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EDITORIALS

The Journal in 2017

The Internal Medicine Journal (IMJ) had a bumper year in 2017 with a full volume plus six supplements published and we managed to maintain and build on our position as the premier vehicle for publication of scientific matters relevant to physicians in New Zealand and its neighbour to the west. I have thanked the Editorial Board and management team annually for the past 12 consecutive years and I never get tired of it. They all work beyond the limits of their briefs throughout the year to provide you with the product you are holding now, one of which we are extremely proud and one that is on a steady upward trajectory regarding quality and reach.

Some of you will be aware that the Editorial Board met in person at the RACP in Sydney this year in September and discussed the current status of the Journal and its future. This was a productive day and you should start to see some outputs from that meeting in the coming issues. I had hoped to have had a summary paper of highlights of the year in many of the disciplines covered in the Journal by this issue but the deadline I set was impossibly short, so hopefully you will see it within the next couple of months. I am hopeful that such an annual report may help to expand the interests and knowledge of an increasingly subspecialised readership into important advances in fields other than its own. When the 2018 version of this does appear, I welcome all comments (even via Twitter: remember, I am @marrow).

The Editorial Board had several changes over the past year starting with the resignation of the Editor for Infectious Diseases, Professor David Gordon (editor since April 2014). We thank David for his patience and application to the editor’s role, especially with the obvious rise in the number of submissions to this specialty. In May 2017, Dr Ian Woolley (Monash Medical Centre, Melbourne) was appointed as Infectious Diseases Editor. Ian has a particular interest in HIV. Associate Professor Fred Khafagi resigned as Nuclear Medicine Editor in September 2017, a role he has held and conducted brilliantly since May 1995. I would like to acknowledge his dedication and loyalty. Associate Professor Sze Ting Lee (Monash Medical Centre Melbourne) was appointed as the new Nuclear Medicine Editor in October 2017. Professor Lee has advised of international developments in this area of medicine with some coverage anticipated for the IMJ readership in an impending editorial. In recognition of the increasing workloads in a number of specialties, the decision was made to appoint an additional editor to the Nephrology portfolio. (This, as you will know, has already happened in other disciplines, such as Haematology, Cardiology and Endocrinology with increased efficiency in these disciplines.) We welcome Professor Karin Jandeleit-Dahm from Monash University who has been appointed to this role.

Our citation index for 2016 was 1.902, showing a significant rise over the year from 1.526 (the 5-year impact factor was 1.788). These figures represent the proportion of citations to published papers over the previous 2 (or 5) years. Our ranking in the ‘medicine, general and internal’ category was 52/154 representing an improvement of 10 places with one additional journal in the mix.

Manuscripts continue to come from all over the world, and China remains a growing source of submissions. I am pleased that our panel of honorary biostatistical advisors has been able to provide very useful assistance to editors when requested. You may remember that last year, I relayed the information that Wiley had partnered with the company called Altmetric to track the ways in which articles are shared, used and discussed including in social media, blog posts, newspapers and magazines. You can see these scores with each published article on Wiley Online Library and a specific example of its value later in this editorial.

The College podcast programme (Pomegranate) continued to highlight interesting matters related to papers published in the Journal. In 2017, the podcast released on 2 August 2017 (Episode 27) discussed the paper on severe asthma by Professor Peter Gibson and Professor Vanessa McDonald (from the Hunter Medical Research Institute), published in the June 2017 issue of the Journal.¹ As guests for this episode, they described emerging diagnostic tools and therapies such as monoclonal antibodies that are targeted to specific disease phenotypes. Another podcast released on 26 September (Episode 29) discussed the paper by Professor Richard Day et al. (St Vincent’s Hospital, Sydney) on drug interactions published in the May 2017 issue of the Journal² and included an external guest, Professor Sarah Hilmer from Royal North Shore Hospital in Sydney for additional viewpoints. You can find the podcasts through the RACP site (https://www.racp.edu.au/pomegranate/), but one can also subscribe to the Pomegranate series through iTunes and other podcast aggregators. There is an added benefit

¹ Internal Medicine Journal 48 (2017) 49–50

² doi:10.1111/imj.13675
for Fellows of listening to these podcasts as CPD credits can be claimed for MyCPD for this activity (as one can for reading the Journal and publishing in it!).

A new solicited series in Addiction Medicine began in 2017 entitled, ‘Addiction medicine: clinical and ethical perspectives’ edited by Associate Professor Yvonne Bonomo. About 10 papers are planned; four were published in 2017, the first one in the February issue.3

The IMJ Twitter account (@The_IMJ) is active and you can link to each issue and highlighted paper directly from there. Follow us, you will not regret it.

There was a considerable amount of media reporting relating to the paper by Ruane et al. entitled ‘Triggering of acute myocardial infarction by respiratory infection’ published in the May 2017 issue of the IMJ.4 Stories reached a global audience and coverage is still ongoing with the article achieving a massive Altmetric score of 594 (a score of 630 as I write). By late May 2017, the article had been mentioned in over 84 news stories from 74 different news outlets globally. The Altmetric score is a calculation based on the quality and quantity of attention a covered article receives in a variety of social media platforms.

Last year, I indicated that Wiley was developing a smart device application (‘app’), which will allow you to access the Journal so much more conveniently. I continue to wait for this as the release has been unfortunately held up for a variety of technical reasons. Hopefully it will be even better when we do see it, possibly soon.

I remain grateful for the work of Virginia Savickis, the editorial manager, and Aparna Avasarala, the editorial assistant, in getting this Journal out on time. Aparna has been essential in getting the Twitter account up and running and is doing an excellent job with it.

Once again, may I remind you to subscribe to the electronic table of contents and automatically include alerts to newly published papers? You can sign up at Wiley Online Library at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1445-5994 and click on the ‘Get New Contents’ alert tab in the upper left corner or for Fellows of the RACP, through the publications link at http://www.racp.edu.au. I would recommend you explore this if you have not done so already.

In closing, I thank, once again, our dedicated team of manuscript reviewers for the excellent and essential work they do for us and the authors whose submissions they review and always improve. Publons (www.publons.com) is an initiative that is now running smoothly and providing some credit for the work reviewers do for this and other publications.

I invite you to read the names of our 2017 reviewers listed after this article and, if possible, thank them personally for the service they selflessly provide for the essential and unpaid work offered to us.

I continue to look forward to the collaboration of the Journal’s readers and contributors.

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Jeff Szer ©
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*Reviewer names recorded from 1 November 2016 to 31 October 2017. Reviewer names not indicated will be published in the next volume.

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Towards a cure for human immunodeficiency virus

The past three decades have seen spectacular advances in the management of human immunodeficiency virus (HIV) infection. Modern antiretroviral therapy (ART) effectively suppresses the virus to undetectable levels in blood allowing for immune recovery and near-normal life expectancy for most people living with HIV. Additionally, it is now clear that commencing ART immediately at any CD4+ T cell count reduces the risk of morbidity and mortality and that HIV-infected individuals with an undetectable viral load on ART are unable to transmit virus sexually. This has led to a global initiative to treat all people living with HIV upon diagnosis and for ART to complement other strategies to prevent new HIV infections. However, in order ultimately to eliminate HIV at a population level, we will still need an effective prophylactic vaccine.

Despite the success of ART, if ART is ceased, virus returns rapidly in blood, usually within weeks. Treatment must therefore be continued lifelong. There are now 19.5 million people living with HIV on ART but this accounts for only 53% of the world’s 36.7 million people living with HIV. In Australia, uptake of ART is approaching 90%, one of the highest rates of treatment uptake globally. The estimated cost of achieving similarly high levels of treatment worldwide by 2020 is US$20 billion per year. In many parts of the world, stigma, discrimination and punitive laws remain significant problems for people living with HIV. Therefore, lifelong treatment for HIV comes at great economic and personal cost and there is now an accelerated global effort to find either a cure or a safe way for individuals to cease ART such that the virus stays at low levels. This is also known as HIV remission.

Why can’t ART cure HIV?

ART works by interrupting viral replication within activated CD4+ T cells, the main target of HIV. However, in resting CD4+ T cells, HIV integrates into human DNA where it is silenced and cannot complete the viral replication cycle. This is known as latent infection and this integrated virus cannot be targeted by ART or the immune system. HIV latency is established within the first few days of infection and persists indefinitely due to the long life-span of infected memory CD4+ T cells and proliferation of these cells. Although infrequent at one in 100 000 cells, these latently infected cells contain infectious virus that can reactivate upon ART cessation. In most people, virus will reactivate within 2–3 weeks of stopping ART.

The earlier ART is commenced, the fewer latently infected cells and the more intact an individual’s immune system. Interestingly, it is now recognised that a small proportion of individuals who commence ART during acute infection and then stop years later are able to maintain low to undetectable levels of virus for prolonged periods. These ‘post-treatment controllers’ are quite distinct from individuals who can naturally control virus without ART, called ‘elite controllers’. Elite control occurs in <1% of people living with HIV whilst the frequency of post-treatment control may be as high as 5–15%. Post-treatment control has also been demonstrated in children infected at birth who start ART within days to months or even several years. Despite these encouraging but rare case reports, lifelong ART remains the recommendation for all HIV-infected individuals outside of clinical studies.

Strategies being evaluated to induce HIV remission

There are multiple approaches that are currently being evaluated to allow people to stop ART safely and achieve remission. These approaches can be broadly divided into four categories: bone marrow transplantation and gene editing, latency activation, latency silencing and immunomodulation. The common aims are to reduce the amount of HIV that persists on ART and/or to boost HIV-specific immunity. Interventional studies in this area are performed in HIV-infected individuals, simian immunodeficiency virus (SIV)-infected macaques and HIV-infected humanised mice. The latter are highly immunodeficient mice which have been given a human haematopoietic stem cell transplant (HSCT) at birth and several months later infected with HIV. ART controls virus replication in all of these settings and therefore interventions to stop ART safely can be evaluated.

The gold standard test to determine if an intervention has worked is to stop ART with regular viral load monitoring. The primary end-point for these studies is the time until virus becomes detectable and/or the frequency of achieving a low viral load steady state, often defined as <50 copies/mL. Many of the earlier studies of cure strategies have not stopped ART but have instead evaluated the effects of an intervention on the frequency of HIV-infected cells measured by polymerase chain reaction (PCR) quantification of HIV DNA or the frequency of infectious genomes. Unfortunately, these
parameters do not predict viral rebound off ART accurately; however, with frequent monitoring, stopping ART is considered to be safe and viral control off ART is now a frequent endpoint to these studies.

**Bone marrow transplantation and gene editing**

Only one person is known to have been completely cured of HIV. Timothy Brown, a US citizen living in Berlin with HIV suppressed on ART, required a HSCT in 2007 for acute myeloid leukaemia (AML).\(^\text{(16)}\) The stem cell donor was homozygous for the Δ32 mutation in CCR5, the chemokine receptor required for HIV entry into the cell. Homozygosity for this mutation means that cells are resistant to HIV infection. Timothy ceased ART upon transplantation and has since remained off ART without any evidence of residual virus 10 years later despite extensive tissue sampling.\(^\text{(16)}\)

Multiple factors may have contributed to Timothy Brown’s cure, including myeloablative conditioning, graft-versus-host disease (which may also have had a graft-versus-virus effect) or a second transplant following AML relapse. Unfortunately, despite multiple attempts, no other recipient of a HSCT from a donor homozygous for the CCR5 Δ32 mutation has had long-term HIV-free survival. This has mostly been due to early fatal complications of the HSCT rather than HIV relapse.\(^\text{(17)}\) Allogeneic HSCT from donors expressing wild-type CCR5 have been associated with marked depletion of residual infected cells to below detectable limits\(^\text{(18,19)}\); however, in all such HSCT recipients to date, viral rebound has occurred post-treatment interruption, albeit significantly delayed in some individuals.\(^\text{(18)}\) Clearly HSCT has unacceptably high risks for a person living with HIV on ART who has a near-normal life expectancy. Therefore transplantation is only suitable for individuals who require it for another indication.

The case of Timothy Brown is proof of concept that HIV cure is possible and has spurred efforts to ‘knock out’ the CCR5 gene from HIV-infected individuals’ haematopoietic stem cells using gene editing technologies such as CRISPR-Cas9 or zinc finger nucleases (ZFN). Clinical trials using infusions of autologous peripheral CD4+ T cells which have had CCR5 gene editing \(\text{ex vivo}\) using ZFN were shown to be safe in HIV-infected individuals on ART and 13.9% of circulating CD4+ T cells were gene modified.\(^\text{(20)}\) This approach is unlikely to work for the small subset of individuals infected with HIV that uses CXCR4, another chemokine receptor that HIV can use to enter a cell. Work continues on nanoparticle or viral vectors for \(\text{in vivo}\) delivery of gene editing enzymes.

**Latency activation**

The most widely studied approach to HIV cure has been to activate latent HIV, often called ‘shock and kill’. This approach attempts to force transcription and protein expression from an integrated virus in latently infected cells so that the immune system can recognise these cells as infected and kill them. ART is continued throughout to prevent infection of neighbouring cells.

Histone deacetylase inhibitors, licensed for use in hematologic malignancy, have been extensively evaluated as a strategy to activate latency. These drugs work by promoting a more open DNA structure which facilitates transcription of HIV DNA to RNA. Whilst these drugs have been shown in HIV-infected individuals on ART to be safe and to increase HIV RNA both inside cells and in plasma, they have not been shown to deplete residual infected cells.\(^\text{(14)}\) It seems that forcing transcription of virus is not enough and a stimulus to help the immune system kill the expressed virus may also be required.

Other agents being evaluated for latency activation include drugs that modify chromatin through changes in DNA methylation. Most promising and least toxic of the latency activation drugs appear to be toll-like receptor (TLR) agonists that activate latency by increasing interferon production. TLR7 and TLR9 agonists have recently been shown \(\text{in vivo}\) and \(\text{ex vivo}\) to activate latent infection and to enhance CD8+ T cell and NK cell activity.\(^\text{(21,22)}\) Therefore, TLR agonists may potentially both ‘shock’ and ‘kill’.

**Latency silencing**

The opposite approach to activating latent infection is to induce a state of deep latency or put the virus to sleep permanently. This has been termed ‘block and lock’. Didehydro-cortistatin A, a novel drug derived from a marine sponge, can induce a state of deep latency in latently infected cells so that the immune system can recognise these cells as infected and kill them. ART is continued throughout to prevent infection of neighbouring cells.

Gene therapy approaches could also be used to silence permanently HIV RNA using small interfering RNA (siRNA).\(^\text{(24)}\) This approach attempts to force transcription and protein expression from an integrated virus in latently infected cells so that the immune system can recognise these cells as infected and kill them. ART is continued throughout to prevent infection of neighbouring cells.

**Immunomodulation**

Targeting the host immune system and not just the virus is also an active area of investigation. Therapeutic vaccination with constructs that boost HIV-specific T cell
function in infected individuals has recently shown promise. Studies in a macaque model show that using a vaccine made from an adenovirus together with a TLR7 agonist could induce post-treatment control after ART cessation. A similar strategy is now being tested in HIV-infected individuals (ClinicalTrials.gov Identifier NCT02616874).

Another promising area of therapeutic vaccination is the passive administration of antibodies that recognise multiple virus strains, known as ‘broadly neutralising antibodies’ (bNAb). There are now many highly effective bNAb that not only block viral infection of cells but also deplete infected cells and may also boost HIV-specific T cell function. Administration of bNAb to HIV-infected individuals on ART has led to significant delays in viral rebound following ART interruption. The challenge now is to increase the half-life of these antibodies or find a strategy that will not require passive administration.

Immunomodulation can also be targeted at immune processes that are not HIV-specific. These include (i) reducing chronic inflammation to improve immune responses, (ii) altering migration of immune cells to tissue sites, such as gut and lymph node where there is a high frequency of infected cells and (iii) boosting T cell function through reversal of T cell exhaustion.

This rapidly expanding field has demonstrated some notable results in animal models that require further evaluation in humans. Interleukin 21 and anti-interferon α/β receptor antibody are examples of agents which have been shown to reduce inflammation and concomitantly deplete the viral reservoir and reduce or delay viral rebound upon ART interruption. αβ7 integrin is a cell surface marker directing immune cells to the gut. A monoclonal antibody against αβ7 integrin given to ART-suppressed SIV-infected macaques has induced post-treatment control for at least 2 years following cessation of both ART and antibody.

