59.

Cricoid Pressure in Contemporary Anaesthesia

Niranjan Sathianathen
Final Year Medicine (Undergraduate)
Monash University

Niranjan is a final year MBBS student with an interest in anaesthetics and surgery.

Aim: To evaluate the role of cricoid pressure in modern day anaesthetics. **Methods**: A literature review was conducted using the following databases: The Cochrane Database of Systematic Reviews, PubMed, Scopus, Ovid MEDLINE and EMBASE. Articles were found using following terms: cricoid pressure, aspiration, laryngoscopy, airway obstruction, anaesthesia, anaesthesiology, airway management, Sellick's and rapid sequence intubation. **Results**: The literature review revealed a lack of high-level evidence supporting the use of cricoid pressure, however, observational studies have suggested a benefit in preventing gastric aspiration. The application of cricoid pressure is inconsistent and generally variable amongst clinicians. Sellick's manoeuvre is occasionally associated with airway obstruction. **Conclusion**: When applied correctly, cricoid pressure may still have a role in preventing pulmonary aspiration of gastric contents. There is however a risk of airway obstruction and given the inconsistencies in technique, cricoid pressure should only be employed by trained individuals.

Introduction

The first description of cricoid pressure (CP) was by Monro in 1774 when he used it to prevent gastric insufflation in near-drowned victims. But it was not until 1961 when Sellick utilised the manoeuvre to prevent regurgitation of gastric contents during the induction of anaesthesia that it came to the forefront of clinical anaesthesiology. [1] Consequently, over the last 50 years, CP has become an integral part of the rapid sequence induction (RSI) – an airway management technique employed in patients at high-risk of aspiration where administration of a sedative and muscle relaxant occurs virtually simultaneously. [2,3] However, more recently, there has been much dispute regarding the efficacy and evidence behind Sellick's manoeuvre leading some anesthetists to even completely abandon it from their practice. [4]

This paper examines the evidence base for the use of cricoid pressure and whether it still has a role in the clinical milieu.

Clinical context

The incidence of pulmonary aspiration of gastric contents has historically been reported as being low overall but it still remains a critical issue in modern anaesthetic practice, as shown by a survey in which 71% of respondents reported encountering at least once case during their careers. [5,6] Importantly, aspiration is associated with severe consequences in regards to morbidity and morality, with a 1999 Australian study reporting a death rate of 3.8%. [6,7]

The purpose of Sellick's method is to decrease the likelihood of Mendelson's syndrome, that is, aspiration pneumonitis – one of the recognised complications of general anaesthesia. The pathophysiology behind Mendelson's syndrome lies in the concept that the unconscious patient has diminished protective airway reflexes placing them at an increased risk of aspiration. [8] This is supported by Vanner and Pryle who displayed an immediate loss of upper oesophageal tone after losing consciousness. [9] Consequently, physical compression of the oesophagus by placing pressure on the cricoid cartilage is expected to prevent the regurgitation of gastric contents.

Aim

To determine whether the application of cricoid pressure decreases the likelihood of gastric aspiration. To evaluate whether the benefits of cricoid pressure outweigh its adverse sequelae.

Search strategy

A search was undertaken of the medical literature using the following keywords and their alternative spellings: cricoid pressure, aspiration, laryngoscopy, airway obstruction, anaesthesia, anaesthesiology, airway management, Sellick's and rapid sequence intubation. Results from all searches were refined with Boolean operators. The search was conducted in the following databases: The Cochrane Database of Systematic Reviews, PubMed, Scopus, Ovid MEDLINE and EMBASE. The search retrieved 571 papers. The reference lists of included studies were also manually reviewed to identify additional relevant literature. Papers including both human and cadaveric studies were included. The author determined which of the retrieved articles were to be included in the review and there were no explicit exclusion criteria.

Results

Evidence for efficacy

Sellick's original articles supporting the use of CP in preventing aspiration are observational studies consisting of 26 and one patient(s) respectively. [1,10] His first article details a successful trial of his technique amongst cadavers by filling their stomach and placing them in a head down position while applying cricoid pressure. It was not until nearly a decade later that four more cadaver-based studies validated Sellick's original findings. [9,11-13] Recently, a case report by Neelakanta further supported the use of cricoid pressure in preventing aspiration. [14] No randomised controlled trials have been conducted to assess the efficacy of CP in the prevention of pulmonary aspiration.

In regards to gastric insufflation, four historical studies have suggested that CP has a positive clinical outcome on decreasing the amount of gas in the stomach amongst patients being ventilated by a facemask. [15-18] It is important to note that that most recent of these studies was conducted in 1993 and consequently clinical protocols used at the time of the cited studies have changed compared to the present day and are inherently more conducive to decreasing aspiration risk, hence potentially undermining this suggested advantage. [19,20]

Anatomical and physiological debate

The crux of the cricoid pressure technique relies on the principle that the cricoid cartilage, oesophagus and vertebral bodies lie in a single axial plane. Subsequently, in theory, backward pressure on the cricoid cartilage against the posterior vertebral bodies should occlude the oesophagus. Studies of both computed tomography and magnetic resonance imaging have disputed this concept and demonstrated

that the oesophagus is naturally displaced laterally in relation to the midline of vertebral bodies in 49% and 53% of individuals respectively. [21,22] With the application of CP, this lateral displacement is further exacerbated thus questioning the primary foundation of Sellick's technique. [23] This phenomenon is not limited to just adults, but also seen in the paediatric population with younger children impacted more than those older. [24] Moreover, Rice *et al.* demonstrated that it is the hypopharynx and not the oesophagus that is situated behind the cricoid cartilage, and further, that the oesopahgus is inferior to the level of the cricoid ring; but interestingly concluded that the alimentary tract is still compressed adequately. [25]

Similar to the debate surrounding the anatomic foundations of CP, there have also been contrasting views regarding its physiological basis. Published papers have suggested that the application of cricoid pressure actually opposes its intended effect of preventing regurgitation by decreasing lower oesophageal sphincter tone. [26] While this has been shown to cause an increase in gastric distention during bag-mask ventilation, Skinner *et al.* suggested that the loss of tone has no significant impact on the risk of gastric reflux amongst healthy individuals. [19,27]

Technical pitfalls

Despite the case reports of CP preventing aspiration, the technique is far from perfect. Surveys revealed that up to 14% of anaesthetists had witnessed aspiration in the presence of cricoid pressure being applied. [28] A potential explanation for this may be the inconsistencies in CP technique between individuals. In his original report, Sellick did not specifically quantify the amount of force necessary to achieve an adequate compression of the alimentary tract other than describing it as "firm". [1] Consequently, the exact amount of force required to achieve the primary aim of preventing aspiration without compromising the ease of laryngoscopy and other complications has been greatly debated. A group of researchers first suggested that a force of 44 Newtons (N) needs to be applied, before Vanner recommended that 20 N be applied in the conscious patient before increasing to 40 N after the onset of anaesthesia. [29,30] In a more recent paper, the optimal amount of force was modified to 10 N and 30 N in the conscious and unconscious patient respectively. [31] Despite these rather precise theoretical recommendations, numerous studies have discovered that the CP forces applied by health professionals are discordant. [32-34] However, additional training was shown to improve staff technique. [33-37]

Adverse sequelae of CP

Whether stemming from the pitfalls in individual technique or not, CP has been associated with airway obstruction. Hartsilver & Vanner found that cricoid pressure applied according to the initial recommendations of Wraight *et al.* resulted in complete airway obstruction in 35% of patients. [29,38] This vastly declined to 2% when the recently suggested 30 N of force was applied; however, if this force is applied in an upward and backward direction as suggested by Vanner *et al.* [39] obstruction was seen in 56% of the population. [38] Another study reported 35% of their cohort as having airway obstruction evidenced by decrease in tidal volume on application of CP, of which 31% had complete obstruction. [40] However, it should be noted that the clinical utility of a decrease in tidal volume as a measure is questionable due to the application of CP during apnoea. Two further randomised controlled studies supported the association between CP and airway obstruction. [41,42] Additionally, the application of CP has been shown to impede laryngeal mask placement in patients who have failed RSI and require an airway resulting in a life-threatening situation as the patient cannot be adequately ventilated. [43,44] The experience is similar when attempting to place a laryngeal tube and laryngeal tube-suction II. [45] However, these difficulties were not encountered when using a cuffed oropharyngeal airway where no significant difference in tidal volume or peak inspiratory pressure was demonstrated when comparing "post-manoeuvre" measurements to baseline, regardless of whether CP was applied or not. [46] It has been reiterated that CP should be removed if any difficulty is encountered during intubation. [40]

The effect of Sellick's manoeuvre on laryngoscopy has been the subject of much research and findings have varied. Vanner *et al.* propose that CP in either the classical form or in the modified upward and backward direction improves views at laryngoscopy compared to no CP, with the best views seen in the modified upward and backward group. [39] Furthermore, CP shows a greater improvement in views in the left lateral than supine position. [47] Nevertheless it should be noted that pressure on the thyroid cartilage resulted in superior views in 88% of patients compared to only 11% when pressure is applied to the cricoid cartilage. [48] In juxtaposition, Haslam *et al.* concluded that the relationship between CP and laryngoscopic views is complex in which low levels of force (< 30 N) may result in improved views but as the pressure increases there is an analogous increased risk of complete obstruction. [49] Similarly, Noguchi *et al.* determined that views are worsened with application of CP, however it is important to note that this was an observational study. [50]

Additionally, the application of cricoid pressure in the conscious patient has been shown to induce vomiting and cause oesophageal injury. [51] In their cadaveric studies, Vanner & Pryle reported oesophageal rupture occurring in 30% of the cadavers studied. [9] Another case report details experiencing this complication in a living patient. [52] Furthermore, by decreasing lower oesophageal sphincter tone, CP increases the likelihood of vomiting. [53,54] In contrast, Khan & ul Haq demonstrated a trend of decreased rates of nausea and vomiting in the postoperative period amid patients that had CP applied compared to the no CP group, but the results were not statistically significant. [55]

Discussion

Although there are studies that support the use of CP in preventing aspiration, it is important to consider that except for Neelankanta *et al.*, they are relatively historical and cadaveric-based which questions its applicability in the modern clinical landscape and in living patients. [14] On the other hand, adverse consequences of CP have been described in both case reports and randomised trials. Furthermore, the debate surrounding the theoretical foundations of Sellick's manoeuvre has cast doubts on its efficacy.

Cricoid pressure was once described as the "lynchpin of physical prevention [of aspiration]" and as a minimum of standard of care, thus implying that any randomised trials evaluating its efficacy would be unethical. [56] However, in light of recent evidence that has suggested several adverse sequelae of utilising Sellick's manoeuvre, it may now be ethically acceptable to conduct a randomised study in order to better evaluate the value of CP. The impetus to perform further research is greater given that evidence supporting the use of cricoid pressure is of poor quality. The results of such a trial would be pivotal in either reaffirming or eradicating CP from the modern anaesthetic landscape.

Although many anaesthetists have already discontinued the use of CP from their practice, this may prove to have been somewhat hasty. While the evidence base exhibiting the benefits of cricoid pressure is scarce, it is important to consider the extremely low levels of aspiration-related death from anaesthesia since its introduction into the clinical domain. It is acknowledged that anaesthetic practice over that time period has undergone considerable change and whilst there are likely to be other factors also responsible for the low mortality rates, the true impact of Sellick's manoeuvre cannot be quantified with any certainty.

Nevertheless, the body of evidence suggesting the cessation of cricoid pressure application needs to be considered carefully. This is especially the case when continued application of pressure results in airway obstruction and, subsequently, difficulty with ventilating the patient. Consequently, the risks and benefits need to be considered on an individual basis and CP should not be applied unless clinical judgment suggests otherwise.

Importantly, this paper has exhibited the substantial inconsistencies in cricoid pressure technique, which demands for better training of health professionals. The importance of this should not be underestimated as rectification of technique may result in both superior efficacy in preventing aspiration as well as a reduction in some of the reported adverse effects.

Conclusion

While there have been a number of reports of the adverse sequelae of applying cricoid pressure, of which complete airway obstruction is the most severe, it may still have a role in preventing aspiration and improving laryngoscopic views – especially at low forces, that is, below 30 N. Subsequently, its use in clinical practice should be evaluated on an individual basis by a risk-benefit analysis.

Overall, cricoid pressure is a pseudoaxiom that has been adopted as part of standard anaesthetic practice without solid evidence supporting its efficacy. In considering the currently available literature, its status as being universally accepted and applied during anaesthetic induction appears to be under threat. Further research is needed in order to more definitively determine whether cricoid pressure has a role to play in clinical practice.

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Conflict of interest

None declared.

Correspondence

N Sathianathen: niranjan19@gmail.com

References

[1] Sellick B: Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961, 19(2):404-406.
[2] Marx J, Hockberger R, Walls R: Airway, 5th edn. St Louis, MO: Mosby; 2002.
[3] Tintinelli J, Kelen G, Strpczynski J: Advanced airway support, 4th edn. New York, NY: McGraw-Hill; 1996.
[4] Priebe H: Cricoid pressure: an alternative view. Seminars in Anesthesia, *Perioperative Medicine and Pain* 2005, 24:120-126.
[5] Warner M, Warner M, Weber J: Clinical significance of pulmonary aspiration during the perioperative period. Anesthesiology 1993, 78:58-62.
[6] Kluger M, Short T: Aspiration during anaesthesia: a review of 133 cases from the Australian Anaesthetic Incident Monitoring Study (AIMS). *Anaesthesia* 1999, 54(1):19-26.
[7] Englehardt T, Webster N: Pulmonary aspiration of gastric contents in anaesthesia. *British Journal of Anaesthesia* 1999, 83(3):453-460.
[8] Holmes N, Martin D, Begley A: Cricoid pressure: A review of the literature. *Journal of Perioperative Practice* 2011, 21:234-238.
[9] Vanner R, Pryle B: Regurgitation and oesophageal rupture with cricoid pressure: a cadaver study. *Anaesthesia* 1992, 47:732-735.
[10] Sellick B: The prevention of regurgitation during induction of anaesthesia. *First European Congress of Anaesthesiology* 1962, 89:1-4.
[11] Fanning G: The efficacy of cricoid pressure in preventing regurgitation of gastric contents. *Anaesthesiology* 1970, 32:553-555.
[12] Salem M, Wong A, Fizzotti G: Efficacy of cricoid pressure in preventing aspiration of gastric contents in paediatric patients. *British Journal of Anaesthesia* 1972, 44:401-404.
[13] Salem M, Joseph N, Heyman H, Belani B, Paulissian R, Ferrara T: Cricoid compression is effective in obliterating the esophageal lumen in the presence of a nasogastric tube. *Anaesthesiology* 1985, 63(4):443-446.
[14] Neelakanta G: Cricoid pressure is effective in preventing esophageal regurgitation. *Anaesthesiology* 2003, 99:242.
[15] Salem M, Wong A, Mani M, Sellick B: Efficacy of cricoid pressure in preventing gastric inflation during bag-mask ventilation in pediatric patients. *Anaesthesiology* 1974, 40:96-98.
[16] Lawes E, Campbell I, Mercer D: Inflation pressire, gastric insufflation and rapid sequence induction. *British Journal of Anaesthesia* 1987, 59:315-318.
[17] Petito S, Russell W: The prevention of gastric inflation - a neglected benefit of cricoid pressure. *Anaesthesia and Intensive Care* 1988, 16:139-143.
[18] Moynihan R, Brock-Utne J, Archer J, Feld L, Kreitzman T: The effect of cricoid pressure on preventing gastric insufflation in infants and children. *Anaesthesiology* 1993, 78:652-656.
[19] Wenzel V, Idris A, Banner M, Kubilis P, Williams JJ: The influence of tidal volume on the distribution of gas between the lungs and the stomach in the non-intubated patient recieving positive pressure ventilation. *Critical Care Medicine* 1998, 26:364-368.
[20] Wenzel V, Keller C, Idris A, Dorges V, Lindner K, Brimacombe J: Effects of smaller tidal volumes during basic life support ventilation in patiets with respiratory arrest: good ventilation, less risk? *Resuscitation* 1999, 43(1):25-29.
[21] Smith K, Dobranowski J: The cricoid cartilage and the esophagus are not aligned in close to half of the adult patients. *Canadian Journal of Anaesthesia* 2002, 49:503-507.
[22] Smith K, Dobranowski J, Yip G, Dauphin A, Choi P: Cricoid pressure displaces the esophagus: An observationsal study using magnetic resonance imaging. *Anaesthesiology* 2003, 99:60-64.
[23] Vanner R, Pryle B: Nasogastric tubes and cricoid pressure. *Anaesthesia* 1993, 48:1112-1113.
[24] Dotson K, Kiger J, Carpenter C, Lewis M, Hill J, Raney L, Losek J: Alignment of cricoid cartilage and esophagus and its potential influence of the effectiveness of Sellick maneuvre in children. Paediatric Emergency Care 2010, 26(10):722-725.
[25] Rice M, Mancuso A, Gibbs C, Morey T, N G, Deitte L: Cricoid pressure results in compression of the postcricoid hypopharynx: The esophageal position is irrelevant. *Anaesthesia & Analgesia* 2009, 109:1546-1552.
[26] Thorn K, Thorn S, Wattwil M: The effects of cricoid pressure, remifentanil, and propofol on esophageal motility and the lower esophageal sphincter. *Anaesthesia and Analgesia* 2005, 100(1200-1203).
[27] Skinner H, Bedforth N, Girling K, Mahajan R: Effect of cricoid pressure on gasto-oesophageal reflux in awake subjects. *Anaesthesia* 1999, 54(798-800).
[28] Howells T, Chamney A, Wraight W, Simons R: The application of cricoid pressure. An assessment and a survey of its practice. *Anaesthesia* 1983, 38:457-460.
[29] Wraight W, Chamney A, Howells T: The determination of an effective cricoid pressure. *Anaesthesia* 1983, 38:461-466.
[30] Vanner R: Tolerance of cricoid pressure by conscious volunteers. *International Journal of Obstetric Anaesthesia* 1992, 1:195-198.
[31] Vanner R, Asai T: Safe use of cricoid pressure. *Anaesthesia* 1999, 54:1-3.
[32] Brisson P, Brisson M: Variable application and misapplication of cricoid pressure. *Journal of Trauma* 2010, 69(5):1182-1184.
[33] Herman N, Carter B, Van Decar T: Cricoid pressure: teaching the recommended level. *Anaesthesia and Analgesia* 1996, 83:859-863.
[34] Meek T, Gittins N, Duggan J: Cricoid pressure: knowledge and performance amongst anaesthetic assistants. *Anaesthesia* 1999, 54:59-62.
[35] Patten S: Educating nurses about correct application of cricoid pressure. *Association of Perioperative Registered Nurses Journal* 2006, 84(3):449-461.
[36] Owen H, Follows V, Reynolds K, Burgess G, Plummer J: Learning to apply effective cricoid pressure using a part task trainer. *Anaesthesia* 2002, 57(11):1098-1101.
[37] Kopka A, Crawford J: Cricoid pressure: a simple, yet effective biofeedback trainer. *European Journal of Anaesthesiology* 2004, 21(6):443-447.
[38] Hartsilver E, Vanner R: Airway obstruction with cricoid pressure. *Anaesthesia* 2000, 55(3):208-211.
[39] Vanner R, Clarke P, Moore W, Raftery S: The effect of cricoid pressure and neck support on the view at laryngoscopy. *Anaesthesia* 1997, 55:896-900.
[40] Allman K: The effect of cricoid pressure application on airway patency. *Journal of Clinical Anaesthesia* 1995, 7:195-199.
[41]Hocking G, Roberts F, Thew M: Airway obstruction with cricoid pressure and lateral tilt. *Ana esthesia* 2001, 56:825-828.
[42] Saghaei M, Masoodifar M: The pressor response and airway effects of cricoid pressure during induction of general anaesthesia. *Anaesthesia and Analgesia* 2001, 93:787-790.
[43] Asai T, Barclay K, Power I, Vaughan R: Cricoid pressure impedes placement of laryngeal mask airway. *British Journal of Anaesthesia* 1995, 74:521-525.
[44] Brimacombe J, White A, Berry A: Effect of cricoid pressure on ease of insertion of the laryngeal mask airway. *British Journal of Anaesthesia* 1993, 71:800-802.
[45] Asai T, Goy R, Liu E: Cricoid pressure prevents placement of the laryngeal tube and laryngeal tube-suction II. *British Journal of Anaesthesia* 2007, 99(2):282-285.
[46] Dravid R, Reed P, Stoneham M, Popat M: Effect of cricoid pressure on insertion of and ventilation through the cuffed oropharyngeal airway. *British Journal of Anaesthesia* 2000, 84(3):363-366.
[47] McCaul L, Harney D, Ryan M, Moran C, Kavanagh B, Boylan J: Airway management in the lateral position: a randomised controlled trial. *Anaesthesia and Analgesia* 2005, 101(4):1221-1225.
[48] Benumof J, Cooper S: Qualitative improvement in laryngoscopic view by optimal external laryngeal manipulation. *Journal of Clinical Anaesthesia* 1996, 8:136-140.
[49] Haslam N, Parker L, Duggan J: Effect of cricoid pressure on the view at laryngoscopy. *Anaesthesia* 2005, 60(1):41-47.
[50] Noguchi T, Koga K, Shiga Y, Shigematsu A: The gum elastic bougie eases tracheal intubation while applying cricoid pressure compared to a stylet. *Canadian Journal of Anaesthesia* 2003, 50:712-717.
[51] Landsman I: Cricoid pressure: indications and complications. *Paediatric Anaesthesia* 2004, 14(1):43-47.
[52] Ralph S, Wareham C: Rupture of the oesophagus during cricoid pressure. *Anaesthesia* 1991, 46(1):40-41.
[53] Tournadre J, Chassard D, Berrada K, Bouletreau P: Cricoid cartilage pressure decreases lower esophageal sphincter tone. *Anaesthesiology* 1997, 86(1):7-9.
[54] Garrard A, Campbell A, Turley A, Hall J: The effect of mechanically-induced cricoid force on lower oesophageal sphincter pressure in the anaesthetised patient. *Anaesthesia* 2004, 59(5):435-439.
[55] Khan F, ul Haq A: The effect of cricoid pressure on the incidence of nausea and vomiting in the immediate postoperative period. *Anaesthesia* 2000, 55(2):163-166.
[56] Rosen M: Anesthesia for obstetrics. *Anaesthesia* 1981, 36:145-146.

Is switching anticoagulant brands safe: Coumadin and Marevan?

Fiona Chen
Fourth Year MBBS
Monash University Medical School, Melbourne
Centre of Cardiovascular Research & Education in Therapeutics, Monash University, Melbourne

Fiona has completed 4 years of medicine and is currently undergoing a BMedSc in Obstetrics and Gynaecology

Ian Wang
Fifth Year MBBS
Monash University Medical School, Melbourne
Centre of Cardiovascular Research & Education in Therapeutics, Monash University, Melbourne

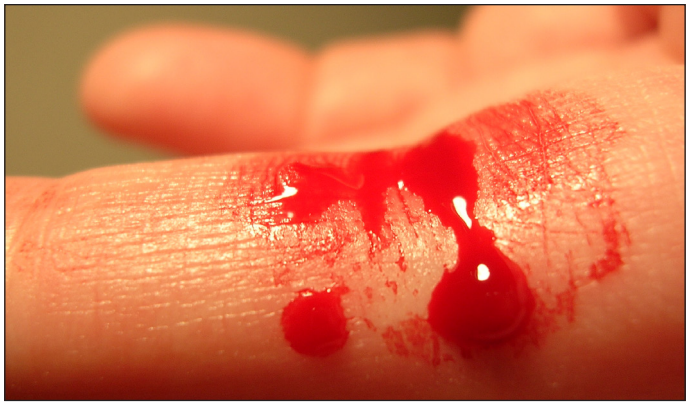
Linda Graudins
Pharmacist
Pharmacy Department, The Alfred Hospital, Melbourne

Ingrid Hopper
Clinical Pharmacologist
Centre of Cardiovascular Research & Education in Therapeutics, Monash University, Melbourne
Clinical Pharmacology Department, Alfred Hospital, Melbourne

Aim: Warfarin is the most frequently prescribed antithrombotic agent, available in Australia as brands Coumadin and Marevan. . Although both are manufactured by Aspen Pharmaceuticals, there are differences in formulation. The product information states they cannot be used interchangeably. Two incident reports of warfarin brand interchange in our hospital prompted a literature review. We aimed to review published evidence on the pharmacokinetics and bioequivalence of different warfarin brands and make brand switching recommendations.
Methods: Systematic review of the literature on warfarin bioequivalence and incidents reported by the Therapeutic Goods Administration (TGA).
Results and discussion: Fifteen studies explored different warfarin formulations. No significant differences were found in efficacy with brand switching in eight studies analysing participants who were healthy, had atrial fibrillation (AF), or a mechanical heart valve. Prospective observational studies demonstrated no significant difference in the International Normalised Ratio (INR) or adverse events, however, a retrospective observational study demonstrated an increase in complications. Of the four population studies, only one demonstrated elevated rates of haemorrhage or thrombosis. No studies directly compared Coumadin and Marevan. Three TGA case reports describe adverse events from brand switching.
Conclusion: Studies of different warfarin formulations demonstrate bioequivalence in population studies, but with marked inter-individual variation, hence the recommendation is to continue the same brand of warfarin where possible. However, brand switching is preferable to withholding a dose of warfarin for inpatients, in the absence of the patient's usual brand. If substituting or brand switching, close monitoring with frequent INR testing is suggested.
Key words: Warfarin, Bioequivalence, Pharmacy, Medication safety, Pharmacodynamics, Generic.

Introduction

Warfarin is the most frequently prescribed antithrombotic agent in Australia. Indications include both prevention and treatment of thrombosis, prevention of strokes associated with atrial fibrillation (AF) as well as clotting on mechanical heart valves. [1] Warfarin is also effective in the treatment of deep venous thrombosis and pulmonary embolism. The benefits of warfarin need to be weighed against



the risk of haemorrhage, a common complication seen in patients prescribed these anticoagulants. Every year 1.2 to 8.1% of patients on long-term warfarin therapy experience a major bleeding complication, attributable to its narrow therapeutic index, as well as susceptibility to other medications interfering with warfarin's absorption, metabolism, and clearance. [2,3]

In Australia, there are two brands of warfarin: Coumadin and Marevan. Both brands are now manufactured by the same company, Aspen Pharmacare Australia Pty Ltd, and previously by Boots Healthcare Australia Pty Ltd. [1] Brands differ in tablet colour, markings and excipients, and were marketed before bioavailability testing was required. Prescribing bodies within Australia, including the Therapeutic Goods Administration (TGA) and the National Prescribing Service do not recommend interchanging warfarin brands, Coumadin and Marevan, due to the lack of information on bioequivalence. [1,4] It has been recommended that patients remain on the same brand of warfarin if possible, with more frequent International Normalised Ratio (INR) testing if switching brands. [5] The practice within hospitals in Victoria has been to prescribe Coumadin preferentially, with Marevan prescribed only if the patient has been previously stabilised on this brand. [6]

Two locally reported incidents involving brand switching led to a review of the literature to inform practice. One of the incidents involved a 52-year-old male patient who mistakenly received Coumadin, when Marevan was his usual brand. The nurse administering the nocte medications quickly discovered this incident. The patient's INR was measured to be sub-therapeutic. The second patient was an 88-year-

old female admitted to hospital after a fall and did not receive her regular prescribed Marevan dose, as staff were unable to source that brand after-hours. This patient had an elevated INR prior to the incident and warfarin was subsequently ceased. The two local incidents did not result in change of therapy or result in harm.

We aimed to review published evidence on the pharmacokinetics and bioequivalence of different warfarin brands and make brand switching recommendations.

Methods

Search strategy

A systematic review of the medical literature was performed by FC using PubMed (1996-Jan 2015). Author IW performed a cross-referencing search of Embase (1974-Jan 2015) to ensure the completeness of the literature review. The search terms included warfarin, bioequivalence, Coumadin, and Marevan. Additionally, the search included unpublished reports from the TGA Database of Adverse Events Notification (DAEN), which was searched by author LG for reports of unexpected therapeutic response from substitution of either Marevan or Coumadin. Search parameters on the DAEN: Date Range: 01/01/1971 to 21/05/2014 'Therapeutic response unexpected with drug substitution'; Medicine Names: Marevan, Coumadin, Warfarin Sodium. [7] Further unpublished information was included from the Danish Health and Medicines Authority (DHMA).

Eligibility Criteria for Studies

Studies that were considered for inclusion included randomised controlled trials (RCTs), crossover trials, retrospective studies, and case reports, published in English and on human participants, with any follow-up time. Systematic reviews and meta-analyses were analysed but not included. The bibliographies of all retrieved articles were manually checked.

Risk of bias

Risk of bias was assessed in each individual study (Table 1).

Summary measures

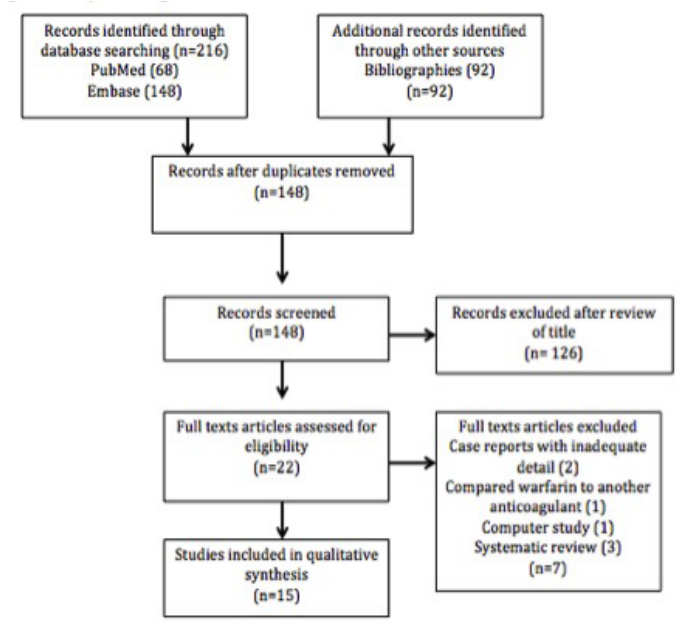


Figure 1. *Study flow diagram.*

Summary measures used include confidence intervals, p-values, and area under the curve (AUC).

The initial search identified 216 records. After duplicates were removed, 148 records were then screened for eligibility, resulting in 125 articles being excluded after review of the titles. A total of seven full-text papers were excluded for reasons stated in Figure 1.

Fifteen studies were included in the analysis, all published between 1971 and 2011. There were three studies in healthy subjects. There were twelve studies of outpatients taking warfarin, including five RCTs, two prospective observational studies, four retrospective studies and one ecological study. The literature search did not identify any studies in which Coumadin and Marevan (Boots or Aspen) were directly compared.

Pharmacokinetic studies in healthy subjects

Three studies in healthy patients demonstrated no difference in average peak plasma concentrations or AUC, but individual patient variability existed. Müller et al. compared the bioavailability of four warfarin tablet formulations. [8] All products were administered as a single 10 mg oral dose to twelve healthy males, and no significant difference was found in the mean average peak plasma concentrations and AUC (for the plasma concentration time curve). Warfarin bioavailability in the four brands differed by less than 20% when compared to the reference product, Marevan, suggesting that all four types of warfarin could be safely interchanged, without any significant bleeding risk. [8] McGilveray et al. assessed the bioavailability of four warfarin products in eight healthy males. Of these, two sodium warfarin products gave AUC ratios of 97.3% and 100.5% and potassium warfarin of 86.6% relative to the reference products. Significant differences were noted in the time to reach peak concentration, as well as concentration at one hour with one of the products reaching its maximum concentration before this first measurement. [9] Wagner et al. found no significant difference in peak plasma concentration or average plasma concentrations measured at 4, 8, 12, 24, 48, 72, and 96 hours in three different brands of warfarin amongst a group of twelve healthy study subjects. However, there was a statistically significant difference in plasma concentration measured at one hour and in peak plasma concentration time, though it was minimal ($p<0.005$ and $p<0.05$ respectively). The three different brands had occurrences of peak plasma concentration at 2.3 hours, 3.6 hours, and 4.1 hours. [10] These studies demonstrate that in healthy males, when brand substitution of warfarin occurred, there was no significant difference in the overall peak concentration of plasma warfarin levels or AUC.

