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AMSJ

Australian Medical Student Journal

Novel oral anticoagulants

Guest — Medical Degrees Being Priced Out of Reach

Review — Stroke Prevention in Non-valvular Atrial Fibrillation: Advances in medical therapy

Original — Specialty choices and rural intentions of students from a private undergraduate medical program compared with other Australian medical students

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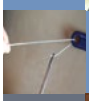
5		Surgical hand ties: A student guide	Jesse Ende
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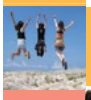
58		Adolescent-onset metabolic syndrome	7 Natalie Ngu
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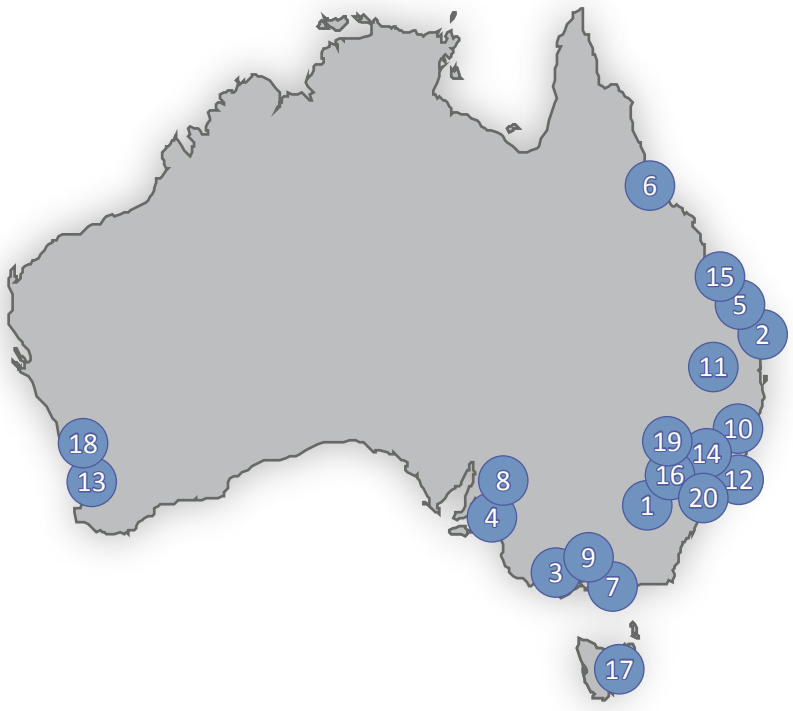

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Editor's welcome: healthcare leaders of tomorrow

Dr. Dylan Morris
Editor-In-Chief, AMSJ

It is with great pleasure that I welcome you to Volume 6, Issue 1 of the Australian Medical Student Journal (AMSJ); the national peer-reviewed journal for medical students. The AMSJ serves two purposes: firstly, to provide a stepping-stone for medical students wishing to advance their skills in academic writing and publication; and secondly, to inform Australian medical students of important news relating to medical education and changes in medical care. This issue of the AMSJ showcases an array of research, reviews, and opinions that address a wide range of contemporary subjects. In particular, there is a trend for articles on translational research and national healthcare matters.

Australia's healthcare system is evolving rapidly to accommodate an ageing demographic, growing epidemics of chronic disease, and the introduction of new and often expensive medical technology. We are concurrently faced with major challenges including declining economic growth and considerable budget cuts in an attempt control national debt. The coming decades will be particularly challenging for our healthcare system, but also for us as future doctors. We will have to make difficult decisions to limit healthcare spending whilst ensuring that Australia maintains a leading world-class healthcare system. More than ever, doctors will be required to be leaders in the national healthcare arena, and it will be up to you and your colleagues to direct our ever-changing healthcare system.

In light of this, I am pleased to introduce this issue with a guest article by Professor Brian Owler, President of the Australian Medical Association. Professor Owler discusses the potential threat of university fee deregulation to Australia's future medical profession. The AMA and others will be launching a social media and public campaign in February to discourage senators from passing a reformed bill.

This issue of the AMSJ has a record number of original research articles, reflecting some of the best research conducted by medical students across Australia. Not only have the authors written excellent papers, they have spent months, even years conducting these extensive projects. Mr Edward Teo reports a large study comparing specialty choices and rural intentions of students graduating from a private medical program compared to those from other Australian medical schools. Ms Skye MacLeod reports on the adequacy of anticoagulation according to the $CHADS_2$ score in patients with atrial fibrillation. Another two studies address the impact of language and literacy respectively on hospital care.

The reviews and feature articles in this issue cover a diverse array of topics. In particular, there are several articles addressing the role of novel oral anticoagulants in the management of atrial fibrillation and venous thromboembolism. This is a large area of interest and transition and we are pleased to inform medical students of the latest evidence and guidelines in this field. It is interesting to observe a growing trend in the publication of systematic reviews in our journal. Systematic literature appraisal and assessment of bias are highly useful skills, which are not only vital for advancing research, but also facilitate the delivery of evidence-based medical care. We encourage students to learn about these

methods and consider writing a systematic review during their medical education.

The AMSJ is staffed by a large team of volunteer medical students from almost every medical school in the country. This issue we received a record number of submissions, with all staff increasing their workload to review and manage each manuscript. I would like to commend the editorial team that have worked tirelessly over the last year. I also acknowledge the new proof-editing team that have been swift at proof-reading all manuscripts and assisting in the development of the new AMSJ style guide. The printed copies of the AMSJ and the AMSJ website would not be possible without help from the print-layout team, IT officers, and sponsorship officers, together led by Miss Biyi Chen. Our Director Mr Christopher Foerster has given his heart and soul to ensure that the AMSJ is of the highest possible standard. Finally, I thank our readers, authors, peer-reviewers, and sponsors who continue to support our journal.

On behalf of the staff of the AMSJ, I hope you enjoy this issue.

Thank you to AMSJ Peer Reviewers

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Surgical hand ties: a student guide

Jesse Ende
Fourth Year Medicine (Undergraduate)
University of New South Wales

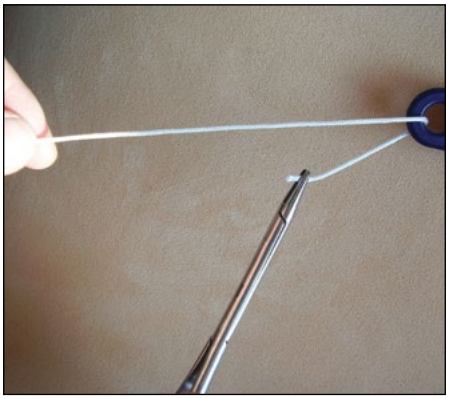
Jesse is a fourth year medical student at the University of New South Wales. He has a passion for surgery and for teaching, both of which he intends to pursue in the future.

Surgical hand ties are a procedural skill commonly employed in surgery; however, student exposure to practical surgical experience is often limited. Students are therefore often excited at the opportunity to learn these skills to practise for themselves. Often the only opportunities to formally learn these skills come in the form of workshops presented at student conferences or run by university special interest groups.

Having attended such surgical skills workshops I have noticed the difficulty demonstrators and students have had in teaching and learning the skill of surgical hand ties. I felt this was the product of two things: the difficulty the tutors had in demonstrating the small movements of the fingers to an audience; and the students' difficulty with remembering each step later. Therefore, I combined an easy to follow graphic with some helpful memory aids into a simple resource to help medical students learn and master hand ties.

In addition to being an individual resource, this guide was also created for use in a workshop setting. Ideally, a demonstrator would show the students the basic steps involved in hand ties. The guide could then be used to reinforce this learning, where the student can practise with the sutures in their hands while following the steps using a combination of pictures, text, and memory aids. This would also have the benefit of letting the demonstrator help students with more specific questions on technique, rather than repeating the same demonstration multiple times.

The overall aim of this guide is to make the process of learning and teaching surgical hand ties to students easier, and to improve recall and proficiency for students performing the skill through the use of simplified steps and diagrams.



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Throwing Hand Ties

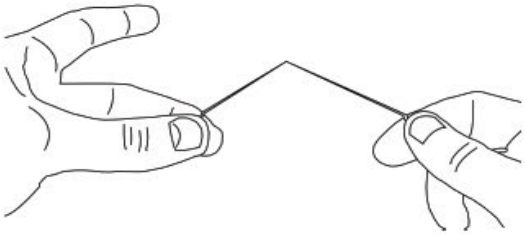
A guide for medical students

Legend

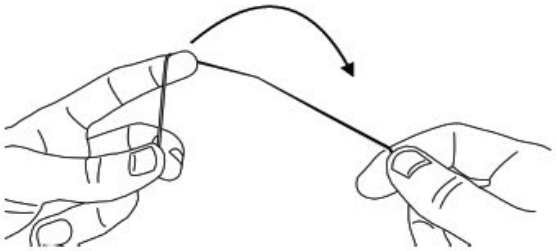
Under → Over

L2 = left hand, finger 2

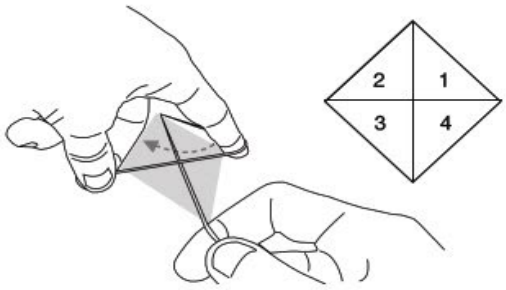
Throw #1



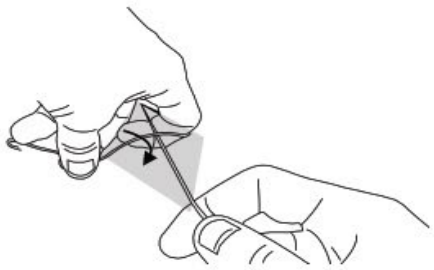
"The mountain"
Start with even lengths. Hold suture between fingers **L1** and **L3**. Keep right hand tight and steady throughout.



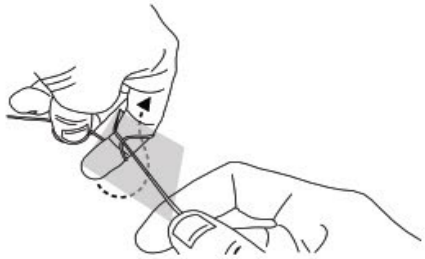
"The mountain"
Make the mountain, and bring it over to make a cross ("The kite").



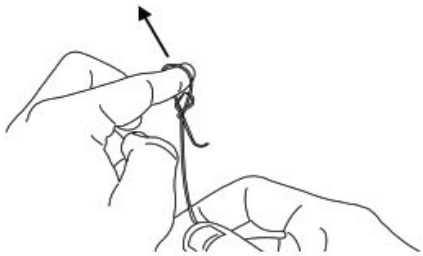
"The kite"
With left hand crossing over right, make a kite with 4 quadrants. **L2** will move from quadrant 1 to quadrant 2, going underneath.



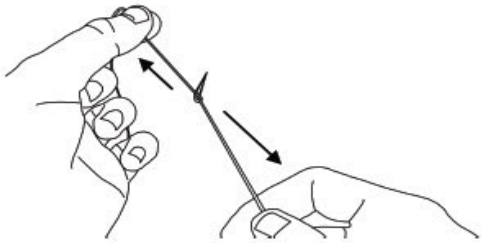
Now move **L2** into quadrant 3, by going over.



"The pull"
With the nail of **L2** pull the suture up and through the loop.



"The pull cont."
Let go with your left hand, and keep pulling the suture through the loop. Then catch it again with **L1** and **L2**.



Now pull your hands away from each other to tighten the throw. Make sure the knot lies flat (check pull direction).

Continued on page 2.

Concept and Design by Jesse Ende, V1.0 July 2014

Throwing Hand Ties

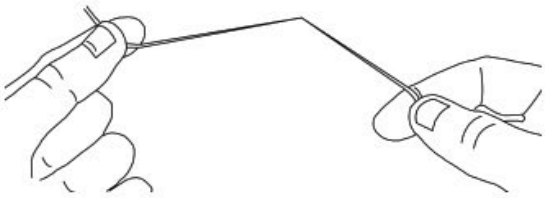
A guide for medical students

Throw #2

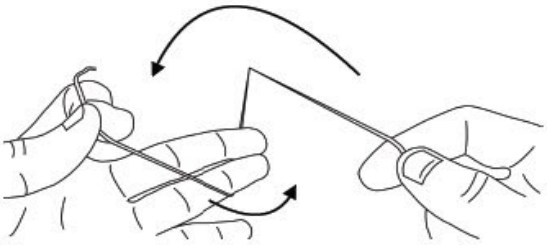
Legend

Under — Over

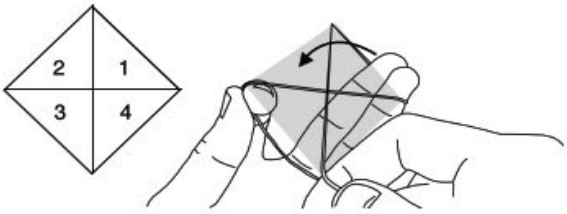
L2 = left hand, finger 2



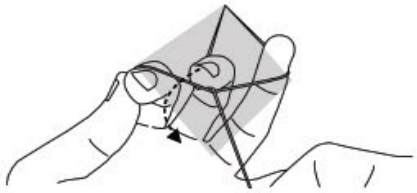
"Part 2"
This time start with suture between **L1** and **L2**. Right hand again stays steady throughout.



"The valley", OR *"The Karate chop"*
Make the valley/karate chop as shown, then bring the right hand over to make another kite.

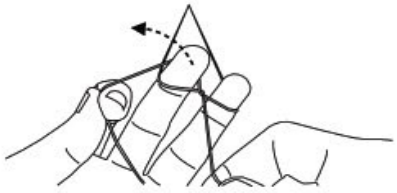


"The kite"
Again, we are going to make our quadrants, this time moving **L3** from quadrant 1 to quadrant 2 (going over).



And now again move **L3** from quadrant 2 to quadrant 3, going underneath.

"The pull"
Using the nail of **L3**, pull the suture into the empty triangle you have made.



And continue using **L3** to pull the length of suture through the loop (by going under as shown).

Keep right hand steady. You will need to let go with your left hand. When it is all pulled through, catch the loose end of suture again, this time between your **L1** and **L3**.

Now take finger out of loop

"The finale"
Again, pull your hands away from each other to tighten the throw. Check the knot is flat (check pulling direction). We are now back to the beginning.

Concept and Design by Jesse Ende, V1.0 July 2014

Page 2 of 2

Medical degrees being priced out of reach

A/Prof Brian K. Owler
MBBS BSc(Med)(Hons) PhD FRACS
President of the Australian Medical Association

A/Prof Brian K Owler is the President of the Australian Medical Association (AMA) and represents surgeons on the Federal Council of the AMA. He is a Consultant Neurosurgeon at the Children's Hospital at Westmead, Norwest Private Hopistal and Westmead Private, and Sydney Adventist Hospital at Wahroonga.

One of the most disappointing and troubling aspects of this year's Federal Budget was the Government's decision to deregulate university fees and to reduce the subsidy for Commonwealth Supported Places by an average of 20 per cent.

It's a decision that the AMA has been fighting, given the harm it could do to the medical profession.

Medicine has always been seen as an attractive career; however, university fee deregulation will mean that medical graduates will be burdened with large debts as they enter the medical workforce as interns. They will carry that debt with them, and this will have consequences that do not seem to have been considered.

At the same time as fee deregulation, the Government is reducing funding for Commonwealth Supported Places.

So, what is the impact of the proposed changes? What will the fees be?

Many medical degrees are now four-year graduate degrees. There are also still a number of undergraduate degrees of five and six years. Let's consider the graduate degree example.

Prior to studying medicine, students have usually completed a science degree of three years, while many others do four or five year degrees. Before they even start medicine, they are likely to have significant debt. Using fees charged to international students as a guide, this debt can be in the order of $50,000.

Medical Deans Australia and New Zealand has estimated that a student completing a four-year professional entry medical course – which is 63 per cent of Australian medical courses − would have a final HECS debt of $55,656, compared to the current debt of $40,340. [1]

The fine print of this modelling is that it is based on the break-even scenario in which fees are limited.

Even the Medical Deans note that their costs are greater than these amounts to provide medical training. Following detailed modelling in 2011, Medical Deans found that it actually costs a University $50,272–51,149 per year to train a single doctor.

The equation does change if universities raise fees past their benchmarked costs to the absolute limit of international student fee levels, which are flexible in their own right.

It is naive to think that universities would not soon raise their fees to the level that covers their costs, even if they would be restrained from going further and making a profit. The current fee for an international medical student at one prominent medical school averages around $76,000 per year.

For a full fee paying domestic student, the fee averages around $64,000 per year.

Indications are that, with fee deregulation, the fee for medicine will likely fall between these numbers, at round $70,000.

They will, of course, be subsidised by the Commonwealth to the order of $18,000.

Therefore the debt accumulated is around $52,000 per year.

Over four years this is more than $200,000 on top of the $50,000 debt

that they are likely to enter medicine with from their undergraduate degrees. So, conservative estimates put the debt at around $250,000 for a medical graduate.

By way of comparison, Bond University has published its fees for 2015. To study a Bachelor of Medicine, Bachelor of Surgery will cost $331,380 − $23,670 per semester x 14 semesters, with the requirement to pay $47,340 in advance for the first two semesters.

Some medical deans will tell you that collection of fees from the Faculty of Medicine will be used to subsidise other areas of the university that are more price sensitive. Bursaries, such as those paid by some universities, will have to be sourced from fees such as those collected from medical students.

There will be immense pressure to raise fees for medical students accordingly. I suspect that the estimate of $250,000 will seem very conservative indeed.

Many reading this may be wondering that, if a medical degree is price insensitive, then what is the issue? Well, there are a number of issues.

There is good evidence that high fee levels and the prospects of significant debt deter people from lower socio-economic backgrounds from entering university.

One of the strengths of medical education in Australia is diversity in the selection of students, including those from lower socio-economic backgrounds. Even under the current arrangements, we still fall short.

In 2009, the former Federal Government outlined a goal that, by 2020, 20 per cent of higher education enrolments at undergraduate level should be filled with students from low socio-economic backgrounds. [2]

A report commissioned on selection and participation in higher education in March 2011 by the Group of Eight (Go8) revealed that low socio-economic status (SES) applicants – from the lowest 25 per cent SES bands − were under-represented at 18 per cent, and high SES applicants – from the top 25 per cent SES bands – were over-represented at 31.6 per cent, relative to their population share in terms of applications for university.

Even now, we are still under the target of 20 per cent.

Closer examination of applications for health disciplines by field of education shows a greater proportion of high SES students – 45 per cent – applying for medicine, compared to 15 per cent applying for medicine from low SES backgrounds. [3]

A significant number of rural students come from a low socio-economic background. High fee levels and the prospect of significant debt will deter them from entering university.

Rural medical students already incur substantive extra costs in accommodation and travel. To place further financial barriers to these students would result in many finding the costs prohibitive. Aboriginal and Torres Strait Islander students may well be hardest hit and discouraged by such measures.

No matter what upfront loan assistance is provided, it will deter students from a low income background from entering medicine. This is a real issue in medicine. We want the best and the brightest, not the wealthiest. And we want the medical profession to have the same diversity as the communities it serves.

I believe Australia has gained significant benefit by attracting medical students from diverse backgrounds who have entered medicine, either through graduate or undergraduate programs, based on merit. That is something that we should continue to value, something that we should continue to benefit from, but it is something that is under threat through these changes.

In the context of this debate, some have suggested that one way to meet demand for medical school places would be to uncap places. The AMA believes this would be a recipe for disaster.

The AMA does not support the creation of new medical schools or additional places until it has been established that there are sufficient training posts and clinical supervisors to provide prevocational and vocational training for the increased numbers of students currently enrolled in Australian medical schools.

Further, any expansion of medical school places should be consistent with workforce planning and the much anticipated five-year training plan we are expecting from the National Medical Training and Advisory Network.

We must not underestimate the impact that an uncapped market would have on demand for health services either.

So, why does graduate debt matter in medicine? There's a perception that doctors earn enough to pay for this level of debt, but the context of debt is important.

A Go8 report on understanding graduate earnings from July 2014 this year suggests that, after 20 years of employment, medicine and law graduates are the top performers, earning $117,000 and $107,000 respectively. [4]

Note, however, that this is after 20 years. In the years preceding that, earnings can be extremely variable depending on individual career paths.

In terms of average earnings, there is a wide variance in the average wage according to discipline.

This also has an impact on the relative financial attractiveness of different medical specialties.

The OECD reports that self-employed general practitioners in Australia earned 1.7 times the average wage in 2011, compared to self-employed specialists who earned 4.3 times the average wage. [5]

Understanding the context of debt incurred by medical students is also important in light of the significant costs of further training required by junior doctors to achieve specialist qualification, and the loss of earning potential for up to 15 years while doing so.

Overseas evidence shows that, in relation to medicine, a high level of student debt is a factor in career choice, driving people towards better remunerated areas of practice and away from less well paid specialties like general practice.

Areas of medicine that are better remunerated will become more attractive. Procedural specialties will be more attractive compared to general practice or areas such as rehabilitation, drug and alcohol, or paediatrics.

Ultimately, these decisions will exacerbate doctor shortages in rural and regional areas.

We do not want to move to a US-style medical training system where students' career choices are influenced by degree of debt. This would have a significant impact on access to services and on workforce planning.

Before its abolition by the Government, Health Workforce Australia published medical workforce projections through until 2025. While these show that, by 2025, the overall medical workforce will be very close to being in balance, there will be geographic shortages as well as shortages in specific specialties.

Encouraging doctors to work in these areas and specialties will be much more difficult if they are saddled with high levels of debt. This would undermine the significant effort that has been made by the Commonwealth to expand doctor numbers, as well as attract graduates to work in underserviced communities and specialties.

Finally, I would like to discuss the implications for higher degrees. These are significant for medical students with an interest in research and academic work.

High debt levels among medical graduates will deter our best and brightest, our future leaders, from undertaking PhD programs.

The numbers of medical graduates in some universities are significant – up to a third.

It is already a major commitment, not only in terms of the minimum three years of time, but also financially.

As a medical graduate, already with significant debt, often at the stage of life of starting a family, it would not be surprising to see commitment to further research, to science, questioned.

This is a real issue for the people who undertake such degrees – our clinician scientists, our future medical leaders. They are the doctors who lead departments, who lead research teams, and run laboratories.

For all the talk of the Medical Research Future Fund, it is disappointing that implications such as these do not seem to have been considered.

The AMA believes that the Commonwealth should be providing additional support for primary medical education, not less, and we do not see fee deregulation as a solution to funding problems.

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Introducing JDocs, a competency framework for junior doctors

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Introduction

The Royal Australasian College of Surgeons is pleased to announce the launch of JDocs, a competency framework supported by a suite of educational resources that have been designed to promote flexible and self-directed learning, together with assessment opportunities to record and log procedural experiences and capture evidence of personal achievements. These resources will be available online later this year, and will continue to evolve and expand over time. Some resources will be available for an annual subscription fee.

Why has College engaged in the prevocational space?

The College recognised the need and importance of re-engagement with prevocational junior doctors to provide guidance and education that would assist with their development towards a proceduralist career. Key to this was to ensure that the doctor entering any procedural speciality program would be well-prepared and clinically competent relevant to their postgraduate year. As a result, the College established JDocs, which is available to any doctor registered in Australia and New Zealand, from and including internship, with the level of engagement determined by the individual doctor.

Junior doctors will also be eligible to apply for the General Surgical Sciences Examination from 2015. This exam tests anatomy, physiology and pathology to a high level.

JDocs does not guarantee selection into any procedural specialty training program, however, engagement with the Framework and its supporting resources describes the many tasks, skills and behaviours a junior doctor should achieve at defined postgraduate levels, and will help the self-motivated junior doctor recognise the skills and performance standards expected prior to applying to a specialty training program.

What does the JDocs Framework cover?

The JDocs Framework is based on the College's nine core competencies, with each competency considered to be of equal importance, and is described in stages appropriate for each of the first three postgraduate clinical years, as well as those beyond. In order to link the many tasks, skills and behaviours of the Framework to everyday clinical practice, key clinical tasks have been developed that are meaningful for the junior doctor. These tasks can be used to demonstrate achievement of the competencies and standards outlined in the Framework, and also make it possible for the junior doctor to show they are competent at the tasks and skills required in order to commence specialty training.

jdocs Best Practice, Better Practitioners

Accessing the JDocs

The first phase of the JDocs website, http://jdocs.surgeons.org/signup.htm, enables the junior doctor to register for updates and download a copy of the Framework. Additionally, the College's website and social media feeds will also deliver updates as to JDocs progression and launch of resources, as they become available later this year.

A shareable app has been developed that provides an overview of JDocs, as well as a sample of learning resources, and can be accessed in the following ways:

- SMS JDocs to 0400813813
- Scan the following QR code

Social media

Twitter: @RACSurgeons, #RACSJDocs

Facebook: Royal Australasian College of Surgeons

Summary

In summary, the JDocs Framework is about the professional standards and learning outcomes to be achieved during the early postgraduate/prevocational clinical years. It describes and assists early career professional development for junior doctors aspiring to procedural medical careers, including surgery.

Bispectral analysis for intra-operative monitoring of the neurologically impaired: a literature review

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Jacob is in his fourth year of medicine at Monash University. He has an interest in anaesthetics.

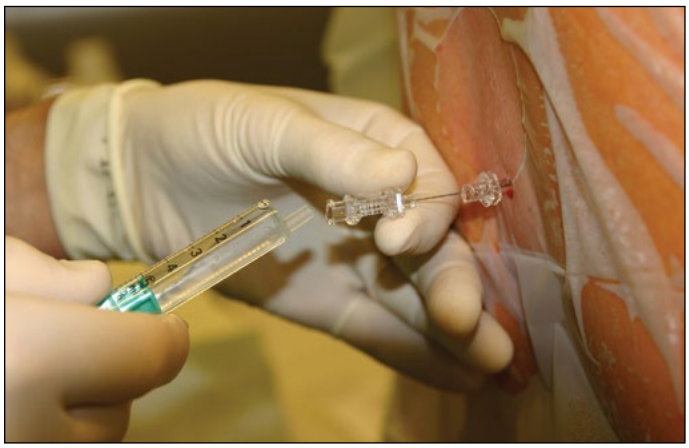
Introduction: The bispectral index (BIS) is a technology which uses a modified electroencephalogram (EEG) to predict the likelihood that an anaesthetised patient has awareness of their surroundings. This method of monitoring was developed by analysing the EEGs of approximately 1000 patients with normal neurological function. It therefore has questionable applicability to those with neurological disability which may cause abnormal EEG patterns. **Aim**: To review the literature and establish whether the BIS monitor can be used to measure depth of anaesthesia in patients with neurologic disability. **Method**: Databases including Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE and PubMed were searched to identify studies investigating the use of the BIS in patients with neurological disability causing atypical EEG patterns. **Results**: Four case reports and four observational studies were found describing patients with Alzheimer's disease, vascular dementia, intellectual disability, epilepsy and congenitally low EEG, who were monitored with the BIS when undergoing anaesthesia. In general, these studies showed patients with neurologic disabilities score lower on the BIS even when fully aware than their non-disabled peers; however, relative changes in BIS score appear to reflect reasonably accurately changes in conscious state and likelihood of awareness. **Conclusion**: The BIS score fails to provide an absolute measure of level of consciousness in patients with neurological impairment and should not be relied upon as the sole measure of awareness. It can, however, provide a relative measure of change in consciousness.

"The anaesthetist and surgeon could have before them on tape or screen a continuous record of the electric activity of… [the] brain."
F. Gibbs, 1937 [1]

Introduction

Originally, monitoring depth of anaesthesia involved the use of clinical signs considered proxies for consciousness, such as those described by Snow in 1847 and later by Guedel. [2,3] Subsequent calculations of the minimum alveolar concentration improved monitoring and reduced the incidence of awareness. More recently, however, it has been recognised that intra-operative awareness can occur independently of sympathetic responses or changes in end tidal concentration parameters. [4] Awareness under anaesthesia is defined as "consciousness under general anaesthesia with subsequent recall", [5] which is commonly detected via patient self-reports or the use of a structured interview, such as a 'Brice' questionnaire. [6] The current incidence of awareness is estimated as occurring in 0.1-0.2% of surgical procedures. [7] Though uncommon, episodes of intra-operative awareness can have significant negative psychological consequences. [8] These consequences have the potential to be greater in patients with neurological disease as they may lack insight into their medical condition and the need for surgery.

The EEG was first suggested as a way to overcome the shortcomings of clinical measures of awareness in 1937. [1] Since then, there have been numerous attempts to achieve this, culminating with the production of the bispectral index (BIS) in 1996. The BIS uses a proprietary algorithm to transform the EEG into a single, dimensionless number between 0 and 100. 100 correlates to "awake", 40 to 60 to "general anaesthesia" and 65-85 to "sedation". The mathematics of bispectral analysis are beyond the purview of this paper but are detailed elsewhere. [9] A trial



in patients at high-risk for awareness, but without neurological illness, found significant reductions in rates of intra-operative awareness, though similar successes have not been replicated elsewhere. [10,11]

Importantly, the algorithm underpinning the BIS was developed by analysing the normal electroencephalograms (EEG) of over 1000 healthy volunteers. Patients with neurologic disease, however, often have underlying structural or physiological abnormalities that manifest themselves as abnormal EEG findings. This has been demonstrated in a variety of psychiatric, degenerative and developmental disabilities. [12] Atypical EEG patterns not taken into consideration during the development of the algorithm can therefore influence BIS levels independently of the depth of anaesthesia. [13] Theoretically, this reduces the BIS's ability to accurately measure depth of anaesthesia in patients with neurological disease. [14]

Aim

To review the literature and establish whether the BIS monitor can be used to measure depth of anaesthesia in patients with neurologic disability.

Search strategy

A search was undertaken of the medical literature. The following keywords and their alternative spellings were mapped to their medical subject headings: neurology, cognitive disability, intellectual disability, BIS, bispectral index and intra-operative monitoring. These keywords were combined with appropriate Boolean operators and used to search databases including Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE and PubMed.

Literature review

There were four case reports and four observational studies found. Conditions described in the literature were Alzheimer's disease and vascular dementia (one observational study), intellectual disability (two observational studies), seizures (three case reports and one observational study), and congenital low amplitude EEG (one case report).

The results of a prospective observational study suggest the BIS may be of limited use in monitoring patients with Alzheimer's disease or vascular dementia. [15] The study compared 36 patients with dementia with 36 age-matched controls. It found that patients with these conditions had an awake BIS on average of 89.1, 5.6 lower than age-

matched controls with a baseline of 94.7, and below 90, considered the cut-off point indicating sedation. [16] These results indicate the BIS values corresponding to awareness validated in normal patients may not apply to those diagnosed with Alzheimer's disease or vascular dementia. Participants in this study were not anaesthetised, so response in BIS to anaesthesia was unable to be assessed. Therefore, it could not be determined whether the BIS intervals which correspond to general anaesthesia and sedation in normal patients were applicable to Alzheimer's patients or alternatively whether they would need to be anaesthetised to a lower BIS given their lower baseline level.

The BIS in intellectually-disabled patients has been investigated in two prospective, observational studies, though these provided conflicting results. The first compared 20 children with quadriplegic cerebral palsy and intellectual disability with 21 matched controls at a number of clinical endpoints. [17] The mean BIS of children with cerebral palsy was significantly lower at sedation (91.63 vs 96.79, p = 0.01), at an end-tidal sevoflurane concentration of 1% (48.55 vs 53.38, p = 0.03) and at emergence (90.73 vs 96.45, p = 0.032). The authors concluded validation of the BIS in children with intellectual disability may be tenuous. However, though the absolute BIS scores were different between these groups, the relative reduction in BIS score and pattern of change at increasing levels of anaesthesia was similar. The BIS may therefore not be a guide to the absolute depth of anaesthesia, but changes indicate increasing or decreasing awareness. It should be noted that this study was performed in children, for whom the BIS was not developed, as opposed to adults. The difference in EEGs between adults and children may therefore have confounded these results.

The second article described a prospective observational study of 80 adolescent and adult patients with varying degrees of intellectual disability undergoing general anaesthesia for dental procedures. [18] The aetiology of intellectual disability varied between patients but was predominately due to autism, cerebral palsy or Down syndrome. The study found no statistically significant difference in BIS scores between patients with mild, moderate, severe or profound disability at eight different clinical endpoints (awake, induction of anaesthesia, intravenous catheter placement, tracheal intubation, start of surgery, end of surgery, awakening to commands, and tracheal extubation). The only statistically significant finding of the study was that patients with more severe intellectual disability took longer to emerge from anaesthesia. The BIS monitor, however, accurately predicted this and provided an additional clue to the anaesthetist of the time required until extubation. These results indicate that intellectual disability does not affect the BIS and support the authors' hypothesis that the BIS score is "a measure of global neuronal function, not a measure of the aberrant neuronal connection" [18] and could therefore be applied to these patients.

Though these two studies provide conflicting results on whether intellectual disability affects the absolute BIS level, both provide good evidence that relative reductions in BIS scores correlate well with increasing depth of anaesthesia in these patients. The BIS may therefore have a role in monitoring changes in conscious states.

Despite the known ability of epilepsy to cause significant derangement of the EEG, only three case reports were found which dealt with this in relation to the BIS. The first describes a patient with pre-existing epilepsy undergoing surgery. [19] Despite no clinical change, the patient's BIS score dropped sharply from 40 to 20 before recovering every five minutes. This occurred over a period of hours until the raw EEG was checked and found to show epileptiform activity. Anticonvulsants were given at which point the BIS stabilised. In another report, seizures were evoked using photic stimulation. [20] Despite the patient remaining conscious, the BIS level dropped to 63 during the seizure. In the third case report, a patient in status epilepticus had a measured BIS of 93 despite being unconscious. [21] This dropped to 23 with control of the seizures. These reports provide strong support for the assertion that "BIS values may not accurately reflect the actual level of consciousness when abnormal EEG activity is evoked in epileptic patients". [20]

In these studies of epilepsy, when patients were not ictal, BIS scores provided measures of depth of anaesthesia that were as accurate as would be expected in non-epileptic patients. The seizures themselves were heralded by large, rapid changes in the BIS, as was their recovery. Epilepsy is not therefore a contraindication to monitoring with the BIS, but anaesthetists should be aware that abnormal BIS scores may be the result of seizures rather than changes in depth of anaesthesia. Furthermore, in instances of sudden changes in the BIS the raw EEG can be checked to determine if the change is due to seizure activity.

The final description of a neurological condition affecting the BIS found in the literature was a congenital, non-pathological low amplitude EEG. In one case report, a man with this condition, despite being fully conscious, had a recorded BIS of 40. [22] This is on the low edge of the level considered ideal for general anaesthesia. As many as 5-10% of the population may show this rhythm when attached to an EEG, which is genetically determined and not associated with any pathology. [23] The current BIS algorithm is incapable of distinguishing awareness from anaesthesia in these patients.

Conclusion

A search of the literature showed almost all neurological conditions which were studied cause abnormal BIS levels. Alzheimer's disease, vascular dementia, intellectual disability, epilepsy and congenitally low amplitude EEG were studied and all disease states, except intellectual disability, in which the results were conflicting, were shown to affect the BIS. It is far from clear whether the BIS may have a role in intra-operative awareness in addition to standard clinical measures in patients with neurological disease. The use of BIS in these cases may therefore mislead the anaesthetist rather than help them. If the anaesthetist does choose to use the BIS to monitor these patients, the BIS should be measured at baseline as the relative reduction in BIS scores may be more important than the absolute value in these patients. Given the lack of published data on this subset of patients, further controlled trials or subgroup analysis of existing trials that compares the use of the BIS against anaesthetic outcomes in patients with neurological disease would be a worthy avenue of future research.

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None.

Conflict of interest

None declared.

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Venous thromboembolism: a review for medical students and junior doctors

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Richard has a keen interest in peripheral vascular diseases and radiology. He will be completing his internship this year in the Bankstown & Campbelltown network.

Venous thromboembolism, comprising deep vein thrombosis and pulmonary embolism, is a common disease process that accounts for significant morbidity and mortality in Australia. As the clinical features of venous thromboembolism can be non-specific, clinicians need to have a high index of suspicion for venous thromboembolism. Diagnosis primarily relies on a combination of clinical assessment, D-dimer testing and radiological investigation. Following an evidence-based algorithm for the investigation of suspected venous thromboembolism aims to reduce over investigation, whilst minimising the potential of missing clinically significant disease. Multiple risk factors for venous thromboembolism (VTE) exist; significant risk factors such as recent surgery, malignancy, acute medical illness, prior VTE and thrombophilia are common amongst both hospitalised patients and those in the community. Management of VTE is primarily anticoagulation and this has traditionally been with unfractionated or low molecular weight heparin and warfarin. The non-vitamin K antagonist oral anticoagulants, also known as the novel oral anticoagulants (NOACs), including rivaroxaban and dabigatran, represent an exciting alternative to traditional therapy for the prevention and management of VTE. The significant burden of venous thromboembolism is best reduced through a combination of prophylaxis, early diagnosis, rapid implementation of therapy and management of recurrence and potential sequelae. Junior doctors are in a position to identify patients at risk of VTE and prescribe thromboprophylaxis as necessary. Although a significant body of evidence exists to guide diagnosis and treatment of VTE, this article provides a concise summary of the pathophysiology, natural history, clinical features, diagnosis and management of VTE.

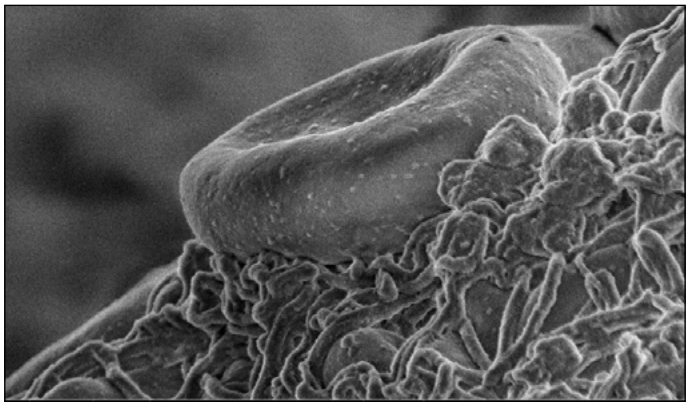
Introduction

Venous thromboembolism (VTE) is a disease process comprising deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a common problem with an estimated incidence of one-two per 1,000 population each year [1,2] and approximately 2,000 Australians die each year from VTE. [3] PE represents one of the single most common preventable causes of in-hospital death [4] and acutely it has a 17% mortality rate. [5, 6] VTE is also associated with a significant financial burden; the financial cost of VTE in Australia in 2008 was an estimated $1.72 billion. [7] Several important sequelae of VTE exist including: post-thrombotic syndrome, recurrent VTE, chronic thromboembolic pulmonary hypertension (CTEPH) and death. [8,9]

Due to the high incidence of VTE and the potential for significant sequelae, it is imperative that medical students and junior doctors have a sound understanding of its pathophysiology, diagnosis and management of VTE.

Pathophysiology and risk factors

The pathogenesis of venous thrombosis is complex and our understanding of the disease is constantly evolving. Although no published literature supports that Virchow ever distinctly described a triad for the formation of venous thrombosis [10], Virchow's triad remains clinically relevant when considering the pathogenesis of venous thrombosis. The commonly cited triad consists of alteration in the constituents of blood, vascular endothelial injury and alterations in blood flow. Extrapolation of each component of Virchow's triad provides a framework for important VTE risk factors. Risk factors form an integral part of the scoring systems used in risk stratification of



suspected VTE. In the community, risk factors are present in over 75% of patients, with recent or current hospitalisation or residence in a nursing home reported by over 50% ofpatients with VTE. [11] Patients may have a combination of inherited and acquired thrombophilic defects. Combinations of risk factors have at least an additive effect on the risk of VTE. Risk factors for VTE are presented in Table 1.

Thrombophilia

Thrombophilia refers to a predisposition to thrombosis, which may be inherited or acquired. [14] The prevalence of thrombophilia at first presentation of VTE is approximately 50%, with the highest

Table 1. *Risk factors for VTE. Adapted from Anderson & Spender (2003) [12] and Ho, Hankey, Lee & Eikelboom (2005) [13].*

Acute provoking factors	Surgery – including orthopaedic, major general and laparoscopic surgery
	Hospitalisation
	Major trauma – including hip or leg fracture and spinal cord injury
	Immobilisation – long haul air travel or prolonged bed rest
	Intravascular device e.g. central venous line
	Heparin induced thrombocytopenia
Chronic predisposing factors	Inherited or acquired thrombophilic defects
	Prior VTE
	Major medical illness – including congestive cardiac failure, respiratory disease, nephrotic syndrome, myeloproliferative disorders
	Malignancy
	Oestrogen therapy
	Paralytic stroke
	Obesity

prevalence found in younger patients and those with unprovoked VTE. [15] Inherited thrombophilias are common in the Caucasian Australian population. The birth prevalence of factor V Leiden heterozygosity and homozygosity, which confers resistance to activated protein C, is 9.5% and 0.7% respectively. Heterozygosity and homozygosity for the prothrombin gene mutation (G20210A) is another common inherited thrombophilia, with a prevalence of 4.1% and 0.2% respectively. [16] Other significant thrombophilias include antithrombin deficiency, protein C deficiency, protein S deficiency and causes of hyperhomocystinaemia. [16,17] Antiphospholipid syndrome is an acquired disorder characterised by antiphospholipid antibodies and arterial or venous thrombosis or obstetric related morbidity, including recurrent spontaneous abortion. Antiphospholipid syndrome represents an important cause of VTE and may occur as a primary disorder or secondary to autoimmune or rheumatic diseases such as systemic lupus erythematosus. [18]

Testing for hereditary thrombophilia is generally not recommended as it does not affect clinical management of most patients with VTE [19,20] and there is no evidence that such testing alters the risk of recurrent VTE. [21] There are few exceptions such as a fertile women with a family history of a thrombophilia where testing positive may lead to the decision to avoid the oral contraceptive pill or institute prophylaxis in the peripartum period. [22]

Natural history

Most DVT originate in the deep veins of the calf. Thrombi originating in the calf are often asymptomatic and confer a low risk of clinically significant PE. Approximately 25% of untreated calf DVT will extend into the proximal veins of the leg and 80% of patients with symptomatic DVT have involvement of the proximal veins. [9] Symptomatic PE occurs in a significant proportion of patients with untreated proximal DVT; however the exact risk of proximal embolisation is difficult to estimate. [9,23]

Pulmonary vascular remodeling may occur following PE and may result in CTEPH. [24] CTEPH is thought to be caused by unresolved pulmonary emboli and is associated with significant morbidity and mortality. CTEPH develops in approximately 1-4% of patients with treated PE. [25,26]

Post-thrombotic syndrome is an important potential long-term consequence of DVT, which is characterised by leg pain, oedema, venous ectasia and venous ulceration. Within 2 years of symptomatic DVT, post-thrombotic syndrome develops in 23-60% of patients [27] and is associated with poorer quality of life and significant economic burden. [28]

Diagnosis

Signs and symptoms of VTE are often non-specific and may mimic many other common clinical conditions (Table 2). In the primary care setting, less than 30% of patients with signs and symptoms suggestive of DVT have a sonographically proven thrombus. [29] Some of the clinical features of superficial thrombophlebitis overlap with those of DVT. Superficial thrombophlebitis carries a small risk of DVT or PE and contiguous extension of the thrombus. Treatment may be recommended with low-dose anticoagulant therapy or NSAIDs. [30]

Deep vein thrombosis

Clinical features

Symptoms of DVT include pain, cramping and heaviness in the lower extremity, swelling and a cyanotic or blue-red discolouration of the limb. [31] Signs may include superficial vein dilation, warmth and unilateral oedema. [31,32] Pain in the calf on forceful dorsiflexion of the foot was described as a sign of DVT by the American surgeon John Homans in 1944. [33] Homans' sign is non-specific and is an unreliable sign of DVT. [34]

Investigations

Several scoring tools have been evaluated for assessing the pre-test probability of DVT. One such commonly used validated tool is the Modified Wells score, presented in Table 3. [35] The Modified Wells score categorises patients as either likely or unlikely to have a DVT.

Table 2. *Key differential diagnoses of DVT*

Key differential diagnoses of DVT
Cellulitis and erysipelas
Calf haematoma
Superficial venous thrombosis
Rupture of a baker's cyst
Varicose veins
Musculoskeletal pathology

D-dimer is the recommended investigation in patients considered unlikely to have a DVT, as a negative D-dimer effectively rules out DVT in this patient group. [36] D-dimer measurements have several important limitations with most studies of its use in DVT being performed in outpatients and non-pregnant patients. As D-dimer represents a fibrin degradation product, it is likely to be raised in any inflammatory response. This limits its use in post-operative patients and many hospitalised patients.

Venous compression ultrasound with Doppler flow is indicated as the initial investigation in patients who are considered likely to have DVT (Modified Wells ≥ 2) or in patients with a positive D-dimer. Compression ultrasonography is the most widely used imaging modality due to its high sensitivity and specificity, non-invasive nature and low cost. Limitations include operator-dependent accuracy and reduction of sensitivity and specificity in DVT of pelvic veins, small calf veins or in obese patients. [32]

Pulmonary embolism

Clinical features

10% of symptomatic PE are fatal within 1 hour of the onset of symptoms [9] and delay of diagnosis remains common due to non-specific presentation. [37] Clinical presentation will depend on several factors including size of the embolus, rapidity of obstruction of the pulmonary vascular bed and patient's haemodynamic reserve. Symptoms may include sudden or gradual onset dyspnoea, chest pain, cough, haemoptysis, palpitations and syncope. Signs may include tachycardia, tachypnea, fever, cyanosis and the clinical features of DVT. Signs of pulmonary infarction may develop later and include a pleural

Table 3. *Modified DVT Wells score. The most symptomatic leg is used.*
≥2 = DVT is likely
<2 = DVT is unlikely
Adapted from Wells et al. (1997) [35] and Wells et al. (2003) [36]

Clinical characteristic	Score
Active cancer	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremities	1
Major surgery within the previous 12 weeks or recently bedridden for ≥ 3 days	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling ≥3cm larger than that of the asymptomatic side	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

friction rub and reduced breath sounds. [31] Patients may also present with systemic arterial hypotension with or without clinical features of obstructive shock. [5,38]

Investigations

The first step in the diagnosis of suspected PE is the calculation of the clinical pre-test probability using a validated tool such as the Wells or Geneva score. Clinician gestalt may be used in place of a validated scoring tool; however it may be associated with a lower specificity and therefore increased unnecessary pulmonary imaging. [39] Neither clinician gestalt nor a clinical decision rule can accurately exclude PE on its own. An electrocardiogram (ECG) will often be performed early in the presentation of a patient with suspected PE. A variety of electrocardiographic changes associated with acute PE have been described. Changes consistent with right heart strain and atrial enlargement reflect mechanical pulmonary artery outflow tract obstruction. [40] Other ECG changes include sinus tachycardia, ST segment or T wave abnormalities, QRS axis alteration (left or right), right bundle branch block and a number of others. [40] The S1Q3T3 abnormality, described as a prominent S wave in lead I with a Q wave and inverted T wave in lead III, is a sign of acute corpulmonale. It is not pathognomonic for PE and occurs in less than 25% of patients with acute PE. [40]

In patients with a low pre-test probability, a negative quantitative D-dimer effectively excludes PE. [39] The conventional D-Dimer cut-off value (500 µg/L) are associated with reduced specificity in older patients leading to false positive results. [41] A recent meta-analysis has found that the use of an age specific D-dimer cut off value (age x 10µg/L) increases the specificity of the D-dimer test with little effect on sensitivity. [42] The pulmonary embolism rule-out criteria (PERC), as outlined in Table 4, may be applied to patients with a low pre-test probability to reduce the number of patients undergoing D-dimer testing. [43] A recent meta-analysis demonstrated that in the emergency department, the combination of low pre-test probability and a negative PERC rule results in a likelihood of PE that is so unlikely that the risk-benefit ratio of further investigation for PE is not favourable. [44]

Patients with a high pre-test probability or with a positive D-dimer test should undergo pulmonary imaging. Multidetector Computed Tomography Pulmonary Angiography (CTPA) is largely considered the imaging modality of choice for PE given its high sensitivity and specificity and its ability to identify alternative diagnoses. [45,46] CTPA must be used only with a clear indication due to significant radiation exposure, risk of allergic reactions and contrast-induced nephropathy. [47] Concerns have also been raised about over diagnosis of PE with detection of small subsegmental emboli. [48]

Table 4. *Pulmonary embolism rule-out criteria. If the patient answers negative to all of these criteria, further investigation for PE is not recommended. This rule is not designed to replace clinical judgment and caution is advised in patients with indeterminate factors (e.g. transient tachycardia). Adapted from Singh, Mommer, Erwin, Mascarenhas & Parasaik (2013) [43].*

Pulmonary embolism rule-out criteria
Age <50 years
Pulse rate <100 beats per min
Pulse oximetry ≥95%
No haemoptysis
No oral hormone use
No recent surgery or trauma requiring treatment with general anaesthesia in the previous 4 weeks
No prior VTE
No unilateral leg swelling

Ventilation-perfusion (V/Q) lung scintigraphy is an alternative pulmonary imaging modality to CTPA. A normal V/Q scan excludes PE; however, a significant proportion of patients will have a 'non-diagnostic' result thus requiring further imaging. [49] Non-diagnostic scans are more common in patients with pre-existing respiratory disease or an abnormal chest radiograph and are less likely in younger and pregnant patients. [48,50] Compared with CTPA, V/Q scanning is associated with fewer adverse effects and less radiation exposure and is often employed when a contraindication to CTPA exists. [49,50]

Bedside echocardiography is a useful investigation if CT is not immediately available or if the patient is too unstable for transfer to radiology. [51,52] Echocardiography may reveal right ventricular dysfunction which guides prognosis and the potential for thrombolytic therapy in massive and sub-massive PE. [51]

The diagnosis of PE during pregnancy is an area of controversy. [54] The diagnostic value of D-dimer during pregnancy using the conventional threshold is limited. With both V/Q scans and CTPA, foetal radiation dose is minimal but higher in the former. CTPA is associated with a much higher dose of radiation to maternal breast tissue thus increased risk of breast cancer. [53,54] In light of these risks, some experts advocate for bilateral compression Doppler ultrasound for suspected PE in pregnancy. [54] However, if this is negative and a high clinical suspicion remains, pulmonary imaging is still required.

Prophylaxis

Multiple guidelines exist to direct clinicians on the use of thromboprophylaxis in both medical and surgical patients. [3,55-58] Implementation of thromboprophylaxis involves assessment of the patient's risk of VTE, risk of adverse effects of thromboprophylaxis, including bleeding and identification of any contraindications.

Patients at high risk include those undergoing any surgical procedure, especially abdominal, pelvic or orthopaedic surgery. Medical patients at high risk include those with myocardial infarction, malignancy, heart failure, ischaemic stroke and inflammatory bowel disease.[3]

Mechanical options for thromboprophylaxis include encouragement of mobility, graduated compression stockings, intermittent pneumatic compression devices and venous foot pumps. Mechanical prophylactic measures are often combined with pharmacological thromboprophylaxis. The strength of evidence for each of the anticoagulant varies depending on the surgical procedure or medical condition in question; however, unfractionated heparin (UFH) and low-molecular weight heparin (LMWH) remain the mainstay of VTE prophylaxis. [3] The NOACs, also referred to as direct oral anticoagulants, notably rivaroxaban, apixaban and dabigatran, have been studied most amongst the hip and knee arthroplasty patient groups, where they have been shown to be both efficacious and safe. [59-61] The use of aspirin for the prevention of VTE following orthopaedic surgery remains controversial, despite receiving a recommendation by recent guidelines. [62] It is recommended that pharmacological prophylaxis should be continued until the patient is fully mobile. In certain circumstances such as following total hip or knee arthroplasty and hip fracture surgery, extended duration prophylaxis for up to 35 days post-operatively is recommended. [3,62]

Management

The aim of treatment is to relieve current symptoms, prevent progression of the disease, reduce the potential for sequelae and prevent recurrence. Anticoagulation remains the cornerstone of management of VTE.