Although the exact mechanism of post-treatment control is not understood, there is some evidence to suggest that this is mediated by natural killer cell and humoral immunity. A single arm study using an anti-human α4β7 monoclonal antibody, vedolizumab, licensed for use in inflammatory bowel disease, is currently underway to determine whether this finding can be replicated in HIV-infected humans on ART (ClinicalTrials.gov Identifier NCT02788175).

Finally, the recent substantial improvements in cancer outcomes with immunotherapy may also provide a promising approach in eliminating HIV persistence and inducing post-treatment control. Immune checkpoint blockers, such as anti-programmed death (PD)-1 and anti-cytotoxic T lymphocyte antigen (CTLA)-4 monoclonal antibodies, licensed for use in melanoma and other solid malignancies, boost cancer-specific T cells, but can also boost HIV-specific T cells ex vivo and SIV-specific T cells in macaque models. Furthermore, in individuals on ART, HIV is concentrated in CD4+ T cells expressing these receptors. Blocking these receptors may potentially increase HIV expression and relieve the block on CD8+ cytotoxic T cell function. Clinical trials evaluating the effect of these antibodies on HIV in the context of HIV-infected individuals requiring immune checkpoint blockade for malignancy have now begun (reviewed by Wykes and Lewin).

**Conclusion**

There have been substantial advances in our understanding of how HIV persists on ART and in testing novel approaches to achieve HIV remission off ART. A wide variety of HIV cure strategies is being evaluated and there is a long list of human clinical studies in the pipeline. However, given that modern ART regimens are simple, non-toxic and confer a near-normal life expectancy and inability to transmit virus, a cure intervention must be both safe and highly effective. An optimal cure regimen would also need to be cheap, stable at room temperature and available orally to facilitate scale-up to developing countries where the epidemic is the worst. Thus the bar is set very high.

Unimaginable advances have been made in HIV treatment and prevention over the past three decades and the hope now is that similar great advances will be made towards achieving a cure. This will need significant funding, investment from the private sector, widespread academic collaboration and most importantly community engagement at every level.

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Dealing with the spiralling price of medicines: issues and solutions

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drug cost, medicine toxicity, financial toxicity, medicine affordability, cost effectiveness, escalating medicine price.

Abstract
Escalating cost of medicines is rapidly becoming a serious threat to patients and health systems. This trend has been documented to impact patient outcomes adversely. As clinicians and tax payers, it is our responsibility to be aware of the potential detrimental effects spiralling costs have on our patients, our community and our health system and to mitigate these effects by exposing this issue to our respective professional societies, representatives of the pharmaceutical companies that we interact with, government regulatory bodies and to patients who we are caring for. Only through understanding and constructive actions will we be able to provide the best quality of care to our patients and continue to enjoy universal healthcare in our country.

Introduction
In Australia and the rest of the world, it has been recognised increasingly that new medications are expensive. In Australia, where the Pharmaceutical Benefits Scheme (PBS) covers the vast majority of prescription medications, the spiralling cost of medicines has a significant impact on the sustainability of our health system. In countries where patients are required to contribute substantially to the medicine cost, high prices can negatively influence their health outcomes. Zafar and Abernethy coined the term ‘financial toxicity’ and used this term to describe the patient-level impact of the high cost of oncology medicines.1 As physicians, it is important that we are aware of the extent of the problem, the limitations of our system and potential roles that we can play in combating this increasingly important problem. The aim of this review is to (i) outline the extent of the problem in Australia as well as globally, (ii) explore the justification for the current trend of increasing prices of medicines, (iii) present some of the mechanisms behind spiralling medicines prices, (iv) reveal the limitations of our government and affiliated agencies to curb price increases, (v) highlight the effects of escalating medicine prices on our patients and our health system and (vi) suggest ways to combat these damaging trends.

The problem in Australia and globally

New medicines are expensive
There has been an explosion of new biological and targeted medicines for cancer and other diseases entering the market over the last decade. Some of these new agents have contributed to the improvement in outcomes of diseases; however, they are also invariably expensive. In Australia, for example, the annual PBS expenditure on oncology medicines rose from AU$65 million in 1999–2000 to AU$466 million in 2011–2012.2 In 2016, the Australian government allocated AU$1 billion for hepatitis C therapy over 5 years, each course of direct acting antivirals costing approximately AU$60 K for a 3-month period.3 While the length of treatment for hepatitis C is finite and has been shown to be cost effective, many biological therapies require ongoing treatment to control diseases, such as rheumatoid arthritis, where etanercept and tocilizumab cost AU$21 1184 and

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Eculizumab, an anti-complement monoclonal antibody used to treat paroxysmal nocturnal haemoglobinuria (PNH), costs AU$576 000 pa per patient, and ongoing chronic treatment is required. Even in an extremely rare condition, such as PNH (up to 400 patients affected in Australia),6 the high cost of eculizumab amounts to AU$280 million pa.

The problem of high medicine cost is not unique to Australia. Taking new oncology medicines as an example, a recent study from the Intercontinental Marketing Statistics (IMS) institute of healthcare informatics estimated that the total cost of oncology medicines was US$107 billion globally, with an expected annual growth of 7.5–10.5%, reaching US$150 billion by 2020.7 The new anti-hepatitis C medicines are expected to cost €50 000–60 000 per 12-week course and will cost 756 times the cost of production in France.8

**New medicines are not necessarily cost effective**

In addition to the high prices, many of the new and rebranded old medicines (such as thalidomide) have not been found to be cost effective. Cost effectiveness has been broadly accepted to be less than US$50 000 per quality-adjusted life year (QALY) gained.9 Between 2003 and 2013, new oncology medicines were associated with an increased overall survival by a modest average of 3.43 months.10 Notwithstanding very variable results for individual patients, this issue is exemplified by the following:

1. Ipilimumab, an anti-melanoma medicine, costs US$120 000 a course, which is associated with an average increase of life expectancy of 4 months.11
2. The FDA approved erlotinib for pancreatic cancer in 2005 based on a median survival prolongation of only 10 days.12
3. Only 1 (enaluzamide) of the 12 new anti-cancer medicines approved by the FDA in 2012 provides survival gains of more than 2 months.13
4. Only 16% of 134 approved anti-cancer medicines in Europe from 2009 to 2016 showed a survival difference of more than 3 months.14

**What is the justification for high medicines pricing?**

Several studies have shown that the cost of medicine production is low, with some oncology medicines costing less than 1% of the selling price.15 A key justification for the high cost of medication is the expense incurred in bringing a new medicine to market, that is, the research and development costs. The Tufts Center estimated that the cost of a medicine’s development was approximately US$2.6 billion in 2014, up from US$802 million in 2003.16 This figure is contested by several authors,16,17 with some independent reports putting it as low as US$100 million or less.18,19 Within the Tuft’s estimate, the cost of other failed medicines, including more than 80% of new compounds that were abandoned at some point during their development, was factored into the cost estimate of successfully developed medicines, apparently a common accounting practice in the pharmaceutical industry.17 Second, this Center is largely funded by pharmaceutical companies, and the methodology of the analysis leading to this report is not readily available for independent evaluation or replication.19 Other independent and transparent estimates of the costs of medicine development are needed to be clearer about this critical point.

The important contribution to research and development of medicines that is borne by the public purse is often overlooked in these estimates. This includes research and development tax credits provided by governments in addition to publicly funded universities and institutions that produce the basic research that elicits disease mechanisms and identifies potential pharmacological targets and medicines.16 It is estimated that publicly funded research from non-profit, university-affiliated centres accounts for more than 84% of all basic research leading to the discovery of new medicines.15

There is mounting evidence that high pricing of medicines is not strictly confined to development costs and is affected by market competition. In South Korea radotinib, a locally developed tyrosine kinase inhibitor, was introduced in competition against imatinib to treat chronic myeloid leukaemia. In South Korea, imatinib costs 61% of the Australian price and 20–30% of the price in the USA.19 Similarly, there is great cost disparity in the market price of new combination hepatitis C medications, ranging from US$175/bottle in Egypt to US$24 890 in Germany.20

A concerning phenomenon related to medicine prices is that, unlike most commodities that depreciate in value with time, some medicine prices increase each year.21 Pyrimethamine (trade name: Daraprim), a medicine developed over five decades ago and used for treating parasitic infections in HIV-AIDS patients, had a price rise of 5500% from US$13.50 per tablet to US$750 following its acquisition by Turing Pharmaceuticals in 2015.22 Similarly, the price of adrenalin (Epi-pen) has soared from US$123 a pack in 2007 to US$799 in 2016, a 6-fold increase, since Mylan pharmaceuticals acquired its marketing rights in 2007.23 Other price increases are more gradual but persistent over the years. Imatinib cost approximately US$30 000 per year in 2001, but the price had steadily increased to US$92 000 per year in 2012.24
Thalidomide, a medicine infamously used to treat nausea in pregnant women in the 1950s and currently used to treat multiple myeloma, has had its price increased nearly 500% between 1999 and 2004. Overall, oncology medicine prices have increased 10-fold over the past 10 years, without a commensurate increase in their effectiveness.

Despite claiming that medicine development is a risky business, the pharmaceutical and biotech industries remain among the most profitable business sectors in the USA. Pharmaceutical companies are private businesses, and their overarching aim is to maximise value for shareholders. As a result, pricing is heavily influenced by what the market can bear rather than just the cost of bringing a medicine to market. There is no obligation to ensure that the product provided is cost effective or to consider the effect on the sustainability of the health system, especially in the USA, where many medicines are developed. In countries where national insurance systems, such as the Australian PBS, determine which medicines are subsidised from the public purse, it is increasingly important that these government agencies are supported by medical professionals and consumers who understand and insist on the cost effectiveness of medicines and contribute to the development of strategies to ensure a sustainable health system for all.

What are the strategies used to maintain high medicines prices?

Several strategies and system features have been used to maintain or escalate the cost of medications.

Market spiral strategy

In this strategy, a medicine is priced 10–20%, and often much more, above the price of an existing medicine recognised as standard of care. In Australia, lenalidomide, a second-generation immune-modulating medicine (IMID) for multiple myeloma that is simply an enantiomer or isomer of thalidomide, is priced at AU $79,049 pa, about four times the price of thalidomide, the first-generation IMID. The third-generation IMID pomalidomide costs AU$126,000 pa, about six times the price of thalidomide. Thalidomide per se is 19 times the cost of previous standard-of-care treatment of multiple myeloma, melphalan and prednisone (Fig. 1). Percentage improvements in time to recurrence or death with each of these new agents have not approached the percentage increases in medicine price.

Patent system

The patent system is intrinsically designed as a time-limited, anti-competitive mechanism, created to reward innovation and research and development with the hope of stimulating further investment in new research and development. It provides the pharmaceutical company exclusive rights in marketing a patented medicine until the patent expires. Generic and biosimilar medicines cannot be marketed for the life of the patent, which is 20 years in Australia, often extended by 5 years depending on the jurisdiction. Selecting a patent length that recognises innovation and development risks, truly stimulates medicine development and does not lead to excessive profits is, however, contentious and is subject to constant debate.

‘Pay for delay’

The medicine patent holder may use a pay-for-delay agreement with their generic competitor to delay the launch of the generic medication, keeping medicine prices high but now sharing the financial benefits with a generic competitor.
‘Product hopping’ and ‘evergreening’

Product hopping occurs when a pharmaceutical company discontinues an old formulation of a medicine when the patent is expired or soon to be expired. This forces consumers to change to the same medicine’s newly patented formulation, in effect extending the monopoly of the same medicine for another 20 years. This tactic is now forbidden by US law. To our knowledge, there are no published reports on this issue in Australia. Another tactic is the marketing of slightly modified ‘follow-on’ medicines, such as moving from a racemate formulation (an equal mixture of R and S enantiomers) to a single enantiomer and claiming benefits in efficacy and/or safety to allow patent extension. Examples include: thalidomide to lenalidomide, citalopram to escitalopram or omeprazole to esomeprazole.

‘Collective monopoly’

Kantarjian et al. reported that there is a tacit, unspoken agreement among competing medicine companies to establish and maintain high medicine prices. However, explicit collective monopoly is illegal and is being monitored by consumer watchdogs, such as the Australian Competition and Consumer Commission.

Challenges in research for cheaper alternatives

The expense of new medicines can be a significant barrier to innovative clinical research. Due to commercial interests, the pharmaceutical company that owns a patented medicine is unlikely to support research looking for cheaper alternatives. A third party who initiates this type of research and wishes to prove superiority will have to purchase the expensive patented medicine and its cheaper alternative, in addition to the costs of running a trial. Unless funding through a large philanthropic organisation is available, public interest studies, such as the ENCORE1 study funded by the Bill and Melinda Gates Foundation, are rare. It is very difficult for any non-commercial third party to engage in this type of research.

What are the limitations of government/regulatory bodies in controlling the escalating cost of medicines?

Most citizens expect governments to regulate the pharmaceutical sector to achieve fair pricing for their products. However, there are barriers that limit the ability of governments to regulate as effectively as desired. As most multinational pharmaceutical companies are headquartered in the USA, prices for their products in the USA have a large influence on prices paid in other markets, including Australia. In the USA, the Medicare Prescription Drug, Improvement, and Modernisation Act of 2003 included legislation that prohibits Medicare from negotiating medicine prices, leading to price determination being left entirely to the pharmaceutical companies. In Australia, consequently, the power of Pharmaceutical Benefits Advisory Committee (PBAC) to negotiate pricing with pharmaceutical companies is affected as the parent organisation cannot accept publicly disclosed ‘list’ prices elsewhere that are significantly lower than their US price for fear of US health insurance providers demanding significantly lower prices.

The influence on Australian medicine prices by USA pricing is further exacerbated by the Australia–US Trade Agreement and the subsequent introduction of the National Health Amendment (Pharmaceutical Benefits Scheme) Act in 2007. This Act effectively segregated patented medicines into a separate formulation (F1), allowing these medicines to be insulated from ‘reference pricing’. Consequently, F1 medicines maintain their original PBS-approved prices until the listing of a bio-equivalent product occurs, resulting in more sustained, and thus greater, profits for US-based pharmaceutical companies. Another challenge for government agencies in negotiating pricing of new medicines is the substantial pressure they receive from patient and medical advocacy groups. Flibanserin, a medicine that increases female sex drive and that was rejected three times by the FDA, was eventually approved after pressure from a medicine company-funded patient advocacy campaign. Industry sponsorship of advocacy groups is not uncommon as a survey by Rose et al. indicated. Rose et al. found that two-thirds of patient advocacy groups reported receiving some industry funding, and the agreements between advocacy groups and industry are generally confidential and not declared. This raises great concerns that industry sponsorship may distort the ‘patient voice’ in order to apply pressure on government bodies for medicine approval.

What are the effects of financial toxicity on patients, pharmaceutical companies and government agencies?

Patients

The effect of the costs of expensive medicines to patients can be immense, particularly when, unlike the case in
Australia, universal health insurance cover is not available, when patients have to finance a considerable co-payment for the required treatment or the whole cost. The effect is worse when the condition is chronic, and there is a requirement for long-term therapy, such as rheumatoid arthritis, chronic myeloid leukaemia (CML) and HIV infection. Kaplan et al. have demonstrated that cancer patients in the USA who have exhausted their financial reserves to pay for their cancer treatment suffer from the loss of access to basic needs, such as light, heat and food, or even suffer bankruptcy. It also creates an inequity of access to healthcare in USA as only patients who can pay or patients who are fortunate enough to have private insurance can access expensive treatments. Moreover, adherence to medications was compromised, with up to 24% of cancer patients non-compliant with their medications due at least in part to the inability to pay for medications. In the USA, increased co-payments are associated with reduced adherence to several classes of chronic medications, including imatinib for CML and statins. The increased financial stress ultimately leads to an increase in emotional distress. Ramsay et al. noted that cancer patients who have severe financial distress requiring bankruptcy protection were more likely to have a shorter survival. In Australia, even the level of co-payments for PBS medicines can add up to significant financial difficulties.