Crossover RCTs

Five RCTs with a crossover design measured the INR of patients with a history of AF or mechanical heart valves who were taking either a branded or generic version of warfarin, having achieved stable anticoagulation with long-term therapy prior to the study. After changing brand, all studies found no statistically significant difference in the average INR of both groups after at least nine weeks of follow-up.

Three studies, Neutel et al., [11] Handler et al., [12] and Weibert et al. [13] examined patients with AF. Neutal et al. demonstrated the bioequivalence of warfarin made by Dupont and Barr Laboratories in a randomised, blinded, crossover study, and showed that the average INR values differed by less than 2% in 55 patients with AF. [11] Handler et al. conducted a study with the objective of substituting warfarin (Dupont) and warfarin (Barr Laboratories) of the same dose and determining its safety and efficacy to confirm bioequivalence results found in other studies. Participants received either warfarin made by Dupont or Barr Laboratories for a period of 28 days and then switched over to the alternate drug for a further two 28-day periods. The mean change in INR measured after every 28 days was -0.17 in patients who began with warfarin (Dupont). After switching, the mean changes were -0.02 and -0.16 respectively. For those starting on warfarin (Barr Laboratories), the mean change from baseline in INR was +0.01, after switching it was -0.16 and -0.18. These differences were not statistically significant, and with the number of dose changes (0.70 ± 0.6 mg for brand A, 0.63 ± 0.9 mg for brand B, and 0.72 ± 0.8 mg for brand C, $p=0.89$) and mean dose for a stable INR (4.6 ± 2.2 mg, 5.3 ± 2.2 mg, and 5.3 ± 2.4 mg), warfarin (Dupont) was determined to be equivalent to warfarin (Barr Laboratories) in safety and efficacy. Eleven participants were

excluded from the study due to dosage adjustments throughout the period, however, an intention-to-treat analysis showed the results fell within the Federal Drug Agency (FDA)'s INR variability values. Handler et al. therefore suggested that additional tests and surveillance are not needed when switching generic with branded warfarin. Weibert et al. performed an RCT crossover comparison of Coumadin and Apothecon warfarin in 19 patients with chronic and paroxysmal AF. [13] Participants already on anticoagulation therapy were randomly assigned to take either Coumadin or Apothecon warfarin for four weeks and then crossed over to receive the alternate for another four weeks. Although seven participants in each group required dosage changes and experienced INR changes outside the desired range, there was no significant change in INR or dosage alteration in either group overall. Therefore, for chronic and paroxysmal AF patients, these brands were considered to be equivalent in anticoagulation action.

Lee et al. studied 35 patients with mechanical valves. [14] This study found no difference in pooled mean INR between Coumadin (Dupont) and warfarin (Lennon) (INR 2.28 and 2.27, respectively) and was within the range for bioequivalence (90% CI for the difference: 96.4 - 104.9). There were also no differences in the adverse event profiles of the two formulations. In a double-blinded crossover RCT, Pereira et al. also suggested that generic and branded warfarin may be used interchangeably. They studied seven patients, and switched them four times between generic Apo-warfarin and to Coumadin over 30 weeks. This study found no significant difference in mean INR results or number of dosage adjustments between patients who switched between the brands and a control group who stayed on Coumadin ($p>0.69$). They also found no patient and warfarin interaction ($p>0.81$). [15]

Observational studies

Observational studies were performed by Swenson et al., Milligan et al., and Richton-Hewett et al., observing patient groups switching from brand-name to generic warfarin. Swenson et al. prospectively studied 210 patients, with 105 controls remaining on Coumadin for the study period and 105 patients switching brands. The mean INR difference between the two groups before and after enrolment was not clinically significant ($p=0.15$). The number of dosage changes required was similar in both groups, with no thromboembolic or haemorrhagic adverse events or any emergency presentations associated with coagulation problems in either group. [16] Milligan et al. prospectively observed 182 participants switching from Coumadin to generic warfarin and demonstrated no significant variation in the parameters studied, including INR ($p=0.3$), adverse events, and frequency of INR monitoring. [17] One small retrospective study demonstrated an increase in complications with brand switching. Richton-Hewett et al. in 1980 assessed the effect of interchanging brand-name and generic warfarin with a retrospective chart review of 55 patients. [18] The 15 patients who switched to generic warfarin were significantly ($p<0.001$) more likely to have a prothrombin time (PT) outside of the therapeutic range and were also more likely to require a dosage change. Notably, one patient required a six-day hospital admission with epistaxis and an elevated PT.

Cohort studies

Regional changes in warfarin formulation afforded the opportunity to examine population-based changes in response to brand switching in three cohort studies and one ecological study. These studies demonstrated safety overall, but with some limitations. Halkin et al. observed 975 participants after a nationwide generic switch of warfarin formulations in Israel. [19] They found that INR values were lower and warfarin doses higher ($p<0.01$), consistent with decreased apparent warfarin sensitivity with the generic brand. Witt et al. found similar results in the United States in a retrospective cohort study of 2299 participants. Calculated INR values were similar, with the average INR decreasing by 0.13 after the switch and no significant differences found in outcomes of hospitalisation, Emergency Department (ED) visits, or bleeding and thromboembolism. However 39% of patients experienced a worsening in therapeutic INR control of more than 10%, whilst 33% experienced INR control that improved by greater than 10%. Witt et al. suggest that receiving long-term anticoagulation therapy with brand-name warfarin can be successfully switched to a generic warfarin, with overall INR levels similar or lower than before such a switch. [20]

A further population-based study was performed by Ghate et al. of 37,756 patients with AF and at least three warfarin prescriptions during the twelve-month follow-up period. The study population was identified via a database of patients receiving commercial health insurance benefits. [19] The patients stayed on Coumadin, generic warfarin, or switched their formulation. An increased risk of thrombotic events was observed in those who switched from Coumadin to generic warfarin compared to those who stayed on Coumadin (hazard ratio (HR)=1.81; 95% CI 1.42 to 2.31, $p<0.001$). Similarly, increased risk of thrombosis was seen in patients changing from generic warfarin to Coumadin (HR=1.76; 95% CI 1.35 to 2.30, $p<0.001$) and generic warfarin to another generic type (HR=1.89; 95% CI 1.57 to 2.29, $p<0.001$). In addition to this, all groups who switched were observed to have an increased risk of haemorrhage. In comparison to the group who remained on Coumadin, switching to the generic formulation was associated with a significantly higher risk of haemorrhagic events (HR=1.51; 95% CI 1.17 to 1.93, $p=0.001$). [21]

Paterson et al. conducted a population-based, cross-sectional, time series analysis of outpatients aged 66 or older in Ontario, Canada following the province's switch to one of two generic warfarin formulations (Apo-warfarin and Taro-warfarin) from Coumadin. [22] Trends in warfarin prescribing, INR testing, and hospitalisations for major haemorrhage and stroke were analysed 40 months before, during the one month of, and the nine months after the mandated switch. No significant differences in the rate of INR testing was found ($p=0.93$), nor hospitalisation for haemorrhage ($p=0.97$), or cerebral thromboembolism ($p=0.89$). [22]

Case reports

Exploration of the TGA DAEN for unpublished Australian case reports revealed two adverse drug reactions involving change of warfarin brand, both of which occurred in 2007. They involved an increased INR when the patient changed from Marevan to Coumadin. One of these reports was complicated with a possible drug interaction with concomitant flucloxacillin. The severities of these two reports were not defined. A third report described a patient who experienced an INR decrease when changed from Coumadin to Marevan.

Other case reports have documented adverse events after switching to generic warfarin. The DHMA has made a precautionary decision to cease switching Marevan to generic warfarin Orion after similar adverse drug reaction reports of elevated INR levels. It is important to note that they have not observed any problems with the generic brand and have not ruled out alternate reasons for the changes in INR. [23] In Oklahoma City, two cases saw subtherapeutic INR levels after a switch from Coumadin to generic warfarin despite the Food and Drug Administration asserting bioequivalence. Both reports conclude that INR levels should be closely monitored if switching is unavoidable. [24]

Discussion

This systematic review of the literature identified a number of studies exploring different warfarin brands, using different methodologies and with a variety of measures of bioequivalence in both healthy subjects and patients. However, the brands raising concern in our hospital, Coumadin and Marevan, have not been directly compared. This review demonstrates that there are conflicting findings in individual versus population studies. Overall, there were no significant differences in plasma drug levels or in efficacy as measured by INR with brand switching on an individual patient level. However, population studies demonstrated an increased risk of thrombosis and haemorrhage with brand switching.

Given the widespread use of warfarin, there are a very low number of reports of issues after brand switching both locally and in the published literature. This may be due to under-recognition and under-reporting of adverse reactions. [7] It may also be that brand switching of warfarin rarely occurs and, if it is occurring, then it may be happening without significant adverse events. In Australia, it is recommended that switching warfarin brands should be avoided. Differences in the excipients between the different brands theoretically may affect bioavailability, however, no comparative trials of the Aspen brands have been published. Another important issue in switching brands is the potential for confusion in patients due to different strengths and colours of the medications, potentially resulting in incorrect dosage.

This review demonstrates that when brand switching does occur in a supervised manner, such as that of a clinical trial, the risks are minimal. For hospital inpatients, we would therefore suggest that giving the alternate brand of warfarin is preferable to withholding a dose. Either a return to the patient's usual brand or a permanent switch to the preferred brand could then be considered. Increased vigilance in following up the INR would be mandatory, due to both the change in formulation and the fact that hospital inpatients are unwell, and that in itself can affect the INR.

The majority of warfarin use, however, is in the community rather than in hospitals. Switching a patient's warfarin brand should be considered on a case-by-case basis. There should be a compelling reason for brand switching, and the patient's ability to comprehend the different dosing between brands should be considered. Most importantly, there should be capacity, both by the patient and the pathology provider, to increase monitoring of INR until clinical stability is established on the new brand.

The strengths of this review are that a variety of methods have been used to address the question of safety of switching warfarin brands, which improves the quality of the evidence. With recent updated information available, paired with case examples, it allows a comprehensive expansion on previous reviews exploring similar topics. However, there are several important limitations. The RCTs reviewed all had small sample sizes, with the largest having only 113 participants. [13] This limits the generalisability of these results. Additionally, RCTs may overstate the safety of brand switching due to selection bias, for example, (1) patients on anticoagulation who agree to enter a trial may manage their anticoagulation better than the general population, (2) well-controlled patients are more likely to participate in a trial, or (3) compliance with medication and dietary restrictions increases during the period of the trial. Studies focusing on pharmacokinetics and bioequivalence may not be adequate to assess clinical outcomes. There are also biases in population studies. For example, factors such as changes to the environment affecting the whole region and contributing to the outcome may not be recognised. Ecological studies cannot be used to prove or explore associations between determinants of disease. There are limitations in the use of a retrospective dataset, such as health insurance claims, in which it cannot be confirmed whether individuals actually took the warfarin dispensed by the pharmacy. Additionally, if the dataset was created for an alternate purpose, such as discharge coding to determine reimbursement, inconsistent definitions, or coding practices may mean the data is of too poor quality to use in a study. There may also be inadequate information about the confounders and data quality. Differential loss to follow-up can introduce bias in retrospective and prospective cohort studies. Across all studies, publication bias and selective reporting within the studies may influence the cumulative evidence.

Conclusion

Studies of different brands of warfarin demonstrate that brand switching is generally safe, although some population studies have demonstrated that INR control may worsen for a period, and that risk of both thrombosis and haemorrhage may increase. Based on the studies reviewed, we support the recommendation to continue with the same brand of warfarin, if possible. However, in the inpatient hospital setting, brand switching is preferable to withholding a dose of warfarin in the absence of the preferred brand, with appropriate INR testing afterwards. We therefore recommend that in an in-patient situation, substitution with an alternate brand of warfarin should occur if one brand is unavailable and INR is monitored daily until stability is assured. In the community, brand switching should be considered on a case-by-case basis with increased INR monitoring until clinical stability is reached. Phasing out formulations of warfarin so only one brand is available, with support from the local regulatory drug agency, including advisory information and support for patients and clinicians, would resolve the confusion.

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None.

Conflict of interest

None declared.

Correspondence

F Chen: fche52@student.monash.edu

Table 1. *Summary of studies.*

Reference Year	Country	Trial design*	Participants	Number of subjects	Follow-up (weeks)	Mean age (years)	Males (%)	Brands
Müller [8] 1988	South Africa	RCT	Healthy males	12	1.14 8 days)	22	100	Warfarin (Petersen), Warfarin (Lennon), Coumadin (Boots), Marevan (Allen & Hanburys)
McGilveray [9] 1978	Canada	Crossover trial	Healthy males	8	None	25-42 (range)	100	Sodium warfarin Potassium warfarin (Manufacturers not stated)
Wagner [10] 1971	US	Crossover trial	Healthy subjects	12	1	25	83	Warfarin (3 different manufacturers not identified)
Neutel [11] 1998		SB crossover RCT	Outpatients Atrial Fibrillation	39	9	70	100	Coumadin (Dupont) Warfarin (Barr Laboratories)
Handler [12] 1998	US	DB crossover RCT	Outpatients Atrial Fibrillation	57	12	69	65	Coumadin (Dupont) Warfarin (Barr Laboratories)
Weibert [13] 2000	US	DB crossover RCT	Outpatients Atrial fibrillation	113	14	70	75	Coumadin (DuPont) Warfarin (Apothecon)
Lee [14] 2005	Taiwan	SB crossover RCT	Mechanical heart valves	35	12	52	71	Coumadin (Dupont) Warfarin (Lennon)
Pereira [15] 2005	US	DB crossover RCT	Outpatients Various indications	7	30	63	43	Coumadin (Bristol-Myers Squibb) Warfarin (Apotex)
Swenson [16] 2000	US	Prospective observational cohort study	Outpatients Various indications	210	20	78	50	Coumadin (Dupont) Warfarin (Barr Laboratories)
Milligan [17] 2002	US	Prospective observational study	Outpatients Various indications	182	78	75	57	Coumadin (Bristol-Myers Squibb) Warfarin (Barr Laboratories)
Richton-Hewett [18] 1998	US	Retrospective cohort study	Outpatients Various indications	55	30	56	47	Coumadin (Du Pont) Panwarfarin (Abbott Laboratories)
Halkin [19] 2003	Israel	Retrospective observational study	Outpatients Various indications	975	52	70	47	Coumadin Sodium (Taro Pharmaceutical Industries) Coumadin Sodium clathrate (Taro, new formulation)
Witt [20] 2003	US	Retrospective cohort study	Outpatients Various indications	2299	26	69	54	Coumadin Warfarin (Barr Laboratories)
Ghate [21] 2011	US	Historical cohort analysis	Atrial fibrillation	37 756	52	71	58	Generic warfarin Coumadin (DuPont/ Bristol-Myers Squibb)
Paterson [23] 2006	Canada	Ecological study	Outpatients Various indications	36 724	200	>65 years old	Not specified	Coumadin (Bristol-Myers Squibb) Warfarin (Apo-warfarin and Taro-warfarin)

Outcomes	Limitations and bias
Test products differed less than 20% from Marevan	Single blind – experimenter's bias Small study size Only male participants
No difference in average peak plasma concentrations. Significant difference in the time required to reach peak concentrations. Two sodium warfarin products gave AUCs of 97.3% and 100.5%. The potassium warfarin gave a lower value of 86.6% relative to the reference products	No mention of blinding – performance bias No mention of randomisation – selection bias Small study size Only male participants
No overall significant difference in average peak plasma concentrations or average time taken to reach peak plasma concentration. A small statistically significant difference in plasma concentration measured at 1 hour and in peak plasma concentration time ($p<0.005$ and $p<0.05$ respectively)	No mention of blinding – performance bias No mention of randomisation – selection bias Small study size Study performed more than 44 years ago
Changes in INR after switching were not significant ($p>0.05$); no differences in adverse effect profiles	AF participants – detection bias Only male participants Small study size
No significant differences in INR ($p=0.40$), dose adjustments, adverse events	AF participants – detection bias Small study size Funded by generic manufacturer
No significant differences in daily dose (0.5 mg/d), average INR difference (< 0.08), adverse events	AF participants – detection bias Small study size Single blind of investigators not patients – performance bias Increased regularity of INR monitoring, which may have detected more variability than normal Funded by generic manufacturer
Dose changes were rare; no significant differences in pooled INRs between Coumadin (Dupont) and warfarin (Lennon) (INR 2.28 and 2.27, respectively). The 90% CI for the difference was 96.4 - 104.9	HV participants – detection bias Observer blinded Small study size
No significant differences in mean INR measurements or variation ($p>0.69$). No patient and warfarin interaction found ($p>0.81$)	Small study size Patients underwent dosage adjustments if INR was out of target range
No significant differences in INR between groups ($p=0.15$); no adverse effects or events	Non-randomised assignment – selection bias Confounding
No significant differences in INR ($p=0.3$), dose adjustments, adverse events	Funded by an insurance company Non-randomised assignment – selection bias Confounding
Higher rate of INR out of range ($p<0.001$), dose changes ($p<0.05$), clinic utilisation ($p<0.03$) with generic group; no significant differences in morbidity/mortality	Non-randomised assignment – selection bias Non-blinded staff – experimenter's bias Confounding Small study size
After the switch, INR values were lower and warfarin doses prescribed were higher ($p<0.01$)	Non-randomised assignment – selection bias Confounding Data from administrative database
INR values below therapeutic range with generic ($p<0.0001$); overall average INR decreased by 0.13 after switch; no significant differences in hospitalisations, ED use, outcomes (bleeding or thromboembolism)	Non-randomised assignment – selection bias Confounding Fatal adverse effects not included in study as post-conversion questionnaire required
Increase in thrombotic events in those groups who had switched Coumadin to generic warfarin (HR=1.81; 95% CI 1.42 to 2.31, $p<0.001$) Generic warfarin to Coumadin (HR=1.76; 95% CI 1.35 to 2.30, $p<0.001$) Generic warfarin to another generic (HR=1.89; 95% CI 1.57 to 2.29, $p<0.001$) Increase in haemorrhagic events in those groups who had switched to generic (HR=1.51; 95% CI 1.17 to 1.93, $p=0.001$)	Non-randomised assignment – selection bias Information from insurance claims database with no available information about INR monitoring, adherence to therapy and missed follow-up appointments Confounding
No significant differences in INR testing ($p=0.93$) or hospitalisation for haemorrhage ($p=0.97$) or thromboembolism ($p=0.89$)	Funded by the government Focussed on major clinical events needing hospitalisation but excluded other outcomes with less reliable code, for example, DVT Cross-sectional – cannot determine causation Administrative health data used

References

[1] Product Information: Marevan, Coumadin. Aspen Pharmacare Australia Pty Ltd. eMIMS (accessed 5/7/2015).
[2] Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant therapy. Chest. 1998;114:511S-523S.
[3] Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ, Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest. 2012;141:1412S3.
[4] Adverse Drug Reactions Advisory Committee, Coumadin and Marevan are not interchangeable, Australian Adverse Drug Reactions Bulletin, June 1999;18:2.
[5] Fry FK, PBAC, Boots. Warfarin tablets, Aust Prescr 1997;20:33.
[6] Dooley M. Recommendations for warfarin in Victorian public hospitals [letter]. Aust Prescr 2003;26:27-9.
[7] Adverse Drug Reaction Reports. Received via personal communication with the Therapeutic Goods Administration. 4th April 2014.
[8] Müller FO, Steyn JM, Hundt HK, Luus HG (1988 Dec 3) Warfarin bio-availability. A comparison of 4 products. S Afr Med J, 74, pp. 1.
[9] McGilveray IJ, Midha KK, Cooper JK: Bioavailability of Canadian tablet formulations of Warfarin Sodium and Potassium. Can J Pharm Sci. 1978;13:9-11.
[10] Wagner JG, Welling PG, Lee KP and Walker JE: In vivo and in vitro availability of commercial Warfarin tablets. J Pharm Sci. 1971;60:666-677.
[11] Neutel JM, Smith DHG. A randomized crossover study to compare the efficacy and tolerability of Barr warfarin sodium to the currently available Coumadin. Cardiovasc Rev Rep. 1998;19:49–59.
[12] Handler J, Nguyen TT, Rush S, Pham NT. A blinded, randomized, crossover study comparing the efficacy and safety of generic warfarin sodium to Coumadin. Prev Cardiol. 1998;4;13–20.
[13] Weibert RT, Yeager BF, Wittkowsky AK, Bussey HI, Wilson DB, Godwin JE et al. A randomized, crossover comparison of warfarin products in the treatment of atrial fibrillation. Ann Pharmacother. 2000;34:981–8.
[14] Lee HL, Kan CD, Yang YJ. Efficacy and tolerability of the switch from a branded to a generic warfarin sodium product: an observer-blinded, randomized, crossover study. Clin Ther. 2005;27:309–19.
[15] Pereira JA, Holbrook AM, Dolovich L, Goldsmith C, Thabane L, Douketic JD et al. Are brand-name and generic warfarin interchangeable? Multiple n-of-1 randomized, crossover trials. Ann Pharmacother. 2005 Jul-Aug; 39:1188-93.
[16] Swenson CN, Fundak G. Observational cohort study of switching warfarin sodium products in a managed care organization. Am J Health Syst Pharm. 2000;57:452-455.
[17] Milligan PE, Banet GA, Waterman AD, Gatchel SK, Gage BF. Substitution of Generic Warfarin for Coumadin in an HMO Setting. Ann Pharmacother. 2002;36: 764-768.
[18] Richton-Hewett S, Foster E, Apstein CS: Medical and economic consequences of a blinded oral anticoagulant brand change at a municipal hospital. Arch Intern Med. 1998;148:806-808.
[19] Ghate SR, Biskupiak JE, Ye X, Hagan M, Kwong WJ, Fox ES, et al. Hemorrhagic and thrombotic events associated with generic substitution of warfarin in patients with atrial fibrillation: a retrospective analysis. Ann Pharmacother. 2011;45: 701-12.
[20] Halkin H, Shapiro J, Kurnik D, Loebstein R, Shalev V, Kokia E. Increased warfarin doses and decreased international normalized ratio response after nationwide generic switching. Clin Pharmacol Ther. 2003;74:215-221.
[21] Witt DM, Tillman DJ, Evans CM, Plotkin TV, Sadler MA. Evaluation of the clinical and economic impact of a brand name-to-generic warfarin sodium conversion program. Pharmacotherapy. 2003;23:360-368.
[22] Paterson JM, Naglie G, Laupacis A, Stukel T. Clinical consequences of generic warfarin substitution. JAMA. 2006;296:1969-1972.
[23] Danish Health and Medicines Authority. Warfarin Orion must not replace Marevan and Waran. Danish Pharmacovigilance. 2015[cited 2015 July 4]. Available from: https://sundhedsstyrelsen.dk/en/news/2015/danish-pharmacovigilance-update,-april-2015.
[24] Hope KA1, Havrda DE. Subtherapeutic INR values associated with a switch to generic warfarin. Ann Pharmacother. 2001 Feb;35:183-7.

Strategies to overcome tamoxifen resistance in breast cancer

Farzana Yasmin Zaman
Final Year Medicine/BMedSci (Undergraduate)
Monash University

Farzana is currently doing a BMedSci in the area of breast cancer research. She hopes to one day be an oncologist and clinician-scientist, and is looking forward to her final year of medical school in 2016. She plays violin in the Monash Medical Orchestra and enjoys devouring novels, travelling and spending time with her cat.

The selective oestrogen receptor modulator (SERM), tamoxifen, is pivotal in treating oestrogen receptor positive (ER+) breast cancers—the most common subtype of breast cancer. As the first targeted therapy for breast cancer, tamoxifen remains the gold standard of adjuvant endocrine therapy. However, this important drug has its limitations: its efficacy is frequently hampered by the phenomenon of tamoxifen resistance.

This article provides an overview of ER+ breast cancer biology relevant to understanding the complexities of tamoxifen resistance. The principal aim is to review the current literature on the mechanisms underpinning tamoxifen resistance and emerging strategies to overcome this challenge, with a focus on those with the greatest translational potential.

Numerous molecular mechanisms of tamoxifen resistance have been proposed and investigated. Well-studied, clinically relevant mechanisms include growth factor receptor signalling, kinase pathway aberrations, cell-cycle dysregulation and epigenetic involvement. Other areas of relevance include the development of new generation SERMs and preclinical studies with novel agents. There is also increasing research into the roles of ER coregulator proteins and cancer stem cells.

Altogether, these areas of interest represent promising opportunities in overcoming the challenge of tamoxifen resistance and ameliorating current breast cancer therapies.

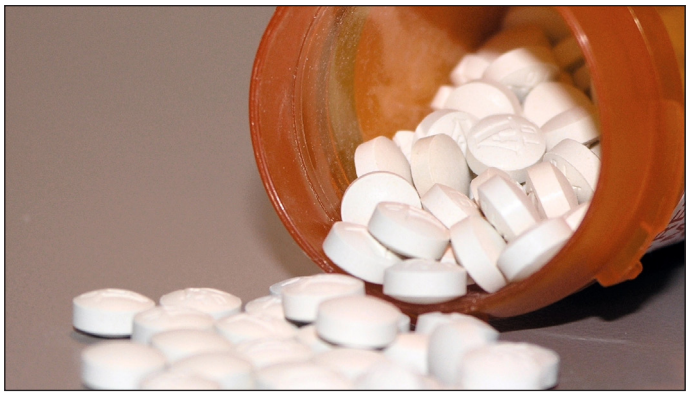
Introduction

Breast cancer is one of the most commonly diagnosed cancers in Australian women. [1] Importantly, breast cancer is a heterogenous disease. It exhibits a wide spectrum of clinical, histopathological and molecular features, which impact prognosis, survival, and response to treatment. In 1896, Sir George Beatson made a landmark discovery: bilateral oophorectomy resulted in tumour remission in a significant proportion of women with metastatic breast cancer. [2] This finding gave birth to the theory that the ovarian hormone, oestrogen, is involved in stimulating the growth of some breast cancers. Indeed, on a molecular level, 70-75% of invasive breast cancers are oestrogen receptor positive (ER+) and proliferate in response to oestrogen, [3] as Beatson deduced.

Patients with ER+ tumours tend to have good prognoses and long-term survival, with a 5-year survival rate of 80-85% in the curative setting. In comparison, ER negative (ER-) cancers are associated with earlier relapses and a lower 5-year survival rate. [3] These discrepancies are partly attributable to availability of effective endocrine therapies, and demonstrate the marked efficacy of such targeted therapies.

Methods

A broad literature review was undertaken on Ovid MEDLINE and PubMed using combinations of the search terms 'tamoxifen resistance OR endocrine resistance'; 'mechanism'; and 'breast cancer'. Limits were set to include articles written in English published since 2000. The search was then further refined to clinical trials published since 2010.



Background

Endocrine therapy

Beatson's findings led to the naissance of endocrine therapies: drugs that either inhibit oestrogen synthesis or block the oestrogen receptor (ER). Indeed, these therapies have revolutionised breast cancer management. There are three main classes of endocrine therapies (Table 1) used as adjuvants to surgery, radiotherapy, and chemotherapy in treating ER+ breast cancers.

Tamoxifen, in particular, has changed the landscape of breast cancer treatment since its discovery over three decades ago. In 1998, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group confirmed that adjuvant tamoxifen treatment substantially improved 10-year survival rates in women with ER+ breast tumours. [4] It has achieved a 39% reduction in disease recurrence and 31% reduction in mortality in early-stage ER+ cancers. [5]

Despite newer drugs, such as aromatase inhibitors (AIs) and selective oestrogen receptor degraders (SERDs), tamoxifen remains the cornerstone of endocrine therapy. Current American Society of Clinical Oncology guidelines outline tamoxifen as first-line adjuvant endocrine therapy in pre-menopausal women and, alongside aromatase inhibitors, in postmenopausal women. [6] Until recently, tamoxifen

Table 1. *Endocrine therapies currently used for ER+ breast cancer.*

Class	Example	Mechanism of action
Selective oestrogen receptor modulators (SERMs)	Tamoxifen	Partial ER agonist and antagonist Binds ER, modulates downstream gene transcription and function
Aromatase inhibitors (AIs)	Steroidal: Anastrozole Letrozole	Blocks peripheral conversion of adrenal androgens to oestrogen
	Non-steroidal: Exemestane	Only successful in women without ovarian function
Selective oestrogen receptor degraders (SERDs)	Fulvestrant	Binds to ER, leads to degradation of receptor

was also recommended for systemic therapy for metastatic hormone-dependent breast cancers. [7] However, AIs are increasingly being used due to the issue of tamoxifen resistance. [8]

Tamoxifen resistance

Approximately 30% of patients with ER+ tumours fail to respond to tamoxifen from the initiation of therapy, [9,10] which is termed de novo or intrinsic resistance. [11] Another 30-40% of patients receiving adjuvant tamoxifen eventually develop disease progression or recurrence within three to five years; this is known as acquired resistance. [10,12]

Understanding tamoxifen resistance is a major focus of current breast cancer research. Before undertaking a literature review on current strategies to overcome tamoxifen resistance, it is necessary to touch on basic ER biology in breast cancer.

Oestrogen receptor biology

There are two ER isoforms, ERα and ERβ, [13] and both are present in normal breast tissue. ERα is clearly associated with breast carcinogenesis and progression, and is the subtype best measured in assays. In contrast, the role of ERβ in breast cancer is still unclear. [13] Use of the term ER hereon refers to ERα, unless otherwise specified.

The classical pathway of ER signalling involves oestrogen binding to the ligand-binding domain of ER. The ligand-activated ER then binds to oestrogen response elements via essential transcription factors that regulate target gene expression. [14] In breast cancer, oestrogen-mediated activation of the ER pathway leads to another chain of events resulting in altered gene transcription, ultimately producing proteins that drive cell division, differentiation, proliferation, and angiogenesis. Subsequently, this leads to tumour growth and progression. [15] Furthermore, coregulator proteins modulate ER transcriptional activities. These proteins either activate or repress transcription of ER-responsive genes and are known as coactivators and corepressors, respectively. [16]

Mechanisms to overcome tamoxifen resistance

Growth factor receptor signalling

Growth factors are involved in regulating the ER signalling pathway. [17] These include membrane receptor tyrosine kinases such as epidermal growth factor receptor (EGFR) and human epidermal receptor (IGFR) (Figure 1). [17,18] If upregulated, these growth factor pathways can provide ER+ breast cancers with stimuli for growth, proliferation, and survival, even when the ER pathway has been inhibited, thus behaving as ER-independent drivers of tumour growth.