Patients with PE and haemodynamic instability (hypotension, persistent bradycardia, pulselessness), so called 'massive PE'may require urgent treatment with thrombolytic therapy. Thrombolysis reduces mortality in haemodynamically unstable patients, however it is associated with a risk of major bleeding. [63] Surgical thrombectomy and catheter-based interventions represent an alternative to thrombolysis in patients with

massive PE where contraindications exist. [64] The use of thrombolytic therapy in patients with evidence of right ventricular dysfunction and myocardial injury without hypotension and haemodynamic instability remains controversial. A recent study revealed that fibrinolysis in this intermediate risk group reduces rates of haemodynamic compromise while significantly increasing the risk of intracranial and other major bleeding. [65]

For the majority of patients with VTE anticoagulation is the mainstay of treatment. Acute treatment involves UFH, LMWH or fondaparinux. [50]

UFH binds to antithrombin III, increasing its ability to inactivate thrombin, factor Xa and other coagulation factors. [66] UFH is usually given as an intravenous bolus initially, followed by a continuous infusion. UFH therapy requires monitoring of the activated partial thromboplastin time (aPTT) and is associated with a risk of heparin-induced thrombocytopenia. [66] The therapeutic aPTT range and dosing regimen vary between institutions. The use of UFH is usually preferred if there is severe renal impairment, in cases where there may be a requirement to rapidly reverse anticoagulation therapy and in obstructive shock where thrombolysis is being considered. [50]

LMWH is administered subcutaneously in a weight adjusted dosing regimen once or twice daily. [51] When compared with UFH, LMWH has a more predictable anticoagulant response and does not usually require monitoring. [67] In obese patients and those with significant renal dysfunction, LMWH may require dose adjustment or monitoring of factor Xa activity. [67]

Therapy with a vitamin K antagonist, most commonly warfarin, should be commenced at the same time as parenteral anticoagulation. Therapy with the parenteral anticoagulant should be discontinued when the international normalised ratio (INR) has reached at least 2.0 on two consecutive measurements and there has been an overlap of treatment with a parenteral anticoagulant for at least five days. [68] This overlap is required as the use of warfarin alone may be associated with an initial transient prothrombotic state due to warfarin mediated rapid depletion of the natural anticoagulant protein C, whilst depletion of coagulation factors II and X takes several days. [69]

The NOACs represent an attractive alternative to traditional anticoagulants for the prevention and management of VTE.

Rivaroxaban is a direct oral anticoagulant that directly inhibits factor Xa.[66] Rivaroxaban has been shown to be as efficacious as standard therapy (parenteral anticoagulation and warfarin) for the treatment of proximal DVT and symptomatic PE. [70,71] When compared with conventional therapy, rivaroxaban may be associated with lower risks of major bleeding. [70] Rivaroxaban represents an attractive alternative to the standard therapy mentioned above as it does not require parenteral administration, is given as a fixed daily dose, does not require laboratory monitoring and has few drug-drug and food interactions. [70,71]

Dabigatran etexilate is an orally administered direct thrombin inhibitor. Dabigatran is non-inferior to warfarin for the treatment of PE and proximal DVT after a period of parenteral anticoagulation. [72] The safety profile is similar; however dabigatran requires no laboratory monitoring. [72]

The lack of a requirement for monitoring is a significant benefit over warfarin for the NOACs. The role of monitoring the anticoagulant activity of these agents and the clinical relevance of monitoring is a subject of ongoing research and debate. [73] Anti-factor Xa based assays may be used to determine the concentration of the anti-factor Xa inhibitors in specific clinical circumstances. [74,75] The relative intensity of anticoagulant due to dabigatran can be estimated by the aPTT and rivaroxaban by the PT or aPTT [76]. There is however, significant variation in the results based on the reagent the laboratory uses. Routine monitoring for the NOACs is not currently recommended.

The major studies evaluating the NOACs carried exclusion criteria that included those at high risk of bleeding, with a creatinine clearance of <30 mL/min, pregnancy and those with liver disease [70-72], thus caution must be applied with their use in these patient groups. The NOACs are renally metabolised to variable degrees. Warfarin or dose adjusted LMWH are preferred for those with reduced renal function (creatinine clearance <30mL/min) who require long-term anticoagulation.

Concern exists regarding a lack of a specific reversal agent for the NOACs. [77,78] Consultation with haematology is recommended if significant bleeding occurs during therapy with a NOAC. Evidence for the use of agents such as tranexamic acid, recombinant factor VIIa and prothrombin complex concentrate is very limited. [77,78] Haemodialysis may significantly reduce plasma levels of dabigatran, as the drug displays relatively low protein binding. [77,78]

Inferior vena cava (IVC) filters may be placed in patients with VTE and a contraindication to anticoagulation. IVC filters prevent PE however they may increase the risk of DVT and vena cava thrombosis. The use of IVC filters remains controversial due to a lack of evidence. [79]

Recurrence

The risk of recurrence differs significantly depending on whether the initial VTE event was unprovoked or associated with a transient risk factor. [9] Patients with idiopathic VTE have a significantly higher risk of recurrence than those with transient risk factors. Isolated calf DVT carry a lower risk of recurrence than that of proximal DVT or PE. The risk of recurrence after the cessation of anticoagulant therapy is as high as 10% per year in some patients groups. [9]

Duration of anticoagulation therapy should be based on patient preference and a risk-benefit analysis of the risk of recurrence versus the risk of complications from therapy. Generally, anticoagulation should be continued for a minimum of three months and the decision to continue anticoagulation should be re-assessed on a regular basis. Recommendations for duration of anticoagulation therapy are presented in Table 5. The currently published guidelines recommend extended anticoagulation therapy with a vitamin K antagonist such as warfarin. Evaluation of the new direct oral anticoagulants for therapy and prevention of recurrence is ongoing. Recent evidence supports the use of dabigatran and rivaroxaban for the secondary prevention of venous thromboembolism with similar efficacy to standard therapy and reduced rates of major bleeding. [70,71,80]

Aspirin has been shown to be effective in reducing the recurrence VTE in patients with previous unprovoked VTE. After up to 18 months of therapy, aspirin reduces the rate of VTE recurrence by 40%, as compared with placebo. [81]

Conclusion

VTE is a commonly encountered problem and is associated with

Table 5. *Recommended duration of anticoagulation. Adapted from Kearon et al. (2012) [82].*

Indication	Duration of therapy
First VTE secondary to transient or reversible risk factor	3 months
First VTE unprovoked – distal DVT	3 months
First VTE unprovoked – proximal DVT or PE	At least 3 months. Long-term treatment if no risk factors for bleeding and good anticoagulant monitoring achievable.
Second VTE unprovoked	Long-term. If high-bleeding risk, 3 months of therapy is recommended.

significant short and long term morbidity. A sound understanding of the pathogenesis of VTE guides clinical assessment, diagnosis and management. The prevention and management of VTE continues to evolve with the ongoing evaluation of the NOACs. Anticoagulation remains the mainstay of therapy for VTE, with additional measures including thrombolysis used in select cases. This article has provided medical students with an evidence based review of the current diagnostic and management strategies for venous thromboembolic disease.

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Conflict of interest

None declared.

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Glass micro-particulate contamination of intravenous drugs – should we be using filter needles?

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After crossing the Tasman from New Zealand, Lewis has developed a wide range of interests including ophthalmology, student and physician wellbeing, rural health and anaesthetics. This article stemmed from ampoule-opening difficulties and discussions with anaesthetists. In 2015 he will be completing a BMedSci, researching and pursuing his keen interest in ophthalmology.

The universal use of filter needles in the aspiration of all medications from glass ampoules for intravenous administration has been recommended due to safety concerns surrounding possible inadvertent injection of glass micro-particulate created from snapping open ampoules. Implementing this would involve significant costs. This article aims to review the relevant literature to evaluate whether sufficient evidence for patient harm due to glass micro-particulate contamination exists to justify the universal introduction of filter needles for the aspiration of medications from glass ampoules for intravenous administration. **Methods**: A search of OVID Medline, TRIP, Embase and Google Scholar databases was conducted with a wide variety of terms with no limitation on publication date. Papers addressing the research question were included in the review. **Result**s: Contamination of drugs by glass micro-particulates does occur with aspiration from glass ampoules. Pathological changes such as granuloma formation, embolic or thrombotic events may occur if these are injected intravenously. There is, however, a lack of evidence of consequent clinical harm in humans. **Conclusion**: A recommendation for the universal introduction of filter needles for aspiration of drugs from glass ampoules for intravenous administration cannot be justified on the basis of the paucity of available evidence showing harm and in light of the significant cost of this recommendation. Concerns regarding the lack of studies demonstrating that particle contamination poses no threat remain valid from a perspective of total patient safety.

Introduction

Glass ampoules are common containers for many drugs. The ampoules are usually broken open by hand and the drugs are then drawn up for administration. In the last 60 years, many questions have been raised over the potential patient safety issues related to glass micro-particulate contamination of drugs from glass ampoules, particularly for intravenous administration. [1-6] There have been few conclusive answers, however there are suggestions it may lead to complications including pulmonary thrombi, micro-emboli, and end-organ granuloma formation. [6]

It has been recommended that filter needles should be used in the aspiration of all medications from glass ampoules. [7] This is not yet standard practice, but follows recommendations made for over forty years that practice should err on the side of caution until further studies can demonstrate that any type of particle contamination poses no threat. [5,6,8,9] This must also be balanced however, against the significant cost the universal use of filter needles would incur. The cost of a 5 µm 18 g filter needle ($0.315) is approximately ten times that of a standard 18 g drawing up needle ($0.029). [10]

For the universal implementation of filter needles to be justified in the light of this expense, three important questions should be satisfied. Firstly, does micro-particulate contamination occur when drugs are aspirated from glass ampoules? Secondly, if so, is this particulate contamination of clinical significance and a threat to patient safety? Thirdly, are filter needles effective in preventing contamination of medications by glass particles? This article reviews the relevant literature and through answering these questions attempts to evaluate whether sufficient evidence exists to warrant the universal introduction of filter needles for the aspiration of medications from glass ampoules for intravenous administration.

Methods

A search of OVID Medline, TRIP database, Embase and Google Scholar databases was conducted. In order to capture all possible evidence and relevant background history on this topic in this review, there was no restriction on date of publication and a wide range of search terms were used. Terms used included (but were not limited to): 'glass', 'ampoule', 'drug contamination', 'intravenous', 'filter needles', 'filter straws', 'filtration' and 'needles'. This search was supplemented with additional papers sourced from reference lists to ensure completeness. Both human and animal studies were included. Papers addressing the research question were included in the review as decided by the author, including papers addressing other micro-particulate contamination. Explicitly defined criteria were not used in the selection of the papers.

Definitions

A filter needle or filter straw is a needle attached to a syringe in place of a drawing up needle, designed to filter out particulates from a contaminated fluid. Generally they contain a 5 micron filter.

Glass ampoules are widely used in the production of parenteral medications. Glass is an attractive material to industry as it can be vacuum-sealed, sterilized, is easy to clean, it is chemically inert, it is difficult to tamper with and is possibly recyclable. [2,4] To access the drug, the top of the ampoule is snapped off by applying manual force at a pre-weakened point. [2]

Results

Does particulate contamination occur?

There is clear evidence that the action of snapping off the top of an ampoule can lead to contamination of ampoule contents, primarily with glass micro-particles. [11-15] Glass micro-particles are primarily composed of inorganic compounds (SiO_2, Na_2CO_2, $CaCO_2$) and metallic oxides. [2] They have a sharp microscopic appearance. [16] Particulate size ranges from 8-172 microns. [15] The amount of particulate matter varies slightly amongst different manufacturers and more particles are found in transparent metal etched ampoules compared with coloured chemically etched ampoules. [17]

Is glass particulate contamination of clinical significance?

Brewer and Dunning (1947) demonstrated that massive micro-particulate infusions in rabbits can cause foreign body reactions which result in pulmonary granulomas, pulmonary silicosis, and cause nodular fibrosis of the liver, spleen and lymph nodes. [1] These were reported as chronic rather than acute changes. Notably, a dose equivalent to a total human dose of 14g of glass over a month given in daily doses was required to produce these effects. Animals receiving small doses, equivalent to those that a human might receive in normal clinical practice, however, exhibited no pathological changes and no glass was found in the lungs. No animals died within the full investigation period of up to a year until euthanised for pathological examination. The authors concluded that "occasional particle contamination of ampoule preparations produces no significant pathology in animals". [1]

Garvan and Gunner (1964) conducted a similar small experiment infusing saline from glass ampoules into an ear vein of three rabbits. [3] After killing the animals, autopsy showed the formation of capillary and arterial granulomas, all containing cellulose fibres. They estimated that every half-litre of IV fluid injected into a rabbit caused the formation of 5000 granulomas scattered through the lungs. They also found similar lesions in the lungs of patients who had died and had received large volumes of IV fluid before death. In this study there was no specific reference to glass as the causative particle of the granulomas, nor was it associated with any morbidity or mortality apart from the histological changes.

Two case reports have been published recently regarding glass contamination. In the first a patient was found on arthroscopy to have glass particles within the right knee joint possibly due to recent steroid or local anaesthetic injection into the joint. [18] In the second report a single glass particle lodged within a cannula caused leakage out of the injection port of the cannula during an infusion. [19]

Contamination with other micro-particulates

Contamination of IV fluids by other materials such as rubber or cellulose has also been shown to occur and these particulates may have similar effects to glass. A review of relevant work concluded however, that although pathological changes had been associated with these various contaminants in both human and animal studies, it was not possible to correlate particular clinical manifestations with a specific contaminant, and nor was there any association with mortality. [20]

Similarly, in an autopsy study Puntis *et al.* (1992) found pulmonary granulomata in two of 41 parentally fed infants who had died of unstated causes following stays in a neonatal intensive care unit with a median duration of 14 days of parenteral feeding. These were compared to 32 control infants who died of Sudden Infant Death Syndrome (SIDS) within the same time period and who had not received any IV treatment. [21] No granulomata or foreign bodies were found in the controls. Of the two cases, some pulmonary granulomas contained cotton fragments or glass, but the majority exhibited no obvious foreign body. The authors point out that the parental nutrition solutions themselves contain many micro-particles that may also have pathological effects. Further to this a recent study found silicon particles (common contaminants in solutions stored in glass ampoules) caused suppression of macrophage and endothelial cell cytokine secretion in vitro, suggesting that micro particle infusion could have immune-modulating effects in vivo. [22]

A recent Cochrane Review of the use of in-line filters for preventing morbidity and mortality in neonates attributable to particulate matter and bacterial contamination, concluded that there is insufficient evidence to recommend the use of these devices. [23] Falchuck *et al.* found that in-line filtration significantly reduced the incidence of infusion-related phlebitis, however a recent meta-analysis of trials investigating the benefit of in-line filters was inconclusive. [24,25]

There is further inconclusive evidence that epithelioid granulomas, containing macrophages and giant cells, can occur at the entry points of silicone coated needles used for acupuncture (a polymer containing the element silicon) but these granulomas can also occur following venipuncture or at skin biopsy sites. [26]

Are filter needles effective in preventing contamination of medications by glass particles?

Sabon *et al.* (1989) found that control ampoules contained an average of 100.6 (SE ± 16.3) particles with size ranging from 10 to 1000 µm. [17] Aspiration through an 18 g needle reduced particulate contamination to a mean of 65.6 (SE ± 18.7) particles with a maximum size of 400 µm, whereas aspiration through a 19 g 5 µm filter needle reduced the number of particles to 1.3 (SE ± 0.3), with a decrease in the average particle size. More recently Zabir *et al.* (2008) found that of 120 ampoules aspirated using a 5 µm filter, 0% of the aspirated fluid samples were contaminated with glass, in comparison to when 120 ampoules were aspirated using an unfiltered 18 g needle, 9.2% of the aspirated fluid samples were contaminated. [27] The use of smaller gauge non-filter needles has also been found to reduce contamination when compared to large bore needles. [5, 27]

In contrast to this Carbone-Traber *et al.* (1986) found no difference between unfiltered and filtered needles or between different needle bore sizes. Using a 3 mm tubing as a control, the contents of ten ampoules were aspirated for each group. The control group was contaminated with a mean of 12 (SD ± 5) glass particles, compared to 13 (SD ± 6) and 13 (SD ± 7) glass particles in the aspirate contents of unfiltered 18 g and 5µm filter needle respectively. [28] The authors suggest that the force of aspiration may cause glass particles to penetrate the filter.

Discussion

The clinical significance of the effects of glass particulates on the human body remains unclear. A number of historical investigations and case reports have been published, however there are no recent systematic reviews or prospective studies relating directly to glass particulates. Perhaps not surprisingly, there are no relevant controlled human studies and much of the data that forms the basis for the evidence of harm comes from animal studies. It is worth noting that while the findings of Brewer and Dunning are often cited as evidence for the harm caused by glass, their clinical conclusions that glass causes no significant pathology in animals are often ignored. [1]

The lack of studies investigating the effects of glass particulate contamination is due to many factors including the ethical difficulties associated with infusing contaminated fluids into human subjects, cost, and the lack of interest by pathologists. [29] The lack of evidence available from high quality and recent investigations is the significant limiting factor of this review.

In this light, a number of recommendations have been made for over forty years that practice should err on the side of caution until further studies can demonstrate that any type of particle contamination poses no threat. [5,6,8,9] This is a valid perspective with a view to ensuring total patient safety.

In evaluating the introduction of any intervention however, both the costs and consequences must be considered. With the current evidence, evaluation of the efficacy or the effectiveness of the global introduction of filter needles cannot be undertaken, nor can cost-benefit be appraised. It is clear however, that the large-scale introduction of filter needle use for all drugs aspirated from glass ampoules destined for intravascular injection would incur a significant cost.

Filter needle use in current practice

Injection of contaminants may occur via various pathways including the intravenous, intramuscular, subcutaneous, intrathecal, epidural, and intraocular routes. There are no data describing the prevalence of filter needle use, and perhaps the most accurate appraisal is that they

are at least widely available. Anecdotally their use seems favoured when drawing up drugs from glass ampoules prior to intrathecal, epidural and intraocular administration, likely due to fear of significant consequences of microbiological contamination of these sites. [30]

Alternatives to filter needles

Several alternative solutions have been considered to reduce glass contamination. The use of a machine that cuts the ampoules and aspirates the contents using a vacuum produced less glass particulate contamination of ampoules compared to opening by hand, however this is impractical for everyday use. [16] The use of prefilled syringes showed far less contamination than aspirating glass ampoule contents into syringes however this a very expensive option. [31,32] A commercial ampoule opener showed no difference in particulate contamination compared to hand-opened. [29] While there have been no recommendations made, the use of smaller gauge needles may reduce contamination as discussed above.

Conclusion

In conclusion, studies have shown evidence of glass particle contamination in injectable drugs drawn from glass ampoules, and have generally demonstrated that use of filter needles would reduce patient exposure to these particulates. There is, however, a lack of definitive evidence for significant harm from the injection of these glass particle contaminants. There is a potential that drugs administered intravenously containing glass fragments may cause granuloma formation, embolic, thrombotic and other vascular events, however this is not supported by any recent literature or conclusive studies. The paucity of evidence further limits economic evaluation into efficacy, effectiveness and cost-benefit analysis, into an intervention that would incur substantial cost. Arguments that practice should err on the side of caution until studies can prove that contamination does not cause harm are valid, however it is unlikely these studies will be able to be conducted. Considering the limited evidence for harm of glass particulate injection found in well over fifty years of observation, it would appear that the cost of filter needles outweighs the questionable benefits gained from their universal introduction for aspiration of intravenously administered drugs from glass ampoules.

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Conflict of interest

None declared.

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Insights into the mechanism of 'chemobrain': deriving a multi-factorial model of pathogenesis

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Kok-Ho's interest lies in infectious diseases and oncology as well as the application of novel theoretical concepts to the development of better cancer treatment strategies. Kok-Ho's primary motivation in medicine is to find a novel therapy for cancers with poor prognosis so that patients who are incurable now may have a new lease of life in the near future.

Chemotherapy-related cognitive impairment, commonly called 'chemobrain', is a potentially debilitating condition that is slowly being recognised. It encompasses a wide range of cognitive domains and can persist up to years after the cessation of chemotherapy. What initially appears to be a straightforward example of neurotoxicity may be a complex interplay between individual susceptibilities and treatment characteristics, the effects of which are perpetuated through mechanisms such as oxidative stress and telomere shortening via cytokines. This article will attempt to propose a multi-factorial model of pathogenesis which may clarify the relationship between these factors and ultimately improve the life of cancer patients through informed decisions during the chemotherapy process.

Introduction

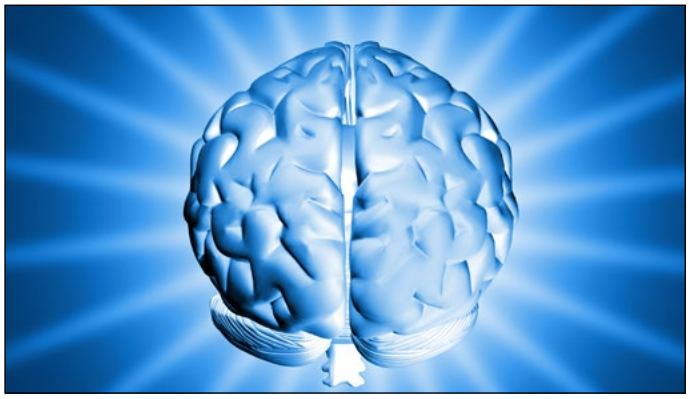
Chemotherapy is a mainstay in modern oncological treatment. Chemotherapeutic drugs are often cytotoxic and this allows cancer cells to be destroyed effectively. However, the systemic nature of chemotherapy means that normal cells are damaged too. If cells in the central nervous system are affected, neurological effects manifesting into cognitive deficits may be evident. The link between chemotherapy and cognitive impairment was first reported by Silberfarb and colleagues in the 1980s. [1] In the past 10-20 years, research in this area further developed due to fairly high rates of cognitive decline in cancer patients receiving chemotherapy. The cognitive sequelae arising from chemotherapy is commonly referred to as 'chemobrain'.

It is estimated that up to 70-75% of cancer patients have cognitive deficits during and post-chemotherapy, and up to half of these patients will have impairment lasting months or years after treatment. [2,3] Transient cognitive impairment during chemotherapy is usually tolerated but persistence of these symptoms can cause significant psychological stress and affect activities of daily living such as work, education, and social interaction.

Understanding chemotherapy-related cognitive impairment can help guide the choice and dosage/duration of chemotherapeutic drugs and ultimately enable us to improve the quality of life of cancer patients undergoing treatment. This article will briefly examine what is known about 'chemobrain' and attempt to propose a multi-factorial model of pathogenesis.

What is 'chemobrain'?

The cognitive domains involved in 'chemobrain' are not fully defined but they are thought to be related to structural and functional changes in the frontal lobes and hippocampus of the brain. [4] Domains affected often include executive functioning, possessing speed, attention/concentration, as well as verbal and visuospatial memory. [5] While the degree of cognitive decline can be subtle in high-functioning individuals with a resultant cognition within the normal range, even a small decline in cognitive function can significantly reduce the quality of life (QOL) of a cancer patient. This is particularly true for those who experience persistent cognitive deficits. 'Chemobrain' can refer to cognitive dysfunction within any time period but recent studies assess cognitive dysfunction in the long-term (i.e. months or years) as immediate cognitive changes are often transient and resolve spontaneously. [6]



Cognitive outcomes in patients undergoing chemotherapy appear to be affected by treatment characteristics. Van Dam and colleagues compared the cognitive function in women receiving high-dose versus standard-dose adjuvant chemotherapy for high-risk breast cancer. The results indicated a dose-related effect whereby a higher proportion of breast cancer patients receiving high-dose chemotherapy had cognitive impairment as compared to patients receiving standard-dose chemotherapy (32% versus 17%). [7] A more recent study by the same team also showed a greater degree of cognitive impairment in breast cancer patients receiving high-dose chemotherapy. [8] However, other studies such as Mehnert *et al.* and Scherwath *et al.* did not find any significant difference in post-chemotherapy cognitive function between high-dose and standard-dose groups. [9,10] These inconsistencies are probably due to methodological differences, such as the choice of chemotherapeutic agent and the time of cognitive testing.

The duration and type of regimen were also implicated as possible treatment factors. In early breast cancer patients, the duration of chemotherapy was positively correlated with the degree of cognitive decline. [11] The previously commonplace cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) regime was also shown to increase the incidence of cognitive dysfunction when compared to published test norms of healthy people. [11] In particular, methotrexate is a known neurotoxic agent which affects cell proliferation and blood vessel density in the hippocampus. [12,13] However, similar regimens substituting methotrexate with etoposide or adriamycin also seem to cause cognitive impairment. [14] This brings into question whether a single or combination of chemotherapeutic agents are largely responsible for the cognitive effects.

Are some individuals more susceptible to 'chemobrain'?

Individual cognitive characteristics

Since 'chemobrain' only occurs in a subset of cancer patients, many researchers have postulated that some individuals may be more susceptible than others. Cognitive decline prior to treatment can contribute indirectly to 'chemobrain' by establishing a lower baseline cognitive function. Individual characteristics such as poor education, reduced cognitive stimulation, old age, and stress are possible risk factors for developing 'chemobrain'. Ahles *et al.* and Adams-Price *et al.* showed that older patients with low cognitive reserve have a lower processing speed as compared to younger patients. [15,16] This is not unexpected as processing speed decreases with age and cognitive disorders in older patients are generally under-diagnosed.

For example, in the United Sates, about 20% of elderly cancer patients screen positively for cognitive disorders, and dementia is clinically diagnosed in one in two cancer patients above the age of 80. [17,18] Earlier studies that have not shown an association between age and cognitive decline often include younger and more highly-educated individuals, and this could have affected the statistical significance of the results. [19]

Most studies failed to find an association between psychological stress and cognitive dysfunction. This is because many neuropsychological tools measure objective (i.e. cognitive function) rather than subjective cognitive impairment (i.e. cognitive symptoms). The latter is, however, equally important and Jenkins *et al.* showed that psychological distress can cause subjective cognitive impairment with a consequent significant reduction in QOL. [20] It is difficult to attribute specific proportions of cognitive decline to chemotherapy or emotional distress, but any declines due to stress/grief are likely to be secondary to chemotherapy.

Genetic susceptibility

The apoliprotein E (APOE) and catechol-o-methyltransferase (COMT) genes are involved in neural repair and neurotransmission. [21,22] The human E4 allele of APOE is associated with cognitive disorders such as Alzheimer's disease, as well as poor prognosis in brain injury and stroke patients. [23,24] One study found that cancer patients with the E4 allele also tend to have poor executive functioning and visuospatial memory irrespective of chemotherapy status. [21]

Interestingly, the brain-derived neurotrophic factor (BDNF) is also implicated as a possible genetic susceptibility factor. The BDNF is involved in neural repair and is preferentially expressed in the frontal lobe and hippocampus. [2] A valine (Val)-to-methionine (Met) amino acid substitution at codon 66 of the BDNF gene confers similar cognitive deficits as those found in APOE E4 carriers. [2,25]

Cognitive performance is dependent on efficient neurotransmission. COMT is required for the metabolism of catecholamines, and this function is especially important in brain regions with low expression of presynaptic dopamine transporter such as the prefrontal cortex. [26] Reduced dopamine level in the prefrontal cortex is associated with a significant decline in executive functioning. COMT-Val allele carriers are rapid metabolisers of dopamine (four times that of COMT-Met allele) and predictably, individuals in the general population with this allele variation were shown to perform poorly in cognitive assessments. [27]

It is worth thinking that chemotherapy may exacerbate cognitive changes in individuals with these specific variations in APOE, BDNF, or COMT.

The current evidence for hormones and cytokines

The fact that cognitive impairment has been shown in diverse types of cancer (breast, CNS, and lymphoma) and even in the presence of the protective blood-brain barrier (BBB), suggests that direct neurotoxicity of chemotherapeutic agents is only partially responsible for 'chemobrain'. It is believed that a reduction in hormones such as oestrogen and testosterone is associated with cognitive decline. Studies have shown that post-menopausal women undergoing chemotherapy have a poorer cognitive performance as compared to pre-menopausal women. Moreover, despite conflicting results in some studies, pre-menopausal breast cancer patients receiving tamoxifen and chemotherapy are often more cognitively impaired (especially verbal memory and processing speed) than those receiving chemotherapy alone. [28,29] Similar results were also found in males undergoing androgen deprivation therapy (ADT) for prostate cancer. One study found that almost half of the prostate cancer patients undergoing ADT scored 1.5 standard deviations below the mean in more than 2 NP measurements. [30] These observations suggest that oestrogen and testosterone may have neuro-protective roles (such as antioxidant or telomere length maintenance) which are vital to cognitive function. [2]

Cytokine imbalance may also be involved in cognitive decline. Cytokines are responsible for maintaining normal neuronal and glial cell function. They also regulate levels of neurotransmitters such as dopamine and serotonin which are necessary for cognition. [31] Increased levels of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and interleukin-6 (IL-6), were found in patients receiving chemotherapy for Hodgkin's disease and breast cancer respectively. [32,33] In particular, an elevated level of IL-6 was associated with a decline in executive functioning. [34] Longitudinal studies of patients receiving immunotherapies consisting of IL-2 or interferon-alpha also found that these therapies result in cognitive decline across a range of domains such as processing speed, spatial ability, and executive functioning. [35] Paradoxically, an elevated level of IL-8 was found to correlate with memory enhancement in acute myelogenous leukemia and myelodyplastic syndrome patients. [34] It is still unclear which cytokines are involved and how they work. Moreover, most studies up to now have focused on acute rather than long-term cognitive changes in cancer patients. Possible roles for hormones and cytokines in chemotherapy-induced cognitive changes will be elaborated in the 'multi-factorial model' section.

Is anaemia related to cognitive function?

In anaemic cancer patients, it is hypothesised that low levels of haemoglobin result in ischaemic damage to the brain. Since many chemotherapeutic agents are cardiotoxic, cerebrovascular changes could also further aggravate the hypoxic condition. [36] Both Vearncombe *et al.* and Jacobsen *et al.* showed that decline in haemoglobin (Hb) levels is a significant predictor of multiple cognitive impairments (such as attention and visual memory) in patients receiving chemotherapy. [37,38] However, Iconomou *et al.* found no association between Hb levels and cognition function, although higher Hb levels were significantly correlated with a better QOL. [39] This conflicting result may be attributed to the use of the Mini-Mental State Examination (MMSE), which is in itself too brief and not a very sensitive measure of subtle cognitive impairment. [3] Conversely, Verancombe *et al.* used a battery of comprehensive neuropsychological assessments to measure different cognitive domains

Establishing a multi-factorial model of 'chemobrain'

Despite all the research so far, there is still no consensus on how 'chemobrain' develops. It is well recognised that oxidative stress is one of the commonest causes of DNA damage in neuronal cells and a number of cognitive disorders such as Alzheimer's disease and Parkinson's Disease are associated with it. [40,41] Chemotherapeutic drugs such as Adriamycin are also known to increase production of reactive oxygen species (ROS) and contribute to reduced anti-oxidant capacity. [42] In addition, chemotherapy has often been associated with telomere shortening in patients with breast cancer and haematological malignancies. [43,44] Telomeres shortening can result in adverse cell outcomes such as senescence and apoptosis, and although most CNS cell types are post-mitotic, some such as glial cells are actively dividing and are vulnerable to this process. [45] Based on these observations, it is conceivable that oxidative DNA damage and telomere shortening could form the basis of a model of CNS dysfunction to explain 'chemobrain'.

As mentioned previously, a lower baseline cognitive function due to individual cognitive characteristics and genetic predisposition can precipitate cognitive difficulties when certain treatment conditions are prevalent. These conditions are not fully understood but may relate to the use of neurotoxic agents, prolonged high-dosage regimens, or simply any therapeutic situation which causes hormonal and/or cytokine imbalances. Cytokines are likely to play a crucial intermediary role linking the neurotrophic effects of chemotherapy to oxidative DNA damage in the CNS as the BBB will limit the entry of most chemotherapeutic agents. [2] Although some animal studies show that a minute dose of these agents can cause cognitive symptoms, such occurrences are typically rare and drug effects may instead follow a

dosage-dependent pattern. [46]

In contrast, cytokines can pass through the BBB and mediate their effects freely. Aluise and colleagues proposed a mechanism of pathogenesis whereby Adriamycin causes the release of peripheral tumour necrosis factor-alpha (TNF-α) via cell injury. These cytokines pass through the BBB and induce glial cells to produce more TNF-α, especially in the hippocampus and frontal cortex. Elevated levels of central TNF- α then damage brain cell mitochondria as well as stimulate production of ROS, which results in oxidative stress and DNA damage. [47]

By extrapolation, other pro-inflammatory cytokines such as IL-6 may play similar roles and different chemotherapeutic agents could induce distinct cytokine profiles with varying CNS effects. It is also worth postulating that the same oxidative stress could have led to telomere shortening and subsequently cell apoptosis/senescence. When this occurs in patients who are post-menopausal or undergoing hormonal therapy, the effects of telomere shortening would predictably be more pronounced. As changes in oestrogen status (such as in the transition from pre-menopause to post-menopause) have been linked to fluctuations in levels of cytokines such as IL-6 and alterations in cortisol rhythm are shown to elevate pro-inflammatory cytokine levels, it is possible that interplay between cytokines and hormones could be significant in the pathogenesis of 'chemobrain'. [48, 49]

How then, does cognitive impairment translate to a diminished QOL? Quantifying cognitive impairment in terms of QOL is difficult due to its objective (assessed by neuropsychological tools) and subjective components (assessed by self-reporting). In some patients, psychological stress coupled with anaemia (and possibly, other side effects of chemotherapy) could have reduced the subjective component of QOL to such an extent that the effects of cognitive difficulties are amplified. This could explain the apparent paradox whereby a subtle change in cognitive function often results in a significant impact on a patient's quality of life.

Lastly, how do we reconcile the delayed effects of 'chemobrain'? The immediate effects of chemotherapy are well-established as a result of acute CNS damage but the persistence of cognitive changes has always remained unclear. A study by Han *et al.* found that systemic administration of the commonly used chemotherapy agent 5-fluorouracil results in a progressively worsening delayed demyelination of the CNS white matter tracts with consequent cognitive impairment. Although this is unlikely to be the only chemotherapy related mechanism of delayed CNS change, it adds to the existing knowledge of prolonged inflammation and vascular damage to the CNS noted in radiotherapy. [50]

A possible multi-factorial model of 'chemobrain' is summarised in Figure 1.

Chemotherapy related cognitive impairment can be affected by a number of possible determinants such as treatment characteristics, genetic susceptibility, cytokine imbalance, and hormonal factors. Mechanisms such as oxidative stress and telomere shortening have been implicated, and studies suggest a mediating role for cytokines. The primary outcome is commonly called 'chemobrain', which encompasses a wide range of cognitive domains including executive functioning, processing speed, attention/concentration, as well as verbal and visuospatial memory. The effects of 'chemobrain' are both acute and delayed, with the latter thought to involve demyelination of CNS tracts. While 'chemobrain' can be subtle, amplifying factors such as psychological stress and anaemia may have a significant impact on the quality of life of a patient in terms of reduced work, education, and social interaction opportunities.

Discussion and conclusion

While good progress has been made in understanding 'chemobrain', further research is required in order for clinical interventions to be effective. A multi-prong treatment approach is widely viewed as necessary to manage this condition due to the complexity of the phenomenon. Pharmacological approaches proposed by researchers revolve around reducing oxidative DNA damage and improving neurotransmission. Examples of drugs considered include antioxidants such as zinc sulfate and N-acetyl cysteine, as well as modulators of the catecholaminergic system such as Methylphenidate and Modafinil. [3] Furthermore, cognitive rehabilitation has shown promise in restoring an acceptable baseline level of cognition. [6] However, these interventions are at most speculative and certain mechanistic questions still need to be addressed.

Firstly, it is important to identify further risk factors which could help us identify the cognitive effects of chemotherapy more precisely. This may involve extending our study beyond purely neurological-related genes such as APOE and COMT. Ahles and Saykin have suggested that genes involved in regulating drug transport across the BBB could be involved

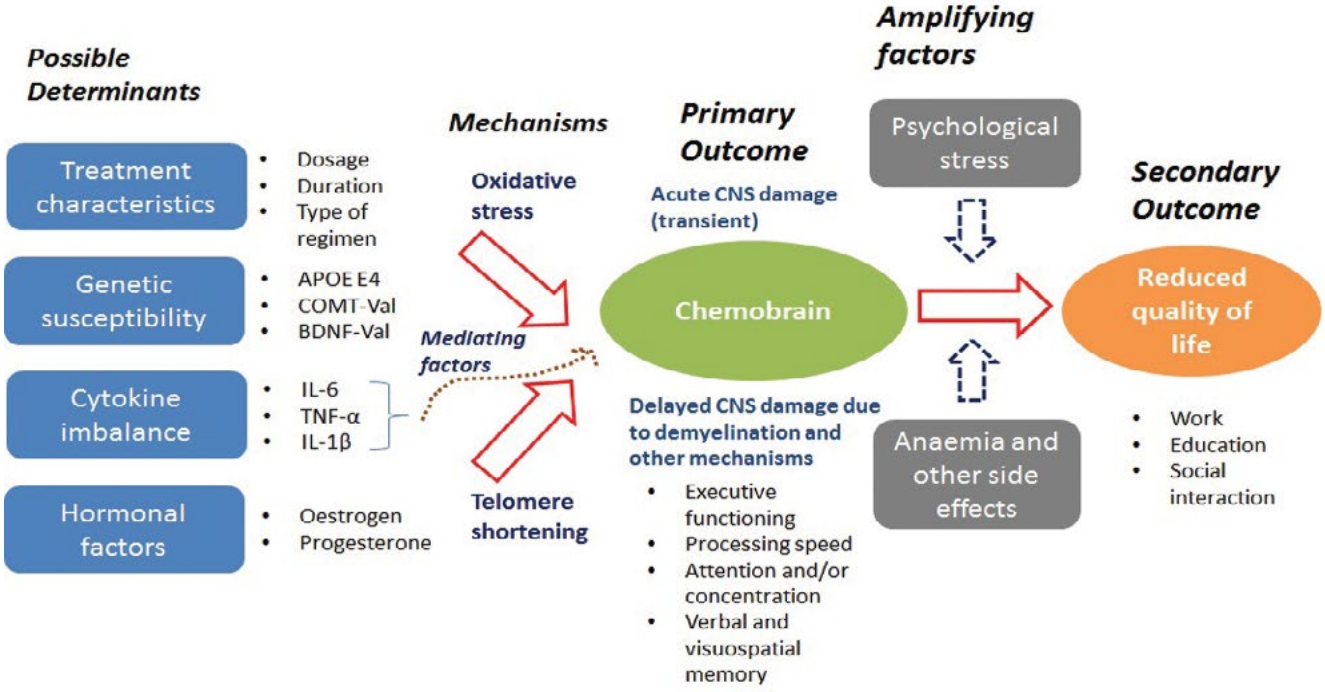


Figure 1. *Pathogenesis of 'chemobrain'.*

in 'chemobrain'. [2] The P-glycoprotein, encoded by the multi-drug resistance 1 (MDR1) gene, is expressed by endothelial cells in the BBB and protects neuronal cells by promoting efflux of drug metabolites. A C3435T polymorphism in exon 26 of the MDR1 gene is associated with reduced efflux capacity of P-glycoprotein and could precipitate buildup of high concentrations of toxic chemotherapy agents. [51] Positron-emission tomography (PET) studies allow monitoring of these concentration changes and may help us understand which drug transporters are involved and how drug doses can affect cognitive function. [52] Evidence of direct chemotherapy neurotoxicity may also be further pinpointed through neuroimaging studies which compare changes in brain integrity on MRI in women treated with chemotherapy compared to cancer patients who did not receive chemotherapy. An example is the study done by Deprez *et al.*, which assessed microstructural changes of cerebral white matter in non-CNS cancer patients. [53]

Secondly, methodological differences between studies pose a serious limitation, which precludes strong conclusions from being derived. Some studies utilize brief assessments, such as the MMSE, which are poor at detecting subtle cognitive changes. There needs to be a battery of NP assessments which are comprehensive yet practical enough to be used in clinical trials (refer to Vardy *et al.*). [54] In addition, many studies often exclude patients with pre-existing conditions (such as neurological disorders or learning disabilities) for fear of aggravating post-chemotherapy cognitive impairment. [19] This meant that high-risk patients are left out of the analysis and consequently, the actual proportion of patients experiencing 'chemobrain' might be underestimated. It is also essential for studies to establish the pre-chemotherapy baseline cognitive level prior to treatment as those, which recruit individuals regardless of cognitive status tend to yield conflicting results. [3] Moreover, studies should endeavour to compare cognitive impairment in the short-term versus the long-term in order to ascertain that cognitive difficulties are persistent and not transient in nature.

The practical implications of understanding 'chemobrain' are forseeable. Chemotherapy regimens can be individualized to fit the physical and psychological constitution of the patient. This helps to improve compliance rate and reduce drop-outs due to adverse treatment-related effects. In addition, the existence of 'chemobrain' may favour the diversification of treatment modalities instead of focusing on chemotherapy alone. For example, immunotherapy can be trialed as adjuvant to chemotherapy with the aim of reducing the latter's side effects and potentiating the overall therapeutic gain, such as in the case of indoximod (an IDO inhibitor) and chemotherapy in metastatic breast cancer.

In conclusion, 'chemobrain' is a phenomenon which needs to be studied in depth. Current observations favour a framework whereby individuals experience cognitive difficulties due to a combination of inherent vulnerabilities and chemotherapy-related side effects. There is also increasing recognition that cytokines might play a crucial supporting role in pathogenesis. Emphasis should be placed on identifying further chemotherapy-related risk factors, as well as improving the sensitivity of methodological approaches with the aim of improving the design of chemotherapy regimens to provide a better quality of life.

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Conflict of interest

None declared.

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HIV/AIDS: let's see how far we've come

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Lauren is a third year medical student at Griffith University. She has an undergraduate degree in science from the University of Sydney, and completed immunology honours in HIV retroviral genetics, studying microRNA changes during HIV infection. She has a passion for the intricacies of the immune system and the pursuit of a cure for HIV.

Now more than ever, HIV positive people are living longer and healthier lives because of access to antiretroviral therapy. Healthcare organisations are working to ensure that HIV positive people all over the world have access to the medical care they need to stay healthy. In the last few years, research into vaccine development, genetics-based approaches and novel therapies have achieved some progress and drug therapy regimens have become more effective. Public health strategies have aimed to reduce transmission, and early access to treatment has dramatically improved quality of life. With resources and funding aimed in the right directions, it will be possible to continue making significant progress towards better prevention, improved treatment options and perhaps even a cure for HIV and the elimination of the global AIDS epidemic. This article reviews some of the successes and difficulties in the scientific, research and treatment arm of combating the HIV epidemic. There is still much work to be done, but for now, let's see how far we've come.

Introduction

The 2011 UNAIDS World Aids Day report concisely outlines the aims of global health efforts against HIV/AIDS: "Zero new infections. Zero discrimination. Zero AIDS-related deaths". [1] As global citizens and future medical practitioners, it is our duty to participate in the medical issues that are of importance to the world. We should work to make the eradication of HIV/AIDS one of those key issues. This paper discusses, from the scientific perspective, some of our triumphs and tribulations with regards to combatting the complex, evasive and resourceful opponent that is the HIV virus.

The Basics

There are two main types of HIV: HIV-1 and HIV-2, with HIV-1 being the more common of the two. [2,3] HIV is a retrovirus with a high degree of variability, attributable to the error prone nature of its reverse transcriptase enzyme and its high recombination rate. [4] The HIV genome consists of a number of genes (see figure 1) including *gag*, *pol*, *env* and *nef* all of which have been used as potential antigens for the generation of vaccines. [5]

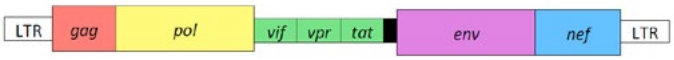

Figure 1. *Simplified diagram of the HIV genome.*

HIV primarily infects cluster-of-differentiation-4 cells (CD4) cells, including CD4 T-cells, macrophages, monocytes and dendritic cells. [6] Initially, the immune response to viral infection (including CD8 T-cell mediated killing, complement activation and antibody production) is effective at removing HIV infected cells [7], but continued immune activation and antigen presentation spreads the virus to the lymph nodes and the rest of the body. [8,9] Continued immune response to replicating virus drives development of escape mutations and ultimately overwhelms the immune system's ability to respond. [10] As the infection progresses, the rate of destruction of infected CD4 T-cells exceeds the rate of synthesis and the CD4 count declines.

The 2008 HIV infection case definition replaces past criteria for HIV

infection progression to AIDS, and divides the infection into stages reflecting the decline in immune function. [11] The stages of infection are:

Stage 1: CD4 T-cells ≥ 500 cells/mm^3 (≥ 29% of total lymphocytes) with no AIDS-defining conditions.

Stage 2: CD4 T-cells 200-499 cells/mm^3 (14-28% of total lymphocytes) with no AIDS-defining conditions.

Stage 3 (Progression to AIDS): CD4 T-cells <200 cells/mm^3 (<14% of total lymphocytes) or the emergence of an AIDS defining condition (regardless of the CD4 T-cell count).

AIDS related conditions include a range of infections, such as esophageal Candidiasis, Cryptococcus, Kaposi sarcoma, *Mycobacterium avium/tuberculosis* and *Pneumocystis jirovecii* pneumonia. [11] AIDS related deaths are usually due to severe opportunistic infection as the immune system is no longer able to fight basic infections. [1]

HIV is primarily transmitted via bodily fluids including blood, vaginal secretions and semen, and across the placenta, however it is not readily found in the saliva, unless there are cuts or ulcers providing access to the bloodstream. [12] Although sexual contact is the most common method of transmission, other mechanisms such as needle-stick injury, sharing needles and transfusion of HIV infected blood are far more likely to result in infection. [12] The infectivity of a person with HIV is proportional to the number of copies per mL of blood. [12]

HAART Therapy

According to UNAIDS estimates, 34 million people around the world were living with HIV in 2010, with 2/3 of the global total in Sub-Saharan Africa. [1] By the end of 2012, this had increased to 35.3 million people. [13] Now more than ever, HIV positive people are living longer and healthier lives. In part, this is due to the provision of effective treatment in the form of Highly Active Anti-Retroviral Therapy (HAART).

The first antiretroviral drug described and approved for clinical use was AZT (3'-azido-3'-deoxythymidine), a thymidine analogue. Now, there are seven categories of antiretroviral drugs, with more than 25 unique drugs. [14] HAART involves taking a combination of at least three drugs from at least two classes of antiretroviral drugs, with the aim of reconstituting lost CD4 T-cells, minimising viral load and reducing viral evolution. [15-17] The efficacy of HAART has changed HIV from a disease of significant morbidity and mortality to a manageable chronic condition. Further, HAART can minimise transmission of the virus, and prolongs the healthy lifetime of the individual by reducing viral load to

undetectable levels. [18]

At present, much research is focused on investigating the timing of initiation of HAART therapy in HIV+ individuals, and the most effective combinations of drugs. [19,20] In general, those who initiate HAART therapy earlier are more likely to die at older ages and of non-AIDS causes. [21] Studies have found conflicting results when tracking the disease outcomes of patients commenced on HAART at different stages of disease. For example, a large collaborative study found that patients who are commenced on HAART with CD4 T-cell counts of 351-450 cells/mm^3 have a lower rate of AIDS and death than patients whose commencement on HAART was deferred until there was further CD4 T-cell decline to below 500 cells. [18,22] Another study has shown that patients commenced on HAART at CD4 counts <500 cells/mm^3 compared to deferring had slower disease progression, but this benefit was not seen with commencing HAART at CD4 T-cell counts of 500-799 cells/mm^3. [19] Recent evidence has shown that early treatment enhances recovery of CD4 T-cells to normal levels. [20,23] The World Health Organisation's HIV treatment guidelines issued in June 2013 now recommend commencing treatment when an individual's CD4 T-cell count falls below 500 cells/mm^3, or immediately on diagnosis for pregnant women, children under 5, those with HIV-associated comorbidities like tuberculosis and Hepatitis B, and for HIV- people in a serodiscordant couple with an HIV+ individual. [13]

HAART requires strict adherence, and side effects can impact on the patient's quality of life. Long-term use is associated with toxicity, particularly to the liver, kidneys, bone marrow, brain, cardiovascular system and gastrointestinal tract. [15,24] Further, It has been noted that illnesses that typically occur with ageing appear prematurely in HIV+ patients on HAART therapy. This is thought to be only partially due to the infection, but also a side effect of the drugs involved in treatment. [25] Torres and Lewis (2014) provide an overview of what is known about premature ageing in the HIV+ patient and how this relates to HAART drugs. [25]

Non-compliance with HAART leads to the resurgence of viral replication with increased viral load and the potential for development of drug resistant mutant strains of HIV. [15,24] This can make it more difficult to treat the patient, as new drug choices may be limited and increases in viral load can lead to risk of further spread of the virus. HAART also does not purge reservoirs of latently infected cells [26], and as such, there is currently no cure for HIV.

Integration, latency and treatment challenges

There are a number of characteristics of the HIV virus that make it challenging to eradicate. HIV exhibits significant genetic diversity, both within an individual patient and within a population. As a retrovirus, HIV has an inherent ability to establish early latency within the DNA of host cells, where it remains for the lifetime of the cells and is unable to be removed by the immune system. [5]

One major development was made in 2013, when Hauber *et al.* reported the successful use of an antiretroviral gene therapy. A site specific recombinase (Tre) targeted to the HIV-1 long terminal repeat (LTR) was used to excise the HIV provirus from infected CD4 T-cells, functionally curing infected cells of their HIV infection, without cytopathic effects. [27] This study provides promising evidence to suggest that in future, genetically oriented antiretroviral technologies may have the potential to provide a cure for HIV infection.

Development of a prophylactic vaccine for HIV

Although it was initially believed that HIV infection was a simple illness of immunosuppression, we now know that HIV sufferers do mount strong immune responses to the HIV virus, although this response is insufficient to control the virus or eradicate the infection. [28] One of the major challenges in producing a prophylactic vaccine is the high variability of the HIV virus. There is a variation of 25-30% between subtypes of HIV-1, and 15-20% variation within any subtype. Furthermore, viral quasi-species in any infected individual can range by 10%. [29] The problem this variation causes is illustrated in natural infection, where the antibodies present in infected individuals are functional, but do not eliminate the infection due to the genetic variety seen in mutants created under the pressure of the immune system. [28,30] This variability makes it difficult to know which antigens to use to generate the required immune response to control the infection. Strategies being explored to combat this include the use of consensus sequences (fusing the most conserved portions of the virus, and trying to produce immunity to such a sequence), conserved region antigens (specifically choosing the most conserved antigens to generate immune responses) and multiple antigen cocktails (vaccination with multiple variants of one immunogen, or several different ones in combination). [31]

The first prototype HIV vaccine tested utilised purified monomeric env gp120 immunogens (a component of the virus's surface envelope protein) in an attempt to generate virus-specific antibody responses. Unfortunately, early trials showed that this vaccine was unable to induce the production of neutralising antibodies, and did not prevent infection with HIV-1 in humans. [31,32] Since then, attempts have been made at prophylactic vaccination using a range of differing immunogens including Tat and Gag. In most cases, these vaccinations have proven safe and well tolerated, and resulted in the production of anti-HIV antibodies that may not be seen in natural infection. [33] Promising results have come from a range of trials, including the control of infected CD4 T-cells by Gag-specific CD8 T-cells, proportionally to the number of Gag epitopes recognised. [34] Success at eliciting immune responses demonstrated thus far with Gag may be to do with its relatively well-conserved sequence patterns. [34]

The STEP Study and Phambili HIV vaccine trials both used an Adenovirus 5 (Ad5) vector and gag, pol and nef immunogens, which was shown to be successful at inducing a good CD8 T-cell response. [35] Subsequent trials demonstrated that the vaccine provided no additional prevention from infection, nor a reduced early viral level. [36] Further, there was an increased rate of HIV-1 acquisition in groups of vaccinated individuals from the STEP study, most particularly in men who were already Ad5 seropositive and uncircumcised. [37]

The primary challenge in the use of viral vectors to deliver a HIV vaccine into cells is the pre-existing immunity of humans to viral vectors, leading to the neutralisation and removal of vectors from the circulation before the transfer of the immunogen to cells. In addition, vectors induce mucosal homing in T-cells, making them more susceptible to infection [38] and explaining the increased susceptibility to infection observed in the Step Study. [37,39]

At present, there is much debate over the necessary aims for a successful HIV vaccine: for example, whether to focus on the development of anti-HIV antibodies, or the induction of a CTL response. [30] Recent papers have described the ability of combinations of broadly neutralising antibodies to successfully neutralise HIV. [40,41]

MiRNAs

A new area of interest is the use of microRNAs (miRNA) as potential next generation therapeutic agents for the treatment of HIV infection and management of viremia. MiRNAs are small, noncoding RNA fragments, responsible for fine-tuning and negatively regulating gene expression. Roles for microRNAs have been found in metabolism, development and growth, and dysregulation of miRNAs have been implicated in loss of tumour suppression and development of cancer. [42,43]

The utility of miRNA-oriented technology has already been illustrated in the context of hepatitis C infection. In 2005, Jopling *et al.* reported that miR-122 was highly abundant in human hepatocytes, and that its presence may facilitate replication of the viral RNA, and encourage survival of the virus in the liver. [44] Since this pivotal paper, the first drug targeting a miRNA has been developed. Miraversen is a miR-122 inhibitor [45], which in human trials has been shown to exhibit dose dependent antiviral activity [46], with no dose-limiting adverse events

or escape mutations observed. [47]

The first attempt to find human cellular miRNAs directly targeting the HIV genome was by Hariharan *et al.* (2005). [48] It was then later shown that one of the miRNAs identified was capable of inhibiting HIV nef expression, and decreasing HIV replication. [49] Further research demonstrates that cellular miRNAs potently inhibit HIV-1 production in resting primary CD4 T-cells, suggesting that cellular miRNAs are pivotal in HIV-1 latency. [50]

In 2007, Triboulet *et al.* reported that HIV-1 infection caused a down-regulation of specific miRNAs in mononuclear blood cells, and that this was necessary for effective viral replication. [51] Witwer *et al.* (2012) subsequently showed that the miRNA profiling of infected cells could be used to distinguish elite suppressors, viraemic HIV-1 patients and uninfected controls from one another [52], indicating significant changes to cellular miRNA profiles of cells when they are infected by HIV. From these studies it is evident that different cellular miRNAs modulate and are modulated by HIV infection, with different miRNAs implicated in different cells, contexts and environments. More research in this area is required, and will hopefully give rise to a new generation of therapeutic agents for HIV. The interested reader is referred to more specific reviews [53-55] for more detailed information.