**Pharmaceutical companies**

One negative impact of high pricing of medicines by pharmaceutical companies is to reduce their willingness to develop novel therapies. The trend is that pharmaceutical companies are more likely to focus on developing second-generation medicines of an existing class of medicine than new medicines that act on a novel pathway. Between 2005 and 2007, only 7 of 217 approvals by the Australian Therapeutic Goods Administration were considered to be important therapeutic innovations. Prescrire, a well-known, independent journal from France that is focused on critical evaluation of the evidence establishing the cost effectiveness and safety of new medicines, reported that only 2% of new medicines or new indications for existing medicines were truly innovative or provided a significant therapeutic advantage over existing medicines.

**Government agencies**

Australia has a highly regarded and robust system for recommending which medicines should be listed on the PBS to the government. This task is assigned to the PBAC, which assesses the cost effectiveness of new therapies submitted by the sponsor company to the PBS for subsidy and negotiates the price, taking into consideration many direct and indirect factors. Unavoidably, there are new and effective medications registered by the Therapeutic Goods Administration (TGA) for particular indications that, at least in initial negotiations, do not fulfil the PBAC criteria for cost effectiveness for subsidy by the taxpayer. Access through our public hospital system can deal with this category to some degree, but hospitals are rightly reluctant to expend scarce resources for medicines and indications not supported by the PBS and for which the evidence of effectiveness is often limited.

An innovative and rarely employed mechanism of bypassing purchasing high-cost medicines with proven effectiveness that are not listed on the PBS due to their excessive cost is to import the raw materials and compound the medicine locally. Prior to the Australian government-funded access to the HCV treatment programme in March 2016, an estimated 1400 Australian patients were treated with the assistance of FixHepC, a web-based platform for the importation of HCV therapies in raw material form from India. Patients were able to access a course of 12 weeks of therapy for AU $1500–$2000 – a fraction (~3%) of what the pharmaceutical company was charging for these treatments.

**How can we address financial toxicity of medicines?**

**Why lowering medicine prices is important**

Lowering of medicine prices would clearly be beneficial to patients, government and the society at large. This includes increasing patient adherence to treatment, with the potential to improve outcomes. For the government and tax payers, lowering medicine prices would provide a more financially sustainable healthcare system. In the USA, the harm to patients caused by the financial toxicity of oncology medicines has resulted in several groups calling for an intervention to moderate the escalating medicine prices (Table 1).

**Role for health professionals**

Modifying prescription habits is an effective means of lowering medicine prices. This is particularly important when it comes to expensive medicines with marginal benefits. The Memorial Sloan Kettering Cancer Center recently stopped their doctors prescribing a medicine for the treatment of colorectal cancer that cost more than US$11 000 a month but had shown no survival advantage over an existing medicine. As a result of this public stance, the manufacturer agreed to reduce the
Role of professional bodies and universities

Professional bodies, such as the Royal Australasian College of Physicians and Therapeutic Guidelines, publish guidelines for the management of various medical conditions and play an important role in guiding prescription habits. In the development of treatment guidelines and protocols, financial impact and cost effectiveness should be, and increasingly is, considered. For example, the American Society of Clinical Oncology (ASCO) is developing scorecards of different cancer treatments, ranking them by their benefits, adverse effects and costs. In Stockholm, Sweden, the regional medicine therapeutics committee issued a ‘Wise List’, which consists of a list of 200 medicines recommended for treating common diseases in ambulatory care, based on efficacy, safety and cost effectiveness. The ‘Wise List’ was found to increase physician adherence to treatment recommendations, and physicians appreciated the assistance this gave them. Universities can play an important role in educating future health professionals about the relevance of health economics for the outcomes of their own patients as well as for the sustainability of an effective healthcare system for all Australians.

It is prudent that professional bodies, universities and healthcare facilities develop robust policies and maintain vigilant oversight to eliminate undue influences from commercial enterprises, such as pharmaceutical company-restricted sponsorships, education sessions where agendas are influenced by the company and conflicts of interest undeclared.

Role of government/regulatory bodies (PBAC)

The most direct way to reduce cost is to disinvest in medications that have subsequently been shown not to provide value. How to achieve such an outcome once the medicine is on the PBS or equivalent is a difficult challenge and, so far, rarely observed.

Another strategy is to innovate to improve outcome assessments, such as validated biomarkers that predict clinical response to a specific medication. This approach, which is increasingly employed, leads to improved selection of patients with likely better responses. The American Society of Clinical Oncology (ASCO), for example, recommends that clinicians not use cetuximab in colorectal carcinomas with a KRAS mutation in codon 12 or 13 as these patients do not respond satisfactorily.

Even more stringent criteria should be considered by the PBAC before recommending the approval of subsidies for medications that do not have evidence of substantive improvement in survival. Again, clinician and consumer education to support the PBAC moving in this direction is essential. Currently, many new medications are being approved based on the improvement in tumour response rates and progression-free survival (PFS), essentially presented as biomarkers for significant clinical benefit valued by patients. However, we have to reconsider if PFS is a valid end-point for approval, especially if overall survival is not improved or if there is no associated and significant improvement of quality of life. End-points that are proven to be clinically meaningful to patients should be advocated instead of excessive focus on statistical significance for improvement in biomarkers. Kantarjian et al. suggests differential

Table 1 Recommendations to address spiralling prices of medicines

<table>
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<tr>
<th>Medical professionals</th>
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<tr>
<td>The need to justify the use of medicines with marginal survival advantage</td>
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<tr>
<td>Be educated about the cost effectiveness and value of new treatments</td>
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<td>Promote public awareness of this healthcare issue</td>
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<td>Openly disclose conflicts of interest</td>
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<td>Professional bodies and universities</td>
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<tr>
<td>Seek sponsorship from non-commercial sources and only accept unrestricted sponsorship from pharmaceutical companies</td>
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<td>Resist publicly endorsing medicines with marginal benefits, such as presentations in plenary meetings</td>
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<td>Develop guidelines on the value of therapies with cost-effective analysis</td>
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<td>Support members who do not wish to treat patients with medicines that have marginal benefits</td>
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<tr>
<td>Educate to raise awareness of health economics and the relationship between pharmaceutical companies, health professionals, Pharmaceutical Benefits Advisory Committee (PBAC) and patient advocacy groups</td>
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<th>Regulatory bodies (PBAC)</th>
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<td>Fund research on the cost effectiveness of new medicines</td>
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<td>Use of clinically meaningful end-points to assess cost-effective benefits</td>
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<td>Support generic markets and address strategies that restrict market competition</td>
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<td>Legally challenge profiteering pharmaceutical companies</td>
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<td>Increase transparency in medicine pricing and assessments</td>
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<td>Patient and community groups</td>
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<td>Understand the impact of financial toxicity</td>
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<td>Advocate for lowering medicine prices by pharmaceutical companies</td>
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<tr>
<td>Resist influences from pharmaceutical companies and sponsorships</td>
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<td>Endorse transparency of sponsorship</td>
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medicine price by half. In Australia, that sort of decision is taken by the PBAC who would not agree to pay more for a medicine compared to a comparator that was similarly cost effective. Physicians should also bear some responsibility in raising public awareness of the effects of financial toxicity and explain to patients why certain therapies with marginal benefits should not be used in their particular setting.

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pricing, with higher remuneration given to medicines that prolong survival for over 6 months, or over one-third of life expectancy without the medicine, and lower remuneration to medicines that provide survival advantage of 2 months or less, or less than 15% of life expectancy.\textsuperscript{13}

Another means of more efficaciously distributing government health funding is to use an indication-based pricing approach where a medicine has multiple indications.\textsuperscript{50} In the USA, the cost of a medication is the same irrespective of the indication for its use. In contrast, Australia utilises an indication-based pricing approach, where a medicine is priced according to its efficacy in different indications; so, for an indication where greater efficacy is shown, a higher PBS price can be agreed on. This will create a fairer system, in which indications with marginal benefits receive a lesser share of total PBS rebates compared to other indications with greater benefits. For medicines that are highly efficacious but expensive, negotiations between the PBAC and the pharmaceutical companies may ensure that the overall cost remains manageable. One example is the direct-acting antiviral (DAA) treatments in hepatitis C, where the Australian government agreed to fund a specific number of HCV treatments over 5 years for $1 billion. The risk-sharing arrangement between the federal government and Pharma meant that if more individuals were treated, the cost would be borne by the pharmaceutical companies rather than the government, which would result in a decrease in the cost per treatment. In the initial 4 months of the DAA programme (March to December 2016), an estimated 33,390 patients initiated therapy, representing 15% of the total chronic HCV infection population in Australia.\textsuperscript{58}

An effective means for lowering the prices of new therapies is to enhance competition by supporting the marketing of generic alternative medications, and many steps along this path have been taken in Australia, although generic prices remain higher than many comparable countries.\textsuperscript{59} Governments can introduce and tighten up laws and regulations deter to companies from the multiple mechanisms used unfairly to delay access to generic medicines,\textsuperscript{13} including continued review of patent and intellectual property laws.

As the free market alone is unable to regulate spiralling medicine prices, government legislation is important to allow legal challenges to prevent companies from profiteering from especially rapidly increasing but unjustified medicine prices. A recent finding against Pfizer by the Competition and Markets Authority in the UK for raising the price of phenytoin sodium capsules by up to 2600% is a good example.\textsuperscript{60}

Finally, we need to advocate for greater transparency surrounding the PBAC assessment and price negotiations with pharmaceutical companies, although this has improved considerably in recent years.\textsuperscript{51} Improving transparency will better inform clinicians and patients about the decision process and the value of a particular therapy. Clinicians, in turn, will be better equipped to provide the most appropriate treatment to patients, making the health system a more sustainable one.

\textbf{Patient and community groups}

Access to new treatments has been a major issue for many patient advocacy groups. The focus, however, is usually on how to promote prompt government approval for subsidy of new medications. Overpricing of new medicines is often overlooked, and yet, the proposed pricing of new medicines is an integral component of submissions for PBAC approval. Therefore, the price proposed by sponsors has a direct impact on whether new medications receive timely approval for the subsidy or not and on how long the negotiations go on. It is therefore vital that patient advocacy groups provide an informed voice to advocate for pharmaceutical companies proposing prices that are demonstrably compatible with cost effectiveness in order to speed up approval processes. Similar to professional bodies, patient advocacy groups should resist undue influences from pharmaceutical companies and their sponsorships and be transparent in addition to being required to declare funding sources as a most important potential conflict of interest.\textsuperscript{61}

\textbf{Conclusion}

Escalation of medicine prices is associated with multiple undesirable consequences, including reduced affordability, limiting access and an unsustainable health system. High prices of medicines are often justified by the costs of development and production; however, the evidence for this is questionable. Studies have shown that increasing the financial cost of medicines adversely affects patients’ lives and can be considered a potential toxicity, specifically financial toxicity, of medicines. In this review, we present the factors responsible for spiralling medicine costs and the limitations of government agencies endeavouring to keep medicine prices in check. We propose several recommendations to address the financial toxicity of medicines, including education to improve public awareness of the issue; proactive

\textsuperscript{50} Ma et al.
participation of clinicians, professional bodies, government agencies and patient advocacy groups and promoting increased transparency around sponsorship and negotiations between consumers, health professional opinion leaders and commercial companies.

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Adult consequences of prenatal drug exposure

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Key words
prenatal drugs, adult outcomes, long-term.

Abstract
Maternal drug use is not new but over the last few decades, the number of mothers using drugs of addiction has escalated to epidemic levels. These drugs are both legal (e.g. prescription medication) and illegal (e.g. heroin) and all will cross the placental barrier into the developing infant. The most immediate and obvious consequence of intra-uterine drug exposure is newborn withdrawal or the Neonatal Abstinence Syndrome (NAS) which is now, with prompt recognition and treatment, an uncommon cause of neonatal death. Thousands (if not millions) of adults most likely would have had a history of passive drug exposure during gestation and the outcomes of these people are unknown. Most are physically healthy and do not need extra medical attention but the effects of prenatal drug exposure may be subtle and extensive. Drug-use disorders are accompanied by a myriad of other adverse problems, including poverty, mental and physical health problems and inadequate parenting ability that may compound the negative effects of drugs. Emerging data suggest that vulnerability to health and neurocognitive issues are pervasive and long-lasting as are lifestyle issues. This review will address current evidence in this area and highlight the knowledge gaps that must be addressed in order to optimise the outcomes for this vulnerable and marginalised but rapidly expanding population of adults.

Introduction
Women have used drugs of addiction for millennia. Until the late 1800s, many drugs, including cocaine and opioids, were freely available and considered medicinal and necessary for the maintenance of the mental and physical well-being of well-bred women.1 Amphetamines and methamphetamine (ice) were used widely as nasal decongestants and ‘nervous system’ aids for housewives and sick children.2 Cannabis had been used since pre-Stone age to treat a variety of ailments, ranging from chronic pain to spasticity, cancer, seizure disorders, nausea, anorexia, hair loss and infection.3 In Ancient Egypt, ground hemp was mixed with honey and inserted directly into the vagina to aid contractions and inhaled as a vapour to ease birth pains. Nowadays, certain contemporary societies, for example, Jamaica, even accept the use of drugs like cannabis (or ganja) as a useful and necessary therapy for ‘female problems’ especially those related to pregnancy and parenting, for example, loss of appetite, nausea, fatigue.4

The impact of maternal drug use on their children is not without concern. For centuries, children were often treated with the same drugs used by their mothers. For example, heroin was aggressively marketed from as early as 1898 by the Bayer pharmaceutical company as a non-addictive and safe medication for childhood ailments, such as bronchitis, tuberculosis, infant colic and dry throat.5,6 In adults, it was approved by the American Medical Association in 1906 as a treatment for morphine addiction. Children were given medications containing cocaine for toothache (banned in the USA in 1920), chloroform for cold symptoms (banned by the US Food and Drug Administration (FDA) in 1976 for human consumption), barbiturates for nervous disorders and both barbiturates and cannabis for insomnia and seizures.5

There are undoubtedly thousands (and probably millions) of children exposed to drugs of addiction throughout the years. The consequences of prenatal (and early childhood) exposure to these drugs on the child and later on the child as an adult are of great concern. This review will thus consolidate available literature on the
impact of maternal drug use on their children as adults. Searches of publically available electronic databases (e.g. Pubmed, Embase and CINAHL) as well as a general internet search (e.g. Google) were employed.

Not all addictive drugs are illegal

It was only in the early 20th century that many drugs of dependency were legally restricted due to realisation of their addictive potential. Drug-trade was rapidly driven underground but made minimal impact on human consumption of addictive drugs. The use of legally prescribed agents is rapidly increasing and is associated with serious impact on the unborn child. Between 2008–2013, at least 1 in 10 American mothers were prescribed an opioid-containing medication during pregnancy, a trend that was associated with 300% increase in the number of infants presenting with withdrawal or the Neonatal Abstinence Syndrome (NAS). Advances in science also provided a means of producing drugs that were not plant based and therefore more easily accessible. Methamphetamines and other amphetamine-type substances, for example, can be easily manufactured in clandestine laboratories using common household agents at ever increasing potencies.

Any drug taken by the mother can affect the foetus and the newborn infant

Most molecules below 500 kDal will cross the placental barrier from the mother into the foetus. Just as in adults, drugs of addiction cause foetal intoxication, tolerance and/or withdrawal, depending on the types of drugs taken by the mother. For example, amphetamines that are taken shortly before birth may result in an intoxicated, sleepy and obtunded infant while heroin and opioids or other drugs, such as benzodiazepines, will lead to NAS.

NAS – what is it?

The most obvious and immediate side-effect of maternal drug use is NAS. The term ‘NAS’ was coined in the 1970s by Loretta Finnegan and her colleagues to describe a syndrome of withdrawal occurring in narcotic-exposed infants. NAS results from drug withdrawal after maternal transplacental drug transfer ceases abruptly at birth. Typically, it starts within a few hours or days after birth but its duration and intensity depend on many factors, including the types and doses of drugs taken by the mother, genetic susceptibility, type of feeding and method of infant care. Untreated NAS is devastating. Infants may fail to thrive, develop seizures or even die. NAS can be protracted with subclinical symptoms lasting for months and is well described in Western literature from as early as the 19th century, accounting for massive healthcare consumption, most of which is met by public health funds.