There is a growing body of evidence that increased growth factor signalling contributes to endocrine therapy resistance. The EGFR/HER2 pathway has been strongly implicated. In fact, preclinical and clinical studies demonstrate that tumours overexpressing EGFR or HER2 are less likely to benefit from endocrine therapy. [19] HER2+/ER+ tumours have poorer prognoses, compared to HER2-/ER+ tumours. [3] In xenograft models, HER2 overexpression leads to tamoxifen-stimulated growth, a potential mechanism conferring intrinsic resistance. Direct interactions between ER and HER2 protect HER2+ cancer cells from tamoxifen-induced apoptosis. [17,20] Consequently, blocking this pathway with the HER2 antibody, trastuzumab, restores tamoxifen sensitivity in resistant cells. [21]

The EGFR/HER2 pathway is also involved in acquired tamoxifen resistance. *In vitro*, long-term tamoxifen treatment leads to stronger EGFR and HER2 expression at the time of drug resistance. A marked increase in EGFR expression is seen in xenograft ER+ tumours with acquired resistance. [12] It has also been shown that EGFR downstream elements that stimulate proliferation and cell survival are overactive in tamoxifen resistant cells. Gefitinib is a selective inhibitor of the tyrosine kinase domain of the EGFR (Figure 1). Adding gefitinib to tamoxifen has been shown to significantly delay the onset of resistance, *in vitro*. [22]

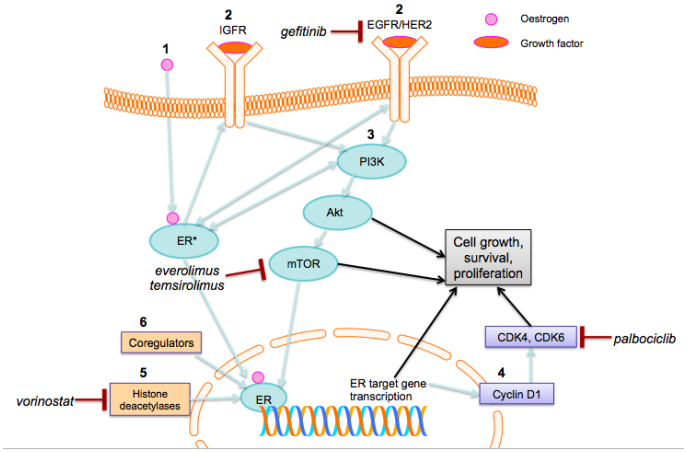


Figure 1. *Pathways upregulated in tamoxifen resistance in ER+ breast cancers and associated drug targets. 1. Oestrogen activates the ER. Oestrogen-bound ER activates ER target gene transcription, which is influenced by ER coregulator proteins and enzymes, such as histone deacetylases. 2. Oestrogen-bound ER also activates growth factor receptors (IGFR, EGFR, HER2). 3. This activates key molecules in the PI3K/Akt/mTOR downstream pathway. In turn, this leads to increased cell growth, survival, and proliferation. There is bidirectional crosstalk among the PI3K/Akt/mTOR pathway, EGFR/HER2 and ER. 4. Cyclin D1 is an ER transcriptional target gene that activates CDK4 and CDK6, leading to cell proliferation. 5. Histone deacetylation and 6. ER coregulator proteins modify ER target gene transcription, which also leads to cell growth, survival and proliferation. Gefitinib inhibits EGFR; everolimus and temsirolimus inhibit mTOR activation, palbociclib; palbocilib is a selective CDK4 and CDK6 inhibitor; and vorinostat inhibits histone deacetylation. (Abbreviations: ER, oestrogen receptor; IGFR, insulin-like growth factor receptor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PI3K, phosphatidylinositol-3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; CDK, cyclin-dependent kinase)*

Based on these promising findings, several phase II clinical trials have combined endocrine and targeted inhibitor therapies. Recent preliminary studies confirm that adding gefitinib to tamoxifen is beneficial compared to placebo, and the combination warrants further clinical investigation. [23]

Kinase pathways

The phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) / mammalian target of rapamycin (mTOR) pathway is an important downstream target in ER+ breast cancer (Figure 1). It has a key role in breast carcinogenesis, and has been linked to endocrine therapy resistance. The mTOR protein controls cellular processes such as growth, survival, and proliferation. Activating mutations in PI3K are known to be oncogenic. [24] Indeed, PIK3CA gene mutations are amongst the commonest somatic mutations in breast cancer and are more frequently identified in ER+ breast cancers than ER- cancers. [25,26]

Crosstalk between ER and the PI3K/Akt/mTOR pathway increases oestrogen-induced transcriptional activity, contributing to tamoxifen resistance. [27] *In vitro*, the PI3K pathway is activated in response to oestrogen depletion, leading to acquired hormone-resistant breast cancer cells. [28] The drug temsirolimus prohibits mTOR activation, thus acting as an mTOR inhibitor (Figure 1). Temsirolimus can restore tamoxifen sensitivity in breast cancer cells. Phase II clinical trials demonstrate the beneficial effects of adding another similarly acting mTOR inhibitor, everolimus, to tamoxifen in patients with metastatic disease that is resistant to AIs. [29] Likewise, clinical trials of everolimus in combination with endocrine therapies (exemestane and letrozole) have led to the first mTOR-inhibitor being approved for postmenopausal women with advanced ER+/HER2- breast cancer. [29,30] Altogether, this points strongly at the role of mTOR inhibitors in overcoming endocrine resistance.

Histone deacetylases

Epigenetic mechanisms, such as histone acetylation and hypoacetylation, modify gene expression. Both histone acetylation and hypoacetylation can contribute to oncogenesis, depending on the target gene. Histone deacetylases (HDACs) are the primary enzymes involved in histone hypoacetylation, and have been associated with breast cancer. Importantly, studies have shown that HDACs interact with the ER signalling pathway (Figure 1), but the precise mechanism remains to be elucidated. [31] Epigenetic modulation of ER signalling by HDAC inhibition is another promising strategy to combat tamoxifen resistance. The drug vorinostat binds to the active site of HDACs, to inhibit their action (Figure 1). *In vitro*, vorinostat downregulates ER transcription and potentiates apoptotic cell death in ER+ cells. [32] In Phase II clinical studies, the combination of vorinostat and tamoxifen appears well tolerated and provides encouraging results for reversing hormone resistance. [33]

Cyclins and cyclin-dependent kinases

Cyclins and cyclin-dependent kinases (CDKs) are involved in cell-cycle regulation. The cyclin D1 gene is a direct transcriptional target of ER signalling. Cyclin D1 activates cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), thus inactivating the retinoblastoma tumour suppressor protein. In turn, this promotes cell-cycle entry and proliferation. [34] *In vitro*, endocrine therapy-resistant breast cancer models exhibit an uncoupling of ER signalling and cell cycle progression: cyclin D1 activity is maintained despite effective blockade of ER with tamoxifen. There is evidence suggesting that resistant cancers remain dependent on cyclin D1-CDK4 to drive proliferation. [35] Palbociclib is a selective CDK4 and CDK6 inhibitor (Figure 1) [34] that has been studied as a potential reverser of endocrine resistance. *In vitro* studies and phase II trials of palbociclib as a synergistic therapy with letrozole in resistant tumours demonstrated that this combination is associated with longer progression-free survival. [36-38] A recent phase III trial involving patients with advanced endocrine therapy-resistant ER+ tumours concluded that palbociclib combined with fulvestrant was more effective than fulvestrant alone. [39] Though these studies do not focus on tamoxifen resistance per se, the results suggest a promising role for this drug in improving treatment outcomes for ER+ cancers.

Alternative endocrine therapies

Aromatase inhibitors (Table 1) are now standard treatment options for postmenopausal women with ER+ tumours. It is commonly accepted that third generation AIs have equivalent or superior efficacy to tamoxifen in postmenopausal women. [8,40-42] Furthermore, AIs appear to be effective in some postmenopausal patients with acquired tamoxifen resistance. [43] However, AI resistance is proving to be as significant a problem as tamoxifen resistance. There is increasing research into the mechanisms behind AI resistance and trials combining targeted therapies with AIs. [44]

The SERD, fulvestrant, binds to the ER, degrades the receptor and inhibits its signalling pathways (Table 1). Unlike tamoxifen, it does not have agonist effects but has comparable efficacy to tamoxifen in postmenopausal women. [45] Importantly, it is not cross-resistant to tamoxifen and is as effective as anastrozole in treating postmenopausal women with acquired tamoxifen resistance. [46, 47] However, the efficacy of fulvestrant is dose-dependent [48] and more studies are needed to optimise treatments. Nevertheless, novel ER antagonists are a growing area in the pursuit to overcome endocrine resistance.

One such novel antagonist is TAS-108, a synthetic ER ligand with pure antagonistic activity that promotes corepressor recruitment without preventing DNA-binding activity. In preclinical studies, TAS-108 successfully inhibits tamoxifen-resistant tumour growth. [49] Phase II trials in postmenopausal patients show that it leads to observable clinical benefits in a proportion of patients. Additionally, it is well tolerated and not associated with significant changes in hormone levels or bone metabolism markers, as is the case with tamoxifen. [50]

New generation SERMs

Another strategy hinges on the development of new SERMs to inhibit ER signalling pathways. Two classes of alternative SERMs have been developed: tamoxifen-like compounds (idoxifene, toremifene, and droloxifine) and fixed-ring compounds (raloxifene, arzoxifene, and EM-800). [51,52]

As a class, new generation SERMs have greater binding affinity for ER and reduced agonist activity, compared to tamoxifen. Preclinical studies (*in vitro* and in vivo) have demonstrated that some alternative SERMs are more effective than tamoxifen in inhibiting ER+ tumour growth, including tamoxifen-resistant tumours. [53-55] However, this efficacy is yet to be recapitulated in clinical trials. [56] The prospect of clinically useful alternative SERMs is clouded by the fact that most known SERMs display a high level of cross-resistance with tamoxifen. [57] Indubitably, further research is required.

Novel agents in preclinical investigation

VEGF inhibitors

Angiogenesis is a hallmark of tumour growth and invasion. This process is modulated by the vascular endothelial growth factor (VEGF) family of growth factors and their associated receptors. Oestrogen enhances angiogenesis via VEGF release. [58] This oestrogen-dependent production of VEGF can be ablated by tamoxifen in tamoxifen-sensitive breast cancer cells. However, in tamoxifen-resistant cells, the VEGF/vascular endothelial growth factor receptor 2 (VEGFR2) signalling loop remains active, despite anti-oestrogenic treatment. [59]

High VEGF/VEGFR2 expression with concomitant elevated p38 mitogen-activated protein kinase activity is associated with poor outcomes in tamoxifen-treated cancers. Inhibition of p38 increases the inhibitory effect of tamoxifen in tamoxifen-resistant cells. [59] In murine xenograft models of tamoxifen-resistant ER+ tumours, low doses of the small-molecule VEGFR2 antagonist, brivanib alaninate, combined with tamoxifen, retards tumour growth and maximises therapeutic efficacy. [60] It remains to be seen whether this approach is effective in the clinic.

Src inhibitors

Src is a membrane-associated non-receptor tyrosine kinase belonging to the Src family kinase group (SFK). [61] Through their involvement in regulating signals from transmembrane receptor-associated tyrosine kinases and in activating intracellular target proteins, [62] SFKs modulate cell survival, proliferation, differentiation and angiogenesis. [63] Src also coordinates ER signalling and plays a role in its non-genomic effects. [63] Studies demonstrate associations between endocrine resistance, elevated Src activity and more aggressive tumour phenotypes. [64,65] Blocking interactions between ER and Src inhibits downstream cellular pathways, leading to decreased cell growth. [66] *In vitro*, Src inhibitors, which target the peptide substrate site of Src, partially restore response to tamoxifen in resistant cells [67] and reduce their invasive ability. [65] The combination of Src and EGFR inhibition has been shown to result in further growth inhibition in tamoxifen-resistant breast cancer cells. [65] These preclinical results suggest a promising role for Src inhibitors in overcoming tamoxifen resistance.

Notch inhibitors

Notch receptors belong to a signalling pathway involved in cell-to-cell communication and regulation of differentiation, proliferation, and apoptosis. [68] Elevated Notch-1 is associated with poor prognosis in breast cancer. In cell models of ER+ breast cancer, small interfering RNA-mediated Notch inhibition potentiates the effects of tamoxifen. When added to tamoxifen in murine xenograft models, such Notch inhibition leads to regression of ER+ tumours. [69]

Other areas of interest

Oestrogen receptor transcription factors and coregulator proteins

ER activity is influenced by ER transcription factors and coregulatory proteins. The ER pioneer transcription factor, forkhead box protein

A1 (FOXA1), and transcription factor GATA3 regulate binding between ER and chromatin, which is vital for tamoxifen's activity on ER. [70] Indeed, FOXA1 has been identified as a positive prognostic marker of ER+ breast cancer and an indicator of endocrine therapy response. [71] GATA3 has received attention, as it is one of three genes mutated in over 10% of breast cancers, however, it is yet to be clearly linked with endocrine response. [72]

ER coregulators have long been known to play a part in tamoxifen's function. When tamoxifen binds to ER in the breast, the resulting receptor conformation favours corepressor recruitment, consequently blocking the proliferative actions of ER signalling. In contrast, oestrogen-bound ER favours coactivator recruitment. [73]

Increased coactivator and decreased corepressor expression is frequently seen in breast tumourigenesis. [74] Coactivator gene AIB1 is amplified in 50% of primary breast tumours and correlates with ER-positivity. [75] AIB1 overexpression is also associated with poorer outcomes in patients receiving tamoxifen, pointing at a link to tamoxifen-resistant tumours. [76] Experimental overexpression of the coactivator, nuclear receptor coactivator 1 (NCOA1), increases tamoxifen's agonist activity. [77] This bolsters the belief that coactivator overexpression contributes to endocrine resistance by enhancing the unfavourable ER agonist activity of tamoxifen.

Conversely, downregulation of the corepressor, nuclear receptor corepressor (NCOR), is observed in xenograft models with acquired tamoxifen resistance. [78] An imbalance in coactivator and corepressor gene expression may impair tamoxifen activity by eliminating its antagonistic effect. [74] Indeed, coregulators appear to be an exciting future drug target.

Cancer stem cells

The cancer stem cell (CSC) hypothesis has established another area of investigation. Tumour-initiating CSCs drive cancer progression and metastasis and may be partly responsible for resistance. In the normal breast, stem cells possess an ER- phenotype. It is postulated that a remaining pool of ER- CSCs in tumour areas continue to develop over growth-arrested ER+ cells. In essence, this converts the bulk of tumour cells from ER+ to ER-. [79] Most current therapies fail to eliminate CSCs, thus potentiating such growth.

Tamoxifen-resistant cells have a larger CSC population than sensitive cells. [80] Furthermore, several groups have identified dysregulated stem cell signalling mechanisms and overexpressed stem cell markers in tamoxifen-resistant cells and tumours that have failed endocrine therapy. [80,81] Significantly, in preclinical studies, downregulation or inhibition of these pathways sensitises resistant cells or decreases progenitor populations. [80,81] Therefore, CSCs hold great potential as putative targets for treating tamoxifen-resistant breast cancers.

Future

It is a fundamental tenet of oncology that no single drug will "cure" cancer. Likewise, no single drug will overcome tamoxifen resistance. It is resoundingly clear that there is no single mechanism underlying tamoxifen resistance. Rather, it involves complex molecular interactions and crosstalk between pathways. The key to overcoming resistance lies in the development of combination therapies. Many promising clinical trials in this area centre on combining tamoxifen with drugs targeting postulated molecular pathways that modulate ER effects. Other approaches aim to build on the principles of tamoxifen therapy by optimising its pharmacology and elucidating methods to increase its favourable antagonist actions.

Moreover, multiple mechanisms may contribute to resistance in an individual patient. This ties in with another principle of modern oncology: the importance of personalised medicine. The concomitant challenge lies in identifying prognostic biomarkers of intrinsic resistance before commencing therapy, and those of acquired resistance as early as possible. The advent of next generation sequencing has already enabled the identification of some genetic and molecular signatures. Hand-in-hand with this, comes the potential need for rebiopsy to detect changes in tumour biology following directed therapies, an area which requires careful consideration. Undoubtedly, in the future, clinically useful biomarkers will facilitate personalised, targeted therapies to overcome the issue of tamoxifen resistance.

Conclusion

There are numerous approaches to addressing tamoxifen resistance. Altogether, this plethora of information sheds light on the clinical conundrum. More importantly, it draws us closer to a multi-faceted strategy; the clinical trials highlighted above are testament to this. With greater research and collaboration, areas currently in the basic scientific or preclinical pipeline may be translated to clinical trials. This will provide clinicians and patients further hope in combating the phenomenon of tamoxifen resistance with more effective therapeutic options.

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None.

Conflicts of interest

None declared.

Correspondence

F Y Zaman: fyzam2@student.monash.edu

References

[1] Australian Institute of Health and Welfare. Cancer in Australia: an overview, 2014. Cancer series no. 78. Canberra: AIHW; 2014. Cat. no. CAN 75.

[2] Beatson G. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet. 1896; 148(3803):162-5.

[3] Sandhu R, Parker JS, Jones WD, Livasy CA, Coleman WB. Microarray-based gene expression profiling for molecular classification of breast cancer and identification of new targets for therapy. Lab Medicine. 2010;41(6):364-72.

[4] Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998;351(9114):1451-67.

[5] Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365:1687-717.

[6] Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol. 2014;32(21):2255-69.

[7] Bernard-Marty C, Cardoso F, Piccart MJ. Facts and controversies in systemic treatment of metastatic breast cancer. Oncologist. 2004;9(6):617-32.

[8] Paridaens R, Dirix L, Lohrisch C, Beex L, Nooij M, Cameron D, et al. Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. Ann Oncol. 2003;14(9):1391-8.

[9] Ring A, Dowsett M. Mechanisms of tamoxifen resistance. Endocr Relat Cance r. 2004;11(4):643-58.

[10] Haldosén L-A, Zhao C, Dahlman-Wright K. Estrogen receptor beta in breast cancer. Mol Cell Endocrinol. 2014;382(1):665-72.

[11] Riggins RB, Schrecengost RS, Guerrero MS, Bouton AH. Pathways to tamoxifen resistance. Cancer Lett. 2007;256(1):1-24.

[12] Massarweh S, Schiff R. Resistance to endocrine therapy in breast cancer: exploiting estrogen receptor/growth factor signaling crosstalk. Endocr Relat Cancer. 2006;13(Supplement 1):S15-S24.

[13] Speirs V, Skliris GP, Burdall SE, Carder PJ. Distinct expression patterns of ERα and ERβ in normal human mammary gland. J Clin Pathol. 2002;55(5):371-4.

[14] Williams C, Lin CY. Oestrogen receptors in breast cancer: basic mechanisms and clinical implications. Ecancermedicalscience. 2013;7:370.

[15] Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med. 2002;346(5):340-52.

[16] Osborne CK, Schiff R, Fuqua SA, Shou J. Estrogen receptor: current understanding of its activation and modulation. Clin Cancer Res. 2001;7(12 Suppl):4338s-42s.

[17] Shou J, Massarweh S, Osborne C, Wakeling A, Ali S, Weiss H, et al. Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. J Natl Cancer Inst. 2004;96:926 - 35.

[18] Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med. 2011;62:233-47.

[19] Arpino G, Green SJ, Allred DC, Lew D, Martino S, Osborne CK, et al. HER-2 amplification, HER-1 expression, and tamoxifen response in estrogen receptor-positive metastatic breast cancer: a Southwest Oncology Group study. Clin Cancer Res. 2004;10(17):5670-6.

[20] Chung Y-L, Sheu M-L, Yang S-C, Lin C-H, Yen S-H. Resistance to tamoxifen-induced apoptosis is associated with direct interaction between Her2/neu and cell membrane estrogen receptor in breast cancer. Int J Cancer. 2002;97(3):306-12.

[21] Chen B, Wang Y, Kane SE, Chen S. Improvement of sensitivity to tamoxifen in ER-positive and Herceptin-resistant breast cancer cells. J Mol Endocrinol. 2008;41(5):367-77.

[22] Gee JM, Harper ME, Hutcheson IR, Madden TA, Barrow D, Knowlden JM, et al. The antiepidermal growth factor receptor agent gefitinib (ZD1839/Iressa) improves antihormone response and prevents development of resistance in breast cancer in vitro. Endocrinology. 2003;144(11):5105-17.
[23] Osborne CK, Neven P, Dirix LY, Mackey JR, Robert J, Underhill C, et al. Gefitinib or placebo in combination with tamoxifen in patients with hormone receptor-positive metastatic breast cancer: a randomized phase II study. Clin Cancer Res. 2011;17(5):1147-59.
[24] Vinayak S, Carlson RW. mTOR inhibitors in the treatment of breast cancer. Oncology. 2013;27(1):38-44, 6, 8 passim.
[25] Hennessy BT, Smith DL, Ram PT, Lu Y, Mills GB. Exploiting the PI3K/AKT pathway for cancer drug discovery. Nat Rev Drug Discov. 2005;4(12):988-1004.
[26] Stemke-Hale K, Gonzalez-Angulo AM, Lluch A, Neve RM, Kuo W-L, Davies M, et al. An integrative genomic and proteomic analysis of PIK3CA, PTEN, and AKT mutations in breast cancer. Cancer Res. 2008;68(15):6084-91.
[27] Tokunaga E, Hisamatsu Y, Tanaka K, Yamashita N, Saeki H, Oki E, et al. Molecular mechanisms regulating the hormone sensitivity of breast cancer. Cancer Sci. 2014;105(11):1377-83.
[28] Beelen K, Opdam M, Severson TM, Koornstra RH, Vincent AD, Wesseling J, et al. Phosphorylated p-70S6K predicts tamoxifen resistance in postmenopausal breast cancer patients randomized between adjuvant tamoxifen versus no systemic treatment. Breast Cancer Res. 2014;16(1):R6.
[29] Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero J-M, Freyer G, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J. Clin. Oncol.. 201; 30(22):2718-24.
[30] Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. N Engl J Med. 2012;366(6):520-9.
[31] Citro S, Miccolo C, Meloni L, Chiocca S. PI3K/mTOR mediate mitogen-dependent HDAC1 phosphorylation in breast cancer: a novel regulation of estrogen receptor expression. J Mol Cell Biol. 2015;7(2):132-42.
[32] Hodges-Gallagher L, Valentine CD, Bader SE, Kushner PJ. Inhibition of histone deacetylase enhances the anti-proliferative action of antiestrogens on breast cancer cells and blocks tamoxifen-induced proliferation of uterine cells. Breast Cancer Res Treat. 2007;105(3):297-309.
[33] Munster PN, Thurn KT, Thomas S, Raha P, Lacevic M, Miller A, et al. A phase II study of the histone deacetylase inhibitor vorinostat combined with tamoxifen for the treatment of patients with hormone therapy-resistant breast cancer. Br J Cancer. 2011;104(12):1828-35.
[34] Rocca A, Farolfi A, Bravaccini S, Schirone A, Amadori D. Palbociclib (PD 0332991): targeting the cell cycle machinery in breast cancer. Exp Opin Pharmacother. 2014;15(3):407-20.
[35] Thangavel C, Dean JL, Ertel A, Knudsen KE, Aldaz CM, Witkiewicz AK, et al. Therapeutically activating RB: reestablishing cell cycle control in endocrine therapy-resistant breast cancer. Endocr-Relat Cancer. 2011;18(3):333-45.
[36] DeMichele A, Clark AS, Tan KS, Heitjan DF, Gramlich K, Gallagher M, et al. CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. Clin Cancer Res. 2015;21(5):995-1001.
[37] Finn RS, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res. 2009;11(5):R77-R.
[38] Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. The Lancet Oncol. 2015;16(1):25-35.
[39] Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med 2015; 373(3)209-19.
[40] Smith IE, Dowsett M, Ebbs SR, Dixon JM, Skene A, Blohmer JU, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol. 2005;23(22):5108-16.
[41] Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol. 2003;21(11):2101-9.
[42] Ellis MJ, Coop A, Singh B, Mauriac L, Llombert-Cussac A, Janicke F, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol. 2001;19(18):3808-16.
[43] Buzdar A, Douma J, Davidson N, Elledge R, Morgan M, Smith R, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol. 2001;19(14):3357-66.
[44] Ma CX, Reinert T, Chmielewska I, Ellis MJ. Mechanisms of aromatase inhibitor resistance. Nat Rev Cancer. 2015;15(5):261-75.
[45] Howell A, Robertson JFR, Abram P, Lichinitser MR, Elledge R, Bajetta E, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. J Clin Oncol. 2004;22(9):1605-13.
[46] Chia S, Gradishar W. Fulvestrant: expanding the endocrine treatment options for patients with hormone receptor-positive advanced breast cancer. Breast. 2008;17 Suppl 3:S16-21.
[47] Robertson JF, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Macpherson E, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. J Clin Oncol. 2009; 27(27):4530-5.
[48] Young OE, Renshaw L, Macaskill EJ, White S, Faratian D, Thomas JS, et al. Effects of fulvestrant 750mg in premenopausal women with oestrogen-receptor-positive primary breast cancer. Eur J Cancer. 2008; 44(3):391-9.
[49] Buzdar AU. TAS-108: a novel steroidal antiestrogen. Clin Cancer Res. 2005;11(2):906s-8s.
[50] Saeki T, Noguchi S, Aogi K, Inaji H, Tabei T, Ikeda T. Evaluation of the safety and tolerability of oral TAS-108 in postmenopausal patients with metastatic breast cancer. Ann Oncol . 2009;20(5):868-73.
[51] Lewis-Wambi JS, Jordan VC. Treatment of postmenopausal breast cancer with Selective Estrogen Receptor Modulators (SERMs). Breast Dis. 2005;24:93-105.
[52] Jiang Q, Zheng S, Wang G. Development of new estrogen receptor-targeting therapeutic agents for tamoxifen-resistant breast cancer. Future Med Chem. 2013; 5(9):1023-35.
[53] Greenberger LM, Annable T, Collins KI, Komm BS, Lyttle CR, Miller CP, et al. A new antiestrogen, 2-(4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-o l hydrochloride (ERA-923), inhibits the growth of tamoxifen-sensitive and -resistant tumors and is devoid of uterotropic effects in mice and rats. J Clin Oncol. 2001;7(10):3166-77.
[54] Freddie CT, Larsen SS, Bartholomaeussen M, Lykkesfeldt AE. The effect of the new SERM arzoxifene on growth and gene expression in MCF-7 breast cancer cells. Mol Cell Endocrinol. 2004;219(1-2):27-36.
[55] Johnston SR, Gumbrell LA, Evans TR, Coleman RE, Smith IE, Twelves CJ, et al. A cancer research (UK) randomized phase II study of idoxifene in patients with locally advanced/metastatic breast cancer resistant to tamoxifen. Cancer Chemother Pharmacol. 2004;53(4):341-8.
[56] Dowsett M, Dixon JM, Horgan K, Salter J, Hills M, Harvey E. Antiproliferative effects of idoxifene in a placebo-controlled trial in primary human breast cancer. J Clin Oncol. 2000;6(6):2260-7.
[57] Gao ZO, Gao ZP, Fields JZ, Boman BM. Development of cross-resistance to tamoxifen in raloxifene-treated breast carcinoma cells. Anticancer Res. 2002;22(3):1379-83.
[58] Hyder SM. Sex-steroid regulation of vascular endothelial growth factor in breast cancer. Endocr-Relat. Cancer. 2006;13(3):667-87.
[59] Aesoy R, Sanchez BC, Norum JH, Lewensohn R, Viktorsson K, Linderholm B. An autocrine VEGF/VEGFR2 and p38 signaling loop confers resistance to 4-hydroxytamoxifen in MCF-7 breast cancer cells. Mol Cancer Res. 2008; 6(10):1630-8.
[60] Patel RR, Sengupta S, Kim HR, Klein-Szanto AJ, Pyle JR, Zhu F, et al. Experimental treatment of estrogen receptor (ER) positive breast cancer with tamoxifen and brivanib alaninate, a VEGFR-2/FGFR-1 kinase inhibitor: a potential clinical application of angiogenesis inhibitors. Eur. J. Cancer. 2010;46(9):1537-53.
[61] Parsons SJ, Parsons JT. Src family kinases, key regulators of signal transduction. Oncogene. 2004;23(48):7906-9.
[62] Belsches-Jablonski AP, Biscardi JS, Peavy DR, Tice DA, Romney DA, Parsons SJ. Src family kinases and HER2 interactions in human breast cancer cell growth and survival. Oncogene. 2001;20(12):1465-75.
[63] Mayer EL, Krop IE. Advances in targeting Src in the treatment of breast cancer and other solid malignancies. Clin Cancer Res. 2010; 16(14):3526-32.
[64] Riggins RB, Thomas KS, Ta HQ, Wen J, Davis RJ, Schuh NR, et al. Physical and functional interactions between Cas and c-Src induce tamoxifen resistance of breast cancer cells through pathways involving epidermal growth factor receptor and signal transducer and activator of transcription 5b. Cancer Res. 2006;66(14):7007-15.
[65] Hiscox S, Morgan L, Green TP, Barrow D, Gee J, Nicholson RI. Elevated Src activity promotes cellular invasion and motility in tamoxifen resistant breast cancer cells. Breast Cancer Res Treat. 2006;97(3):263-74.
[66] Varricchio L, Migliaccio A, Castoria G, Yamaguchi H, de Falco A, Di Domenico M, et al. Inhibition of estradiol receptor/Src association and cell growth by an estradiol receptor α tyrosine-phosphorylated peptide. Mol Cancer Res. 2007; 5(11):1213-21.
[67] Anbalagan M, Carrier L, Glodowski S, Hangauer D, Shan B, Rowan BG. KX-01, a novel Src kinase inhibitor directed toward the peptide substrate site, synergizes with tamoxifen in estrogen receptor alpha positive breast cancer. Breast Cancer Res Treat. 2012;132(2):391-409.
[68] Miele L, Golde T, Osborne B. Notch signaling in cancer. Curr Mol Med. 2006; 6(8):905-18.
[69] Rizzo P, Miao H, D'Souza G, Osipo C, Song LL, Yun J, et al. Cross-talk between notch and the estrogen receptor in breast cancer suggests novel therapeutic approaches. Cancer Res. 2008;68(13):5226-35.
[70] Hurtado A, Holmes KA, Ross-Innes CS, Schmidt D, Carroll JS. FOXA1 is a critical determinant of estrogen receptor function and endocrine response. Nat Genet. 2011; 43(1):27-33.
[71] Mehta R, Jain R, Leung S, Choo J, Nielsen T, Huntsman D, et al. FOXA1 is an independent prognostic marker for ER-positive breast cancer. Breast Cancer Res Treat. 2012;131(3):881-90.
[72] Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61-70.
[73] Heldring N, Nilsson M, Buehrer B, Treuter E, Gustafsson J-Å. Identification of tamoxifen-induced coregulator interaction surfaces within the ligand-binding domain of estrogen receptors. Mol Cell Biol. 2004;24(8):3445-59.
[74] Girault I, Bieche I, Lidereau R. Role of estrogen receptor alpha transcriptional coregulators in tamoxifen resistance in breast cancer. Maturitas. 2006;54(4):342-51.
[75] Bautista S, Vallès H, Walker RL, Anzick S, Zeillinger R, Meltzer P, et al. In breast cancer, amplification of the steroid receptor coactivator gene AIB1 is correlated with estrogen and progesterone receptor positivity. Clin Cancer Res. 1998; 4(12):2925-9.
[76] Osborne CK, Bardou V, Hopp TA, Chamness GC, Hilsenbeck SG, Fuqua SAW, et al. Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER-2/neu in tamoxifen resistance in breast cancer. J Natl Cancer Inst. 2003; 95(5):353-61.
[77] Smith CL, Nawaz Z, O'Malley BW. Coactivator and corepressor regulation of the agonist/antagonist activity of the mixed antiestrogen, 4-Hydroxytamoxifen. Mol Endocrinol. 1997;11(6):657-66.
[78] Lavinsky RM, Jepsen K, Heinzel T, Torchia J, Mullen T-M, Schiff R, et al. Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes. Proc Natl Acad Sci U.S.A. 1998;95(6):2920-5.
[79] O'Brien C, Howell S, Farnie G, Clarke R. Resistance to endocrine therapy: are breast cancer stem cells the culprits? J Mammary Gland Biol Neoplasia. 2009; 14(1):45-54.
[80] Dubrovska A, Hartung A, Bouchez LC, Walker JR, Reddy VA, Cho CY, et al. CXCR4 activation maintains a stem cell population in tamoxifen-resistant breast cancer cells through AhR signalling. Br J Cancer. 2012;107(1):43-52.
[81] Piva M, Domenici G, Iriondo O, Rabano M, Simoes BM, Comaills V, et al. Sox2 promotes tamoxifen resistance in breast cancer cells. EMBO molecular medicine. 2014;6(1):66-79

A review of current and novel treatment strategies for chronic plaque psoriasis

Yiliang Zheng
MBBS

Yiliang Zheng is a graduate of Monash University in Melbourne. He has a broad range of interests within internal medicine, such as cardiology, rheumatology, and dermatology, and is still actively exploring each subspecialty with an open mind. He also enjoys teaching junior medical students, finding it challenging, enriching and fulfilling.