Where to from here?

HIV has proven itself a formidable opponent to our aims at a global improvement in healthcare and quality of life. However, recent research gives hope that advanced treatments, better prevention and even a cure may one day be possible. It is clear that the best way to tackle HIV is by a coordinated approach, where global health strategies, clinical medicine and research work together to help eradicate this epidemic.

We have had some success in the use of novel approaches like targeting cellular miRNAs and excising HIV DNA from the human genome, and there have also been some promising results in the generation of immunity to infection through a HIV vaccine. We are constantly learning more about how HIV interacts with the host immune system, and how to overcome it. However, progress on the development of a HIV vaccine has stalled somewhat after the findings of the STEP and Philambi studies.

It is important to acknowledge the significant achievements that have been made worldwide through HIV public health campaigns. In 2012, a record 9.7 million people were receiving antiretroviral therapy, and the incidence of HIV is falling each year, with a 33% decline from 2001 to 2012. [56] However, there is still much work to be done to ensure all people are able to access HIV testing and treatment. One of the aims of the Millennium Development Goals is to provide universal access to treatment for HIV/AIDS to all those who need it, although this is yet to be achieved. [56,57]

Medicine has come a long way in the understanding and treatment of the complex and multifaceted problem that is the global AIDS epidemic. I urge medical students to be informed and interested in the HIV epidemic, and to be involved in the clinical, research and community groups tackling this multifaceted problem. With continued efforts and dedication, there is hope that in our lifetime, we may see the realisation of the ambitious aims of the 2011 UNAIDS World AIDS Day report: "Zero new infections. Zero discrimination. Zero AIDS-related deaths".

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Conflict of interest

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Complementary medicine and hypertension: garlic and its implications for patient centred care and clinical practice

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This review aims to explore the impact that patient attitudes, values and beliefs have on healing and the relevant implications these have for clinical practice and patient centred care. Using a Cochrane review as a platform, garlic as a complementary medicine was evaluated based on current societal trends and pertinent clinical practice points. The study found that when engaging with a patient using complementary medicine it is important to consider not only the efficacy of the proposed treatment, but also variation in preparations, any possible interactions and side effects, and the effect of patient beliefs and the placebo effect on clinical outcomes. The use of garlic in the treatment of hypertension could serve to enhance the therapeutic alliance between clinician and patient and potentially improve clinical outcomes.

Introduction

Hypertension is the most common cardiovascular disease in Australia. Approximately eleven percent of the population (2.1 million people) are affected by the condition. [1] The prevalence is twice as high in the indigenous population, affecting 22 percent of those aged 35 or older.[1] Hypertension is a significant risk factor for transient ischaemic attack, stroke, coronary heart disease and congestive heart failure, increasing the risk of these by two to three fold. [2] Cardiovascular disease accounts for 47,637 or 36 percent of deaths in Australia each year and costs the economy a total of $14.2 billion AUD per annum – 1.7 percent of GDP. [3,4] Hypertension also accounts for six percent of all general practice consultations, making it the most commonly managed condition. [5] Given the significant effect hypertension has on society, it is imperative to evaluate potential therapies to combat hypertension.

Hippocrates is quoted as saying "*let food be thy medicine and medicine be thy food*". [6] A considerable number of complementary therapies are thought to be effective in the treatment of hypertension by the general public. Such medicines include cocoa, acupuncture, coenzyme Q10 and garlic. [7] Medical texts from the ancient civilisations of India, China, Egypt, Rome and Greece all reference the consumption of garlic as having numerous healing properties. [8] Garlic (*Allium sativum*) was selected as the medicine of choice for this review as it is one of the most widely used and better studied complementary therapies in the management of hypertension. [9]

In addition to the effect of garlic on blood pressure, it is interesting to consider the implications of using this complementary medicine in light of patient centred care and clinical practice. It is highly recommended to medical students and clinicians that a patient's cultural attitudes, values and beliefs are recognised and incorporated into clinical decision-making. The incorporation of patient perspectives into clinical practice may be done by negotiating the use of garlic as a complementary medicine alongside the use of a recognised antihypertensive drug. This study therefore aims to explore the findings and implications of controlled studies on the use of garlic to prevent cardiovascular morbidity and mortality in hypertensive patients in relation to good clinical practice and patient centred care. The aim of this investigation is to use a Cochrane review as a platform to explore garlic as an antihypertensive, and to discuss this treatment in the context of patient centred care and clinical practice.

Methods

The review focused on recent literature surrounding the use of garlic as an antihypertensive. A Cochrane review was used as an exemplar to discuss the broader implications of using garlic as a therapy for hypertension. Use of garlic was explored through the framework of current societal trends, clinical practice and patient centred care. Selected publications present both qualitative and quantitative data.

Results

While the literature search retrieved a number of randomised controlled studies suggesting a beneficial effect of garlic on blood pressure, [5,10] the most recent Cochrane review by Stabler *et al.* retrieved only two controlled studies that assessed the benefit of garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients. [5,11,12] Of the two studies, Kandziora did not report the number of people randomised to each treatment group, meaning their data could not be meta-analysed. [5] They did report however, that 200mg of garlic powder in addition to hydrochlorothiazide-triamterene baseline therapy produced a mean reduction of 10-11 mmHg and 6-8mmHg in systolic and diastolic pressure respectively, compared to placebo therapy. [5] Auer's 1990 study randomised 47 patients to receive either 200 mg garlic powder three times daily or placebo determining that garlic reduces mean arterial systolic blood pressure by 12mmHg and diastolic blood pressure by approximately 6-9mmHg in comparison to a placebo. [5] Ried's meta-analysis revealed a mean systolic decrease of 8.4mmHg ± 2.6mmHg ($P \leq 0.001$) and a mean diastolic reduction of 7.3mmHg ± 1.5mmHg ($P \leq 0.001$) in hypertensive patients. [10]

Given these findings fall within the normal parameters for blood pressure measurement variability, the efficacy of garlic as an antihypertensive is inconclusive. It is also difficult to ascertain the implications of the Cochrane review for morbidity and mortality as neither of the trials reported on clinical outcomes for patients using garlic as a hypertension treatment and insufficient data was provided on adverse events. As such, garlic cannot be recommended as a monotherapy for the reduction of hypertension. [13] Despite this, there are other potential uses for garlic in the treatment of hypertension which encompass both patient centred care (PCC) and evidence based practice.

Different garlic preparations

Several garlic preparations are available for the treatment of hypertension including: garlic powder (as per the Cochrane studies),

garlic oil, raw garlic, cooked garlic and aged garlic extract. [5,14] Ried and colleagues suggests that aged garlic extract is the best preparation for treatment of hypertension, and may reduce mean systolic blood pressure by 11.8mmHg ± 5.4mmHg over 12 weeks compared to placebo (P=0.006). Ried also noted that aged garlic extract did not interact with any other medications, particularly warfarin. [14]

Drug interactions

A number of drug interactions may occur when using garlic. Edwards *et al.* noted an increased risk of bleeding in patients who take garlic and blood thinning agents such as aspirin and warfarin. The same study also noted that the efficacy of HIV medications such as saquinavir may be reduced by garlic interactions, and some patients suffer allergies to garlic. [15]

Patient beliefs and the placebo effect

Patient beliefs must be incorporated into clinical practice not only for adherence to PCC but also as a therapy itself. Numerous studies have suggested that placebo treated control groups frequently experience a relevant decrease of blood pressure in pharmacological investigations into hypertension. [16]

Discussion

The findings of the Cochrane review are useful in making evidence based decisions regarding patient care, yet it is important to reflect on the issue of hypertension holistically and to consider what the review may have overlooked. Given that the Cochrane review provided insufficient data on the potential adverse effects, including drug interactions, of garlic consumption, prescribing garlic as a therapy for hypertension at this stage would be a failure to uphold best evidence based practice and would breach ethical principles such as non-maleficence.

Different types of garlic preparation are available. If a patient wishes to use this complementary therapy they should be guided to the most appropriate type. On a biochemical level, aged garlic extract has two main benefits for clinical practice. It contains the active and stable component (S)-allyl-cysteine which is measurable, and may allow for standardisation of dosage. [14] Aged garlic extract is also reportedly safer than other preparations and does not cause the bleeding issues associated with blood thinning medications such as warfarin. [15]

Patient centred care is particularly important as patient centred approaches have numerous influences over clinical outcomes. Bauman *et al.* proposes that PCC reduces patient anxiety and morbidity, improves quality of life, patient engagement and both patient and doctor satisfaction. [17] Evidence also suggests PCC increases treatment adherence and results in fewer diagnostic tests and unnecessary referrals, which is important to consider given the burden of hypertension on the health care system. [17,18] Particularly significant for all stakeholders (patients, clinicians and financiers) is the use of PCC as a dimension of preventative care. For the primary prevention of disease, clinicians should discuss risk and lifestyle factors with patients and the detrimental effects they can have on a patient's health. [2,5] Given the effect of PCC on treatment adherence it is important to consider open communication and discussion with patients not only as a part of treatment, but also as a part of preventative medicine. Further, if a patient is willing to take garlic for hypertension it may be a tool for further discussion between clinician and patient, especially if the treatment sees some success. This success may open windows for a clinician to discuss further the effects of lifestyle modification on health. [7]

Being a multifaceted dimension of health, PCC recognises each patient is a unique individual, with different life experience, cultural attitudes, values and beliefs. Capraz *et al.* found that a percentage of patients use garlic in preference to antihypertensive drugs whilst others use it as a complementary medicine in combination with another antihypertensive drug. [19] This affirms the potential for disparity in patient ideals. A patient may prefer garlic because of concern over the addictive potential of drugs (including antihypertensive). [19] Such concerns should be explored with the patient to ensure patients can make informed decisions about their healthcare. Other viewpoints may be complex, for example mistrust in pharmaceutical companies, or simply having a preference for natural therapies. [19] Again, these somewhat concerning perceptions are worthy of discussion with a willing patient.

Amongst all the information provided it is worth taking the time to appreciate the role of demographic and religious factors. The social context of a patient's health may influence how a patient considers the findings of the review. [20] It may also provide an indicator for the likelihood of complementary medicine use. [20] Xue *et al.* suggests that females aged 18-34 who have higher-than-average income, are well educated and had private health cover were more likely to use a complementary or alternative medicine, such as garlic for hypertension. [20] Religion is also a significant determinant in patient centred care. Adherents to Jainism are unlikely to be concerned with the findings of the review, as they do not consume garlic, believing it to be an unnecessary sexual stimulant. [21] Similarly, some Hindus have also been noted to avoid garlic during holy times for the same reason. [21] A clinical decision regarding garlic as a complementary medicine would have to consider these factors in consultation with the patient.

When making decisions about the course of clinical practice in consultation with a patient, it is important to remember patients have a right to making a well informed decision. [22] It would be appropriate to disclose the findings of this review to patients considering the use of garlic so that a patient can make an informed decision regarding treatment options. It is essential that patients seeking treatment for hypertension understand the true extent of the efficacy of garlic: that it only has minimal (if any) blood pressure lowering effects. Patients should also be advised against garlic as a monotherapy for the reduction of hypertension until there is sufficient evidence to support its use. It is also important to inform patients of their right to use garlic as a complementary medicine if the patient so wishes to do so. [13,19] Given the potential detrimental effects of some garlic preparations, the implications of these effects should also be discussed with patients. If there is discrepancy between the views of the patient and the clinician, then the clinician must remain professional, upholding the codes of ethics which necessitates clinicians respecting the needs, values and culture of their patients. [23] The clinician must also provide the best clinical advice, and negotiate an outcome that is agreeable to both parties' agendas. [23]

Conclusion

Hypertension is the most commonly managed condition in general practice. A Cochrane review assessing the benefit of garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients found a negligible effect on morbidity and mortality. [5] The study did not reflect on clinical outcomes for patients and neglected to discuss different garlic preparations used in the studies, potential differences this may have had on patient outcomes or any pertinent side effects. It is recommended that more studies be performed on the clinical effectiveness and side effects of different types of garlic preparations, particularly aged garlic extract. Patient centred care is important for the best clinical outcomes and for disease prevention. [17,18] Regardless of the efficacy of garlic, it is highly recommended to clinicians that a patient's cultural attitudes, values and beliefs are recognised and incorporated into clinical practice. This may be done by negotiating the use of garlic as a complementary medicine, along with the use of a prescribed recognised antihypertensive drug if the patient desires a complementary medicine. The significant effect that patient values have on healing should be realised and utilised by clinicians and students alike. Ultimately, the use of garlic in the treatment of hypertension could serve to enhance the therapeutic alliance between clinician and patient and potentially improve clinical outcomes.

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Does increased geographical distance to a radiation therapy facility act as a barrier to seeking treatment?

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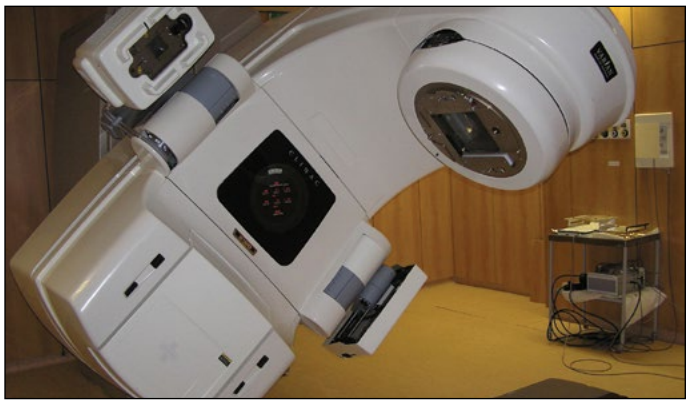
Introduction: Radiation Therapy (RT) is a common treatment modality for cancer management. Due to specific licensing and expertise requirements, RT tends to be centralised in larger urban centres resulting in restricted geographical access for many. Several studies conducted have examined the relationship between distance to treatment and utilisation of RT, however there remains a gap in literature with regards to Australian geography, particularly in rural areas where land is vast and treatment facilities are few. This review aimed to address the question: "Does increased geographical distance to a RT facility act as a barrier to seeking treatment?" **Methods**: The SCOPUS and Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases were searched for articles pertaining to geography, access, and radiotherapy for all cancer diagnoses. Specific inclusion criteria were applied and the quality of the studies were assessed. **Results**: Twelve studies were eligible for inclusion in the review. Of these, nine studies identified a negative relationship between distance to RT facility and RT treatment, one study determined a positive relationship between geographical distance and RT treatment, and two studies noted public transportation as a barrier to RT treatment. **Conclusion**: This review suggests that there may be an inverse association between distance to treatment and utilisation of RT. However, studies were limited by retrospective design and prospective studies are required before firm conclusions can be drawn. In order to apply these findings to rural Australian settings, it would be ideal to examine data in local areas to determine if these populations are serviced adequately and where there are areas of underutilisation of RT.

Introduction

Radiation Therapy (RT) is a common treatment modality for a multitude of cancer diagnoses. RT may be used for radical or palliative intent; to provide disease control or improve quality of life. [1] The radiation dose is fractionated, delivered daily over weeks, and can in some cases take as many as nine weeks to achieve prescribed radiation doses. [2-4] It is a highly technical treatment that uses imaging options such as: Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) scanning to accurately delineate the tumour volume. Utilising the skills of radiation oncologists and radiation therapists, a precise dose of radiation is delivered to this targeted volume, destroying cancer cells whilst sparing normal tissue where possible.

Radiotherapy requires multidisciplinary input, for example from nursing, medical oncology, palliative care, dietetics and speech pathology. [5,6] For many patients it is the treatment of choice and yields excellent five year survival rates for localised solid tumours. [7] Due to the specific quality control measures, equipment and licensing requirements, substantial cost of treatment machines and the expertise required, the location of RT facilities tends to be centralised in larger urban centres, subsequently restricting access to those located in more regional and rural areas. [3,8,9]

Despite its therapeutic advantages, there are several factors that patients may consider prior to attending RT facilities, one of which is accessibility. For many patients the distance to a RT facility and the protracted course of treatment means that RT is not a feasible option. Challenges in accessing RT may lead to suboptimal treatment



and subsequently poor outcomes for cancer patients. [1,3,7] Several studies have investigated the association between geographical distance to radiotherapy and radiotherapy utilisation, however they are limited by small sample sizes and differ in their conclusions. Accordingly, a systematic review was conducted to assess whether greater geographical distance to a RT facility was a barrier to RT treatment.

Methods

Search-strategy

A search strategy was devised according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. [10] The SCOPUS (incorporating 100% of Medline titles) and Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases were searched using the following search terms: *(geograph* distance OR access)* AND *(radiation therapy OR radiotherapy)*, from January 1, 2000 to June 26, 2013 applied to abstracts.

Inclusion criteria

Studies were included if factors associated with access to or inequalities in receiving RT or cancer treatment were noted on all diagnoses of cancer. Studies were included if they were in the English language, pertinent to humans and linked to publically available full text articles.

Exclusion criteria

Studies were excluded if the primary objective did not include geographical distance or access barriers to RT facility or cancer treatment; if the study focused on treatments rather than barriers to treatment; or if the data was published prior to 2000.

Data extraction and quality assessment

Studies were independently abstracted for quality assessment by the primary author with corroboration from co-authors. Quality assessment was based on the study design, sample size, control for confounders, and control of bias. [11,12] The studies were rated as high (H), moderate (M) or low (L) quality based on study design, execution, and reporting. High quality suggested a prospective study design with a large sample size, considerable control of confounders, and little bias, whereas low quality reflected a small sample size, limited control of confounders, and significant bias.

Results

The search of the SCOPUS database yielded 57 results, of which 22 met the eligibility criteria, with 11 that were relevant to geographical

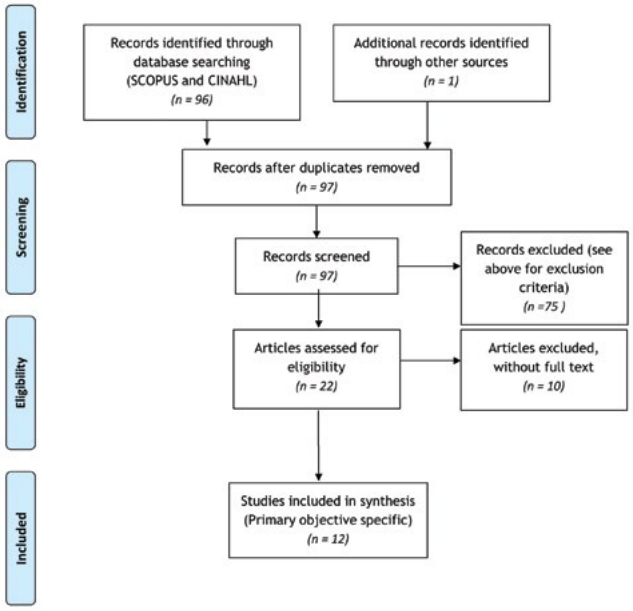


Figure 1. *PRISMA Flow Diagram*

distance and variations in access to RT and available in full text. Repeating the search in CINAHL provided 39 additional results of which no articles were deemed relevant to the primary aims of this systematic review. One additional study was identified from grey literature searching and was included in the review, resulting in a total of 12 studies (Figure 1).

The quality of the included studies is shown in Table 1. As most of the studies were retrospective in study design where data examined was retrieved from cancer registries, they tended to be of moderate quality assessment. Overall, two studies were deemed to be high quality and ten studies were considered to be of moderate quality. None of the included studies were considered to be of poor quality.

The geographical location of each study is summarised in Table 2. Of the 12 studies, eight were conducted in the United States, one study was conducted in Canada, one study was conducted in the United Kingdom and two studies were conducted in Australia with a mixture of urban and rural settings. Several studies utilised geographic information system (GIS) software to map and measure the distance from the patient's residence to the RT facility to give an indication of the accessibility of the RT clinics. Distances were calculated using straight line measurements rather than the actual route travelled by the patient via the software.

Of the 12 studies that met the inclusion criteria, nine identified a negative relationship whereby the greater the distance to the RT facility, the less likely the patient would be to undergo RT. [1,3,4,7-9,13-15] One prospective study with moderate control for confounders determined a positive relationship, whereby the greater the distance to the RT facility, the greater the likelihood of receiving RT. [16] There were two studies that did not address the distance to the RT clinic, but instead noted that lack of public transportation to RT facility was an access barrier, and that the presence of a radiation oncologist reduced mortality rates. [2,17] Although these two studies did not specifically address the primary objective, their results indicate that travel time to RT clinics is a major barrier to patients and that local resources such as radiation specialists can improve prognoses. Synthesis of the study data yielded a list of factors that were considered to influence access to RT (Box 1). The most influential factors contributing to radiotherapy access included: shorter distance to the RT facility, higher socio-economic status (SES), and increased education.

Box 1. *Factors identified that influence access to RT.*

- Resource availability of RT [1]
  - o Adequate staff in RT [9]
- Geographical distance to RT facility
  - o ↑ distance from patient residence to RT facility ↓utilisation of RT [1,3,9,13]
  - o ↑distance to RT facility ↑increased utilisation of RT [16]
- Physician preference and training [3,7,14]
- Accessibility of the RT facility (public transport) [14]
- Socioeconomic Status (SES)
  - o higher SES corresponds to increased RT utilisation [3,7,8,13-17]
- Level of patient education [2,7,14,17]
- Age
  - o Younger more likely to undergo RT [2,4,14]
  - o Older more likely to undergo RT [16]
- Hospital reputation [14]
- Referral patterns [8,14]
- Health insurance [2,4,8,13]
- Marital status
  - o Married more likely to undergo RT [4]
  - o Social support [13,15]
- Travel subsidy or reimbursement [7,9]
- Culture [7,14]
- Race
  - o Caucasian population are more likely to undergo RT [2,4,17]

Discussion

The findings of this review suggest that geographical distance to RT facilities is a barrier to RT treatment. The majority of the studies included found that with increased distance to the RT facility, there was lower utilisation of RT as a treatment. One study conducted in Queensland, Australia reported conflicting findings, suggesting that with increasing distance to RT facilities there was higher utilisation of RT. This study focussed specifically on the prostate cancer population in Queensland, which is often an older population and therefore may have other factors that influence RT accessibility, such as retirement, income, and doctor preferences, whereas other studies often looked at cancer patient populations in younger cohorts. Older populations may not have to factor in time away from employment, and may have family they can reside with that live in regional centres. They may have previous exposure to hospitals and specialists, and therefore may have alternative factors that impact on preferences for location. [16] The findings of this study were potentially also limited by confounding bias as stated by the authors.

It is important to note that there was considerable variability in the geographical setting of the included studies. One study was conducted in a metropolitan city in the USA and the results may not be applicable to Australian settings. Interestingly, at least one study from each nation and the majority of research included in this review found that increased distance to RT facilities can act as a barrier to utilisation of RT, suggesting that this is a global phenomenon.

It would be useful to qualitatively investigate why patients select RT as their treatment option to ascertain insight into the barriers patients subjectively experience. With lower population density and lack of available RT facilities in rural areas such as Northern Queensland, there are great distances that must be traversed in order to receive life-saving treatment. Public transportation alone cannot be considered a barrier in instances where it is not available to patients, as is the case in remote areas. Therefore it is important to investigate area-specific geographical barriers, as rurality may pose other obstacles to overcome. It would also be interesting to explore whether variations exist in the acceptance of RT during the wet season when driving

conditions could be challenging. This area of cancer care deserves much attention, especially in areas with vast land and few facilities. Identifying barriers to receiving RT is crucial to addressing the needs of the population.

Limitations of the studies synthesised in this review include the fact that many studies investigated distance to treatment rather than actual road travel times, which can vary significantly in many areas in Australia due to factors such as traffic, road works, the wet season and mountainous regions. There remains controversy in the optimal methodology used to assess accessibility to treatment. The GIS methods that were cited in this review were variable in their measurement of distance, often utilising straight line methods or mile radius buffer zones, which are not representative of the course travelled by the patient and do not give a clear indication of travel time. It is likely that increasing the accuracy of GIS distance measurements, by using round distance or alternatives as opposed to straight line measurements would exaggerate rather than minimise these differences.

This systematic review has a number of limitations. Firstly, two databases were utilised in the literature search and only open-access full text manuscripts were included, therefore restricting the amount of literature reviewed. Secondly, the methodological quality of the majority of included studies was moderate. The studies examined were either of retrospective or prospective study design. Most studies identified that the decision to proceed with RT is multifactorial, and many adjusted for a limited number of confounders. An ideal study would follow each patient with a diagnosis of cancer prospectively through a questionnaire or interview to ascertain which factors act as barriers or enablers to the decision for treatment. It would then revisit the patient post treatment to assess for any changes or additional challenges met. This would be a time-intensive process which would involve long follow up of patients, and may potentially be intrusive to patients during an emotional and difficult period in their life. Finally, the scope of the literature search was expanded to include all geographical locations rather than confining the search to rural areas in Australia alone due to the paucity of literature available. The results are therefore limited in their transferability to Australian settings.

Creating new technologies to deliver better dose profiles to tumour volumes is an integral part of radiation therapy, but however precise these treatments can be, their use is of limited value to populations who are not able to access RT. [18,19] Uniquely, radiotherapy will always need to be delivered in larger centres unlike other areas of oncology where initiatives such as tele-oncology are overcoming geographical access barriers. Therefore, further work in determining the role of innovative strategies to minimise the time patients spend away from home in rural areas and the burden associated with receiving treatment would be useful. [20,21]

Conclusion

Multiple factors are considered in the decision making process to have radiotherapy versus alternative treatments and these remain individual and context specific. Access to the RT facility is one important factor considered in this review. [22] The preference for modalities is important to investigate as studies have indicated a discrepancy between evidence based optimal and actual utilisation rates of RT. [1,23,24] The multitude of factors and social context that influences the patients' choice for and satisfaction with treatment makes this a complex and significant area of research. [22,25] This review indicates that most likely rurality and increased distance from RT centres are important considerations, thus there is also the requirement for additional research into areas that may improve access for the rural cancer patient population, including travel subsidies, accommodation, and location of treatment facilities. However, there is a need for further studies, ideally prospective, and geography specific, before firm conclusions can be drawn.

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Conflict of interest

None declared.

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Table 1. *Quality assessment of articles meeting inclusion criteria. Study Quality: High (H) Moderate (M) or Low (L).*

Study	Study Design	Sample size	Control for confounders	Methodological issues
Soo J, *et al.* (2010)	Retrospective cohort study investigating all invasive prostate cancer patients diagnosed from January 1st 1986 – December 1999 and all RT treatment from January 1986-April 2005. (M)	Not reported.	Incident data and treatment data are not coincident, however prostate cancer disease time may be long and this enables lengthy follow up. (M)	No sample size and no measure of effect bias. Did not examine other factors that may impact access, e.g. resource availability. (L)
Aneja S, *et al.* (2012)	Mapping of primary care physicians in non-rural counties. (H)	2472 non-rural counties. (H)	Used a 5 year time period to account for changes in the workforce. Considered socioeconomic and demographic factors. (H)	No identified bias or problems with methodological rigour. (H)
Schroen AT, *et al.* (2005)	Retrospective cross-sectional analysis of early-stage invasive female breast cancer patients comparing distance to RT facility vs mastectomy rates. (M)	20,094 women. (H)	Large sample size study that examined distance as a single factor to investigate its influence of patient decision. Compared similar stages of breast cancer patients. (H)	As comparisons were made based on distance as the exclusive factor and with patients of similar staging, no biases were identified. (H)
Voti L, *et al.*(2005)	Retrospective analysis using GIS software to measure the distance from patient address to the facility. (M)	18,903. (H)	Considers other factors that may influence treatment choice i.e. health insurance, marital status, etc. (H)	Euclidean distance measurement used. Other factors that may promote use of mastectomy i.e. pregnancy, previous RT of the breast etc) not accounted for with retrospective registry data (L)

Cetnar JP, *et al.* (2013)	Retrospective analysis using GIS software to measure the distance from patient address to the facility. (M)	Random selection of 1096 men from 3220 eligible. (H)	Selection of patients across race/ethnicity and state specific factors. Oversampling of minorities for comparison of race and ethnicity. (H)	Non-curative treatment was deemed as hormonal therapy, active surveillance or watchful waiting, but may be the first line choice for some. (M)
Athas WF, *et al.* (2000)	Retrospective analysis using GIS software to measure the distance from patient address to the facility. (M)	1122. (M)	Use of centroids for PO BOX when ZIP codes only were available. (M)	Assumed that each patient was treated at the nearest facility. ZIP code centroids may cause a spurious result. Did not include Native American women. (L)
Underhill C, *et al.* (2009)	Self-administered survey completed by regional hospitals administering chemotherapy (RHAC). (M)	157 RHAC (98% response rate). (H)	Survey rather than retrospective analysis. (M)	Variable interpretation of the survey by participants. De-identified participants may have led to duplicated responses. Quantity of services investigated, not quality. (L)
Baldwin LM, *et al.* (2012)	Retrospective analysis of SEER data from 2000 to 2004 of breast cancer and four "other cancers". (M)	122,526 cancer patients. (H)	Addressed primary variable (urban vs rural residence) and secondary variables (poverty, low employment, low education and availability of radiation oncologist). Controlled for patient socio-demographics, and regional practice variation. (H)	Unable to use patient address from database, therefore reliant on county level distance to RT facility rather than individual travel distance. (M)
Boscoe FP, *et al.* (2011)	Retrospective analysis using GIS software to measure the distance from patient address to the facility. (M)	104,730. (H)	Both centroid distance via census tract to RT facility and residential address used. Considered confounding variables i.e. age, primary tumour etc. (H)	Incomplete radiation data limited results. Potentially underestimated distance to surgery and inaccuracies in geocoding. (M)
Williams MV, *et al.* (2009)	Analysis of a retrospective audit of wait times for RT during one week: 24 September 2007 to 30 September 2007. (M)	2504 patients excluding skin cancer (H)	A one week snapshot in time project, with little control for confounders. (L)	Primary outcome defined as 1st course of RT, as opposed to completed treatment, cure or survival. (M)
Baade PD, *et al.* (2012)	Prospective trial of men diagnosed with prostate cancer between 2005 and 2007. Data obtained via telephone and self-administered questionnaires. (H)	956 men. (M)	Prospective study. Confounding factors considered ie. demographic and Quality of Life (QoL) indicators. (H)	Stage recorded based on the patient's description of local, locally advanced, or advanced disease – recall bias may skew results (95% concordance with registry). (M)
Peipins LA *et al.* (2013)	Cross-sectional GIS and network analysis to quantify spatial accessibility to RT. (M)	282. (M)	Considered race, household income and access to a vehicle. Multimodal transport including bus, rail and wait times/walking to transport compared with personal vehicle transfer. (H)	Did not account for daily variations, traffic, parking time etc. Assumed those without a private vehicle were taking public transport and that all subjects would go to the nearest facility. (L)

Table 2. *Literature summary.*

Article	Setting	Participants	Geographical details	Results
Soo, J. *et al.*	British Columbia, Canada	Palliative prostate radiotherapy patients from January 1986 – December 2005.	Mix of urban, suburban, rural and remote.	Increased utilisation rate of RT for rural and remote patients. Increased distance to RT clinic led to less usage of RT. Opening additional RT facility increased RT utilisation. N.B. No measure of effect size given.
Aneja S, *et al.*	2472 non-rural counties in United States	Radiation oncologist, primary care physician and urologist density per 100,000 people mapped to the included counties.	Only non-rural counties considered.	Presence of a Radiation Oncologist (RO) had a significant reduction on the mortality rate of prostate cancer patients until "plateau effect". ≤1 RO: 3.65% mortality reduction, 95% CI 5.54-1.76% (p = 0.031). 2 – 4 ROs: 1.48% mortality reduction, 95% CI 2.73 – 0.23% (p = 0.045).

Schroen AT, *et al.*	Virginia, United States	All female Virginia residents diagnosed with local or regional breast cancer (SEER) between January 1st 1996 and December 31st 2000.	Variations in access to health care and SES. Mix of rural, suburban and highly urbanised areas.	Greater distance to RT decreased the likelihood of receiving breast conserving treatment (BCT), independent of tumour size ($p < 0.001$). Patients further from a RT facility were more likely to receive a mastectomy (OR = 1.45; 95% CI = 1.30 - 1.62).
Voti L, *et al.*	Florida, United States	Local stage female breast cancer patients (SEER) from July 1997 and December 2000.	Rurality index not specified, likely all urban participants.	Greater distance to a RT facility decreased RT use: OR decreased 3% per 5 mile increase in distance. Younger ages had increased utilisation of BCT, with the OR decreasing 1% per year increase in age.
Cetnar JP, *et al.*	Wisconsin, United States	Random selection of men with a confirmed diagnosis of prostate cancer in the Wisconsin Cancer Reporting System in 2004 with specified exclusions.	Mix of rural and urban setting. 95% of the population live within 15 miles of a hospital.	Rural patients were equally as likely to receive radiotherapy as their urban counterparts • Rural/urban setting OR = 1.01; 95% CI = 0.59 – 1.74 • Rural setting OR = 0.96; 95% CI = 0.52 – 1.77
Athas WF, *et al.*	New Mexico, United States	All cases of localised (SEER) breast cancer diagnosed between 1994 and 1995 in female residents of New Mexico, excluding Native American women due to lack of address.	Vast setting with large distances to travel between population districts with 12 facilities.	Lower likelihood of receiving RT post breast conserving surgery with increased travel distance. 51% living > 75miles from a facility received RT (OR = 0.26; 95% CI = 0.14-0.5) vs 82% living ≤50miles away (OR = 1.00).
Underhill C, *et al.*	All Australian states and territories except ACT	Staff self-administered cross-sectional survey administered between June and December 2005 to 161 RHAC. Responses completed by hospital manager, chemotherapy nurse, oncologist, or delegate (n=157).	Mixed urban and rural, classified under Australian Standard Geographical Classification (ASGC) Remoteness Areas (RAs).	46% of RT facilities were fully staffed with an average wait time of three weeks. The study indicated difficulties for patients and their families relating to travel and transport refunds. Shortages in the medical and radiation oncology field were identified.
Baldwin LM, *et al.*	8 states across the United States	Patients with a diagnosis of one of anal, rectal, lung, breast or cervical cancers through NCNN and SEER staging. Exclusion of male breast cancer. Years included: 2000-2004.	Mixture of rural (14,692) and urban (107,834) patients.	Older ages received less RT amongst all diagnoses. Breast cancer patients further from a RT facility had less RT utilisation compared with urban counterparts (62.1% vs 69.1%; $p \leq 0.001$). Other cancers demonstrated equal rural vs urban utilisation.
Boscoe FP, *et al.*	10 states across the United States	All early stage female breast cancer cases (SEER) from 2004 and 2006.	Mixture of settings: 73% 0-15km from RT facility, 5.4% 30-45km, <1% >100km from facility.	With further distance from a RT facility, rate of mastectomies increased (in the group >60km from surgery and <30km from RT, 42.2% received mastectomy rather than BCT; OR = 1.27). Opening of a new RT facility was associated with a reduction in mastectomy rates from 61% to 45%.
Williams MV, *et al.*	United Kingdom: England, Scotland, Wales, Northern Ireland	2504 RT patients who were newly commencing RT during the week of September 24, 2007.	Mix of urban and rural settings.	Variations were observed in wait times, access rates and dose fractionation across the UK. Deprivation (economic, social, and housing indices) affects access rates.
Baade PD, *et al.*	Queensland, Australia	Men with newly diagnosed prostate cancer residing in Queensland (Brisbane, Townsville, and Mackay). Data extracted from registry.	Mixture of regional and urban areas within Queensland.	RT utilisation with adjuvant androgen deprivation therapy increased with older age and greater distance from a RT facility. RT alone had greater utilisation in retired patients, those who were asymptomatic, had low Gleason scores/localised prostate cancer, or who had a smoking history. Prostatectomy results were ↑ in patients who lived closer to the RT facility.
Peipins LA *et al.*	Atlanta, Georgia metropolitan area, United States	Year 2000 Census data for all women ≥40 years old in specified counties.	Urban only with access to public transportation options. 18 RT facilities were geocoded.	Public transportation resulted in a travel time of 56 minutes vs private transport which took 8 minutes, though the distances were similar. Public transport remains a barrier to accessibility of RT.

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Chronic obstructive pulmonary disease: extrapulmonary manifestations, pulmonary rehabilitation programs and the role of nutritional biomarkers on patient outcomes

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Melissa has always had a strong interest in health and initially pursued this interest by undertaking a Bachelor of Biomedical Science. As she has a passion for lifestyle and preventative medicine, she completed her third year research project on chronic obstructive pulmonary disease. As a doctor Melissa would like to focus on preventative medicine and research.

Until recently, chronic obstructive pulmonary disease (COPD) received little research attention, as it was perceived as a self-inflicted condition that was difficult to treat. As COPD now affects one in seven Australians over 40 and is a leading cause of disease burden and death, research into this condition has intensified. Traditionally, research focused on the pulmonary effects and yet it is starting to emerge that the condition encompasses a range of extrapulmonary manifestations, such as weight loss and skeletal muscle dysfunction, which significantly affect the health and functioning capacity of COPD patients. There are many unanswered questions about the disease process and the role of the extrapulmonary manifestations. The aim of the current review is to explore two critical extrapulmonary manifestations of COPD: weight loss and skeletal muscle dysfunction, to investigate how pulmonary rehabilitation aims to improve these pathological processes and, lastly, to investigate the role of nutritional biomarkers and how these may predict outcomes in the pulmonary rehabilitation programs. Ultimately, it is anticipated that research into nutritional biomarkers may lead to the development of a screening tool that can be used to identify COPD patients who may benefit from nutritional supplementation prior to the commencement of a pulmonary rehabilitation program. It is hoped that identifying and managing those patients that require nutritional support will lead to greater improvements in rehabilitation and overall quality of life.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic obstructive lung disease, primarily caused by smoking. It affects one in seven Australians over 40 [1] and is a leading cause of disease burden and death. [2-4] The morbidity and mortality rates associated with COPD are continuing to increase, and it has been predicted that COPD may be the third most common cause of death worldwide by 2020. [5,6] In the past, COPD has been perceived as a self-inflicted condition, which was difficult to treat. Although the perceptions surrounding COPD have changed and research has shed more light on the disease processes, there are still many gaps in the scientific knowledge regarding this condition.

One such gap, which has only recently been explored, is the role of extrapulmonary manifestations associated with COPD. Previously, clinicians and researchers solely focused on the structural and functional changes occurring in the pulmonary system of patients with COPD. However, in recent years, it has become increasingly evident that the disease encompasses a range of other manifestations outside the lungs, including weight loss and skeletal muscle dysfunction. [7] Weight loss, which is a very common manifestation in patients with COPD, causes a reduction in respiratory and skeletal muscle function, which is associated with reduced quality of life and increased mortality rates. [8] Weight loss, skeletal muscle dysfunction and some of the other manifestations associated with COPD can be managed through pulmonary rehabilitation programs, although these are costly, time consuming and individual success is highly variable. [9] Furthermore, there is currently no dedicated funding for these programs in Australia. [10]

In order to improve the effectiveness and outcomes achieved

through pulmonary rehabilitation programs, researchers have begun investigating the role of nutrition in COPD patients. Ultimately, it is anticipated that the identification of important nutritional biomarkers that predict improved outcomes in pulmonary rehabilitation, may lead to the development of nutrient supplementation strategies to improve success in rehabilitation programs and optimise the quality of life of patients with COPD. The aim of the current review is to explore two critical extrapulmonary manifestations of COPD: weight loss and skeletal muscle dysfunction, to investigate how pulmonary rehabilitation aims to improve these effects and lastly, to investigate the role of nutritional biomarkers in COPD and how these may predict outcomes in the pulmonary rehabilitation programs.

Extrapulmonary manifestations

Recent research has found that patients with COPD suffer a range of extrapulmonary manifestations that were not previously related to the condition. Two of the major extrapulmonary manifestations seen in COPD patients that have a critical impact on quality of life and prognosis are weight loss and skeletal muscle dysfunction.

Weight loss

Although traditionally research focused on the pulmonary effects of the disease, it was evident as early as the 1960's that a low body weight and weight loss were associated with an increased mortality rate in COPD patients. [11] However, at the time weight loss was believed to be only associated with the terminal phase of the disease, and hence it was considered inevitable and irreversible. [11] Currently, excessive weight loss, especially loss of fat-free mass, is very common in COPD patients and is associated with poor functional capacity, reduced quality of life and increased mortality. [8] Although the exact cause of excessive weight loss in COPD remains unclear, the proposed mechanisms include low testosterone levels, increased pro-inflammatory cytokines and increased catecholamine synthesis. [12-14]

Skeletal muscle dysfunction

A common extrapulmonary manifestation that significantly affects the quality of life of a COPD patient is skeletal muscle dysfunction. Skeletal muscle dysfunction is characterised by increased muscle fatigability, and a reduction in muscle endurance and strength. [15] In many studies, body mass index (BMI) (which is calculated as weight/height squared in kg/m^2) is used as a basic indicator of weight loss

or possible muscle alterations, although these measures can be further investigated by evaluating skeletal muscle strength and body composition. [16] COPD patients with skeletal muscle dysfunction have increased mortality rates and are likely to place a significant burden on healthcare resources. [17,18] The precise mechanisms causing skeletal muscle dysfunction in COPD patients are still unclear, although several factors that may contribute include sedentary lifestyle, nutritional abnormalities, tissue hypoxia, systemic inflammation, skeletal muscle apoptosis, oxidative stress, tobacco use and medications. [7] In patients with COPD, skeletal muscle dysfunction is characterised by two different phenomena: (1) net loss of muscle mass; and (2) dysfunction or malfunction of the remaining muscle. [7] One of the key features involved in the loss of muscle mass is increased protein catabolism. The major pathway involved in the degradation of proteins, which relates to muscle wasting, is the ATP-ubiquitin dependent proteolytic system (Figure 1). [19] This system can be activated by several factors such as cytokines, glucocorticoids, acidosis, inactivity or low insulin levels. [20-22] Following the activation of this pathway, proteins are marked for degradation by ubiquitination, and then they are recognised and processed in the proteasome. [4] Pro-inflammatory cytokines may also play a role in muscle deterioration by producing reactive oxygen species, which modify skeletal muscle proteins allowing them to be easily degraded by the proteasome. [4]

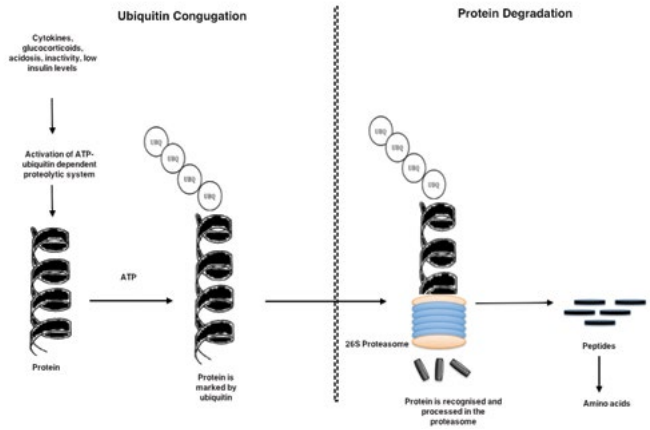

Figure 1. *ATP-ubiquitin dependent proteolytic system. A trigger such as cytokines, glucocorticoids, acidosis, inactivity or low insulin levels causes the activation of this pathway. Initially, proteins are conjugated with ubiquitin and then they are recognised and bound to the proteasome. The protein enters the proteasome, which contains multiple proteolytic sites. Peptides are then released from the proteasome and are rapidly degraded into amino acids by peptidases in the cytoplasm. The ubiquitin is released and is reused. [23]*

The exact trigger for the development of the extrapulmonary manifestations is unknown, although it is thought that the process is mediated by systemic inflammation. [24] As COPD is a condition primarily caused by smoking, it could be questioned whether smoking is the major cause for the development of systemic inflammation and in turn the extrapulmonary manifestations. As multiple studies have found that persistent inflammation is still present in ex-smokers, [25] it is possible that tobacco smoke may initiate the inflammatory process, however it does not explain the sustained inflammatory state evident in COPD patients. [24] Instead, it is possible that the systemic inflammation arises from pathological changes occurring within the lungs of COPD patients. [24] This is supported by other studies that have found that inflammation is still present in COPD patients who have ceased smoking. [26,27] In light of these observations, some researchers have speculated that part of the COPD pathogenesis process involves an autoimmune component. [28]

The discovery that COPD encompasses both pulmonary and systemic manifestations has created new possibilities for rehabilitation and treatment targets. As weight loss and skeletal muscle dysfunction are reversible and treatable, pulmonary rehabilitation programs have been reorientated in order to focus on improving skeletal muscle function and the overall quality of life of COPD patients.

Pulmonary rehabilitation programs to improve patient outcomes

In response to the growing prevalence and burden of COPD, the Australian Lung Foundation and Thoracic Society of Australia and New Zealand developed clinical guidelines (COPDX) for the diagnosis and management of COPD. [29] One of the main aims of COPDX is to optimise patient function using pulmonary rehabilitation programs. [29] Pulmonary rehabilitation programs are composed of exercise training, behavioural and psychosocial interventions and nutritional therapy. [30]

Exercise training

Prior to the work by Barach *et al.* [31] in the 1950's, who suggested that exercise may be beneficial, the only recommendations for the management of respiratory conditions were rest and avoiding breathlessness. [32] Since this suggestion, there have been many experimental findings, randomised controlled trials and observations supporting the benefits of exercise training for patients with COPD. Based on the most recent evidence, patients with COPD undergoing pulmonary rehabilitation should participate in exercise training at least 2-5 days per week, for at least 20-30 minutes per session, over an 8-12 week period. [33, 34] Exercise programs involve endurance and strength training, mainly focusing on the lower limbs. [30] In patients with COPD, exercise training has been shown to significantly improve exercise tolerance and endurance time and it is also able to improve or reverse the physiological, metabolic and structural skeletal muscle abnormalities seen in COPD patients [35], suggesting that pulmonary rehabilitation is an anabolic stimulus. [36] Although, it is unknown how pulmonary rehabilitation improves skeletal muscle dysfunction and the role of specific nutrients during this process.

Nutritional approaches to improving muscle function and body composition in COPD

The role of nutritional therapy in the management of COPD has changed dramatically during the past twenty years. Although it was widely known that a large proportion of COPD patients experienced significant weight loss, it was viewed as irreversible and nutritional support was not considered. [37] This concept has been challenged by recent studies, which have revealed that nutritional depletion affects functional performance and exercise intolerance. [37] After this discovery, many trials have investigated the benefits and effects of nutritional support in patients with COPD, although the initial results from these studies were disappointing. A meta-analysis of the available literature conducted by Ferreira *et al.* [38] concluded that nutritional support, defined as any caloric supplement administered for more than two weeks, had no significant effect on 6-min walk distance, anthropometric measures, respiratory muscle strength, weight gain or FEV_1. These results led to the suggestion that in order to improve muscle mass and physiologic function, nutritional support must be combined with an anabolic stimulus such as exercise training. [39] In a large clinical trial combining nutritional therapy (daily high caloric supplement (420 kcal)) with an 8-week pulmonary rehabilitation program, patients showed an increase in body weight and a significant improvement in fat-free mass and respiratory muscle strength. [40] These results were further supported by a more recent study by Creutzberg *et al.* [39], who observed that the combination of nutritional therapy with pulmonary rehabilitation was effective in improving physiological measures such as body composition, muscle function, exercise capacity, serum protein, as well as the health status and well-being of patients with COPD. [39] Since the use of nutritional support has been shown to be beneficial, research needs to shift towards investigating the effectiveness of different types of nutrients and how these may be used in combination with pulmonary rehabilitation programs in order to maximise patient outcomes.

Protein supplementation

There are two main pathways involved in the synthesis and breakdown

of proteins (Figure 2) and recent research has shown that the loss of fat-free mass in patients with COPD is caused by an imbalance between these two pathways. A reduction in fat-free mass causes the loss of protein-rich tissues, particularly skeletal muscle [36] and the imbalance in protein metabolism leads to increased whole-body protein turnover. [41] This has led researchers to investigate the use of protein supplementation in improving fat-free mass in COPD patients.

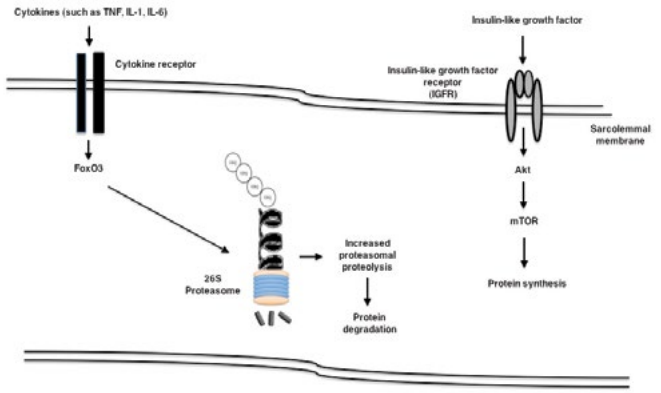

Figure 2. *Mechanisms of protein synthesis and degradation in skeletal muscle. The balance between protein synthesis and degradation determines whether muscles hypertrophy or atrophy. If hypertrophy occurs, protein synthesis exceeds degradation, as the Akt pathway stimulates protein synthesis and the FoxO pathway is inactivated. In certain disease states, such as muscle wasting, insulin signalling is suppressed, and therefore the Akt pathway is not activated and protein synthesis cannot occur. The FoxO pathway is activated and proteins are degraded in the proteasome. [42-44]*

In skeletal muscle, the regulation of protein initiation, translation and synthesis relies on the activation of two signalling proteins called the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK). [45] In a study by Fujita *et al.* [45] Protein supplementation, which provides the essential amino acids necessary for protein synthesis, alters the phosphorylation status of AMPK and mTOR signalling proteins, and increases the synthesis of proteins in healthy adults. As mentioned previously, for patients with COPD, nutritional supplementation must be combined with an additional anabolic stimulus in order to be effective and therefore recent studies have investigated the effectiveness of protein supplementation combined with exercise training. Laviolette *et al.* [46] conducted a study observing the effects of supplementation with pressurised whey or casein combined with an 8-week exercise-training program in patients with COPD. From the study, they concluded that combining whey supplementation with exercise training caused an improvement in exercise capacity (cycle endurance time), fatigue and emotional control. [46] Although these results are promising, there is emerging evidence that other nutrients such as vitamin D and B, calcium, zinc, magnesium, fatty acids and antioxidants can influence lung function and stimulate the anabolic pathways involved in protein synthesis and muscle function.