NAS is not the only problem

If promptly treated, NAS seldom causes death. However, NAS is not the only problem faced by children of drug-using mothers. Many mothers with drug-using disorders use multiple drugs and have poor lifestyle issues that worsen the outcomes for their children. For example, parents affected by drug-use disorders may be unable to parent adequately, with parenting styles ranging from being neglectful, to being over-authoritative and inappropriate, putting their children at risk of physical, emotional and sexual harm. In Australia, more than 50% of methadone-maintained mothers were placed into foster care by age 5 and in a data linkage study, Uebel et al. showed that children with a post-birth diagnosis of NAS were 21 times more likely to be hospitalised during childhood for assaults, injuries and maltreatment and three times more likely to die before the age of 12 than other Australian children. This all adds up to great social vulnerability and chronic stress, which in turn, potentially impairs adequate development of adult working memory, general cognitive functioning, attention and executive function.

Can gestational chronic drug exposure itself lead to cognitive dysfunction?

All drugs of addiction, regardless of their eventual clinical effect, elicit the pleasurable sensations associated with drug use by modulating neurotransmitter levels and function. Repetitive stimulation of neurotransmitter neurons eventually results in neurotransmitter depletion, oxidative stress and finally, neuronal death. Chronic drug users show evidence of brain volume loss, particularly within deep nuclear structures. These deficits are associated with functional abnormalities that may persist for years even after abstinence. Downregulation of neurotransmitter function is linked to neurocognitive impairment and dysfunction in both animals and humans and indeed, drug addiction is hypothesised to be the result of enduring changes to ventral striatal and prefrontal cortical circuits that receive input from midbrain dopaminergic neurons governing affective and cognitive functions. Babies who are exposed to intra-uterine opioids have significantly smaller whole brain, basal ganglia and cerebellar volumes than other children but whether this is caused by drug exposure or other factors (e.g. poor nutrition, chronic
stress) during gestation or whether these findings persist as the child grows into an adult, is as yet, unknown.62

What are the drug-exposed children like as adults?

Determining long-term outcomes for drug-exposed babies beyond childhood is difficult because most of these children, apart from withdrawal or intoxication, are healthy.12,17 Few seldom need medical attention20 and many may also have unstable home lives resulting in frequent shifts between multiple carers, homes and schools,51 making them difficult to locate for any protracted time. Also, most mothers use multiple drugs,19 have multiple environmental, psychiatric and lifestyle co-morbidities and stressors15 that make isolating any specific long-term outcomes to a single drug, exceedingly difficult.

What do we know so far?

Neurodevelopment and cognitive function

The most enduring neurodevelopmental and cognitive outcome data have examined persons prenatally exposed to cannabis, the most commonly used illicit drug in the world.34 The Ottawa Prenatal Prospective Study (OPPS) recruited a middle-class, low risk group of Caucasian babies born in Canada from 1978 and has since reported on outcomes to 22 years of age.35 Although there were earlier concerns for behavioural problems (e.g. aggression36), adults no longer displayed any evidence of major impairment in the second decade of life. However, subtle changes persisted. Prenatal cannabis-exposed adults (n = 16) performed similarly on cognitive testing (e.g. Visuospatial 2-Back, Go/NoGo, Letter 2-Back and Counting Stroop tasks) to non-exposed adults (n = 15) but functional magnetic resonance imaging demonstrated that their efforts were associated with significantly different brain blood flow responses, especially in the left posterior brain, suggesting persistence of prenatal cannabis effect even until adulthood.39

Studies of other drugs, for example, opioids, are not so enduring and are contaminated by exposure to other drugs and adverse lifestyle issues. Nygaard et al. compared cognitive function in 45 youths between 17 and 21 years of age who were exposed in utero to heroin and multiple drugs, to 48 non-drug-exposed youths. As adults, the drug-exposed cohort had significantly worse cognitive and fine motor function but whether this was due to heroin-exposure was uncertain as most had been placed in foster care from as early as 1 year of age.37

Certainly, the compounded factors of adverse environmental situations, such as unstable and chaotic home lives and poverty, add to poor outcomes with or without intra-uterine drug exposure.38

Risk to addiction

Addiction is a complex chronic psychiatric illness with a high relapse rate. The predisposition to addiction is intimately influenced by genetic and environmental factors. Compared with non-exposed children, the children of drug-using parents are more than twice as likely to develop an alcohol and/or drug use disorder themselves in adulthood.39 For example, 53% of children of alcoholics develop alcohol or drug use disorders in adulthood40 and also start using substances earlier and at faster rates.39 Twin studies show that 48–58% of the variation in liability to alcoholism is genetically modulated41 with certain genes (e.g. JUN, CEBPB, PRKCB, ENO2 or CEBPG) capable of predicting risk to heroin addiction with 85% accuracy in known drug users.42

Gestational drug exposure may represent the first hit to a susceptible, developing neurological system. Prenatal cannabis, for example, may interfere with the endocannabinoid system, an important modulator and influence of neurodevelopment until adulthood.43 Indeed, long-term studies of prenatal cannabis exposure show an increased risk of poor social outcomes, including criminal activity, lower education levels, having children without being married, unemployment44 and psychiatric dysfunction.44–46

Emotional, behavioural and social adjustment

Emotional, behavioural and social adjustment is crucial for productive social functioning. Poor emotional and behavioural function is evident in children of substance users from early as 2–3 years of age47 with increased rates of anxiety, depression, oppositional behaviour, conduct problems and aggressive behaviour as well as lower rates of self-esteem and social competence.48–50 A range of adverse adult problem behaviours, such as externalising behaviours, impulsivity and attention problems, is particularly associated with gestational cocaine51 and methadone.52 In later life, offspring of heroin dependent parents have an 8-fold risk of depression, a 3-fold risk of attention disorders and a 16-fold risk of substance use disorders in young adulthood (average 17.9 years53) but despite this, the exact relationship between prenatal drugs and future mental health issues in offspring remain unclear.54

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Resilience

Despite these problems, more than 50% of children of substance users are resilient to poor outcomes. In the general population, certain behaviours predict resilience. For example, a survey of 19 303 middle to high school students from 82 Norwegian schools found that specific factors, such as the quality of parent–child relationships and absence of negative drug-related beliefs, close relationships with drug users, low delinquency rates, regular tobacco use and alcohol intoxication, predicted resilience to teenage cannabis use. Behavioural resilience, defined as the lack of early (<14 years) substance use, risky sexual behaviour or delinquency, is also positively influenced by strict caregiver supervision, lower violence exposure and absence of intra-uterine tobacco exposure even in children exposed to prenatal drugs, such as cocaine. There is ample evidence to show that programmes designed to enhance and support individual and family resilience have lasting effects, not only on drug use but also on suicidal risk, depression, anxiety, disruptive behaviours and even intergenerational vulnerability to such adversities.

Physical health

Even though most drug-exposed children are healthy as infants, up to 25% of them may not receive adequate healthcare within the first 2 years of life. The impact of this neglect on long-term health is unknown. Similar findings to Uebel et al.’s Australian data were shown in a data linkage study of 55 369 children born in Finland in 2002. In this study, children of drug-using mothers were hospitalised more frequently for injuries and infection, and the risk of health problems was increased if the mother abused both alcohol and drugs rather than drugs alone, suggesting that physical health problems may be an acquired issue rather than being a consequence of intra-uterine drug exposure.

Academic outcomes

School performance is one of the most important achievements of childhood. School failure leads to poor adult outcomes. Low education levels, cognitive deficits, deprived upbringing and delinquency are consistent childhood traits in prisoners, the unemployed, the poor and in drug users. Indeed, an individual’s IQ at age 8–9 years consistently predicts future poor outcomes, including crime, substance use disorders, mental health, sexual adjustment (number of sexual partners, pregnancy) and lower educational achievement (school leaving qualifications, tertiary qualifications) and occupational status (unemployment, income). Conversely, higher intelligence is linked to better physical health at age 50, such as lower risk of diabetes and stroke.

To date, there is no study examining the relationship between intra-uterine drug exposure and adult academic achievement. At most, follow-up has been truncated at adolescence or even prior. There are consistent indications that prenatal drug exposure, for example, to marijuana, cocaine and opioids compromises school performance and cognitive skills from as early as 8–9 years of age and until high school. Oei et al. used linkage data to examine the performance on Australian standardised curriculum based tests for 2234 children diagnosed with NAS as infants to the first year of high school. Compared to children without a diagnosis of NAS, mean test scores (range 0–1000) for children with NAS were significantly lower from as early as Grade 3. By Grade 7, or the first year of high school, the differences had increased. Children with NAS scored lower than other children in Grade 5 who were on average, 2 years younger, even after accounting for confounding factors, such as indigenous status, male gender and parental education. Again, these studies cannot apply causality but suggest that cognitive support and educational intervention must be provided for any child known to be exposed to intra-uterine drugs to decrease the risk of poor school outcomes.

Criminal activity, involvement with the justice system and other deviant behaviours

The offspring of drug users have earlier and more frequent engagement in criminal activity. In 206 cases of serious child abuse or neglect in the juvenile court system of Boston, Murphy et al. found that 43% of cases had at least one parent with a substance use problem, with the proportion increasing to 50% when alleged substances included alcohol, cocaine and heroin. Problems with criminal activity increased when there was concurrent school failure, truancy, suspension or expulsion and the need for drug and alcohol treatment. A series of interviews with 70 substance abusers about their 188 children found that 80% had been arrested, 34% reported being treated for an emotional disorder and 17% were abusing drugs and alcohol.

What really happens to the adults?

Currently, the information we have do not, and cannot, definitively link intra-uterine drug exposure to adult
adverse outcomes. Herranz et al. conducted a series of interviews with 30 heroin-exposed adults (mean age 22.3 years) with a postnatal diagnosis of NAS and found that adverse problems were common from early childhood. Of the original cohort of 151 children, five had died (four from acquired immune deficiency syndrome, one of unknown reasons) and 94 were not locatable. More than 50% of their mothers were HIV positive and 40% of mothers and 30% of fathers died after birth. Almost a quarter (23%) were adopted/fostered before childhood and >25% reported emotional and physical abuse. Attention deficit hyperactivity disorder was diagnosed in 20%, 76% smoked, five reported hazardous drinking, 87% had used cannabis at least once and almost half (47%) had used cocaine. Half undertook post-school studies but 37% were unemployed. More than half (57%) had received psychiatric treatment during childhood.72

**Conclusion**

This review highlights the concerns and lack of information about the long-term outcomes of adults with a history of intra-uterine drug exposure. Studies are confounded with the many problems associated with a drug-using lifestyle, including socio-economic, emotional and psychological adversities. However, the limited data available suggest that the impact of intra-uterine drug exposure, regardless of drug type, can be subtle but may be pervasive and detrimental to future adult outcomes. Whether these problems can transmit into future generations is yet to be determined. Considering the rapidly escalating magnitude of perinatal drug use, efforts must be urgently made to determine these consequences so that children can be provided with opportunities to mitigate future vulnerability not only for themselves as adults, but for future generations of children.

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ORIGINAL ARTICLES

Statin-associated immune-mediated necrotising myopathy: a New Zealand case series showing possible overrepresentation in Pacific Islanders

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Key words
immune-mediated necrotising myopathy, statin, anti-HMGCR antibodies, idiopathic inflammatory myopathy, HLA-DRB1*11:01.

Abstract
Background: Statin-associated immune-mediated necrotising myopathy (IMNM) is an emerging entity. Being an uncommon condition, our knowledge and understanding is largely based on case series.

Aim: To review incident cases of statin-associated IMNM associated with anti-3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) antibodies in a single New Zealand centre over a 2-year period.

Methods: Four incident cases of statin-associated IMNM were seen between 2014 and 2016. Their presentation, investigation, treatment and current response to treatment are summarised. Two of the four patients were Pacific Islanders despite a small Pacific Island population in the southern district health board. A literature search was performed focusing on the presentation, investigation and treatment of statin-associated IMNM and also genetic associations with this entity to determine whether Pacific Islanders may be at increased risk.

Results: All four patients presented with profound weakness and recent exposure to atorvastatin. All proceeded to muscle biopsy. Two biopsies showed typical IMNM. One biopsy had mild changes, reported as possibly being compatible with anti-HMGCR antibodies. The final biopsy had features consistent with IMNM, with some features suggestive of polymyositis. Two recent studies have shown an association between anti-HMGCR antibodies and the HLA-DRB1*11:01 haplotype. Interestingly, HLA-DRB1 alleles (including HLA-DRB1*11:01) were observed to be among the most frequent alleles in a Pacific Island population study.

Conclusion: This is the first case series of statin-associated IMNM with a focus on Pacific Islanders and raises the possibility that Pacific Islanders exposed to statins may be at increased risk of developing an immune-mediated myopathy.

Introduction
In recent years, major advances have been made in the differentiation of the idiopathic inflammatory myopathies (IIM). The recognition and clinical availability of antibody testing have revealed distinct clinical presentations that had previously been unrecognised. Several case series of statin-associated immune-mediated necrotising myopathy (IMNM) have been reported. Most notably, in 2007, Needham et al.1 reported eight cases of statin-associated myopathy, which, unusually, continued to progress after cessation of the drug; all cases were trialled on immunosuppressive therapy, and seven responded to treatment (one was lost to follow-up). In all eight cases, muscle biopsy findings included scattered necrotic and regenerating fibres. Grable-Esposito et al.2 studied 25 patients who developed necrotising myopathy in the setting of statin use; all biopsies showed a mixture of necrotic and regenerating muscle fibres without inflammatory infiltrate, and all patients responded to immunosuppressive therapy, although 23 patients required more than one immunosuppressive agent. In 2010, Christopher-Stine et al.3 identified 26 patients with a necrotising myopathy of unclear aetiology and identified an autoantibody specificity against 200-kd and 100-kd proteins in 16 of these patients. Of these 16 patients, 10 had been exposed to...
statins. The 100-kd protein was subsequently found to be 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) (an enzyme in the cholesterol biosynthesis pathway inhibited by statins).4

It is largely on the basis of the above studies that the entity of statin-associated IMNM has been defined. IMNM is now recognised as one of the idiopathic inflammatory myopathies.9 Other IIM include dermatomyositis, polymyositis and inclusion body myositis. IMNM can be associated with anti-signal recognition particle antibody, statins/anti-HMGCR antibodies, viral infection, an underlying malignancy or an autoimmune disease.5–10 IMNM tends to present with subacute, progressive, symmetrical, proximal muscle weakness.5,9,11–13 Creatine kinase (CK) is often significantly elevated,3,6–8,11,12 and there can be an associated rise in transaminases and lactate dehydrogenase.9 Electromyography (EMG) shows an irritable myopathy,3,12,14,15 and magnetic resonance imaging (MRI) typically shows muscle oedema with atrophy, fatty replacement and fascial oedema occurring in some cases.13,16 Clinical suspicion of IMNM should prompt muscle biopsy for a definitive diagnosis.

Mononuclear cell infiltrates in the muscle biopsy specimen are the hallmark of IIM.11 Necrotising myopathy is distinguished by the presence of many necrotic and regenerating muscle fibres without significant inflammatory cell infiltrate, aside from myophagocytosis of necrotic muscle fibres.2,3,5,7,9,11,13,16 This pattern can also be seen in toxic myopathies and dystrophies,6,13,20 but upregulation of the MHC class I antigen in non-necrotic muscle fibres can be used to help identify those who have IMNM.20

Methods

Characteristics of the four patients seen in the Southern District Health Board (SDHB) over a 2-year period (December 2014 to September 2016) are summarised in Table 1. All of our cases had a subacute onset of weakness with histories ranging from 3 to 8 months. The two Pacific Island males had classical proximal symmetrical muscle weakness. Case 2 also had some involvement in the small muscles of her hands, and Case 4 had lower limb myositis only. CK at diagnosis ranged from 4200 to 21 856 μmol/L. Cases 1 and 3 had EMG confirming an inflammatory myopathy, while Case 2 had myopathic changes (polyphasic motor unit potentials of small amplitude and short duration). The EMG for Case 4 showed full-motor unit recruitment with polyphasic and unstable motor unit potentials and was reported as showing ‘recent denervation/renervation’, which can be associated with muscle splitting and therefore could be consistent with myositis’. MRI showed extensive muscle oedema consistent with myositis in all four cases. In Cases 1 and 3, the shoulder girdle and hip girdle, as well as intercostal (Case 1 only) and abdominal wall muscles, were involved. In Case 2, only the shoulder and hip girdle muscles were involved. In Case 4, the hip girdle, as well as calf muscles, was involved.