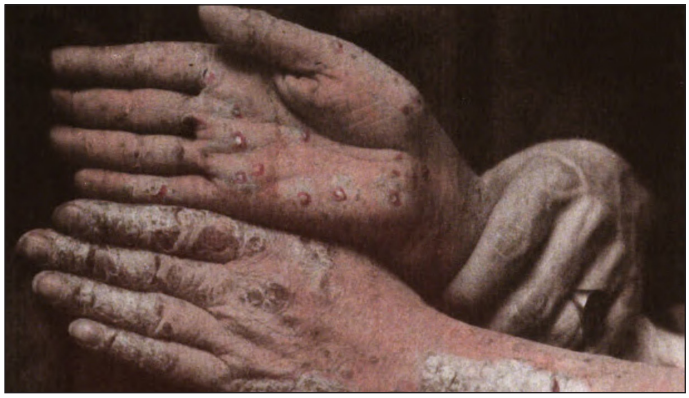
Psoriasis is a chronic, immune-mediated inflammatory dermatosis with many comorbidities, particularly psoriatic arthritis, metabolic syndrome, and depression. Psoriasis has a significant impact on quality of life, especially for those with severe disease. It is therefore important for the physician to evaluate patient preferences and choices when considering an optimal treatment approach and therapeutic regimen for the individual patient. Currently, the physician can select from multiple treatment options. Lifestyle modifications should be considered for all patients to minimise triggering factors. Topical therapy, particularly corticosteroids and vitamin D creams, are first-line for most patients with chronic plaque psoriasis. Other conventional therapies for psoriasis include phototherapy and systemic agents. Over the past decade, advances in the understanding of psoriasis pathogenesis have allowed the emergence of newer biologic agents that have significantly improved disease outcomes for patients with moderate-to-severe psoriasis. These include tumour necrosis factor alpha (TNFα) inhibitors, such as infliximab, adalimumab, and etanercept; an interleukin-12/interleukin-23 (IL-12/IL-23) inhibitor, namely ustekinumab; and the latest class of biologics, IL-17 inhibitors, such as secukinumab. New oral molecule inhibitors, such as phosphodiesterase-4 inhibitors and Janus kinase (JAK) inhibitors are currently being trialled in severe psoriasis.

Introduction

Psoriasis is a chronic, recurrent, immune-mediated inflammatory dermatosis with wide-ranging systemic effects. It affects approximately 2-3% of the population worldwide, with an estimated prevalence of 2.3-6.6% in Australia, where it is reported to be almost twice as prevalent in men as in women. [1] Psoriasis is currently understood as a multifactorial disorder with immune dysregulation, genetic susceptibility, and internal and environmental factors contributing to the disease onset. [1,2] The most common form of psoriasis is chronic plaque psoriasis, where salmon-pink plaques with silvery scales develop over the scalp, extensor surfaces, elbows, and knees, (due to the Koebner phenomenon). Sometimes it develops over the entire body surface and patients can become erythrodermic. Other subtypes of psoriasis are well described, such as guttate, flexural, pustular, and erythrodermic psoriasis.

Psoriasis is associated with several comorbidities, including psoriatic arthritis (PsA), cardiovascular disease, metabolic syndrome, hypertension, diabetes mellitus, dyslipidaemia, malignancies (skin cancers and lymphomas), inflammatory bowel disease, and psychiatric illness, including depression and anxiety. [1,3,4] It can have a significant impact on the patient's quality of life (QOL) and cause considerable psychosocial distress and disability.

The management of psoriasis, therefore, necessitates that the physician develop a holistic approach towards the patient. It is important for the patient to develop an understanding of the disease to allow discussion of therapeutic strategies with the physician and for the patient to express his/her treatment preferences. Common goals of therapy in psoriasis include complete remission of skin disease, optimising QOL, preserving functional status, and minimising or controlling comorbidities, particularly diseases of the joints.



Over the past decade, increasing understanding of the molecular and immunological mechanisms of psoriasis pathogenesis and the advent of newer monoclonal antibodies that demonstrate immense efficacy in treating psoriasis have dramatically expanded the treatment strategies that the physician can employ to treat an individual patient's condition. This paper will review and examine the various treatment modalities that are currently available to treat psoriasis, as well as highlight several upcoming novel agents for psoriasis treatment. It will focus on the Australian patient context, which will be relevant and practical to the Australian medical student.

Methods

A computerised search strategy was performed using MEDLINE and EMBASE up to November 2015. The search was limited to human studies of adults published in the English language and included reference lists of papers published.

Severity and impact of disease

Severity of disease can be measured using the Psoriasis Area and Severity Index (PASI) or body surface area (BSA) affected by psoriatic lesions. Mild disease is considered with lesions covering <10% of BSA or PASI ≤ 10. [5] PASI is one of the most commonly used measures of a clinically meaningful improvement. Clinical trials often use PASI 75 as a primary outcome, where the percentage of patients having at least 75% reduction in baseline PASI is evaluated. [6] Dermatology Life Quality Index (DLQI) is a quantitative measure examining the patient's perspective of the disease impact on his/her life. [7]

The impact of psoriasis on the patient's QOL cannot be underestimated. Various studies have assessed and evaluated DLQI and the clinical severity of psoriasis. QOL of psoriasis patients, in general, is strongly reduced and there is a linear, positive correlation between DLQI and BSA. [8] Patients suffer in many aspects of their lives, most frequently in social and emotional areas. [9] With the use of biologics, patients report satisfaction with their treatment, and DLQI and PASI decline and remain low for prolonged periods, with improvement in QOL. [10,11] It is important for the physician to evaluate patient preferences, choices regarding dosing frequency, and satisfaction with prior treatments in order to determine appropriate treatment regimens for the individual patient.

Considerations to treatment approach

Currently, the physician can select from a range of treatment strategies for psoriasis, from topical therapy and phototherapy to systemic oral agents and novel biologics,. However, there are currently no consensus

guidelines that provide a specific treatment algorithm. [12] Treatment regimens should hence be considered and individualised to each patient.

There are several factors that have to be considered by the physician in selecting an appropriate treatment regimen. The physician has to consider the patient's ability to apply and comply with topical therapy, which can be influenced by factors, such as the patient's age (young or elderly patients), presence of lesions over inaccessible areas, and the ease of application of topical therapy. [13,14] Extensive psoriasis-afflicted areas, such as in moderate or severe disease affecting large body surface areas, may be better treated with UV therapy, systemic therapy, or biologics, as compared to topical therapy, which may be a less practical treatment option. [14] The presence of PsA may suggest use of systemic therapies or biologics, which can be efficacious against both skin and joint diseases. [14]

Lifestyle modifications

Obesity has a strong known association with psoriasis severity. [4] Lifestyle weight loss intervention, by dieting or exercise, has been shown to reduce severity of psoriasis by a PASI score of 2.5, compared to a non-intervention group. [4] It is postulated that weight loss and the consequent decrease in adipose tissue decreases inflammatory cytokines, contributing to the improvement in severity of psoriasis. [4] Other modifiable lifestyle factors, such as stress, smoking, and trauma (in cases of the Koebner phenomenon) are also well-documented triggers of psoriasis. [1] Active steps can be taken by the patient, supported by their physician, to modify such factors to help decrease psoriasis flares and disease severity.

Topical therapies

Topical therapies are the first-line treatment for most patients with psoriasis, as most patients tend to have mild or limited disease. [13,14] It is common practice for patients to be on combination therapies, such as multiple topical agents, or topical therapies with a systemic or biologic therapy. [13]

Topical corticosteroids, such as hydrocortisone, mometasone and clobetasol, are the most frequently used treatments for psoriasis and remain the mainstay of therapy, having anti-inflammatory and anti-proliferative activity. [14,15] Topical steroids are classified based on potency and the selection of the steroid class depends on the location and sensitivity of the lesion to topical steroids. [14] High potency preparations are required for scalp and palmoplantar lesions and low potency preparations are used for facial and genital lesions. Ointments are considered the most efficient delivery systems, being more occlusive than creams or lotions. [14] Side effects of topical steroids include skin atrophy, telangiectasia, and easy bruising. [14]

Topical vitamin D3 analogues, calcipotriol and calcipotriene, have anti-proliferative properties and provide significant improvement after a three-month course of therapy. [14] Calcipotriene is one of the most commonly used non-corticosteroid treatments for psoriasis. [15] Topical vitamin D3 analogues can cause perilesional skin erythema and irritation. [14] Recent studies have demonstrated that a combination of topical steroids and calcipotriene is more effective and safer than either agent alone. [16]

Other topical therapies may be used with corticosteroids or vitamin D analogues. Tar is sometimes used as an adjunct therapy, having some anti-inflammatory and anti-pruritic properties. [14] It is, however, messy to use and can cause skin irritation and folliculitis, especially in higher concentrations. [14] Dithranol, an anthracene derivative, is postulated to work by inhibiting keratinocyte proliferation and has been shown to produce prolonged, sustained remission of psoriasis. [14,17] It can cause skin irritation and staining. [14] Topical retinoids, such as tazarotene, may also be used in localised psoriasis. Compounded creams with salicyclic acid have been used for thickened scales, as salicyclic acid has anti-inflammatory and desquamative effects and increases corticosteroid penetration. [2]

Phototherapy

Phototherapy is a second-line treatment modality that is often used in eczema and other pruritic dermatoses, and has been shown to be safe and effective. [18] Narrow-band ultraviolet B radiation (NB-UVB) and psoralen and ultraviolet A radiation (PUVA) are the current phototherapy treatments used in psoriasis. UVB radiation primarily acts on epidermal and epidermodermal junction components, while UVA radiation affects epidermal and dermal components. [18] Phototherapy has both immediate and delayed effects on the skin. Immediate effects include formation of DNA photoproducts and damage, which cause apoptosis of resident skin cells and inflammatory cells, while delayed effects include local and systemic immune suppression, leading to suppression of disease activity. [18] As a monotherapy, PUVA has been demonstrated to be more effective than NB-UVB, with respect to achieving PASI 75. [19] Although short-term adverse effects are shown to be mild with a low withdrawal rate, use of PUVA has been consistently shown to be associated with increased risk of skin cancer. [19,20] Phototherapy with NB-UVB, now more commonly used in Australia instead of PUVA, can be an appropriate treatment for moderate-to-severe psoriasis and may be combined with other systemic therapies, such as methotrexate, that, overall, may be more efficacious than monotherapy. [12]

Systemic therapies

Various systemic immunosuppressants have been used for decades in the treatment of psoriasis. Used in other diseases, such as rheumatological diseases and inflammatory bowel disease, their long-term safety and side effect profiles are well documented and understood. Approximately 20-30% of patients suffer from moderate-to-severe disease and often require systemic therapies, in addition to conventional therapies. [3] Data of head-to-head studies on these systemic therapies, however, are lacking and insufficient. [21]

Methotrexate is a systemic drug that has been proven to have great efficacy as a monotherapeutic option in the treatment of psoriasis, though it can be considered with other agents or phototherapy to maximise its effectiveness. [12] It has long-term potential in causing hepatotoxicity, bone marrow suppression, and lung fibrosis.

Cyclosporine, a calcineurin inhibitor, is similarly very efficacious in the treatment of moderate-to-severe psoriasis as monotherapy by inducing immunosuppression. [22] It can sometimes be used in combination with methotrexate or tumour necrosis factor (TNF) inhibitors. [3] Cyclosporine is associated with hypertension and impaired renal function.

Acitretin is a vitamin A derivative that is often used for palmoplantar, pustular, and erythrodermic psoriasis, but has lower efficacy in chronic plaque psoriasis. [22] Unlike methotrexate and cyclosporine, acitretin is not immunosuppressive. [22] Acitretin can cause hyperlipidaemia, hepatitis, and alopecia.

Biologics

The traditional systemic therapies, such as methotrexate, have been the mainstay of therapy, particularly in moderate-to-severe psoriasis. However, some patients suffer loss of efficacy, adverse effects, cumulative organ-specific toxicity and inadequacy or inability to clear resistant lesions with the use of these conventional therapies. [3] With rapid advances in the understanding of psoriasis pathogenesis, newer biologic agents, such as monoclonal antibodies targeting TNFα and interleukin-12/interleukin-23 (IL-12/IL-23), have emerged over the past decade. These agents have broadened treatment options for patients with moderate-to-severe psoriasis and have demonstrated high efficacy and favourable safety profiles, improving disease outcomes.

TNFα inhibitors

TNFα inhibitors represent the first wave of biologics in the therapeutic strategy for treatment of psoriasis. TNFα inhibitors that are US Food and Drug Administration (FDA)-approved and Australian Pharmaceutical

Benefits Scheme (PBS)-approved for use in psoriasis include etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicade). All three agents have been shown in various trials to produce significant benefits to psoriasis outcomes in terms of PASI and DLQI. [23-26] Etanercept has been shown to produce 59% PASI 75, versus taking placebo, at week 12, with improvement in DLQI. [23] A twice-weekly regimen has been demonstrated to be more beneficial than a once-weekly regimen, producing a more rapid and greater response in the PRISTINE trial. [27] Infliximab produced 81% PASI 75 and 88% clearance at week 10. [25] Infliximab has been shown to be superior to etanercept, in terms of efficacy, at 24 weeks. [28] Adalimumab has demonstrated improvement in self-reported work productivity, total productivity impairment, and total activity impairment. [26]

There are currently limited direct, long-term, head-to-head trials comparing the efficacy of the three TNFα inhibitors in treating psoriasis. [21] Use of these TNFα inhibitors, in particular infliximab and adalimumab, has been associated with a higher risk of serious infections, compared to non-methotrexate and non-biologic therapies. [29]

IL-12/IL-23 inhibitors

Molecular studies in recent years have shed light on the immuno-pathogenesis of psoriasis. IL-12 is a cytokine involved in stimulating naïve T cells to differentiate into CD4 cells and natural killer cells (NK cells) and upregulating production of interferon-γ (IFNγ). [30] IL-23 is a heterodimeric cytokine consisting of IL-23p19 and IL-12/23p40 subunits. [28] Recent evidence suggests that IL-12 antagonism inhibits T helper cell type 1 (Th1) development or responsiveness, while IL-23 antagonism impairs survival, expansion, or function of IL-17-producing T cells (Th17). [30] IL-23 has been proven to be a necessary upstream mediator to the Th17 pathway, as it activates Th17 cells to produce IL-17. [30] IL-23 is thought to be significantly important in psoriatic inflammation and specific inhibition of IL-23 is speculated to have profound therapeutic value.

This is clearly seen in the use and subsequent FDA-approval of ustekinumab (Stelara) in 2009 for use in psoriasis and PsA, where it demonstrated 81% achievement of PASI 75, versus 2% by placebo, at week 12. [31] It was found to be superior to etanercept. [32] More than 80% of patients were able to maintain PASI 75 for more than 3 years, without evidence of cumulative damage, in the POENIX 1 trial. [33]

IL-17 inhibitors

Along with IL-12 and IL-23, molecular studies have brought attention to a central pathogenic pathway in psoriasis, where interleukin-17A (IL-17A) is regarded as the most critical T-cell-derived cytokine in altering growth and differentiation of skin cells. [3,6] IL-17A acts on endothelial cells, fibroblasts, chondrocytes, osteoblasts, monocytes, synovial cells, and keratinocytes. [6] The main physiological function of IL-17A is protection from infections by recruiting inflammatory cells to local sites of infection. [6] However, in psoriasis, there is hyperproliferation of keratinocytes driven by these cytokines from T cells. The psoriatic plaque typically shows infiltration of activated T cells, especially Th1 and Th17 cells that produce large amounts of IL-17, interferon-α (IFNα), and TNFα. [6] Hence, IL-17A is considered as a potential therapeutic target that may reduce the inflammation seen in psoriasis.

The results of phase II trials using IL-17 inhibitors support the hypothesis that IL-17 is indeed an essential target in treatment of chronic plaque psoriasis. [34] Targeting the IL-17 pathway may result in additional systemic benefits, particularly to arthritis and cardiovascular risk. [34] These novel agents acting on the IL-17 pathway have shown promising results in the therapeutic management of psoriasis.

Secukinumab (Cosentyx) was the first IL-17 inhibitor and was approved by the FDA in January 2015 for use in psoriasis treatment. It is also approved for PBS-subsidised treatment for chronic plaque psoriasis. Secukinumab neutralises IL-17A and had achieved 63% PASI 50 at week 12 in phase I trials. [35] Subsequent phase II and III clinical trials showed more than 80% of patients achieve PASI 75 at week 12. [36] Phase III trials have demonstrated that patients taking secukinumab are less likely to experience loss of response and showed superior PASI outcomes, compared to placebo, etanercept, and ustekinumab groups. [36-38]

Two other IL-17 inhibitors, brodalumab and ixekizumab, are in the last stages of development before they are approved for use. Ixekizumab is similar to secukinumab, as it inhibits IL-17. Phase II trials have shown significant scores of PASI 75 in 76.7%, 82.8% and 82.1% of patients receiving 25mg, 75mg, and 150mg, respectively, of ixekizumab at week 12, with significant and sustained reduction in DLQI scores. [39] Interestingly, use of ixekizumab has resulted in a reduction in inflammatory infiltrate, with modulation and normalisation of psoriasis disease-related genes. [6] Brodalumab inhibits the receptor subunit IL-17RA. Phase II trials have showed improvements, with a PASI scores of 85.9% and 86.3% using 210mg and 140mg, respectively, at 12 weeks, with significantly lower DLQI. [40] Both ixukizumab and brodalumab are currently in phase III trials to investigate their safety and efficacy.

Adverse effects of the three IL-17 inhibitors are reported in their respective trials. They are generally well-tolerated, but may show various drug reactions, such as nasopharyngitis, arthralgia, injection-site erythema, headache, and pruritus. [6] There are theoretical concerns that suppressing IL-17, which is a pro-inflammatory cytokine that activates innate immune responses against extracellular organisms, will increase the risk of neutropaenia with the decreased attraction of neutrophils. [3,6,34] However, these trials have not found that bacterial or fungal infections pose a significant problem. [6] It should be noted that most of these trials are short in duration and long-term efficacy, safety, and tolerability are not yet fully established. [34] Further longitudinal studies will be required to follow these trial patients.

Novel molecule inhibitors

New oral molecule inhibitors that are awaiting PBS approval include apremilast and tofacitinib. Apremilast, a phosphodiesterase-4 inhibitor, is a new oral agent approved in 2014, which has been shown to be effective against moderate-to-severe plaque psoriasis. [41] An oral inhibitor of the JAK/STAT signalling pathway, tofacitinib, is being trialled and will soon receive PBS-approval for subsidy. [42,43]

Biologic therapies for patient use in Australia

Given their hefty cost, these biologic agents are heavily subsidised under the PBS and strict qualifying criteria are applied to prescribe them in Australia. To qualify for the five currently approved biologic agents (adalimumab, etanercept, infliximab, secukinumab, and ustekinumab), patients must have failed to achieve an adequate response to at least three of the four treatments of: phototherapy, methotrexate, cyclosporine, or acitretin. [44] The biologic agent must be used as systemic monotherapy and the patient must subsequently be assessed to have demonstrated an adequate response to this current treatment by having a PASI score of greater than 15 in order to be eligible for continuing treatment. [44]

Future directions

We need to further explore and deepen our understanding of the pathogenic pathways in psoriasis to uncover components that can be potential therapeutic targets. Further understanding of the impact of psoriasis on other systemic co-morbidities is required, such as evaluating and quantifying the risk of cardiovascular disease. We will need to have more long-term, head-to-head trials to allow comparison of efficacy and safety of these novel biologics. We need further evaluations of combination regimens using traditional and biologic therapies to increase efficacy of treatment, decrease cumulative

dose, and minimise side effects. This ultimately allows us to establish combined, multi-modal therapies for the individual patient to produce complete remission of skin disease and optimal QOL and functional status. Our healthcare system should explore various strategies aimed to reduce the cost of biologics and improve their accessibility to patients.

Conclusion

Advances that have been made into understanding psoriasis have led to emerging, promising, and effective treatments. As we witness an ever-expanding treatment armamentarium with novel agents, further work is still required to examine their efficacies and evaluate their use in combination regimens. Future understanding of disease pathogenesis, stratification of disease, outcome measures, and novel therapeutics will allow physicians to optimise disease and functional outcomes for patients.

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None.

Conflict of interest

None declared.

Correspondence

Y Zhang: zheng.yiliang90@gmail.com

References

[1] Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systemic review of incidence and prevalence. *J Invest Dermatol*. 2013;133:377-85.

[2] Thaci D, Augustin M, Krutmann J, Luger T. Importance of basic therapy in psoriasis. *Journal of the German Society of Dermatology*. 2015;13(5):415-8.

[3] Chiricozzi A, Krueger JG. IL-17 targeted therapies for psoriasis. *Expert Opin Investig Drugs*. 2013;22(8):993-1005.

[4] Upala S, Sanguankeo A. Effect of lifestyle weight loss intervention on disease severity in patients with psoriasis: a systematic review and meta-analysis. *Int J Obesity*. 2015;39(8):1-6.

[5] Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res*. 2011;303(1):1-10.

[6] Lonnberg AS, Zachariae C, Skov L. Targeting interleukin-17 in the treatment of psoriasis. *Clinical, Cosmetic and Investigational Dermatology*. 2014;7:251-9.

[7] Finlay AY, Khan GK. Dermatology life quality index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-6.

[8] Çakmur H, Derviş E. The relationship between quality of life and the severity of psoriasis in Turkey. *Eur J Dermatol*. 2015;25(2):169-76.

[9] Pariser D, Schenkel B, Carter C, Farahi K, Brown TM, Ellis CN. A multicenter, non-interventional study to evaluate patient-reported experiences of living with psoriasis. *J Dermatolog Treat*. 2015:1-8.

[10] Zhang M, Brenneman SK, Carter CT, Essoi BL, Farahi K, Johnson MP, et al. Patient-reported treatment satisfaction and choice of dosing frequency with biologic treatment for moderate to severe plaque psoriasis. *Patient Prefer Adherence*. 2015;8:777-84.

[11] Chaptini C, Quinn S, Marshman G. Durable dermatology life quality index improvements in patients on biologics associated with psoriasis areas and severity index: a longitudinal study. *Australas J Dermatol*. 2015.

[12] Soliman A, Nofal E, Nofal A, Desouky FE, Asal M. Combination therapy of methotrexate plus NBUVB phototherapy is more effective than methotrexate monotherapy in the treatment of chronic plaque psoriasis. *J Dermatolog Treat*. 2015;26(6):528-34.

[13] Van de Kerkhof PC. An update on topical therapies for mild-moderate psoriasis. *Dermatol Clin*. 2015;33(1):73-7.

[14] Simpson KR, Lowe NJ. Trends in topical psoriasis therapy. *Int J Dermatol*. 1994;33(5):333-6.

[15] Feldman SR, Fleischer AB, Cooper JZ. New topical treatments change the pattern of treatment of psoriasis: dermatologists remain the primary providers of this care. *Int J Dermatol*. 2000;39(1):41-4.

[16] Ma L, Yang Q, Yang H, Wang G, Zheng M, Hao F, et al. Calcipotriol plus betamethasone dipropionate gel compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized, controlled trial investigating efficacy and safety in a Chinese population. *Int J Dermatol*. 2016;55(1):106-13.

[17] Hollywood KA, Winder CL, Dunn WB, Xu Y, Broadhurst D, Griffiths CE, et al. Exploring the mode of action of dithranol therapy for psoriasis: a metabolomic analysis using HaCaT cells. *Mol Biosyst*. 2015;11(8):2198-209.

[18] Situm M, Bulat V, Majcen K, Dzapo A, Jezovita J. Benefits of controlled ultraviolet radiation in the treatment of dermatological diseases. *Coll Antropol*. 2014;38(4):1249-53.

[19] Almutawa F, Alnomair N, Wang Y, Hamzavi I, Lim HW. Systematic review of UV-based therapy for psoriasis. *Am J Clin Dermatol*. 2013;14(2):87-109.

[20] Archier E, Devaux S, Castela E, Gallini A, Aubin F, Le Maitre M, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol*. 2012;26(S3):22-31.

[21] Nast A, Jacobs A, Rosumeck S, Werner RN. Efficacy and safety of systemic long-term treatments for moderate-to-severe psoriasis – a systemic review and meta-analysis. *J Invest Dermatol*. 2015.

[22] Mahmood T, Zaghi D, Menter A. Emerging oral drugs for psoriasis. *Expert Opin Emerg Dr.* 2015;20(2):209-20.

[23] Tyring S, Bagel J, Lynde C, Klekotka P, Thompson EH, Gandra SR, et al. Patient-reported outcomes in moderate-to-severe plaque psoriasis with scalp involvement: results from a randomized, double-blind, placebo-controlled study of etanercept. *J Eur Acad Dermatol Venereol*. 2013;27(1):125-8.

[24] Gottlieb AB, Langley RG, Strober BE, Papp KA, Klekotka P, Creamer K, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. *Br J Dermatol*. 2012;167(3):649-57.

[25] Yang HZ, Wang K, Jin HZ, Gao TW, Xiao SX, Xu JH, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicentre trial. *Chin Med J (Engl)*. 2012;125(11):1845-51.

[26] Kimball AB, Yu AP, Signorovitch J, Xie J, Tsaneva M, Gupta SR, et al. The effects of adalimumab treatment and psoriasis severity on self-reported work productivity and activity impairment for patients with moderate to severe psoriasis. *J Am Acad Dermatol*. 2012;66(2):e67-76.

[27] Kemeny L, Amaya M, Cetkovska P, Rajatanavin N, Lee W-R, Szumski A, et al. Effect of etanercept therapy on psoriasis symptoms in patients from Latin America, Central Europe, and Asia: a subset analysis of the PRISTINE trial. *BMC Dermatol*. 2015;15:9.

[28] Sandoval LF, Pierce A, Feldman SR. Systemic therapies for psoriasis: an evidence-based update. *Am J Clin Dermatol*. 2014;15(3):165-80.

[29] Kalb RE, Fiorentino DF, Lebwohl MG, Toole J, Poulin Y, Cohen AD, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *JAMA Dermatol*. 2015;151(9):961-9.

[30] Adriane AL, Gottlieb AB. Specific targeting of interleukin-23p19 as effective treatment for psoriasis. *J Am Acad Dermatol*. 2014;70(3):555-61.

[31] Krueger GG, Langley RG, Leonardi C, Yeilding N, Guzzo C, Wang Y, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med.* 2007;356(6):580-92.

[32] Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A. Ustekinumab for the treatment of moderate to severe psoriasis. *Health Technol Assess*. 2009;13(S3):61-6.

[33] Kimball AB, Gordon KB, Fakharzadeh S, Yeilding N, Szapary PO, Schenkel B, et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis: results from the POENIX 1 trial through up to 3 years. *Br J Dermatol*. 2012;166(4):861-72.

[34] Brown G, Malakouti M, Wang E, Koo JY, Levin E. Anti-IL-17 phase II data for psoriasis: a review. *J Dermatolog Treat*. 2015;26(1):32-6.

[35] Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, et al. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis and uveitis. *Sci Transl Med*. 2010;2(52):52ra72.

[36] Lopez-Ferrer A, Vilarrasa E, Puig L. Secukinumab (AIN457) for the treatment of psoriasis. *Expert Rev Clin Immunol*. 2015;11(11):1177-88.

[37] Warren R, Guettner A, Morita A, Gisondi P, Cooper S. Secukinumab efficacy in subjects with moderate to severe plaque psoriasis: pooled subgroup analyses by patient age of 4 phase 3 clinical studies. *J Am Acad Dermatol*. 2014;70(5,S1):AB186.

[38] Garnock-Jones KP. Secukinumab: a review in moderate to severe plaque psoriasis. *Am J Clin Dermatol*. 2015;16(4):323-30.

[39] Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med.* 2012;366(13):1190-9.

[40] Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med.* 2012;366(13):1181-9.

[41] Kang EJ and Kavanaugh A. Psoriatic arthritis: latest treatments and their place in therapy. *Ther Adv Chronic Dis*. 2015;6(6):196-203.

[42] Papp KA, Menter A, Strober B, Langley RG, Buonanno MS, Wolk R. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol*. 2012;167(3):668-77.

[43] Menter A, Papp KA, Tan H, Tyring S, Wolk R, Buonanno M. Efficacy of tofacitinib, an oral Janus kinase inhibitor, on clinical signs of moderate-to-severe plaque psoriasis in different body regions. J Drugs Dermatol. 2014;13(3):252-6.

[44] Pharmaceutical Benefits Scheme [Internet]. Commonwealth of Australia: Australian Government Department of Health; 2015. Etanercept [updated 2015; cited 2015 Dec 3]. Available from: http://www.pbs.gov.au/medicine/item/1954W-3445H-3448L-5734T-6367D-8637N-8638P-8778B-8779C-9035M-9036N-9037P-9429G.

Arthroplasty & infection: The bane of the orthopaedic surgeon

Diane Quach
Fifth Year Medicine (Undergraduate)
James Cook University

Diane is a fifth year medical student with an interest in academic writing and research.

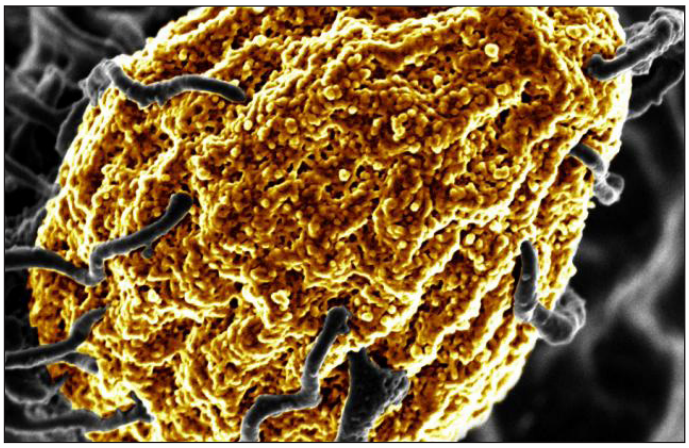
Dr. Mark Wilson
MBBS
Orthopaedic Registrar
North West Regional Hospital, Burnie, Tasmania

Mark is a surgical trainee with an interest in orthopaedics, sports medicine, and clinical anatomy education.

The last 50 years have ushered in an era of rapid technological development in the domain of joint replacement surgery and subsequently improved the lives of millions, both in terms of alleviation of pain and functional restoration. In spite of this technical progress, periprosthetic joint infection remains a barrier in achieving entirely successful outcomes for all joint replacement surgery patients. Once a periprosthetic joint infection has been diagnosed, there exists a vast array of adjuvant treatment modalities. A combination of clinical signs, laboratory and microbiological tests, histopathology, and imaging studies are required to meaningfully diagnose a periprosthetic joint infection, but the increasing incidence of morbid obesity, diabetes, and the rise of the 'metabolic syndrome' has been associated with a perceived increase, amongst clinicians, in the rate of periprosthetic joint infections. Indeed, the rising prevalence of this complication demands considerable clinical acumen from the orthopaedic surgeon. It has become increasingly challenging to treat patients who develop infections in the setting of total joint replacement. Surgical options include single or serial washouts vs. single stage or multi-stage exchange procedures, but the utilisation of adjuvant broad-spectrum intravenous antibiotics with myriad systemic side effects is required for adequate treatment. Furthermore, the emerging and proven value of the multidisciplinary team brings together orthopaedic surgeons and infectious disease physicians to act in the best interests of their patients by limiting the considerable morbidity associated with periprosthetic joint infections.

Introduction

Since the developments of Charnley in the 1960s, [1-4] joint replacement surgery has revolutionised the treatment of joint pain, most commonly due to osteoarthritis, and served to restore function and productivity in an increasingly afflicted population. [5] Despite these technical and surgical advances, periprosthetic infections have been an important barrier in achieving successful joint replacement surgery in some patients. [6] In the context of an ageing population, surgeries such as this are becoming evermore prevalent, and hence the frequent review of its process is warranted to achieve the best possible patient outcomes. There are several aspects of arthroplasty that need to be taken into account. Given that prevention is always better than cure, surgical sterility and asepsis is by far the most important factor in preventing periprosthetic infections and maintaining the efficacy of joint replacement surgery as a therapeutic modality. [3] Contributing to this are the various adjuvant treatments included in current perioperative protocols widely used by modern orthopaedic surgeons. However, despite the multitude of additional precautions, it is revealed that infection rates persist at one to four percent in most modern facilities. [6,7] Various patient factors such as obesity and diabetes have also been implicated in the development of periprosthetic joint infections. In considering the contributing factors, an evaluation will also be made of the current treatment options and outcomes for patients in terms of quality of life and economic burden on the



healthcare system. Infections of orthopaedic prostheses prove to be a considerably disastrous event for both patients and surgeons, and hence warrant close review of the options available and their value to patient management.