Vitamins

Vitamin D

One of the first studies to investigate the association between vitamin D and muscle metabolism was by Birge and Haddad [47], who observed that 25-hydroxy vitamin D altered muscle metabolism causing an accelerated incorporation of amino acids into muscle protein. They postulated that vitamin D acts directly on muscle [47] and this theory was confirmed in 1985, when a vitamin D receptor (VDR) was discovered in cultured rat myoblast cells. [48] Further research has discovered VDR in a range of tissues, and recently, it was isolated from human skeletal muscle. [49] Recent studies have shown that COPD patients, particularly those with severe COPD, have low levels of vitamin D. [50] In order to investigate the link between vitamin D depletion and muscle function, Bjerk *et al.* [51] performed a randomised pilot trial in which patients with COPD were supplemented with vitamin D for 6 weeks. Although the supplementation group had a significant increase in mean vitamin D levels compared to the control, there were no significant improvements in physical performance or respiratory symptoms. [51]

Vitamin B

A recent study examining hyperhomocysteinaemia discovered that COPD patients had reduced plasma concentrations of vitamin B, particularly folate [52], which is an essential co-factor involved in protein synthesis. [53] Another study found an association between folate intake and lung function. In this study, participants with COPD had lower folate levels than controls, and their folate intake was below the recommended dose. [54] Based on epidemiological data, it has been suggested that an increased folate intake could lead to reductions in the prevalence of COPD and breathlessness. [54]

Minerals

Calcium, Zinc and Magnesium

Currently, there is very limited human research on the role of minerals in muscle function and most of the available data is based on experimental animal models. Early evidence of the role of calcium in protein synthesis emerged from experimental rat studies, which revealed that maintenance of optimal rates of protein synthesis was dependent on the availability of calcium. Furthermore, calcium depletion led to the inhibition of protein synthesis, which was characterised by a reduced rate of peptide chain initiation. [55] Recently, it has been identified that an increase in the concentration of intracellular calcium triggers the activation of the mTOR pathway, leading to skeletal muscle hypertrophy. [56]

Zinc and magnesium are essential minerals required for growth in humans. [57,58] Both minerals play an important role in the synthesis of proteins, with deficiencies leading to the down-regulation of protein synthesis. [59] An experimental study revealed that protein synthesis in muscle was inhibited in zinc deficient rats [60] and a more recent study confirmed these results, by finding a reduction in protein synthesis and enhanced protein degradation in muscle tissue from zinc-deficient rats. [59] Unfortunately, the literature on the calcium, zinc and magnesium levels of COPD patients is limited and further research is warranted.

Fatty acids

In order to prevent or reverse muscle loss, interventions must target the abnormal anabolic pathways. The dysfunctional anabolic pathway is partly caused by defects in the anabolic signalling cascade in muscle, such as decreased activation of the mTOR signalling pathway. [61,62] In various animal studies, fish-oil-derived omega-3 fatty acids have been used to target the protein synthesis pathways. In one study, growing steers received feed enriched with menhaden oil, which increased the activation of anabolic signalling proteins in muscle. [63] In a more recent human study, omega-3 supplementation in older adults increased the rate of muscle protein synthesis, which suggests that omega-3 fatty acids reduce anabolic resistance. [64] It is not entirely clear how omega 3-fatty acids act on the muscle protein synthesis pathway, although it may be partially mediated via increased activation of the mTOR signalling pathway. [64] Based on the limited evidence, supplementation with fatty acids may be a beneficial treatment, although as of yet there are no published studies exploring this. [65]

Antioxidants

Antioxidants are considered to be protective factors in the lungs as they can scavenge endogenous and exogenous reactive oxygen species. [66] There is increasing evidence that oxidative damage and the failure of antioxidants to protect lung tissue are partly responsible for the development of COPD. [67,68] Studies examining the effect of antioxidant supplementation on oxidative damage and pulmonary function are incredibly conflicting. Habib *et al.* [69] observed that vitamin E supplementation had no effect on pulmonary function. Another study found that when used in addition to standard therapy,

an antioxidant supplement (containing vitamin A, C, E, zinc, copper, selenium and manganese) had a positive effect on the oxidant-antioxidant balance in COPD patients, however it had no effect on pulmonary function tests. [70]

Although research has focused on oxidative stress caused by the production of free radicals in the lungs in patients with COPD, there is emerging evidence that exercising skeletal muscle may also produce free radicals and contribute to oxidative stress. [71] Free radicals produced during exercise depress muscle force production [72] and increase the discharge frequency of thin-fibre muscle afferents [73] and thus, targeting oxidative stress may improve exercise tolerance and reduce the development of fatigue.

Based on all of the available evidence, it is apparent that patients with COPD suffer from nutritional abnormalities, which may contribute to muscle dysfunction and weight loss. An altered nutritional status may affect a patient's ability to synthesise protein and lead to less effective outcomes in pulmonary rehabilitation programs. Although some studies have shown that protein supplementation combined with exercise training can be beneficial, evidence is limited and somewhat conflicting. Apart from protein and amino acids, other nutrients have a direct effect on the synthesis of protein and the function of skeletal muscles, although research into these effects is lacking. Nutritional support is an important part of COPD management, however there is no definitive evidence about what types of nutrients should be used and how they may influence the outcome of rehabilitation programs. Ongoing and future research is expected to provide further insight in this area, and hopefully improve the quality of life and survival of COPD patients.

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Conflict of interest

None declared.

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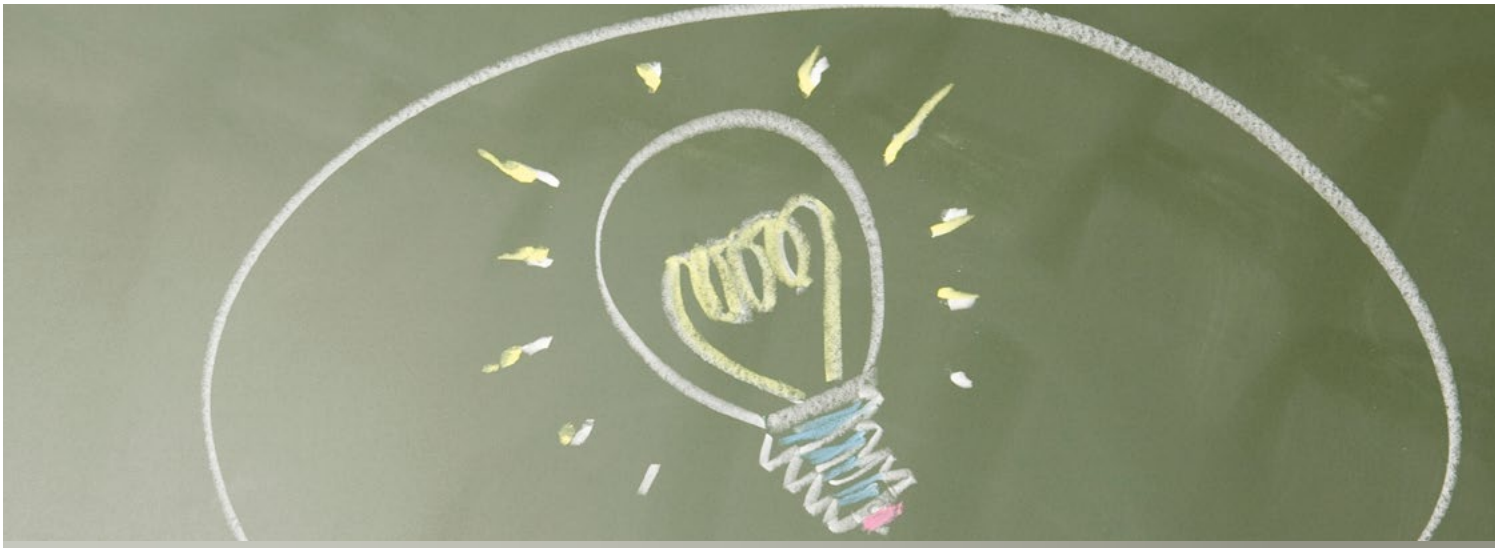

Stroke prevention in non-valvular atrial fibrillation: advances in medical therapy

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Karishma has currently started her internship year at Blacktown Hospital in NSW. Although still undecided about a career path, Karishma is very interested in obstetrics and gynaecology as well as internal medicine especially cardiology, gastroenterology and endocrinology.

Introduction: The aim of this article is to review the literature and evaluate the evidence of the different medical treatments for stroke prevention in non-valvular atrial fibrillation. **Methods**: A literature search using MEDLINE plus OvidSP, PubMed, CINAHL and the New England Journal of Medicine databases was performed with the search terms stroke prevention, atrial fibrillation, anticoagulation, novel anticoagulants, direct thrombin inhibitors and factor Xa inhibitors. **Results**: Eight studies were identified which assessed the efficacy and adverse effects of the different treatments in stroke prevention in those with non-valvular atrial fibrillation. **Conclusion**: Evidence suggests that target specific oral anticoagulants have similar or superior efficacy compared to warfarin for stroke prevention in patients with non-valvular atrial fibrillation, however more long term follow-up studies are required.

Introduction

Atrial fibrillation (AF) is defined as an arrhythmia caused by rapid and irregular depolarisation and contraction of the atrium and is the most common sustained cardiac arrhythmia. [1] It is classified into three subgroups: paroxysmal, persistent and permanent. [2] Paroxysmal AF is recurrent AF where the rhythm disturbance terminates spontaneously within seven days, persistent AF is where the rhythm disturbance is sustained for greater than seven days, and permanent AF is where the rhythm disturbance has lasted for longer than one year and not been terminated by medical intervention. [2] AF affects 1–2% of the general Australian population and importantly this incidence increases with age, with 9% of people over the age of 80 being affected. [3] Although often considered a benign arrhythmia, AF is a major cause of morbidity and mortality. [3] The most feared complication is systemic embolism leading to stroke. [3] AF accounts for 1 in 5 strokes, [4] with morbidity and mortality determined by the vessel that is occluded and the extent of ischaemia. This is reflected in the stroke prognostic scores (PLAN) which take into account preadmission comorbidities, level of consciousness, age and neurologic deficit, and predict patients who will have a poorer outcome after hospitalisation for acute ischaemic stroke. [5] Treatment of AF consists of rate and rhythm control as well as antithrombotic therapy to prevent stroke.

There are multiple mechanisms responsible for the increased risk of thromboembolic stroke in individuals with AF. Firstly, altered atrial contraction results in blood stasis in the atria. Secondly, the left atrial appendage acts like a pocket to promote platelet aggregation and thrombus formation. Changes in systemic circulation also increase the risk of clot formation.

Evidence-based guidelines support the use of warfarin and aspirin as the two leading medical therapies for stroke prevention in AF. [6] Warfarin has been used as the mainstay treatment for the last 60 years, but this has not been without problems. There has been a recent emergence of new therapies, with 20 new novel anticoagulants currently under investigation, many showing promising results in phase III trials. [7] These drugs have been collectively referred to as new oral anticoagulants (NOACs), and more recently, target specific oral anticoagulants (TSOACs). Recently in Australia the Therapeutic Goods Administration (TGA) has approved a direct thrombin inhibitor, dabigatran, and two factor Xa inhibitors, rivaroxaban and apixaban, for stroke prevention in AF patients. [8,9] The recent attention on emerging treatment options makes us question what the evidence is behind their use in the context of stroke prevention in AF patients as compared to traditional therapies.

Objective

The objective of this review was to compare the efficacy and safety profile of TSOACs, in particular the TGA-approved TSOACs, dabigatran, rivaroxaban and apixaban, to standard medical therapy for stroke prevention in AF.

Methods

Search criteria

A literature search of MEDLINE plus OvidSP, NCBI PubMed and CINAHL via EBSCOhost and the New England Journal of Medicine databases was conducted. Limits were set to include articles published between the years 1999 to current to reflect modern practice. The search terms used were “stroke prevention” AND “atrial fibrillation” AND “anticoagulation” AND “novel anticoagulants” OR “direct thrombin inhibitors” OR “factor Xa inhibitors”. The reference lists of included studies were also manually reviewed to identify additional relevant literature.

Eligibility criteria

Studies were included if they assessed the efficacy and safety profile of TSOACs as well as standard medical therapy for stroke prevention in those with non-valvular AF. Only studies conducted in humans and published in English were included. There was no restriction on publication type and no limit on study size.

Results and discussion

Search results

Database and reference searches yielded 1149 articles of which 89 full text papers were selected and reviewed. 81 articles were excluded, mainly due to lack of focus on the standard medical therapies and TGA-approved TSOACs (dabigatran, rivaroxaban and apixaban) in those with non-valvular AF. Based on the inclusion and exclusion criteria, eight studies were eligible for inclusion in the review. These studies varied in their characteristics with participant groups. Of these studies there were two meta-analyses (level I evidence), one prospective open-label randomised trial, one randomised double-blind controlled trial (level II evidence) and four randomised controlled trials (level II evidence).

Current guidelines

Treatment for stroke prevention in patients with AF is guided by risk stratification by the $CHADS_2$ or the CHA_2DS_2-VASc scores. [10] In the $CHADS_2$ score, patients are given one point each for age greater than 75, hypertension, diabetes mellitus and heart failure, and two points

if they have a history of previous stroke or transient ischaemic attack (TIA). A $CHADS_2$ score of zero confers low risk, one confers moderate risk and a score of equal or greater than two means the patient is at high risk of stroke. [10] In those with a $CHADS_2$ score of 0, there is a risk of 0.6 events per 100 person-years and this increases to 13.0 events per 100 person-years in those with a $CHADS_2$ score of 6. Compared to the $CHADS_2$ score, the CHA_2DS_2-VASc score for non-valvular AF has a larger score range (0 to 9) and incorporates a greater number of risk factors (female sex, 65 to 74 years of age, and vascular disease). The $CHA2DS_2$-VASc score has been shown in several studies to better discriminate stroke risk among patients with a baseline $CHADS_2$ score of 0 to 1, as well as in older women. Furthermore there are a range of scores to identify patients at increased bleeding risk. These include the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalising ratio (INR), Elderly, Drugs/alcohol concomitantly) and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) scores to name a few. Although helpful clinically, they are not used in the current treatment guidelines. [11]

In Australia, current therapeutic guidelines recommend that those with a $CHADS_2$ score of 0 should be treated with aspirin or no therapy, with a preference for no therapy. Those with a score of 1 should be treated with oral anticoagulation with warfarin, dabigatran or aspirin with a preference for oral anticoagulation. Those with a score of 2 or more would benefit from oral anticoagulation with warfarin or dabigatran. Warfarin should be maintained at therapeutic levels with INR between 2.0 and 3.0 with a target INR of 2.5. [10] Although not in the guidelines, the TGA has approved the use of rivaroxaban 20mg once daily and apixaban 5mg twice daily for stroke prevention. [8,9]

The European Society of Cardiology recommends that the CHA_2DS_2-VASc score should be used to assess stroke risk. Warfarin is the drug of choice in those with mechanical heart valves. In those with a prior stroke, TIA, or CHA_2DS_2-VASc score greater than 2, oral anticoagulation is recommended with warfarin, dabigatran, rivaroxaban, or apixaban. If therapeutic INR is unable to be maintained then a direct thrombin inhibitor or factor Xa inhibitor is recommended. In those with non-valvular AF and CHA_2DS_2-VASc score of 0, the guidelines state that it is reasonable to omit antithrombotic therapy. In those with a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered. [12]

The American College of Cardiology / American Heart Association recommend that antithrombotic therapy should be based on the presence of risk factors for stroke and thromboembolism. They recommend that the $CHADS_2$ stroke risk stratification should be used to assess stroke risk. In patients with a $CHADS_2$ score of greater than 2, long term oral anticoagulation therapy, for example with warfarin, is recommended. In patients with a $CHADS_2$ score of 0 to 1, they recommend CHA_2DS_2-VASc be used to further stratify their risk. They further go on to state that in those with a CHA_2DS_2-VASc score of 1, aspirin may be considered rather than oral anticoagulation therapy. [11] The importance of shared decision-making, the patient's preferences as well as discussion of risks of stroke and bleeding is recommended in all guidelines. [11,12]

Traditional medical therapy

Vitamin K antagonist – warfarin

Historically warfarin has been the cornerstone of pharmacological therapy in stroke prevention in those with AF. [13] Since approval in 1954 warfarin has been the leading oral anticoagulant choice especially in those at high risk. [14]

Warfarin interferes with the cyclic interconversion of vitamin K and its 2,3-epoxide. Vitamin K is a cofactor in the pathway of synthesis of vitamin K-dependent coagulation factors (factors II, VII, IX, and X). Warfarin may have a procoagulant effect during initiation of treatment due to earlier clearance of the protein C (half-life 8 h) which is an antithrombotic, compared to prothrombin (50–72 h) which is a prothrombotic. [15] The dose is titrated with the level of the INR and hence INR needs to be monitored regularly. [16] Treatment with vitamin K will reverse the anticoagulant effect of warfarin. Plasma products such as fresh frozen plasma and prothrombin complex concentrate may also be used when urgent reversal is required. This is seen as one of the main advantages in choosing this treatment. [14]

The efficacy of warfarin has been extensively proven. In six trials of warfarin versus placebo warfarin showed a 62% reduction in stroke. Number to treat analysis revealed that one would need to treat 32 patients for one year to prevent one stroke. [2,17]

Although warfarin has been widely proven to be efficacious in stroke prevention, it still remains under-prescribed. The Canadian Stroke Network study found that in high-risk patients with pre-existing AF with no contraindications to anticoagulation, only 40% received warfarin and the majority were not in the therapeutic range. [18]

Treatment with warfarin is not without limitations. At supra-therapeutic levels warfarin predisposes patients to fatal bleeding. A meta-analysis by Haft *et al.* found that, compared with placebo, adjusted-dose warfarin was associated with a 130% increase in the relative risk for major extracranial haemorrhage. [19] The therapeutic range is relatively narrow, resulting in the need for frequent monitoring. [19,20] As one can imagine patient compliance becomes a big factor in the success of treatment.

In addition to this, keeping the INR in therapeutic range is challenging and the dose of warfarin is subject to change as there are many drug–drug, drug–disease and drug–food interactions. Certain medications such as rifampicin, metronidazole and amiodarone can affect INR. Foods that have high vitamin K content such as leafy green vegetables can potentially reverse the anticoagulant effects of warfarin. Medical conditions like diarrhoea, fever, heart failure, liver disease and hyperthyroidism can potentiate warfarin's anticoagulant effects whereas hypothyroidism can reduce its effects. [16]

Furthermore what cannot be underestimated is the deep-seated fear in clinical practice of the adverse effect of fatal bleeding leading to reluctance in prescribing. Practitioners tend to overestimate warfarin's bleeding risk while at the same time underestimate the benefits in stroke prevention. [18]

Acetylsalicylic acid – aspirin

Acetylsalicylic acid directly and irreversibly inhibits the activity of cyclooxygenase (COX-1 and COX-2) to reduce the formation of thromboxane A2 and inhibit platelet aggregation. [21] A pooled analysis of the AFASAK I and Stroke Prevention in Atrial Fibrillation (SPAF) I studies on aspirin for stroke prevention found that aspirin reduced the risk of stroke by 36%. [17]

Like warfarin, the concern with aspirin, especially in the elderly, is the risk of fatal bleeding. The BAFTA trial found that elderly AF patients randomised to warfarin treatment experienced a 52% lower risk of fatal or disabling stroke or intracranial haemorrhage compared to aspirin. This was further confirmed by the WASPO trial which reported higher rates of adverse events and intolerance to aspirin in 80–90–year-old patients. Interestingly the effect of aspirin on stroke attenuates with age and randomised controlled trials found no evidence that aspirin reduces the risk of cardioembolic stroke in those greater than 80 years old. [2]

Warfarin vs. aspirin

There is significant evidence to suggest superiority of warfarin to aspirin in primary stroke prevention. Five randomised controlled trials showed that adjusted-dose warfarin resulted in a relative risk reduction of 36% when compared with aspirin. Meta-analysis of 13 trials found that warfarin was superior to both aspirin and placebo in reducing the risk of stroke or embolism. [13] For combination therapy, results from the SPAF III trial found a relative risk reduction of 74% with standard intensity warfarin (INR 2.0–3.0) compared to aspirin plus low intensity warfarin (INR 1.2–1.5). [17]

Dual antiplatelet therapy (aspirin plus clopidogrel)

Dual antiplatelet therapy has also been studied in two large randomised control trials: ACTIVE-W and ACTIVE-A. [2,22] ACTIVE-W compared aspirin plus clopidogrel with warfarin. The trial was stopped early due to the clear superiority of warfarin with the risk of stroke lower in those treated with warfarin as compared to dual antiplatelet therapy (3.9% vs. 5.6% per year). The risk of major haemorrhage was similar between the two groups but minor bleeding was significantly higher in the dual antiplatelet group. [22]

New advances in therapy: target-specific oral anticoagulants

Direct thrombin inhibitors - dabigatran

Dabigatran is a direct competitive inhibitor of thrombin, blocking directly at factor IIa, the final step in blood coagulation. The onset of action is two hours and the half-life is 12–17 hours. [7] Dabigatran is eliminated by renal excretion, making its use difficult in patients with renal insufficiency. [13]

The Randomised Evaluation of Long Term Anticoagulation Therapy (RE-LY) study was a multicentre, prospective open label randomised controlled trial which included patients with non-valvular AF at moderate to high risk of stroke or systemic embolism as determined by the $CHADS_2$ score. 18113 patients were randomised to receive dabigatran 110 mg twice daily, 150 mg twice daily or warfarin. The mean duration of follow up was two years. The trial found that dabigatran 110 mg twice daily was non-inferior to warfarin in preventing stroke or systemic embolism (1.53% vs. 1.69% per year, p<0.001) and superior to warfarin in regards to major bleeding (2.71% vs. 3.36% per year, p=0.003). The higher dose of 150 mg twice daily was found to be superior to warfarin in preventing stroke and systemic embolism (1.11% vs. 1.69% per year, p<0.001) and non-inferior to warfarin in terms of major bleeding. Although both doses resulted in fewer intracranial haemorrhages compared to warfarin, there was a higher incidence of gastrointestinal bleeding in the higher dose group. [7,23] Importantly discontinuation rate was also higher in the dabigatran group with the most common reason being gastrointestinal symptoms. [6,7,14,20,23–25]

Furthermore the study by Salazar *et al.* found that direct thrombin inhibitors were as efficacious as vitamin K antagonists for the outcomes of vascular death and ischaemic events. Importantly they found that only the dose of dabigatran 150 mg twice daily was found to be superior to warfarin. Direct thrombin inhibitors were also associated with fewer major haemorrhagic events. Interestingly, adverse events occurred more frequently with direct thrombin inhibitors and led to the discontinuation of treatment. [26]

Factor Xa inhibitors

These drugs bind directly to the active site of factor Xa, which is located on the convergence of the intrinsic and extrinsic pathways. This inhibits thrombin formation from both pathways and inhibits thrombin formation upstream. [7]

Rivaroxaban

Rivaroxaban is a potent selective reversible factor Xa inhibitor which inhibits free factor Xa. The time to peak concentration is three hours with a half-life of 9–13 hours. [7] Rivaroxaban is partially metabolised by the cytochrome P450 (CYP450) system making it subject to drug interactions, and two-thirds is eliminated by the kidneys. [6,7,14]

The Rivaroxaban once daily Oral direct factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was a randomised double-blind study enrolling 14264 patients allocated either rivaroxaban 20 mg once daily (or 15 mg once daily if creatinine clearance was 30–49 ml/min), and dose-adjusted warfarin with target INR 2.0–3.0. [7,27] ROCKET-AF was different from other trials due to the medical comorbidities of the study population: 55% of the participants had a history of stroke, 62% had heart failure and 87% had a CHADS2 score of 3 or greater, indicative of a high risk population. [7] ROCKET-AF found rivaroxaban to be non-inferior to warfarin for stroke and systemic embolism (1.7% vs. 2.2% per year, p<0.001) and the rates of major bleeding were similar between the two groups (14.9% vs. 14.5% per year, p=0.44). Importantly, the rivaroxaban group had significant reductions in intracranial haemorrhage (.5% vs. 0.7%, p=0.02) and fatal bleeding (0.2% vs. 0.5%, p=0.003), suggesting that rivaroxaban may be safer than warfarin. [7,27]

Furthermore in a study by Bruins Slot *et al.* it was shown that in patients with AF, factor Xa inhibitors significantly reduced the number of strokes and systemic embolic events compared with warfarin. [28] Factor Xa inhibitors also appeared to reduce the number of major bleeds and intracranial haemorrhages compared with warfarin. [28] Further head-to-head studies of the different factor Xa inhibitors are required and are currently underway to conclusively determine the most effective and safest factor Xa inhibitor for patients with AF.

Apixaban

Apixaban is an oral factor Xa inhibitor with a half-life of 8–15 hours. [7] It is eliminated in various pathways, and among the TSOACs has the lowest renal elimination of 25%. [25] It does not inhibit or induce CYP450 therefore has a low potential for drug interactions. [7]

There have been two major studies assessing its use in stroke prevention: the Apixaban Verses acetylsalicyclic acid to prevent stroke in AF patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial and Apixiban for prevention of stroke in subjects with atrial fibrillation (ARISTOTLE) trial. [29,30]

The AVERROES trial was stopped early due to clear benefits of apixaban compared with aspirin. It included 5599 patients in whom vitamin K antagonist therapy was unsuitable. Patients were randomised to receive apixaban 5 mg twice daily or aspirin 81–325 mg once daily. Patients with apixaban had significantly lower rates of stroke and systemic embolic events (1.6% vs. 3.7%, p<0.001) with no increase in bleeding (1.4% vs. 1.2%, p=0.57). Patients receiving apixaban also had fewer cardiovascular hospitalisations. [29]

The ARISTOTLE study compared apixaban to warfarin in 18201 AF patients who had at least one other cardiovascular risk factor. This study found that the annual rate of stroke and systemic embolism was 1.27% in the apixaban group compared to 1.60% in the warfarin group (p=0.01). Apixaban was also associated with fewer major haemorrhages (2.13% vs. 3.09% per year, p<0.001) and overall adverse events were similar with a lower discontinuation rate in the apixaban group. Importantly the apixaban group had a lower mortality rate compared to the warfarin group and is the first oral anticoagulant to show a significant mortality benefit over warfarin. [30]

It is unclear which of these TSOACs is most effective and safe in patients with AF. These trials provide the strongest evidence for apixaban, however there have been no head-to-head trials comparing different TSOACs. The described studies had differing patient demographics and baseline characteristics making it difficult to make comparisons between trials. [7] Further investigation is needed before one can be said to be superior to another.

Advantages and disadvantages of target specific oral anticoagulants

The TSOACs offer many advantages over traditional therapy. They have predictable anticoagulation effects, which allow fixed dosing. [6,14] They also have a wider therapeutic index therefore avoiding the need for routine monitoring. [6] In general they have lower potential for interactions; dabigatran and apixaban in particular have fewer drug and food interactions as they are not metabolised by CYP450 isoenzymes. [7] Rivaroxaban however is metabolised to some degree by CYP450 and so there is potential for medication interactions. [7,14,19,24]

Nevertheless they too have their own limitations. Like warfarin, bleeding is the main adverse effect in all the TSOACs. A recent meta-analysis by Chai-Adisaksopha *et al.* found that, when compared with vitamin K antagonists, TSOACs are associated with less major bleeding,

fatal bleeding, intracranial bleeding, clinically relevant non-major bleeding, and total bleeding. Additionally, TSOACs do not increase the risk of gastrointestinal bleeding. [31]

The main limitation of TSOACs is the lack of specific antidotes to reverse their anticoagulant effects. Although the short half-lives are reassuring in the sense that drug concentrations should decline rapidly when it is discontinued, in situations where reversibility is an emergency, such as trauma, life-threatening bleeding, emergency surgery or in renal insufficiency, it may well be a deadly disadvantage. [15] Additionally in the absence of monitoring it may be difficult to assess patient compliance. [10]

While many of the novel agents do not utilise the CYP450 pathway they are still subject to interactions to some degree as all three are p-glycoprotein (P-GP) substrates. P-GP is an intracellular drug transport system that has a role in drug absorption and distribution. Food and drugs can affect its activity. For example rifampicin, a P-GP inducer, results in decreased serum concentration of dabigatran and should be avoided. Likewise antifungals and HIV proteases are contraindicated as they can result in increased serum concentration and may therefore increase the risk of haemorrhage. [7]

Use of these new agents can only be confidently endorsed once long term follow-up studies are conducted, as anticoagulation therapy is a lifelong treatment. Many of the aforementioned studies had a follow-up period of 2–3 years, however are expected to report long term follow-up results in the coming years. [7] The long term safety profile of these drugs will need to be considered before widespread transition to TSOACs can be recommended. [19]

The United States Food and Drug Administration (FDA) has issued boxed warnings on dabigatran, rivaroxaban and apixaban in their use for non-valvular AF. It has been shown in clinical trials that discontinuation of these agents without appropriate cover by another anticoagulant places patients at an increased risk of thrombotic events. Therefore it is recommended to strongly consider replacement with another anticoagulant if these agents are to be discontinued for any reason other than pathological bleeding. [32-34] Additionally the FDA has reported that epidural and spinal hematomas have occurred in patients treated with dabigatran who receive neuraxial anesthesia or spinal puncture. These may result in long-term or permanent paralysis. [32]

Exciting new research is underway to identify an antidote for the TSOACs. Phase I trials demonstrate that idarucizumab produces an immediate, complete and sustained reversal of the anticoagulant effect of dabigatran in healthy participants. [35] Patient enrolment has also started into a randomised, double-blind, placebo-controlled phase III trial. [35,36] This trial will assess the efficacy of andexanetalfa, a factor Xa inhibitor reversal agent, in rapidly reversing rivaroxaban induced anticoagulation. The safety profile will also be evaluated with a follow up period of 43 days. [36] The synthetic molecule PER977 is also being studied in its ability to reverse the anticoagulant effect of edoxaban. In this study, haemostasis was restored within 10–30 minutes of administration of 100–300 mg of PER977 and was sustained for 24 hours. Additional phase II clinical studies are ongoing. [37] These 'FDA-designated breakthrough therapies' are under an accelerated approval pathway with the hope of bringing the agent into market as soon as possible and potentially overcoming the biggest drawback in the use of TSOACs. [36]

Conclusion

This review suggests that TSOACs have similar or superior efficacy than warfarin for stroke prevention in patients with non-valvular AF. Importantly, trials consistently demonstrate a favourable side-effect profile for these drugs. Research is currently underway into development of an antidote, overcoming the main argument against their use. [35] This advancing research will likely see TSOACs replace warfarin as the treatment of choice for stroke prevention in non-valvular AF.

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Conflict of interest

None declared.

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Pathogenesis of severe allergic asthma and the therapeutic use of anti-immunoglobulin E antibody

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Rukaiya is a medical student with a variety of interests that currently include paediatrics, infectious disease and addressing the needs of under-served populations particularly. She enjoys researching into the effectiveness of treatment options for medical conditions as they assist us, as future doctors, in making evidence-based clinical decisions.

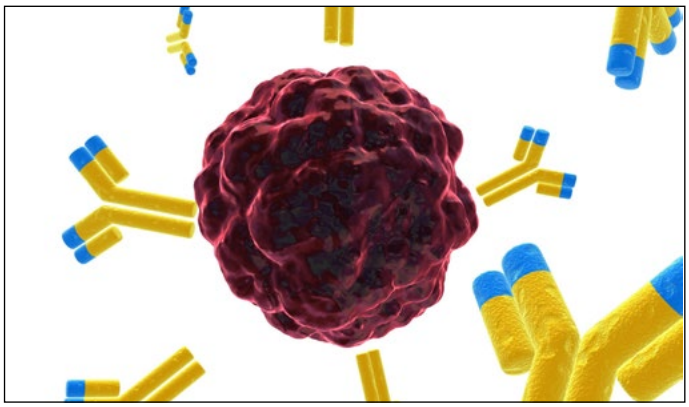
Allergic asthma involves type 1 hypersensitivity, which is driven by immunoglobulin E (IgE) dependent immunological mechanisms. Severe asthma is associated with chronically persisting inflammation and is often relatively unresponsive to conventional treatment with corticosteroids. This review article summarises the best treatment for severe persistent asthmatics based on current understanding of its pathogenesis. The efficacy and need for the recent therapeutic intervention of anti-immunoglobulin E (anti-IgE) monoclonal antibodies is explored. Further discussion includes drug efficacy and limitations, a summary of cost–benefit analyses, and comparison of anti-IgE to alternative treatment options for asthma. Literature was searched using MEDLINE database to obtain relevant articles. Currently, there is glucocorticoid resistance in certain cases of severe asthma. Hence the viability and safety of anti-IgE antibodies in the treatment of severe asthma was a significant breakthrough. Anti-IgE therapy enhances lung function whilst it reduces number of hospitalisations, frequency of exacerbations and need for inhaled corticosteroids (ICSs). Potential future therapies include monoclonal antibodies against interleukins 5 and 13 (IL-5 and IL-13) for severe asthmatics with persisting eosinophilia. Patients with severe asthma who have become unresponsive to high dose inhaled corticosteroids and who are above the age of six should be prescribed anti-IgE therapy – an effective treatment option that is currently available under the Pharmaceutical Benefits Scheme (PBS).

Introduction

Allergic asthma is a type 1 hypersensitivity reaction that occurs in response to an antigen which would not normally trigger an immune response. Only a small proportion of asthmatics are classified as being severe, yet they contribute to a disproportionately high percentage of health care costs in comparison to mild–moderate asthmatics whose diseases are well-controlled. [1] A cross-sectional study in Barcelona identified that severe asthmatics contributed towards 41% of their total asthma-derived healthcare costs. [1] This review focuses on the pathogenesis of severe allergic asthma, especially the important role of IgE antibodies in the degranulation of mast cells and eosinophils, leading to severe inflammation and contributing to airway remodelling. It also focuses on the mechanism of action and side effects of corticosteroids and anti-IgE antibodies. Glucocorticoid resistance is an important issue in severe asthma and understanding anti-IgE therapy involves having insight into the pathogenesis of allergic asthma. This article also explores the efficacy and limitations of anti-IgE therapy, including a summary of cost–benefit analyses, and a comparison to other options for treatment of asthma.

Pathogenesis

The pathogenesis of asthma involves three major phases (Figure 1): initial sensitisation, and subsequent early and late phase reactions. The initial contact with a particular inhaled allergen is recognised by antigen presenting cells (APCs) such as dendritic cells in the airway tissue. These APCs migrate to bronchus associated lymphoid tissues and lymph nodes and interact with naïve T cells to induce a type 2 T helper (Th2) cell response. Th2 cells stimulate B cell proliferation and isotype switching within germinal centres, resulting in plasma cells switching from producing IgM to IgE antibodies specific to the allergen. [2-4] The



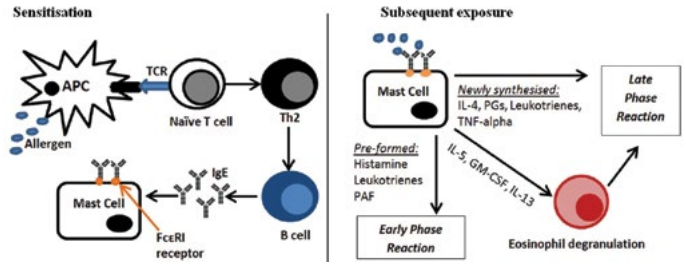


Figure 1. *Diagram explaining the pathogenesis of allergic asthma, including sensitisation, and the early and late phase reactions. APC= Antigen presenting cell, TCR= T cell receptor, Th2= Type 2 T helper cell, IgE= Immunoglobulin E, FcεRI= high affinity receptor for the Fc region of IgE, PAF=platelet activating factor, IL= Interleukin, PG= prostaglandin, GM-CSF= granulocyte-macrophage colony stimulation factor.*

Fc portions of IgE antibodies bind to high affinity FcεRI receptors on mast cells and basophils in the submucosa of bronchial tissues, hence completing the sensitisation process. Subsequent contact, when the same allergen binds to and cross-links adjacent Fab portions of IgE molecules present on the surface of mast cells, results in degranulation of the mast cells and release of their mediators. The immediate early phase response involves pre-formed mediators in granules such as histamine being released, which causes bronchoconstriction as well as greater vascular permeability and hence oedema of the bronchial walls and narrowing of the airways. The late phase allergic reaction occurs due to newly synthesised mediators from mast cells such as interleukin 4 (IL-4), prostaglandins, leukotrienes and tumour necrosis factor alpha (TNF-α), which cause infiltration of the bronchial walls with inflammatory cells, especially Th2 cells and eosinophils, leading to increased oedema and airway narrowing. Furthermore, the release of IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-13 from mast cells induces the degranulation of eosinophils. These release even more mediators that further perpetuate the condition and can lead to chronic inflammation as seen in severe asthmatics who suffer from frequent exacerbations. Evidently there are serious consequences to the downstream effects of an IgE-mediated response. [5,6]

In the pathogenesis of severe persistent allergic asthma, the activation of IgE that results in Th2-driven chronic inflammation is linked to the development of fibrosis and airway remodelling. [7, 8] The Th2 cytokines, IL-4 and IL-13 along with transforming growth factor beta

(TGF-β) increase collagen synthesis and the synthesis of eotaxin which chemically attracts eosinophils. Studies on murine models demonstrate that IL-13 plays a direct role in mucus production. [9] Myofibroblasts that synthesise collagen are responsible for the fibrotic changes seen in airway remodelling in chronic asthma. Other changes seen in airway remodelling include goblet cell metaplasia of airway epithelium and hence increased mucus synthesis and secretion. One possible reason for this could be stimulation by TGF-β. [7] Overall, the resulting disease profile for severe asthma involves persisting symptoms of dyspnoea, coughing and chest tightness, greatly compromised airflow, high eosinophil and Th2 cell differential counts within their full blood count profiles, as well as repeated hospitalisations for severe exacerbations. [10-13]

Management

Inhaled corticosteroids (ICSs)

The current standard treatment for asthma is ICSs, an anti-inflammatory medication, which is often combined with a bronchodilator for symptomatic relief. [10] The mechanism of action of corticosteroids involves binding to the glucocorticoid receptor in the cytosol, which stimulates the receptor to translocate and bind to DNA in the nucleus in order to alter the expression of a variety of genes. [13,14] For instance, corticosteroids inhibit nuclear transcription factor NF-κB and activator protein 1 (AP-1) complex, resulting in decreased production of Th2 pro-inflammatory cytokines. [13-15] Overall, ICSs prevent excessive inflammation involving infiltration by eosinophils and other leukocytes, as well as release of pro-inflammatory mediators that lead to airway remodelling. [13,16]

Even though corticosteroids successfully address the inflammatory consequences of the hypersensitivity reaction, severe asthmatics can become unresponsive to even high doses of ICSs, as well as to oral corticosteroids. The development of glucocorticoid resistance in severe asthmatics is relatively rare but requires appropriate management. [13,17] There are many theories to explain the development of glucocorticoid resistance, including an abnormal interaction between the large amounts of pro-inflammatory mediators and glucocorticoid receptors. [9,18] Hence, in June 2003 the Federal Drug Administration approved the use of omalizumab, the only recombinant human anti-IgE monoclonal antibody (mAb) currently available. [2,16]

Anti-IgE therapy

As previously illustrated, IgE antibodies play a crucial role in the pathophysiology of allergic asthma. The synthesis of therapeutically viable anti-IgE mAbs that can target the specific mechanisms of disease

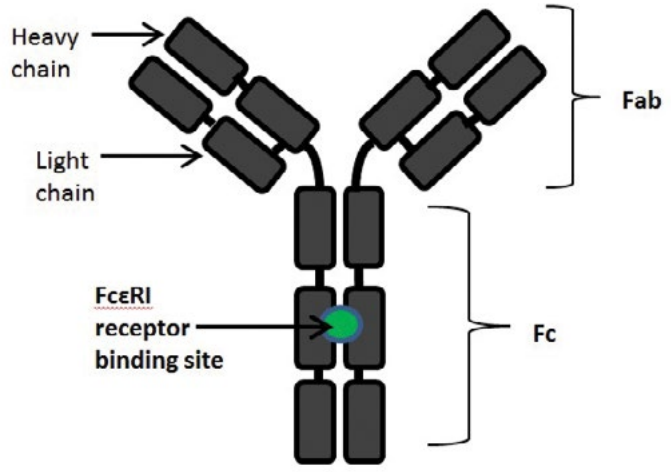


Figure 2. *The structure of Immunoglobulin E Antibody. It highlights the Fab and Fc portions, as well as the FcεRI receptor binding site, which is the same site at which anti-IgE antibody binds.*

pathogenesis is an important breakthrough. [4] Anti-IgE mAb binds to the site on the Fc portion of IgE antibodies that normally binds to FcεRI receptors on mast cells and basophils. [4] Hence once anti-IgE binds to unbound IgE molecules, these IgE antibodies are unable to attach onto mast cells and hence no degranulation and release of inflammatory mediators occurs upon allergen exposure. However anti-IgE is unable to bind to IgE molecules that are already attached to mast cells or basophils due to a conformational change of the Fc portion of IgE once it is bound to the FcεRI receptor on mast cells. [2,4] Consequently, anti-IgE mAb are not able to cross-link IgE on mast cells and basophils and are fortunately non-anaphylactic. [4,8] Circulating anti-IgE:IgE immune complexes are removed by the reticuloendothelial system and do not accumulate in the kidneys, and hence omalizumab has no renal toxicity. [3,16]

Furthermore, complement components do not bind to these immune complexes, no antibodies are produced against anti-IgE, and hence no serum sickness or anaphylaxis occurs. [2,3] This is because the mAb has been carefully manipulated to become "humanised" through the removal of murine components. [4,16] The emphasised safety of the drug is supported by multiple-double blind, randomised control trials (RCT) consisting of greater than 300 participants to compare the effects of omalizumab to placebos in moderate to severe asthmatics. [4,16,19] The reported significant adverse events were primarily injection site reactions. [19,20,21] The drug has only been used for the last eleven years since its approval in the United States and hence the long term side effects are unknown.

Overall, there are many therapeutic benefits of anti-IgE antibodies. These include serum IgE levels diminishing by greater than 95% compared to before treatment and consequently weakening early and late phase reactions. [2,16] Clinical outcomes commonly assessed in trials include the rate of exacerbations, unscheduled healthcare use, asthma-related mortality and quality of life. The 2013 Cochrane review and other systematic reviews identify that omalizumab significantly reduces asthma exacerbations, and specifically that there was a reduction in the rate of exacerbations from 26% to 16% when comparing patients given a placebo to patients receiving omalizumab. [21-23] Similarly, there was a reduction in hospitalisations from 3% to 0.5% when moderate to severe asthmatics were treated with anti-IgE therapy. Furthermore, once treatment with omalizumab begins, patients are more likely to reduce or completely withdraw their use of ICSs, which is further supported by individual RCTs. [19] The RCT conducted by Busse et. al. showed a significant reduction in the number of days with asthma symptoms in comparison to placebo group, a reduction in the need for ICSs as well as a reduction in exacerbations from 48.8% to 30.3% when participants were given omalizumab. [20] Overall, anti-IgE therapy enhances lung function whilst it decreases bronchoconstriction, sputum eosinophilia, hospitalisations, frequency of exacerbations and the need for ICSs. This occurs due to inhibition of the downstream effects of IgE antibodies. [24] Hence anti-IgE mAb provides effective symptom control and improves quality of life.

Current guidelines provided by the National Institute for Health and Care Excellence (NICE) clearly state that omalizumab is recommended as an add-on therapy only for severe persistent asthmatics in individuals above the age of six years old, who are commonly already on high dose ICSs and possibly oral corticosteroids. [25] Safety of omalizumab use among young children has not been determined and therefore there is an age restriction. [20] The pooled analysis of two RCTs involving 1070 moderate–severe asthmatics by Bousquet et al. interestingly showed that patients who had lower lung function or were taking high doses of corticosteroids, or patients who had been hospitalised for asthma treatment in the past year before beginning omalizumab therapy, all displayed the greatest benefit from treatment. [15] Mild to moderate asthmatics would still benefit from anti-IgE therapy; however its use is limited to severe asthmatics primarily due to the large cost of the drug.

The incremental cost effectiveness ratio (ICER) per quality adjusted life year gained for omalizumab is above conventional thresholds – the average annual cost of treatment per patient is £8056 in the UK.

[22,25] However the cost effectiveness of omalizumab is justified in severe asthmatics due to their high risk of asthma-related mortality and hence the considerable improvement in quality of life provided by omalizumab. [21,22] Specifically it is reported that severe asthmatics cost the National Health Service (NHS) in the UK approximately greater than £680 million annually. Hence it is subsidised in the UK under the NHS. [25] Initially omalizumab was not PBS-listed until adequate cost–benefit analysis had been conducted. Currently, under Medicare Australia, omalizumab is available under the PBS. [26] However there are strict criteria for satisfying requirements to obtain omalizumab under the PBS. These include having a formal assessment, a corrected inhaler technique, a completed Asthma Control Questionnaire five-item (ACQ-5) and an IgE pathology report. Omalizumab is administered subcutaneously either every two or four weeks, depending on the baseline serum total IgE levels and the patient's body weight. [26]

Potential future treatment options

Following the successful use and implementation of anti-IgE, there is significant investigation into the efficacy of other mAbs targeting specific inflammatory mediators involved in the pathogenesis of severe allergic asthma. Experimental trials involving monoclonal antibodies against TNF-α and interleukins 4, 17 and 9 (IL-4, IL-17 and IL-9) have not been successful in treating severe allergic asthma. [23,27-29] However mAbs against IL-5 and IL-13 are promising due to their success in trials with reducing frequency of severe exacerbations in patients with severe asthma with persistent eosinophilia. [23,27,30,31] Similar to omalizumab, mAbs against IL-5 such as mepolizumab, relizumab or benzalizumab reduce rate of exacerbations, reduce need for corticosteroids, and improve lung function and asthma control. Clinical trials for use of such immune-modulators have only occurred recently, however it is likely to become a therapeutic option for patients with the specific phenotype of severe asthma with persisting airway eosinophilia. [23,30] Furthermore, several recent studies identify the importance of phenotyping severe asthmatics in order to tailor the most appropriate treatment to each patient. [27,32,33] Personalised treatment will be greatly beneficial for severe asthmatics, however the cost of such endeavours must be considered simultaneously.

It is also important to consider whether there are any currently available alternative treatment options for severe asthmatics. Hence, we shall quickly consider leukotriene receptor antagonists (LTRAs), such as montelukast, and mast cell stabilisers, such as nedocromil. There are several types of leukotrienes (LTs), such as cysteinyl LTs (CysLTs) and LTB4, and their release plays an important role in the pathogenesis of asthma. Montelukast is specifically a CysLT1 receptor antagonist which does not affect LTB4, an important inflammatory LT in the pathogenesis of airway inflammation in severe asthma. Evidently this drug is not effective in the treatment of severe asthma. [34] As montelukast provides some asthma symptom control, treatment guidelines from the Global Initiative of Asthma (GINA) and the US National Asthma Education and Prevention Program (NAEPP) recommend LTRAs as second-line treatment to ICSs for mild persistent asthma only. [35,36] Nedocromil is a G-protein coupled receptor 35 agonist, which is expressed on human mast cells, and hence causes mast cell stabilisation. [37] This leads to an improvement in lung function and reduces asthma symptoms. Similarly to montelukast, nedocromil only plays a role in mild asthmatics as an alternative treatment to ICSs and there is no current evidence for its role in the treatment of severe asthma. [35,38]

Conclusion

Evidently, severe uncontrollable asthma requires new treatment options other than corticosteroid anti-inflammatory medication due to some patients developing glucocorticoid resistance. Fortunately, numerous randomised control trials have proved the efficacy of anti-IgE therapy for severe asthmatics and now omalizumab is being used clinically. Anti-IgE therapy is particularly effective as it specifically inhibits the IgE-mediated severe inflammatory response which is a critical process in the pathogenesis of allergic asthma. Anti-IgE therapy enhances lung function whilst it reduces number of hospitalisations, frequency of exacerbations and need for ICSs, and greatly improves patient quality of life. It is an effective treatment option that is currently available under the PBS. Potential therapies that may be used in the near future in severe asthmatics with persisting eosinophilia include monoclonal antibodies against IL-5 and IL-13. Future research into reducing the cost of omalizumab and consequently expanding its use for mild–moderate asthmatics would be beneficial.

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Conflict of interest

None declared.

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Efficacy of mirtazapine as adjunct therapy to antipsychotics in the treatment of chronic schizophrenia

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Karen completed her undergraduate training last year at James Cook University and has recently commenced internship in NSW. She has thoroughly enjoyed studying in Far North Queensland and learning about the various tropical disease presentations in this region.

Aim: The aim of this article was to review the literature and evaluate the evidence that is available on the effectiveness of mirtazapine as adjunct therapy to antipsychotics for chronic schizophrenia. **Case Study:** SC, a 44 year old male with a previous psychiatric history of chronic paranoid schizophrenia, voluntarily presented to an acute mental health service with insomnia, delusional ideations, and negative symptoms. He was subsequently diagnosed with relapse of his schizophrenia and prescribed olanzapine. He responded poorly and slowly, which then prompted the addition of mirtazapine as an augmenting agent to the regimen. His insomnia resolved shortly after and significant improvement of his negative symptoms was observed. **Methods:** A literature search was conducted using the ScienceDirect and Pubmed databases. The search terms mirtazapine AND chronic schizophrenia; mirtazapine AND antipsychotics AND chronic schizophrenia AND efficacy were used. **Results:** Four randomised controlled trials and one open-label trial were identified. Two of the randomised trials demonstrated substantial reduction in the total scores of the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS) when mirtazapine was combined with the antipsychotics, risperidone and clozapine, respectively. The remaining studies showed that mirtazapine in combination with risperidone yields greater improvement in neurocognition. There were no studies identified that directly investigated the efficacy of a combined olanzapine and mirtazapine treatment strategy. **Conclusion:** Current level II evidence suggests that mirtazapine may be beneficial as an adjunct agent in patients with chronic schizophrenia. However, this evidence is limited to a select number of primary therapies and the mechanism and long term effects are currently unclear.

Case Report

SC, a 44-year-old Caucasian male with a background of chronic paranoid schizophrenia, was brought in by his sister to an Acute Mental Health Service with a 12 month history of insomnia which he believed was a consequence of the depot (Risperidone Consta) he was given a year ago. He averaged two to three hours of sleep most nights and had delusional beliefs about needing two to three blood transfusions to remove the "chemicals from the depot" from his blood stream. He also appeared to have somatic delusions as he believed that the contents of the depot were slowly being leached out through his sweat and feet as "aqua ammonia".

SC had previously worked as a banana farmer, but was currently unemployed and lived alone. Collateral history from his sister further revealed that SC was socially withdrawn from his family and friends, lacked motivation to resume his job as a banana farmer or any other employment and failed to look after his personal hygiene. He had no other significant past medical history. His only treatment for schizophrenia prior to admission had been with olanzapine 10mg, however, his compliance with this medication had been poor, according to his sister.

On assessment, SC looked unkempt with long, dry, frizzy hair and a long, scraggly beard. He had a lean build and was dressed in worn-out jeans and a faded, dirty t-shirt. He had downcast eyes but was passively cooperative. His speech was slow with low volume and he needed to be prompted repeatedly. He said he always had a frustrated mood

due to his lack of sleep and rated it "0/10". His affect was stable and blunted. He had delusional beliefs regarding his health and persecution but no perceptual changes. Both his insight and judgment were poor and he was assessed to have a moderate risk for suicide/self-harm.

SC was diagnosed with a relapse of his chronic paranoid schizophrenia. He was continued on olanzapine, with an increased dose, which saw a reduction in his delusional thought processes and an improvement in his insight and judgment. However, he continued to suffer from insomnia and his avolition, reduced socialisation, and diminished emotional responsiveness remained unchanged. Mirtazapine was added to the regimen and improvement in all these domains was seen within one to two weeks.