All patients were screened for malignancy. Case 1 was found to have hypercalcaemia and a parathyroid nodule on ultrasound as well as a right hilar node on computed tomography (CT) of the chest and abdomen. Subsequent parathyroidectomy showed the nodule to be benign, and the right hilar node was stable in appearance with no

Table 1 Clinical characteristics of cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at onset</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>CK (μmol/L) at diagnosis</th>
<th>EMG</th>
<th>MRI</th>
<th>Statin exposure</th>
<th>HMGCR Antibodies (AU)†</th>
<th>Muscle biopsy</th>
<th>Treatment</th>
<th>Current response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>Male</td>
<td>Pacific Islander</td>
<td>21 856</td>
<td>Extensive muscle oedema with infiltrating macrophages</td>
<td>Prednisone + methotrexate</td>
<td>Normal CK, minimal weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>Female</td>
<td>Caucasian</td>
<td>9433</td>
<td>Myopathic changes with distal involvement</td>
<td>Prednisone, methotrexate + IVIg</td>
<td>Normal CK, minimal weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>Male</td>
<td>Pacific Islander</td>
<td>8499</td>
<td>Extensive muscle oedema</td>
<td>Prednisone + methotrexate</td>
<td>Normal CK, moderate residual weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>Female</td>
<td>Caucasian</td>
<td>4200</td>
<td>Extensive muscle oedema</td>
<td>Methylprednisolone/ prednisone + methotrexate</td>
<td>Normal CK, ongoing significant proximal weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Normal range: 0–3 AU; 3–10 AU ‘equivocal’. CK, creatine kinase; EMG, electromyography; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; IVIg, intravenous immunoglobulin; MRI, magnetic resonance imaging.
suspicous features on repeat CT at 6 months. Case 2 had a small 5 mm right upper lobe nodule; repeat CT after 6 months showed no change. Cases 3 and 4 had no evidence of malignancy.

All cases had been on long-term atorvastatin. This had been discontinued in the community in Cases 3 and 4 within the last month, and 6 months earlier in Case 2 with no improvement in symptoms. Atorvastatin was discontinued in Case 1 while he was being investigated as an inpatient. All cases were tested for myositis-specific antibodies prior to treatment, and all were strongly positive for anti-HMGCR (enzyme-linked immunosorbent assay). Other myositis-specific antibodies were negative. Muscle biopsy for Case 1 was reported as showing an ‘inflammatory myopathy consistent with polymyositis or related disorder’ but showed prominent fibrosis with infiltrating macrophages and patchy sarcolemmal upregulation of MHC Class 1 (features consistent with an IMNM). Chronic endomysial inflammation was also observed, along with increased numbers of endomysial CD8-positive T cells infiltrating non-necrotic fibres. Cases 2 and 3 showed prominent myofibre necrosis and regeneration with myophagocytosis, consistent with a necrotising myopathy. Case 4 showed features of myocyte regeneration with infiltrating macrophages suggesting necrosis, on a background of chronic denervation; it was thought this may be compatible with anti-HMGCR antibodies, although changes were mild.

All cases were initially treated with corticosteroids. Cases 1–3 were treated with 60 mg of prednisone; Case 4 was treated with pulse methylprednisolone followed by 40 mg of prednisone. Methotrexate was started at the initiation of treatment in Cases 2–4 and was added at 6 weeks in Case 1 due to ongoing significant weakness despite a dramatic improvement in his CK from 21 856 to 4904 μmol/L and a subjective improvement in strength. Case 2 was approved to start intravenous immunoglobulin (IVIg) after 1 month of treatment with prednisone and methotrexate due to ongoing significant weakness. Case 1 now has a normal CK with some mild weakness of wrist extension only. He is currently on prednisone 7.5 mg and methotrexate 20 mg. Case 4 now has a CK of only 35 presumed secondary to sarcopenia. She has ongoing significant hip flexor weakness, which is likely to be multifactorial. In particular, she sustained an undisplaced fracture of the right femoral neck during follow-up. This has resulted in deconditioning/disuse atrophy in her pelvic girdle musculature. She is currently receiving prednisone 7.5 mg and methotrexate 20 mg.

**Discussion**

The estimated incidence of statin-associated IMNM is 2/million/year. At the time of the last New Zealand census (2013), the SDHB had a population of only 297 423; four incident cases over 2 years in this population is therefore unusual. As with all autoimmune diseases, it is likely that both genetic and environmental factors play a role in the development of IIM. Familial, seasonal and geographic clustering, as well as temporal associations between environmental triggers and development of myositis, has been observed. Of note, a survey of rheumatology centres in Europe demonstrated a difference in the frequency of dermatomyositis based on latitude. This raises the question could there be an association between latitude and statin-associated IMNM given that the SDHB is the southern most DHB in New Zealand? It would be interesting to look at incident cases of IMNM in other New Zealand centres between December 2014 and September 2016.

Of the 297 423 people in the SDHB in 2013, only 5856 (1.97%) were of Pacific Island descent. At that time, 6.98% of the New Zealand population identified as Pacific Islanders. It is therefore also of interest that two of our patients were Pacific Islanders. In a study by Velickovic et al., allele frequency distribution of the HLA-DRB1 (and HLA-DQB1 genes) were investigated in Cook Islanders, Samoans, Tokelauans and Tongans. They found that six DRB1 alleles (including DRB1*11:01) accounted for more than two thirds of all observed alleles in all four populations despite these genes being highly polymorphic in general. **HLA-DRB1*11:01** is strongly associated with the development of statin-associated IMNM, with an odds ratio of 24.5 in Whites and 56.5 in Blacks in those with the disease when compared to the general population. This represents one of the strongest associations between an immunogenetic risk factor and a myositis autoantibody. While it is difficult to comment on a possible association between Pacific Island ethnicity and statin-associated IMNM based on a case series of just four patients, the known genetic associations with **HLA-**
DRB1*11:01 suggest that Pacific Islanders may be at increased risk, and certainly appeared to be overrepresented in our case series. All of our patients were exposed to atorvastatin. However, previous studies have noted that atorvastatin is the most commonly prescribed statin in their centre.2 We suspect that this is also the case in the SDHB, and there have been no studies showing any relationship between choice of statin and the risk of IMNM. All of our patients presented with classical subacute symmetrical proximal muscle weakness, apart from Case 2 who had some involvement in the small muscles of her hands. Two biopsies showed typical IMNM. Case 4 had mild changes, which were reported as possibly being compatible with anti-HMGCR antibodies. Case 1 had features consistent with IMNM, but biopsy also showed chronic endomysial inflammation. While this can be seen in up to 30% of patients with IMNM,3 increased numbers of endomysial CD8-positive T cells were also seen infiltrating non-necrotic fibres, which is a feature of polymyositis or inclusion body myositis.17 Interestingly, the study by Limaye et al.25 found a non-preferential distribution of anti-HMGCR antibodies in all myositis subgroups, despite the majority of the literature focusing on the association of anti-HMGCR antibodies and IMNM. Like most autoimmune conditions, the IIM subgroups appear to lie on a spectrum of disease with overlapping features, rather than fitting neatly into diagnostic categories.

Statin exposure may increase the risk of developing an inflammatory myopathy after the age of 50 by three-fold.22 This includes inflammatory myopathies, such as dermatomyositis and polymyositis,8,28 although an IMNM is more commonly seen.28 We therefore suggest that patients exposed to statins, who are anti-HMGCR positive and have a clinical presentation of an inflammatory myopathy, are likely to have a statin-associated myopathy even if this is not classically necrotising on biopsy.

Current treatment of IMNM is not evidence-based and is influenced by individual physicians’ experience6,17,18 as well as extrapolation of treatment experience of the other inflammatory myopathies.18 On review of the literature, however, expert opinion suggests corticosteroids as first-line treatment.3,6,12,17 Many physicians co-administer a second immunosuppressant as this may allow earlier tapering of corticosteroids.3 However, there are concerns that this then makes it unclear as to which agent is the most effective.6,17 If there is a response to corticosteroids, it is generally agreed that steroid-sparing agents, such as methotrexate, azathioprine, mycophenolate or cyclosporine, be added.3,5 All but one of our cases were started on methotrexate in conjunction with corticosteroids at the outset of treatment; methotrexate was added at 6 weeks in Case 1 due to ongoing significant weakness. Cases 1–3 are now stable on the combination of prednisone and methotrexate, although Case 2 also required 1 year of treatment with IVIg. Case 4 still has ongoing significant weakness on the combination of prednisone and methotrexate, which is thought to be multifactorial and includes disuse atrophy, despite her low CK. In the event of inadequate response to corticosteroids, expert opinion favours IVIg as second-line treatment.5,7,17 In several open-label trials, IVIg has been shown to be effective in polymyositis and IMNM,6,7 and its efficacy in dermatomyositis has been demonstrated in a double-blind, placebo-controlled trial.5,7,17 Case 2 was approved to receive IVIg after 1 month of treatment with prednisone and methotrexate due to ongoing significant weakness and responded well to this treatment. Rituximab has also been found to be useful in some cases.3–7,17

This is the first case series of statin-associated IMNM with a focus on Pacific Islanders. All of our patients were over 50 and exposed to statins. Interestingly, patients with no prior exposure to statins can develop an IMNM associated with anti-HMGCR, although this tends to occur in patients younger than 50.4 In fact, in two recent studies investigating IMNM in European and Japanese populations, of all anti-HMGCR-positive patients, only 44% and 38%, respectively, were exposed to statins.13,29 In earlier studies in an American population, 72.7% of patients were exposed to statins.30 Those patients who have been exposed to statins may be more responsive to immunosuppressive therapy,14,30 particularly IVIg.14,20 The response to IVIg in Case 2 further supports this statement.

**Conclusion**

Statin-associated IMNM is still an emerging entity. Our case series shows that recognition and early treatment was associated with good outcomes in three of the four cases, although relapse and partial response to standard therapy required escalation of treatment in two of these three patients. Our case series also raises further questions: could there be an association with latitude, and also, are Pacific Islanders at increased risk? Given that statin-associated IMNM is uncommon, it is important that case series in different populations around the world continue to be reported to improve our understanding of this disease.
References


Survival difference according to mutation status in a prospective cohort study of Australian patients with metastatic non-small-cell lung carcinoma

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Key words
non-small-cell lung cancer (NSCLC), molecular testing, EGFR, ALK, KRAS.

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Background: Non-small-cell lung cancer (NSCLC) is a heterogeneous disease comprising not only different histological subtypes but also different molecular subtypes.
Aim: To describe the frequency of oncogenic drivers in patients with metastatic NSCLC, the proportion of patients tested and survival difference according to mutation status in a single-institution study.
Methods: Metastatic NSCLC patients enrolled in a prospective Thoracic Malignancies Cohort Study between July 2012 and August 2016 were selected. Patients underwent molecular testing for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) gene rearrangements, Kirsten rat sarcoma (KRAS), B-Raf proto-oncogene (BRAF) mutations and ROS1 gene rearrangements. Survival was calculated using the Kaplan-Meier method for groups of interest, and comparisons were made using the log-rank test.
Results: A total of 392 patients were included, 43% of whom were female with median age of 64 years (28–92). Of 296 patients tested, 172 patients (58%) were positive for an oncogenic driver: 81 patients (27%) were EGFR positive, 25 patients (9%) were ALK positive, 57 patients (19%) had KRAS mutation and 9 patients (3%) were ROS1 or BRAF positive. Patients with an actionable mutation (EGFR/ALK) had a survival advantage when compared with patients who were mutation negative (hazard ratio (HR) 0.49; 95% confidence interval (CI) 0.33–0.71; P < 0.01). Survival difference between mutation negative and mutation status unknown was not statistically significant when adjusted for confounding factors in a multivariate analysis (HR 1.29; 95% CI 0.97–1.78, P = 0.08).
Conclusion: In this prospective cohort, the presence of an actionable mutation was the strongest predictor of overall survival. These results confirm the importance of molecular testing and suggest likely survival benefit of identification and treatment of actionable oncogenes.

Introduction

Lung cancer remains the leading cause of cancer-related mortality in Australia, representing an estimated 9.4% of all new cancers in 2016 and accounting for nearly one in five (18.8%) cancer deaths.1,2 Approximately 85% of all lung cancer cases are non-small-cell lung cancer (NSCLC), the majority of whom present with locally advanced or metastatic disease.3 These patients have a median survival of 8.0 months despite available standard first-line treatment, with a 5-year overall survival of less than 14%.4,5 NSCLC includes three major histological subtypes of adenocarcinoma, squamous cell carcinoma and large cell carcinoma.6 Adenocarcinoma, the most common histological subtype of NSCLC, has a higher than 50% estimated frequency of potentially identifiable oncogenic driver mutations.6 The frequency is much lower in squamous cell and large-cell carcinomas. Alterations in several oncogenes, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), Kirsten rat sarcoma (KRAS), ROS1 rearrangement, B-Raf proto-oncogene (BRAF), human epidermal growth factor 2 (Her-2), neurotrophic receptor tyrosine kinase

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1 (NRTK-1), ret proto-oncogene (RET) and proto-oncogene MET (MRT), have been reported in NSCLC. To date, only EGFR and ALK mutation-positive NSCLC have approved targeted therapies in Australia.

Activating EGFR mutations are key drivers in NSCLC in approximately 10–15% of Western patients and 30–35% of Asian patients.7 The clinically relevant and most frequent EGFR mutations are in-frame deletions/insertions of exon 19 (40–50%) and L858R mutations of exon 21 (30–40%). Lung cancers with EGFR mutations depend on EGFR signalling for growth and survival, which confers sensitivity to treatment with EGFR tyrosine kinase inhibitors (TKI).8 EGFR TKI gefitinib, erlotinib and afatinib have been shown in seven randomised phase III trials to improve progression-free survival (PFS), objective response rate and quality of life of patients with EGFR-mutant NSCLC over standard first-line doublet chemotherapy. However, an overall survival advantage has not been clearly demonstrated, most likely due to cross-over designs confounding survival data.9–15 Current treatment guidelines recommend EGFR mutation testing in all patients with adenocarcinoma or in whom adenocarcinoma cannot be excluded.16

ALK gene rearrangements occur in about 3–5% of NSCLC patients, with a higher frequency in adenocarcinomas, never or light smokers and younger patients, but can occasionally be found in older patients and smokers.17,18 Crizotinib, a first-generation, oral, TKI inhibiting ALK, ROS1 and MET, has been shown to have superior response rates and prolonged PFS over standard chemotherapy and is now the standard first-line treatment of advanced ALK-rearranged NSCLC.19 Once again, no survival benefit was identified, likely due to a high rate of cross-over from chemotherapy to crizotinib arm on progression.

Activating KRAS mutations, which occurs in about 20–25% of lung adenocarcinomas,20 were shown to have a poorer prognosis,21 with a meta-analysis of 28 studies validating it as an unfavourable prognostic marker.22 More recent data from a pooled analysis of four trials of adjuvant chemotherapy showed that KRAS mutation is not significantly prognostic in patients with resected NSCLC.23 Due to the functional complexity of the RAS–RAF–MEK–ERK signalling pathway, there has been no successful therapeutic treatment for KRAS mutant tumours to date despite multiple Phase II studies, with agents targeting downstream molecules.24,25

While molecular testing for EGFR and ALK has been recommended by international guidelines since 2012, the results of molecular testing and the associations with patient outcome have not previously been reported in the Australian setting. Here, we describe the frequency of EGFR mutations, ALK rearrangements, KRAS mutations, BRAF mutations and ROS1 rearrangements in patients with metastatic NSCLC at diagnosis, together with survival differences according to mutation status, using prospectively collected data from an Australian cohort of NSCLC patients. Furthermore, we examined reasons why mutation testing was not performed in some patients in this group.