Current perioperative protocols

Perioperative protocols now include a multitude of adjuvant treatments that are very much part of the modern orthopaedic surgeon's armamentarium. Regimes including perioperative antibiotic therapy, the use of 'space suits' by surgeons and theatre nurses, double gloving, antiseptic-coated skin adhesives, adherence to sterile surgical practices, and the utilisation of antibiotic-impregnated bone cement are just some of a number of steps taken to reduce the likelihood of superficial and deep wound infections, [8-11] which in the setting of an artificial prosthesis can lead to limb, and occasionally, life-threatening complications. [12]

These methods have a sound theoretical and clinical basis, [8] and are well-accepted in the orthopaedic surgical community as a means of preventing multiple surgeries to salvage or revise infected prosthetic joints and the toxicity of protracted, high-dose intravenous antibiotic therapy. Despite these measures, a review of the available literature reveals an infection rate of between one and four percent in most modern hospitals [6,7]; importantly, these figures are expressed to patients prior to joint replacement surgery as part of the process of informed consent, as an act of best practice. Although the use of antibiotics has a clear clinical benefit in the setting of periprosthetic infection, it is difficult to discern how useful the other approaches are in helping to reduce infection in joint replacement surgery. [9,13,14]

Basic microbiology of joint infections

Evaluation of microorganisms associated with perioperative infections demonstrate the existence of a wide range of Gram-positive and negative bacteria and fungi that may cause infection. [15] However, there is an overwhelming association between Gram-positive bacteria and perioperative infections, particularly *Staphylococcus spp.*, compared to any other known causative organism. [15-17]

There is particular concern for the growing prevalence of *methicillin-resistant Staphylococcus aureus* (MRSA) associated with perioperative infections. [16,17] *Staphylococcal spp.* has also been associated with higher risk of re-infection and persistence of infection in the setting of arthroplasty. [16] *Propionibacterium acnes* is also reported to be of growing concern, especially in the context of shoulder surgery, for reasons yet to be clearly delineated. [15,18,19]

Patient factors: obesity, diabetes and immunosuppression

Obesity

Obesity is fast becoming an epidemic for the Australian healthcare system. Not only has high body mass index (BMI) been implicated in the increased number of total joint replacements, owing largely to accelerated osteoarthritis (OA), but obesity as a health condition in itself complicates arthroplasty surgery and deleteriously impacts patients' functional outcomes. Australia has one of the highest rates of obesity in the world, with a quarter of the population being classified as obese, and the incidence is increasing, with 34% of the population predicted to be obese in 2015. [20] Furthermore, because obesity is a risk factor for OA due to increased mechanical joint loading, the proportion of those presenting for joint replacement surgery is even greater and is also set to increase in the short to medium-term. Obesity is associated with a number of co-morbidities such as heart disease, hypertension, diabetes, and the 'metabolic syndrome', the latter two of which complicate surgery and independently increase the risk of periprosthetic infection.

There is, however, a degree of ambiguity in the orthopaedic literature, with arguments for and against obesity in itself being an independent risk factor for periprosthetic infection. One centre's study demonstrated that morbid obesity, or a BMI of > 40, increases the risk of deep prosthetic infection by eight to nine times; however, obesity and a BMI of 30-39, increased the risk by two to three times. [21,22] These rates are also related to the anatomical site of the joint replacement itself. With regards to the knee, only the relationship between morbid obesity and prosthetic infections was found to be statistically significant. [22,23] Addressing the issue of surgery for obese patients is one of the modern-day challenges for orthopaedic surgeons and much work remains to be done in developing a clear framework for addressing this clinical problem.

Diabetes

Diabetes mellitus and hyperglycemia have been indicated as risk factors for various complications in orthopedic surgery, including surgical site infections, pneumonia, prolonged hospital admissions, stroke, and deep vein thrombosis. [24-27] This increased risk is often attributed to the common co-morbidities that exist in diabetic patients, which are of a particular vasculopathic nature. [24] However, it appears that a direct correlation between diabetes mellitus and incidence of periprosthetic joint infection is yet to be clearly delineated. One study has demonstrated an important distinction between controlled and uncontrolled metabolic syndrome (defined as diabetes, dyslipidemia, hypertension, and obesity) and risk of periprosthetic joint infection; however, when compared to healthy patients, both groups appeared to yield non-significant results. [28] Another study investigating rates of infection after total joint arthroplasty has found up to 11.4 times higher incidence of infection in diabetes mellitus patients compared to non-diabetic patients in total hip arthroplasty and 2.6 times higher in total knee replacement. [29] Contrary to this, it was found that the blood glucose level (BGL), measured by HbA1c readings pre- and post-operatively, were not significantly associated with infection risk. [30] Hence, it appears that BGL alone is not an adequate indicator of perioperative infection risk, though it remains an important risk factor for other complications, such as length of stay, in orthopaedic surgery. [30] Therefore, the evidence to support the direct relationship between diabetes mellitus as an independent risk factor for periprosthetic joint infections remains an area requiring further research.

Rheumatoid arthritis

Rheumatoid arthritis (RA) patients are not only at higher likelihood of requiring joint arthroplasty, but also have an innate immunosuppressed profile due to their management regimes. There is a paucity of recent literature that discusses the relationship between perioperative infections and RA. Of the available most recent data, RA patients have been indicated as being at higher risk of complications when compared to OA patients, another prominent group undergoing joint arthroplasty. RA is also reportedly associated with higher length of hospital stay, cost of hospitalisation, and need for blood product transfusion compared to OA patients. [31] Other studies have found that RA is associated with a higher incidence of prosthesis infection compared to matched OA controls. [32]

Interestingly, contrary to previous studies, a study comparing RA and 'non-RA' patient sequelae after total shoulder arthroplasty found that RA patients actually had lower length and less complex stays in hospital post-surgery, and that RA patients were more often routinely discharged home with fewer complications. [33] It has been suggested that the advent of newer RA treatments, such as disease-modifying antirheumatic drugs (DMARDs) and anti-tumour necrosis factor (anti-TNF) inhibitors may contribute to this altered risk for perioperative complications in RA patients. [32]

A further recent study has attempted to compare DMARDs with newer biological agents such as infliximab and rituximab, amongst many others, and their risk association need for total joint arthroplasty and associated periprosthetic infection risk. [34] It appears that the use of biological agents was associated with a higher and earlier, need for joint replacement when compared to DMARDs; however, it was also noted this may be attributed to the fact that patients using biological agents tend to have more aggressive RA. [34] Moreover, it appears that although biological agents tend to require less revision surgeries, there is no significant difference in the rate of joint infection between the two treatment regimens. [34]

Solid organ transplant patients

Solid organ transplant patients are becoming increasingly common as total joint arthroplasty candidates. This is due to the increased rate of solid organ transplants, but reasons for total joint arthroplasty in this group are not much different to otherwise healthy individuals and include osteonecrosis of the femoral head for total hip arthroplasty (THA), and osteoarthritis. [35-37] It has been postulated in the past that this group of patients may be more susceptible to periprosthetic infection due to their use of immunomodulators such as tacrolimus, mycophenolic acid, and corticosteroids such as prednisone. [38] Joint replacement surgery in this patient group has traditionally involved the prophylactic use of antibiotics, presumably for this reason, although the use of perioperative intravenous antibiotics for all patients has become standard practice in orthopaedic surgery. [35-38]

Most recent studies are largely retrospective when observing the rate of perioperative infection, as well as other complications in this highly select patient group. However, contrary to what may be presumed, the most recent literature suggests that patients undergoing THA still have low rates of periprosthetic joint infection as a perioperative complication, despite the nature of the transplant undertaken and the subsequent immunosuppression regime. [36-38] In some studies, the periprosthetic infection rate in the transplant patient group following THA was zero. [37,38] Other cases observed only one wound infection amongst the 55 THAs performed in various solid organ transplant patients. [36] However, the situation appears to be different for this patient group in regards to total knee arthroplasties (TKA). Two studies consistently report the rate of periprosthetic infection as being higher in TKA compared to THA. [36,37]

Another study observing only TKA reported an infection rate of 4 out of the 24 (17.3%) TKAs performed on various solid organ transplant patients. Contrary to these numbers, there have been reports of no

statistically significant difference between TKA and THA, with both yielding no increased periprosthetic infection risk. [38] Given all of this recent evidence, it appears that we are yet unable to discern whether there is any true significance between solid organ transplant subgroups and their relative risk of periprosthetic infection in total joint arthroplasty. The conclusion may perhaps be drawn, that it is relatively safer to perform total hip replacements in this patient group compared to total knee replacements. However, one must be cognisant of the fact that most of these studies are retrospective analyses of specific patient cases with relatively small statistical power.

HIV patients

Patients with human immunodeficiency virus (HIV) are also becoming increasingly common candidates for total joint arthroplasty, perhaps owing to the improved efficacy of antiretroviral treatments available to the community and increased longevity of these patients in general. [39] One study reported that HIV patients undergoing joint replacement tend to be younger than matched controls and also yielded non-significant results in its investigation of whether this immunocompromised group will experience higher rates of periprosthetic infection. [40] This suggests periprosthetic infection rates in the HIV population are not as striking as they used to be in the context of total joint arthroplasty. [40] This has been attributed to the advent of more effective antiretrovirals and their increased uptake in this patient population, as well as more effective intravenous drug user (IVDU) education producing a lower bacteraemia risk to seed infection. [40] Other similar studies appear to reflect those previously found in producing either none, [41] or very low rates (one hip in 41 THAs) [39] of periprosthetic infection for total knee or hip arthroplasties in HIV patients.

Recognising perioperative joint infections

It must be borne in mind that recognising infection after total joint replacement remains clinically difficult. A combination of clinical signs, laboratory and microbiological tests, histopathology, and imaging studies are required to meaningfully suggest a prosthetic infection. [42] More important, is the ability to predict and diagnose the early stages of a prosthetic joint infection as prompt intervention and management has the best chance of salvaging the prosthesis and preserving optimal joint function. [9] Given that plain radiographs have low sensitivity and low specificity for detecting early infections, the efficacy of new imaging techniques involving scintigraphy, positron emission tomography, and computerised tomography imaging is currently under investigation, but remains contentious. [9] What is becoming clear is the fact that treatment of orthopaedic infections is no longer solely in the domain of the orthopaedic surgeon. Modern multidisciplinary care now demands a team approach between surgeons and infectious diseases specialists; the need for an evidence-based approach should take priority when managing both superficial and deep infections.

Treatments: antibiotic therapy & surgical revision

Infections of joint replacement components and other implantable orthopaedic hardware are some of the most disastrous events in clinical orthopaedics, especially in terms of patient outcomes, and often considerable and prolonged resource expenditure. Not only is the ordeal of having a prosthetic infection protracted with an increased risk of recurrent infections, there are also a wide range of possibly devastating outcomes, including sepsis and limb amputation. [12] The financial burden is also significant, with the cost of successfully treating an infected joint replacement conservatively placed at approximately $50,000 for early interventions and $100,000 for late interventions. [6] In revising joint replacements for infection, several important questions arise, namely, “Should failed total joints be revised in single or multi-stage operations?” and “What should be done in those situations where bone loss is considerable and metallic structural augmentation is required to restore anatomy?” These and other questions demand attention.

It has become an increasing challenge to treat patients who develop infections in the setting of total joint replacement. Literature is scarce in regards to accepted modes of treatment, particularly with hip, knee, and shoulder prostheses, and moreover, few publications specifically outline the most effective therapeutic regimes. [13] It is problematic for treating teams to appreciate what best clinical practice may be; indeed, the removal and revision of the prosthesis as a single or two-staged procedure is often the fallback position for orthopaedic surgeons. [7,13] The evidence suggests that this approach is one of a number of potential options. At the other end of the spectrum, reports of high rates of successful salvage of prosthesis in situ are also achievable with aggressive debridement and targeted antibiotic therapy alone. [14,43] However, the prevalence of resistant bacteria should be borne in mind and appropriate consultation with an infectious diseases physician is also wise. Moreover, there are other strategies such as MRSA screening and other prophylactic practices that increase the success of an arthroplasty, the discussion of which is beyond the scope of this article.

Patient outcomes & quality of life issues

Of the available treatment outcomes, it appears the most long-standing debate still appears to be between one-stage and two-stage revisions, in terms of surgical interventions. For patients that are unfit for surgery, long-term suppressive antibiotic therapy seems to be a viable option, though the ideal regimen is yet to be delineated. [44] Two-stage revision also appears to be accepted as a ‘gold-standard’ for the management of periprosthetic infections. [45-48] The most recent literature remains rather mixed about the efficacy of one-stage over two-stage revisions in hip and knee arthroplasties. Of the most recent studies, some yield better success rates [45,49] and patient-rated outcomes for one-stage revision [45] or lower than expected success rates for two-stage revision [50]; while others are in support of two-stage revision. [48] Nonetheless, it appears that the success rate of one-stage over two-stage or vice versa is by a small difference in percentage, suggesting perhaps that these methods are quite comparable. Other than the previously noted study, it appears that there are few other available studies that present measurable patient outcomes, aside from the success rate of the treatment method.

It has also been found that patient transfers during the two-stage revision period may negatively impact on its success rate due to various possible reasons. [47] Perhaps as an alternative to either one-stage or two-stage revision alone, a Singaporean hospital has introduced its findings based on a periprosthetic joint infection protocol that reflects progression from incision and drainage (washouts) to two-stage revision depending on patient outcome for the management of MRSA infections. [51] It reports one third of its patients being successfully treated by first-line washouts alone and an 88% success rate in the remaining patients who underwent two-stage revision as second-line treatment. In consideration of new or alternative methods to manage periprosthetic joint infection, one group found that irrigation and debridement may hold promise as a treatment method alone, with a success rate of 55.1% in their study, given its association with lower morbidity, tissue fibrosis, and better functional outcomes when compared to two-stage revision. [46] However, this study also found that successful treatment with single or serial washouts is significantly more likely to fail if conducted after 5 days of symptom onset or clinical detection. [46] Related to this discussion, it was found that pulse lavage to remove biofilm has variable efficacy and is largely dependent on prosthesis material (cobalt chrome vs. polymethyl methacrylate vs. polyethylene) and reaffirms that it alone is not adequate in the management of periprosthetic infection, but must be combined with suppressive antibiotic therapy and/or meticulous debridement for optimal results. [52]

Conclusion

It has become an increasing challenge to treat patients who develop infections in the setting of total joint arthroplasty. The surgical options of single or serial washouts with or without debridement vs. single-stage or multi-stage exchange procedures are all reasonable options, but there is no clear, uniform consensus in the literature that favours one approach over the others. The utilisation of broad-spectrum intravenous antibiotics with myriad systemic side effects is required for adequate treatment and is considered best practice. The value of the multidisciplinary team consisting of the orthopaedic surgeon and the infectious disease physician is brought to bear when these patients are at their most vulnerable. Ultimately, it falls upon the treating clinician to act in the best interests of their patients by limiting the substantial morbidity and impact on quality of life associated with periprosthetic joint infections.

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None.

Conflict of Interest

None declared.

Correspondence

D Quach: 93dquach@gmail.com

References

[1] Charley J. A sterile-air operating theatre enclosure. *Brit J Surg.* 1964;51(3):195-202.
[2] Charnley J, Eftekhar N. Postoperative infection in total prosthetic replacement arthroplasty of the hip-joint with special reference to the bacterial content of the air of the operating room. *Brit J Surg*. 1969;56(9):641-9.
[3] Lidwell OM. Sir John Charnley, surgeon (1911-82): the control of infection after total joint replacement. *J Hosp Infect*. Jan 1993;23(1):5-15.
[4] Toledo-Pereyra LH. John Charnley-father of modern total hip replacement. *J Invest Surg*. Nov-Dec 2004;17(6):299-301.
[5] Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. Apr 2007;89(4):780-5.
[6] Poultsides LA, Liaropoulos LL, Malizos KN. The socioeconomic impact of musculoskeletal infections. *J Bone Joint Surg Am*. Sep 1 2010;92(11):e13.
[7] Lentino JR. Prosthetic joint infections: bane of orthopedists, challenge for infectious disease specialists. *Clin Infect Dis*. May 1 2003;36(9):1157-61.
[8] Byrne AM, Morris S, McCarthy T, Quinlan W, O'Byrne J M. Outcome following deep wound contamination in cemented arthroplasty. *Int Orthop*. Feb 2007;31(1):27-31.
[9] Cataldo MA, Petrosillo N, Cipriani M, Cauda R, Tacconelli E. Prosthetic joint infection: recent developments in diagnosis and management. *J Infect*. Dec 2010;61(6):443-8.
[10] Lindsay W, Bigsby E, Bannister G. Prevention of infection in orthopaedic joint replacement. *J Perioper Pract*. Jun 2011;21(6):206-9.
[11] Luessenhop CP, Higgins LD, Brause BD, Ranawat CS. Multiple prosthetic infections after total joint arthroplasty. Risk factor analysis. *J Arthroplasty*. Oct 1996;11(7):862-8.
[12] Ritter MA, Farris A. Outcome of infected total joint replacement. *Orthopedics*. Mar 2010;33(3).
[13] Weber P, Utzschneider S, Sadoghi P, Andress HJ, Jansson V, Muller PE. Management of the infected shoulder prosthesis: a retrospective analysis and review of the literature. *Int Orthop*. Mar 2011;35(3):365-73.
[14] Choong PF, Dowsey MM, Carr D, Daffy J, Stanley P. Risk factors associated with acute hip prosthetic joint infections and outcome of treatment with a rifampinbased regimen. *Acta Orthop*. Dec 2007;78(6):755-65.
[15] Bjerke-Kroll BT, Christ AB, McLawhorn AS, Sculco PK, Jules-Elysee KM, Sculco TP. Periprosthetic joint infections treated with two-stage revision over 14 years: an evolving microbiology profile. *J Arthroplasty*. May 2014;29(5):877-82.
[16] Zmistowski B, Tetreault MW, Alijanipour P, Chen AF, Della Valle CJ, Parvizi J. Recurrent periprosthetic joint infection: persistent or new infection? *J Arthroplasty*. Oct 2013;28(9):1486-9.
[17] Ridgeway S, Wilson J, Charlet A, Kafatos G, Pearson A, Coello R. Infection of the surgical site after arthroplasty of the hip. *J Bone Joint Surg Br.* Jun 2005;87(6):844-50.
[18] Hudek R, Sommer F, Kerwat M, Abdelkawi AF, Loos F, Gohlke F. Propionibacterium acnes in shoulder surgery: true infection, contamination, or commensal of the deep tissue? *J Shoulder Elbow Surg*. Aug 29 2014;23(12):1763-71.
[19] Singh JA, Sperling JW, Schleck C, Harmsen W, Cofield RH. Periprosthetic infections after shoulder hemiarthroplasty. *J Shoulder Elbow Surg*. Oct 2012;21(10):1304-9.
[20] Dowsey MM, Choong PF. Early outcomes and complications following joint arthroplasty in obese patients: a review of the published reports. *ANZ J Surg*. Jun 2008;78(6):439-44.
[21] Dowsey MM, Choong PF. Obesity is a major risk factor for prosthetic infection after primary hip arthroplasty. *Clin Orthop Relat Res*. Jan 2008;466(1):153-8.
[22] Dowsey MM, Choong PF. Obese diabetic patients are at substantial risk for deep infection after primary TKA. *Clin Orthop Relat Res*. Jun 2009;467(6):1577-81.
[23] Peel TN, Dowsey MM, Daffy JR, Stanley PA, Choong PF, Buising KL. Risk factors for prosthetic hip and knee infections according to arthroplasty site. *J Hosp Infect*. Oct 2011;79(2):129-33.
[24] Toor AS, Jiang JJ, Shi LL, Koh JL. Comparison of perioperative complications after total elbow arthroplasty in patients with and without diabetes. *J Shoulder Elbow Surg*. Sep 9 2014:23(11):1599-606.
[25] Li GQ, Guo FF, Ou Y, Dong GW, Zhou W. Epidemiology and outcomes of surgical site infections following orthopedic surgery. *Am J Infect Control*. Dec 2013;41(12):1268-71.
[26] Pope D, Scaife S, Tzeng TH, Vasdev S, Saleh KJ. Impact of diabetes on early postoperative outcomes after total elbow arthroplasty. *Journal Shoulder Elbow Surg*. Mar 2015:24(3):348-52.
[27] Ponce BA, Menendez ME, Oladeji LO, Soldado F. Diabetes as a risk factor for poorer early postoperative outcomes after shoulder arthroplasty. *J Shoulder Elbow Surg*. May 2014;23(5):671-8.
[28] Zmistowski B, Dizdarevic I, Jacovides CL, Radcliff KE, Mraovic B, Parvizi J. Patients with uncontrolled components of metabolic syndrome have increased risk of complications following total joint arthroplasty. *J Arthroplasty*. Jun 2013;28(6):904-7.
[29] Iorio R, Williams KM, Marcantonio AJ, Specht LM, Tilzey JF, Healy WL. Diabetes mellitus, hemoglobin A1C, and the incidence of total joint arthroplasty infection. *J Arthroplasty*. May 2012;27(5):726-9 e721.
[30] Maradit Kremers H, Lewallen LW, Mabry TM, Berry DJ, Berbari EF, Osmon DR. Diabetes mellitus, hyperglycemia, hemoglobin A1C and the risk of prosthetic joint infections in total hip and knee arthroplasty. *J Arthroplasty*. Mar 2015:30(3):439-43.
[31] Stundner O, Danninger T, Chiu YL, Sun X, Goodman SM, Russell LA et al. Rheumatoid arthritis vs osteoarthritis in patients receiving total knee arthroplasty: perioperative outcomes. *J Arthroplasty*. Feb 2014;29(2):308-13.
[32] Bongartz T, Halligan CS, Osmon DR, Reinalda MS, Bamlet WR, Crowson CS et al. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. Arthritis Rheum. Dec 15 2008;59(12):1713-20.
[33] Hambright D, Henderson RA, Cook C, Worrell T, Moorman CT, Bolognesi MP. A comparison of perioperative outcomes in patients with and without rheumatoid arthritis after receiving a total shoulder replacement arthroplasty. *J Shoulder Elbow Surg*. Jan 2011;20(1):77-85.
[34] Aaltonen KJ, Virkki LM, Jamsen E, Sokka T, Konttinen YT, Peltomaa R et al. Do biologic drugs affect the need for and outcome of joint replacements in patients with rheumatoid arthritis? A register-based study. *Semin Arthritis Rheum*. Aug 2013;43(1):55-62.
[35] Klatt BA, Steele GD, Fedorka CJ, Sanchez AI, Chen AF, Crossett LS. Solid organ transplant patients experience high rates of infection and other complications after total knee arthroplasty. *J Arthroplasty*. Jun 2013;28(6):960-3.
[36] Ledford CK, Watters TS, Wellman SS, Attarian DE, Bolognesi MP. Risk versus reward: total joint arthroplasty outcomes after various solid organ transplantations. *J Arthroplasty*. Aug 2014;29(8):1548-52.
[37] Ledford CK, Watters TS, Wellman SS, Attarian DE, Bolognesi MP. Outcomes of primary total joint arthroplasty after lung transplantation. *J Arthroplasty*. Jan 2014;29(1):11-5.
[38] Leonard GR, Davis CM, 3rd. Outcomes of total hip and knee arthroplasty after cardiac transplantation. *J Arthroplasty*. Jun 2012;27(6):889-94.
[39] Snir N, Wolfson TS, Schwarzkopf R, Swensen S, Alvarado CM, Hamula M et al. Outcomes of total hip arthroplasty in human immunodeficiency virus-positive patients. *J Arthroplasty*. Jan 2014;29(1):157-61.
[40] Capogna BM, Lovy A, Blum Y, Kim SJ, Felsen UR, Geller DS. Infection rate following total joint arthroplasty in the HIV population. *J Arthroplasty*. Sep 2013;28(8):1254-8.
[41] Wang TI, Chen CF, Chen WM, Chiang C, Huang C, Liu C et al. Joint replacement in human immunodeficiency virus-infected patients. *J Chin Med Assoc*. Nov 2012;75(11):595-9.
[42] Marculescu CE, Cantey JR. Polymicrobial prosthetic joint infections: risk factors and outcome. *Clin Orthop Relat Res*. Jun 2008;466(6):1397-404.
[43] Shuman EK, Malani PN. Prevention and management of prosthetic joint infection in older adults. *Drugs Aging*. Jan 1 2011;28(1):13-26.
[44] Prendki V, Zeller V, Passeron D, Desplaces N, Mamoudy P, Stirnemann J et al. Outcome of patients over 80 years of age on prolonged suppressive antibiotic therapy for at least 6 months for prosthetic joint infection. *Int J Infect Dis*. Oct 30 2014;29C:184-9.
[45] Choi HR, Kwon YM, Freiberg AA, Malchau H. Comparison of one-stage revision with antibiotic cement versus two-stage revision results for infected total hip arthroplasty. *J Arthroplasty*. Sep 2013;28(8 Suppl):66-70.
[46] Triantafyllopoulos GK, Poultsides LA, Zhang W, Sculco PK, Ma Y, Sculco TP. Periprosthetic knee infections treated with irrigation and debridement: outcomes and preoperative predictive factors. *J Arthroplasty*.Apr 2015;30(4):649-57.
[47] Dietz MJ, Choi HR, Freiberg AA, Bedair H. Transfer of patient care during two-stage exchange for periprosthetic joint infection leads to inferior outcomes. *J Arthroplasty*. Jul 2014;29(7):1426-9.
[48] Romano CL, Gala L, Logoluso N, Romano D, Drago L. Two-stage revision of septic knee prosthesis with articulating knee spacers yields better infection eradication rate than one-stage or two-stage revision with static spacers. *Knee Surg Sports Traumatol Arthrosc*. Dec 2012;20(12):2445-53.
[49] Bori G, Munoz-Mahamud E, Cune J, Gallart X, Fuster D, Soriano A. One-stage revision arthroplasty using cementless stem for infected hip arthroplasties. *J Arthroplasty*. May 2014;29(5):1076-81.
[50] Stammers J, Kahane S, Ranawat V, Miles J, Pollock R, Carrington R et al. Outcomes of infected revision knee arthroplasty managed by two-stage revision in a tertiary referral centre. *Knee*. Jan 2015;22(1):56-62.
[51] Siddiqui MM, Lo NN, Ab Rahman S, Chin PL, Chia SL, Yeo SJ. Two-year outcome of early deep MRSA infections after primary total knee arthroplasty: a joint registry review. *J Arthroplasty*. Jan 2013;28(1):44-8.
[52] Urish KL, DeMuth PW, Craft DW, Haider H, Davis CM, 3rd. Pulse lavage is inadequate at removal of biofilm from the surface of total knee arthroplasty materials. *J Arthroplasty*. Jun 2014;29(6):1128-32.

Failing the Frail

Dr. Hannah Ireland
BA (Comms) (Hons), MBBS
University of Notre Dame, Fremantle

Hannah is a former Sydney journalist who, after working in the field for several years, embarked on a sea change and began medicine in Fremantle, Western Australia. She has a keen interest in otolaryngology, oncology, and Aboriginal health. Hannah is a subscriber to the Stoppardian notion that words are powerful beyond measure and if you get the right ones in the right order, you can nudge the world a little.

Currently our elderly are enduring the harsh rationing of medical care. Their age rather than their capacities and needs is directing the treatment, or the lack thereof, that they receive in hospital. As a student walking the wards, I've heard clinicians exiting the room of a grey-haired, frail grandmother saying, "What kind of life is that?", "What's the point in transfusing her?", "Treatment is futile, she should be palliated." All of these phrases and the derivations of them grate on me. I am not a proponent of over-treating, over-testing, and needless infliction of pain against a patient's wishes. However, when I hear these utterings I wonder whether the elderly patient's interests are at heart. I wonder if the fact that they are an octogenarian influences the doctor's view of futility. Futile for whom? Is the treatment futile because it is evident that it won't cure the patient? Is a cure even what we are looking for in multi-morbid geriatric patients? What if it buys more time for the patient and their family? What if that patient and their family think a few extra days or weeks are exactly what they need to say goodbyes? Surely that is not futile.

Futility can be subjective. We attempt to deny this fact. Doctors are not obliged to give treatment that they consider to be futile. However, prognostication is inexact. It is extremely difficult to determine when treatment is futile for an elderly patient with another infective exacerbation of their chronic obstructive pulmonary disease. No one can tell if this will be the infection that literally knocks the wind right out of them or if they will respond to antibiotics, nebulisers and fluids as they have before and return home. Nothing we have in our vast medical arsenal can precisely determine when a person will die. Therefore, the concept of withholding futile treatment is benevolent in intention but may be treacherous in practicality.

Knowing this, it is important that doctors present the options and possibilities to the patient and their family. This is not something that can be done with speed in the chaos of a morning ward round. It takes time, careful consideration, and discussion of uncertainty. It requires looking at the patient as a whole, identifying their wishes, fears and goals [1] and their family's desires for them. It is a process that acknowledges that medical treatment extends to an understanding of both the social and psychological needs, not just the medical history and vital signs. It is a deviation from the traditional medical approach, which makes us uncomfortable. But it is undoubtedly the approach that patients need and deserve, especially as they enter the final years, months and days of their life.

In relatively recent times a new medical discourse has emerged. It is peppered with words like "advance care directive", "not for resuscitation", and "end-of-life planning". These concepts are admirable. [2] They are a step towards ensuring that appropriate treatment is given to elderly patients. They are a systematised way of elucidating the patient's desires for the end of their life in the event that they are not able to communicate these intentions independently. They can give another degree of certainty that doctors are doing the right thing by the patient when caring for those who are very ill and elderly. They attempt to ensure that patient autonomy is upheld even in their final days. It has been shown by randomised trials that this end-of-life planning, when done thoroughly and correctly, results in increased patient and medical team satisfaction. [3] However, when

done poorly they have the capacity to collapse into a paper storm of inadequately completed forms, unchecked tick-boxes and a flurry of confusion.

The danger with this contemporary discourse and ever-evolving multitude of forms is that they become a veil for sanctioned ageism in our hospitals. [2] They pretend to address the patient as a whole but have the potential to bolster the fiscal constraints placed on hospitals that indirectly promote limitation of treatment according to age. They may even deny the elderly the empathy that other younger patients with better chances of full recovery receive without question. They are supposed to empower the patient but can instead circumvent the need for physicians and surgeons to learn how to have iterative meaningful conversations with the elderly and their families about their medical care. [2] There is a danger that these forms emerge as yet another mechanism for denial of deserved medical attention. They support the tired cry to create a "sustainable" medical system by discretely refusing the most vulnerable people in hospitals adequate medical consideration and thus further cement the lowly position of our elderly in our health care system. [2] Most worryingly, they delay the important recognition that we are failing our elderly and that our approach needs to change.

Part of the reason I believe that we avoid real discussions with elderly patients with complex health requirements is because it requires us to see ourselves in these osteoporotic, hard-of-hearing folk. [2,4] Too often we separate ourselves from them. We label them as "acopics" on "social visits". We fail to see the aged as depicting our own destination in life. Perhaps we do this because recognising the elderly as related to us requires us to confront our mortality and contemplate our own ageing and death which is understandably uncomfortable. We don't want to become them so we run from them as if avoiding the elderly will make us immune to ageing.

I hear doctors and students joke, in tutorials and at the end of a ward round, "I never want to get that way, I hope I die suddenly at 75". They click their fingers to emphasis the swiftness with which they wish to depart the earth. They all want to spare their inner light from the ravages of time. They playfully ask their colleagues to just titrate morphine up to toxic doses if they have a stroke or become

demented. They talk about growing old as if it is a fate worse than death. In doing so, they devalue the elderly that populate the busy wards. [3] Our grandparents become the least worthy of treatment because the implication is that they, as a collective, have nothing to contribute anymore. [4] They have lost their social worth. These phrases perpetuate ageism and they erect barriers which shut out the elderly from an impartial medical system. These jovial remarks are said without any consideration of the fact that they too will grow old. Most probably, they will grow older than the grey-haired people they walk past on the wards because that is the way our demography is headed, largely thanks to modern medicine. By "othering" the elderly, by failing to see the individual behind the date of birth, the connection is never made between doctor and patient, and austerity of care creeps in.