Introduction

Schizophrenia is characterised by psychotic symptomatology being present for longer than a one-month period, with some symptoms persisting for at least six months. [1] It is a multi-domain disorder that typically consists of a combination of positive symptoms such as delusions, hallucinations, disorganised speech, or grossly disorganised or catatonic behaviour, negative symptoms such as affective flattening, alogia, or avolition, and cognitive symptoms such as deficits in working memory, attention, or executive functions. These symptoms are further associated with social/occupational dysfunction and are not accounted for by another disorder. [1] Whilst DSM-5 does not specifically classify schizophrenia into acute or chronic forms, it indicates that the course of schizophrenia varies, with some patients showing exacerbations and remissions, whilst others remain chronically ill with symptoms lasting greater than 1 year. [1] The pharmacological management of schizophrenia primarily addresses the positive symptoms of the disorder as they are responsive to all approved antipsychotics, however, negative symptoms only respond modestly at best to these antipsychotics. [2] This is of particular concern in patients with chronic schizophrenia as this form of the illness is usually characterised by an increasing prominence of negative symptoms throughout its course, leading to poor functional outcomes and quality of life for these patients. [2] Literature suggests that certain antidepressants may have a beneficial impact on negative symptoms. [2] In the above case, SC was first given olanzapine however responded only partially which in turn prompted the addition of mirtazapine. This makes us question whether the use of mirtazapine as add-on therapy to antipsychotics is efficacious in the treatment of chronic schizophrenia.

Objective

The objective of this article was to evaluate the evidence that is available on the effectiveness of mirtazapine as adjunct therapy to antipsychotics for chronic schizophrenia.

Data Collection

To address the objective identified above, a literature search of the ScienceDirect and Pubmed databases was done with limits set to include articles that were written between the year 2000 and the present time. References from retrieved articles were also reviewed for relevance and inclusion in the review. The search terms were mirtazapine AND chronic schizophrenia; mirtazapine AND antipsychotics AND chronic schizophrenia AND efficacy. The search identified five studies: four randomised, double-blind, placebo-controlled trials (Level II Evidence) and one open-label trial (Level III-3 Evidence). Of these studies, none specifically investigated the combination therapy of olanzapine and mirtazapine (that which is relevant to the patient described in the case report). They did, however, investigate the efficacy of mirtazapine with other related second-generation antipsychotics.

Discussion

Pharmacology of mirtazapine

According to the dopamine hypothesis, schizophrenia is attributed to an excess of dopamine in the striatum and a deficiency of dopamine in the frontal cortex. [3] The excess dopamine is responsible for the positive symptoms of the condition whilst the negative symptoms are thought to be a result of the frontal dopaminergic deficiency. [3]

Mirtazapine selectively antagonises post-synaptic 5-HT_2 (subtypes 2A and 2C) and 5-HT_3 receptors, which may contribute to its anxiolytic properties as well as enhance dopaminergic neurotransmission. [4] Specifically, combined mirtazapine and antipsychotic therapy results in concurrent blockade of 5-HT_2A and D_2 receptors. This is thought to selectively stimulate dopaminergic activity in the mesocortical pathway or frontal cortex without increasing its activity in the mesolimbic and nigrostriatal areas of the brain, thereby improving the negative and cognitive symptoms of the disorder. [3]

Mirtazapine may also indirectly increase dopamine output in the medial prefrontal cortex. [3] One preclinical study suggested that noradrenaline reuptake transporters clear extracellular dopamine into noradrenergic nerve terminals. [3] As mirtazapine increases noradrenaline levels, greater competition between dopamine and noradrenaline for the same reuptake transporter may exist, which can subsequently cause elevation in dopamine levels. [3]

Another primary mechanism of action is antagonism of central presynaptic α_2-adrenergic inhibitory autoreceptors, leading to increased release of noradrenaline. [4] It also blocks α_2-heteroreceptors in serotonergic nerve terminals, resulting in enhanced 5-HT_{1A}-mediated serotonin neurotransmission. [4] Increased central noradrenergic and serotonergic activity helps alleviate symptoms of inattention, impaired concentration, and anxiety. [4]

Whilst no drug has received Therapeutic Goods Administration approval for the treatment of negative symptoms of schizophrenia, [3] the continually improving understanding of mirtazapine's mechanisms of action has prompted several clinical trials to investigate its role, as well as the role of other antidepressants, in the management of this disorder.

Effects of mirtazapine on the negative symptoms of chronic schizophrenia

One study was identified that evaluated the efficacy of mirtazapine as add-on therapy to risperidone in patients with chronic schizophrenia and prominent negative symptoms. It was an eight week, randomised, double-blind, placebo-controlled trial involving a sample of 40 in-patients who met the DSM-5 criteria for schizophrenia with 20 participants assigned to risperidone 6mg/day + mirtazapine 30mg/day and 20 participants assigned to risperidone 6mg/day + placebo. [5] All participants were acutely psychotic on a background of chronic schizophrenia. Patients were assessed at baseline and at the end of the study using the Positive and Negative Syndrome Scale (PANSS) as the primary outcome measure. [5]

The study found that the mirtazapine group had a greater mean improvement in the negative symptoms ($p<0.001$) and PANSS total scores over the eight-week period. [5] Furthermore, clinical response (characterised by a 50% or more reduction in the PANSS total score) was seen in 68.18% of patients receiving mirtazapine compared to 31.81% of those assigned to placebo. The difference was significant ($p=0.03$). [5] This study showed the superior efficacy of mirtazapine in comparison to placebo in the augmentation of risperidone treatment in chronic schizophrenia. Given that no significant adverse effects were observed with the administered dose of mirtazapine, [5] the study further suggests its use as a potential combination treatment strategy particularly when negative symptoms prevail. Whilst no issues were observed in this study period, mirtazapine is notoriously known for its propensity to cause weight gain. [6] Its use as add-on therapy must therefore be judiciously tailored given the higher prevalence of metabolic syndrome in patients with chronic mental illnesses such as schizophrenia. [6]

A similar eight week, randomised, double-blind, placebo-controlled trial tested the role of mirtazapine in augmenting clozapine therapy for patients with chronic schizophrenia. [7] Its methodology and criteria for inclusion were similar to that of the aforementioned study. The study involved 48 in-patients, half of whom were assigned to mirtazapine 30mg/day and the other half administered placebo. [7] Each patient was on a stable dose of clozapine monotherapy for at least one month prior to the study. Their doses ranged from 150-650mg daily and did not change throughout the study. [7] The primary efficacy measure was the Scale for the Assessment of Negative Symptoms (SANS) total scores. The study saw a substantial reduction in scores for the mirtazapine group compared to the placebo group with particular improvements on the SANS subscales avolition/apathy and anhedonia/asociality. [7] Mirtazapine also showed greater superiority over placebo in the Brief Psychiatric Rate Scale (BPRS) total score at the end of the trial. [7]

The evidence from both studies indicates that the combination of antipsychotics and mirtazapine may be more effective for the treatment of negative symptoms in chronic schizophrenia than antipsychotics alone. However, both studies had limitations, namely the small sample sizes and the short treatment period, given the long-term nature of the illness. Furthermore, whether these findings can be generalised to all second-generation antipsychotics such as olanzapine is also worthwhile questioning.

Effects of mirtazapine on neurocognition

The efficacy of adjunctive mirtazapine in chronic schizophrenia does not appear to be limited to improving the negative symptoms of the illness. The literature suggests that add-on mirtazapine may also have desirable effects on neurocognition. [8, 9] An eight week, double-blind clinical trial was conducted whereby 21 patients with chronic schizophrenia, stabilised on risperidone, were randomly assigned to adjunctive treatment with either mirtazapine or a placebo. Cognitive performance was measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). [8] Unlike the placebo group, the mirtazapine group saw statistically significant improvements in the RBANS total scores, and also in the subscales for immediate and delayed memory. [8] Like all other studies discussed so far, the short treatment period was a major limitation.

This shortcoming was addressed in another study with a similar methodology and criteria for inclusion. It was a six week double-blind, randomised trial with a six week open label extension phase, designed to explore the effects of prolonged mirtazapine treatment. [10, 11] During the extension phase, the twelve week mirtazapine exposure group (i.e. those who received mirtazapine from the beginning) and the

six week mirtazapine exposure group (i.e. those who received placebo initially and were then shifted to mirtazapine at the extension phase) both showed improvement in the areas of visual-spatial functions, verbal/visual memory, executive functions, verbal fluency, and general mental and psychomotor speed. [10, 11] However, the twelve week mirtazapine exposure group was found to convey neurocognitive superiority over the six week mirtazapine exposure group, [10, 11] suggesting that additional benefits may be yielded with prolonged treatment.

Conclusion

Chronic schizophrenia is a complex illness that is characterised by a combination of positive, negative and cognitive symptoms. [1] Whilst antipsychotics are the recommended first-line treatment, the prolonged nature of the illness often results in residual negative symptoms and sustained neurocognitive deficits that tend to have a poor response to antipsychotics. [2] Current level II evidence suggests that the use of adjunct mirtazapine to antipsychotics may augment the treatment of chronic schizophrenia by alleviating the negative symptoms of the disorder. However, this evidence is limited to a select number of primary therapies and the long-term effects are currently unclear. Given that no studies were identified that specifically addressed the efficacy of a combined treatment strategy of olanzapine and mirtazapine, it is difficult to determine the appropriateness of the management approach taken for SC's illness.

Before the use of mirtazapine as an adjuvant to antipsychotics in chronic schizophrenia can be recommended for clinical practice, it is important to conduct large-scale, placebo-controlled studies that are lengthy in duration, so that the full efficacy and potential side effects of mirtazapine can be properly explored. Its tendency for weight gain/exacerbation of metabolic syndrome, especially in combination with atypical antipsychotics which share a similar risk profile, is of particular concern. [6] It may also be worthwhile to determine whether mirtazapine is synergistic with most or only selective antipsychotics.

Nonetheless, SC's considerable improvement upon administration of mirtazapine provides the grounds for questioning what treatment approach is best for a patient with chronic schizophrenia.

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Consent declaration

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

Conflict of interest

None declared.

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Adolescent-onset metabolic syndrome

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Natalie is a fourth year medical student at Monash University with a particular interest in women's and children's health. She has spent some time researching which enabled her to realise that she would rather be on the ward than in the lab.

Obesity is a common cause of insulin resistance (metabolic syndrome) in adults, however in recent years this has extended into much younger age groups. Associated conditions including dyslipidaemia, type 2 diabetes mellitus, and cardiovascular complications are all major components of metabolic syndrome. This case report describes a sixteen-year-old with features typical of adult-onset metabolic syndrome. The patient described in this report did not receive adequate treatment for three years after her initial diagnosis, which highlights challenges in engaging with and managing this age group. This report discusses the use of a biopsychosocial approach in managing metabolic syndrome in the adolescent population.

Case

DT is a sixteen-year-old female who was referred to the emergency department by her general practitioner (GP) after she was found to have a blood glucose level of 14.1mmol/L. She was commenced on intravenous saline and short-acting insulin, and transferred to the paediatric ward.

DT had been diagnosed with a cluster of health problems collectively known as the metabolic syndrome at 13 years of age, but subsequently ceased prescribed medication and failed to attend follow-up appointments. Her co-morbidities at the time included type 2 diabetes mellitus (T2DM), dyslipidaemia, obesity, and non-alcoholic fatty liver disease. She was also found to have obstructive sleep apnoea and polycystic ovarian syndrome.

She reported that most of her adult relatives were overweight, however denied any family history of T2DM or any hereditary conditions. She had never smoked, or participated in alcohol or recreational drug use.

Having emigrated from Samoa at age 11, DT said she had few friends, although she socialised within her church community. DT dealt with domestic violence in her immediate family, parental separation, and was responsible for the care of her seven siblings.

On examination, DT was severely obese with a body mass index (BMI) of 41.8kg/m^2. Her vital signs were all within the normal ranges and she had no signs of diabetic ketoacidosis. Of significance was the presence of acanthosis nigricans on her neck, elbow creases, and axillae, indicating longstanding insulin resistance. She had a deep voice, but no other signs of hyperandrogenism.

DT's investigations revealed a HbA1c of 12.2% (reference range [RR]<6.5%), fasting glucose level of 14.1mmol/L (RR: 4.0-6.0), alanine transaminase of 56 mmol/L (RR <30), aspartate amino transferase of 44mmol/L (RR <30), and gamma-glutamyl transferase of 64 mmol/L (RR <30). Ketones, fasting lipid profile, and thyroid function tests were all within the normal ranges, and no insulin autoantibodies were present. Urinalysis demonstrated glycosuria but not ketonuria.

These results confirmed the previous diagnosis of T2DM. However, due to the resolution of dyslipidaemia and her normal blood pressure, DT no longer met the International Diabetes Federation criteria for metabolic syndrome. The deranged liver function tests were consistent with her previous diagnosis of non-alcoholic fatty liver disease.

DT was managed in a multidisciplinary setting involving a paediatrician, endocrinologist, diabetes educator, dietician, and a social worker. She received ongoing care from a local GP and the paediatric endocrinology

hospital outpatient service. The GP initially checked her blood glucose level weekly and adjusted the metformin dosage (1 x 850mg mane, 2 x 850mg nocte) [1] as required. The allied health team provided her with a lifestyle plan to reduce her dietary energy intake, to include incidental exercise as part of a regular exercise regimen, and distraction strategies to address overeating. DT was also booked for appointments to monitor diabetes-related complications (ophthalmology, renal, and podiatry clinics). Due to difficulty locating an appropriate interpreter, DT's mother was not actively involved in discussions regarding her ongoing management. This made it incredibly difficult for the treating team to include DT's family in the management plan, despite family involvement being a crucial component of care of the adolescent.

DT was involved in many discussions around her extensive management plan, however she asked upon discharge, "*What if I can't?*" Her self-doubt demonstrates a normal, adolescent response to an overwhelming challenge and is worsened by a lack of family involvement in her care. It remains uncertain as to whether DT will attend any follow-up appointments.

Discussion

Adolescent obesity

With obesity rates in Australians being very high, the public eye has long been focused on the health impacts of the modern lifestyle. The 2007 Australian National Children's Nutrition and Physical Activity Survey found that 17% of Australian children were overweight and 6% were obese. [2] Despite these figures, only a minority of Australian GPs routinely perform measurements such as height, weight, and calculation of body mass index in children, relying on visual inspection alone to assess weight. In addition, many GPs find it difficult to raise the issue of weight management with children and their families, resulting in delayed or lack of dietary control and lifestyle modification. [3]

Adolescence is a time when the ability to learn increases and new habits are adopted yet the ability to self-regulate is not fully developed. [4] Overweight adolescents may desire the improved body image and self-esteem that weight loss might entail but lack an understanding of the practical steps that need to be undertaken in order to achieve that goal. [5]

The Metabolic Syndrome in the Paediatric Population

The metabolic syndrome is a term used to describe the co-occurrence of a range of metabolic risk factors including abdominal obesity,

Age (years)	Obesity	Triglycerides	HDL-C	Blood pressure	Glucose
6-9	≥90th centile				
10-16	≥90th centile or adult cut-off	>1.7mmol/L	<1.03mmol/L	Systolic BP >130 or diastolic BP ≥85mmHg	BGL≥5.6mmol/L or known T2DM
>16 (adult criteria)	WC≥94cm (male) or ≥80cm (female) Or BMI >30kg/m2	≥1.7mmol/L or treated	<1.03mmol/L (male) or <1.29mmol/L (female) or treated	Systolic BP >130 or diastolic BP ≥85mmHg or treated	BGL≥5.6mmol/L or known T2DM

Table 1. *International Diabetes Federation-modified definition of metabolic syndrome in children and adolescents [8] (WC=waist circumference). HDL-C, high density lipoprotein cholesterol; BP, blood pressure; BGL, blood glucose level; T2DM, type II diabetes mellitus; WC, weight circumference; BMI, body mass index.*

hyperglycaemia, dyslipidaemia, and hypertension. [6] While the overt disease is rare in the paediatric population, adult cardiovascular disease is more common in those who exhibited metabolic syndrome traits as children compared to those who did not. [7]

The International Diabetes Federation requires the presence of central obesity as well as two other metabolic abnormalities to reach a diagnosis of metabolic syndrome (Table 1). [8] While DT did not meet the full diagnostic criteria for metabolic syndrome on her current presentation she previously fulfilled these criteria and has extensive metabolic derangements consistent with this syndrome, including cardiovascular disease, non-alcoholic fatty liver disease, chronic kidney disease, and diabetic retinopathy. [6] A New Zealand study of adolescents with a Pacific Island ethnicity (including Samoan) found that although rates of overweight and obesity were high (40% and 36%), only a small proportion had aberrant glucose metabolism. This is thought to be due to better insulin secretory reserves in these populations, and thus the fact that DT has T2DM is of particular concern given that she is at an extreme end of an already at-risk population. [9] Early onset T2DM is closely associated with hereditary risk factors such as increased BMI, lower threshold for insulin resistance, and dyslipidaemia. [6] Given the established heritability of these conditions it would be suitable to test DT's immediate family members for T2DM and dyslipidaemia.

Managing metabolic risk factors

Optimal management of co-morbidities reduces both the occurrence and severity of complications. Regular monitoring should be undertaken, including assessment of blood pressure, waist circumference, fasting lipid profile, fasting blood glucose, urinalysis and renal function, HbA1c, visual acuity, and pedal sensation. [6] First line management in individuals with obesity as well as obesity-associated complications includes weight loss, as well as lifestyle interventions such as diet and exercise modification, glycaemic control, and optimisation of lipid profile. Such monitoring may present a burden on both the patient and healthcare providers but is an important secondary prevention strategy to reduce the risk of major long term complications.

The identification of risk factors for metabolic complications is crucial in adolescents for two reasons: 1) many risk factors can be modified to reduce future disease burden; [6] 2) adolescents are more likely to misjudge their weight status and thus feel either overwhelmed or unable to recognise the need to make lifestyle adjustments. [10] Clinicians play an important role in providing support and initiating lifestyle changes.

Adolescent attitudes to chronic disease management

For DT, the prospect of dietary restriction, an exercise regime, daily medication, and multiple appointments may have appeared overwhelming. The transition from childhood to adolescence is marked by heightened social awareness and often a struggle to form an individual identity. [11] A study of adolescent females found that deviation from the BMI norm is associated with greater social anxiety, depression, and lower self-worth, all of which affect not only the mental health of the individual but also their engagement with healthcare professionals. [11] In DT, these factors may also impact on the day-to-day management of her health.

Another study investigating the experience of adolescents with T2DM, found that three main factors influence the maintenance of health and end-health outcomes: concept of illness, adjustment to diagnosis, and motivation to maintain good health. [12] The study suggests that the adolescent's beliefs about both the cause of the condition and the ability to adhere to advice are affected by motivation stemming from immediate and future consequences. If adolescents cannot yet fully understand the consequences, their motivation is sourced from family, health professionals, and their own perceptions of their health status. [10, 12] In DT's case, family dysfunction and lack of continuity of care due to emigration may have contributed to her apparent lack of motivation to comply with health recommendations.

What went wrong in DT's care?

Although several of DT's health concerns were identified when she was thirteen years old a combination of factors, including emigration and family dysfunction, meant that DT did not have adequate support. These issues might be overwhelming to an adult, and are further amplified in an adolescent who does not yet have the understanding and motivation to adhere to treatment. She may have been prevented from 'falling through the gaps' if a treating team in Australia had been established by her New Zealand doctor before she emigrated. With a comprehensive handover, DT may have been better supported by a team who at least had some information about her history. The central problem however, is the family dysfunction meaning that her parents have had very little insight into her medical issues. Also considering that she has seven siblings and her parents are estranged, her health concerns are less likely to be managed outside of the hospital environment. This complex set of issues is difficult to address and may require support from a social worker and GP. Cultural issues including language, home life, and diet may be best evaluated with a home visit by a community nurse and the assistance of an interpreter. Cultural sensitivity is imperative to establishing rapport, so input from a Pacific Islander social worker may be beneficial.

The biospsychosocial approach

When addressing chronic disease, the biopsychosocial approach is appropriate for individuals of any age. This involves consideration of the medical aspects, which for DT includes medication and specialist reviews, as well as consideration of the psychological and social factors that influence attitudes and behaviours. Traditionally, the focus has been on addressing lifestyle factors in the individual, when there are perhaps better long-term outcomes by addressing wider, societal issues. [13] Family-centred models are the current mainstay of treatment and in DT's case, will require consideration of culturally appropriate ways to engage with her family such as with social workers, interpreters, ethnic health workers, and members of her church community.

By addressing her individual concerns, which may include self-esteem and self-confidence, and by improving communication with her healthcare providers, DT may be given a better chance at improving her long-term health outcomes. As mentioned previously, by improving self-efficacy, adolescents such as DT are given the confidence in their

own ability to manage their health, and thus are more likely to be able to sustain a healthy lifestyle.

It is important to consider DT's Samoan origin, as factors such as family commitments, roles within the community, and societal expectations will influence her motivation and ability to improve her health. An investigation into the facilitators of healthy lifestyles in the Pacific Islands found that supportive role models and making physical activity more enjoyable were the most effective ways in which the health of communities could be improved. [14] These utilise the existing social structures of Pacific Island populations to provide motivation to make positive lifestyle choices and also support for long-term maintenance. Interventions should therefore focus on improving self-efficacy and providing realistic strategies. Motivational interviewing could be used by a GP to identify key goals for the individual patient to be achieved through a lifestyle plan. [4]

The increasing occurrence of typically adult-onset metabolic syndrome in children is a public health concern and DT is a prime example of the potential for patients to 'slip through the gaps'. While there are multiple public campaigns aimed at improving the modifiable risk factors in the paediatric population, the rates of obesity and associated complications remain high. Another concern involves the many challenges unique to adolescent medicine, as the patients are not only dealing with chronic health issues but the individual changes in body and mind that are characteristic of that stage of life. This case demonstrates that a multi-faceted approach aimed at engaging, motivating, and empowering adolescents is required to optimise health outcomes in this population.

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Consent declaration

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

Conflict of interest

None declared.

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English-speaking background and its relationship with length of stay in elderly patients admitted to a subacute setting: a retrospective study

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Introduction: Despite the resource implications of extended inpatient stays, the impact of a non-English speaking background (NESB) on length of stay (LOS) has not been studied in the subacute geriatric population. We investigated the relationship between language background and LOS in elderly subacute inpatients. **Method**: A retrospective file audit of subacute inpatients (aged ≥75) was conducted. LOS, language background, interpreter requirement, comorbidities, functional status (Functional Independence Measure (FIM)), history of dementia/delirium, and discharge destination were noted. **Results**: 121 records were audited. 45 (37%) were identified as NESB with a median LOS of 21 days [IQR 13.0, 41.0] compared to 19 days for patients with an ESB [IQR 8.8, 35.8]. The median LOS for NESB patients who required an interpreter (n=24) was 27.5 [IQR 14.4, 44.8] compared to 17.0 [IQR 10.0, 40.0] for those who did not (n=21). There were no statistically significant differences in LOS found between ESB patients and NESB patients who required an interpreter (p=0.272), or NESB patients who required and did not require an interpreter (p=0.232). When short LOS patients (<22 days) were compared to long LOS patients (≥22 days), we found a significant association between a longer LOS and history of dementia/delirium (p=0.038), lower admission FIM score (p<0.001) and discharge destination. Those with short LOS were significantly more likely to be discharged to acute care, and those with long LOS to home or residential care (p=0.003). **Conclusion**: We did not find a statistically significant difference in LOS between ESB and NESB in subacute patients aged over 75. However, an association between longer LOS and a history of dementia, delirium or cognitive impairment; lower admission functional status; and discharge to home or residential care was found.

Introduction

Australia is a multicultural country. Persons from a Non-English Speaking Background (NESB) now comprise a large and growing proportion of Australia's ageing population. [1] The 2011 census revealed that greater than thirty-two percent of households in Greater

Melbourne reported speaking two or more languages at home. [2] Language barriers have the potential to impact multiple aspects of health care delivery for older people, including effects on diagnosis, prevention of complications, engagement in treatment decisions, and timely discharge planning. [3] These factors have been shown to increase hospital length of stay (LOS), which is undesirable for both patients and the health care system. [3]

Associations between NESB and LOS have been mostly investigated in acute care settings and younger populations, with mixed results. [3-8] A retrospective study in a Canadian Paediatric Emergency Department (ED) revealed longer LOS for families that did not speak English. [4] A prospective cohort study in another Paediatric ED in Chicago (USA) found a 20 minute longer stay for patients who spoke a different language to the clinician. [5] A retrospective study by John-Baptiste *et al.* in a heterogeneous inpatient population in Canada showed a 0.5 day longer LOS for patients with limited English proficiency. [3] Conversely, studies in a psychogeriatric setting in Western Melbourne and medical inpatient settings in Californian hospitals found no significant difference in LOS between English speaking background (ESB) and NESB patients. [6-8]

Elderly patients admitted to subacute care such as a rehabilitation ward or Geriatric Evaluation and Management (GEM) unit typically have a longer LOS to address complex needs. [9] A number of factors influencing LOS in subacute care have been identified, including pre-existing disability, cognitive impairment, recurrent falls, urinary incontinence and lack of supportive living arrangements. [10-12] However, the impact of a NESB in elderly patients on LOS in a subacute setting has not been investigated to our knowledge, and is of particular relevance in the context of an ageing and diverse population due to the resource implications of an extended LOS. [13]

Our primary aim was to investigate the relationship between language background (ESB vs. NESB) and LOS in older patients in a subacute setting in metropolitan Melbourne. Our secondary aim was to explore other factors associated with an increased LOS in this setting.

Methods

Study setting and participants

Monash Health caters for the South Eastern catchment area of Melbourne, which is the largest in Victoria in terms of population. The 2011 census found that 44.4% of people living within the City of Monash reported speaking a language other than English at home, compared to 29.1% in Greater Melbourne. [14] Monash Health services a large NESB population and as such, it is ideally placed to research the impact of linguistic diversity on health care delivery.

Study participants were older patients (aged 75+) admitted to any subacute medical ward within Monash Health. Subacute care in Monash Health is located across the South-Eastern Region in three centres. The term 'subacute' encompasses two inpatient streams: GEM and Rehabilitation (Rehab). GEM encompasses the subacute care of chronic or complex conditions associated with ageing, cognitive dysfunction, chronic illness or disability. It is conducted by a geriatrician and a multi-disciplinary team for a defined episode of care. [15] Rehabilitation aims to maximise independence and quality of life for people living with a disabling medical condition. Multidisciplinary care is provided in an inpatient setting with an aim to minimise long-term care needs and community support to bring about considerable cost savings both in acute health care, and in long-term social security. [15]

Study design

This project was a retrospective file audit of consecutive discharges from subacute wards between February 2012 and February 2013. Inclusion and exclusion criteria are detailed in Table 1.

The lower age limit for our study was selected as being 75 because this age range captures the 'old' and 'oldest-old' categories, while excluding the 'young-old' (65-74 years) category who are likely to have less complex care needs.

Ascertainment of English speaking background

Language background status was ascertained from the patient admission cover sheet. Assessment of whether an interpreter was 'required' was made via allied health admission notes. The standardised Monash Health admission forms require the health care provider to indicate in a checkbox item whether an interpreter is required. The language status and requirement of an interpreter was corroborated with medical, nursing and allied health progress notes.

Inclusion Criteria	1.	Age ≥ 75 years
	2.	Admission and discharge from a subacute setting at Monash Health
	3.	Patient data available and language background recorded in the medical record
Exclusion Criteria	1.	Conflicting or no reports of language background within the records
	2.	Transfer to an acute inpatient unit in less than 24 hours from admission to subacute

***Table 1**. Inclusion and Exclusion Criteria*

Length of stay data

Length of stay was calculated from the admission date and discharge date in the discharge summary of each participant record.

Other variables collected

Based on our literature review, other variables collected were: Patient demographics: age, gender and primary language spoken, Clinical characteristics: admission type (GEM or Rehab), discharge destination, diagnosis on admission to subacute, functional status (Functional Independence Measure (FIM) [16]), comorbidities (used to calculate the Charlson Comorbidity Score [17]), and a history of dementia, delirium, or cognitive impairment.

Statistical analysis

Extracted data were analysed descriptively in Excel and the following statistical tests were applied in SPSS (version 22) to assess differences between groups: Mann-Whitney U test for non-normally distributed continuous data, Chi-square test for categorical data and independent samples and t-test for normally-distributed continuous data.

Three comparative analyses were conducted. Comparison 1 sought associations between language background (ESB vs. NESB patients who required an interpreter) and LOS. Comparison 2 involved a subset analysis of NESB patients, where difference in LOS was investigated for NESB patients who *did not require* an interpreter compared with NESB patients who *required* an interpreter. Comparison 3 sought associations between prolonged LOS and all clinical/demographic variables collected, where long LOS was defined as ≥ 22 days (based on average length of stay of 20.8 days for patient with orthopaedic impairments in New South Wales rehabilitation units in 2010). [18]

Ethics

The project was approved as a Low/No Risk research activity by the Monash Health Ethics Committee (Ref: 13048L).

Results

Participant characteristics

There were 201 discharges from subacute settings within Monash Health between February 2012 and February 2013, of which a total of 121 discharges met the eligibility criteria. The average age of the patients was 83.2 years old (SD=5.2). Male patients represented 46%. The languages spoken by NESB patients were most commonly Greek (16%) and Italian (13%).

The three most common primary diagnoses at admission were fractures from any cause (17%), stroke (both ischaemic or haemorrhagic) (12%) and intracranial haemorrhage (8%). The median FIM score for ESB and NESB was 68.0 [46.3, 81.8] and 65.6 [42.0, 79.3] respectively (FIM score possible range: 18 to 126). 32% of ESB patients had a history of dementia, delirium or cognitive impairment compared to 29% of the NESB group.

As shown in Table 2, mean age, mean Charlson co-morbidity score, and distribution of admission care types were very similar for ESB and NESB groups. There was a small difference in gender distribution for ESB and NESB groups, but this was not statistically significant ($\chi^2[2, n = 121] = 3.82, p = 0.15$).

In terms of discharge destination, more patients from the NESB group were discharged home with supports (33%) compared to the ESB group (21%). A large proportion of both ESB and NESB patients were discharged to an acute inpatient unit; 55% and 53% respectively.

Length of stay

Comparison 1 revealed a median difference in LOS of 8.5 days between ESB patients and NESB patients who required an interpreter, although this was not statistically significant (Table 2, Figure 1). Comparison 2 sought differences in LOS between NESB patients who required an interpreter and those who did not (Table 2). The difference in LOS was not statistically significant (Figure 1).

The purpose of Comparison 3 was to identify other variables associated with LOS status (long LOS ≥ 22 days, short LOS < 22 days). The long LOS group was associated with a history of dementia/delirium/cognitive impairment, lower functional status (FIM score) at admission, and discharge to home or residential care (Table 3). No relationship was found between age or interpreter requirement and LOS status (Table 3).

Discussion

The study confirmed that a large number of Monash Health's elderly subacute patients are from a Non-English Speaking Background (NESB), consistent with the proportion reported by 2011 Census data. [2]

Demographic and clinical data	ESB (N=76)	NESB (N=45)	NESB subset: Interpreter not required (N=21)	NESB subset: Interpreter required (N=24)
Mean age (years)	83.6	82.6	82.4	82.7
Male gender N (%)	30 (40%)	26 (58%)	12 (57%)	14 (58%)
Admission care type N (%) • GEM • Rehabilitation	 59 (78%) 17 (22%)	 34 (76%) 11 (24%)	 15 (71%) 6 (29%)	 19 (79%) 5 (21%)
Charlson Comorbidity Score • Mean raw score (SD) • Mean age adjusted score (SD)	 2.2 (1.8) 6.1 (1.9)	 2.7 (1.7) 6.5 (1.8)	 3.0 (1.3) 6.7(1.4)	 2.5 (2.0) 6.3 (2.1)
Transfer to acute inpatient unit N (%)	42 (55%)	24 (53%)	11 (52%)	13 (54%)
History of dementia/delirium or cognitive impairment noted N (%)	24 (31.6%)	13 (28.9%)	7 (33.3%)	6 (25%)
Median length of stay (days) [Interquartile Range]	19.0 [8.8, 35.8]	21.0 [13.0, 41.0]	17.0 [10.0, 40.0]	27.5 [14.3, 44.8]

Table 2. *Summary of patient groups, demographics and clinical data versus LOS. ESB = English Speaking Background; NESB = Non-English Speaking Background.*

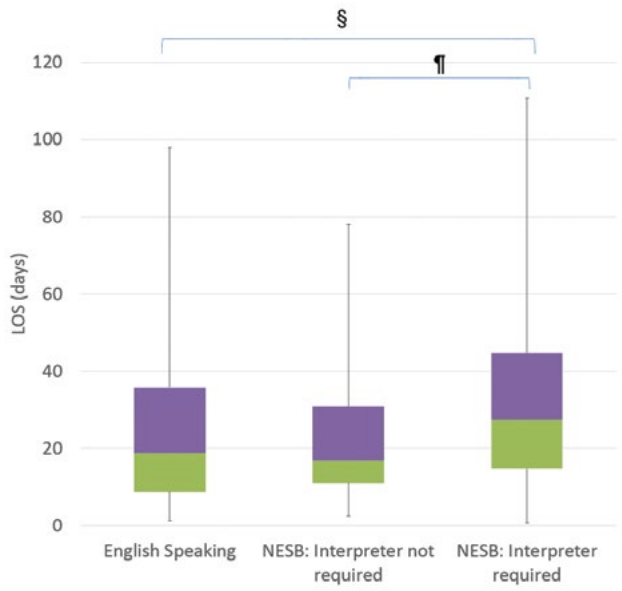

Figure 1. *Length of Stay (LOS) distribution by language background*
¶Mann-Whitney test, p=0.232; §Mann-Whitney test, p=0.272
NESB = Non-English Speaking Background

NESB patients in Australia may find it difficult to communicate with the doctor and navigate the health care system. [19] This may be especially the case for elderly Non-English Speaking patients, as they have a high burden of chronic disease, disability and impairments, and have complex medical, functional and social needs. [20] A survey of Aged Care Assessment Service clinicians in Victoria cited the availability and quality of interpreters as a significant challenge in assessing culturally and linguistically diverse clients. [21] Communication difficulties have been found to make the assessment of cognitively impaired patients more challenging. [21]

Both Rehabilitation and GEM require high levels of patient cooperation and understanding in order to engage with multidisciplinary care, including physiotherapy, occupational therapy, and social work. [9] We hypothesised NESB status would be associated with a longer LOS for elderly patients in subacute care due to language barriers faced during complex multi-disciplinary care. However, we did not find a significant difference between the patients who were NESB compared to ESB patients. Comparison 1 found a trend towards a longer median LOS between patients who were from NESB requiring an interpreter, compared to ESB patients, although this was not statistically significant.

Our finding of a similar LOS for ESB and NESB is not unique. A study of a psychogeriatric unit in Melbourne [6] and American studies of inpatients in acute medical settings found no difference in LOS between ESB and NESB patients. [7,8]

These findings are interesting because they are counterintuitive, and the reasons for the lack of relationship deserve further investigation. It is possible that health services that provide care for a large NESB population, such as Monash Health, already have effective procedures in place to support communication between staff and NESB patients and their families. Alternatively, it may be that NESB patients are consulted less often due to language barriers, and decision-making is conducted without involvement of the patient. While such practice could reduce LOS, it may result in lower satisfaction with care and quality of care. For example, research conducted in North America has shown language discordance in the physician-patient relationship may result in reduced satisfaction and poorer health outcomes. [22,23] While a study of NESB patients in a Queensland Emergency Department reported increased rates of patient satisfaction when an interpreter was used compared to patients who did not utilise an interpreter. [24] Future studies of the subacute population could focus on satisfaction and health outcomes of NESB patients.

Although NESB was not associated with increased LOS in our study, we did identify a number of other factors associated with a longer LOS. When short LOS patients (<22 days) [18] were compared to long LOS patient, we found a significant associated between a longer LOS and patients with dementia/delirium, lower admission FIM score and discharge destination. Those with a short LOS were more likely to be transferred to acute care and those with a long LOS to home or residential care.

One of the limitations of this study is that it was retrospective. Retrospective analyses suffer from the fact that the data being analysed was not originally collected for the purpose of the study. The accuracy of data depends upon diligently prepared medical records by medical, nursing and allied health professionals. There were instances in this study where the language background of the patient was not clearly recorded in the patient's medical record, which led to the file being excluded from the study. This study also revealed that Allied Health

	LOS < 22 days (N=63)	LOS ≥ 22 days (N=58)	Outcome of analysis
Mean age (years)	83.4	83.0	NS
Interpreter not required (%) **Interpreter required (%)**	63% 16%	62% 24%	NS
Median FIM score at admission [IQR]	75.0 [62.0, 85.5]	52.0 [36.0, 74.0]	p<0.001
History of dementia, delirium or cognitive impairment N (%)	14 (22%)	23 (40%)	p=0.038
Discharge destination • Home • Residential care • Transfer to acute inpatient unit • Other	 13 (21%) 4 (6%) 44 (70%) 2 (3%)	 23 (40%) 12 (21%) 22 (38%) 1 (2%)	p=0.003

Table 3. *LOS Category [18] versus demographics and clinical data.*
NS = Not significant
IQR = Interquartile range
FIM = Functional Independence Measure [16]

and Nursing staff noted the language and social background of the patient in their notes more often than Medical staff. In addition, the generalizability of this study is limited in that it was conducted within one health service and in one state of Australia. The power of the study is limited by the fact that only 121 patient records were studied.

A final limitation of the study is the high number of patients who were transferred back to an acute inpatient unit during their subacute stay (Tables 1 and 2). The LOS for some of these patients may have been underestimated as the majority actually returned to subacute and continued their rehabilitation following the resolution of their acute medical problem. Future work could include repetition of this analysis with LOS calculated using combined admission times and/or exclusion of cases where patients were transferred unexpectedly and did not return to subacute care.

Conclusion

Our study did not reveal a statistically significant difference in LOS between subacute inpatients aged over 75 of English speaking and non-English speaking backgrounds. Variables that were related to longer LOS were a history of dementia, delirium or cognitive impairment, lower admission functional status, and discharge to home or residential care.

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Conflict of interest

None declared.

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Impact of socioeconomic status on the provision of surgical care

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In Australia, there is an association between low socioeconomic status (SES) and poor health outcomes. Surgical conditions account for a large portion of a population's disease burden. The aim was to determine the difference in provision of surgical care and patient satisfaction between low and high SES communities in Sydney, Australia. A cross sectional analytical study was conducted using questionnaire-based data. Patients were recruited from five general practice centres across low and high SES areas. Participants were eligible for this study if they had surgery performed under general anaesthesia within the last five years. Analysis was performed to determine whether waiting times for surgery and surgical consultations were different between low and high SES groups, and whether private health insurance impacted on waiting times. A total of 107 patient responses were used in the final data analysis. Waiting times for elective surgery were longer in the low SES group ($p=0.002$).The high SES group were more likely to have private health insurance ($p<0.001$) and were 28.6 times more likely to have their surgery in a private hospital. Private health insurance reduced waiting times for elective surgical procedures ($p = 0.004$), however, there was no difference in waiting times for initial surgical consults ($p=0.449$). Subjective patient satisfaction was similar between the two groups. In conclusion, our study demonstrates that SES does not impact on access to a surgical consultation, but a low SES is associated with longer waiting times for elective surgeries. Despite this, patients in both groups remained generally satisfied with their surgical care.

Introduction

In Australia, low socioeconomic status (SES) has been linked to poor health outcomes [1] with a 1.3 times greater mortality risk in low SES areas when compared to the highest SES areas. [2-3] Individuals living in more disadvantaged areas are more likely to engage in unhealthy behaviours, and their poorer health is reflected in more frequent utilisation of health care services. [4] Greater Western Sydney represents one of the lowest SES areas in Sydney, Australia [5] and according to the Socio-Economic Indexes of Areas (SEIFA), contains eight of the ten most disadvantaged areas in Sydney. [5-6] For general elective procedures, average waiting times in Greater Western Sydney hospitals varied from 23 to 93 days, compared with 4 to 36 days in other areas of Sydney. [6] Thus, timely and easily accessible provision of surgical services is a growing necessity for the expanding population of Greater Western Sydney.

Methods

The research was approved by the University of Western Sydney Human Research Ethics Committee (H9067). The SEIFA [7] score was used to determine the areas chosen for data collection. A total of five Sydney General Practices, three located in low SES areas and two in high SES areas, were chosen randomly for patient recruitment.

The data collection tool employed was a survey which included questions relating to SES factors, health fund status, comorbidities, details of the surgical procedures undertaken, waiting times for operations, follow-up consultations, post-operative complications and patient satisfaction. The survey and written consent were offered to all General Practice waiting room patients over a period of two weeks by the authors. Patients were eligible to participate if they had undergone a surgical procedure in Sydney, performed under general anaesthesia within the last five years. The survey was anonymous with no personally identifying information recorded.

Data were analysed using Microsoft Excel 2010 and SPSS software version 22.0. Logarithmic values were calculated for all data sets and t-tests performed for analysis. Chi-squared analyses were conducted to assess the effect of private health insurance on hospital choice.

Results

A total of 107 surveys were eligible for analysis after excluding dental procedures, colonoscopies, procedures performed outside Sydney, emergency procedures, caesarean sections and respondents under 18 years of age.

Table 1 illustrates the characteristics of the sample studied. Notable

differences between responses from high and low SES areas include level of education and private health insurance status. The median ages were 56 for low SES and 66 for high SES (p=0.02). Table 2 displays the types of surgical procedures that were included in the study.

Waiting times

The average waiting time for consultation with a surgeon was 2.5 weeks in the low SES group and two weeks in the high SES group (p=0.449). Private health insurance status did not influence this waiting time. Waiting times for elective surgery were on average six weeks in the low SES group and 2.5 weeks in the high SES group (p=0.002). Possession of private health insurance was associated with a decreased waiting time (p=0.004).

Private health insurance and choice of hospital

Responders with private health insurance were 28.6 times (p < 0.001) more likely to have surgery performed at a private hospital.

Patient satisfaction

Table 3 demonstrates rates of patient satisfaction between the low and high SES groups. There was an overall trend for patients in the lower SES groups to be dissatisfied with waiting times but be generally satisfied with other aspects of surgery.

Demographic	**Low SES (N = 53) n (%)**	**High SES (N= 54) n (%)**
Male Female	22 (41.5) 31 (58.5)	19 (35.2) 35 (64.8)
Age median *(IQR)*	56 (43-72)	66 (54-77)
Employed	20 (37.7)	19 (35.2)
High School education Tertiary education	28 (52.8) 20 (37.7)	15 (27.8) 37 (68.5)
Income: $0-18000 $18001-$37000 $37001+	N = 37 12 (32.4) 7 (18.9) 18 (48.7)	N = 29 6 (20.7) 4 (13.8) 19 (65.5)
Private Health Insurance	18 (34.0)	50 (92.6)
Public hospital procedure Private hospital procedure	34 (64.2) 19 (35.9)	13 (24.1) 41 (75.9)

Table 1. *Sample Demographics*

Discussion

The study found that patients from lower SES groups had less private health insurance and longer wait times for surgery. Despite this, a high level of satisfaction was expressed across both SES groups regarding surgical outcomes and overall medical care during hospital admission.

These findings were anticipated and are consistent with previous research which has shown that patients in the public system experienced longer waiting times and were 60-95% less likely to undergo surgery than private patients. Furthermore, privately insured patients were also found to have greater access to surgical care, shorter overall length of stay and lower mortality rates. [8] This relationship creates the premise that increasing access to private care will relieve the burden on the public system and reduce waiting times. However, the converse has been shown to be the case, with an increase in waiting times for surgery when access to private hospitals is increased. [9] The trend for generally high levels of satisfaction is counter-intuitive, however, is consistent with the literature. [10-11]

The implications of longer waiting times in Western Sydney is of concern because the region's population is expected to grow by 50% over the next 20 years, a growth of 1 million people [12], and the availability of health care services will have to expand to accommodate this increasing population. There are increasing numbers of additions to public hospital elective surgery waiting lists every year. [13] Availability and staffing of beds in public hospitals are lower in the Western Sydney region, and there is a relative lack of private hospitals compared to the wider Sydney metropolitan area [6]. Compounding the issue of access

	Low SES (N = 53) n (%)	**High SES (N= 54) n (%)**
General	17 (32.1)	11 (20.4)
Orthopaedic	19 (35.8)	17 (31.5)
Obstetrics/Gynaecology (excluding Caesarean sections)	5 (9.4)	8 (14.8)
Other*	12 (22.6)	18 (33.3)

Table 2. *Types of surgical procedures*
** includes cardiothoracic, vascular, urological and neurosurgical procedures*

Question	**Low SES (N= 53)**				**High SES (N= 54)**			
	Strongly agree (%)	Agree (%)	Disagree (%)	Strongly disagree (%)	Strongly agree (%)	Agree (%)	Disagree (%)	Strongly disagree (%)
Satisfaction with operation outcomes	56.0	36.0	6.0	2.0	71.7	20.8	5.7	2.0
Satisfied with medical care during admission	63.3	28.6	4.1	4.1	76.9	19.2	3.9	0.0
Dissatisfaction with access to care	8.2	8.2	51.0	32.7	4.0	6.0	24.0	66.0
Waiting time too long	16.3	6.1	49.0	28.6	5.9	2.0	29.4	62.8
Satisfaction with follow-up care	57.8	33.3	9.0	0.00	70.8	27.1	2.1	0.0

Table 3. *Patient Satisfaction*

to healthcare are lower rates of private health insurance membership and the generally poorer health of low SES populations. [6] It becomes apparent that there is a relative lack of services available in low SES areas of Sydney. It is estimated that the cost of funding enough public hospital beds to accommodate a populace of this size would be a minimum of $1.29 billion a year. This poses the risk of escalating inequality in access to health services between the low SES areas of Western Sydney and the wider metropolitan area. [6] The NSW government has invested $1.3 billion from the recent health budget to upgrade existing hospitals [14], however, ongoing funding of these hospitals will need to increase to accommodate the growing demand. [6]

Data were collected from a small number of locations across only three SES regions in Sydney, providing a limited sample size for analysis. Recall bias would also have an impact on accuracy of responses, despite the criteria for a five year cut off. Future research would benefit from increasing data collection across a larger number of SES sites to reduce any possible sample bias. Furthermore, expanding data sources to include hospital databases would minimise recall bias, allowing for more objective and accurate data regarding the length of time spent on surgical waiting lists and utilisation of private health cover.

Conclusion

It is well established that a low SES is associated with poorer health. This study has found that patients from low SES areas experienced longer waiting times for elective surgery. A contributing factor to the longer waiting times was possession of private health insurance. Patients from low SES areas felt that they waited too long for their surgery; however, overall satisfaction ratings were generally high across both SES groups. The interplay between SES and the public and private health systems has created a disparity in access to timely elective surgery.

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Conflict of interest

None declared.

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How do the specialty choices and rural intentions of medical students from Bond University (a full-fee paying, undergraduate-level medical program) compare with other (Commonwealth Supported Places) Australian medical students?

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Introduction: Australian medical schools are demonstrating an increased interest in full-fee paying education, which warrants assessment of possible ramifications on the profile of the Australian medical workforce. This study aims to identify differences in demographics, specialty preferences and rural intentions between domestic full-fee paying undergraduate medical students and all other (CSP) Australian medical students. **Methods:** The data of 19,827 medical students was accessed from the Medical Schools Outcomes Database from 2004-2011. This was then analysed using logistic regression and McNemar's test to identify differences in specialty choice and preferred location of practice. **Results:** Demographically, full-fee paying medical students of Bond University and other Australian medical students were similar in age and gender. However, Bond medical students were less likely to come from a rural background (10% versus 21.7%) and, even after performing logistic regression analysis, still showed a greater preference for future urban practice at both entry and exit of medical school than all other students (entry questionnaire OR = 3.3, $p < 0.01$, and exit questionnaire OR = 3.9, $p < 0.05$). There was no significant difference in preference for higher-paid medical specialties or those in short-supply between Bond medical students and all other Australian medical students.**Conclusion:** Full-fee paying medical students of Bond University demonstrate similar future specialty preferences but are far more likely to come from an urban background and choose urban over rural practice than other medical students. Further research is necessary to better understand the implications of full-fee paying education on the medical workforce.

Introduction

Australian medical schools are demonstrating an increased interest in providing full-fee paying education; in 2004 there were 160 places

for domestic full-fee paying Australian medical students (1.6% of all students), which increased to 932 (7%) by 2008 and 871 (5.1%) in 2013. [1,2] This trend warrants the assessment of possible ramifications on the profile of the Australian medical workforce in terms of specialty and geographical distribution. [3]

There are a number of medical student characteristics and experiences that are known to guide medical training and ultimately impact on the nature and location of their specialty choices. [4-8] This includes demographic characteristics such as gender, background (rural or urban origin), personal and family factors (whether a student has a partner or children), education, personality and interests. [9] Previous research has indicated a pattern of gender distribution amongst medical specialties, where women are more likely to choose general practice and men are more likely to enter other specialist careers (such as surgery, which remains a very male-dominated field). [9] Similarly, male doctors tend to place a higher emphasis on financial remuneration and women are generally more concerned about working hours and flexibility of practice. [8] The perceived prestige and

lifestyle factors associated with certain specialties plays a significant role in specialisation choice. [8,10-12] Clinical exposure to specialty fields is key in influencing some of these preconceived views. [10,13]

It is well documented that there is a significant shortage and maldistribution of doctors in remote and rural Australia, reflecting an increasing awareness that this inadequacy of healthcare needs to be addressed in these communities. [5,6,8-10,12,14-19] Only 23% of Australian doctors practise in places of significant workforce need, where the number of doctors per head of population is 54-65% of that in metropolitan areas. [16] Although programs, research and government incentives have been introduced over the past 20 years to address these problems, the Rural Doctors Association of Australia has reported that less than 5% of medical school graduates have taken up rural practice in the last 15 years and the majority of doctors working in rural areas are international medical graduates on restricted provider numbers. [12,19,20]

Among the many factors that influence medical students to take up rural practice after graduation, the strongest indicator is a rural background, closely followed by positive rural placements. [5,9,15,16,20,21] Rural-practicing doctors are two to four times more likely to be of rural background than those practising in urban areas. [5] However, between 34% – 67% of rural doctors originate from urban backgrounds which is attributed in part to students' rural clinical exposure through scholarships and placements such as the John Flynn Placement Program and the Rural Undergraduate Support and Coordination (RUSC) funded rural experience. [5,22] Training opportunities such as Rural Clinical Schools are also effective in influencing students towards a rural career by allowing students to experience the benefits of rural life first-hand whilst providing effective and innovative medical education. [7,22,23] Now many programs are available for medical students that offer exposure to rural practice. [6,12,17,23,24]

Bond University was the first institution to offer a full-fee paying undergraduate medical course in Australia in 2005 [25], with no direct funding from the Australian Government. Several well-established medical schools followed suit by introducing up to 50% more full-fee paying places in their current medical programs to cater for the student surplus, including international students. [26] While fees vary amongst medical schools for both domestic and international full-fee paying places, they are generally between of $30,000 to $60,000 per annum for a four to six year education. [27] Domestic full-fee paying students do have the option of accessing loans under the Government 'Fee-Help' program to cover a portion of their tuition fees; they are entitled to a lifetime maximum of $112,134 for a medical education (as of 2013) with 20% simple interest, repayable upon graduation and employment. [27]

The aim of this study was to determine whether full-fee paying Australian medical students differ significantly from other medical students in terms of future intended specialty career and rural/urban location of practice. This level of financial burden has raised significant concerns about its implications of medical education accessibility and future workforce specialty distribution. We hypothesised that full-fee paying students would indicate an increased preference for pursuing future urban practice and higher-paying specialties.

Methods

Data was provided by the Medical Schools Outcomes Database (MSOD), a project of the Medical Deans Australia and New Zealand association that is funded by Health Workforce Australia as a means of evaluating rural medical education initiatives. [19] Commencement of Medical School Questionnaires (CMSQ) and Exit Questionnaires (EQ) are administered to all medical students on entry to and graduation from all Australian medical schools and at the end of the first postgraduate year.