Methods

A review was performed on all patients with a diagnosis of Stage IV NSCLC between July 2012 and August 2016 using prospectively collected data from the Thoracic Malignancies Cohort (TMC) database at Peter MacCallum Cancer Centre. Ethics approval was obtained from the Peter MacCallum Cancer Centre Clinical Research and Ethics Committee (PMCC 11/88).

Patients with metastatic NSCLC at diagnosis, adenocarcinoma, squamous cell carcinoma, large cell and NOS histology were included. The disease stage was determined by radiological findings according to the TNM classification system, and stage IV patients were eligible. Eastern Cooperative Oncology Group (ECOG) performance status26 was determined according to the records for the patients’ activity of daily life and the extent of dependence. The molecular status of patients’ tumour was determined by histopathology results available in the hospital’s electronic medical records and in the database. Results for EGFR mutations, ALK rearrangements, KRAS mutations, BRAF mutations and ROS1 rearrangements were identified.

The following details were collected for the 392 patients included in the study: age, gender, ethnicity, ECOG performance status, smoking history, respiratory comorbidity, weight loss at diagnosis, histology and molecular pathology, previous treatment, date of last follow-up and date of death.

Statistical methods

Descriptive statistics, including median along with percentages and frequencies for categorical variables, were tabulated and presented here. Overall survival was defined as the time from date of diagnosis of metastatic lung cancer to date of death or last follow up. Patients who were alive at the time of analysis were censored at the latest date of assessment.

Survival curves were calculated by the Kaplan-Meier method for groups of interest and were compared using the log-rank test. Hazard ratio (HR) and 95% CI were reported, with a P-value less than 0.05 considered to indicate statistical significance. The association between patient- and disease-related variables and overall
survival was assessed by univariate and multivariate Cox proportional hazards regression using Stata 14.0 software (Stata Statistical Software: Release 14, 2015; StataCorp., College Station, TX, USA). All baseline variables collected in the TMC were included in univariate analyses, and those demonstrating significant association with survival ($P < 0.05$) were carried forward to multivariate analyses.

**Results**

From July 2012 to August 2016, 1352 patients were enrolled in the TMC database, including 392 patients with stage IV NSCLC. The cut-off date of analysis was 31 August 2016. Nine patients with ROS1 rearrangements and BRAF mutations were excluded from survival analyses due to small numbers. A total of 383 patients was included in the survival analysis (103 alive and 280 dead) with a median study time for all patients of 8.9 months (range 0–55 months) and for living patients 17.5 months (range 0–55 months).

**Patient demographics**

The characteristics of the patients are summarised in Table 1. The median age of patients at diagnosis was 64 years (28–92), and 43% of patients were female, with a predominant Caucasian population of 77%. Adenocarcinoma was the most frequent histology (73%), and 24% of patients were never smokers. The majority of patients were ECOG performance status 1 at diagnosis (64%).

**Reasons mutation testing not performed**

Of the 392 patients, 296 (76%) were tested for at least one gene. Among these, 124 (124/296, 42%) patients were found to be mutation negative. In 96 patients (96/392, 24%), tumour mutation status was unknown

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics ($n = 392$)</th>
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<tbody>
<tr>
<td>No. (%)</td>
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<td>---------</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Median age at diagnosis (years)</td>
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<tr>
<td>Current smoker</td>
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</table>

† Never smoker refers to <100 cigarettes per lifetime. ALK, anaplastic lymphoma kinase; BRAF, B-raf proto-oncogene; ECOG PS, Eastern Cooperative Group Performance Status; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NOS, NSCLC otherwise specified; NP, not performed; NSCLC, non-small-cell lung cancer.
due to molecular testing not being performed, with the most common reason being squamous histology (Table 2).

**Molecular subtypes**

Of the 296 patients who underwent testing, *EGFR* mutations were the most frequent, with 81 patients (81/296, 27%) testing positive, followed by *KRAS* mutations in 57 patients (57/296, 19%), *ALK* rearrangements in 25 patients (25/296, 8%) and 9 patients (9/296, 3%) who were either *BRAF* positive (5 patients) or *ROS1* positive (4 patients).

Of the 81 patients with *EGFR* mutation, 68 patients (84%) received first-line TKI, whereas only 9 patients with *ALK* rearrangements (36%) received a first-line *ALK* inhibitor. All patients with identified *EGFR* or *ALK* rearrangements eventually went on to receive a TKI (targeting *EGFR* or *ALK* as relevant) as a subsequent line of treatment. All four patients with *ROS1*-positive NSCLC were treated with an *ALK* inhibitor either in the first-line setting or in a subsequent line of treatment. More than half of the patients (31/57, 54%) with *KRAS* mutation received systemic therapy, whereas only three out of five patients (40%) with *BRAF*-positive NSCLC received chemotherapy.

**Survival according to mutation status**

Survival by oncogenic driver mutation type compared with patients without a driver mutation is shown in Figure 1. The survival difference between mutation-negative and mutation not performed shown in Figure 2 is statistically significant using univariate analysis: HR 1.71 (95% CI 1.31–2.22, *P* < 0.01); however, this result is not statistically significant with multivariate analysis: HR 1.29 (95% CI 0.97–1.78, *P* = 0.08) when corrected for confounding factors. Patients who were mutation negative and mutation not performed had median survival times of 9.0 months (range 0–46 months) and 5.0 months (range 0–37 months) respectively. Patients with *EGFR* mutations had a median survival of 25 months (0–53 months), patients with *ALK* rearrangements had a median survival in excess of 24 months (0–51 months), and patients with *KRAS* mutations had a median survival of 7.0 months (range 0–39 months).

**Univariate analysis**

In univariate analyses (Table 3), the following variables were associated with improved overall survival: adenocarcinoma histology, presence of *EGFR* or *ALK* mutation, Asian ethnicity, absence of smoking history, respiratory comorbidity and no weight loss at diagnosis. Survival differences were not observed between *EGFR*- and *ALK*-positive patients who were combined as a single group for future analyses (actionable mutation positive). Similarly, *KRAS* mutation did not confer any survival benefit compared with mutation-negative status, and therefore, these groups were combined for future analyses (actionable mutation negative).

**Multivariate analysis**

In multivariate analysis (Table 4), the presence of an actionable mutation (*EGFR/ALK*) conferred a twofold survival benefit compared to patients who were mutation negative or not tested. Univariate survival differences between patients not tested and negative for mutation were no longer significant (HR 1.31, 95% CI 0.97–7.78, *P* = 0.08). Similarly, associations between survival and ethnicity and age were no longer observed in the multivariate model.

**Discussion**

Combination platinum-based chemotherapy regimens are still considered to be standard care for the majority...
of patients presenting with newly diagnosed metastatic NSCLC, with an improvement in median survival from 4.0 to 8.0 months. The discovery of oncogenic drivers together with the development of targeted therapies has revolutionised the management of advanced NSCLC for a subgroup of mutation-positive patients, leading to improved outcomes. Here, we present the differences in survival of patients with metastatic NSCLC at initial diagnosis according to the presence or absence of an oncogenic driver mutation in the Australian setting.

Our analyses confirmed the known poor survival rates of patients without an oncogenic driver mutation. In this cohort, patients were often older, male and smokers as reported in previous studies. More than half the patients (74/124, 60%) whose tumours do not harbour a mutation received standard first-line chemotherapy, with a median survival of 9.0 months, which is comparable to reported literature. The short survival time of only 5.0 months in patients whose mutation testing was not performed could be due to various poor prognostic factors, such as older age, smoking history and multiple comorbidities. More than a third of these patients had a performance status (PS) of ≥2, which is a good predictor of shorter survival time and the most common reason for not receiving active treatment. It also influences the decision not to request mutation testing in patients whom clinicians judge as not fit to receive any form of systemic therapy.

Multivariate analysis confirmed that the presence of an actionable mutation was the strongest predictor of overall survival in this cohort of patients with metastatic NSCLC, where mutation testing was conducted according to

---

### Table 3 Association between patient- and disease-related variables and overall survival by univariate Cox proportional hazards regression

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell</td>
<td>1.82</td>
<td>1.32–2.54</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Large cell</td>
<td>2.67</td>
<td>1.35–6.15</td>
<td>0.01</td>
</tr>
<tr>
<td>NSCLC NOS</td>
<td>2.64</td>
<td>1.56–3.12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Histology (non-adeno vs adeno)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adeno</td>
<td>2.04</td>
<td>1.58–2.65</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mutation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK positive</td>
<td>0.28</td>
<td>0.15–0.52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EGFR positive</td>
<td>0.40</td>
<td>0.27–0.58</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>KRAS positive</td>
<td>1.27</td>
<td>0.88–1.82</td>
<td>0.20</td>
</tr>
<tr>
<td>Not tested</td>
<td>1.86</td>
<td>1.39–2.50</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EGFR versus ALK positive</td>
<td>1.42</td>
<td>0.75–2.71</td>
<td>0.29</td>
</tr>
<tr>
<td>Actionable mutation‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.34</td>
<td>0.24–0.47</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Not tested</td>
<td>1.71</td>
<td>1.31–2.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ethnicity (Asian vs non-Asian)</td>
<td>0.53</td>
<td>0.37–0.76</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ECOG PS (≥2 vs ≤2)</td>
<td>1.91</td>
<td>1.46–2.50</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking status Current</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>0.94</td>
<td>0.70–1.26</td>
<td>0.67</td>
</tr>
<tr>
<td>Never</td>
<td>0.28</td>
<td>0.18–0.42</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking (ever vs never)††</td>
<td>3.43</td>
<td>2.44–4.81</td>
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</tr>
<tr>
<td>Weight loss (0–10% vs &gt;10%)††</td>
<td>1.59</td>
<td>1.20–2.10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Respiratory comorbidity‡‡</td>
<td>1.80</td>
<td>1.38–2.33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender (male vs female)‡‡</td>
<td>1.72</td>
<td>1.34–2.20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (continuous) ≤65</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td>0.11</td>
</tr>
<tr>
<td>Age (≥65)</td>
<td>1.74</td>
<td>1.37–2.20</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

†P-value for the comparison of overall survival for patients with and without the specified factor or for actionable mutation as compared with that for patients in the reference group. ‡Adeno refers to adenocarcinoma. ‡‡Colinet definition: Respiratory comorbidity was defined as the presence of one or more of the following: history of tuberculosis, history of pleural effusion or pneumonia, asthma, pulmonary embolism, chronic pulmonary insufficiency as defined by a chronic hypoxemia less than 60 mmHg and/or chronic obstructive pulmonary disease (COPD) inducing an FEV1 less than 1.5 L.27 ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Group Performance Status; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma.

### Table 4 Association between patient- and disease-related variables and overall survival by multivariate Cox proportional hazards regression

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actionable mutation‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.49</td>
<td>0.33–0.71</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Not tested</td>
<td>1.31</td>
<td>0.97–1.78</td>
<td>0.08</td>
</tr>
<tr>
<td>Ethnicity (Asian vs non-Asian)</td>
<td>1.21</td>
<td>0.90–1.65</td>
<td>0.20</td>
</tr>
<tr>
<td>ECOG PS (≥2 vs &lt;2)</td>
<td>1.37</td>
<td>1.02–1.84</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking (ever vs never)‡‡</td>
<td>1.60</td>
<td>1.06–2.42</td>
<td>0.03</td>
</tr>
<tr>
<td>Weight loss (0–10% vs &gt;10%)††</td>
<td>1.37</td>
<td>1.03–1.83</td>
<td>0.03</td>
</tr>
<tr>
<td>Respiratory comorbidity‡‡</td>
<td>1.44</td>
<td>1.10–1.90</td>
<td>0.01</td>
</tr>
<tr>
<td>Gender (male vs female)‡‡</td>
<td>1.43</td>
<td>1.11–1.85</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (continuous) ≤65</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td>0.53</td>
</tr>
</tbody>
</table>

†P-value for the comparison of overall survival for patients with and without the specified factor or for actionable mutation as compared with that for patients in the reference group. ‡Adeno refers to adenocarcinoma. ‡Ever smoker refers to past or current smokers; never smoker refers to <100 cigarettes per lifetime. ††Colinet definition: Respiratory comorbidity was defined as the presence of one or more of the following: history of tuberculosis, history of pleural effusion or pneumonia, asthma, pulmonary embolism, chronic pulmonary insufficiency as defined by a chronic hypoxemia less than 60 mmHg and/or chronic obstructive pulmonary disease (COPD) inducing an FEV1 less than 1.5 L.27 ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Group Performance Status; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma.
international recommendations\textsuperscript{16} and targeted therapies were available. The median survival of patients with an actionable mutation (EGFR/ALK) in our study was comparable to reported data from the Lung Cancer Mutation Consortium.\textsuperscript{6} Additionally, regardless of mutation status, improved survival was associated with the female gender and the absence of adverse prognostic factors, including ECOG $\geq 2$, smoking history, weight loss and respiratory comorbidity. Evaluation of these patient- and disease-related variables for all patients in the TMC (stages I–IV) has been utilised to improve prognostic estimation at the time of NSCLC diagnosis (Alexander et al., Lung cancer prognostic index – a risk score to predict overall survival after the diagnosis of NSCLC in the era of targeted therapies (2017), unpublished manuscript).

Our study recorded that in a setting with available molecular testing, a low but significant number of patients did not have molecular testing performed (96/392, 24%). According to recommended guidelines, EGFR and ALK testing is not recommended in NSCLC that lacks any adenocarcinoma component, such as pure squamous cell carcinoma or large-cell carcinomas. However, if the adenocarcinoma component cannot be completely excluded in the setting of limited tissue specimen, EGFR and ALK testing may be performed in cases showing squamous or large-cell histology. Clinical characteristics, such as Asian ethnicity and a lack of smoking history, may guide decisions in this setting.\textsuperscript{18} It is currently local practice for molecular testing to be ordered at the time of diagnosis for patients with adenocarcinoma presenting with advanced stage disease. A lung panel consisting of EGFR, ALK, KRAS, ROS1, BRAF and MET is available upon request, with EGFR mutation and ALK rearrangement prioritised over other molecular tests unless clinically indicated or patients are being considered for a clinical trial.

It was noted that although 84% of patients with EGFR mutation-positive NSCLC received first-line EGFR TKI, only 36% of patients with ALK-rearranged NSCLC received an ALK inhibitor at diagnosis. This most likely reflects a period of limited availability of crizotinib in Australia as it was only available on the Pharmaceutical Benefit Scheme in August 2015. Nevertheless, all patients subsequently received targeted therapy (targeting EGFR or ALK as relevant) in their subsequent line of treatment.

The acquisition of tissue for biopsy continues to be a challenge, and when available, immunohistochemistry for diagnosis of lung cancer is generally prioritised over molecular testing. In our study, 20% of patients (19/96) had insufficient tissue for molecular testing, which is higher compared with the initial Canadian experience with an EGFR testing programme, which found that 12% of cases had insufficient tissue.\textsuperscript{28} The French Cooperative Thoracic InterGroup (IFCT) has shown that routine nation-wide molecular profiling for advanced NSCLC is feasible, and at least one potentially actionable mutation was detected 50% of the time and changed treatment options for at least half of the patients.\textsuperscript{29} Comparatively, 36% of patients in our cohort had at least one potentially actionable mutation (EGFR/ALK).

Johnson et al. reported that the KRAS mutation is strongly associated with shorter survival period even after adjusting for age, gender and performance status.\textsuperscript{30} We demonstrated that patients whose tumour harbours KRAS mutations had a worse prognosis when compared with those patients with an EGFR and ALK mutation. The higher frequency of patients with EGFR mutations compared with KRAS mutations seen in this study is atypical for an Australian population, likely due to referral bias to a tertiary cancer centre, with a high number of migrants, who have higher population rates of EGFR mutations. The declining rates of smoking in Australia\textsuperscript{11} may have also contributed to a higher percentage of non-smoking-related lung cancer in our study; however, it is uncertain if this is due to a declining rate of smokers in general or an increase in lung cancer incidence amongst never smokers.\textsuperscript{12}

This study has several limitations, such as the retrospective nature of the analysis, albeit prospectively collected data in a single institution. We only included patients with de novo metastatic disease, and survival was measured from date of diagnosis of metastatic disease, distinguishing the group of patients with poorest survival. This study was not designed to compare the survival of patients according to the type of treatment received; rather, it was more an observation of the number of patients with an actionable mutation receiving first-line targeted therapy. The median survival of patients with ALK-rearranged NSCLC is longer than

\begin{figure}
\centering
\includegraphics[width=\textwidth]{survival.png}
\caption{Survival of patients without oncogenic driver mutations; mutation negative versus mutation not performed. Mutation Neg indicates mutation not performed; Mutation NP indicates mutation not performed.}
\end{figure}
expected; however, with only a small number of patients, this should be interpreted with caution.