The other reason I believe we relegate the elderly to the medical scrap heap is because they challenge our medical capacities. They sit uncomfortably outside the modus operandi we learn at medical school. In the current hospital system, doctors approach patients with a view to compartmentalise them and break them down into discrete systems and then further into isolated organs within those systems. This method is neat and tidy. It is an efficient method that seeks to unravel dense biological complexities into manageable medical and surgical problems. It is goal-oriented and treatment-focused and on many occasions it makes patients better. However, the flaws in the system present themselves when the geriatric patient arrives in the emergency department. These patients can't be dissected and deconstructed so easily and consequently they challenge our method. They test our Sherlockian reasoning and routinely disprove our beloved Occam's razor theory that each and every patient can be summarised with a unifying diagnosis. They stand in the lesser known Hickam's dictum camp that states that, "Patients can have as many diseases as they damn well please". [4] This is daunting for us in the medical world. It signals longer assessment times, more complex diagnostics, less reliability in old-faithful heuristics and the possibility that the patient's problems won't be neatly tied up at the conclusion of the consult. The elderly are often perceived as a potential threat to our diagnostic and management skills simply because it feels strange to settle with a management plan where a medical cure and resolution is not the endpoint. We perceive this as some sort of failure on our part or a compromise of our identity, [1] but really it is an indication that we, as a group, are not equipped to deal adequately with the elderly patients that are populating our hospitals. It is an indication that we are failing them and that a cultural shift needs to occur within the medical fraternity.

Atul Gawande, the famous American surgeon responsible for the now commonly used "surgical checklist", describes the inevitable population change occurring in developed nations in his latest book Being Mortal. [1] Traditionally, our demography has been pyramidal in configuration. The broad base of the population is occupied by those under the age of five and the small pointed apex accommodates a much smaller number of those over 80 years of age. However, with the passing of time and the impressive acceleration of modern medicine the shadow this traditional pyramid casts has begun to change shape. Gawande describes it as a "rectangularisation" [1] of the population, whereby the over-80-year-olds are increasing to be greater in proportion with the under-five-year-olds. [1] In essence, people are living longer and the elderly now represent a greater proportion of our society. I believe this new longevity of humanity is exciting as it presents an abundance of new possibilities; however, not all people see it that way. The growth of the elderly is often viewed with the gaze of a miserly economist, where the elderly are seen as a huge financial burden and are simply mopping up valuable health dollars. Whatever your view, it doesn't really matter as the growth of the elderly is not reversible. It is happening and we as a medical community must shift to accommodate it and work with it, not against it. As such, the medical treatment of the elderly can no longer be the job of the specialised geriatricians alone. In fact, the number of training geriatricians is amongst the lowest of all the specialties in this time of their greatest demand. [1] This means that we all have a role to play in the care of the elderly in our hospitals. We must use the knowledge that we have to the benefit of our elderly and ensure that the medical treatment they receive supports their individuality and healthy ageing.

Unquestionably this will require a seismic cultural shift amongst doctors. It will require doctors to have that prickly confrontation with their own mortality and to acknowledge the limitations of their skills in this area. It will require openness to learning new skills and a reordering of priorities of treatment in some cases. It will involve an abandonment of the inertia that medical traditions and systems have created in favour of necessary innovation for the future. This seems a daunting task to embark on, but without change we will undoubtedly find ourselves living in a society that displeases us, a society that is fraught with injustice and inequity. The changes we make now must ensure that in the future our society is one that Simone de Beauvoir [5] describes, where a man in his last years might still be a man. [5] Where the vulnerable, those unable to work and those who are grey and tired are protected and their humanity is respected and upheld.

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Correspondence

H Ireland: hannah_ireland@hotmail.com

References

[1] Gawande A. Being Mortal: Medicine and what matters in the end. New York: Metropolitan Books, Henry Holt and Company; 2014.
[2] Hitchcock K. Dear Life: On caring for the elderly. Quarterly Essay. Issue 57, Australia: Penguin Books; 2015.
[3] Detering K, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. *BMJ*. 2010;340:c1345. DOI: 10.1136
[4] Montgomery K. How Doctors Think: Clinical Judgment and the Practice of Medicine. Oxford: Oxford University Press; 2006.
[5]De Beauvoir S. The Coming of Age. New York: G.P. Putnam & Sons; 1972.
[6] Hitchcock K. Little White Slips, Australia: Pan Macmillan Australia; 2009.

Inequality and mangoes in the Wild West: An elective perspective

Anna Elliston
Final Year Student (Undergraduate)
University of Tasmania

Anna is a final year medical student at the University of Tasmania. She is interested in medicine as a vehicle for science communication, for the expression of stories and for social change.

Kununurra, at the top end of Western Australia, is a stark place. Red dust, mangoes, boab nuts, and the sibilance of deafening cicadas. Brilliant sunsets and fearsome lightning storms. Air so thick in the wet season it feels as though you could slice through it with the ragged, broken edge of a turfed XXXX beer can. Baubles hang on boab trees at Christmas. The occasional croc attack might be the nonchalant topic of yarns weaved between yawns of people sitting in the shade, listless in their efforts to escape the unrelenting heat.

I was lucky enough to spend three weeks there on an elective placement at the end of 2014. Coming from my beloved, yet sheltered Tasmania, I was ignorant enough not to have any correct preconceptions about Kununurra and its people. Tassie has also had a unique history with regard to its Indigenous population so our present situation is different to that of the mainland. Although I had listened to lectures on the cultural and geographical determinants of health in the early years of med school, it was only when witnessing firsthand the discrepancies in health outcomes between rural and urban, as well as Indigenous and non-Indigenous Australians, that I started to understand how rife inequality still is. Perhaps I should be ashamed of my naïvety as it was, but I'd rather use it as a basis to discuss these inequalities and my experiences. Australia still has huge gaps in health outcomes and without personally experiencing this it's easy to become blinkered and immune. Australia is not necessarily a lucky country. It is sprawling and diverse, with ingrained inequality that should be confessed and addressed.

Kununurra has a population of about 7000 and was originally set up as a town for workers in the Ord River Irrigation Scheme. The name means "Big Waters" in the local Miriwoong language, and it's pretty much the big smoke of the East Kimberley. Kununurra is home to many members of the Malngin, Miriwoong, Wadainybung, Dulbung, Gidja, and Kuluwaring groups. [1] There are three pubs and three bottle shops, one small hospital with a five bed emergency department, and a service that picks up drunk people off the street at night and takes them to a place where they can dry out. There's a Subway and the singularly enticing Rosie's Chicken at the servo, but happily not yet a McDonald's or KFC. I point this out because large fast-food chains serve up super-sized helpings of poor health outcomes in the communities they penetrate. [2,3] This, combined with the fact cooking skills have been lost through generations of previously institutionalised Aboriginal people, creates the ultimate combo of cardiovascular risk, diabetes, and obesity. A basket of healthy food at the supermarket is around 20% more expensive than in the city, leaving many people with even less choice. [4]

My experience in Kununurra was often confronting and sad, leaving me with a deep impression of the past and present traumas. For example, I met a twelve-year-old Indigenous girl who tried to hang herself – she was one of many. A doctor told me the tiny hospital had seen nine suicides in three months. Sadly, because of the small population, there is no mental health facility in Kununurra and psychiatric patients are sometimes flown to Perth, Broome, or Darwin which may require sedation, for safety. Face-to-face mental health services are generally rare in remote Australia, which is nonsensical since rates of suicide increase with geographical isolation. Rates of suicide are 66% higher in remote places than in the city and 2.7 times higher for Aboriginal and Torres Strait Islander people, and highest in Indigenous youth. [5]

Rates of drinking are also higher in rural areas than in Australian cities, for many reasons. However, it is very important to mention that

Indigenous Australians are 1.4 times more likely than non-Indigenous people to abstain from alcohol altogether. Even so, it is a dangerous cocktail of easy accessibility, unfortunate role modelling, boredom, and cultural decimation, as well as so many other complex risk factors, that mean that those who do drink are 1.5 times more likely to drink at risky levels. [6]

I saw so many medical, psychological, and relationship problems related to alcohol in Kununurra. I saw a lot of alcohol-related injuries in the emergency department - injuries from fights, car and motorbike accidents, as well as simply tripping over and kicking stuff. I heard stories of family violence. I also saw many kids with physical and behavioural signs of Foetal Alcohol Spectrum Disorder (or "Fazz-Dee" as it is referred to with dismayed familiarity), which has implications for mental health, education, drug and alcohol abuse, and crime. [7]

I saw a 14-year-old girl have her Implanon changed. She had recently been released from gaol and she liked it there because it gave her relative safety, three meals a day, and her own room with a TV. Implanon (also known as "Slutstick" in the local slang) is the first and only type of contraception you can see or feel on the person's body. One of the doctors I worked with said this may, horribly, increase the risk of rape.

I spent a day with a community nurse who was going around the town, changing people's ulcer dressings. Much of the housing in Kununurra is new, and much of it is already wrecked. I didn't understand why, but the nurse suggested it was related to alcohol use. At one house we stopped at, there was an immaculately dressed, yet frustrated woman holding a takeaway coffee in her hand. She was a social worker, and her job that morning was to get the little boy in the household to school. It was difficult: his mum was sleeping off a heavy night of drinking and he couldn't find his shoes. The scene spoke loudly of rifts and differing agendas.

Speaking of rifts, Australia still struggles with huge differences in lifespan. We may have among the longest average lifespan, but we still have a gap of up to four years' difference between rural and metropolitan areas. [9] The lifespan gap between Indigenous and non-Indigenous people is worse: 11.5 years for males and 9.7 years for females. [10] The life expectancy for Indigenous Australians is 67.2 for males and 72.9 for females, which is about on par with many developing countries worldwide. [10,11] Lifespan is just one way of demonstrating the differences in health outcomes across Australia and should serve as a serious reminder that we still have a lot of work to do in making Australia as equal and developed as we would like to imagine it is.

"Take any pathology from a textbook," one doctor said to me, "and look at the age of onset. Here - you need to take ten or twenty years off that. So there's people with chronic kidney disease in their forties, sometimes their twenties. People have heart attacks in their thirties." I didn't quite believe him until I saw that Kununurra has as big a dialysis clinic as Hobart does. In fact, rates of end-stage kidney disease can be up to four times higher in remote parts of Australia compared to metropolitan areas, which has serious consequences on quality and quantity of life for individuals in those communities. [8]

I met an Indigenous lady in the Kununurra emergency department who looked incredibly weathered and whom I innocently imagined to be about 90 years old. She had congestive heart failure secondary to chronic hypertension and rheumatic heart disease, atrial fibrillation and she was on warfarin. But what dose of warfarin? There were discrepancies between her Webster pack, her doctor's progress notes and her medical records. No one, let alone the patient herself, had any idea what was going on. Her INR was eight, when it should be between two and three. In her case, her alcohol use and the fact that she travelled from a nearby community with different doctors were the main problems causing the confusion. I was shocked to learn that she was only 60. There were countless others like her.

All this also reminded me that we are, as doctors in training, taught on a basis of ideals. The ideal HbA1c or blood glucose level. The ideal blood pressure. An acceptable number of years lived. These ideals are targets, but there were rarely any bullseyes in Kununurra. It seemed too easy to say, well, this is a different population, so the numbers are different. But I also thought, why lower the standard because of the social and political history of the region? The professionals I shadowed took all this into account and just got on with things.

I was very impressed by the health workers I met in Kununurra - midwives, doctors, nurses, podiatrists, physios and others. There's a saying that the only people who get jobs in the Wild West are missionaries, mercenaries and misfits. Those that don't fit in the city. Or worse, that "Kartiya [which means 'non-Indigenous people' in some north-western Indigenous languages] are like Toyotas: when they break down, we get a new one". [11] My experience was the opposite: on the whole the professionals I met are incredible, culturally sensitive, passionate and welcoming people. Most of them live in Kununurra long-term, despite short-term locum stereotypes. They are generalists who make the most of the few resources they have. They made their jobs look rewarding and even sexy. Yes, they are mostly non-Indigenous: currently, only 1% of the health workforce is Indigenous. [12] Hopefully this is changing with slow-yet-celebrated increases in numbers of Aboriginal and Torres Strait Islander medical students and doctors. [13]

While in Kununurra I came to realise that the meaning of 'health' for Indigenous people in the region differed from my own. A sense of belonging and of being on country was important, and this has effects on mental and physical health. [15] Even direct questioning can be confronting for Indigenous people - yet it is an everyday technique of history taking. The Western paradigm of health and healthcare fails to take into account these fundamental differences, which leads to a lack of necessary services. Australia needs more Indigenous doctors and impassioned advocates to guide us on these matters.

My time was marvellous as well as confronting. I was privileged to hear stories and meet people, gather different perspectives and increase my confidence in medicine. Friends and I explored Lake Argyle and the surrounds of Kununurra. I got to fly to a remote community and help out in clinics with the Royal Flying Doctors. We did veranda clinics on some cattle stations the size of Tasmania, which was no big deal to anyone except me. We swatted flies while we discussed blood pressure tablets and aphthous ulcers. I was lucky enough to see meet some famous Aboriginal painters and see them working. I went to a whole-day Fazz-Dee workshop, focussing on a culturally sensitive approach to it, how to recognise it and how to educate mothers and families.

I went to Kununurra as a blank slate, simply from having experienced nothing like it before. I left humbled, indebted and passionate, having pieced together a bit of an understanding of the challenges faced by the community, as well as an aptitude for plucking high-up mangoes out of trees. The Wild West can be beautiful, but its social circumstances are not pretty. We live in a country that still struggles with many problems and I hope that this snapshot of my experiences serves as an honest memo. As students, it is difficult to see that our contribution is meaningful, but it is still important to go on placements even if just to listen, observe, absorb stories and try to understand. But as future health professionals, we're well-placed and arguably obliged to act.

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Correspondence

A Elliston: anna.elliston@utas.edu.au

References

[1] Barber K, Rumley H. Gunanurang: (Kununurra) Big River Aboriginal cultural values of the Ord River and wetlands - a study and report prepared for the water and rivers commission. 2003 [cited 2015 April 20th]. Available from http://www.water.wa.gov.au/PublicationStore/first/51768.pdf

[2] Saunders P, Saunders A, Middleton J. Living in a 'fat swamp': exposure to multiple sources of accessible, cheap, energy-dense fast foods in a deprived community. *Br J Nutr.* 2015 Apr 17; 1-7.

[3] Thornton LE, Jeffrey RW, Crawford DA. Barriers to avoiding fast-food consumption in an environment supportive of unhealthy eating. *Public Health Nutr*. 2013 Dec. 16 (12): 2105-13.

[4] National Rural Health Alliance Inc. Obesity in rural Australia. Deakin West ACT: September 2013 [cited 2015 April 20th]. Available from http://ruralhealth.org.au/sites/default/files/publications//nrha-obesity-fact-sheet.pdf

[5] National Rural Health Alliance Inc. Mental health in rural and remote Australia. Deakin West ACT: September 2015 [cited 2015 June 15th]. Available from http://ruralhealth.org.au/sites/default/files/publications/fact-sheet-mental-health-2015.pdf

[6] National Rural Health Alliance Inc. Alcohol use in rural Australia. Deakin West ACT: March 2014 [cited 2015 June 15th]. Available from http://ruralhealth.org.au/sites/default/files/publications/nrha-factsheet-alcohol.pdf

[7] Government of Western Australia Department of Health. Child and youth health network: foetal alcohol spectrum disorder model of care. Perth WA: 2010 [cited 2015 June 29th]. Available from http://www.healthnetworks.health.wa.gov.au/modelsofcare/docs/FASD_Model_of_Care.pdf

[8] National Rural Health Alliance Inc. Kidney disease in rural Australia. Deakin West ACT: March 2013 [cited 2015 June 15th]. Available from http://ruralhealth.org.au/sites/default/files/publications/nrha-factsheet-35.pdf

[9] National Rural Health Alliance Inc. Measuring the metropolitan-rural inequity. Deakin West ACT: September 2010 [cited 2015 June 15th]. Available from http://ruralhealth.org.au/sites/default/files/fact-sheets/Fact-Sheet-23-%20measuring%20the%20metropolitan-rural%20inequity_0.pdf

[10] Australian Bureau of Statistics. The health and welfare of Australia's Aboriginal and Torres Strait Islander people: life expectancy. Canberra ACT: February 2011 [cited 2015 June 21st]. Available from http://www.abs.gov.au/AUSSTATS/abs@.nsf/lookup/4704.0Chapter218Oct+2010

[11] World Health Organisation. Life expectancy at birth. 2015 [cited 2015 June 21st]. Available from http://gamapserver.who.int/gho/interactive_charts/mbd/life_expectancy/atlas.html

[12] Mahood K. Kartiya are like Toyotas. Griffith Reivew: 2012 [cited 2015 April 20th]. Available from https://griffithreview.com/articles/kartiya-are-like-toyotas/

[13] Australian Government Australian Institute of Health and Welfare. Indigenous Australians. Canberra: 2015 [cited 2015 June 21st]. Available from http://www.aihw.gov.au/indigenous-australians/

[14] Australian Medical Association. Indigenous doctors double. Barton ACT: 2014 Oct 28th [cited 2015 April 20th]. Available from https://ama.com.au/ausmed/indigenous-doctors-double

[15] Australian Indigenous Health Info Net. Background information. 2015 [cited 2015 June 29th]. Available from http://www.healthinfonet.ecu.edu.au/other-health-conditions/mental-health/reviews/background-information

Smoke on the water: a student based guide to electronic cigarettes

Damian J Ianno
B. Biomedicine (Hons)
Third Year Medicine (Postgraduate)
University of Melbourne

Damian's medical interests lie in surgery, anaesthetics, and psychiatry. Non-medical interests include writing, soccer, and philosophy. Having completed an honours degree and worked as a researcher he plans to be heavily involved in research throughout his medical career.

Diseases attributed to tobacco smoking are some of the most prevalent and preventable in the world. Therefore, smoking cessation programs and interventions are crucial components of population health strategies. Currently used interventions and medications have proved effective in aiding patient abstinence from tobacco, yet they are often met with low patient uptake, satisfaction, and compliance. Electronic cigarettes pose a new challenge for clinicians as minimal evidence exists on their safety, health impact and effectiveness as smoking cessation tools.

The evidence to date on electronic cigarettes was reviewed and this guide was developed to assist medical students in providing information and advice to patients about electronic cigarettes. The guide includes information on types of electronic cigarettes, how they work, their health effects, their use in smoking cessation and, current regulation in Australia. The article also includes patient-centred frequently asked questions, with evidence-based answers.

Behind the smoke screen

What are e-cigarettes?

Electronic cigarettes, also known as e-cigarettes, e-cigs, personal vaporisers or electronic nicotine delivery systems (ENDS), are battery-operated devices used to simulate the experience of smoking by delivering flavoured nicotine, in the form of an aerosol (Figure 1). Despite the original design dating back to 1963, [1] it was only in 2003 that the Chinese inventor and pharmacist, Hon Lik, was able to develop the first commercially viable modern e-cigarette. [2]

People use e-cigarettes for many reasons, including: To make it easier to reduce the number of cigarettes you smoke (79.0%), they may be less hazardous to your health (77.2%), they are cheaper than regular cigarettes (61.3%), they are a quitting aid (57.8%), so you can smoke in places where smoking regular cigarettes is banned (57.4%), as an alternative to quitting (48.2%), e-cigarettes taste better than regular cigarettes (18.2%). [3]

Figure 1. *Aerosol from an e-cigarette.*

What makes up an e-cigarette?

There are various classes of e-cigarette, but all follow a simple design. A lithium ion battery is attached to a heating element known as an "atomiser" which vaporises the e-liquid. The e-liquid, sometimes called "juice", is traditionally held in a cartridge (the mouth piece) and usually consists of a combination of propylene glycol and glycerine (termed humectants) to produce aerosols that simulate conventional cigarette smoke. [4] Liquid nicotine, water, and/or flavourings are commonly included in e-liquids as well. Some devices have a button designed to activate the atomiser; however, more recent designs work via a pressure sensor that detects airflow when the user sucks on the device. This pressure sensor design emits aerosolised vapour, which the user inhales. This practice is known as 'vaping'.

What types of e-cigarettes exist?

Currently, three classes of e-cigarettes exist on the market [5]:

The first class is commonly referred to as 'cigalikes' and, as the name would suggest, they resemble traditional combustion tobacco cigarettes (Figure 2).

"e-Go's" comprise the second class. These are larger than cigalikes and have removable tanks that can be refilled with e-liquid (Figure 3).

Finally, there are modular e-cigarettes (or 'mods'), which are usually larger than e-Go's. They have a removable tank and can be customised to the user's preferences (Figure 4).

Why is this important?

E-cigarette devices vary vastly between developers. [6] Users are able to modify their e-cigarette atomisers, circuitry, and battery power to alter vapour production. [7-9] By 2014, there were an estimated 466 brands of e-cigarette with 7764 flavours. [10] Users are also able to select their own e-juice, with 97-99% of users choosing e-liquid containing nicotine. [6,11] Despite devices on the market delivering less nicotine than conventional combustible cigarettes, [12] many health professionals are concerned about the short and long-term health effects of e-cigarettes. [13]

Demystifying the situation

How safe are e-cigarettes?

Given that e-cigarettes have been available for just under a decade, no long-term studies into their health effects currently exist. However, several short-term studies have been conducted on the health implications of e-liquids, e-cigarette devices, and vapour.

Figure 2. *A cigalike.*

Figure 3. *An e-Go.*

Figure 4. *A modular e-cigarette, or "mod".*

Nicotine

The e-cigarette market is largely unregulated. One study found nicotine amounts in e-liquids varied greatly, with concentrations ranging from 0-34 mg/mL. [14] Of additional concern, further studies found significant discrepancies between 'label concentration' of nicotine and 'actual concentration', [15] with one reporting that 'nicotine free' e-liquids actually contained nicotine. [16] This is of ethical concern given that nicotine is a highly addictive drug [17] likely to influence usage patterns and dependence behaviours. There is a need to assess nicotine dependence in e-cigarette users. [18] One study looked at pharmacokinetic absorption of nicotine by comparing nicotine delivery via e-cigarettes, combustion cigarettes, and nicotine inhalers. It found that e-cigarette absorption rates lay between those of combustion cigarettes and nicotine inhalers, implying that nicotine is absorbed though both buccal (slow, nicotine inhaler) and pulmonary (fast, combustion cigarette) routes. As nicotine dependence is related to absorption rate and exposure, this suggests e-cigarettes users are at risk of dependence. This claim was verified by other studies, which conclusively demonstrated e-cigarette users can achieve nicotine exposure similar to that of combustion cigarette smokers. [19,20]

Propylene glycol and glycerine (humectants)

Propylene glycol and glycerine have not been deemed safe for inhalation [21] because little is known about their long-term impacts on health when inhaled. [22] By-products of heating both propylene glycol (propylene oxide) and glycerine (acrolein) have been found to be potentially carcinogenic and irritating to the respiratory tract. [23] A systematic review of contaminants in e-cigarettes concluded that humectants warrant further investigation given the precautionary nature of threshold limit values (TLVs) for exposures to hydrocarbons with no established toxicity (The TLV of a substance being the level to which it is believed a worker can be exposed, day after day, for a working lifetime without adverse health effects). [24]

Flavours

There are over 7000 flavours of e-liquid as of January 2014. Despite nearly all of these flavourings having been approved for human oral consumption, their safety when heated and inhaled remains questionable. [25] In fact, many flavourings have been shown to be cytotoxic when heated and others resemble known carcinogens. [26] One study found heating cinnamon flavoured e-liquid produced cinnamaldehyde, a highly cytotoxic substance, [27] while another study found balsamic flavour e-cigarettes triggered pro-inflammatory cytokine release in lung epithelium. [28] Furthermore, a recent study looking at 30 e-fluids found that the majority of flavours consisted of aldehydes which are known 'primary irritants' of the respiratory mucosa. [29] Manufacturers do not always disclose the exact ingredients in their e-liquids and many compounds are potentially cytotoxic, pro-inflammatory and/or carcinogenic. Thus, the safety of e-liquids cannot be assured. [25,30]

Toxins

In the US, the Food and Drug Administration analysed the vapour of 18 cartridges from two leading e-cigarette manufacturers and confirmed the presence of known and potentially carcinogenic or mutagenic substances. These included diethylene glycol (DEG, an ingredient used in antifreeze that is toxic to humans), tobacco-specific nitrosamines (TSNAs, human carcinogens) and tobacco-specific impurities suspected of being harmful to humans (anabasine, myosmine, and β-nicotyrine). [31] To put these findings into context, the concentration of toxins in e-cigarettes ranged between 9 and 450 times less than those in conventional cigarettes. [19] Secondly, they were found to be at acceptable involuntary work place exposure levels. [24] Furthermore, levels of TSNAs were comparable in toxicity to those of nicotine inhalers or patches, [32] two forms of nicotine replacement therapy (NRT) commonly used in Australia. [33] Lastly, e-cigarettes contain only 0.07-0.2% of the TSNAs present in conventional cigarettes. [34] Of note, in 15 subsequent studies that looked at DEG in e-cigarettes, none was found. [34]

E-cigarette device

Many chemicals used in e-liquids are considered safe for oral ingestion, yet their health effects when inhaled as vapour remain uncertain. This applies not only to e-liquids but also the e-cigarette device itself. Many e-cigarette devices are highly customisable, with users able to increase voltages, producing greater toxin levels. One study identified arsenic, lead, chromium, cadmium and nickel in trace amounts not harmful to humans, while another found these elements at levels higher than in combustion cigarettes. [36,37] Lerner et al. looked at reactive oxygen species (ROS) generated in e-cigarette vapour and found them similar to those in conventional smoke. They also found metals present at levels six times greater than in conventional cigarette smoke. [38] A recent review noted that small amounts of metals from the devices in the vapour are not likely to pose a serious health risk to users, [24] while other studies found metal levels in e-cigarette vapour to be up

Table 1. *Frequently reported hazards of electronic cigarette smoking [43].*

Respiratory system	Upper respiratory tract irritation, dry cough, dryness of the mucus membrane, nose bleeding, release of cytokines and pro-inflammatory mediators, allergic airway inflammation, decreased exhaled nitric oxide (FeNO) synthesis
Nervous system	Headache, dizziness, nervousness, insomnia, sleeplessness
GIT	Nausea, vomiting, dry mouth, mouth or tongue sores/inflammation, black tongue, gum bleeding, gingivitis, gastric burning, constipation
CVS	Palpitation, chest pain
Eye	Irritation, redness and dryness of the eyes, can cause eye damage
Choking hazards	Accidental exposure to high concentrations of e-liquids can cause choking hazards
Malignancy	Change in bronchial gene expression and risk of lung cancer
Miscellaneous	Shortness of breath, shivering etc

to ten times less than those in some inhaled medicines. [39] Given that metals found in e-cigarette vapour are likely a contaminant of the device [6, 40], variability in the e-cigarette manufacturing process and materials requires stricter regulation to prevent harm to consumers.

Effects on health

E-cigarettes appear to be safer than combustion cigarettes, [15] but they should not be considered harm free. [41] A 2014 Cochrane review found no 'serious' adverse effects from e-cigarette trials to date, [42] yet another review which included 28 publications found hazards related to e-cigarettes (Table 1). [43].

Other large studies supported this information. [23,44-46] Research on short-term changes to cardiorespiratory physiology following e-cigarette use included increased airway resistance [25] and slightly elevated blood pressure and heart rate. [47] As the short- and long-term consequences of e-cigarette use are currently unclear, [47] a conservative stance would be to assume vaping as harmful until more evidence becomes available.

Where there's smoke, there's fire

Australian law and e-cigarettes

In Australia there is currently no federal law that specifically addresses the regulation of electronic cigarettes; rather, laws that relate to poisons, tobacco, and therapeutic goods have been applied to e-cigarettes in ways that effectively ban the sale of those containing nicotine. In all Australian states and territories, legislation relating to nicotine falls under the Commonwealth Poisons Standard. [49,50] In all states and territories, the manufacture, sale, personal possession, or use of electronic cigarettes that contain nicotine is unlawful, unless specifically approved, authorised or licenced. [49,50]

Under the Commonwealth Poisons Standard nicotine is considered a Schedule 7 – Dangerous Poison. E-cigarettes containing nicotine could be removed from this category in the future should any device become registered by the Therapeutic Goods Administration (TGA), thus allowing it to be sold lawfully.

There are currently no TGA registered nicotine containing electronic cigarettes [51] and importation, exportation, manufacture and supply is a criminal offence under the Therapeutic Goods Act 1989. [52] It is, however, possible to lawfully import electronic cigarettes containing nicotine from overseas for personal therapeutic use (e.g. as a quitting aid) if one has a medical prescription as this is exempt from TGA registration requirements outlined in the personal importation scheme under the Therapeutic Goods Regulations 1990.

Therefore, it is up to the discretion of the medical practitioner if they provide a prescription for a product not yet approved by the TGA. Given that legislation currently exists to permit medical practitioners to assist individuals in obtaining e-cigarettes, it is imperative we understand both the legal environment at the time and the health consequences.

Stick that in your e-cig and vape it!

E-cigarettes as smoking cessation aids

A debate continues as to whether e-cigarettes – with or without nicotine – are able to play a role in smoking cessation (Figure 5). In the absence of large scale clinical trials it is impossible to answer this question definitively. What is clear from smoking statistics worldwide is that more needs to be done regarding smoking cessation. E-cigarettes may be another tool to help achieve a tobacco free future. Thus far, conventional NRT has been rated by most smokers attempting to quit as unappealing [53] despite evidence that NRT increases quit rates by 50-70% compared to placebo. [54] Few trials have been conducted to investigate whether e-cigarettes are effective tools for smoking cessation, but one recent systematic review and meta-analysis found that nicotine containing e-cigarettes were associated with both a

Figure 5. *Quitting tobacco cigarettes through vaping.*

significant reduction in the number of combustion cigarettes smoked as well as complete smoking tobacco abstinence. [53] This suggests that e-cigarettes have potential as cessation aids and tobacco harm reduction devices.

E-cigarettes containing nicotine were more successful in helping patients reduce or quit smoking than those without nicotine according to a recent Cochrane review, [42] a finding in-line with conventional NRT vs. placebo studies. The review was unable to compare e-cigarette trials to conventional NRT trials given differences in study designs but commented that on average quit rates using conventional NRT at 12 months were 10%, while e-cigarette use corresponded with quit rates of 20%.

E-cigarettes, unlike conventional NRT products, are not only able to provide smokers with nicotine to satisfy their pharmacological addiction, but by design simulate many of the behaviours that have been psychologically ingrained through long-term smoking. E-cigarettes allow users to inhale and exhale a smoke-like substance. They can handle a device of similar shape to satisfy the oral fixation. Psychological triggers from 'smoker-friendly venues' can be relieved by using e-cigarettes, and flavourings can be customised to tobacco or menthol. These factors may prove e-cigarettes a valuable ally in the fight on tobacco. However, there is concern among some health practitioners that e-cigarettes may be a gateway to use of combusted tobacco. [55] If a patient is seeking advice about quitting, it is important to provide them with well tested NRT and medications. These include nicotine delivery preparations for oromucosal (nicotine gum and spray) and transdermal (nicotine patches) routes as well as other drugs including bupropion, varenicline and cytisine medications, [56] with varenicline being the most effective in improving likelihood of quitting. [53]

Questions you may be asked by patients

My partner and I are looking to start a family soon. Is it safe to use electronic cigarettes during pregnancy?

As e-cigarettes lack many of the harmful carcinogens found in regular tobacco cigarettes, consumers might be misled into believing these products are safe. This is of great concern to traditionally high-risk groups, such as pregnant women. In a 2015 review, the author concluded that, based on current evidence, no amount of nicotine is known to be safe during pregnancy. [40] To date, there is no evidence looking specifically at e-cigarette use in pregnant women, however much is known about nicotine exposure in pregnancy. Nicotine is metabolised faster in pregnant women [57] and easily crosses the placental barrier to enter fetal circulation, [40,58] and nicotinic receptors implicated in brain development [59,60] are present in the fetal brain from the first trimester of pregnancy. Many women may seek to use e-cigarettes since conventional NRT in pregnant women has been highly unsuccessful for smoking cessation. [61] Nicotine is considered a Category D drug under Australian pregnancy guidelines

(formerly ADEC) and exposure during pregnancy has been found to cause significant health consequences in the fetus and neonate. [62] It is important to inform patients that current evidence suggests nicotine, at any concentration, during pregnancy is not considered safe and all efforts should be made to ensure a nicotine-free pregnancy with effective strategies implemented prior to conception.