Independent variables

The main independent binary variable of comparison represented whether the student attended Bond University's full-fee paying undergraduate medical program or not. Other independent variables included in each analysis were the student's sex, age when they began medical school, the year they began medical school, whether they are of rural background and their marital status.

Dependent variables

Preference for urban versus rural future medical practice was re-categorised into a binary variable from the original questionnaire categories: Those who chose to practice in a small community, small town, regional city or town were considered to be rural candidates. Those who chose to practice in a capital or major city centre were considered to be urban candidates.

Two variables were created to explore preferences for future medical specialty. The first of the two is a binary variable that assesses the preference for choosing a higher-paying specialty. Students who chose surgery, obstetrics and gynaecology, radiology, intensive care medicine or emergency medicine—which are the top five specialties rated as the highest paid in the '2010 Medicine in Australia: Balancing Employment and Life (MABEL)' study—were considered in pursuit of a higher-paying specialty. The second binary variable examined the preference for choosing a specialty in-demand (not necessarily highest paid). [24] Students who chose general practice, psychiatry, obstetrics and gynaecology, pathology, ophthalmology or radiology—which are predicted to be the top six specialties in short supply by 2025 by the Health Workforce of Australia (HWA)—were considered in pursuit of a specialty in-demand. [28]

Statistical analysis

Independent samples t-tests were used to compare differences between medical students of Bond University and all other Australian medical students on demographic background variables (Table 1). Logistic regression was used for comparisons between full-fee paying medical students of Bond University and all other Australian medical students in analyses of preferences for the three dependent variables listed above. Data on preferences for rural versus urban practice, for the top five paid, and six most in-need specialties were analysed at two data collection time points: on entry to medical school (CMSQ) and exit from medical school (EQ), resulting in six logistic regression models comparing full-fee paying undergraduate medical students with all other medical students. McNemar's test was used to analyse changes in student rural future practice and specialty preferences between the time that they entered and exited medical school, and logistic regression to explore changes through time between cohorts in these preferences.

Demographics	Bond University full-fee paying medical students	Other Australian medical students
Commencement Questionnaire	496	18,161
Exit Questionnaire	116	5,426
Male : Female	48.8% : 51.2%	46.6% : 53.4%
Mean Age (yrs)*	21.82	21.28
Rural Background^*	10.0%	21.7%

Table 1. *A summary and comparison of the baseline demographics for full-fee paying medical students of Bond University and students of other Australian medical schools.*
**p<0.01 ^Students who have chosen on their questionnaire that they are from a small community or smaller town; versus, those considered as not rural who indicated that they were from a regional city, large town, major urban centre, or capital city.*

Preference for	Bond University full-fee paying medical students		Other Australian medical students	
	Entry	Exit	Entry	Exit
Rural practice	33 (6.7%)	4 (3.5%)	3868 (21.3%)	841 (15.5%)
Top 5 Best Paid Specialties	166 (33.5%)	55 (47.4%)	5503 (30.3%)	2138 (39.4%)
Top 6 in Short Supply Specialties	105 (21.2%)	19 (16.4%)	3650 (20.1%)	1346 (24.8%)

Table 2. *Numbers and proportions of students who stated a preference for rural practice, any of the top 5 paid specialties, and any of the 6 specialties predicted to be in short supply by 2025.*

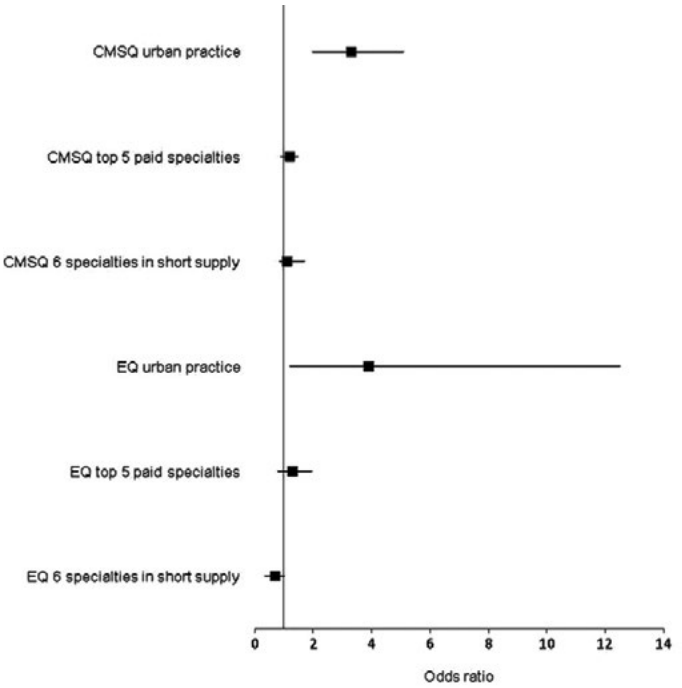

Figure 1. *Summary of results for specialty and urban/rural practice preference.*

Ethics Approval

Approval was provided by all universities for the MSOD project, which applies to this paper. Permission was requested and approval given by MSOD to use their data for this research article (MR-2013-002).

Results

The results of the McNemar's tests showed no statistically significant difference for full-fee paying medical students of Bond University who completed both entry and exit questionnaires (n = 94), but that in all other medical students (n = 3760) there was a significant drop in intention to practice rurally, and an increase in preference for a top 5 paid specialty and specialties predicted to be in short supply (p-values < 0.001). In addition, there was evidence of cohort effects in CMSQ preferences amongst all medical students: between 2005 and 2011 cohorts entering medical school, later cohorts of students had a greater preference for urban future practice. The cohort effect odds ratio was 1.07 (p < 0.001; 95% CI: 1.04-1.10). Later cohorts were less likely to select a future specialty on the list of six most in-need (OR = 0.95, 95% CI: 0.94-0.98, p < 0.001) but were not more or less likely to prefer a top 5 paid specialty. No significant cohort effects were observed in the exit questionnaire analyses, although it should be noted that the exit data only included four cohorts (2008-11).

Demographics and practice choices	OR	95% CI	p-value
Selecting a higher paying specialty			
Older students+	0.98	0.97-0.98	< 0.0001
Male (vs female) students	1.40	1.31-1.50	< 0.0001
Male (vs female) graduates++	1.53	1.33-1.76	< 0.0001
Married graduates	0.89	0.83-0.96	< 0.001
Selecting a specialty in short supply			
Older students	1.02	1.02-1.03	< 0.0001
Married students	1.34	1.12-1.53	< 0.0001
Rural background students	1.41	1.30-1.54	< 0.0001
Males (vs female) students	0.61	0.55-0.66	< 0.0001
Married graduates	1.16	1.09-1.24	< 0.0001
Male (vs female) graduates	0.60	0.52-0.68	< 0.0001
Choosing future urban practice			
Male (vs female) students	1.49	1.36-1.64	< 0.0001
Male (vs female) graduates	1.26	1.03-1.54	0.03
Unmarried students	0.74	0.63-0.88	< 0.0001
Unmarried graduates	0.84	0.77-0.92	< 0.0001
Choosing future rural practice			
Urban students	0.08	1.30-1.54	< 0.0001
Urban graduates	0.18	0.15-0.22	< 0.0001
Younger students	0.97	0.95-0.98	< 0.0001
Younger graduates	0.96	0.94-0.98	< 0.0001

Table 3. *Odds ratio comparing students and graduates of Bond against other universities on practice choices.*
+ 'Students' denotes results taken from the commencement of medical school questionnaire (CMSQ)
++ 'Graduates' denotes results taken from the exit (of medical school) questionnaire (EQ)

Both commencement and exit of medical school surveys showed that full-fee paying medical students of Bond University had a significantly greater preference for future urban practice than other Australian medical students (Figure 1).

Age on entry to medical school, gender, marital status and whether the student was from a rural background were statistically controlled in all six analyses.

Analyses performed using logistic regression; 95% CIs aforementioned in Results text; p < 0.05.

OR > 1.0 indicates variable in favor of full-fee paying medical students of Bond University.

OR < 1.0 indicates variable in favor of other Australian medical students.

Analyses shows that full-fee paying medical students of Bond University were neither more likely to have a preference for the top five paid medical specialties, nor more likely to pursue the top 6 specialties predicted to be in need by 2025, when compared with all other medical students in Australia (Figure 1).

Of the variables which were statistically controlled in the logistic regression analyses, a number were significant predictors of the three outcomes. These findings have been summarised in Table 3. At entry to medical school, older students and women were less likely to select a top five paid specialty and women remained less likely to select a top five paid specialty at exit. Married students were significantly less likely to choose any top five paid specialty as their first preference on exit. Specialties in short supply were selected at entry by those who were older, married, from a rural background or female and at exit by those who were married or female. Coming from an urban background was a strong predictor of not preferring future rural medical practice at both entry and exit from medical school and men were oriented towards urban practice. Younger students stated less preference for rural practice and unmarried students stated a lesser preference for future urban practice.

Discussion

Interestingly, in contrast to our hypothesis, we found that full-fee paying medical students of Bond University were not more or less likely to prefer the highest-paid medical specialties when compared with other Australian medical students. There were also no significant differences in preference for specialties predicted to be in short supply. This result implies that the full-fee paying nature of education is not a significant influential factor in future specialty preferences whilst supporting the idea that this choice may be guided by other demographic and experiential factors documented in the literature.

More students in general (that is, including students of Bond and all other medical schools) had a tendency to select a top-paid specialty by the end of medical school compared to entry.

So the potential generalised 'commercialisation' of students' motivations during medical training remains a point of concern despite the apparent validation of full-fee paying training as an unlikely implicating factor. There are no papers in the current Australian literature specifically exploring the factors influencing medical students in this choice, so we can only theorise on the circumstances affecting the decisions to pursue a higher-paid specialty. This trend may indicate that students begin medical school with more altruistic and rural intentions, but change their minds during training and come to place greater importance on financial return as they mature through their educational experience. Cohort effects may also play a role (that is, whether more recent student cohorts are more oriented towards future urban practice and career earnings). The trends of student specialty preference being affected by financial debt obtained during training and potential remuneration in higher paid specialties are being increasingly explored in American and Canadian literature. [29, 30]

At exit from medical school, fewer Australian medical students, in general, planned to work in a rural area than at entry, despite the numerous incentives and rural programs to encourage rural medical practice. The decrease in preference for rural practice by graduation in all Australian medical students may reflect the small number of regional medical schools or limited opportunity for rural placements, and factors such as specialty choice and training in urban areas. It is nonetheless clear that full-fee paying Bond medical students are more likely to prefer urban practice when compared against other Australian medical students. This may suggest the need for further modification of medical school recruitment and admission processes at privately funded institutions to focus on students who demonstrate either a rural background or interest in rural practice. There are current opportunities for students who are keen to undertake rural clinical clerkships at all medical schools through various in-curricular and extra-curricular activities. However, unlike their commonwealth-supported counterparts, privately-funded medical schools are not mandated to enforce their students to receive this rural exposure. Ensuring a rural clinical rotation could be a potential avenue for encouraging more students to pursue rural and remote practice. James Cook University (JCU) has designed its medical program specifically to recruit and prepare doctors to work in rural and remote locations. Their program is characterised by a selection process targeting students of regional and remote backgrounds, a rural community orientated curriculum, increased engagement with Aboriginal and Torres Strait Islander health issues and more frequent and extended rural clinical placements. [31] As a result, at graduation, 88% of JCU medical students intend to practise outside Australian capital cities, compared to 31% of graduates from other medical schools. [31]

The conclusions of this study are limited by the difference in sample size between full-fee paying undergraduate medical students and all other students (496 compared to 18161). This restricted the potential for statistically significant subgroup data analysis. A further qualitative study would be useful in clarifying student motivations and influencing factors in decision making of future specialty choice and location of practice. There is, as yet, no long-term data of how students' preferences translate to actuality, with the first students who contributed to the MSOD project still in their early postgraduate years. Ongoing follow-up of students may also shed further light on factors that influence doctors at all stages of training. There is an increasing emphasis on medical schools becoming 'socially accountable' in their training of physicians, in order to respond to current and future health needs and challenges in society, which includes the maldistribution of doctors. [32] The initiatives that medical schools undertake in an effort to fulfil the criteria presented by the World Health Organisation (WHO) for social accountability are designed to impact the training of medical students and therefore may be partially accountable for graduate specialty preferences. Further research is being conducted to clarify whether a full-fee-paying medical student education and potential associated debts can influence specialty choice, particularly higher income specialties. [33]

Conclusion

Full-fee paying medical students of Bond University are more likely to come from an urban background and prefer urban over rural practice at exit of medical school when compared with all other Australian medical students. This is a point of concern and may inform future modifications to medical school admission processes as well as more opportunities for rural clinical exposure in the curriculum. Nonetheless, they remain similar to all other Australian medical students in terms of demographic characteristics and preference for higher-paying specialties and those in short supply. Future research is directed to assess the long term impact on medical workforce distribution and specialty choice of full-fee paying medical education in Australia.

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Conflict of interest

None declared.

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Health literacy and patient comprehension in the pre-anaesthetics consultation

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Background: The concept of health literacy and patient comprehension is important, especially in the area of patient consent for surgical procedures. This extends to the pre-admissions anaesthetic consultation where poor patient health literacy can have an impact on the patient's comprehension of risks. **Objectives**: This exploratory study aims to investigate the level of health literacy and comprehension in a population of patients attending a pre-admissions anaesthetic clinic. **Methods**: A cross-sectional study design was used to survey adult participants (≥18yrs old) attending a regional based pre-anaesthetics clinic. Information gathered as part of the survey included demographic information, health literacy scores (via a previously validated tool), and questions pertaining to the comprehension of their consultation. **Results**: In total, 51 patients participated in the study. Patients were divided into two subgroups (inadequate/marginal vs. adequate), depending on their screened level of health literacy. Those with inadequate/marginal health literacy were significantly more at risk of having inadequate comprehension than those with adequate health literacy (p = 0.01). There was no statistically significant difference between health literacy levels and a variety of demographic indicators, including education level and employment status. **Conclusion**: Patients with inadequate or marginal screened health literacy scores were less likely to comprehend the information provided to them as part of their pre-admissions consultation. These results suggest that screening patients for their health literacy levels may be advantageous, in that information provided can be tailored to their individual needs. Further research is however required.

Introduction

Health literacy is broadly defined by the World Health Organisation (WHO) as the "cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health". [1] By using this definition, the concept of health literacy is more than just encompassing health education and communication – it also addresses the underlying environmental, political, and social factors that can determine health. It is important to note that health literacy does not just encompass the ability of a patient to understand a diagnosis or make an appointment, but is also critical for good patient engagement with the medical system. This is important in an Australian context as research suggests that up to 59% of Australians have inadequate health literacy skills. [2]

Inadequate or poor health literacy has been linked with poor health outcomes. [3,4] These poor health outcomes result from a combination of factors which include but are not limited to: poorer health-related knowledge and comprehension, [3] difficulty understanding diagnosis and treatment recommendations, [5] inappropriate use of resources – including decreased use of preventative health measures and an increase in emergency department presentations [4] and poor medication compliance. [6] Poor health literacy can further negatively impact on older adults, who are more likely to experience poorer overall health status [7] and higher mortality rates, [8,9] as compared to older adults with adequate health literacy.

Pre-admissions anaesthetic clinics are used to deliver important information to patients. Consultations within these clinics aim to ensure that the patient is optimally prepared for the operation or surgical procedure by providing them with relevant and essential information. [10] A comprehensive pre-admissions anaesthetic consultation and assessment is a valuable exercise because it can result in reduced: in-patient length of stay following the procedure/surgery, [11] case cancellations and/or further delays on the day of the procedure/surgery. [12] Two of the key elements communicated to patients during the pre-anaesthetics consultation include the risks involved with the procedure/surgery and the potential risks associated with receiving anaesthetic agents. This information is typically provided to patients using both verbal and written communication strategies, [13] which can be inadequately comprehended by the patient with poor health literacy skills. [14]

A recent study conducted by Kadakia et al., [15] identified that inadequate health literacy could potentially predict poor patient

comprehension of their orthopaedic injury and surgical intervention – including understanding the risks involved with the procedure. It could be argued therefore, that there is a rationale for screening for health literacy levels, and identifying those at risk of poor comprehension, as part of the pre-admissions anaesthetic clinic routine practices. By screening and identifying these patients, additional measures could be used by the physician to ensure the optimisation of patient understanding, including understanding of potential risks associated with the procedure. However, there appears to be a paucity of evidence regarding a patient's understanding of the pre-admission anaesthetic consultation, and the effect of health literacy in predicting comprehension of information provided to them during these consultations.

This exploratory pilot study aimed to assess the level of health literacy and comprehension of health information delivered to patients attending a regional pre-admissions anaesthetic clinic.

Methods

Following human ethics approval from the University of Wollongong Human Research Ethics Committee (Ethics No. GSM13/048), this study utilised a cross-sectional survey design which included the self-completion of an anonymous questionnaire. Upon verbal consent being given, participants aged 18 years and above were provided with a questionnaire by the clinic nursing staff, which was to be completed at the end of the pre-anaesthetics consultation. The clinics were run either by an anaesthetic consultant, or by a qualified GP anaesthetist, and was set in a New South Wales based regional pre-admissions anaesthetics clinic.

Potential participants presented to the pre-admissions anaesthetics clinic for a wide range of elective surgical procedures, including; ophthalmic, Ear/Nose/Throat (ENT), orthopaedic, and general surgical procedures. The anonymous questionnaire comprised three components. The first component gathered demographic information. The second component included the following three validated health literacy questions, [16,17] which were rated on a 5-point Likert scale:

- How often do you have someone help you read hospital materials? (5 = 'Never'; 4 = 'Occasionally'; 3 = 'Sometimes'; 2 = 'Often'; 1 = 'Always').
- How confident are you filling out medical forms by yourself? (5 = 'Extremely'; 4 = 'Quite a Bit'; 3 = 'Somewhat'; 2 = 'A Little Bit'; 1 = 'Not At All').
- How often do you have problems learning about your medical condition because of difficulty understanding written information? (5 = 'Never'; 4 = 'Occasionally'; 3 = 'Sometimes'; 2 = 'Often'; 1 = 'Always').

These three questions were chosen based on a previously validated system for stratifying health literacy in an efficient and rapid manner. [17] In order to analyse health literacy in this patient population, participants were stratified into either adequate or inadequate/marginal health literacy. Those participants with a response of 'Somewhat' or 'Sometimes' (correlating with a Likert score of 3) and below were deemed to have either inadequate or marginal health literacy. Deficiency in one or more of the three questions was deemed sufficient to classify patients as having overall inadequate or marginal health literacy. Those above this cut-off for all three questions were deemed to have adequate health literacy.

The third component of the questionnaire included seven questions about the patient's comprehension of information provided during the pre-anaesthetics consultation, which have not been previously validated. They included a range of questions about health information, which is commonly discussed during pre-anaesthetic consultations. Responses to the following seven questions were categorised via three responses; yes, no, and unsure:

- Do you know what operation or procedure you are having? (Yes, No or Unsure).
- Do you understand why you are having the operation or procedure? (Yes, No or Unsure).
- Do you understand the potential complications of your operation or procedure? (Yes, No or Unsure).
- Do you understand the potential complications of the anaesthesia? (Yes, No or Unsure).
- Do you understand where you will be after your operation or procedure? (Yes, No or Unsure).
- Do you know what to expect after you wake up? (Yes, No or Unsure).
- Was there one or more times during your time with the doctor where you were not sure of what he was saying? (Yes or No).

To score patient comprehension, the results of this third component of the anonymous questionnaire were tabulated and a score out of seven given. A score of 1 was given for each affirmative response for the first six questions. For the final question, a score of 1 was given if the patient understood the anaesthetist throughout the entirety of the consultation. A patient with a total score of ≥6 was deemed to have adequate comprehension of the consultation, whereas any patient with a total score <6 was deemed to have inadequate comprehension. This measure of patient comprehension was devised for this study, and is not based on any previously validated tools. Consequently, this is an exploratory study and the scoring system for comprehension will need validation in the future. Descriptive statistics were used to analyse the data. Associations between variables were analysed using chi-square analysis. [18] The level of significance was set at $p < 0.05$.

Results

Patient Characteristics

A total of 51 responses were received from study participants between February and April 2014, with all received questionnaires completed in a satisfactory manner. The mean age of the participants was 64.8 ± 13.6 years, with the ages ranging from 18 to 84 years. In the majority of cases, participants were from either the category "had completed high school" or "had not finished ", and 61% of the participants were not in the labour force. (Table 1)

Health Literacy and Patient Comprehension

Of the total participants, 76% (n = 39) were deemed to have adequate health literacy, as compared to 24% (n = 12) with inadequate/marginal health literacy. In addition, the majority of the participants (n = 43; 84%) had adequate comprehension scores of the consultation, rather than inadequate comprehension scores (n = 8; 16%). When the comprehension scores are viewed within each health literacy grouping, 42% (n = 5) of those with inadequate/marginal health literacy also had inadequate comprehension. The proportion of those with inadequate comprehension was less amongst those with adequate health literacy (n = 3; 8%). These statistics are reflected in figure 1.

Analysis

Chi-square analysis demonstrated that there was a statistical difference between the two groupings of health literacy in relation to their comprehension of the anaesthetics consultation ($p = <0.01$). Chi-square analysis was also performed in regards to employment status (employed vs. unemployed/not in labour force) and education level attained (education of High School or lower vs. education beyond High School). These groupings were used due to the low level of participants in some groups. There was no statistically significant difference between the previously stated health literacy groups in regards to both level of education attained ($p = 0.356$) and employment status ($p = 0.494$) at the time.

Discussion

The issue of patient comprehension in the delivery of information regarding the pre-admissions anaesthetic consultations and procedural risks cannot be understated. Without the ability to correctly understand and interpret both verbal and written information patients

Variable	*Category*	*Number of Participants (%)*
Gender	Male Female	30 (59%) 21 (41%)
Level of Education Attained	Did Not Complete High School Completed High School Diploma or Advanced Degree Bachelor Degree and Above	10 (20%) 28 (55%) 6 (12%) 7 (14%)
Employment	Not in Labour Force Unemployed Employed	31 (61%) 6 (12%) 14 (27%)

***Table 1**: Participant Characteristics*

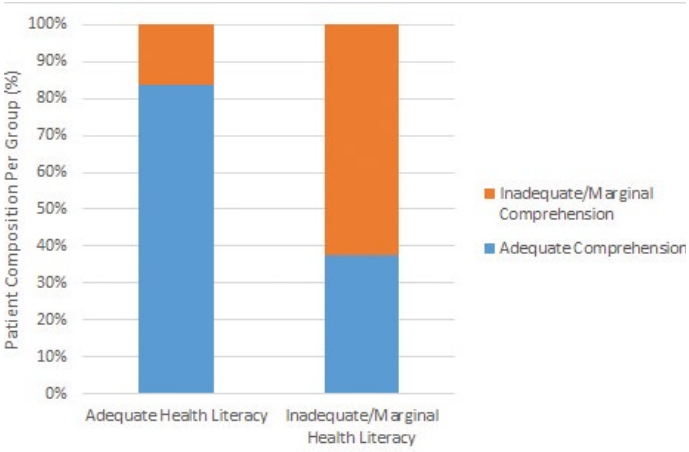

Figure 1: *Associations of Health Literacy with Patient Comprehension*

will be unable to provide accurate consent to their procedure, and they will also be at risk of poor health outcomes because they may have misunderstood important information regarding their procedures. If we could identify this at-risk patient group by using a quick and cheap assessment of health literacy, additional resources and techniques could be utilised to improve patient understanding that would otherwise be absent in the standard pre-admissions anaesthetic consultation. Upon analysis of the data, a significant difference was found between the health literacy groups in terms of comprehension of the pre-anaesthetics consultation.

The findings of patient comprehension in the pre-admissions anaesthetics consultation mirror that of a number of other studies. Similar findings by Kadakia [15] and Wallace [19] show that a lower level of health literacy can place patients at risk of poor comprehension. This can and has been used as a predictor for patients at risk of misinterpreting health care information. For example, the study by Kadakia [15] examined comprehension and health literacy in an orthopaedic trauma patient population. They used the same questions by Chew et al. [16] to delineate patients into inadequate and adequate health literacy, and then tested patient comprehension and knowledge of their procedure. They found a significant link between poor health literacy and poor patient comprehension and retention of information about their procedure. However they also found that patient comprehension depended on educational level, which was not replicated in this study. This may have been due to the larger sample size of the Kadakia study. However, their suggestion of an increased focus on patient communication by medical staff can also be applied in the pre-anaesthetics consultation.

Predicting Patient Comprehension

Since this study demonstrated that health literacy can have an impact on overall patient comprehension, it could be recommended that screening of health literacy should be an important addition to pre-anaesthetic clinic consultations. Doing so would help to identify those patients at greatest risk of poor comprehension and would allow for the delivery of information, which was targeted toward individual patient needs. The anaesthetists in this study could then have improved patient comprehension by employing a variety of techniques. These could include using simple and easy to understand language and by speaking slowly, [20] asking patients to repeat back basic information [21], and by having a longer consultation time. [22]

One component that this study did not explore was the effect that supplementary information can have on further improving patient comprehension. In theory patient leaflets should be a very useful tool in assisting patients with comprehension of their medical procedure and management of their condition, before and after their procedure. However, many patient information leaflets are written at levels in excess of the mean patient literacy, [23] often including too much information, which may be irrelevant to the patients' needs. [24] Information provided to patients during these education sessions, should therefore be aimed at an appropriate level for the target audience. Furthermore, using culturally appropriate images that are linked to either spoken or written information can also be additional useful strategies to help improve patient retention and comprehension of health information provided during consultations. [25]

Limitations and Future Research

The nature of the current study resulted in a small sample size, without the assumed entirety of patients presenting to the pre-anaesthetics clinic being sampled. This small sample size limits the statistical power of the study. It is also possible that some of the non-significant differences may trend towards significance with a larger sample size. Due to the study being an anonymous survey, it would be speculative to estimate patient uptake of surveys. In addition, those patients with poor health literacy and/or patient comprehension may not have attempted to complete the questionnaire. This introduces a level of selection bias towards those with higher levels of health literacy, something that could be potentially avoided if it was a compulsory part of the pre-anaesthetics consultation workup. In addition, assistance could be provided to these patients in completing the survey after their consultation. The exploratory nature of the study, as well as the use of a scoring system for comprehension that has not been validated, also limit this study. In particular, validation of the scoring criteria for comprehension would be vital. Furthermore, measurements of both inter-rater and intra-rater reliability were not performed.

There were also a number of confounding factors, which need to be considered as part of the current study. For instance, different anaesthetists were involved throughout the duration of the study. As a result this study was unable to allow for the potential differences in information delivery from each of these health professionals. It is also feasible that word of mouth from the study may have led to the anaesthetists themselves changing their approach to information delivery. Additionally, due to the variety of surgical specialties and procedures that were included, it is possible that the complexity of the procedure would have influenced the patient's comprehension. In light of this variety in the delivery of information, perhaps future inclusion of a patients' overall satisfaction with the delivery of health information would be beneficial, as well as the anaesthetists overall impression of the patient's level of health literacy and comprehension of the consultation.

Language could be seen as another confounding factor and barrier to comprehension of the anaesthetic process. In fact, this could also have led to some patients declining to enter the study itself. This could be avoided in future studies by either excluding patients from a Non-English Speaking Background (NESB), or utilising this as an additional demographic data for future analysis. The patient's postcode and socio-economic status could also have a profound effect on health literacy and patient comprehension, and were not assessed in this study.

In terms of the patient understanding the anaesthetist, perhaps a qualitative component could be included in future studies. From this, we could further investigate barriers and facilitators, which may have impacted upon the patient's ability to understand their anaesthetist. Moreover, future studies could also assess patient recall regarding important information imparted to them as part of the consultation. An additional component that should be included in future analysis is the proportion of patients who returned surveys out of the entire population presenting to the pre-anaesthetics clinic.

The results of this study warrant further research, potentially by addressing the limitations addressed above. This would include a larger sample population size, over a longer period of time, and should potentially include multiple sites. In addition, developing a validated scoring of comprehension would be beneficial in future analysis. By increasing the sample size and including a validated score of comprehension, stronger statistical analysis could be performed. A study of this kind could be replicated in a variety of areas of medicine where comprehension of risks and complications is needed.

Conclusion

The results of this study suggest that screening for at-risk patients prior to attending a pre-admissions anaesthetic clinic may be beneficial in identifying patients with poor health literacy. Such individuals could have information tailored to maximise comprehension of the pre-admission anaesthetic consultation. Further research in these areas is warranted.

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Conflict of interest

None declared.

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General practitioner awareness of pharmacogenomic testing and drug metabolism activity status amongst the Black-African population in the Greater Western Sydney region

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Background: Individuals of black-African background have a high variability in drug metabolising enzyme polymorphisms. Consequently, unless these patients are tested for these polymorphisms, it becomes difficult to predict which patients may have a sub-therapeutic response to medications (such as anti-depressants) or experience an adverse drug reaction. Given the increasing population of black-Africans in Australia, GPs are on the front line of this issue, especially in Greater Western Sydney (GWS) – one of the country's rapidly increasing populations due to migration. **Aim:** To ascertain the awareness of GPs regarding drug metabolising enzyme polymorphisms in the black-African population and pharmacogenomic testing in the GWS community. **Methods:** A descriptive, cross-sectional study was conducted in GWS by analysing GP responses to a questionnaire consisting of closed and open-ended questions. **Results**: A total of 46 GPs completed the questionnaire. It was found that 79.1% and 79.5% of respondents were unaware of: the high variability in drug metabolism enzyme activity in the black-African population and pharmacogenomic testing (respectively). No respondents had ever utilised pharmacogenomic testing. Only a small proportion of GPs "always" considered a patient's genetic factors (13.9%) and enzyme metaboliser status (11.1%) in clinical practice. Preferred education media for further information included written material, direct information from other health professionals (such as pharmacists) and verbal teaching sessions. **Conclusion:** There was a low level of awareness of enzyme metaboliser status and pharmacogenomic testing amongst GPs in GWS. A future recommendation to ameliorate this includes further education provision through a variety of media noted in the study.

Introduction

Depression accounts for 13% of Australia's total disease burden, making it an important health issue in the current context. [1] General Practitioners (GPs) are usually the first point of contact for patients seeking help for depression. [2,3] Antidepressant prescription is the most common treatment form for depression in Australia with GPs prescribing an antidepressant to treat up to 40% of all psychological problems. [2] This makes GP awareness of possible treatment resistance or adverse drug reactions (ADRs) to these medications vital.

Binder et al. [4] described pharmacogenomics as "the use of genome-wide approaches to elucidate individual differences in the outcome of drug therapy". Detecting clinically relevant polymorphisms in genetic expression can potentially be used to identify susceptibility to ADRs. [4] This would foster the application of personalised medicine by encouraging an inter-individual approach to medication and dose prescriptions based on an individual's predicted response to medications. [4,5]

Human DNA contains genes that code for 57 cytochrome (CYP) P450 isoenzymes; these are a clinically important family of hepatic and gastrointestinal isoenzymes responsible for the metabolism of over 70% of clinically prescribed drugs. [5-10] The CYP family of enzymes are susceptible to polymorphisms as a result of genetic variations, influenced by factors such as ethnicity. [6,5,10] Research has shown that polymorphisms in certain CYP drug metabolising enzymes can result in phenotypes that class individuals as "ultrarapid metabolisers (UMs), extensive metabolisers (EMs), intermediate metabolisers (IMs) and poor metabolisers (PMs)."[6,10] These categories are clinically important as they determine whether or not a drug stays within the therapeutic range. Individuals with PM status may be susceptible to experiencing ADRs as a result of toxicity, and conversely, those with UM status may not receive a therapeutic effect. [5,6,10,11]

When considering the metabolism of antidepressants, the highly polymorphic CYP enzymes: CYP2C19 and CYP2D6 are known to be involved. [5,10,12] A study by Xie et al. [13] has shown that for the CYP2D6 enzyme alone, allelic variations induce polymorphisms that result in a PM phenotype of "~1%" in Asian populations, "0-5%" among Caucasians and a variation of between "0-19%" in black-African populations. This large disparity of polymorphism phenotypes was reproduced in a recent study, which also showed that the variation is not exclusive to the CYP2D6 enzyme. [6] It has been reported that the incidence of ADRs among PMs treated with drugs such as antidepressants is 44% compared to 21% in other patients. [5,14] Consequently, increased costs have been associated with the management of UM or PM patients. [5]

The black-African population in Australia and specifically Sydney (where GWS is one of the fastest growing regions) continues to rise through migration and humanitarian programs. [15-18] Almost 30% of Africans settling in Australia in the decade leading to the year 2007 did so under humanitarian programs including under refugee status. [15-17] As refugees are at a higher risk of having mental health problems including depression due to their traumatic histories and post-

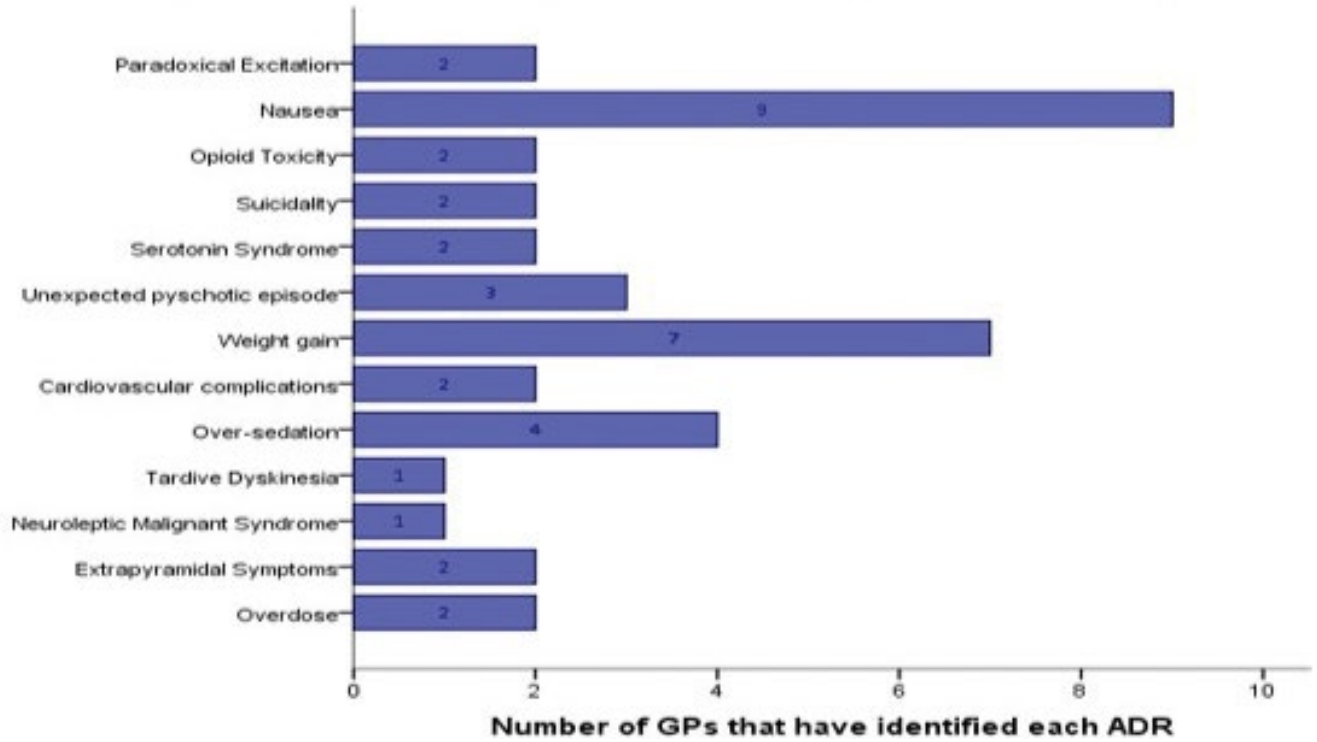

Figure 1: *The total number of GPs identifying each of the 13 ADRs in patients of black-African background being treated with antidepressants. A total of 18 GPs responded to this question.*

migratory difficulties, GPs in GWS face increased clinical interactions with black-Africans at risk of depression. [19,20] Considering the high variability of enzyme polymorphisms in this population, pharmacogenomic testing may play a role in the primary care of these patients. We therefore conducted a study to assess GP awareness of pharmacogenomic testing and the differences in enzyme metaboliser status (drug metabolism phenotypes). We also investigated the GP preferences of media for future education on these topics.

Methodology

Study Design and Setting

This is a descriptive, cross-sectional study. Ethics approval was granted by the Human Research Ethics Committee.

Considering GWS is the fastest growing region in Sydney, we focussed on particular suburbs in GWS (Blacktown, Parramatta and Holroyd Local Government Areas). [17-20] Using geographical cluster sampling, a list of GP practices were identified with the aim of recruiting 50 participants.

Study tool

Data was collected using a questionnaire validated by university supervisors and designed to elicit the level of understanding and awareness among GPs. The main themes of the questionnaire involved: questions regarding basic demographic information; questions aimed at determining the level of GP awareness regarding differences in drug metabolising phenotypes and pharmacogenomic testing; and open-ended questions eliciting the preferred methods of education with respect to pharmacogenomic testing.

Data Collection

We invited 194 GPs between April and May 2014 to participate in the study. The questionnaire and participant information sheet were either given to the practice managers or to the GPs in person. Questionnaires were collected in person within the following two weeks.

Data Analysis

Data was analysed using SPSS (version 22, IBM Australia). Descriptive statistics were used to summarise findings, with p-values calculated using Chi-square analysis (with Yates correction) to compare two sets of data. A p-value of <0.05 indicated statistical significance.

Influencing factor	***No. of GPs***
Clinical picture (patient age, ethnicity, response to drugs, disease severity and drug class being prescribed)	5 out of 9
Patient factors (including: compliance and cost of testing)	3 out of 9
Reliability of testing (including: sensitivity and specificity)	1 out of 9

Table 1: *Factors influencing the potential use of pharmacogenomic testing in GPs who are already aware of testing methods.*

Medium	***No. of GPs using each medium***
Direct information from other specialties	3 out of 8
Written material (online or hard copy)	4 out of 8
Verbal teaching, peer discussions, presentations	4 out of 8

Table 2: *Learning media used by aware GPs to find out about pharmacogenomic testing.*

Medium	***No. of GPs using each medium***
Written material (online or hard copy)	32 out of 39
Verbal teaching, peer discussions, presentations	15 out of 39

Table 3: *Preferred learning mediums proposed by GPs for gaining education regarding pharmacogenomic testing.*

Results

The overall response rate was 23.7% (46/194). Our respondents included: 27 females and 19 males. The mean number of years of experience in general practice was 13.9 and most GPs (93.4%, 43/46) had received some form of training in antidepressant prescription in the last 5 years. The number of patients of black-African background seen in the last 6 months ranged from 0 to greater than 100. Only 26.1% (12/46) of GPs reported no consultations with a patient of black-African background within this timeframe. Of the 73.9% (34/46) of GPs who had seen at least one patient from this cohort, 55.9% (19/34) had treated at least one patient for depression with antidepressants.

GPs experience of ADRs in patients of black-African background treated for depression

From 46 participants, 19 had treated a patient of black-African background with antidepressants, 18/19 reported having identified at least one ADR (Figure 1).

GP awareness and consideration of drug metabolism activity status and genetic factors

Awareness amongst GPs of the different drug metabolism activity phenotypes in black-Africans was low with 79.1% (34/43) being unaware. Patients' genetic factors and enzyme metaboliser status were "always" considered by only 13.9% (5/36) and 11.1% (4/36) of GPs, respectively. There was no statistically significant difference regarding awareness between GPs who had treated black-African patients and those who had not (21.1% vs 13.3% respectively, p=0.89).

GP awareness and use of pharmacogenomic testing

The awareness of methods for testing a patient's key drug metabolising enzymes, also known as pharmacogenomic testing, was extremely low with 79.5% (35/44) of GPs being unaware of the testing methods available in Australia. Of the 20.5% of GPs (9/44) who were aware, none had utilised pharmacogenomic testing for their black-African patients. These nine GPs then nominated factors that would influence their utilisation of pharmacogenomic testing on these individuals. Three main categories of influence emerged (Table 1). When specifically asked whether they would be more inclined to utilise pharmacogenomic testing on black-African patients who had previously experienced ADRs, 88.9% (8/9) GPs stated that they would be more inclined.

Preferred education media

GPs that were aware of pharmacogenomic testing were asked, through an open-ended question, how they obtained information regarding these methods. Three main categories were identified based on their responses (Table 2). All GPs were then asked to note down their preferred medium of education for pharmacogenomic testing (Table 3). Multiple responses were allowed.

Discussion

This study showed that there is a low level of awareness regarding pharmacogenomic testing and the differences in drug metabolism phenotypes among GPs. Additionally, we identified the preferred education media for providing information to GPs (Table 3). Awareness of pharmacogenomic testing and of the differences in drug enzyme metaboliser status (phenotype) could be valuable in the clinical setting. Improved patient outcomes have been noted when doctors are able to personalise management based on information from pharmacogenomic testing,[21] with Hall-Flavin et al. [21] noting significantly improved baseline depression scores amongst patients with depression whose doctors were provided with information on pharmacogenomics.

A previous study reported that a high proportion (97.6%) of physicians agreed that differences in genetic factors play a major role in drug responses. [22] Whilst it is arguable that knowledge of genetic factors holistically playing a role in drug response may be universal, our study specifically focussed on the knowledge of differences in enzyme metaboliser status. It was found that 79.1% of GPs (34/43) were unaware, with only a small number of GPs "always" considering enzyme metaboliser status (11.1%) in their management. Given the aforementioned importance of genetic factors and the potential to reduce ADRs using personalised medicine, this is an area for improvement.

When considering pharmacogenomic testing, we found 79.5% (35/44) of GPs to be unaware of testing methods. No GP had ever utilised pharmacogenomic testing, this low rate of utilisation is also reported previously in other several studies. [22-24] A lack of utilisation and awareness arguably forms a barrier against the effective incorporation of personalised medicine in the primary care setting. These low figures represent a lack of education regarding pharmacogenomics and its clinical applications. This is an issue that has been recognised since the arrival of these testing methods. [25] McKinnon et al. [25] highlighted that this lack of education across healthcare professionals is significant enough to be considered a "barrier to the widespread uptake of pharmacogenomics". To ameliorate the situation, the International Society of Pharmacogenomics has issued recommendations in 2005 for pharmacogenomics to be incorporated into medical curricula. [26] Another contributing factor to the low utilisation of testing could include the lack of subsidised tests available through Medicare. Currently, pathology labs do provide pharmacogenomic testing (such as Douglas Hanley Moir and Healthscope), however this is largely done so through the patient's expenses as only two methods are subsidised by Medicare. [23,27,28]

Amongst those aware of pharmacogenomic testing, eight out of nine GPs answered that they would be more likely to utilise pharmacogenomic testing in black-African patients who had previously experienced ADRs; this is consistent with findings noted by van Puijenbroek et al. [29]. Among these GPs, factors that were noted to be potential influences in their utilisation of testing included: patient factors such as compliance and the reliability of the test, and, factors affecting the clinical picture (as described in Table 1). This is consistent with findings by studies that have also identified cost and a patient's individual response to drugs as influential factors in a physician's decision making. [29,30]

Considering that the majority of information regarding enzyme metabolism and pharmacogenomic testing was published in pharmacological journals,[6,8-14,30-32] much of this knowledge may not have been passed on to GPs. In order to understand the preferred media of information for GPs, we posed open-ended questions and discovered that the majority of GPs who answered the question (32/39), would prefer information in the form of writing (Table 3). This could be either in the form of online sources (such as guidelines, summaries, the National Prescribing Service or the Monthly Index of Medical Specialities) or peer reviewed journal articles. Current literature also reflects this preference for GPs to gain education regarding pharmacogenomics through journal articles. [22] The other preferred medium of education was through verbal teachings, peer discussions and presentations (Table 3), with there being specific interest in information being disseminated by clinical pathology laboratories; this is also reflected in the literature. [22,29]

Strengths and limitations

Small sample size is a limitation of this study with possible contributing factors including: the short amount of time allowed for data collection and the low response rate due to GP time constraints. Strengths of the study include the use of a validated questionnaire catered to our target population and open-ended questions which gave us further insight into GP preferences.

Implications and future research

Currently, anti-coagulants provide an example of the clinical applications of considering enzyme polymorphisms in patient management. [33,34] Warfarin is a particular example where variability in INR has been associated with enzyme polymorphisms, leading to the utilisation of dosage algorithms to optimise clinical outcomes. [34] Similarly, when using antidepressants, pharmacogenomic testing could

play a role in clinical decision making with Samer et al. [5] suggesting dose reductions and serum monitoring for those with known PM status. However, as identified in our study, there is an overall lack of awareness regarding the differences in enzyme metaboliser status and the methods available for pharmacogenomic testing.

Future studies should focus on the clinical practicality of utilising these tests. Additionally, future studies should determine the effectiveness of the identified GP preferred modalities of education in raising awareness.

Conclusion

There is a low awareness among GPs regarding both the differences in enzyme metaboliser status in the black-African community, and the methods of pharmacogenomic testing.

To optimise clinical outcomes in black-African patients with depression, it may be useful to inform GPs of the availability and application of pharmacogenomic testing. We have highlighted the preferred education modalities through which this may be possible.

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Conflict of interest

None declared.

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Adequacy of anticoagulation according to $CHADS_2$ criteria in patients with atrial fibrillation in general practice - a retrospective cohort study

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Skye's current interests include critical care and emergency medicine.

Background: Atrial fibrillation (AF) is a common arrhythmia associated with an increased risk of stroke. Strategies to reduce stroke incidence involve identification of at-risk patients using scoring systems such as the $CHADS_2$ score (Congestive Heart Failure, Hypertension, Age ≥75 years, Diabetes or Stroke) to guide pharmacological prophylaxis. **Aim**: The aim of this research project was to determine the prevalence and management of AF patients within the general practice (GP) setting and to assess the adequacy of anticoagulation or antiplatelet prophylaxis according to the $CHADS_2$ score. **Methods**: This study was a retrospective cohort study of 100 AF patients ≥50 years conducted at a South Coast NSW Medical Centre over a 3-year period. Data was obtained from existing medical records. $CHADS_2$ scores were determined at baseline, 12 months and 3 years and were compared with medications to assess whether patients were undertreated, adequately treated or over-treated according to their $CHADS_2$ score. **Results**: Prevalence of AF in patients >50 years was 5.8%. At baseline, 65% of patients (n=100) were at high risk of stroke ($CHADS_2$ score ≥2). This increased to 75.3% of patients at 12 months (n=89) and 78.4% of patients at 3 years (n=60). Adequate treatment occurred in 79.0% of patients at baseline and 83.1% and 76.7% at 12 months and 3-years, respectively. There were three instances of stroke or trans-ischemic attack during the study period. **Conclusion**: GPs play a critical role in prevention of stroke in patients with AF. Adequate pharmacological interventions occurred in the majority of cases, however, identification and treatment of at-risk patients could be further improved.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in Australia, affecting 8% of the population over the age of 80 years. [1,2] The morbidity and mortality associated with AF is primarily due to an increased risk of thromboembolic events such as stroke, with studies reporting up to a five-fold increase in the annual risk of stroke among patients with AF who have not received prophylaxis with either anticoagulant or antiplatelet therapies. [3,4]

It has been demonstrated that the incidence of stroke in patients with AF can be significantly reduced with the use of pharmacological agents, such as anticoagulant and antiplatelet medications including warfarin and aspirin, respectively. [5] More recently, the development of new oral anticoagulant (NOAC) medications such as dabigatran and rivaroxaban have also been approved for use in patients with AF. [6] However, several studies indicate that the use of anticoagulants and antiplatelets for the prevention of thromboembolic events is often underutilised. [7,8] It is estimated that up to 51% of patients eligible for anticoagulant therapy do not receive it. [9] Furthermore, an estimated 86% of patients who suffer from AF and have a subsequent stroke were not receiving adequate anticoagulation therapy following their AF diagnosis. [10]

In contrast, pharmacological treatments for stroke prophylaxis have been associated with an increased risk of intracerebral haemorrhage, particularly amongst the elderly. [11] A study of 170 patients with AF over the age of 85 years demonstrated that the rate of haemorrhagic stroke was 2.5 times higher in those receiving anticoagulant therapy compared to controls (OR=2.5, 95% CI: 1.3-2.7). [12] Therefore, the need to optimise the management of patients with AF in the general

practice (GP) setting is of high importance for stroke prevention and requires an individualised pharmacological approach in order to achieve a balance between stroke reduction and bleeding side effects.

Consequently, the development of validated risk stratification tools such as the $CHADS_2$ score (Congestive Heart Failure, Hypertension, Age ≥75 years, Diabetes, Previous Stroke or Trans-ischemic Attack (TIA)) has enabled more accurate identification of AF patients who are at an increased risk of stroke by assessing co-morbidities and additional risk factors to determine the appropriateness of anticoagulation or antiplatelet prophylaxis to reduce the risk of thromboembolic events. [13]

The aim of this research project was to determine the prevalence of AF among patients within a GP cohort and to assess the adequacy of pharmacological stroke prophylaxis according to the $CHADS_2$ criteria. The results of this study will enable GPs to determine whether the current management of patients with AF is adequate and whether closer follow-up of these patients needs to occur in order to minimise associated bleeding and stroke complications.

Methods

Study design and ethics

This study was a retrospective cohort study of the prevalence, patient characteristics and adequacy of anticoagulation according to the $CHADS_2$ score in GP patients with AF over a 3-year period. The study was approved by the University of Wollongong Human Research Ethics Committee (Appendix 1, HREC 13/031).

Participants

Participants were identified using a search of the practice database (Best Practice, Version 1.8.3.602, Pyefinch Software Pty Ltd), at a South Coast NSW Medical Centre using the database search tool. Search criteria included any patient (recorded as alive or deceased) who attended the practice with a recorded diagnosis of AF over a 3-year period (between November 2010 – November 2013) and were ≥50 years of age. This included both patients with long-term AF diagnosed before the study period in addition to those newly diagnosed with AF during the study period. The total number of all patients aged ≥50 years who attended the practice at least once during the same period was recorded to determine the prevalence of AF at the practice.

Exclusion Criteria

Exclusion criteria included patients <50 years of age, patients with incomplete medical records or those diagnosed with AF who subsequently moved from the practice during the study period.

$CHADS_2$ Score (NB1)	Risk Level	Treatment Recommendations (NB2)
0	Low	No therapy or Aspirin
1	Moderate	Oral anticoagulant or Aspirin
2 or more	High	Oral anticoagulant

NB1: $CHADS_2$ score derives from adding the following points:

- 1 point each for age more than 75 years, hypertension, diabetes mellitus, heart failure
- 2 points for previous stroke or transient ischemic attack.

NB2: Treatment recommendations are based on the $CHADS_2$ score.

Figure 1: *Therapeutic Guidelines - Treatment Recommendations for Prophylaxis of Stroke in Patients with AF (Reproduced with permission) [17]*

$CHADS_2$ Score

The $CHADS_2$ score was chosen for the purpose of this study as it is a validated risk-stratification tool for patients with AF. [13-15] The scoring system assigns one point each for the presence of Congestive Heart Failure, Hypertension, Age ≥75 years or Diabetes and assigns two points if a patient has a history of previous Stroke or TIA. AF patients with a $CHADS_2$ score of 0 are considered to be at low risk of a thromboembolic event (0.5 – 1.7% per year stroke rate); a score of 1 indicates intermediate risk (2.0% per year stroke rate) and a score ≥2 indicates high risk (4.0% per year stroke rate). [16]

Data Search and Extraction

Patient data was manually extracted from individual patient records, coded and recorded into a spreadsheet (Microsoft Excel, 2007). Basic data including date of birth and sex were recorded. Date of AF diagnosis (assessed as the first documented episode of AF within the patient record) and co-morbidities including hypertension, congestive heart failure, diabetes, stroke or TIA were included if documented within the patient medical record. Correspondence from specialists and hospital discharge summaries were also analysed for any diagnosis made outside of the medical centre and not subsequently recorded in the medical record.

Lifestyle factors were recorded from the practice database including alcohol use (light/moderate/heavy or none) and smoking status (non-smoker, ex-smoker or current smoker). Complications arising from pharmacological prophylaxis (including any documented bleeding or side-effects) or discontinuation of treatments were included. Individual patient visits were analysed for any documented non-compliance with medications. Where possible, cause of death was also recorded.