Conclusion

We conclude that there is a significant difference in survival of patients with an oncogenic driver mutation and treated with a therapeutic targeted agent compared with patients without a mutation. These data confirm that it is imperative to test upfront for somatic mutations in patients diagnosed with metastatic NSCLC as the identification of an oncogenic driver mutation can guide therapy and is prognostic for survival in the context of available targeted therapies.

References


Early use of peripherally inserted central catheters is safe in Staphylococcus aureus bacteraemia

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¹Infection Management Services, Princess Alexandra Hospital; ²School of Medicine, University of Queensland, Brisbane, Queensland, Australia

Abstract

Background: Management of Staphylococcus aureus bacteraemia (SAB) includes prolonged intravenous antibiotics often administered through a peripherally inserted central catheter (PICC). Optimal timing of PICC insertion for SAB treatment is unknown. There are concerns that early insertion may increase the risk of subsequent line infection.

Aims: This retrospective audit aims to determine if early PICC insertion is safe. The outcomes considered included crude mortality, attributable mortality, PICC line infections, duration of bacteraemia and relapsed SAB.

Methods: Patients with SAB at our institution between March 2013 and September 2016 were identified. Early PICC line insertion was defined as occurring within 48 h of index positive blood culture.

Results: This retrospective audit identified 357 patients with SAB who subsequently received a PICC. This study did not show any significant differences between the early and late PICC insertion groups for attributable mortality (6.3% and 4.8%, \( P = 0.27 \)), duration of bacteraemia (median 2 days for both groups, \( P = 0.48 \)) and relapsed SAB (4.7% and 4.1%, \( P = 0.74 \)). Importantly, no confirmed PICC infections were identified in either group.

Conclusions: Early PICC insertion in SAB appears safe in this retrospective audit. If validated in prospective studies, this should allow for the early establishment of safe, reliable intraveneous access in SAB patients.

Introduction

Staphylococcus aureus bacteraemia (SAB) is common and serious, with an estimated 6900 cases occurring in Australia annually¹ and a contemporary 30-day mortality of 16.1%.² Management of SAB is a core service responsibility of infectious disease services.³ The
management of SAB is also of interest to the broader clinical community, with 87% of SAB cases being admitted under non-infectious disease home teams. There remain important questions regarding the optimal investigations and treatment of SAB. Management of SAB has been identified as one of the key areas for ongoing clinical research by the Australasian Society for Infectious Diseases Clinical Research Network.3

Bacteraemia can occur secondary to a wide range of sources, with skin and soft tissue sources predominating in community-onset SAB, while infected vascular access devices, surgical site infections and infected prosthesis are more common in healthcare-associated SAB.6 S. aureus is highly virulent and is associated with haematogenous seeding of infection in up to 34% of cases.7 These features of SAB mandate repeat blood cultures until clearance of bacteraemia is confirmed, a careful assessment for primary and secondary sites of infection and a minimum 14-day course of intravenous (IV) antibiotics.8,9 Administration of these prolonged courses of IV antibiotics is increasingly occurring through peripherally inserted central catheter (PICC); these allow safe and reliable IV access for inpatients and, when appropriate, allow for treatment to be completed through outpatient IV antibiotic programmes.

However, there is a concern that early PICC insertion, particularly within the period of bacteraemia, may predispose to S. aureus infection of the new line. Consequently, the practice at some centres is to delay PICC insertion until clearance of bacteraemia can be demonstrated by negative blood cultures. Reflecting these clinical concerns, the guidelines around PICC use remain cautious regarding insertion during periods of bacteraemia, with recommendations for delayed insertion; notably, these recommendations are based on expert consensus only.10 There is currently no published evidence to support or refute this practice. Delays in PICC insertion can delay establishment of safe reliable IV access for antibiotic administration. These delays can also prolong the length of inpatient stay by impeding transfer to outpatient IV antibiotic programmes.

This single-centre, retrospective audit compared the outcomes for patients with SAB and early PICC insertion with outcomes of patients with SAB and late PICC insertion. We considered the primary outcomes measures of duration of bacteraemia, confirmed PICC infection, SAB relapse and attributable mortality.

Methods

Patients were eligible for inclusion in this study if they had a positive blood culture for S. aureus from samples collected at Princess Alexandra Hospital between March 2013 and September 2016 and had a PICC inserted during their subsequent treatment. Early PICC insertion was defined as occurring within 48 h of the first positive blood culture; late PICC insertion was defined as occurring later than this but prior to completion of IV antibiotic therapy. The duration of bacteraemia was determined from the number of days, inclusive, between the first and last positive blood cultures time periods were measured in 24-h increments based on the date of the event being recorded, and patients with a single positive blood culture were assumed to have a 1-day duration of bacteraemia. We assessed for the outcomes of crude mortality, attributable mortality at 30 days, Catheter-Related Blood Stream Infection (CRBSI) from the PICC, duration of bacteraemia and relapsed SAB.

Presence and duration of SAB, timing of clearance cultures and culture-positive PICC tips were identified from the state-wide laboratory information service (Auslab). The medical record of each case was reviewed to collect demographic data and timing of PICC insertion. We defined a PICC CRBSI as per the Infectious Diseases Society of America, with continuing or recrudescent positive blood cultures with S. aureus in association with a positive culture of the PICC tip after removal.11 The Australian Commission on Safety and Quality in Health Care catheter-associated BSI guidelines, defined as new positive blood cultures, in association with a central line in situ for >2 calendar days12 were inappropriate for this study as they are a surveillance tool intended to identify catheter-associated BSI rather than demonstrate a causative role and could have classified ongoing bacteraemia after insertion of a PICC line as a CRBSI. Relapse was defined as microbiologically confirmed SAB occurring greater than 2 days and less than 365 days after the first negative blood culture. We performed sub-analyses of patients with methicillin-resistant S. aureus (MRSA) and of those who received a PICC within the period of confirmed bacteraemia, as defined by positive blood cultures on the day of, or subsequent to, PICC insertion. Information regarding source of infection and treatment was obtained by cross-referencing cases with the local Australian Group on Antimicrobial Resistance prospective dataset. The medical records of patients who died were reviewed independently by both authors to determine if these deaths were attributable to the SAB; factors considered included ongoing bacteraemia, uncontrolled signs and symptoms of infection or otherwise unexplained death.13

Data were de-identified and recorded in a secure electronic database (excel). Statistical analysis was performed using statistical software (Stata 13, Stata...
Statistical Software: Release 13, 2013; StataCorp., College Station, TX, USA). Categorical values were analysed by Fisher’s exact test and continuous values analysed using Student’s t-test. Given the right skewed distribution in duration of bacteraemia, these differences were analysed using the Mann–Whitney U-test.

This retrospective quality assurance study was submitted to the Metro South Human Research Ethics Committee and received an exemption from ethical review (HREC/16/QPAH/756).

Results

Our study identified 433 patients with SAB, of whom 357 subsequently received a PICC. The median duration to PICC insertion was 5 days (Fig. 1). The overall 30-day mortality in the total population was 15% (65/433), with a mortality of 53% (40/76) in the subset not receiving a PICC as compared to 7% (25/357) in the population receiving a PICC.

No significant differences in the populations who received an early or late PICC were identified (Table 1). There was a trend towards increased intensive care unit (ICU) admissions among the group with late PICC insertion; this reflects the alternative lines used for central venous access in the ICU.

The focus of the SAB was similar among the early and late PICC insertion groups (Table 2). There was a trend towards increased device-associated infection as the initial focus of SAB among the early PICC insertion group. This, in part, indicates the subset of patients with ongoing requirements for central or reliable IV access, which prompted early PICC insertion.

Attributable outcomes were similar for both early and late PICC insertion. Our population had a mean duration of bacteraemia of 3.7 and 3.3 days in the early and late PICC insertion groups, respectively, with a median bacteraemia duration of 2 days in both groups (Table 3). Among all patients receiving a PICC, 48.5% (173/357) had a duration of bacteraemia of 1 day. Eleven patients did not have clearance blood cultures performed, and this may underestimate the duration of bacteraemia for this subset. Attributable mortality was similar in the early and late PICC insertion groups (Table 3). However, there was an increased crude 30-day mortality rate in the early PICC insertion group as compared to late PICC insertion (Table 3). The increased crude 30-day mortality rate in the population not receiving any PICC (53%, 40/76) as compared to the population receiving a PICC

![Figure 1](http://example.com/figure1.png)

**Figure 1** Days from index blood culture to peripherally inserted central catheter (PICC) insertion.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early PICC insertion† (64)</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>57.6</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>35 (54.7)</td>
</tr>
<tr>
<td>MRSA (%)</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Inpatient onset‡ (%)</td>
<td>9 (14.1)</td>
</tr>
<tr>
<td>ICU admission (%)</td>
<td>5 (7.8)</td>
</tr>
</tbody>
</table>

†PICC insertion within 48 h of index positive blood culture. ‡Onset > 48 h from hospital admission. ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; PICC, peripherally inserted central catheter.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Focus of SAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus of SAB</td>
<td>Early PICC insertion (64)</td>
</tr>
<tr>
<td>Infective endocarditis (%)</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>Device-related infection (%)</td>
<td>25 (39.1)</td>
</tr>
<tr>
<td>Skin and soft tissue (%)</td>
<td>12 (18.8)</td>
</tr>
<tr>
<td>Osteomyelitis or septic arthritis (%)</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>8 (12.5)</td>
</tr>
</tbody>
</table>

PICC, peripherally inserted central catheter; SAB, *Staphylococcus aureus* bacteraemia.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early PICC insertion (64)</td>
</tr>
<tr>
<td>Mean duration of bacteraemia (days)</td>
<td>3.7</td>
</tr>
<tr>
<td>Median duration of bacteraemia (days) (IQR)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Crude mortality (%)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Attributable mortality (%)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Relapse (%)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>PICC infections (%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

†Mann–Whitney U-test. IQR, interquartile range; PICC, peripherally inserted central catheter.
SAB secondary to MRSA, and this could increase the risk of PICC line while still bacteraemic. There were no PICC CRBSI among the group receiving an early PICC insertion and 40 had late PICC insertion.

We also performed a sub-analysis of patients who received a PICC within the period of confirmed bacteraemia. This group included 67 patients, of which 27 had early PICC insertion and 40 had late PICC insertion. There were no PICC CRBSI among the group receiving a PICC line while still bacteraemic.

<table>
<thead>
<tr>
<th>Table 4: MRSA subgroup analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early PICC insertion (11)</td>
</tr>
<tr>
<td>Mean duration of bacteraemia (days)</td>
</tr>
<tr>
<td>Median duration of bacteraemia (days) (IQR)</td>
</tr>
<tr>
<td>Crude mortality</td>
</tr>
<tr>
<td>Attributable mortality (%)</td>
</tr>
<tr>
<td>Relapse (%)</td>
</tr>
<tr>
<td>PICC infections (%)</td>
</tr>
</tbody>
</table>

†Mann-Whitney U-test. IQR, interquartile range; PICC, peripherally inserted central catheter.

Discussion

This study suggests that early PICC insertion in SAB is safe, with no differences between the early and late PICC insertion groups in attributable mortality, duration of bacteraemia and relapsed SAB. Importantly, there were no PICC CRBSI in either group.

The difference in crude mortality is notable. However, we believe this result to be confounded by several factors. We acknowledge that the determination of deaths as being attributable to SAB is made difficult by the multiple factors that contribute to outcomes and is vulnerable to interpretive bias. Patients in the early PICC insertion group were more likely to have pre-existing medical conditions that mandated prolonged IV access and PICC insertion, often prior to the recognition of SAB, although this dataset does not include formal comorbidity scores. The timings of the non-attributable deaths were also relatively distant from onset of bacteraemia, occurring a median 26 days post-bacteraemia as compared to 16 days for the attributable deaths, which also suggests a greater role for non-sepsis mechanisms. Additionally, the lack of difference in other outcome measures argues against any mechanistic role that early PICC insertion could have had in increasing mortality.

PICC infections occur at a rate of approximately 2 per 1000 patient days. The risk of line infection is increased by the formation of a non-infective biofilm on the external surface of the catheter within 3 days of insertion as well as subsequent intra-luminal biofilm formation.

The concerns around secondary infection of the PICC have biological plausibility. Antibiotic therapy does not lead to immediate sterilisation of the blood stream, with a typical mean duration of bacteraemia of 3 days for MSSA and 9 days for MRSA bacteraemia. Haematogenously infected lines of MSSA are well described. However, the risk of this complication developing is not understood in the presence of effective antimicrobial therapy at the time of line insertion, as is the case in this study population. The presence of appropriate antibiotics may be adequate to prevent the establishment of a microbial biofilm on the PICC even in the presence of persistent bacteraemia. This may be analogous to the situation in prosthetic joint infection revision surgery where single-stage revisions, with a new prosthesis being implanted into a potentially non-sterile site, still lead to the cure of infection in 90–95% of cases at 5 years. Similarly, central venous access is often required for community-onset septic shock requiring ICU admission; when blood cultures taken at admission subsequently become positive, it does not routinely indicate a line change.
There remains the possibility that microbial seeding of the PICC occurs at the time of insertion and that this infectious inoculum remains suppressed while there is ongoing administration of antibiotics. Most patients with a SAB and subsequent PICC have the line removed at the completion of antibiotic therapy. There is a potential risk for shearing of infected biofilm at the time of removal, with subsequent haematogenous seeding of infection. Our study did not demonstrate any increased relapse rates in the cohort receiving early PICC insertion, indicating that this process, if occurring, was unlikely to be clinically significant.

There was a reduced proportion of patients with ICU admission in the early PICC insertion group, which was due to the alternative lines used for establishing IV access in the critical care setting. We do not consider this a weakness of the study. The rationale for early PICC access is the establishment of reliable IV access and potentially to expedite discharge in patients with early clinical improvement and no metastatic source of infection identified, which requires further intervention. Neither of these criteria is relevant to the shocked patient with SAB requiring ICU admission.

Our institution contributes to the Australian Group on Antimicrobial Resistance data, which include ongoing surveillance of SAB. No significant differences have been noted in our population with SAB, compared with aggregated Australian data, other than a slightly lower MRSA rate, for which there is significant state-to-state variation within Australia. This indicates that our population is representative of the broader Australian population with SAB and that our results are externally applicable.

This study has some shortcomings. The absence of any confirmed PICC CRBSI in this study raises the possibility of this study being underpowered for this outcome measure. There are no published data on the rates of PICC CRBSI occurring during a SAB while receiving appropriate antimicrobial therapy. As such, we were unable to perform a power calculation prior to data collection. The absence of any PICC CRBSI in the 357 patients suggests that this is a rare event. It is possible that infected PICC tips were not sent for culture; however, this is unlikely given that the infectious diseases unit consults closely on all cases of SAB and would recommend tip culture in cases of suspected PICC infection. Our relapse data are limited by the absence of strain typing to distinguish SAB relapse from recurrence. Finally, the retrospective nature of this study, and lack of comorbidity assessment, cannot exclude the impact of unappreciated confounders, a factor discussed above with respect to the different crude mortality rates.

**Conclusion**

In summary, our data suggest that the risk of PICC infection secondary to SAB in the presence of effective antimicrobial therapy is low, and there was no apparent increased risk with early PICC insertion or insertion during bacteraemia. Given the limitations inherent in a retrospective audit, these results require validation in a prospective study with formal comorbidity assessment. If validated, these findings should impact routine management of SAB and increase the safety and reliability of IV access and delivery of IV antibiotics, as well as facilitate early discharge to outpatient antibiotic programmes for patients with uncomplicated SAB.