My housemates are always using e-cigarettes near me. Can I get sick if I am around them when they use one?

Evidence, especially long-term data, is lacking on the effects of e-cigarettes on bystanders. [13] What is known is e-cigarette vapour contains nicotine and particles that may be inhaled by persons in the vicinity of e-cigarette users. [28] One study found low levels of formaldehyde and nicotine among several other chemicals emitted into the air. It was subsequently concluded that toxins in e-cigarette aerosols were emitted at much lower levels compared with conventional cigarette emissions. [63] A 2014 systematic review [24] compared TLVs to the "worst case" assumptions about both chemical content of aerosols and liquids as well as behaviour of e-cigarette users and concluded "there is no evidence that vaping produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces". Any effect on bystanders from e-cigarette vapour is likely to be much less than combustion cigarettes, a similar conclusion reached by other studies. [39,64] However, some studies have shown serum cotinine levels (the primary metabolite of nicotine) to be increased in non-smokers exposed to e-cigarette vapour, [65,66] though only to levels ten percent of that of second-hand smoke from conventional cigarettes. Even if toxins in vapour are likely to pose little harm to bystanders, the very presence of toxins and nicotine in vapour is inconsistent with the claim most e-cigarette companies make of vapour being 'just harmless water vapour'.

So I've heard e-cigarettes may be unhealthy, but are they dangerous?

There are potential dangers surrounding e-cigarettes arising from their design and engineering. The United States Fire Administration recently compiled a report of over 25 fires or explosions from e-cigarettes, either while being used or charged, many of which resulted in serious burns to individuals and damage to property. [67]

Nicotine in the e-liquid refill packs is considered a potentially lethal poison. [11] If ingested or in direct contact with skin it poses a potential serious health risk, [68] including the potential for overdose in children. [69] There has been at least one known fatality in a toddler from accidental ingestion and overdose of liquid nicotine intended for e-cigarette use. There have been over 3500 liquid nicotine exposure related incidents recorded by the American Association of Poison Control Centres since November 2014. [70]

What are tobacco companies doing about e-cigarettes?

It is worth noting that many tobacco companies have opted to include e-cigarettes in their product portfolio. [6] Thus ethically speaking, it is vital for doctors to understand that by recommending e-cigarettes they may indirectly be supporting the tobacco industry.

Conclusion

E-cigarettes are a growing market and present a novel challenge to clinicians and medical students. Traditional approaches of obtaining pack-year histories or relying on tell-tale signs of smoking such as tar stained fingers or smoke odour will not work for e-cigarette users. We must ask specifically about use of e-cigarettes when taking a smoking history, use terms like 'vaping', ask whether the e-juice contains nicotine and if they have customised their devices. We must not become complacent simply because e-cigarettes are currently viewed as the lesser of two evils with regards to impact on health. As medical students, deciding whether or not to endorse e-cigarettes as smoking cessation aids is a complex issue given that proven, safe, and effective treatments currently exist, and those should be used as primary cessation aids. If a patient has used these primary aids and failed to quit, it is worthwhile considering e-cigarettes as an avenue for achieving tobacco abstinence. It is unlikely that the clinicians we encounter in our studies will have a detailed understanding on e-cigarettes and vaping practises; it is therefore up to us to keep abreast of such knowledge to provide patients with quality information and care.

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Conflict of interest

None declared.

Correspondence

D J Ianno: dianno@student.unimelb.edu.au

References

[1] A GH. Smokeless non-tobacco cigarette. Google Patents; 1965.
[2] Hancock T. Chinese e-cigarette inventor fights for royalties. The Japan Times [Internet]. 2013 Oct 4 [cited 2015 27th July]. Available from: http://www.japantimes.co.jp/news/2013/10/04/business/chinese-e-cigarette-inventor-fights-for-royalties/#.VbXikPmqqkq.
[3] Hummel K, Hoving C, Nagelhout GE, de Vries H, van den Putte B, Candel MJ, et al. Prevalence and reasons for use of electronic cigarettes among smokers: Findings from the International Tobacco Control (ITC) Netherlands Survey. *Int J Drug Policy*. 2015;26(6):601-8.
[4] Cheng T. Chemical evaluation of electronic cigarettes. Tob Control. 2014;23 Suppl 2:ii11-7.
[5] Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*. 2014;11(4):4356-73.
[6] Born H, Persky M, Kraus DH, Peng R, Amin MR, Branski RC. Electronic Cigarettes: A Primer for Clinicians. *Otolaryngol Head Neck Surg*. 2015;153(1):5-14.
[7] Cooper S. What you need to know about vaporizers: Engadget [Internet]. 2014 May 23 [cited 2015 28 July]. Available from: http://www.engadget.com/2014/05/23/vaporizers-explainer/.
[8] Larson E. Pimp My Vape: The rise of e-cigarette hackers. Mashable Australia [Internet]. 2014 Jan 25 [cited 2015 28 July]. Available from: http://mashable.com/2014/01/25/vaping-subculture/.
[9] Ebbert JO, Agunwamba AA, Rutten LJ. Counseling patients on the use of electronic cigarettes. Mayo Clin. Proc. 2015;90(1):128-34.
[10] Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control*. 2014;23 Suppl 3:iii3-9.
[11] Brandon TH, Goniewicz ML, Hanna NH, Hatsukami DK, Herbst RS, Hobin JA, et al. Electronic nicotine delivery systems: a policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. *Clin. Cancer Res*. 2015;21(3):514-25.
[12] Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep*. 2014;4:4133.
[13] Callahan-Lyon P. Electronic cigarettes: human health effects. *Tob Control*. 2014;23 Suppl 2:ii36-40.
[14] Goniewicz ML, Hajek P, McRobbie H. Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications. *Addiction*. 2014;109(3):500-7.
[15] Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. *Ther Adv Drug Saf*. 2014;5(2):67-86.
[16] Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control.* 2014;23(2):133-9.
[17] Nestler EJ. Cellular basis of memory for addiction. *Dialogues Clin Neurosci*. 2013;15(4):431-43.
[18] Fagerstrom K, Eissenberg T. Dependence on tobacco and nicotine products: a case for product-specific assessment. *Nicotine Tob Res*. 2012;14(11):1382-90.
[19] Schroeder MJ, Hoffman AC. Electronic cigarettes and nicotine clinical pharmacology. *Tob Control*. 2014;23 Suppl 2:ii30-5.
[20] Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology.* 2014;231(2):401-7.

[21] Jimenez Ruiz CA, Solano Reina S, de Granda Orive JI, Signes-Costa Minaya J, de Higes Martinez E, Riesco Miranda JA, et al. The electronic cigarette. Official statement of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) on the efficacy, safety and regulation of electronic cigarettes. *Arch Bronconeumol*. 2014;50(8):362-7.
[22] Pepper JK, Brewer NT. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. Tob Control. 2014;23(5):375-84.
[23] Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation*. 2014;129(19):1972-86.
[24] Burstyn I. Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks. *BMC Public Health*. 2014;14:18.
[25] Bertholon JF, Becquemin MH, Annesi-Maesano I, Dautzenberg B. Electronic cigarettes: a short review. *Respiration*. 2013;86(5):433-8.
[26] Bahl V, Lin S, Xu N, Davis B, Wang YH, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. Reprod Toxicol. 2012;34(4):529-37.
[27] Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicol In Vitro.* 2014;28(2):198-208.
[28] Rom O, Pecorelli A, Valacchi G, Reznick AZ. Are E-cigarettes a safe and good alternative to cigarette smoking? *Ann. N. Y. Acad. Sci*. 2015;1340:65-74.
[29] Tierney PA, Karpinski CD, Brown JE, Luo W, Pankow JF. Flavour chemicals in electronic cigarette fluids. *Tob Control*. 2015.
[30] Schraufnagel DE, Blasi F, Drummond MB, Lam DC, Latif E, Rosen MJ, et al. Electronic cigarettes. A position statement of the forum of international respiratory societies. *Am J Respir Crit Care Med*. 2014;190(6):611-8.
[31] FDA. Public Health Focus - Summary of Results: Laboratory Analysis of Electronic Cigarettes Conducted By FDA [WebContent]. 2015 [cited 2015 28 July]. Available from: http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm173146.htm.
[32] Stepanov I, Jensen J, Hatsukami D, Hecht SS. Tobacco-specific nitrosamines in new tobacco products. *Nicotine Tob Res*. 2006;8(2):309-13.
[33] Quit Victoria. Nicotine replacement products 2015 [cited 2015 28 July]. Available from: http://www.quit.org.au/preparing-to-quit/choosing-best-way-to-quit/nicotine-replacement-products.
[34] Cahn Z, Siegel M. Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes? *J Public Health Policy*. 2011;32(1):16-31.
[35] Chausse P, Naughton G, Dutheil F. Electronic Cigarettes: The Resistance Value of the Heating Filament Could Be the Key to Lung Toxicity. *Chest*. 2015;148(1):e29-30.
[36] Cobb NK, Abrams DB. E-cigarette or drug-delivery device? Regulating novel nicotine products. *N Engl J Med*. 2011;365(3):193-5.
[37] Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PloS one*. 2013;8(3):e57987.
[38] Lerner CA, Sundar IK, Watson RM, Elder A, Jones R, Done D, et al. Environmental health hazards of e-cigarettes and their components: Oxidants and copper in e-cigarette aerosols. *Environ Pollut*. 2015;198:100-7.
[39] Hajek P, Etter JF, Benowitz N, Eissenberg T, McRobbie H. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. *Addiction*. 2014;109(11):1801-10.
[40] Suter MA, Mastrobattista J, Sachs M, Aagaard K. Is there evidence for potential harm of electronic cigarette use in pregnancy? *Birth Defects Res A Clin Mol Teratol*. 2015; 103(3):186-95.
[41] Pisinger C, Dossing M. A systematic review of health effects of electronic cigarettes. *Prev Med*. 2014;69:248-60.
[42] McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev*. 2014;12:CD010216.
[43] Meo SA, Al Asiri SA. Effects of electronic cigarette smoking on human health. *Eur Rev Med Pharmacol Sci*. 2014;18(21):3315-9.
[44] Gualano MR, Passi S, Bert F, La Torre G, Scaioli G, Siliquini R. Electronic cigarettes: assessing the efficacy and the adverse effects through a systematic review of published studies. *J Public Health*. 2014.
[45] Franck C, Budlovsky T, Windle SB, Filion KB, Eisenberg MJ. Electronic cigarettes in North America: history, use, and implications for smoking cessation. *Circulation*. 2014;129(19):1945-52.
[46] Hua M, Alfi M, Talbot P. Health-related effects reported by electronic cigarette users in online forums. *J Med Internet Res*. 2013;15(4):e59.
[47] Orellana-Barrios MA, Payne D, Mulkey Z, Nugent K. Electronic Cigarettes-A Narrative Review for Clinicians. *Am J Med.* 2015;128(7):674-81.
[48] Chapman S, Byrne F, Carter SM. "Australia is one of the darkest markets in the world": the global importance of Australian tobacco control. Tob Control. 2003;12 Suppl 3:iii1-3.
[49] Victoria Q. Legal status of electronic cigarettes in Australia. 2015 [cited 2015 26 July]. Available from: http://www.quit.org.au/downloads/resource/policy-advocacy/policy/legal-status-electronic-cigarettes-australia.pdf.
[50] The Poisons Standard (the SUSMP) | Therapeutic Goods Administration (TGA). 2015 [cited 2015 26 July]. Available from: https://www.tga.gov.au/publication/poisons-standard-susmp.
[51] TGA. Electronic cigarettes | Therapeutic Goods Administration (TGA) 2015 [cited 2015 26 July]. Available from: http://www.tga.gov.au/community-qa/electronic-cigarettes.
[52] Therapeutic Goods Act Section 19B, (1989).
[53] Rahman MA, Hann N, Wilson A, Mnatzaganian G, Worrall-Carter L. E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. *PloS one.* 2015;10(3):e0122544.
[54] Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2012;11:CD000146.
[55] Klein JD. Electronic Cigarettes Are Another Route to Nicotine Addiction for Youth. *JAMA Pediatr*. 2015:1-2.
[56] Green G. Nicotine Replacement Therapy for Smoking Cessation. *Am Fam Physician.* 2015;92(1):Online.
[57] Dempsey D, Jacob P, 3rd, Benowitz NL. Accelerated metabolism of nicotine and cotinine in pregnant smokers. *J Pharmacol Exp Ther*. 2002;301(2):594-8.
[58] Luck W, Nau H, Hansen R, Steldinger R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. *Dev Pharmacol Ther.* 1985;8(6):384-95.
[59] Hellstrom-Lindahl E, Nordberg A. Smoking during pregnancy: a way to transfer the addiction to the next generation? *Respiration*. 2002;69(4):289-93.
[60] Nasrat HA, Al-Hachim GM, Mahmood FA. Perinatal effects of nicotine. *Biol Neonate*. 1986;49(1):8-14.
[61] Coleman T, Chamberlain C, Cooper S, Leonardi-Bee J. Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis. *Addiction*. 2011;106(1):52-61.
[62] Bruin JE, Gerstein HC, Holloway AC. Long-term consequences of fetal and neonatal nicotine exposure: a critical review. *Toxicol Sci*. 2010;116(2):364-74.
[63] Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? *Indoor Air*. 2013;23(1):25-31.
[64] McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhal Toxicol*. 2012;24(12):850-7.
[65] Drummond MB, Upson D. Electronic cigarettes. Potential harms and benefits. *Ann Am Thorac Soc*. 2014;11(2):236-42.
[66] Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. *Nicotine Tob Res.* 2014;16(6):655-62.
[67] Administration USF. Electronic Cigarette Fires and Explosions 2014 [cited 2015 30 July]. Available from: https://www.usfa.fema.gov/downloads/pdf/publications/electronic_cigarettes.pdf.
[68] Yang L, Rudy SF, Cheng JM, Durmowicz EL. Electronic cigarettes: incorporating human factors engineering into risk assessments. *Tob Control*. 2014;23 Suppl 2:ii47-53.
[69] Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, et al. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation*. 2014;130(16):1418-36.
[70] Gillian Mohney. First Child's Death From Liquid Nicotine Reported as 'Vaping' Gains Popularity. ABC News [Internet]. 2014 Dec 12 [cited 2015 30 July]. Available from: http://abcnews.go.com/Health/childs-death-liquid-nicotine-reported-vaping-gains-popularity/story?id=27563788.

Primary prevention of dengue: A comparison between the problems and prospects of the most promising vector control and vaccination approaches

Aran Sandrasegaran
3rd year, James Cook University

Aran is a third year medical student at James Cook University in Townsville. He graduated from Trinity Grammar School in Sydney, but was born in Singapore and lived in London. During his spare time, he enjoys running and playing chess online.

Dengue fever has the highest and fastest-rising morbidity and mortality of any vector-borne viral disease. The growing global impact of dengue is a public health challenge with an economic burden that is currently unmet by licensed vaccines or vector control strategies. Therefore, effective, efficient, safe, and sustainable interventions are a public health priority. However, interventions also must be applicable to tropical and less developed regions where dengue is prevalent. Vector control, the principal method for dengue prevention, is not sustainable because current methodology is expensive and of limited effectiveness. Innovative candidate vaccines, including live-chimeric, live-attenuated, inactivated, subunit, and DNA vaccines, and vector control approaches, such as the release of mosquitoes carrying the dominant-lethal allele or *Wolbachia*, are in trials. The most advanced and promising new dengue control measures are the Sanofi Pasteur live-attenuated ChimeriVax vaccine (CYD-TDV) and infection of the *Aedes* mosquito vector with the endosymbiotic *Wolbachia* bacteria. While vaccination shows slightly more promise than vector control, in terms of effectiveness and sustainability, integration of both interventions may be more effective than either approach alone.

Relevance to medical students

The rapid pace of development of vaccines for dengue fever will rapidly reduce the over-100-million dengue fever cases and their associated morbidity and mortality within the next few years. A candidate vaccine against dengue viruses called, CYD-TDV, could reach registration and review by the World Health Organization in 2016. If countries do license CYD-TDV, future doctors will need to understand the costs and benefits of vaccination, particularly any undesirable outcomes after vaccination, and whether alternatives exist.

Introduction

There are more than 100 million dengue cases annually and the financial cost of this disease has been estimated to be more than $2 billion in the Americas and $1 billion in South-East Asia each year. [1] The 30-fold increase in the incidence of dengue in the last 50 years has highlighted the failure of existing vector control strategies and the need for new vaccine or vector control approaches. [1] The most advanced of these are the mosquito-infecting bacteria *Wolbachia*, and Sanofi Pasteur's chimeric tetravalent dengue vaccine (CYD-TDV). A comparison of their problems and prospects based on effectiveness, efficiency, safety, sustainability, economy, and universality may guide their adoption. While these approaches have been developed in isolation, their combination may help achieve the World Health Organization (WHO) goals of reducing dengue mortality by 50% and morbidity by 25% by 2020. [2]

Vaccinations

Prospects

The ideal dengue fever vaccine would induce a neutralising and balanced response for all four dengue serotypes, provide long-lasting or life-long protection, be safe and stable, balance reactogenicity and immunogenicity, and be cost-effective and context-appropriate. A more universal vaccine would confer "herd immunity" to the general

population by reducing the reservoir of infected individuals and infection transmission. Vaccine candidates should be evaluated in trials spanning different populations and patterns of dengue transmission. [2] Several vaccine types are under development, including live-attenuated, live-chimeric, inactivated, subunit, and DNA vaccines (Table 1). [3] Inactivated and subunit vaccines are safer, in principle, due to a lower risk of reversion to virulence and are under evaluation in pre-clinical or early clinical trials. [4] Several more cost-effective and immunogenic live viral vaccines are under evaluation in late-stage clinical trials. [17]

The leading vaccine candidate is the tetravalent Sanofi CYD-TDV that recently completed phase III clinical trials. [4] Phase I and II trials have established the vaccine is safe and immunogenic, inducing neutralising antibody responses in 77–100% of recipients receiving three doses of the vaccine. [13] A neutralising immune response is achieved through inserting dengue structural protein genes for the four serotypes onto a yellow fever virus backbone. [14] The multi-centre Phase III efficacy studies have further supported this effectiveness and safety. [17] The vaccine reduces dengue fever incidence by 56% and dengue haemorrhagic fever by 88%. [15] More than 28,000 subjects have been immunised with this vaccine. [18] CYD-TDV is based on the safe and effective YF-17D vaccine. [18] Pre-clinical and phase I studies have suggested that the incorporation of four dengue serotypes into the YF-17D RNA backbone has not come at the cost of the vaccine's stability. [19] The reactogenicity profile is similar to the YF-17D control. [20] A more robust immune response, with no adverse reactions, has been observed post-injection in flavivirus-vaccinated individuals. No cases of dengue-like disease that could arise from reversion of live vaccine strains to virulence were observed in studies on younger subjects. [21] There was a low vaccine viraemia and similar rates of adverse events compared to the YF-17D control. The vaccine's commercial prospects are still uncertain, but it has a low production cost. [22] Over 20 clinical trials and 20,000 subjects have therefore found the Sanofi vaccine safe and immunogenic. [16]

Problems

The major challenge with the Sanofi Pasteur vaccine has been to induce a balanced immune response against all four dengue virus serotypes (DENV 1-4). The vaccine has needed to elicit protective responses against all four serotypes and not produce sub-neutralising levels of antibody that might enhance subsequent DENV infections.

Table 1. *Candidate vaccine approaches.*

Vaccine type	Developer	Process	Progress
Live, attenuated chimeric (recombinant)	Acambis / Sanofi Pasteur	Insertion of genes coding for DENV structural proteins into a yellow fever virus (17D) backbone. [1]	Phase III tetravalent – leading candidate [4]
	Centre for Disease Control (CDC) / Inviragen	Insertion of serotype genes into serotype II (DENV2-PDK53) DNA backbone. [2]	Phase II monovalent [3]
	National Institutes of Health (NIH) / University of Maryland	Insertion of serotype II and III genes into safer, more immunogenic serotype I and IV DNA backbone. Live attenuated DENV Delta-30 mutation. [4]	Phase I tetravalent
Live, traditionally attenuated	Walter-Reed Army Institute of Research (WRAIR) / GlaxoSmithKline (GSK)	Attenuation achieved by growing the virus in cultured cells and selecting strains	Phase II tetravalent; technical issues [6]
	Mahidol Institute / Sanofi Pasteur		Phase II tetravalent
Inactivated	GSK	Viruses cultured and killed [5]	Phase I tetravalent
Subunit	Hawaii Biotech	Viral immunogenic envelope is combined with viral non-structural protein antigens to produce recombinant 80% E subunit vaccine [6]	Phase I tetravalent [7]
DNA	WRAIR	Dengue prM-E DNA vaccine incorporating membrane and envelope genes into a plasmid vector [8]	Phase I monovalent

ChimeriVax proved notably inefficient in protecting against DENV-2. [23] The efficacy of ChimeriVax was found to be 61%, 82%, and 90% against DENV-1, DENV-3, and DENV-4, respectively, and only 3.5% against DENV-2 after a single dose and 9.2% against DENV-2 after three doses. [24] Other challenges are the three six-monthly doses of vaccine, which could reduce patient compliance and reduce its utility as a traveller's vaccine.

Vector control

Prospects

Vector control methods, which seek to eliminate the hosts of disease-transmitting pathogens, need to reduce dengue incidence in an efficient and economical manner without burdening local health infrastructure. While transient control has value in dengue prevention, ideal methods should be sustainable, require minimal reapplication of insecticide, and account for external factors, such as climate change. [15] Safety is paramount and the effects of preventive interventions on health and ecology should be monitored or the strategy may be limited in its use, for example, in the case of the carcinogenic, toxic, and polluting, but highly efficient insecticide, dichlorodiphenyltrichloroethane (DDT). [25] Ultimately, the proposed intervention will need to be based on scientific evidence as well as public and government support. Current chemical, environmental, biological, and genetic vector control methods are not successfully mitigating dengue's increasing prevalence, geographical distribution, and severity (Table 2). [26] Whether inserting the endosymbiotic *Wolbachia* bacteria into *A. aegypti* mosquitoes will be effective in controlling dengue remains to be seen.

Wolbachia promises to be the equivalent of a human "vaccine" for dengue vectors, by inducing a natural biologic resistance to dengue infection in dengue-carrying *A. aegypti* mosquito populations. *Wolbachia* occurs naturally in approximately 40% of arthropods and reduces *A. aegypti's* ability to respond to viruses, life-span, and reproduction. [30,31] All three forms of *Wolbachia* (wAlbB, wMelPop, and wMel), inhibit DENV replication and dissemination within the host mosquito and may block viral transmission. [32,33] *Wolbachia* strains can dramatically reduce the lifespan of the female *A. aegypti* mosquito so that virus transmission may not occur before the insect dies. [34,35] However, some *Wolbachia* strains are transmitted from mother to offspring in *A. aegypti* populations resulting in rapid spread throughout a population. [35] Risk assessments failed to identify significant risks associated with releasing *Wolbachia*-infected *A. aegypti*. [36] Safety concerns relate to the possible transfer of Wolbachia to humans by mosquito bites, and to non-target species and mosquito predators. [37] *Wolbachia* infection rates remain at 100% one year after Wolbachia wMel release in Cairns. [38] This intervention has now received regulatory approval. The success of field trials such as this would allow this innovation to move to countries where dengue is endemic.

Table 2. *Candidate vector control approaches..*

Vector control type	Process	Progress
Chemical [1]	Insecticides, larvicides, pest control	Popular and evidence-based
		Concerns about significant financial and logistical costs, contamination and toxicity and insecticide resistance
Environmental [2]	Eliminating mosquito breeding grounds, screens, water and waste management	Appropriate strategies have the potential to reduce vector transmission and benefit overall health of people and the environment
		Significant infrastructure needed
Biological [3]	Natural predators and pathogens, (for example, *Wolbachia*)	Successful in local elimination of mosquitoes
		Significant infrastructure needed
Genetic	Release of insects carrying dominant-lethal allele (RIDL), Sterile insect technique (SIT), HE gene, RNAi	Limited field trials and mixed data on effects in reducing target populations in field trials. Large release numbers required

Problems

The challenge now remains to make *Wolbachia*-based vector control strategies more universally applicable and sustainable. Some effects of specific *Wolbachia* strains on DENV transmission may be inappropriate for certain contexts. For example, wMelPop has a more significant impact on DENV transmission in dengue-endemic settings than wMel due to a stronger DENV transmission-blocking effect. [39] However, the wMelPop strain reduces the fitness of *A. aegypti* more than wMel, so would require additional *Wolbachia* mosquito deployment to maintain sufficient levels of *Wolbachia*-infected vectors to prevent dengue transmission. The sustainability of *Wolbachia*-based strategies is challenged by the significant financial and operational costs for rearing, releasing and re-establishing Wolbachia-infected mosquito populations. [40] As with insecticides, the evolution of resistance poses a risk. [41] *A. aegypti* could evolve resistance against particular strains of *Wolbachia*, similar to the resistance of *Drosophila simulans* after transinfection with *Wolbachia* wMelPop. [42] Furthermore, dengue virus strains could develop a means of evading *Wolbachia*-based transmission blocking. Longer-term, larger-scale trials are needed to assess how *Wolbachia* can reduce the burden of dengue in a sustainable manner.

Vaccination and vector control have the potential to be effective, safe, and sustainable, despite their failure to control dengue to date (Table 3). Two large-scale phase III trials in the Americas and Asia involving 40,000 participants have demonstrated an efficacy of 60.8% for CYD-TDV. [16] However, *Wolbachia*-based vector control is still at the small-scale trial stage in Australia in order to refine methods with further large-scale trials in Indonesia, Vietnam, and Brazil. Small scale trials have been completed in Vietnam. Licensing of the Sanofi Pasteur vaccine is expected with Australian Pesticides and Veterinary Medicines Authority (AVPMA) approval already achieved in Australia. [4] Licensing of *Wolbachia* will require further field trials, risk assessment, and time. Both vaccination and *Wolbachia* involve fixed, front-loaded establishment costs that are significantly lower than traditional vector control methods. The risk of adverse events is increased with the Sanofi Pasteur CYD-TDV vaccine that had an efficacy ranging from 56 to 100% against DENV-1, DENV-3 and DENV-4, but not against DENV-2. It may be that incomplete protection can be achieved through combining vaccine and vector control approaches to reduce DENV-2 transmission.

Combinations

Modelling shows that combining vector control with vaccination could increase intervention effectiveness by reducing vector density and therefore infections. One compartmental model found that an imperfect vaccine could reduce dengue incidence by 57%, ten years post-vaccination, but when combined with other strategies, there was a greater reduction in incidence with a rate of 81%, ten years post-vaccination. [43] Another model demonstrated that less efficacious vaccines should not be applied without concurrently applying vector control approaches. [44] Computer simulations suggest that in areas of high mosquito density, vector control followed by vaccination programs could reduce potential surges in dengue virulence. [45] Vector control and vaccination approaches therefore need context-sensitive and coordinated integration. Applied together, vector control and vaccination interventions could reduce DENV transmission significantly and prove to be cost effective. [46] Vaccines for other diseases have previously been paired with vector control methods with few safety issues, better protection against disease risk, and extended efficacy. [47]

Conclusion

The development of safe, effective, and affordable dengue vaccines and new vector control methods promise to rapidly reduce dengue incidence and therefore morbidity and mortality. The most advanced vaccine candidate has proven safe and protective against three of the four dengue virus serotypes. Of the emerging genetic, biological, and environmental vector control methods, the closest to clinical application is the release of mosquitoes infected with specific strains of *Wolbachia* that can reduce dengue virus replication, reproduction, and life span. The vaccine shows slightly more promise than the *Wolbachia* vector control method. History has shown that no single approach is able to control dengue and the future of dengue fever prevention may be integrated immunisation, vector control, and social mobilisation.

Correspondence

A Sandrasegaran: arans@rocketmail.com

Table 3. *Overview of promising vaccine and vector control approaches.*

	Vaccination – Sanofi Pasteur	**Vector control – Wolbachia**
Mechanism	Vaccine contains strains against the four dengue virus serotypes	Natural arthropod *Wolbachia* bacteria injected into *A. Aegypti* eggs
	Dendritic cells carry strains to lymph nodes to activate B cell proliferation and antibody production	Reduce mosquito reproduction, lifespan and pathogen replication
	When bitten by infected mosquitos, antibodies neutralise the virus	*Wolbachia* passed between generations
Efficacy/efficiency	Neutralising and immunogenic; reduces dengue fever by 56% and dengue hemorrhagic fever by 88%; inefficient in tackling DENV-2 in trials	Inhibits DENV replication and dissemination and reduces vector lifespan and reproduction; predicted to reduce transmission by 60–100%
Safety	YF-17D is a safe, stable vaccine backbone; low viraemia, reactogenicity, and adverse events	Minimal safety concerns, such as *Wolbachia* transfer to humans, non-target species, and mosquito predators
Sustainability	Long-term waning of vaccine-elicited immunity may require boosters	Stable in short-term, but potential for *Wolbachia* resistance in the long-term
Economy	Low production cost	Large operational and re-establishment costs
Universality	Most useful in tropical regions, rather than as a traveller's vaccine	Mainly effective in urban centers and tropical regions

References

[1] Bhatt S, Gething P, Brady O, Messina J, Farlow A, Moyes C. The global distribution and burden of dengue. Nature. 2013;496(7446):504-507.

[2] Guzman M, Halstead S, Artsob H, Buchy P, Farrar J, Gubler D. Dengue: a continuing global threat. Nat Rev Micro. 2010;8(12):S7-S16.

[3] Hombach J, Jane Cardosa M, Sabchareon A, Vaughn D, Barrett A. Scientific consultation on immunological correlates of protection induced by dengue vaccines. Vaccine. 2007;25(21):4130-4139.

[4] Guy B, Barrere B, Malinowski C, Saville M, Teyssou R, Lang J. From research to phase III: Preclinical, industrial and clinical development of the Sanofi Pasteur tetravalent dengue vaccine. Vaccine. 2011;29(42):7229-7241.

[5] Durbin A, Whitehead S. Next-Generation Dengue Vaccines: Novel Strategies Currently Under Development. Viruses. 2011;3(12):1800-1814.

[6] Sun W, Cunningham D, Wasserman S, Perry J, Putnak J, Eckels K. Phase 2 clinical trial of three formulations of tetravalent live-attenuated dengue vaccine in flavivirus-naive adults. Hum Vaccin. 2009;5(1):33-40.

[7] Huang C, Butrapet S, Pierro D, Chang G, Hunt A, Bhamarapravati N. Chimeric Dengue Type 2 (Vaccine Strain PDK-53)/Dengue Type 1 Virus as a Potential Candidate Dengue Type 1 Virus Vaccine. J Virol. 2000;74(7):3020-3028.

[8] Osorio J, Huang C, Kinney R, Stinchcomb D. Development of DENVax: A chimeric dengue-2 PDK-53-based tetravalent vaccine for protection against dengue fever. Vaccine. 2011;29(42):7251-7260.

[9] Halstead S, Deen J. The future of dengue vaccines. Lancet. 2002;360(9341):1243-1245.

[10] Putnak R, Coller B, Voss G, Vaughn D, Clements D, Peters I. An evaluation of dengue type-2 inactivated, recombinant subunit, and live-attenuated vaccine candidates in the rhesus macaque model. Vaccine. 2005;23(35):4442-4452.

[11] Lazo L, Izquierdo A, Suzarte E, Gil L, Valds I, Marcos E. Evaluation in mice of the immunogenicity and protective efficacy of a tetravalent subunit vaccine candidate against dengue virus. Microbiol Immunol. 2014;58(4):219-226.