Adequacy of Anticoagulation

Individual $CHADS_2$ scores were determined for each patient at baseline, 12 months and 3 years. At each of these time points, $CHADS_2$ scores were compared to each patient's medication regime (i.e. no medication use, an anticoagulant agent or an antiplatelet agent). The use of other medications for the treatment of AF (for example, agents for rate or rhythm control) was not assessed. Patients were then classified as being undertreated, adequately treated or over-treated according to the $CHADS_2$ score obtained at baseline, 12 months and 3 years as per the current therapeutic guidelines (Figure 1). [17]

Adequate treatment was considered to be patients receiving treatments in accordance with the therapeutic guidelines. [17] Undertreated patients included those who received no treatment when an oral anticoagulant was indicated ($CHADS_2$ score ≥2). Over-treated patients included those treated with an oral anticoagulant where it was not indicated according to the current guidelines ($CHADS_2$ score = 0).

Statistical Analysis

Results are presented as mean ± standard deviation. A p-value of <0.05 was considered to be statistically significant. One-way ANOVA was used to assess between-group differences in $CHADS_2$ scores at each time point (Baseline, 12 months and 3 years). Descriptive data is presented where relevant. Prevalence of AF at the practice was calculated using the formula; (patients with AF ≥50 years / total number of patients ≥50 years at the practice, X 100).

Results

A total of 346 patients with AF aged ≥50 years were identified. Of these, 246 participants were excluded - (n=213 due to insufficient data within their medical record, and n=33 patients had left the practice during the study period) leaving a total of 100 patients for inclusion in the analysis (Figure 2). Due to the nature of the search strategy (which identified any patient with AF during the period of November 2010-November 2013), both newly-diagnosed patients and patients with long-term AF were included in the analysis. Therefore, long-term data was available for n=89 participants at 12 months, and n=60 participants at 3 years. There were no statistically significant differences in age (p=0.91) or sex (p=0.86) between the included and excluded participants.

Including all patients initially identified with AF (n=346), the overall prevalence of AF among patients at the practice was 5.8%. Participant characteristics are presented in Table 1. The mean age of participants at diagnosis was 74.9 ± 10.0 years, with more males suffering from AF (60%) compared to females (40%). Over half of patients had a history of smoking (57%), and hypertension was the most common co-morbidity (74%). 13% of participants were listed within the practice database as being deceased.

At baseline, 65.0% of patients were classified as high risk of stroke ($CHADS_2$ score ≥2). This increased to 75.3% of patients and 78.4% of patients at 12 months and 3 years, respectively (Graph 1). There were

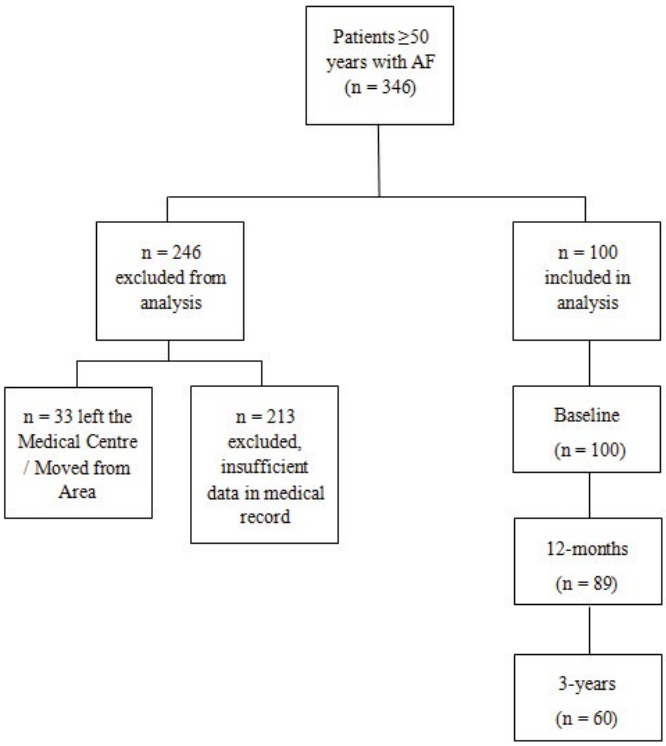


Figure 2: *Flowchart of study patients with AF at a South Coast, NSW General Practice*

Patient Demographics	*n = 100*
Age (Years)	
50 - 59	8
60 - 69	22
70 - 79	36
80+	34
Males (%)	60
Deceased (%)	13
Ex-Smoker (%)	57
Current Smoker (%)	4
Alcohol Use (n=77)	
Nil (%)	10.0
Light (%)	56.0
Moderate (%)	7.0
Heavy (%)	4.0
Unknown (%)	23.0
Co-morbidities	
Congestive Heart Failure (%)	16
Hypertension (%)	74
Diabetes (%)	26
Stroke (%)	7
TIA (%)	17

Table 1. *$CHADS_2$ scores at baseline, 12-months and 3-years in Patients with AF*

no patients with a $CHADS_2$ score of 6 at any of the study time points.

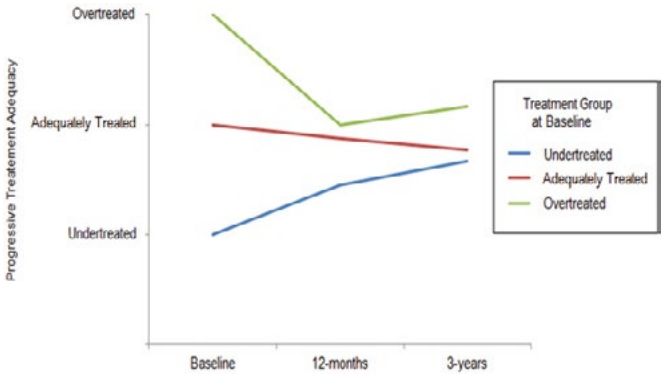
Analysis of participants who had 3-year follow-up data available (n=60) demonstrated a statistically significant increase in average $CHADS_2$ scores among patients between baseline vs. 12 months ($p<0.05$) and baseline vs. 3 years ($p<0.01$). There was no statistically significant difference in $CHADS_2$ scores between 12 months vs. 3 years ($p=0.54$).

Graph 2 demonstrates changes in treatment adequacy over time based on patients' initial treatment group allocation at baseline. For patients who were initially identified as being undertreated at baseline, there was a trend toward adequate treatment by 3-years. For patients initially identified as over-treated at baseline, the trend towards adequate treatment occurred more rapidly (p=non-significant) (on average by 12 months).

Patient pharmacological treatments and adequacy of treatment at baseline, 12 months and 3 years are shown in Table 2.

There were several reported side-effects and documented instances of medication cessation from anticoagulation and antiplatelet therapy. A total of eight patients were non-compliant and ceased warfarin during the study period and eight patients had their warfarin ceased

Graph 1. *Risk of stroke according to $CHADS_2$ scores at baseline, 12-months and 3 years in Patients with AF*



Graph 2. *Progression of Treatment Adequacy over time in Patients with AF based on initial baseline Treatment Adequacy.*

by their treating doctor (reason for cessation unknown). A further eight patients ceased warfarin therapy due to side-effects (Intracranial haemorrhage (n=1), Gastrointestinal bleeding (n=3), Haematuria (n=1), Unknown bleeding (n=3)). One patient ceased aspirin due to oesophageal irritation. No other pharmacological therapies were ceased due to side-effects. Warfarin was ceased in one case due to an elective surgical procedure.

A total of two patients suffered an embolic or haemorrhagic stroke and a further two patients suffered a TIA during the study period. Prior to their thromboembolic event, one patient was undertreated with aspirin ($CHADS_2$ score = 2), one was adequately treated with clopidogrel ($CHADS_2$ score = 1) and a further one patient was undertreated on aspirin ($CHADS_2$ score = 3). Cause of death was unknown in six patients. No patients had stroke or TIA listed as their cause of death in their medical record.

Discussion

It has been suggested that Australian patients with AF may not be receiving optimal prophylactic anticoagulant and antiplatelet medications for the prevention of thromboembolic events. [7,8] The aims of this retrospective cohort study were to assess stroke risk and the adequacy of anticoagulation in 100 AF patients ≥50 years over a 3 year period in a GP setting.

Results from the current study indicate that overall, the use of anticoagulant and antiplatelet strategies for stroke prophylaxis was appropriate in the majority of cases and consistent with published therapeutic guidelines. [17] The prevalence of AF at the practice of 5.8% was similar with other studies, which report a prevalence of AF in the GP setting of between 4-8%. [18, 19] In the current study, there were more males with AF than females, however this trend has also been found in several other studies which have reported a higher prevalence of AF amongst males. [15,18]

$CHADS_2$ scores increased between baseline and 12 months and baseline and 3 years. This increase was to be expected as patients are likely to gain additional risk factors as they age. The majority of patients at all time points were at high risk of stroke ($CHADS_2$ score ≥2), with warfarin or similar anticoagulation therapy being indicated.

Anticoagulant / Antiplatelet	Baseline (n=100)	12-months (n=89)	3-years (n=60)
Aspirin	20 (20.0%)	19 (21.3%)	13 (21.7%)
Warfarin	73 (73.0%)	60 (67.4%)	39 (65.0%)
Clopidogrel	3 (3.0%)	3 (3.4%)	4 (6.7%)
Dabigatran (Pradaxa®)	2 (2.0%)	2 (2.2%)	0 (0.0%)
None	2 (2.0%)	5 (5.6%)	4 (6.7%)
Adequacy of Anticoagulation			
Undertreated	13 (13.0%)	15 (16.9%)	13 (21.7%)
Adequately Treated	79 (79.0%)	74 (83.1%)	46 (76.7%)
Over-treated	8 (8.0%)	0 (0%)	1 (1.7%)
Adequacy of Anticoagulation according to Age Group			
50 - 59 years	(n=8)	(n=8)	(n=4)
Undertreated	1 (12.5%)	0 (0.0%)	0 (0.0%)
Adequately Treated	4 (50.0%)	8 (100.0%)	4 (100.0%)
Over-treated	3 (37.5%)	0 (0%)	0 (0%)
60 - 69 years	(n=22)	(n=19)	(n=13)
Undertreated	0 (0.0%)	1 (5.3%)	2 (15.4%)
Adequately Treated	19 (86.4%)	18 (94.7%)	10 (76.9%)
Over-treated	3 (13.6%)	0 (0.0%)	1 (7.7%)
70 - 79 years	(n=36)	(n=33)	(n=23)
Undertreated	6 (16.7%)	9 (27.3%)	6 (26.1%)
Adequately Treated	28 (77.8%)	24 (72.7%)	17 (73.9%)
Over-treated	2 (5.6%)	0 (0%)	0 (0%)
80+ years	(n=34)	(n=29)	(n=20)
Undertreated	6 (17.6%)	5 (17.4%)	5 (25.0%)
Adequately Treated	28 (82.4%)	24 (82.8%)	15 (75.0%)
Over-treated	0 (0%)	0 (0%)	0 (0%)

Table 2. *$CHADS_2$ scores at baseline, 12-months and 3-years in Patients with AF*

Overall, treatment adequacy increased between baseline and 12 months (79% versus 83.1%), then decreased by 3 years (83.1% versus 76.7%). This trend is likely to represent aggressive management of AF at the initial diagnosis then a decline in optimal stroke prophylaxis as patients age, develop additional side-effects or become at increased risk of falls. Additionally, older patient groups (those >70 years) were more likely to be undertreated. This may be due to several factors, including patient non-compliance with warfarin therapy, doctor reluctance to prescribe warfarin to patients at risk of falls, and the incidence of side-effects such as bleeding. Similar causes of under-treatment of elderly patients with AF have been outlined in other studies. [20,21] In younger patients, there was a trend towards over-treatment at the time of diagnosis.

In the current study, one patient suffered an embolic stroke during the study period and two patients had a TIA. Appropriately, all three of these patients were subsequently changed to warfarin. One patient who was adequately treated on warfarin with a $CHADS_2$ score of 1 was changed to aspirin following an intracranial haemorrhage (and

consequently remained classified as adequately treated). Although these were isolated cases within the study, it should be noted that the life-long morbidity of stroke for these individuals is significant.

Strengths of the current study include the large number of patients and the comprehensive assessment of medical records for the main study outcomes of $CHADS_2$ scores and anticoagulation or antiplatelet therapies. By assessing individual medical records, a comprehensive assessment of patient data was available for inclusion in the study analysis.

There are some limitations in the current study. As data was extracted from an existing database of patient medical records (which was not kept for the purpose of conducting research) there were some instances of missing or incomplete data. However, the majority of missing data was, in general, relating to the patient's social history (such as smoking rates and alcohol use), which were not central to the main research aims and would not have influenced the results.

A thorough assessment of medication regimes was able to be carried out for the purpose of this study. As all medication changes are automatically recorded by the Best Practice program at each visit, the author is confident that this aspect of the data is accurate. However, it should be noted that it is possible that some patients may have been taking over the counter aspirin, which may not have been recorded on their medication list and consequently some patients may have been assessed as 'undertreated'. An additional consideration relates to the use of warfarin and whether patients' prescribed warfarin were within the therapeutic range, however, the assessment of multiple INR readings for each patient over a 3-year period was thought to be beyond the scope of this study. Only two patients at the practice had been prescribed NOACs (Dabigatran) for anticoagulation, therefore analysis of this medication was limited.

The calculation of $CHADS_2$ scores was able to be assessed for all patients. Although most co-morbidities were well documented, there may have been some limitations with regards to the identification of some co-morbidities such as hypertension, diabetes and the presence of congestive heart failure among some patients. For example, in some instances some patients did not have a recorded diagnosis of hypertension, but a review of blood pressure readings demonstrated several high systolic blood pressure readings which could have been diagnostic for hypertension. Where this occurred, patients were not considered to have hypertension or congestive heart failure and were not assigned an additional $CHADS_2$ point.

The $CHADS_2$ score was chosen for the purpose of this study due to its simplicity and validation for the identification of patients at risk of stroke [13-15]. More recently, refinements to the $CHADS_2$ score has led to the development of the CHA_2DS_2-VASC score, which assigns additional points to higher age groups, female patients and patients with vascular disease. [22] The CHA_2DS_2-VASC score provides a more comprehensive overview of stroke risk factors in an individual and has also been validated for the purpose of determining the need for pharmacological stroke prophylaxis. More recently, studies have shown that application of the CHA_2DS_2-VASC score is most useful for clarifying the stratification of patients within the low-intermediate stroke risk categories (i.e. determining those with $CHADS_2$ scores of 0-1 who are truly at low risk and do not require aspirin). [23] Because the aims of the current study were to identify patients at high risk of stroke and determine the appropriateness of their treatment, the CHA_2DS_2-VASC score was not utilised in this study. However, it should be noted that the CHA_2DS_2-VASC may provide additional clarification in the assessment of patients with low-intermediate $CHADS_2$ scores.

An additional consideration in this study relates to the nature of the AF suffered by patients. Although patients were included if they had a known diagnosis of AF, it is almost impossible to determine how long patients had already been suffering from AF prior to and after their diagnosis. In addition, it was not possible to determine whether patients had paroxysmal or sustained/chronic AF. However, it has been demonstrated that there may be little difference in outcomes for patients with paroxysmal versus persistent AF, [24,25] with a large cohort study comparing stroke rates in patients with paroxysmal versus sustained AF reporting no significant difference in rates of stroke (3.2% versus 3.3%, respectively). [24] Therefore, it is unlikely that determination of paroxysmal and sustained AF patterns would have influenced results of the current study.

Conclusion

The results obtained from this study will allow GPs to optimise the management of patients with AF in the community setting. Although this study found that the management of patients with AF at the practice is consistent with the current guidelines in the majority of cases, further improvements can be made to minimise the risk of stroke among patients with AF, especially with regards to targeting undertreated patients. Additionally, the current study may raise greater awareness of the incidence of AF within the practice and the need to assess stroke risk and treat patients accordingly, especially as $CHADS_2$ scores were rarely recorded formally at the time of diagnosis. GPs are well placed to optimise the treatment of AF and prevent strokes though treatment of co-morbidities and implementing lifestyle interventions, such as encouraging smoking cessation and the minimisation of alcohol use, and may further reduce the incidence of stroke and TIA in patients with AF.

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Conflict of interest

None declared.

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Personal reflection: how much do we really know?

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"Hurry up with that blood pressure and pulse," blurts the ED registrar. "And make sure to do it on both arms this time." Before I can ask him what's going on, he's teleported to the next bed. Great. I'm alone again. But I don't blame him; it's a Saturday night, and a volunteer medical student is the least of his worries.

I fumble for what seems like an eternity with the blood pressure cuff, but eventually get it on, much to the amusement of a charge nurse eyeballing me from the nurses' station. Recording the right arm was textbook, so now it was just the left arm to do. I listen hard for the Korotkoff sounds, but there was nothing. I shut my eyes in a squeamish hope that it might heighten my hearing, but nothing again. I can feel the charge nurse staring again; I fluster and break a cold sweat. I feel for the left radial pulse, but it repeatedly flutters away the moment I find it. I remember thinking: Gosh. Am I really that incompetent? Embarrassed, I eventually concede defeat and ask for a nurse who tells me she'll be there "in a minute."

Amidst all this confusion, was John—my patient. I'd gotten so caught up with 'Operation Blood Pressure' that I completely forgot that he was lying there with a kind of graceful patience. I quickly apologised and introduced myself as one of the students on the team.

"It's all right. You're young; you'll eventually get the hang of it… Have to start somewhere, right?" His voice had a raspy crispness to it, which was quite calming to actually hear against the dull rapture of a chaotic emergency room.

John was one of those lovely elderly persons who you immediately came to admire and respect for their warm resilience; you don't meet too many gentlemen like John anymore. Despite his discomfort, he gave me a kind smile and reached out with his right hand to reassuringly touch my hand. It was a beautifully ironic moment: There he lay in bed, and there I stood by his bedside. And for a moment, there I was the patient in distress, and there he was the physician offering me the reassurance I so desperately needed.

Patients teach us to be doctors. Whether it is a lesson in humility or a rare diagnostic finding, patients are the cornerstone of our ongoing clinical expertise and development; they are why we exist. The more we see, the more we learn. The more we learn, the better doctors we become. Sir William Osler was perhaps the first one to formally adopt this into modern medical education. After all, the three-year hospital residency program for training junior medicos was his idea, and is now a curriculum so widely adopted that it's almost a rite of passage all doctors make.

But how much clinical exposure are we really getting nowadays? With the betterment of societal health, there is a reduced prevalence and incidence for rarer diseases. Epidemiologically this is undoubtedly a good thing, but it does sadly reduce learning opportunities for upcoming generations of doctors. Our clinical accruement is premised on seeing and doing; through experiences that shape our clinical approach. Earlier this year, an African child presented with mild gut disturbances and some paralysis of his lower limbs. The case baffled three residents and a registrar, but after a quick glance from a consultant, the child was immediately diagnosed with polio (which was confirmed later by one of the myriad of tests the panicking residents had ordered earlier). We'd all read about polio, but either through the lack of clinical exposure or careless assumptions that polio was all

cured; we were quick to overlook it. We can only diagnose if we know what we are looking for.

It's not surprising that preceding generations of senior doctors (and those before them) have such perceived superior clinical intellect, not just with the breadth of their clinical knowledge but with their almost Sherlock Holmes senses of acuity to formulate diagnosis based primarily off history taking and physical examination. Traditionally it is advertised in textbooks that 90% of diagnoses should be made from the history and examination alone. Nowadays, with the advent of improving diagnostic technologies in radiology and pathology, it isn't surprising that a number of us have replaced this fundamental skill with an apparent dependence on expensive invasive tests. In a recent study physicians at their respective levels were assessed on their ability to identify heart murmurs and associate it with the correct cardiac problem. Out of the 12 murmurs: interns correctly identified 5, senior residents 6, registrars 8 and consultants 9. Makes you wonder how long ago it was when physicians could identify all twelve. I remember an ambitious surgical resident saying - Why bother diagnosing murmurs when you can just order an echocardiogram? And I remembered the humbling answer a grandfather consultant had for him - Because I'm a real doctor and I can.

As for poor John, I was still stuck with getting a blood pressure for his left arm. Two hours earlier, I responded with the ambulance to John at his home, a conscious and breathing 68 year old complaining of severe headaches and back pain. John was a war veteran who lived independently and sadly had no remaining family to care for him. He has had a month's history of worsening headaches and lumbar back pain with associated sensory loss particularly in his lower limbs that has been affecting his walking recently. Physical exam confirmed his story and he was slightly hypotensive at 100/65 mmHg, but otherwise his ECG and vitals were generally unremarkable. He otherwise looked to be a healthy 68 year old with no significant past medical history. Funnily enough, he'd just been sent home from ED earlier in the day for the same complaint. As far as we could tell, he was just another old guy with a bad headache, back pain, and possibly sciatica. It wasn't surprising that he was sent home from ED this morning with a script for Celecoxib, Nurofen, and instructions to follow-up with his GP.

I'll remember from this moment onwards that when a nurse says that they'll be a minute, it's actually a metaphor of an ice age. I eventually decide to fess up to the registrar that I couldn't do the blood pressure properly. He gives me a disappointing look but I concluded that honesty

is usually the best option in healthcare — well, at least, over pride. I remembered reading a case earlier that week about a medical student who failed to admit that he was unable to palpate the femoral and left radial pulses in a neonate, and subsequently missed an early diagnosis of a serious aortic coarctation, which in the end was discovered the following morning after the baby had already become significantly blue and cyanosed overnight.

Much to my relief, the registrar couldn't find the blood pressure either and ruled it as pathologic. He disappeared to have a word with his consultant, with both of them quickly returning to the bedside to take a brief history from the patient. By that point, the nurse had finally arrived along with a couple more students and an intern. John had an audience. It was bedside teaching time.

"So apparently you're God?" John asked the consultant, breaking the seriousness of the moment. We all simultaneously swivel our heads to face the consultant liked starved seagulls, only we weren't looking for a fried chip but craving for a smart response to scribble in our notebooks.

"To them," the consultant looks at us, "I am. As for you, I'm not sure."

"I survived getting shot you know, during the war…it just nicked some major artery in my chest…clean shot, in the front and out the back... army docs made some stitches, and I healed up just fine by the end of the month. I've been fit as a fiddle since—well, at least, up until these last few months."

The rest of the history was similar to what I'd found out earlier, but I was slightly annoyed and almost felt betrayed that he'd failed to mention this to me earlier.

The fictional TV Dr Gregory House has a saying that "everybody lies." It's true to an extent, but I don't think patients do it deliberately. They generally might discount or overlook facts that are actually an essential part of the diagnostic process; they are human after all (and so are we). There are the psychiatric exceptions, but for the most part, patients do have the good faith of wanting to help us to help them get better. While sending a team of residents to break into a patient's house is not usually the preferable choice (unless you're Dr House), we usually try and pick up these extra clues by knowing what questions to ask and through the comfortable rapport we build with our patients as we come to understand them as a person. The trick is to do all of this in a 10 to 15 minute consult.

The consultant quickly did a physical exam on John. He closed his eyes as he listened to his chest. And then, a very faint smile briefly came across his face — the epiphany of a pitifully murmuring heart.

"We're probably going to run some tests to confirm this," he informs John before turning to us, "but I suspect we might have a case of a dissecting aorta." Of course; why didn't I think of that? Hindsight's always 20-20, but I continue to kick myself for missing that murmur, and not making the (now obvious) connection.

The consultant continues to command his lackeys to request an alphabet of tests. Soon enough the CT images return and it's evident that there was blood dividing into a false lumen of the descending aorta (likely to have torn at the site where his gunshot injury had traumatised the vascular tissues from decades ago). Urgent surgery was booked, a range of cardiac medications commenced, and by the time I returned from documenting the notes, there was now a bunch of tubes sticking out of him.

The next time I see John is after his surgery and before he was transferred to the rehabilitation unit. I treasure our final meeting.

"So I beat the odds," John threw a beaming smile towards me. He's a trooper — I'll definitely give him that. Assuming his initial dissectional tear occurred when he reported the onset of his headaches and lower back pain, he'd survived a dissecting aortic aneurysm for at least one whole month, not to mention a war before that. (The odds of dropping dead from an aortic dissection in the first 24 hours alone it's 25%, in 48 hours it's 50%, in the first week it's 75% and in the first month it's 90%.)

"Yes, you definitely beat the odds." I smile back at him with a certain amount of gained confidence. Our eyes meet briefly, and beneath the toughened exterior of this brave man is the all-too-familiar softened reservoir of unannounced fear. Finally, I extend my hand to shake his and gently squeeze it; it is the blessing of trust and reassurance he first showed me as a patient that I am now returning to him as a physician.

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Conflict of interest

None declared.

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The blind spot on Australia's PBS: review of anti-VEGF therapy for neovascular age-related macular degeneration

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Case scenario

A 72 year old male with a two-day history of sudden blurred vision in his left eye was referred to an ophthalmologist at a regional Australian setting. On best corrected visual acuity (BCVA) testing his left eye had reduced vision (6/12-1) with metamorphopsia. Fundoscopy showed an area of swelling around the left macula and optical coherence tomography and fundus fluorescein angiography later confirmed pigment epithelial detachment of his left macula and subfoveal choroidal neovascularisation. He was given a diagnosis of wet macular degeneration and was commenced on monthly ranibizumab (Lucentis®) injections – a drug that costs the Australian health care system approximately AUD $1430 per injection and will require lifelong treatment. Recent debate has risen regarding the optimum frequency of dosing and the necessity of this expensive drug, given the availability of a cheaper alternative.

Introduction

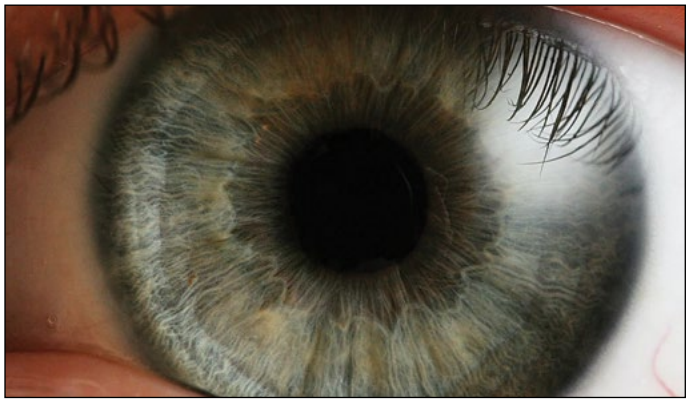
Age-related macular degeneration (AMD) is the leading cause of blindness in Australia. [1] It predominantly affects people aged over 50 years and impairs central vision. In Australia the cumulative incidence of early AMD for those aged over 49 years is 14.1% and 3.7% for late AMD. [1] Macular degeneration occurs in two forms. Dry macular (non-neovascular) disease comprises 90% of AMD and has a slow progression characterised by drussen deposition underneath the retinal pigment epithelium. [2] Currently there is no agreed treatment of advanced dry AMD and is managed only by diet and lifestyle. [3,4] Late stages of dry macular degeneration can result in "geographic atrophy" causing progressive atrophy of the retinal pigment epithelium, choriocapillaries and photoreceptors. [2]

Wet (neovascular) macular degeneration is less common and affects 10% of AMD patients but causes rapid visual loss. [2] It is characterised by choroidal neovascularisation (CNV) secondary to the effects of vascular endothelial growth factor (VEGF) causing blood vessels to grow from the choroid towards the retina. Leakage of these vessels leads to retinal oedema, haemorrhage and fibrous scarring. When the central and paracentral areas are affected it can result in loss of central vision. [2,5] Untreated, this condition can result in one to three lines of visual acuity lost on the LogMAR chart at three months and three to four lines by one year. [6] Hence visual impairment from late AMD leads to significant loss of vision and quality of life.

Currently there are three main anti-VEGF drugs available for wet macular degeneration: ranibizumab (Lucentis®), bevacizumab (Avastin®) and aflibercept (Eylea®). This feature article attempts to summarise the development in treatments of wet macular degeneration and highlights the current controversies regarding the optimal drug and frequency of dosing in context of cost to the Australian Pharmaceutical Benefits Scheme (PBS).

Earlier treatments for wet AMD

Neovascular (wet) AMD was largely untreatable over a decade ago but the management has transformed over this period. [2] Initially laser photocoagulation was used in the treatment of wet AMD with the aim of destroying the choroidal neovascular membrane by coagulation. During the 1980s, the Macular Photocoagulation study reported favourable outcomes for direct laser photocoagulation in small classic extrafoveal and juxtafoveal choroidal neovascularisation



(CNV). However the outcomes for subfoveal lesions were poor and laser photocoagulation was limited by lack of stabilisation of vision, high reoccurrence rates in 50%, risk of immediate moderate visual loss in 41% and laser induced permanent central scotomata in sub-foveal lesions. [2,7]

During the 1990s photodynamic therapy (PDT) with verteporfin was introduced. It involved a two stage process: an intravenous infusion of verteporfin that preferentially accumulated in the neovascular membranes, followed by activation with infrared light that generated free radicals promoting closure of blood vessels. The TAP trial reported that the visual acuity benefits of verteporfin therapy in predominantly classic CNV subfoveal lesions was safely sustained for five years. [8] However the mean visual change was still a 13-letter average loss for PDT compared with a 19-letter average loss for untreated controls. [2,9] In addition, photosensitivity, headaches, back pain, chorioretinal atrophy and acute visual loss were observed in 4% as adverse effects. [2]

Anti-VEGF therapies

A breakthrough in treatment came during the mid-2000s with the identification of VEGF as the pathophysiological mechanism in driving the choroidal neovascularisation and associated oedema. This led to the establishment of the first anti VEGF drug, pegatanib sodium, an RNA aptamer that specifically targeted VEGF-165. [10] The VISION trial, involving 1186 patients with subfoveal AMD receiving pegatanib injections every six weeks, had 70% of patients with stabilised vision (less than three lines of vision loss) compared to 55% of sham controls; yet still only a minority of patients actually gained vision. [10]

A second anti-VEGF agent, bevacizumab (Avastin®) soon came into off-label use. Bevacizumab was initially developed by the pharmaceutical company Genetech® to inhibit the tumour angiogenesis in colorectal cancer but its mechanism of action as a full length antibody that binds to all VEGF isoforms proved to have multiple purposes. Despite a lack of clinical trials to support its use in wet AMD, anecdotal evidence led ophthalmologists to use it in an off-label fashion to inhibit angiogenesis associated with wet macular degeneration. [11,12]

In 2006, however, Genetech® gained Food and Drug Administration (FDA) approval for the anti-VEGF drug ranibizumab, a drug derived from the same bevacizumab molecule, as a fragment but with a smaller molecular size to theoretically aid retinal penetration. [13] Landmark clinical trials established that ranibizumab not only prevented vision

loss but also led to a significant gain in vision in almost one-third of patients. [14,15] The ANCHOR trial, involving 423 patients, compared ranibizumab dosed at 0.3 mg and 0.5 mg given monthly over two years with PDT and verteporfin given as required. This trial found 90% of ranibizumab treated patients achieved visual stabilisation with a loss of < 15 letters compared to 65.7% of PDT patients. Furthermore, up to 41% of the ranibizumab treated group actually gained >15 letters compared to 6.3% of the PDT group. [15]

Further trials including the MARINA, [14] PRONTO, [16] SUSTAIN, [17] and PIER [18] studies confirmed the effectiveness of ranibizumab. Despite these results and the purpose built nature of ranibizumab for the eye, in countries like the US and other countries around the world where patients and health insurance companies bear the cost burden of treatment, bevacizumab (Avastin®) is more frequently used, and constitutes nearly 60% of injections in the US. [19] This occurrence is explained by the large cost difference between ranibizumab (USD $1593) and bevacizumab (USD $42) in context of apparent similar efficacy. [19] The cost difference is due to the fact that one vial of bevacizumab can be fractioned by a compounding pharmacy into numerous unit doses for the eye. [20]

Given the popular off-label use of bevacizumab, the CATT trial was conducted by the US National Eye Institute to establish its efficacy. The CATT trial was a large US multicentre study involving 1208 patients randomised to receive either bevacizumab 1.25 mg or ranibizumab 0.5 mg (monthly or as needed). The CATT trial results demonstrated that monthly bevacizumab was equivalent to monthly ranibizumab (mean gain of 8.0 vs 8.5 letters on ETDRS visual acuity chart in one year). [21] The IVAN trial, a UK multi-centre randomised controlled trial (RCT) involving 628 patients, showed similar results to the CATT trial with a statistically insignificant mean difference in BCVA of 1.37 letters between the two drugs. [22]

Hence debate has mounted in regards to the substantial cost difference in the face of apparent efficacy. [23] On the backdrop of this costly dilemma are three major pharmaceutical companies: Genetech®, Roche® and Novartis® Although bevacizumab was developed in 2004 by the pharmaceutical company Genetech®, the company was taken over in 2009 by the Swiss pharmaceutical giant Roche®, which is one-third owned by another pharmaceutical company, Novartis®. [24] Given that both ranibizumab and bevacizamab are produced essentially by the same pharmaceutical companies (Genetech/Roche/Novartis) there is no financial incentive for the company to seek FDA or Therapeutic Goods Administration (TGA) approval for the cheaper alternative, bevacizumab. [13,24]

Another major concern that is emphasised in the literature is the potentially increased systemic adverse effects reported with bevacizumab. [22] The systemic half-life of bevacizumab is six days compared to ranibizumab at 0.5 days and in theory it is postulated that systemic inhibition of VEGF could cause higher systemic vascular events. [2] The CATT trial reported similar rates of adverse reactions (myocardial infarction, stroke and death) in both bevacizumab and ranibizumab groups. [21] However, a meta-analysis of the CATT and IVAN data showed that there was an increased risk of serious systemic side effects requiring hospitalisation in the bevacizumab group (24.9% vs 19.0%). Yet this statement is controversial as most events reported were not identified in the original cancer trials involving patients receiving intravenous doses of bevacizumab (500 times the intravitreal dose). [21,22] Hence it has been questioned whether this is more attributable to chance or imbalance in the baseline health status of participants. [2,22] An analysis of US Medicare claims demonstrated that patients treated with bevacizumab had significantly higher stroke and mortality rates than ranibizumab. [25] However this data is inherently prone to confounding bias considering the elderly at risk of macular degeneration are likely to have risk factors for systemic vascular disease. When corrected for comorbidities there were no significant differences in outcomes between ranibizumab and bevacizumab. [23,25] It has been argued that trials to date have been underpowered to investigate adverse events in bevacizumab. Hence until further evidence is available, the risk of systemic adverse effects favouring the use of ranibizumab over bevacizumab is unclear. [22]

Adding to the debate regarding the optimum drug choice for AMD, is the newest anti-VEGF, aflibercept (Eylea®) which attained FDA approval in late 2011. Aflibercept was created by the pharmaceutical companies Regeneron/Bayer® and is a novel recombinant fusion protein designed to bind to all isoforms of VEGF-A, VEGF-B and placental growth factor. [20] Aflibercept has a dispensed price the same as ranibizumab at AUD $1430 per injection on the PBS. [26] The binding affinity of aflibercept to VEGF is greater than ranibizumab and bevacizumab which allows for longer duration of action and hence extended dosing intervals. [27]

The VIEW 1 study, a North American multicentre RCT with 1217 patients, and the VIEW 2 study, with 1240 patients enrolled across Europe, the Middle East, Asia-Pacific and Latin America, assigned patients into one of four groups: 1) 0.5 mg aflibercept given monthly, 2) 2 mg aflibercept given monthly, 3) 2 mg aflibercept at two-monthly intervals after an initial 2 mg aflibercept monthly for three months, or 4) ranibizumab 0.5 mg monthly. The VIEW 1 trial demonstrated that vision was maintained (defined as losing less than 15 ETDRS letters) in 96% of patients on 0.5 mg aflibercept monthly, 95% of patients receiving 2 mg monthly, 95% of patients on 2 mg every two months and 94% of patients on ranibizumab 0.5 mg monthly. [28] Safety profiles of the drugs in both the VIEW 1 and VIEW 2 trials showed no difference between aflibercept and ranibizumab in terms of severe systemic side effects. Hence aflibercept has been regarded as equivalent in efficacy to ranibizumab with potentially less frequent dosing.

Frequency of injections

In addition to the optimal drug of choice for AMD, the optimal frequency of injection has come into question. Given the treatment burden of regular intravitreal injections and risk of endophthalmitis with each injection, extending treatment using “as-required” dosing is often used in clinical practice. Evidence from the integrated analysis of VIEW trials is encouraging as it showed that aflibercept given every two months after an initial loading phase of monthly injections for three months was non-inferior to ranibizumab given monthly in stabilising visual outcomes [28] Although the cost is similar to ranibizumab, the reduced number of injections may represent significant cost savings.

A meta-analysis of the IVAN and CATT trials showed that continuous monthly treatment of ranibizumab and bevacizumab, gives better visual function than discontinuous treatment with a mean difference in BCVA at two years of -2.23 letters. [22] The pooled estimates of macular exudation as determined by optical coherence tomography (OCT) favoured a continuous monthly regimen. However, there was an increase in the risk of developing new geographic atrophy of the retinal pigment epithelium (RPE) with monthly treatment when compared to the as-needed therapy, therefore visual benefits from the monthly treatment may not be maintained long-term. [22] It is unclear whether the atrophy of the RPE represents a drug effect or the natural history of AMD. Interestingly, mortality at two years was lower with the continuous compared to the discontinuous group. In relation to systemic side effects, the pooled results slightly favoured continuous therapy although this was not statistically significant. This appears to contradict the normal dose response framework, however it is hypothesised that immunological sensitisation with intermittent dosing may account for this. [22]

Hence it appears that continuous therapy for bevacizumab and ranibizumab may be favourable in terms of visual outcome. However in clinical practice, given the treatment burden for patients and their carers, the risk of rare sight threatening endopthalmitis and possible sustained rise in intraocular pressure with each injection, [29] the frequency of injections is often individualised based on maintenance of visual acuity and anatomic parameters of macular thickness on OCT.

Currently the "inject and extend" model is recommended, whereby after three monthly injections treatment is extended to five or six weeks if the OCT shows no fluid. Depending on signs of exudation and BCVA, treatment may be reduced or extended by one or two weeks per visit to a maximum interval of ten weeks. Although there are no large prospective studies to support this, smaller studies have reported encouraging results which offers another cost saving strategy. [30] However, given the use of the more expensive ranibizumab, it is still a costly endeavour in Australia.

Current Australian situation

Other practical issues play a role in the choice of anti-VEGF therapy in Australia. For instance, the subsidised cost of ranibizumab to the patient is lower than the unsubsidised full cost of bevacizumab. [13] Patients must pay between AUD $80 and $159 out-of-pocket per injection for bevacizumab, whilst ranibizumab costs the government AUD $1430 and the maximum out of pocket cost for the patient is around AUD $36. [26] Among ophthalmologists there is favour towards the use of ranibizumab because of its purpose built status for the eye. [13] It seems the quantity and quality of evidence for ranibizumab compared to bevacizumab is greater. [29] As bevacizumab is used off-label, its use is not monitored, hence there is no surveillance. Lack of appropriate surveillance has been argued as a case to favour the use of the FDA approved ranibizumab. Essentially the dilemma faced by ophthalmologists is summarised in the statement: "*I would personally be reluctant to say to my patients, 'The best available evidence supports the use of this treatment which is funded, but are you interested in changing to an unapproved treatment [Avastin] for the sake of saving the community some money?*" [31]

Another issue in Australia is the need for bevacizumab to be altered and divided by a compounding pharmacist into a product that is suitable and safe for ocular injection. A recent cluster of infectious endophthalmitis resulting in vision loss occurred in the US from non-compliance to recognised standards. [32] The CATT and IVAN studies had stringent quality and safety control with the bevacizumab repackaged in glass vials using aseptic methods. In these trials, the risk of sight-threatening endophthalmitis was rare for both ranibizumab (0.04%) and bevacizumab injections (0.07%). [21] However, in clinical practice, it is argued that many of the compounding pharmacies may not be as regulated as that of the clinical trials to give comparable inferences about safety.

Conclusion

Prior to development of anti-VEGF therapies, patients with wet macular degeneration were faced with a progressive and permanent decline in vision. Today the available treatments not only stabilise vision but also lead to an improvement in vision in a significant portion of patients. Currently there are no published "head-to-head" trials comparing the three available drugs – bevacizumab, ranibizumab and aflibercept – together, which is warranted. In addition, further analyses of the safety concerns of bevacizumab are required. Current research is focusing on improving anti-VEGF protocols to reduce injection burden and combination therapies with photodynamic therapy or corticosteroids. [3] However, topical therapies such as pazopanib, a tyrosine kinase inhibitor that targets VEGF receptors, currently in the pipeline, may offer a possible non-invasive therapy in the future. [2,33]

At present, the evidence and expert opinion is not unanimous in allowing health policy makers to rationalise the substitution of bevacizumab over ranibizumab or aflibercept. Practical concerns in terms of FDA or TGA approval, surveillance, compounding pharmacy and safety are still major issues. In 2013, ranibizumab was the third-highest costing drug on the PBS at AUD $286.9 million and aflibercept prescriptions cost the Australian government AUD $60.5 million per annum. [26] From a public health policy perspective, Australia has an ageing population and with eye health burden only to increase, there is need to prioritise resources. The cost–benefit analysis is not limited to AMD but applies to other indications of anti-VEGF therapy such as diabetic macular oedema and retinal vein occlusion. Substitution of first-line treatment with bevacizumab, which has occurred elsewhere in the world, has the potential to save the PBS billions of tax-payer dollars over a few years and its review should be considered a high priority in current health policy.

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Conflict of interest

None declared.

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Trust me, I'm wearing my lanyard

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The medical student's first lanyard represents much more than a device which holds clinical identification cards – it symbolises their very identity, first as medical students and eventually as medical practitioners. The lanyard allows access to hospitals and a ready way to discern who's who in a fast paced environment. It is the magic ticket that allows us to wander hospital corridors (often aimlessly) without being questioned.

Despite this, the utility of the lanyard as a symbol of "an insider" is being questioned, with mounting evidence showing it to be a harbour for the indirect transmission of bacteria from health care staff to patients. It may be time for the lanyard, like the white coat before it, to be retired as a symbolic but potentially harmful relic of the past. This essay investigates the validity of these concerns by examining available literature and the results of a small pilot study.

Background

In May 2014 Singapore General Hospital announced a new dress policy for all staff. Hanging lanyards were banned and replaced with retractable identification card holders. Dr Ling Moi Lin, the hospital's director of infection control, explained that the hospital aimed "to ensure that ties and lanyards do not flap around when staff examine patients, these objects can easily collect germs and bacteria – we do not want to carry them to other patients." [1]

This hospital is not alone on their stance against hanging lanyards. The British National Health Service (NHS) Standard Infection Prevention and Control guidelines published in March 2013 lists wearing neckties or lanyards during direct patient care as "bad practice". The guidelines state that lanyards "come into contact with patients, are rarely laundered and play no part in patient care". [2] Closer to home the current 2013 Bare Below the Elbows campaign, a Queensland Government initiative aiming to improve the effectiveness of hand hygiene performed by health care workers, recommends that retractable (or similar) identification card holders are used in place of lanyards. [3] Other Australian states and many individual hospitals have adopted similar recommendations. [4,5]

However, some hospitals and medical schools continue to require staff and students to wear lanyards. For example James Cook University medical students are provided with one lanyard, which must be worn in all clinical settings (whether that be at the medical school during clinical skills sessions or at the hospital) for the entire duration of their six-year degree. [6] The University of Queensland 2013 medical student guide for their Sunshine Coast clinical school states that students must wear their lanyards and display identification badges at all times in teaching locations. [7] This is not concordant with the current Queensland Government initiative recommendations.

The NHS Standard Infection Prevention and Control guidelines are also being breached by medical schools requiring their students to wear lanyards. London Global University states that lanyards are important in that they remind patients who students are and clinical teachers and other professionals that they are in a teaching hospital. However students are required to use a safety pin to attach the end of their lanyard to fixed clothing. [8] A similar policy is in place in Cardiff University where students must wear lanyards but ensure that they are not "dangling" freely when carrying out examinations and procedures. [9] So how harmful could the humble, dangling lanyard really be?

How harmful could the lanyard be?

Each year there are around 200,000 healthcare-associated infections in Australian acute healthcare facilities. Nosocomial infections are the most common complication affecting patients in hospital. These potentially preventable adverse effects cause unnecessary pain and suffering for patients and their families, prolong hospital stays and are costly to the health care system. [10]

Improving hand hygiene among healthcare workers is currently the single most effective intervention to reduce the risk of nosocomial infections in Australian hospitals. [11] The World Health Organisation guidelines on Hand Hygiene in Health Care indicate five moments when the hands must be washed. Two of these are before and after contact with a patient. [12]

In between these two crucial hand washes several objects are frequently touched by health care staff. Objects such as a doctor's neckties [13-17], stethoscopes [18-20] and pens [21,22] have all been shown to carry pathogenic bacteria. The bacteria isolated include methicillin resistant *Staphylococcus aureus* (MRSA), found on doctors' ties [14,16] and stethoscopes. [19] Making contact with these objects during an examination can result in the indirect transmission of microorganisms, transferring the infectious agents to a susceptible host via an intermediate object termed a fomite.

The infectious agents must be transferred from the fomites to the hands of the health care practitioners before they can be spread to patients. The efficiency of transfer of a pathogen on a surface to a practitioner's hand after a single contact was tested by a recent study published in 2013. It isolated five known nosocomial pathogens and placed them on non-porous surfaces; after 10 seconds of contact time between a finger and the surface under a known pressure the microorganism transferred to the finger was examined. It showed that under relative humidity non-porous surfaces had a transfer efficiency of up to 79.5%. [23] This study indicates that after one contact with a contaminated fomite there is a significant transfer of microorganisms to the hands, these can then be transferred to patients.

Furthermore, if no regular preventative disinfection is performed the most common nosocomial pathogens may survive or persist on inanimate surfaces for months and can therefore be a continuous source of transmission. [24] One study conducted in the United Kingdom in 2008 approached 100 hospital staff randomly and asked them to state the frequency and method by which their lanyards were

washed or decontaminated. Only 27% had ever washed their lanyards and 35% of lanyards appeared noticeably soiled. [25] This suggests that the lanyards, which doctors carry with them daily, could potentially harbour acquired infectious agents for an extended periods of time.

Two recent studies have shown that lanyards do carry pathogenic bacteria. [25,26] An Australian study by Kotsanas et al. tested lanyards and identification cards for pathogenic bacteria and found that 38% of lanyards harboured these. Nearly 10% of lanyards grew *MRSA*, and other pathogens found included methicillin sensitive *Staphylococcus aureus*, enterococci and Gram-negative bacilli. The bacterial load on lanyards was 10 times greater per unit surface area than the identification cards themselves. [26]

It has been suggested that contaminated fomites are a result of poor hand hygiene. As such it is assumed that with good hand hygiene practices wearing these objects is acceptable. It has been widely reported that nurses have far better hand hygiene habits than doctors. A recent Australian study conducted in 82 hospitals reports that nurses consistently have significantly higher levels of hand hygiene compliance. [27] If the fomite pathogenic carriage is dependent on hand hygiene then one might expect that lanyards worn by nurses would have lower pathogenic carriage. However Kotsanas et al. showed that although there was a difference in organism composition there was no significant difference between total median bacterial counts isolated from nurses' and doctors' lanyards. [26] This suggests that the carriage of pathogens on lanyards is not solely dependent on compliance with hand hygiene protocols.

Lanyards have thus been shown to carry bacteria, which may remain on them for months, regardless of hand hygiene practices, and have high rates of transfer to the hands of practitioners. However there have been no studies conducted to directly show that their use results in the increased transmission of bacteria. There are however some studies which have shown bacterial transfer from neckties to patients. Lanyards are similar to neckties in that they have been shown to carry pathogenic bacteria, are made of a textile material which is rarely laundered, are positioned at the waistline, have a nature to swing and inadvertently touch patients or the practitioner's cleansed hands and have no direct role in patient care. [13-17]

A study in Pakistan found that the bacteria collected from the lower part of neckties worn by physicians correlated with bacteria isolated from their patients' wounds after surgical review. [17] This suggests that bacterial transmission occurred. More convincingly, a recent study by Weber et al. tested the transmission of bacteria, to dummies, from doctors wearing different combinations of clothing inoculated with comparable levels of bacteria to those previously reported. After a brief 2.5-minute history and exam, cultures were obtained from the dummies at three sites. The number of contaminated mock patients was six times higher and total colony units cultured was 26 times higher when the examiner was wearing an unsecured necktie. [28] This showed that unsecured neckties do result in greater transmission of bacteria from doctors to patients. The ties may swing to directly transmit bacteria to the patient or to the cleansed hands of the doctor, which are then transferred to the patient. Lanyards would likely pose a similar risk.

In my clinical experience, unlike ties, lanyards are often inadvertently touched and fiddled with by medical students and doctors during the clinical examination of a patient. This can recontaminate hands with pathogens even after hand-washing procedures have been followed. Thus, because of this additional contact, lanyards potentially have a higher rate of bacterial transmission than neckties.

What did my pilot study show?

To test this theory I conducted a small observational study, in which 20 James Cook University fourth-year medical students were observed during the focused examination of a volunteer, posing as a patient in an imitated hospital bed setting. Twelve students conducted a focused head and neck examination whilst eight conducted an abdominal examination. The students were unaware of the nature of the study. All students observed washed their hands prior to and at the end of each clinical examination. I observed the students from when they washed their hands prior to the physical exam until their last physical contact with the patient. The mean time taken was 12 minutes. During this period two things were noted: the number of times that their hands made contact with their lanyards and the number of times that the lanyard made contact with the patient. 70% of the students' lanyards touched their patient during the exam at least once; the mean number of times was 2.65 (SD = 2.99). 95% of students touched their lanyards during the exam; the mean number of times was 7.35 (SD = 5.28).

Many made contact with their lanyard as part of their introduction to the patient, holding their lanyard to "show" that they are in fact a medical student. Some held the lanyards to their abdomen with one hand whilst examining the patient with the other hand to prevent it making contact with the patient. Others fiddled with the lanyard whilst talking to the patient. During hand gestures, the lanyards often collided with the student's hands and the students' stethoscopes, prominently displayed around their necks, were often entangled with their lanyards. The amount of contact was to the extent that some students default position was standing with their hands holding their lanyards. After each forced hand movement their hands were returned to holding their lanyards.

It is also interesting to note that several students had attached objects such as pens, USBs and keypads to their lanyards. The attachment of additional objects had a slightly increased correlation with the amount of times that their hands made contact with the lanyard but almost doubled the times the lanyard made contact with the patient (2.65 to 4.67).

One student had a lanyard clip which fastened the end of his lanyard to his shirt. This student did not touch his lanyard once during the exam and his lanyard also did not make contact with the patient. There may thus be some benefit in following the lead of London Global University and Cardiff University in enforcing the use of lanyard clips or safety pins to prevent their students' lanyards from dangling. [8,9]

This observational study adds another dimension to the argument against wearing lanyards. Like neckties, lanyards have been shown to carry pathogenic bacteria, swing to make contact with the patient, are rarely laundered, and have no direct part in patient care. This small observational study confirmed my assumption that lanyards also come into contact with examiners' hands a significant number of times during an examination.

Role models

During the influential years at some medical schools, it is standard policy that students are required to wear a hanging lanyard even though there is a growing body of evidence which indicates that hanging lanyards should not be worn. These students can only dream of the day when their blue medical student lanyards are replaced with the lanyards with "DOCTOR" repeatedly printed. Our role models are wearing improved, larger, better lanyards. It has been proposed that advocating the presentation of up-to-date evidence based information with an emphasis on role modelling should be made an educational priority to improve hand hygiene rates. [29] Research has indicated that targeting medical students may be an effective approach to raising the low compliance rates of hand hygiene procedures of doctors. [29] Clearly advocating the role that fomites like lanyards play in the spread of nosocomial infections has not been made an educational priority and may be part of the reason why compliance with current health hygiene policies regarding their use are low.

It seems contradictory that if I do not to wash my hands at the start of a clinical examination I will fail but I could, like one student in the

observation study did, touch an object shown to carry pathogenic bacteria, which I am required to wear, 23 times and still pass. Making contact with an object shown to carry pathogenic bacteria more than once per minute of clinical examination is alarming and arguably diminishes the purpose of rigorous hand washing procedures.

Conclusion

Lanyards are an easy way to carry identification cards that identify who's who in a fast paced environment. However there is a growing body of evidence that indicates that they may be the harbour for the indirect transmission of infectious agents to patients. Several health hygiene policies have been updated to encourage health professionals not to wear lanyards during direct patient care. Some medical schools have not followed these guidelines and still require students to wear lanyards. While there is no definitive link showing the transmission of an acquired infection from the tip of a medical student's lanyard, there is very reasonable circumstantial evidence indicating that this could easily happen. Obeying current state infection prevention guidelines and swapping hanging lanyards for retractable identification cards or simply preventing them from dangling may be useful in reducing nosocomial infections in Australia. It is about time that the lanyard is retired as a symbolic but potentially harmful relic of the past.

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Conflict of interest

None declared.

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Making the cut: a look at female genital mutilation

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Female Genital Mutilation (FGM) is a procedure of historical, cultural and religious derivation that continues its practice worldwide, involving partial or total removal of the external female genitalia. The stand of many international bodies, including the United Nations, is that it epitomises a violation of the human rights of girls and women. Australian state and territorial law prohibits and categorises FGM as a criminal offence, as do RANZCOG guidelines for medical practitioners. Reducing the practice of FGM worldwide encompasses involvement in awareness and education programs at an individual and societal level, beginning with local communities, elders/leaders, young men and women, and traditional health practitioners. Approaching the request for FGM or reinfibulation in an Australian healthcare setting requires an understanding of the socio-cultural influences surrounding the practice and empathy towards the needs of the patient and their cultural identity. It also requires a comprehensive understanding of the myriad physical and psychological health risks posed by FGM.

Introduction

The continued worldwide practice of female genital mutilation (FGM) or traditionally, 'circumcision' is one that has sparked much controversy within the ethics of Western medicine. Is the centuries old socio-cultural ritual a violation of the rights of a woman or child hiding behind the label of 'custom'? Or has the Western world perceived 'degradation' where there is only an exercising of free will that is perhaps unfathomable but not necessarily unethical? How much of 'free will' is truly an expression of an individual's autonomy? To what extent does culture impinge upon it? And how do we as health practitioners balance this societal commentary with the bioethical principles underlying medical practice? These are questions that have come to the forefront of the FGM debate and that will be examined here. Perhaps, one of the more overarching issues we should also ponder is this: *are and should the principles of what is 'ethical' be derived from socio-cultural forces?*

According to the World Health Organisation (WHO), female genital mutilation (FGM) comprises all procedures that involve partial or total removal of the external female genitalia, or other injury to the female genital organs for non-medical reasons.[1] The current position of the WHO is that 'FGM is a violation of the human rights of girls and women'.[1]

The World Health Organisation (WHO) estimates 100-140 million women worldwide are affected by female genital mutilation.[1] 28 countries of Africa, as well as a few countries of Middle East and Asia have documented practice of FGM.[1] Of these, the four countries with highest prevalence are Somalia, Sudan, Guinea and Djibouti (>90% of women). 1] In Australia, there have been an increasing number of migrants from countries practising FGM, particular over the past decade.[2]

The current laws and guidelines surrounding FGM

Under NSW Law, FGM is prohibited; Section 45 of the 1900 NSW Crimes Act extensively covers prohibition of female genital mutilation. [3] In fact, in all jurisdictions of Australia (though covered exclusively by differing states and territories), FGM is considered a criminal offence. [3] Current Royal Australian and New Zealand College of Obstetricians

and Gynaecologists' (RANZCOG) guidelines strongly recommend that all health practitioners do *not* acquiesce to the requests for elective reinfibulation or indeed other forms of FGM.[2] The United Nations has, as of December 2012, passed a resolution banning the practice of FGM worldwide, as a violation of human rights and dignity.[1]

The arguments 'for' prohibition of FGM

In terms of establishing a perspective on the matter, the tone of the commentary to follow is *ultimately averse to the practice of FGM*. At the forefront of this argument are the adverse health effects. A study by Hosken et al showed that 83 percent of women who had undergone FGM would require medical attention at some point in their lives for a condition resulting from the procedure.[4] In terms of a statistical look at the associated health problems, according to a survey of 55 health providers in the Nyamira District of Kenya, 49.1% reported obstructed labour, dyspareunia, bleeding, urinary problems, and fear and anxiety. [5] The World Health Organisation (WHO) estimates that women who have undergone FGM are twice as likely to die during childbirth and are more likely to give birth to a stillborn child when compared to those women who have not undergone FGM.[1]

Central to the argument is that it confers no health benefit to a woman, and contrarily presents a myriad collection of damaging consequences upon one's health. Proponents of prohibiting the practice, such as Toubia et al, suggest that non-therapeutically excising an otherwise functioning body part is not simply abhorrent; it is a violation of the codes of medical practice and an obstruction to the bioethical principles of non-maleficence and beneficence.[6]

An important detail is that the procedure is often performed on children (a large proportion pre-pubertal), who by virtue of medical ethics are not able to provide informed consent. But what of consenting adults? Whilst it is difficult to ignore the requests made by consenting adults in a sterile, medical environment within the healthcare systems of the Western World, this could condone the practice worldwide.[6] In many instances FGM has (despite it being a social custom of historical derivation) signified the degradation of the rights and dignity of women internationally.[1,6,7] Many argue that if health practitioners do not perform the procedure in a safe sterile manner, women will seek infibulation/reinfibulation from an untrained and often medically unsafe source.[8] However, the underlying point remains that it is the responsibility of the medical profession to uphold certain ethical

principles of beneficence, non-maleficence and justice that are violated by FGM. The harm minimisation of performing re-infibulation/ infibulation sterilely as opposed to at the hands of a non-medical entity is ultimately not outweighed by the consequences of condoning said practice and failing to reduce the practice worldwide.[6,7]

Elchalal et al, in *Female Genital Mutilation: the peril remains*, consolidated the views of Toubia et al, in elucidating that societies and countries that promote the practice of FGM should seek to empower their women (over time) and symbolise social acceptance and respectability in practices that do not confer such negative health risks and psychological trauma.[6,7] What must be highlighted is the importance placed on healthcare workers to utilise their position of trust and objectivity, when relaying the health risks associated with FGM to patients.[6,7]

The arguments 'against' prohibition of FGM

It is important that whilst being in support of eradicating FGM, one examines the counter arguments. Those who defend the practice, hold the value of social integration and cultural importance to the sense of identity held by many consenting adult women, in a higher regard. [8,9] Bronnit et al identifies the psychological health benefits that can be derived from compliance with the practice of FGM, as often outweighing the adverse health risks.[8] Defenders of FGM question the betterment of the cultural and ritualistic component of mental health as being a valid justification for performing FGM.[8,9]

Whilst many commentators also refuse to condone the practice on children, Bronnit states that in denying requests for reinfibulation/ infibulation to consenting adults, you risk retreating to the 'archaic' models of paternalism.[8] It is an interesting argument to consider here: what of the adult woman who, in full knowledge of the risks of the procedure, requests it as it holds importance to her cultural and personal identity? It is undeniably difficult to criticise the respect for patient autonomy.

In response to this argument, the facet of autonomy that can be questioned in these scenarios is whether the request for FGM is a product of cultural embedding. [1,2,5,6] This does not mean to demean the cultural background of the patient. It instead allows us to contemplate the possibility that what is desired by the patient is the sociocultural integration and acceptance FGM affords them.[1,2,5] There is anecdotal evidence in current literature to suggest that fear of rejection by family and community is a potent driving force in desiring FGM.[1,5] It is difficult to assess what component of the request is entrenched in a socio-cultural need for assimilation, and this could impede the voluntariness of consent. It is important to assert that fear is no justification for condoning what is unquestionably a practice with harmful health consequences. The solution is not to acquiesce to pressure to perform FGM but to educate the community as to the risks and impacts of FGM.

Some commentators reinforce that if patient autonomy is stated to be an adequate justification for performing female cosmetic genital surgery, it should also apply as adequate justification for medically performed FGM.[8,9] Many advocates of similarly banning labioplasty argue that certain forms of cosmetic surgery on female genitalia pose similar health risks to FGM. [10] However, perhaps what this should invoke is a questioning of the ethical soundness of female genital cosmetic surgery. Despite said assertions that the legal permitting of labioplasty should likewise permit FGM, the converse can and must be argued. Performing one potentially unethical procedure should not allow the medical practice of other unethical procedures.

The final stance

It is of great interest in finally evaluating this argument, to return to a question posed at the beginning of this paper: should ethics be removed from socio-cultural standpoints? The answer is yes, and herein lies the core opposition to the practice of FGM. Ethics are grounded in the basic human rights and preservation of the dignity of a person. As E.H Kluge postulates in *Female Genital Mutilation, Cultural Values and Ethics*, ethics apply to the nature of what it is to be human, and consequently apply to all human beings irrespective of their background or belief system.[11] Therefore, if cultural frameworks fail to meet these universal standards, they can be subject to ethical critique.[11] Consequently despite having respect for the autonomy of the patient, this writer holds the opinion, as do several international bodies, that FGM has led to worldwide incidences of violations of the rights of a woman, and degradation of their inherent dignity and should be prohibited.[1] Also as health practitioners objectively upholding what is in the best health interests of the patient, we cannot ignore the high risks of varying adverse physical and psychological health outcomes that are often inevitable with FGM.[1,4,5]

Reducing the practice of FGM internationally

Legislation that is effective in countries condoning FGM is well and good, but how does one begin to turn a centuries old wheel? International organisations, such as UNICEF, have mapped out goals for eliminating FGM internationally.[12] These are mainly aimed at affecting change at an individual and societal level by challenging age-old customs. [12] Koso-Thomas et al found, in examining populations and countries that practice FGM, levels of education and literacy were inversely proportional to rates of FGM, so these are areas to be addressed in terms of empowering women to have the correct educational tools for informed decision making.[13] Community based interventions, which bring together leaders and elders of local communities as well as women and their families, are one method. They can permit open discourse and awareness programs to take effect.[12,13] An intriguing concept in implementing strategies for change is that of decreasing the 'supply and demand' of FGM.[12] This involves educating target groups such as the local health practitioners carrying out the infibulations.[12] It encompasses educating them as to the dangers of FGM or retraining practitioners of traditional medicine in women's health and midwifery, hence providing them with a more ethically suitable position.[12,13] Educating young men and their families is also vital in terms of reducing the stigma surrounding women who do not receive FGM.[12] This will assist in challenging the association of FGM with marriageability.[12]

Managing requests for FGM in medical practice

The views of Elchalal et al and RANZCOG guidelines still hold; cultural sensitivity and probing the cross cultural barrier is necessary in providing comprehensive healthcare whilst denying the request of FGM. [2,7] Extensive antenatal/gynaecological counselling may allow a healthcare practitioner to not only build rapport and trust, but also allow one to elicit details of what influences requests for the procedure.[2] This therefore reduces adverse mental health outcomes that may arise from a refusal of the request. The inclusion of family members (whilst carefully documenting their views), is not only in keeping with the desire of the patient; it allows you the unique opportunity to hear their opinions, understand their influence on the patient, and incorporate them into your educational strategies.[2] The guidelines have stressed the vital importance of treating women who have undergone FGM without 'alarm or prejudice', as allowing them the confidence to access healthcare is an imperative outcome of treatment.[2] Educational outreach programs, namely the National Education Program on Female Genital Mutilation and FARREP (Family and Reproductive Rights Education Program) utilise both multilingual and multicultural health workers who can assist in offering culturally sensitive healthcare.[2] Ultimately, it is important to uphold the quality of life of the patient and identify the factors that contribute to it.

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Managing complicated malaria in pregnancy: beating the odds

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Malaria, especially *falciparum* malaria, has the potential to cause multi-organ failure and is a major cause of morbidity and mortality in pregnant women. It is defined by the World Health Organisation (WHO) as the presence of asexual parasitaemia and one or more of the following manifestations: cerebral oedema; severe anaemia; renal failure; pulmonary oedema; adult respiratory distress syndrome (ARDS); disseminated intravascular coagulation (DIC); acidosis; hypotension or shock. [1] The pathophysiology underlying this disease will be discussed in this paper and will serve as a basis for outlining the importance of immediate supportive management and prompt administration of appropriate anti-malarial chemotherapy.

Introduction

Malaria is an infectious, tropical disease caused by parasitic protozoa of the species *Plasmodium*. The malaria parasites are transmitted via the bite of an infected female *Anopheles* mosquito (vector), the most virulent species being *Plasmodium falciparum* (*P. falciparum*). [2,3] Malaria in pregnancy is a major public health concern and contributes heavily to maternal and neonatal deaths worldwide. [3] In this article, the pathophysiology of *P. falciparum* malaria will be discussed to provide a background for the relevant management options and ethical decisions faced when treating pregnant women with complicated *P. falciparum* malaria.

Case Presentation

History

A 22-year-old woman, Ms AP, was admitted to Colombo General Hospital with high-grade fever, tremors and confusion. A detailed history revealed that she was a married, small business owner from a rural, farming region located in a malaria endemic area in Sri Lanka. [2] Her medical history was clear of any clinically significant past or current illnesses. However, it was found that she was four weeks pregnant with her first child.

Findings

On examination, she was alert but appeared fatigued with visible jaundice. Her blood pressure was 110/60mmHg and she was tachypnoeic and tachycardic with a heart rate of 110bpm. Her temperature was 37.8°C, indicating a pyrexial illness and her oxygen saturation was 94% on room air. Further physical examination revealed scleral icterus and splenomegaly but was otherwise unremarkable with no elevated jugular venous pressure or signs of pulmonary oedema. Laboratory investigations revealed normocytic normochromic anaemia (haemoglobin (Hb) 90 g/L), thrombocytopenia (platelet count 100 x 10^9 cells/L) and hypoglycaemia (blood glucose 3 mmol/L). Ms AP's liver function tests were also abnormal, with raised liver enzymes and increased total bilirubin (12 mmol/L). Importantly, her blood results showed stage 3 kidney failure, with increased serum urea (12mmol/L), creatinine (180mmol/L) and reduced glomerular filtration rate (36 ml/min). While viral serology and bacterial culture were negative, thick and thin blood films for malaria revealed ringed trophozoites, typical of *P. falciparum* (Figure 1), and parasitemia with more than 6% infected erythrocytes. Based on the World Health Organisation (WHO) criteria for severe malaria and her above presentation, indicating major organ dysfunction and asexual parasitemia, Ms AP was diagnosed with complicated malaria.

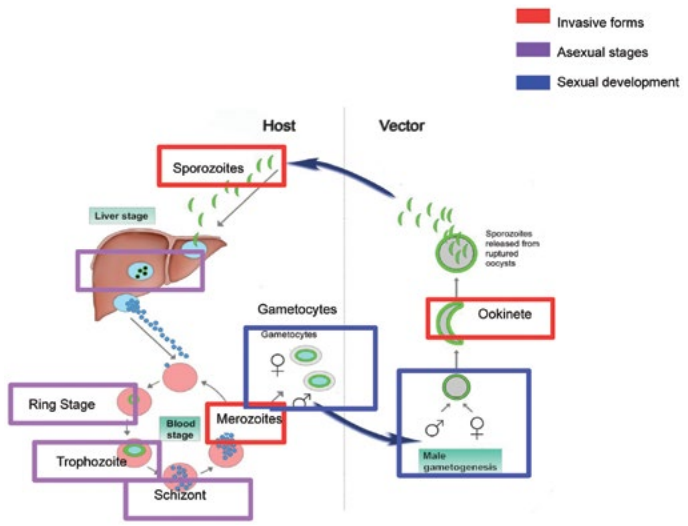

Figure 1. *Malaria life cycle*

Discussion

Effect of malaria in pregnancy

Infection of red blood cells by the asexual forms of *P. falciparum* and the involvement of inflammatory cytokines result in the prototypical clinical manifestations of malaria. [4] The initial paroxysm of *P. falciparum* malaria presents as non-specific 'flu-like' symptoms including malaise, headache, diarrhoea, myalgia and periodic fever every 48 hours. [4,5] These symptoms are associated with an immune response which is triggered when infected red blood cells (RBCs) rupture, releasing RBC remnants, parasitic antigens, and toxins into the bloodstream. [4,5] If untreated, this fairly un-alarming presentation can quickly progress to complicated malaria involving vital organ dysfunction. [4,5] In pregnancy, complicated malaria is more common due to altered immune function.[5,6].Discussed below is the pathophysiology and supportive management of the major manifestations of complicated malaria in pregnant women.

Severe anaemia (Hb less than 80g/L) is a major manifestation of pregnant women with *P. falciparum* complicated malaria and has the potential to cause maternal circulatory collapse. This is due to additional demands of the growing foetus and the ability of *P. falciparum* to invade RBCs of all maturities. [6,7] Both chronic suppression of erythropoiesis

by tumour necrosis factor alpha (TNF-α) and synchronous eruption of erythrocytic schizonts contribute to severe anaemia. [6,7] *P. falciparum* also derives energy via breakdown of haemoglobin, making infected RBCs more rigid and less able to navigate the micro-circulation. [6,7] This, along with alteration of non-infected RBC membranes, by addition of glycosylphosphatidylinositol (GPI), cause increased haemolysis and accelerated splenic clearance of RBCs. [6,8] Increased activity of the spleen manifests clinically as splenomegaly. [8] In pregnant women, like Ms AP, who present with severe anaemia, packed red cells are transfused when a safe blood supply is acquired. [9] However, blood transfusions should be used sparingly in resource poor areas where the risk of negative outcomes, such as incidental transfer of human immunodeficiency virus (HIV), is great. [9,10]

Cerebral malaria is an ominous sign in pregnant women and is a neurological syndrome characterised by altered consciousness (Glasgow Coma Scale ≥ 8) and uncontrolled, sub-clinical seizures. The precise mechanisms involved in the onset of this phenomenon remains unclear; however, localised perfusion defects, metabolic disturbances, and host immune responses all play a critical role. [11,12] Decreased localised perfusion is primarily due to microvascular changes. *P. falciparum* proteins, such as *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP-1), form knobs on the surfaces of infected RBCs and bind to receptors such as intracellular adhesion molecule 1 (ICAM-1) on the endothelium. This ability to cyto-adhere to cells results in sequestration of infected RBCs in blood vessels, causing endothelial inflammation and obstruction. [7,11] Interestingly, in *P. falciparum* malaria, a phenomenon known as rosetting also occurs. [11,12] Here, PfEMP-1 on infected RBCs bind to glycosaminoglycan receptors on uninfected RBCs, causing aggregation. [11,12] This further slows microcirculatory flow, reducing perfusion and causing ischemia-induced functional deterioration in organs such as the brain. [9,10] Mechanical ventilation in conjunction with appropriate anti-malaria drugs may be life-saving; preventing fatal hypoxemia and organ failure. [13,14] Seizures and other complications of cerebral malaria are treated with anti-convulsants to protect against rapid neurologic deterioration. [13,14]

Hypoglycaemia is a common manifestation in pregnant women with complicated malaria and arises from increased anaerobic glycolysis when P.*falciparum* metabolises glucose to lactic acid for energy. [7,8] In addition, decreased hepatic gluconeogenesis and increased demands of a febrile illness contribute to lowered blood glucose levels. [7,8] Intravenous administration of 25-50% dextrose solution injection is standard treatment and benefits both mother and foetus. [9,10]

Hepatic and renal failure occurs in complicated malaria due to mechanical obstruction of blood vessels by infected erythrocytes and via immune-mediated destruction of cells. [15,16] Loss of function of these organs result in poor lactate clearance, which along with increased anaerobic glycolysis and parasitic lactate production, potentiate metabolic acidosis. [15,16] Ultimately, these changes can progress to respiratory and circulatory distress. [15,16] In conjunction with anti-malarial agents, the best supportive therapy is fluid resuscitation or if required, renal replacement therapy. [15-19] Caution should be taken when treating malaria-induced hypertension in pregnancy as excessive fluid resuscitation via intravenous (IV) saline could worsen pulmonary oedema, triggering respiratory failure. [18, 19]

ARDS is more common in pregnant women and can be precipitated by pulmonary oedema, compensatory metabolic acidosis, sepsis, and severe anaemia. [11] It stems primarily from increased vascular permeability due to ongoing inflammation, as well as reduced pulmonary micro-circulatory flow. [11,12] Mechanical ventilation is essential in patients with ARDS as it helps maintain positive expiratory pressure and oxygenation. [13, 14] In patients presenting with hypotension, secondary sepsis due to bacterial co-infection should be suspected. Appropriate bloods including blood cultures should be taken and immediate treatment with broad-spectrum antibiotics such as clindamycin commenced. [14,19]

Effect of malaria on the foetus

Foetal distress is a concern in complicated malaria. Sequestration of RBCs in the placenta, via the binding of PfEMP-1 to chondroitin sulphate A (CSA) on the syncytiotrophoblast, can cause placental insufficiency. This results in poor oxygen supply to the foetus and may cause miscarriage, premature labour, still birth, growth restriction, and low birth weight. [20,21] This phenomenon is more likely in primigravida patients, such as Ms AP, and is thought to be due to lack of a specific immune response to the unique placental variant surface antigens (VSA) expressed by placental parasites. This hypothesis is supported by a longitudinal study by Maubert et al. which showed that antibodies against CSA-binding parasites were present in 76.9% of multigravida women by 6 months compared to only 31.8% of primigravida women. [22] In addition, severe fever and hypoglycaemia disrupts normal fetal development, which may induce premature labour and cause intrauterine growth restriction. [20,21] Micro-trauma to the placenta also increases the risk of infected maternal erythrocytes crossing into foetal circulation. Inevitably, this has the potential to cause congenital malaria and adds to the burden of complicated malaria in pregnant women. [20,21] Evidently, promoting prompt and efficacious drug treatment of malaria is necessary to reduce the systemic impact of malarial hyperparasitemia and to reduce foetal distress and mortality. Furthermore, due to the risk of congenital malaria, placenta, cord blood and neonatal thick and thin blood films should be considered for detection of malaria at an early age. [23]

Anti-malarial drugs and pregnancy

According to the South East Asian Artesunate Malaria Trial (SEAQUAMAT) study, a multi-centred, randomised controlled trial in South East Asia, artemisinin derivatives such as parenteral artesunate are the drugs of choice in pregnant women with complicated malaria. [24] These drugs are superior to quinine which is associated with a

Complicated P. falciparum malaria in pregnancy	
Supportive	1. Primary resuscitation survey [13-19] 2. Consider oxygen and mechanical ventilation [13-19] 3. Gain IV access, start fluid resuscitation and anti-malarial therapy [13-19] 4. Administer antipyretics for fever [19] 5. Determine fluid requirements and prevent fluid overload [20] 6. Administer intramuscular dextrose to avoid hypoglycaemia [21] 7. Consider anti-convulsants and antibiotics if seizures or sepsis are present [13-19] 8. Admit to intensive care unit (ICU) and monitor parasite levels, cardiac and renal function [13-21] 9. Consider blood transfusion if severe anaemia is present [21] 10. Consider renal dialysis if in kidney failure [19]
Chemotherapy *	1. Parenteral artesunate 2. Switch to oral anti-malarial medication when possible [25]
Follow Up	1. Counsel mother about vertical transmission and recurrence [23] 2. Test for congenital malaria [23]

***Table 1**. Key management points - Summary of relevant management options in complicated malaria in pregnancy*

narrow therapeutic window, hypotension, and hyperinsulinemic hypoglycaemia. [24] While quinine was the traditional drug of choice, it is now considered outdated and the drug artemenisin is currently used. [24,25] Artemisinin derivatives work by producing cytotoxic oxygen radicals within the parasite.[24] Unlike other anti-malarial drugs, such quinine and chloroquine, artesunate is toxic not only to mature schizont forms of *P. falciparum* but also to early ring stage endoerythrocytic trophozoites. [24,25] Therefore, they work faster to clear parasites from the blood, reducing complications linked with micro-vascular damage and parasite glucose consumption. [24-27] While relatively safe, these drugs have been associated with foetal anaemia and lowered bone density in early trials. [23-28] However, it is important to remember that in complicated malaria the mother is the priority as without her survival, foetal mortality is highly likely. Importantly, efficacy of above drugs in pregnancy should also be monitored as pregnancy appears to alter the efficacy of anti-malarial agents. [23]. Patients should be advised of the risk of recurrence and offered regular blood films throughout their pregnancy. [23]

Conclusion

Complicated malaria in pregnancy is a medical emergency and can result in death if not treated properly. Like in Ms AP's case, prompt administration of parenteral artesunate in conjunction with general supportive therapy is required for the best chance of survival for both the mother and foetus. [29]

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Consent Declaration

Informed consent was obtained from the patient in regard to publication of this article for educational purposes.

Conflict of interest

None declared.

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Ki-67: a review of utility in breast cancer

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Ki-67 is a protein found in proliferating cells that is identifiable by immunohistochemistry (IHC). Its prognostic and predictive value in breast cancer has been an area of avid research in recent literature and is increasingly shown to be of value. Identifying the presence of Ki-67 protein is now an accepted technique to differentiate hormone receptor (HR)-positive breast malignancies, and as a marker of prognosis in these tumours. It is also shown to have predictive value in neoadjuvant chemotherapy, and post-neoadjuvant endocrine therapy. Whilst it is not currently recommended as a routine investigation in the diagnosis of breast cancer, with standardisation of its methodology it has potential to become so.

Introduction

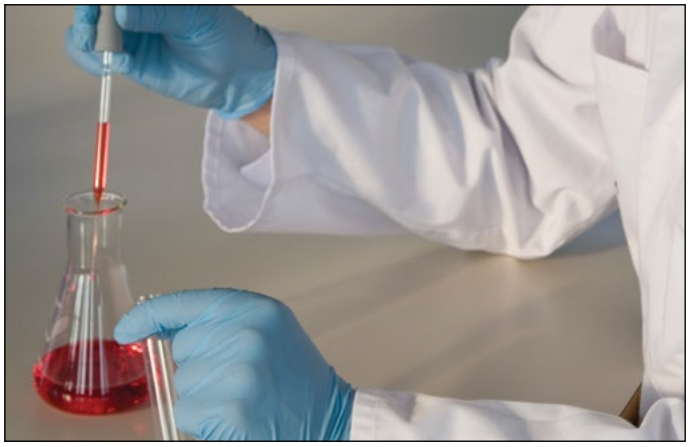
Breast cancer is the most frequent cancer of women (excluding non-melanoma skin cancer) in Australia. Survival of breast cancer has improved significantly in recent decades, with five-year relative survival increasing from 72% in the mid-1980s to 89% by 2010. [1] Survival rates have improved as a result of developments in screening, treatment and also diagnosis.

It is currently an exciting era in diagnostic medicine, with rapidly increasing knowledge and research leading to increased availability of diagnostic techniques. Improved diagnostics are allowing us to classify tumours not only based on their anatomical location and pathological appearance, but also by molecular and genetic typing. This increasing complexity of diagnosis and subtyping is allowing for more individualised cancer treatments and better outcomes for patients. Immunohistochemistry is an area of diagnostics that has blossomed over the past two decades. One of the most frequent uses of diagnostic IHC is in breast pathology. IHC techniques may have prognostic and predictive value, [2] and contribute to the trend towards targeted and bespoke therapies. Numerous tests have now been developed and some have become a standard part of the diagnostic work-up, such as for oestrogen receptors (ER) and progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2).

Despite the improvements in diagnosis, there remains a group of patients whose risk of recurrence is indistinguishable based on current standard tests. This leads to potential overtreatment of patients who would not benefit from therapy, and potential under treatment of those who would. [3] Other tests include multi-gene predictors and urokinase plasminogen activator testing that also have proven benefit as prognostic factors, and possibly have predictive value. The Ki-67 protein is a marker of proliferation that has been known for over two decades and has been the subject of renewed study and reporting of late. However, its popularity and integration into practice has been somewhat controversial.

Ki-67 as a proliferation marker

Ki-67 is a unique protein that is found exclusively in proliferating cells. It is present in the nuclei of cells in the G1, S and G2 phases of cell division and peaks in mitosis. Cells in the G0 phase do not express Ki-67. It is present in all cells, both tumour and non-tumour, and its presence is a marker of growth fraction for a certain cell population. [4] Despite the numerous studies demonstrating its presence in proliferating cells, the exact role of Ki-67 in cell division is as yet unknown. [5] Ki-67 was



first assessed for prognostic value in non-Hodgkin's lymphoma, but is increasingly used in various malignancies, [4] most notably in breast cancer. It has now been proven that a higher fraction of stained nuclei is associated with worse prognosis, and healthy breast tissue exhibits low levels of Ki-67 (<3%). [6]

Counting mitoses, flow cytometry (for determining S-phase fraction), and IHC for Ki-67 are common techniques for determining growth fraction. Flow cytometry is not recommended in prognostication due to difficulty with methodology. [7] Logically, counting mitoses and Ki-67 should correlate highly but clinical studies have shown that only 51% of high Ki-67 expressing breast tumours have a high mitotic index. [8] Ki-67 and the other proliferation markers, despite showing promise, are not recommended as a routine part of breast cancer workup currently. [3]

Ki-67 as a surrogate genetic marker

Ki-67 and mitotic rate are both considered markers of cell proliferation, however Ki-67 is considered a superior prognostic marker. [6] One reason it can be used for prognostication is that it may act as a surrogate for genetically different tumours. Patients with ER-positive tumours, like other malignancies, are known to display a great variance in behaviour, including response to therapy. This occurs because tumours display a heterogeneous mix of gene expression grade index. [9] To improve prognostication and therapy recommendations, breast malignancies were genetically subclassed into five subtypes (luminal A, luminal B, HER2-enriched, basal-like, and normal breast-like). Of most interest is the differentiation between luminal A and luminal B, which (by one author's definition) are both ER-positive and HER2-negative tumours but display contrasting behaviour. [10] Luminal B tumours typically have worse outcomes and demonstrate higher proliferation. Genetic typing showed certain genes (such as CCNB1, MK167, and MYBL2) have higher expression in luminal B tumours. [10] Given that genetic testing is expensive, and hence impractical, as a routine test in some settings, [8] Ki-67 can be used as a surrogate measure. This phenomenon has been studied wherein the combined prognostic value (IHC4) of ER status, PR status, Ki-67, and HER2 was shown to be of similar prognostic value to a more expensive 21-gene test. [11] Very recent Australian data shows that when tumours are divided into luminal A and B with the use of Ki-67 "the 15-year breast cancer specific survival was 91.7% [and] 79.4%" respectively. [8] This confirms the clinical variation in these tumours. These figures were only in

lymph node-negative breast cancer treated with breast-conserving surgery and postoperative radiotherapy.

Prognostic value

Ki-67 has been accepted to differentiate between luminal B and luminal A tumours without additional genetic testing. [12,13] The best cut-off score to differentiate ER-positive HER2-negative tumours is currently thought to be around 14%. At or above this figure, a tumour can be regarded as luminal B subtype and hence having a poorer prognosis. However Ki-67 is also associated with "younger age at diagnosis, higher grade, larger tumor size, positive lymph node involvement, and lymphovascular invasion.' [10] This is echoed in other large preclinical trials. [14]

A high Ki-67 is also shown to be associated with poorer ten-year relapse-free survival and breast cancer specific survival. This has been demonstrated in node-positive tumours, node-negative tumours, those treated with tamoxifen as the only agent, and those who are treated with combination therapy of tamoxifen and a chemotherapeutic agent. [6,10] A large retrospective Australian study has confirmed that Ki-67 appears to have significant mortality prediction. In their experience, a Ki-67 cut-off of 10% yielded the highest sensitivity and specificity, and at this level patient mortality rose from 3% in the low-Ki-67 group to 22%, and 15-year survival increased from 3% to 22%. Of note, this study did not differentiate luminal A and luminal B, and this did not exclude ER-negative tumours, nor-HER2-negative tumours, and so only looked at outcomes based on Ki-67. Interestingly, all HER2-positive tumours were high-Ki-67 tumours. The difference in the Ki-67 cut-off when compared with the 14% from previous trials is likely explained by the lack of inter-laboratory validation. The poorer 15-year survival of the high-Ki-67 tumours, compared with Pathmanathan's [8] study, can be partially explained by the inclusion of HER2-positive tumours and triple negative tumours, which are known to have poorer prognosis.

Aleskandarany et al. [15] in their larger study confirmed the variation between luminal tumour but also suggest that there is little prognostic value in Ki-67 in subcategorising HER2-positive and triple negative tumours[16]. Further, they revealed that " [a high Ki-67 is] associated with premenopausal status, larger tumor size, definite vascular invasion, and lymph node involvement", thus in non-luminal tumours may be selecting a patient group with other predictors of poor prognosis.

Ki-67 predictive value

Studies regarding the predictive value of the test are not yet as convincing as for prognostication, but continue to be an area of continued research and debate.

There are potential roles for Ki-67 in directing therapy in primary chemotherapy, neoadjuvant chemotherapy, neoadjuvant endocrine therapy, and in radiotherapy case selection. Chang et al. [17] suggested that tumours with a high Ki-67 are likely to respond more favourably to chemotherapeutic agents in the primary setting and that Ki-67 as a marker may be measured temporally during treatment to assess response. This study, however, had a small sample size and a single therapeutic regime, making it difficult to adopt in clinical practice.

Viale, [18] in his large retrospective review, showed that Ki-67 did not predict the relative efficacy of neoadjuvant chemoendocrine therapy in node-negative hormone receptor (HR)-positive tumours. However, this does not imply that Ki-67 has no role in directing adjuvant chemotherapy in other groups of breast malignancy. This has been further studied in a group of high risk breast malignancies by Denkert et al. [19] Denkert's group demonstrated that Ki-67 predicts response to neoadjuvant chemotherapy in HR-positive, HR-negative, HER2-negative, and triple negative groups. It also shows an effect on disease free survival (DFS), and overall survival (OS) in HR-positive and HER-negative groups. This study also reveals that Ki-67 percentage is a continuum and subsets may not be simply broken down into 'high' and 'low'; rather, multiple cut-off points may be required for a single tumour type and a variation of cut points required based on the studied endpoint (e.g. DFS or pathological response) and different tumours. To achieve this, further trials recording information prospectively will be necessary.

Ellis studied Ki-67 in the neoadjuvant endocrine therapy setting, and reported that it has limited role in pre-treatment biopsies, but its post-neoadjuvant treatment value predicts relapse-free survival. [20] Ellis suggests that when Ki-67 and ER status are combined post-surgery, a low value is correlated with low levels of relapse, and states that therapy beyond continuation of endocrine agent is likely unnecessary. In contrast, poor biomarker profile post-surgery is associated with significantly earlier relapse, more typical of ER-negative tumours; patients should be "offered all adjuvant treatments". [20]

Ki-67 also has predictive value outside of HR-positive tumours. There is evidence showing that in HR-negative tumours, a Ki-67 >20% is a predictor for clinical and pathological response in the neoadjuvant setting with anthracycline-based chemotherapy. [21] It showed that patients with HR-negative status and Ki-67 >20% were much more likely to respond to their prescribed regime. However the authors did not give the absolute variation in response based on Ki-67, and did not test with a variety of agents or protocols to see if IHC could be used to recommend a particular agent.

Another role for Ki-67 in the neoadjuvant chemotherapy setting is in reviewing the response to therapy. A number of authors have shown that Ki-67 percentage often decreases after adjuvant therapies, and that reduction may correlate with pathological response and DFS. [22] Dowsett and colleagues [23,24] measured Ki-67 both at baseline and two-week post-neoadjuvant endocrine therapy. These authors suggest that the Ki-67 after two weeks of neoadjuvant therapy is of greater prognostic value than at baseline. They hypothesised that a great change in Ki-67 should also be predictive of outcome, but the trial failed to show this.

Despite the scarcity of high-quality data the latest St Gallens consensus supports the use of Ki-67 in defining luminal B tumours and states, "For patients with luminal B (HER2-negative) disease, the majority of the panel considered chemotherapy to be indicated. Chemotherapy regimens for luminal B (HER2-negative) disease should generally contain anthracyclines and… taxanes". [12] This suggests that some groups have already adopted Ki-67 as a significant predictive factor in the management of HR-positive tumours.

Barriers to Ki-67 being used as a routine component of breast cancer workup

When Ki-67 staining is performed, nuclei display brown pigmentation. The area of greatest staining is used for counting, and the fraction of nuclei stained by the antibody is used to determine a percentage score. Ki-67 score is the first IHC marker that requires exact quantification to assess its benefit and there is currently no standardised methodology to do this. [25,26] This has led to a broad range of recommendations regarding the minimum number of cells analysed to accurately ascertain the percentage. [19] There are also many antibodies that are commercially available which may display subtle variances in result. [27] Further variations may also be seen based on the method of counting, i.e. computer aided versus human analysis. [28] The lack of a standard method to ascertain the percentage in a reproducible way combined with the other variances in techniques leads to inter/intra operator and laboratory variances. These have made it currently difficult to incorporate Ki-67 into routine use. [26]

Other IHC assays have been validated in the field of breast malignancies, such as for HER2, [29] and have led to more concrete recommendations. [12] Validation involves standardised recommendations for numerous factors including tissue handling, fixation, assay selection, comparison to standards, and ensuring inter and intra-laboratory concordance. [30] Further, this has been complimented by the development of HER2 in-situ hybridisation (ISH) to assess the underlying gene expression,

which may be superior or complimentary. [30] These advancements are yet to be achieved in Ki-67 analysis. Validation and standardisation of Ki-67 in a similar way has been called for by many authors, and if achieved will increase confidence in results and may allow for it to be used as part of routine testing. [25]

Conclusion

The renewed interest in Ki-67 in breast malignancies has proved its prognostic value, particularly in subgrouping HR-positive HER2-negative breast cancers. There is now increasing evidence to show that it may have a predictive role, with most evidence pointing to its role in both directing neoadjuvant chemotherapy and in assessing tumours post-neoadjuvant therapy to help direct further adjuvant therapy. Ki-67, along with other commonly used IHC assays and genetic testing are facilitating a move away from previously crude methods of treatment to increasingly tailored treatment solutions for our patients. Once standardised, Ki-67 may provide a cost-effective contribution to this trend.

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Conflict of interest

None declared.

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The role of general practice in cancer care

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Kok-Ho's interest lies in infectious diseases and oncology as well as the application of novel theoretical concepts to the development of better cancer treatment strategies. Kok-Ho's primary motivation in medicine is to find a novel therapy for cancers with poor prognosis so that patients who are incurable now may have a new lease of life in the near future.

The incidence of cancer has risen in Australia and globally over the past few decades. Fortunately, advances in medicine have enabled cancer patients to live longer. We now have the means to provide better healthcare and support for this group of 'survivors'. However, this situation also poses unique challenges to the healthcare system as resources are limited but healthcare professionals are required to do more. In recent years, there has been a call for an expansion of the role of general practitioners (GPs) in cancer care. Such a primary care-based approach allows GPs to pursue their interests in cancer management and enables diversification of healthcare resources. This article will attempt to examine how general practice can be involved in cancer care in Australia.

Introduction

Cancer is a chronic disease on the global scale. In Australia, cancer accounts for approximately a quarter of all deaths. [1] By the age of 75, one in three males and one in four females will be expected to be diagnosed with cancer. [1] These figures may be attributed to higher population growth and an ageing population. [2] As patients are diagnosed earlier and receive better treatment, more cancer patients transit into survivorship. [3] Consequently, the immediate demands of cancer care extend beyond diagnosis and treatment and towards multi-disciplinary care, which focuses on providing support and improving the quality of life of patients. This article will briefly examine the factors influencing the involvement of primary care physicians in cancer care in Australia and reference initiatives implemented by other countries.

Patterns of cancer care and areas of GP involvement

Cancer management is complex and involves different healthcare providers. According to Norman et al., cancer care patterns may be sequential, parallel or shared. [4] In sequential care, patients are mainly cared for by oncology teams while parallel care requires general practice (GP) management of non-cancer problems. Shared care has the greatest GP involvement and requires joint management of cancer care by GP and oncology teams. GPs in Australia are mostly involved in screening and diagnosis of cancer and, eventually, referral to specialists who take over treatment and patient follow-up. GPs also play a role in managing the side effects of treatment as well as education (including prevention measures) of patients and their families. Depending on the treatment outcome, supportive or palliative care may also be provided by GPs.

In the future, it is expected that GPs will need to accept responsibilities outside their remit. This is due to a limited number of specialists in rural and remote areas and the need to diversify and expand the healthcare workforce. [5] Furthermore, health systems that include strong primary medical care were shown to be more efficient and have better health outcomes. [6] Therefore, there is a gradual move towards shared care models with GPs playing a central role alongside other healthcare providers. In this context, it will be important to understand the factors influencing the involvement of GPs in cancer care and how to maximize their involvement throughout the spectrum of cancer care.

Factors influencing GP involvement in cancer care

Location of GPs

The degree of involvement of GPs may depend on where they are based. [7] Out of necessity, GPs in rural and remote areas could be involved in coordination of cancer care and also some aspects of treatment (e.g. pre-chemotherapy checks) and follow-up of side effects. Conversely, GPs working in urban settings were more likely to refer patients upon diagnosis.

Studies have shown that indigenous Australians and other minority groups living in rural or remote areas have higher cancer mortality rates due to reduced access to healthcare. [8] GPs working in these settings could reduce this inequality through better prevention and diagnosis, timely referrals as well as treatment of co-morbidities-areas which are traditionally within the remit of primary care. [9] Although the cancer curriculum in Australian GP training focuses on these areas, it is estimated that GPs only encounter about four new cancer cases each year with cases exhibiting huge variability in cancer types and treatment requirements. [7] Such a scenario necessitates opportunities for GPs to improve their skills and experience through case-based learning and seminars. [7] Online learning modules offered by Cancer Australia are a good starting point but more effort will be required to promote these learning opportunities as GPs may not be aware of such resources. [7,10]

In recent years, the rise of telemedicine has provided an important tool in connecting rural GPs and specialists. This has enabled rural GPs to be more involved in cancer care as they can easily gain access to specialist knowledge. In Queensland, medical oncology services via videoconferencing were trialed and provided to remote and rural communities. [11] Satisfaction levels were high among both patients and rural health workers with such benefits as reduced time and money, improved communication between specialists and patients and greater access to specialist support by rural GPs. [11]

Communication pathways

Communication between GPs and hospital-based services is regarded as a major challenge facing general practice in Australia. The main form of communication from hospitals to GPs is the discharge summary and specialist letter with GPs receiving information mainly from hospital medical officers. [5] The variable quality and poor

timeliness of information received has been shown to impede quality communication between GPs and hospitals. These factors were attributed to poor understandings of GP roles in cancer care and their information needs, as well as inexperience of medical officers. [5] It was found that hospital communications to GPs tend to omit social information about the patient. As cancer patients have been shown to be dependent on GPs for psychosocial support, the social needs of cancer patients may not be addressed adequately by GPs if poor communication persists. [1]

It was also shown that GPs preferred to receive a multi-disciplinary discharge summary containing input from all health professionals involved. [5] The creation of electronic health records may facilitate the development of such a discharge summary. In Canada, the British Columbia (BC) e-health initiative allows authorized health professionals working in BC to access complete patient records when and where they were required. [12] This initiative was shown to reduce patient delays and costs to healthcare providers and patients and is a great demonstration of how improved communication via improved access to patient records may improve healthcare outcomes of cancer patients. Nonetheless, it is important that such electronic platforms are developed for and with healthcare practitioners to allow them to tackle the patient's needs without being burdened by technology. [12]

Regular meetings may also improve communication between GPs and specialists. Mitchell et al. suggested that GPs should be regularly involved in hospital-based multi-disciplinary team (MDT) meetings. [13] It is heartening that a national survey found that 84% of GPs would consider taking part in MDT meetings should the opportunity arise. [14] This suggests that formalization of MDT meetings is highly feasible. Cancer patients may benefit from the sharing of experiences between members of a formalized MDT team and this could be crucial to patients who suffer from low-incidence cancers where experience of the team matters and also to GPs, who would otherwise have little awareness about which specialists to approach for specific cancers. [13]

Remuneration and financial incentives

Inadequate remuneration may also deter GPs from accepting additional responsibilities. A recent study found an increasing proportion of Australian GPs are not involved in palliative care (25%) as compared to previous rates of 5% and 8% in 1993 and 1998 respectively. [15] Poor remuneration in relation to the time and knowledge required for palliative care may be a deterring factor. There is currently no requirement for GPs to provide after-hour services for palliative care and some GPs also reflect that they are not confident enough to manage the technical and psychosocial aspects of palliative care. [15]

Financial incentives may be helpful as the workload of GPs has increased but their incomes have decreased relative to specialist incomes. [6] In the United Kingdom, the Gold Standards Framework for palliative care rewards GPs who are interested in palliative care and demonstrate quality care through regular meetings and maintenance of a patient register. [16] Such a scheme may attract GPs to be more involved in palliative care. In addition, to increase involvement of GPs in population-based screening programs, the current payment scheme in Australia should be revised to reward service not just based on service to symptomatic patients but also asymptomatic cancer patients who approach GPs for counseling and other psychosocial issues. [8]

Role of healthcare providers

The roles of healthcare providers are often unclear. Holmberg et al. reported that while some people understand the role of GPs in cancer care, others felt that their roles were not stated explicitly in guidelines. [17] The varying perception of GP roles may hinder GPs from expressing their information needs and prevent their expanded involvement in treatment and follow-ups. It has been shown that patients prefer to know who is in charge and parallel care may provide a clearer definition of GP and specialist roles. [18] Moreover, parallel care is not as demanding as shared care in terms of the level of communication required to facilitate coordination of cancer care and may therefore be favoured by both GPs and specialists. [18] While it is important to align patients' perception with the preferences of healthcare providers, a parallel pattern of care may not be necessarily be the most effective. This explains why there is now a gradual move towards multi-disciplinary care based on shared care models, which was highlighted in Australia's 2009 report on 'A healthier future for all Australians'. [19]

A shared care model would require clarity of roles and a need to recognize and expand the role of primary care without compromising healthcare outcomes. Two randomized control trials in the United Kingdom (UK) and Canada showed that follow-up of breast cancer patients by GPs was as safe as follow-up by specialists while an Australian study showed no difference in recurrence rates of colorectal cancer patient after follow up by GPs or specialists. [20,21] These studies imply that GPs may undertake a greater role in the follow-up phase. Similarly, there may also be a growing role for GPs in the treatment phase, in terms of management of toxicity episodes or pre-chemotherapy checks, as new oral chemotherapeutic agents are developed. [13]

Access to protocols such as The Cancer institute NSW Standard Cancer Treatment Program (CI-SCaT) may allow GPs to manage cancer patients without requiring too much reliance on specialist expertise. [13] Similarly, GPs can access wiki-based clinical practice guidelines which are developed and constantly updated by Cancer Council Australia. [22] GPs based in rural/remote areas have been relying on generic clinical skills adapted to cancer care to manage cancer patients for years and supplementation of these skills by specialized cancer information may improve the feasibility and practicality of GP-based cancer management. [23]

GP preferences and input

While there is much potential for the expansion of GP roles, GP preferences and their input in cancer plans needs to be valued. GPs generally express interest in being involved in areas that are traditionally within their remit such as prevention, diagnosis, surveillance and psychological support but less than 50% of GPs expressed a desire to undertake coordination roles in treatment and supportive care. [7] These observations may reflect underlying structural and systemic constraints (e.g. workload and payment structures) that could only be addressed effectively at a governmental level. Conversely, as mentioned previously, GPs in rural/remote areas are already actively involved in coordination of cancer and psychological care and thus they may accept expanded roles more readily.

Ultimately, there needs to be a buildup of trust and confidence in GP capabilities and increased involvement of GPs in cancer control plans will be necessary. Internationally, the UK National Health Service (NHS) has involved GPs in its cancer plan since 2000. [1] Similarly, in Australia, GPs have been involved in the National Service Improvement Framework for Cancer while a scoping exercise undertaken by the National Cancer Control Initiative in 2004 has sought to identify areas of priority to support cancer care by primary healthcare providers. [1] A result of which was the Cancer Service Networks National Demonstration Program (CanNET) which was funded by the Australia government in seven states. It was conceived as a means of identifying opportunities to improve the organization and delivery of cancer care via MDTs and managed clinical networks (MCNs) so as to improve outcomes and reduce disparities in cancer survival rates across population groups. [24]

Lessons from CanNET

The evaluation of CanNET provided valuable insights into the provision of multi-disciplinary cancer care. For example, in addition to effective communication, it was found that networking events and activities were essential to building up professional relationships between

healthcare providers. [24] Moreover, although GPs were willing to be involved in MDT sessions, engaging GPs was found to be difficult due to constraints imposed on general practice. [24] This suggests that while examining constraints on the specialist side is important and has been researched extensively, increased focus should also be placed on alleviating constraints on the GP side.

CanNET was also found to increase the work burden for healthcare providers. [24] This has prompted a re-think of healthcare providers' roles to incorporate more flexibility. A number of innovative roles are found overseas and could be trialed in various CanNET networks. For example, the Uniting Primary Care and Oncology Network (UPCON) in Manitoba advocated the use of medical leaders in the form of lead family physicians (FPs). [25] These lead FPs are primary care physicians within a practice who have an interest in cancer care and constantly engage in regular education programs and meetings jointly organized by oncologists and FPs. They disseminate useful information to colleagues and also play an advisory role by raising issues pertaining to primary care during meetings with oncologists and the Manitoba cancer agency. Besides occasionally accepting referrals, lead FPs did not have to perform difficult or unfamiliar tasks and they were remunerated according to their level of involvement. [25] This program managed to improve the partnership between GPs and other healthcare providers and could potentially fit into the Australian system.

Consistent with the theme of medical leadership, it was found that the introduction of continuing professional development (CPD) was effective in promoting local champions in some CanNET networks. CPD opportunities such as mentoring and clinical placements were received positively and more than half of the healthcare providers surveyed acknowledged that these activities helped increased their knowledge and skills and provided valuable networking opportunities. [24] Nonetheless, more work is required to address potential constraints such as workload and staff shortages. This again raises the importance of tele-oncology as a possible solution as essential oncology skills may be learnt during GP sit-ins with patients, therefore reducing the need for face-to-face attendance of workshops.

Looking to the future- the ideal oncology curriculum

The Oncology Education Committee of Cancer Council Australia has developed an ideal oncology curriculum for medical schools with the aim of equipping students with the knowledge, skills and attitude to provide quality care to cancer patients and their caregivers. This curriculum has been reviewed recently to include more emphasis on clinical experiences such as 'observing all components of multi-disciplinary cancer care'. [26] These changes reflect the need for future doctors who are able to work within a multi-disciplinary cancer care setting and who can understand the role of healthcare providers (including GPs) in different phases of a cancer patient's journey. [26] Students who are interested in becoming GPs will need to be familiar with the specific needs and requirements of cancer patients as GPs are often the first point of call. Furthermore, students who take up the Medical Rural Bonded Scholarship Scheme (MRBS) and end up in rural settings will be expected to take up more responsibility than their urban counterparts. As such, changes in medical education may pave the way for changes in future medical practice.

Conclusion

Cancer management in Australia is gradually changing toward a shared care model with a focus on multi-disciplinary care. In this context, there is an increasing demand for GPs to expand their roles to relieve the pressure on other healthcare providers. Existing constraints that impede the involvement of GP will need to be addressed. These include issues pertaining to communication, remuneration, role clarity as well as GP preferences and input. A number of initiatives such as CanNET were implemented and has helped identify areas which could promote a greater role for general practice in cancer care. Overseas healthcare initiatives such as UPCON and the BC e-health initiative will also provide further valuable lessons in our search for solutions. Currently, tele-oncology appears to be a viable approach in improving rural GP involvement in cancer care and alleviating workload and staff shortages.

In conclusion, GPs have the capacity to provide quality cancer care alongside their specialist counterparts and it would be a more efficient use of healthcare resources to involve rather than neglect them. It is unlikely that specialist cancer care will be compromised as they form the core component of the actual treatment process whereas GPs are envisioned to take up coordinating as well as diagnosis and follow-up roles. As the roles of the GP can be flexible depending on preference and expertise, this is in itself advantageous as cancer care is no longer limited by the number of specialists. Specialist care may also be enhanced due to a more focused and individualized approach afforded by the less workload taken on by the specialists.

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Conflict of interest

None declared.

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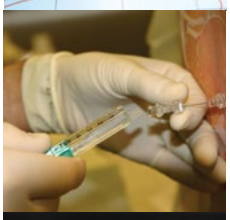

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