[12] Clements D, Coller B, Lieberman M, Ogata S, Wang G, Harada K. Development of a recombinant tetravalent dengue virus vaccine: Immunogenicity and efficacy studies in mice and monkeys. Vaccine. 2010;28(15):2705-2715.

[13] Putri D, Sudiro T, Yunita R, Jaya U, Dewi B, Sjatha F. Immunogenicity of a candidate DNA vaccine based on the prM/E genes of a dengue type 2 virus Cosmopolitan genotype. Jpn J Infect Dis. 2015.

[14] White L, Sariol C, Mattocks M, Wahala M. P. B. W, Yingsiwaphat V, Collier M. An Alphavirus Vector-Based Tetravalent Dengue Vaccine Induces a Rapid and Protective Immune Response in Macaques That Differs Qualitatively from Immunity Induced by Live Virus Infection. J Virol. 2013;87(6):3409-3424.

[15] Guy B, Saville M, Lang J. Development of sanofi pasteur tetravalent dengue vaccine. Hum Vaccin. 2010;6(9):696-705.

[16] Capeding M, Tran N, Hadinegoro S, Ismail H, Chotpitayasunondh T, Chua M. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet. 2014;384(9951):1358-1365.

[17] Lang J. Recent progress on sanofi pasteur's dengue vaccine candidate. J Clin Virol. 2009;46:S20-S24.

[18] Kanesa-thasan N, Sun W, Kim-Ahn G, Van Albert S, Putnak J, King A. Safety and immunogenicity of attenuated dengue virus vaccines (Aventis Pasteur) in human volunteers. Vaccine. 2001;19(23-24):3179-3188.

[19] Bonaldo M, Caufour P, Freire M, Galler R. The yellow fever 17D vaccine virus as a vector for the expression of foreign proteins: development of new live flavivirus vaccines. Instituto Oswaldo Cruz. 2000;95:215-223.

[20] Guirakhoo F, Pugachev K, Zhang Z, Myers G, Levenbook I, Draper K. Safety and Efficacy of Chimeric Yellow Fever-Dengue Virus Tetravalent Vaccine Formulations in Nonhuman Primates. J Virol. 2004;78(9):4761-4775.

[21] Guirakhoo F, Kitchener S, Morrison D, Forrat R, McCarthy K, Nichols R. Live Attenuated Chimeric Yellow Fever Dengue Type 2 (ChimeriVax-DEN2) Vaccine: Phase I Clinical Trial for Safety and Immunogenicity: Effect of Yellow Fever Pre-immunity in Induction of Cross Neutralizing Antibody Responses to All. Hum Vaccin. 2006;2(2):60-67.

[22] Guy B, Guirakhoo F, Barban V, Higgs S, Monath T, Lang J. Preclinical and clinical development of YFV 17D-based chimeric vaccines against dengue, West Nile and Japanese encephalitis viruses. Vaccine. 2010;28(3):632-649.

[23] Dayan G, Garbes P, Noriega F, Izoton de Sadovsky A, Rodrigues P, Giuberti C et al. Immunogenicity and Safety of a Recombinant Tetravalent Dengue Vaccine in Children and Adolescents Ages 9-16 Years in Brazil. Am J Trop Med Hyg. 2013;89(6):1058-1065.

[24] Mahoney R, Francis D, Frazatti-Gallina N, Precioso A, Raw I, Watler P. Cost of production of live attenuated dengue vaccines: A case study of the Instituto Butantan, Sao Paulo, Brazil. Vaccine. 2012;30(32):4892-4896.

[25] Halstead S. Dengue vaccine development: a 75% solution? Lancet. 2012;380(9853): 1535-1536.

[26] Sabchareon A, Wallace D, Sirivichayakul C, Limkittikul K, Chanthavanich P, Suvannadabba S. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet. 2012;380(9853):1559-1567.

[27] Amarasinghe A, Mahoney R. Estimating potential demand and supply of dengue vaccine in Brazil. Hum Vaccin. 2011;7(7):776-780.

[28] Maguire S, Hardy C. Discourse and Deinstitutionalization: the Decline of DDT. Academy of Management Journal. 2009;52(1):148-178.

[29] Gubler D. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. Trends in Microbiology. 2002;10(2):100-103.

[30] Maciel-de-Freitas R, Aguiar R, Bruno R, Guimares M, Loureno-de-Oliveira R, Sorgine M. Why do we need alternative tools to control mosquito-borne diseases in Latin America? Instituto Oswaldo Cruz. 2012;107(6):828-829.

[31] Thammapalo S, Meksawi S, Chongsuvivatwong V. Effectiveness of Space Spraying on the Transmission of Dengue/Dengue Hemorrhagic Fever (DF/DHF) in an Urban Area of Southern Thailand. J Trop Med. 2012;2012:1-7.

[32] Nam V, Yen N, Duc H, Tu T, Thang V, Le N. Community-Based Control of Aedes aegypti By Using Mesocyclops in Southern Vietnam. Am J Trop Med Hyg. 2012;86(5):850-859.

[33] Mousson L, Zouache K, Arias-Goeta C, Raquin V, Mavingui P, Failloux A. The Native Wolbachia Symbionts Limit Transmission of Dengue Virus in Aedes albopictus. PLoS Negl Trop Dis. 2012;6(12):e1989.

[34] Moreira L, Saig E, Turley A, Ribeiro J, O'Neill S, McGraw E. Human Probing Behavior of Aedes aegypti when Infected with a Life-Shortening Strain of Wolbachia. PLoS Negl Trop Dis. 2009;3(12):e568.

[35] Yeap H, Mee P, Walker T, Weeks A, O'Neill S, Johnson P. Dynamics of the "Popcorn" Wolbachia Infection in Outbred Aedes aegypti Informs Prospects for Mosquito Vector Control. Genetics. 2010;187(2):583-595.

[36] Moreira L, Iturbe-Ormaetxe I, Jeffery J, Lu G, Pyke A, Hedges L. A Wolbachia Symbiont in Aedes aegypti Limits Infection with Dengue, Chikungunya, and Plasmodium. Cell. 2009;139(7):1268-1278.

[37] Lu P, Bian G, Pan X, Xi Z. Wolbachia Induces Density-Dependent Inhibition to Dengue Virus in Mosquito Cells. PLoS Negl Trop Dis. 2012;6(7):e1754.

[38] Min K, Benzer S. Wolbachia, normally a symbiont of Drosophila, can be virulent, causing degeneration and early death. National Academies Press. 1997;94(20):10792-10796.

[39] McMeniman C, Lane R, Cass B, Fong A, Sidhu M, Wang Y. Stable Introduction of a Life-Shortening Wolbachia Infection into the Mosquito Aedes aegypti. Science. 2009;323(5910):141-144.

[40] De Barro P, Murphy B, Jansen C, Murray J. The proposed release of the yellow fever mosquito, Aedes aegypti containing a naturally occurring strain of Wolbachia pipientis, a question of regulatory responsibility. J Verbr Lebensm. 2011;6(S1):33-40.

[41] Popovici J, Moreira L, Poinsignon A, Iturbe-Ormaetxe I, McNaughton D, O'Neill S. Assessing key safety concerns of a Wolbachia-based strategy to control dengue transmission by Aedes mosquitoes. Instituto Oswaldo Cruz. 2010;105(8):957-964.

[42] Hoffmann A, Iturbe-Ormaetxe I, Callahan A, Phillips B, Billington K, Axford J. Stability of the wMel Wolbachia Infection following Invasion into Aedes aegypti Populations. PLoS Negl Trop Dis. 2014;8(9):e3115.

[43] Ferguson N, Hue Kien D, Clapham H, Aguas R, Trung V, Bich Chau T. Modeling the impact on virus transmission of Wolbachia-mediated blocking of dengue virus infection of Aedes aegypti. Sci Trans Med. 2015;7(279):279ra37-279ra37.

[44] Hoffmann A, Montgomery B, Popovici J, Iturbe-Ormaetxe I, Johnson P, Muzzi F. Successful establishment of Wolbachia in Aedes populations to suppress dengue transmission. Nature. 2011;476(7361):454-457.

[45] McMeniman C, Lane A, Fong A, Voronin D, Iturbe-Ormaetxe I, Yamada R. Host Adaptation of a Wolbachia Strain after Long-Term Serial Passage in Mosquito Cell Lines. J Appl Environ Microbiol. 2008;74(22):6963-6969.

[46] McGraw E, Merritt D, Droller J, O'Neill S. Wolbachia density and virulence attenuation after transfer into a novel host. National Academies Press. 2002;99(5):2918-2923.

[47] Knerer G, Currie C, Brailsford S. Impact of combined vector-control and vaccination strategies on transmission dynamics of dengue fever: a model-based analysis. Health Care Manag Sci. 2013;.

[48] Boccia T, Burattini M, Coutinho F, Massad E. Will people change their vector-control practices in the presence of an imperfect dengue vaccine? Epidemiol Infect. 2013;142(03):625-633.

[49] Thavara U, Tawatsin A, nagao Y. Simulations to compare efficacies of tetravalent dengue vaccines and mosquito vector control. Epidemiol Infect. 2013;142(06):1245-1258.

[50] Knerer G, Currie C, Brailsford S. The Cost-Effectiveness of Combined Vector-Control and Vaccination Strategies on Prevention of Dengue Fever: A Dynamic Model-Based Analysis. Value in Health. 2014;17(7):A806.

[51] Lipsitch M, O'Neill K, Cordy D, Bugalter B, Trzcinski K, Thompson C. Strain Characteristics of Streptococcus pneumon Vaccine. J. Infect Dis. 2007;196(8):1221-1227.

Expect the unexpected: A case of malignant hyperthermia in a 14-year-old boy undergoing gastroscopy

Dr. Annie Xin
MD

Annie is a final-year medical student at the University of Melbourne. She has a keen interest in paediatric anaesthesia.

Malignant hyperthermia (MH) is a rare pharmacogenetic disorder, in which volatile anaesthetic agents trigger deregulated calcium release causing hypermetabolic crisis in susceptible individuals. MH is an anaesthetic emergency that requires prompt recognition due to the high mortality related to delayed treatment. This report documents an unexpected case of MH during an elective gastroscopy at the Royal Children's Hospital in a 14 year old boy who had previously undergone uneventful general anaesthesia. The patient developed early signs suggestive of MH after exposure to sevoflurane and was treated with dantrolene. He made a full recovery and a later muscle biopsy confirmed MH susceptibility. This case highlights the importance of clinical vigilance for this rare condition, especially in "low risk" patients without any past or family history for MH. This case also illustrates how early recognition of non-specific clinical signs and efficient implementation of a local MH action plan can lead to successful outcomes despite the potential life-threatening nature of an acute MH crisis.

Introduction

Malignant hyperthermia (MH) is a life-threatening anaesthetic emergency most commonly triggered by inhalational anaesthetic agents. The disease was first described in 1962, after ten members in a Melbourne family died after general anaesthesia with ether. [1] It was later found to be an inherited pharmacogenetic disorder where anaesthetic agents cause abnormal calcium release in skeletal muscle leading to a hypermetabolic crisis. MH is a rare disease with an estimated incidence of <0.02%. [2] It may only be encountered once in an anaesthetist's career, but prompt r ecognition and treatment may make the difference between life and death for the patient. This case report describes an unexpected occurrence of MH in a low-risk paediatric patient undergoing routine gastroscopy. This case highlights the importance of clinical vigilance and a well-implemented action plan in achieving good clinical outcomes in an acute MH event. The key points in the clinical diagnosis and management of MH as well as the values of genetic testing are discussed.

Case report

A 14 year old boy with a five week history of intermittent epigastric pain associated with food was referred to the Royal Children's Hospital (RCH) Day Surgery for an elective gastroscopy under general anaesthesia (GA) for investigation of peptic ulcer disease. He had previously undergone wisdom tooth extraction under GA at another Victorian hospital without any adverse reaction to volatile anaesthetics. There was no known family history of unexpected intraoperative deaths. Except for an enlarged body habitus (body weight of 110 kg), his peri-operative assessment was unremarkable, and he was an otherwise healthy boy.

On the day of the gastroscopy, anaesthesia was induced with IV fentanyl (100 mcg) and propofol (200 mg). A size 4 laryngeal mask airway (LMA) was inserted and the patient maintained spontaneous ventilation on 2.8% sevoflurane. The first 20 minutes after the induction of anaesthesia were uneventful. However, over the following ten minutes, the patient became increasingly diaphoretic with signs of abdominal distension. His heart rate increased from 80 to 120 bpm, mean arterial blood pressure from 80 to 140 mmHg and end-tidal pCO2 (ETCO2) from 45 to 60 mmHg. Gastroscopy was suspended. The LMA was exchanged for a size 7.5 cuffed endotracheal tube for airway

protection. A senior staff anaesthetist was consulted. Although possible diagnoses including pain, light anaesthesia, and obstructed ventilation were considered, there were no obvious painful stimuli or signs of emergence, and the minute ventilation volumes as well as normal chest movement and breath sounds were inconsistent with obstructed ventilation. MH was strongly suspected. An oral temperature probe was inserted and measured a temperature of 40°C, and arterial blood gas (ABG) revealed mixed respiratory and metabolic acidosis (pH 7.02, pCO2 102 mmHg, lactate 8.8 mmol/L, base excess -8 mmol/L). The RCH Malignant Hyperthermia Crisis Plan was activated. The patient was given 250 mg of dantrolene in a large, single IV bolus. Sevoflurane was ceased immediately and he was hyperventilated on 100% oxygen using a Laerdal bag and a separate oxygen source. GA was maintained using a target-controlled infusion of propofol. Cooling was achieved with topical application of ice packs to the neck, axillae and groin. Within ten minutes, the patient's body temperature returned to 37 °C, heart rate to 80 bpm, ETCO2 to 45 mmHg and his ABG improved dramatically (pH 7.46, pCO2 28 mmHg, lactate 3.7 mmol/L, base excess -3 mmol/L).

He was transferred to the paediatric intensive care unit (PICU) for further management and monitoring. His blood test showed acute hyperkalaemia with an elevated K+ of 7.0 mmol/L but no major elevation in his creatine kinase level. After an overnight stay in PICU, the patient made a full recovery and was discharged from hospital five days later. He subsequently underwent a muscle biopsy, and the caffeine-halothane contracture test confirmed a genetic susceptibility to MH. The patient and his parents were informed of the diagnosis and educated about the condition, with an emphasis on future precautions with undergoing anaesthesia. Genetic counselling was offered to the family.

Discussion

Background

MH is an autosomal-dominant disorder of myocyte hypermetabolism most commonly triggered by volatile anaesthetic agents (e.g. halothane, isoflurane, sevoflurane, desflurane) and in rare cases by the depolarising muscle relaxant suxamethonium. [2] MH is estimated to occur once in every 5,000 to 100,000 cases of anaesthesia [2]. About 20-50% of all MH presentations occur in children, with a male-to-female ratio of 2:1. [3,4] The majority of susceptible individuals carry mutations in calcium channel genes, most commonly in the ryanodine receptor gene RYR1 (70%), and occasionally in the CACNA1S gene (1%)

that encodes the α-subunit of the dihydropyridine receptor. [2] Through mechanisms still unknown, an encounter with a triggering anaesthetic agent causes deregulated calcium release from the abnormal channels in skeletal muscle, leading to a hypermetabolic crisis. If left untreated, MH carries a mortality rate of >80%. [5]

Clinical features

Timely recognition of the condition is key to patient survival. As demonstrated in this case, previous uneventful anaesthesia with triggering agents does not rule out MH. Although a detailed anaesthetic history is an important part of peri-operative assessment, 21% of MH patients report previous uneventful anaesthesia and 75% a negative family history. [4] In fact, it has been estimated that on average three anaesthesias are required before an adverse event is triggered in an MH-susceptible patient. [6] The reason for this variability in clinical penetrance is unclear; however, results from animal studies suggest that co-administration with other anaesthetic drugs could influence the onset of MH. [7] Ultimately, the diagnosis of MH falls on the vigilant mind of the anaesthetist. As in this case, the clinical signs are often non-specific (Table 1). Early signs may include increased oxygen consumption (detected by a widened FiO2 and end-tidal O2 gradient), metabolic derangement (hypercapnia, respiratory and metabolic acidosis, diaphoresis, skin mottling), cardiovascular instability (tachycardia, labile blood pressure) and masseter spasm following exposure to succinylcholine. [8]. Masseter spasm has been reported as the earliest sign of acute MH [9] but is present in less than half of paediatric presentations. [10] In children, sinus tachycardia and hypercapnia have been shown as the two most reliable early clinical signs. [10] Fever, hyperkalaemia, and elevated creatine kinase are late signs and their absence does not exclude the diagnosis. [8] The only existing set of diagnostic criteria in the literature was proposed in 1994 by Larach and colleagues [11], which is a clinical grading scale integrating some of the aforementioned early and late signs. However, its diagnostic performance has not been assessed due to the rarity of the condition, and this grading scale is not widely used in Australia. Overall, the anaesthetist needs to apply good clinical judgement and have a strong suspicion for MH if ETCO2 continues to rise despite increased minute ventilation. Other possible differential diagnoses include inadequate anaesthesia or analgesia, insufficient or obstructed ventilation, sepsis, anaphylaxis, endocrine disorders (e.g. thyroid storm, phaeochromocytoma), and neuroleptic malignant syndrome. In this patient, the combination of fever, hypertension, respiratory and metabolic acidosis, lack of exposure to neuroleptic medication, and the time course of clinical deterioration in relation to inhalational anaesthetic exposure made the diagnosis of MH most likely.

Management

This case illustrates the value of a well-rehearsed local management protocol in an acute MH event. At RCH, a detailed MH action plan and an emergency MH trolley are readily available in the operating suite. The immediate management includes cessation of the offending anaesthetic agent, termination of surgery, recruitment of additional personnel (especially the most senior anaesthetic staff), and prompt preparation of dantrolene. [13] Dantrolene inhibits calcium release from the sarcoplasmic reticulum by antagonising the ryanodine receptor RYR1, [14] and is the only definitive treatment for MH. Dantrolene is given at 2-3 mg/kg IV every 10-15 minutes until the patient is clinically stable. [15] In this overweight boy, there was the consideration whether to administer the dose according to his true body weight or ideal weight. The MH Association of the United States recommends that dose calculation be based on the patient's true weight rather than ideal weight, as the major site of action of dantrolene is in the tissue space, and up to 10 mg/kg can be safely administered in boluses. [16] In this case, 250 mg of dantrolene (~2.5 mg/kg at the patient's true weight) posed a logistical challenge. Dantrolene is manufactured in a powder form and is notoriously slow to dissolve in water. [17] Six nurses had to be recruited to mix 13 ampoules of dantrolene for the patient.

	Clinical signs	Changes in monitored variables	Changes in biochemistry
Early	Tachypnoea	Increased FiO2 and ETO2 gradient Rising ETCO2 Increased minute ventilation	Increased PCO2 Decreased pH
	Tachycardia	Sinus tachycardia	
	Masseter spasm		
Late	Diaphoresis	Rising core body temperature	
	Cyanosis	Decreased SpO2	Decreased PaO2
	Generalised muscle rigidity		Elevated creatine kinase
	Dark urine Oliguria		Haemoglobinuria Deranged UEC
	Arrhythmia	Widened QRS, VT, VF	Hyperkalaemia
	Prolonged bleeding		Low platelets and fibrinogen Prolonged prothrombin time Elevated D-dimer
	Death		

Table 1. *Clinical features of MH (adapted from Hopkins TM, 2000 [12]*

Concurrent supportive therapies for MH include hyperventilation with 100% oxygen using a clean source (not the original machine that may retain traces of volatile anaesthetic), maintenance of IV anaesthesia, and in the event of rising core body temperature, employment of cooling methods such as topical application of ice packs to vascular plexuses, cold IV fluids, forced-air cooling blankets, bladder irrigation, and nasal/peritoneal lavage. [15]

Continued monitoring of the patient in an intensive care unit is crucial in the detection and early correction of complications of MH such as hyperkalaemia as seen in this case. Other serious complications include rhabdomyolysis, acidosis, arrhythmias, disseminated intravascular coagulation, and multi-organ failure. [6] Aside from regular observation of the patient's vital signs and urine output, serial ABGs, FBEs, UECs, coagulation studies, creatine kinase, and ECGs are useful investigations in the ongoing management of MH. Continued monitoring is of particular importance as recrudescence of symptoms has been reported in 14.4% paediatric patients after the initial treatment. [10]

Confirmatory diagnosis

Confirmatory diagnosis of MH susceptibility is made with muscle biopsy that is used for in vitro caffeine-halothane contracture testing (CHCT). Currently, all of the Australian testing centres adopt the protocol recommended by the European Malignant Hyperthermia Group and the test has an estimated sensitivity of 99% and specificity of 94%. [18] In Australia, CHCT is only available to children over 12 years of age, because a relatively large piece of vastus lateralis muscle (0.5 g) is required. The muscle is immersed in a tissue bath with various concentrations of caffeine or halothane, and the test yields a positive, negative or equivocal result for MH susceptibility (Table 2). Although

	Contraction in caffeine	Contraction in halothane
Positive (susceptible)	+	+
Negative (normal)	-	-
Equivocal	+	-
	-	+

Table 2. *Caffeine-Halothane Contracture Test result for MH susceptibility.*

an equivocal CHCT result does not confirm the diagnosis, the patient should be treated clinically as having MH. With advancement in DNA sequencing technologies over the past decade, some American centres now offer genetic testing for families with MH. However, challenges remain in the interpretation of the results. Almost 400 RYR1 mutations have been identified in MH-affected families, but only a few are causal. [19] Additionally, for affected families with normal RYR1 and CACNA1S sequences, DNA testing is of limited value with the causal genes yet to be identified. For the moment, CHCT remains the gold standard of MH testing in Australia.

Future anaesthetic considerations

It is essential that patients with suspected or confirmed MH avoid any triggering anaesthetic agent in future surgeries, and be anaesthetised with regional anaesthesia or total intravenous anaesthesia assisted by bispectral index monitoring to reduce the risk of intraoperative awareness. Patients should be ventilated on a clean circuit purged of any residual volatile anaesthetic and closely monitored during the procedure. Theatre staff should anticipate acute MH crisis and be ready to act with dantrolene on standby. Where appropriate, sedation and local anaesthesia are also good options for consideration.

Conclusions

Death under general anaesthesia is a medical disaster dreaded by patients and anaesthetists alike. MH is a rare but preventable cause of anaesthetic-related morbidity and mortality, and an acute MH event can be treated with an effective antidote. This case is a reminder that early recognition of MH is often based on pattern recognition of non-specific clinical signs; and excellent clinical outcomes can be achieved when the crisis is acted upon promptly by a trained team. Although a patient who reports a positive MH history invariably puts every anaesthetist on alert, as illustrated in this case report, it is often the "low risk" elective patient who is more likely to develop an acute MH crisis and put the doctor's clinical skills to the test. For the anaesthetist, continued training on the subject will ensure a low threshold for clinical suspicion when the unexpected case arises. For the hospital, a well-rehearsed local MH action plan is paramount for an efficient response to the emergency to achieve improved patient safety.

Consent declaration

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

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Conflict of interest

None declared.

Correspondence

A Xin: dr.annie.xin@gmail.com

References

[1] Denborough MA, Forster JF, Lovell RR, Maplestone PA, Villiers JD. Anaesthetic deaths in a family. *Brit J Anaesth*. 1962 Jun;34:395-6. PubMed PMID: 13885389. Epub 1962/06/01.
[2] Rosenberg H, Sambuughin N, Riazi S, Dirksen R. Malignant Hyperthermia Susceptibility. In: Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong CT, et al., editors. *Gene Reviews*. Seattle (WA)1993.
[3] Salazar JH, Yang J, Shen L, Abdullah F, Kim TW. Pediatric malignant hyperthermia: risk factors, morbidity, and mortality identified from the Nationwide Inpatient Sample and Kids' Inpatient Database. *Paediatr anaesth*. 2014 Dec;24(12):1212-6. PubMed PMID: 24974921. Epub 2014/07/01.
[4] Strazis KP, Fox AW. Malignant hyperthermia: a review of published cases. *Anesth and analg*. 1993 Aug;77(2):297-304. PubMed PMID: 8346828. Epub 1993/08/01.
[5] Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in north america from 1987 to 2006: a report from the north american malignant hyperthermia registry of the malignant hyperthermia association of the United States. *Anesthesiology*. 2008 Apr;108(4):603-11. PubMed PMID: 18362591. Epub 2008/03/26.
[6] Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. *Orphanet j rare dis*. 2007;2:21. PubMed PMID: 17456235. Pubmed Central PMCID: 1867813. Epub 2007/04/26.
[7] Gronert GA, Milde JH. Variations in onset of porcine malignant hyperthermia. *Anesth and analg*. 1981 Jul;60(7):499-503. PubMed PMID: 7195665. Epub 1981/07/01.
[8] Glahn KP, Ellis FR, Halsall PJ, Muller CR, Snoeck MM, Urwyler A, et al. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. *Brit J anaesth*. 2010 Oct;105(4):417-20. PubMed PMID: 20837722. Epub 2010/09/15.
[9] Pollock AN, Langton EE, Couchman K, Stowell KM, Waddington M. Suspected malignant hyperthermia reactions in New Zealand. *Anaesth intens care*. 2002 Aug;30(4):453-61. PubMed PMID: 12180584. Epub 2002/08/16.
[10] Nelson P, Litman RS. Malignant hyperthermia in children: an analysis of the North American malignant hyperthermia registry. *Anesth and analg*. 2014 Feb;118(2):369-74. PubMed PMID: 24299931. Epub 2013/12/05.
[11] Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology*. 1994 Apr;80(4):771-9. PubMed PMID: 8024130. Epub 1994/04/01.
[12] Hopkins PM. Malignant hyperthermia: advances in clinical management and diagnosis. *British J anaesth*. 2000 Jul;85(1):118-28. PubMed PMID: 10928000. Epub 2000/08/06.
[13] Harrison GG. Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. *Brit J anaesth*. 1975 Jan;47(1):62-5.
[14] Paul-Pletzer K, Yamamoto T, Bhat MB, Ma J, Ikemoto N, Jimenez LS, et al. Identification of a dantrolene-binding sequence on the skeletal muscle ryanodine receptor. *J biol chem*. 2002 Sep 20;277(38):34918-23. PubMed PMID: 12167662. Epub 2002/08/09.
[15] MHANZ. MH Resource Kit 2012 [cited 2015 June 20]. Available from: http://www.anaesthesia.mh.org.au/mh-resource-kit/w1/i1002692/.
[16] MHAUS. Emergency Treatment for An Acute MH Event 2015 [cited 2015 Aug 15]. Available from: http://www.mhaus.org.
[17] Kugler Y, Russell WJ. Speeding dantrolene preparation for treating malignant hyperthermia. *Anaesth intens care*. 2011 Jan;39(1):84-8. PubMed PMID: 21375096. Epub 2011/03/08.
[18] Ellis FR, Halsall PJ, Ording H. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. The European Malignant Hyperpyrexia Group. *Brit J Anaesth*. 1984 Nov;56(11):1267-9. PubMed PMID: 6487446. Epub 1984/11/01.
[19] Stowell KM. DNA testing for malignant hyperthermia: the reality and the dream. *Anesth analg*. 2014 Feb;118(2):397-406. PubMed PMID: 24445638. Epub 2014/01/22.

The Digital Doctor

By Robert Watcher

Sarah Yao
Third Year Medicine (Undergraduate)
Monash University

Sarah is a hopeful third year medical student at Monash. She has a keen interest in your eye and her food, separately of course.

Modern medicine in the 21st century is an evolving enterprise of knowledge and technology. In The Digital Doctor, Dr. Robert Wachter, one of America's 50 most influential physician- executives, discusses the wiring of the healthcare system in the form of electronic health records and 'big data' today. While there is hope digitised healthcare will increase the efficiency of practitioners and improve clinical practice, Wachter reports less than optimal experiences - interrupted work flows in the clinic to attend to electronic databases, decreased opportunities for the practitioner to establish healthy doctor-patient relationships, and occasionally, fatal consequences when the technology we so heavily rely on fails us. Indeed, Wachter succinctly summarises today's epoch of computerised healthcare in his title - "hope, hype and harm."

As a medical student, The Digital Doctor has been thought provoking. My generation of medical students are digital natives who, having grown up with technology, are comfortable with it. Yet, as Wachter points out in his book, by being too comfortable with computerised healthcare, we are less critical of its shortcomings. It is hence imperative to reflect on the importance of striking a balance between being technologically-competent and being vigilant in the age of digitised healthcare.

Through interviews with prominent health professionals and vivid anecdotes, the picture Wachter paints is realistic but solemn. When patient history, drug doses, and investigations are electronically recorded, bedside treatment shifts to the computer. Electronic health records and digital monitoring of the patient, which may come in the form of electronically updated investigation results, introduces the concept of the 'iPatient'. The iPatient is monitored online, and only attended to when the electronic healthcare system sends out reminders. The fundamental concern is that less time is spent taking a history or physically examining the patient. The end result being that we might overlook diagnoses and unnecessarily invest in costly technological interventions. When these amount to hastened patient interactions and increased billing costs, the patient's experience with the healthcare system will be an unsatisfactory one.

Digitised healthcare may have also fallen short of the areas in which it has sought to improve. Although digitised healthcare was designed for convenience, electronic documentation is burdensome when one must adhere to strict formatting when recording data. Additionally, the availability of patient information at the click of a mouse means that any data stored online is just as easily lost, possibly through software malfunction or accidental deletion. Furthermore, there is the possibility that digitised healthcare undermines the skill of practitioners, where practitioners are too trusting on the computer to speak up when in doubt. The Digital Doctor draws up a real incident whereby a computer error led to a teenager being prescribed an overdose of 38.5 antibiotic tablets. The error, despite raising suspicions amongst the nurses, was not corrected, and resulted in the patient taking the prescribed medication overdose. This raises the concern of the quality of education students receive to prepare them for transitioning to practitioners. Are we adequately trained to confidently apply our knowledge in real life situations where the patient is more than an illness defined by exam buzzwords? Is there the possibility that we give ourselves room for mistakes because we trust that computerised healthcare will always correct us when we are wrong? As current medical students undergoing traditional medical school teaching methods, are we sufficiently prepared to become future doctors competent both in our practice, and in the technology that accompanies it?

It is crucial to note that this narrative is set in America. While there are differences between the American and Australian healthcare system, we too practice digitised healthcare, and there are lessons to learn. We should accept that this technology is inevitable alongside advancements in diagnostic and therapeutic equipment. We need to understand that technology is an aid to improve our practice. It is not an alternative or a distraction. We must remember that it is still our patients we are treating, not digital data presented to us.

The Digital Doctor is a cautionary narrative that is highly relevant, albeit critical. We need to accept that the interface of medicine, as The Digital Doctor rightfully highlighted, is changing. The future of technology in healthcare is dynamic and promising - it can be our Mecca if we are adaptive practitioners in using this technology. While we are never fully prepared for what lies ahead of us in our medical careers, we are at the very least, enlightened by the age of computerised medicine and what it has in store for us, both good and bad.

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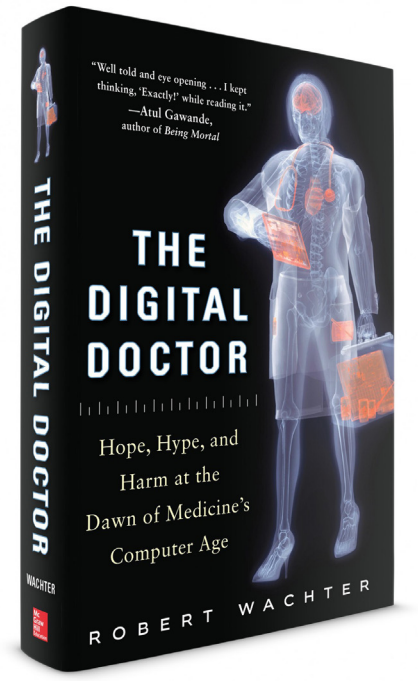
Correspondence

S Yao: hwyao2@student.monash.edu



Reference

[1] Wachter R. The Digital Doctor: Hope, Hype and Harm at the Dawn of Medicine's Computer Age. United States of America: McGraw- Hill Education; 2015.

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