**Acknowledgements**

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**References**


Postural change in convulsive seizures: a retrospective review of video-electroencephalographic recordings

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Key words
sudden death, seizure, prone position, posture.

Abstract

Background: Prone position has been identified as an important risk factor for sudden unexpected death in epilepsy raising the possibility of avoidance of this posture in sleep as a preventative measure.

Aims: To evaluate the potential utility of prone posture position, we studied patterns of postural change during generalised tonic clonic seizures.

Methods: Video-electroencephalographic recordings of patients undergoing investigations at the Royal Brisbane and Women’s Hospital between 2005 and 2013 were reviewed independently by two raters. Head and truncal positions (left and right lateral, supine, sitting, prone) at seizure onset and offset, before and after nurse interventions were recorded. Post-ictal postural changes and evidence of stertorous respirations were also recorded.

Results: Thirty-one seizures from 27 patients were included in the study. One seizure began with the patient asleep in the prone position. One patient became prone during a seizure, having previously been asleep in the left lateral position. Nine patients changed position during a seizure. Seven of these patients were sitting or in a lateral position at the time of seizure onset, two patients were supine at seizure onset. No patient rolled by more than 90° during a seizure. Post-ictal stertorous respirations were observed in 14 patients, one of whom was prone.

Conclusion: The incidence of patients attaining a prone position during a seizure was low. Given that no patient rolled more than 90°, patients are least likely to attain a prone position if they are supine at the beginning of a seizure.

Introduction

The annual incidence of sudden unexpected death in epilepsy (SUDEP) is estimated to be 1.16 per 1000 patients with epilepsy.1 It is the second cause of years of potential life lost next to stroke in patients with an underlying neurological condition.1 Patients most at risk have a history of primary or secondarily generalised tonic clonic seizures (GTCS) and high seizure frequency.2–5 The pathophysiology of SUDEP is unclear, but possibilities include cardiac and/or respiratory compromise.

Respiratory compromise, as evidenced by hypoxaemia and hypercapnia, is common during the ictal and post-ictal periods.3,5,6 Prone sleeping position has also been identified as an important risk factor for SUDEP. Most cases of SUDEP are unwitnessed, occur in bed (presumably during sleep) and the deceased is often found in the prone position.2,5,3 A recent meta-analysis of publications documenting body position in patients who died from SUDEP found that 73% of patients died in the prone position.7

An interesting parallel exists with sudden infant death syndrome (SIDS), for which risk factors include the prone and side sleeping positions.8,9 Whether these risk factors contribute to sudden infant death through hypoventilation remains to be proved, but the ‘Back to Sleep’ campaign which addressed these risk factors by encouraging parents to have their infants sleep in a supine position, was associated with a decline in the incidence of SIDS to more than 50% in Western countries.8,9

Given that a prone position may contribute to SUDEP, it is important to understand how patients become prone during seizures if measures to prevent patients attaining this position during or after a seizure are to be devised. In this study, we aimed to: (i) estimate the frequency with which convulsive seizures end in a prone position; and (ii) document positional changes that occur during GTCS.
Methods

Ethics approval for the study was obtained from the Human Research Ethics Committee of the Royal Brisbane and Women’s Hospital prior to commencing the study.

Video-EEG for patients with epilepsy undergoing investigations at the Royal Brisbane and Women’s Hospital between 2005 and 2013 were reviewed to identify patients with recorded GTCS. Videos were reviewed by two independent investigators (JR and KI). The following data were recorded: sleep/wake state at seizure onset, time of behavioural and electrographic onset and offset of seizures, time of nurse interventions that resulted in postural change, and head and truncal positions (left and right lateral, supine, sitting, prone) at seizure onset and offset, before and after nurse interventions. We also recorded post-ictal postural changes until the patient was sufficiently alert to converse or move independently without nursing staff.

Evidence of respiratory compromise by way of stertorous respiration or respiratory obstruction and any influence of bedding on posture were also recorded. Clinical information, including subject age, gender, seizure type and focus, seizure frequency and medication changes were obtained from patient charts.

Statistical analysis

Twenty-seven patients were identified as having GTCS. For patients with more than one seizure, multiple seizures were only included if seizures were not stereotypical or if the seizures began with the patient in different positions or different physiological state. Otherwise, the seizure with the greatest proportion of time without nurse intervention to alter posture was selected to include in data analysis.

Head and truncal positions at seizure onset and at seizure end or at the time of nurse intervention were compared to assess concordance between head and truncal positions. Concordance was high and analyses of postural change were therefore undertaken for truncal position only. Cohen’s kappa coefficient was calculated to assess inter-rater reliability. The strength of agreement was considered moderate for coefficient values 0.41–0.60, good for 0.61–0.80 and very good for 0.81–1.16.

Results

Data from 27 patients (11 males, 16 females) were included in the study. Mean patient age was 32.4 years (range 16.3–55.8 years). All patients had focal epilepsy; electroclinical localisation of the seizure focus is shown in Table 1. There were no cases of SUDEP amongst the study population.

Fourteen patients reported that prior to admission, convulsive seizures occurred on average at least once a month. Of the remainder, three patients reported that convulsive seizures occurred at 1- to 6-month intervals, in one patient at 6- to 12-month intervals and in seven patients at greater than 12-month intervals; GTCS frequency was not recorded in two patients.

Video-EEG monitoring

Antiepileptic medications were reduced for 13 patients and ceased for 4 patients during monitoring. An additional four patients were not on antiepileptic medication at the time of admission. Thirty-seven GTCS were identified and six stereotypical seizures were excluded from the analysis in patients in whom multiple GTCS were recorded.

Postural changes

Head and truncal posture at seizure onset and at seizure end or at the time of nurse intervention are shown in Figure 1. There was very little discordance between head and truncal position at seizure onset (Fig. 1). Truncal position at seizure end or at the time of nurse intervention was the same for most patients, but some patients in the supine or sitting position had their head rotated to the left or right. The patients in whom the trunk was in the prone position at seizure onset had their head in the right lateral position. As truncal position identified all patients who attained a prone position, subsequent data analysis considered only truncal position.

Position at seizure onset was influenced by physiological state (awake or asleep) (Fig. 2). Fifteen seizures began while patients were asleep and 16 whilst awake. In patients who were awake at seizure onset, most were in the supine or sitting position (Fig. 2). Seizures beginning with patients in a lateral position were more likely if patients were asleep than awake (Fig. 2). One patient was asleep in a prone position at the time of seizure onset, and maintained this position throughout the seizure (Fig. 2).

Table 1 Localisation of seizure focus

<table>
<thead>
<tr>
<th>Seizure focus</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right TLE</td>
<td>13</td>
</tr>
<tr>
<td>Left TLE</td>
<td>10</td>
</tr>
<tr>
<td>Frontal</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
</tbody>
</table>

TLE, temporal lobe epilepsy.
Truncal posture at seizure end or at the time of nurse intervention was judged to be different to that at onset in nine seizures (Table 2). Six of these nine seizures began during wakefulness in the sitting or supine posture. In the patient who became prone during a seizure, the seizure commenced during sleep in the left lateral position (Table 2).

Seizure type amongst patients who changed position during a seizure reflected that of the study population, with four patients having right temporal, three left temporal and two bi-frontal seizure onset. Three patients were observed to turn their head into the pillow for 5–10 s. Two of these patients had right temporal lobe and the other had frontal lobe epilepsy with no electroclinical lateralising features.

Two patients were prevented from falling out of bed by bed rails. Neither rater considered that bedding influenced posture in other seizures observed.

Seventeen patients changed truncal position during the post-ictal period (Table 3). Some positional changes were due to nursing intervention, others were initiated by patients. One prone patient was rolled into a lateral recovery position (Table 3). The other sat up and later got out of bed (Table 3). No patient became prone during the post-ictal period.

Respiratory compromise

Fourteen patients were judged to have stertorous respirations post-ictally (Table 4). Most patients were in either the left or right lateral position at that time. One of the two patients who were prone had stertorous respirations (Table 4). No patients obstructed their airway during the ictal or post-ictal period.

Inter-rater reliability

Inter-rater reliability was generally high. Cohen’s kappa coefficient calculated for head and truncal position at seizure onset was 0.92 and 0.87 respectively. Cohen’s kappa coefficient for postural change was 0.70. Discordant ratings occurred when truncal rotation towards the

<table>
<thead>
<tr>
<th>Truncal position</th>
<th>Left lateral</th>
<th>Right lateral</th>
<th>Supine</th>
<th>Sitting</th>
<th>Prone</th>
<th>Out of bed</th>
</tr>
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<tr>
<td>at seizure onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lateral</td>
<td>1†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right lateral</td>
<td>1†</td>
<td></td>
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<tr>
<td>Supine</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Patients with seizure onset in sleep.

<table>
<thead>
<tr>
<th>Truncal position</th>
<th>Post-ictal trunk position</th>
</tr>
</thead>
<tbody>
<tr>
<td>at seizure end</td>
<td>Left lateral</td>
</tr>
<tr>
<td>Left lateral</td>
<td></td>
</tr>
<tr>
<td>Right lateral</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Truncal postural changes during generalised tonic clonic seizures (number of patients)

Table 3 Change in truncal position during the post-ictal period

Table 4 Truncal position of patients observed to have post-ictal stertorous respiration

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The frequency of apnoeas in patients with Cheynes–Stokes respiration, with a Cohen’s kappa coefficient equal to 0.5. Discordant ratings were resolved by joint review of videos.

Discussion

In this review of generalised tonic clonic seizures, we observed that patients attained a prone position during or after a seizure infrequently. Postural change was rare, regardless of the physiological state at seizure onset, with no patient changing truncal position by more than 90°. In two of the 31 seizures, patients attained a terminal prone position, one having been in a prone position at seizure onset and the other rolling from the left lateral position to a prone position during the seizure. Both patients were asleep at seizure onset.

Prone sleeping position has been identified as an important risk factor for SUDEP. Hence, our findings support the possibility that interventions that modify sleep posture may be able to influence this SUDEP risk factor. Our results suggest that patients are least likely to attain a terminal prone position if seizures begin whilst in a supine position. This position would also ensure that dystonic head posturing is unlikely to result in a patient turning their head into the pillow.

Several strategies have been devised to help control sleep posture, including modified bedding or sleepwear and wearable devices that monitor sleep posture and awaken the patient if they move into specific postures. If a positional strategy to modify the risk of SUDEP is to be pursued, knowledge of concurrent obstructive sleep apnoea and other co-morbidities, such as heart failure, is important for the treating physician to ensure that patients are not put at risk of apnoea through other mechanisms. The frequency of apnoeas in patients with Cheynes–Stokes respiration is increased in the supine position relative to non-supine positions.11 Furthermore, the patient tolerability of a positional strategy to modify the risk of SUDEP also needs to be explored. Positional devices employed in the treatment of obstructive sleep apnoea (OSA) have generally had poor compliance.12 Given that sleep deprivation also affects seizure threshold, the effects of postural manoeuvres on sleep quality and duration also need to be ascertained.

How a prone position contributes to the mechanism of SUDEP remains unclear. If it is through hypoventilation, then arousal must be impaired for patients not to change position during the post-ictal period. Patients are frequently observed to be drowsy during the post-ictal period, and this state is often accompanied by generalised EEG suppression.7 It is important to note that SUDEP may be a heterogeneous disorder with more than one underlying mechanism,5,7 such that a positional strategy may not mitigate the risk of SUDEP in all patients. In a review of 253 cases of SUDEP, whilst the predominant terminal position was prone, 27 patients were found supine.7

A recent review of 88 cases of SUDEP, in which the circumstances of mortality were documented, identified 21 cases of SUDEP during wakefulness.7 Postural changes observed during GTCS that begin during wakefulness are therefore also relevant. There is also evidence that in some patients, hypoxaemia and hypercapnia persist despite increased respiratory rate.5,6 This is suggestive of ventilation-perfusion mismatch, possibly as a result of right to left pulmonary shunting or neurogenic pulmonary oedema.3 Respiratory compromise may also come about due to central apnoea, which occurs in 42% of seizures.6 The brainstem hypothesis for SUDEP, like theories for SIDS, proposes that the normal arousal and stimulatory responses to hypoxia and hypercapnia are impaired.1 Neurocardiogenic theories propose that seizures precipitate cardiac repolarisation abnormalities that lead to fatal cardiac arrhythmias. Studies have shown that ion channels known to cause long QT syndrome are also expressed in the central nervous system,5,6 and functional variants of genes implicated in long QT syndrome have also been identified in SUDEP patients.6 Genes for ion channels precipitating arrhythmias other than long QT syndrome have also been implicated in SUDEP.5

The relationship between stertorous respiration during or after convulsive seizures and risk of SUDEP is unclear. Surprisingly, most patients were in the left or right lateral position at the time when stertorous respiration occurred. This is in contrast to patients with obstructive sleep apnoea, where upper airway obstruction predominantly occurs in the supine position.12

Mechanisms underlying airway obstruction in patients with OSA in the supine position are thought to be a combination of unfavourable airway geometry with increased collapsibility, reduced lung volume and an inability of the airway dilator muscles to compensate.12 There is little information on the effect of lateral position on airway obstruction.12

Postural change in convulsive seizures

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Limitations

This was a phenomenological study and the relatively small sample size precluded extensive examination of risk factors in patients attaining a prone position. Patients were also observed in a clinical environment, rather than their home environment. This may affect patient posture. For example, the head of a hospital bed is more easily elevated than a domestic bed and patients were often semi-reclined or sitting in bed at the time of seizure onset. Nurses intervened to alter posture during a seizure in approximately 50% of cases. Although postural change was analysed only for the period prior to nurse intervention, it is possible that more patients would have changed position in the absence of intervention. Sleep quality may also differ in hospital and home. Physiological state at seizure onset did not appear to affect the propensity for positional change, but the predominant position at seizure onset was different between the asleep and awake groups.

Conclusion

GTCS uncommonly result in patients attaining a terminal prone position. Most patients did not change position during a seizure and postural change was minimal in those who did change position (rolling no more than 90°). It may therefore be possible to prevent patients attaining a terminal prone position by encouraging patients to sleep in a supine position, and to develop strategies or devices to maintain this position. Larger studies of postural changes during GTCS are needed to confirm these findings in clinical and non-clinical environments.

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Predictive value of symptoms, signs and biomarkers on computed tomography pulmonary angiogram results

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Key words
pulmonary embolism, computed tomography pulmonary angiogram, troponin, D-dimer.

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Abstract

Background: Pulmonary embolism (PE) is associated with significant morbidity and mortality. PE is a heterogeneous entity that causes a wide variety of clinical presentations, making it imperative to establish which clinical symptoms, signs and biomarkers can influence the pretest probability of PE to aid clinicians and reduce over testing.

Aim: To analyse the clinical parameters used by clinicians to order a computed tomography pulmonary angiogram (CTPA) and establish which were associated with the presence of PE.

Methods: Medical records of patients who underwent CTPA from December 2015 to March 2016 were extracted. Patient demographics, clinical symptoms, diagnostic and radiological results were analysed.

Results: The study included 150 CTPA studies. Of the studies, 25 were positive for PE and 125 were negative. There was no significant relationship between the presence or character of chest pain and a positive CTPA result (P = 0.216). Previous history of venous thromboembolism (VTE) (P < 0.0001), one or more risk factors for VTE and positive troponin (P < 0.002) were all predictive of PE. None of the patients with a negative D-dimer had a positive CTPA.

Conclusion: This study supports the negative predictive value of the D-dimer for excluding PE and demonstrates that the strongest pretest predictors of PE in our population are a prior history of VTE, risk factors for VTE and elevated troponin. None of the parameters that often generate requests for CTPA, including vital signs or the presence of chest pain, was associated with the presence of PE in our study population.

Introduction

Pulmonary embolism (PE) is defined as an occlusion of the main or branching pulmonary arteries. It has an estimated annual incidence of 1.22–1.83 per 1000 patients. The actual incidence, however, is likely to be greater because up to 50% of patients with deep vein thrombosis (DVT) develop silent PE. Together with DVT, PE is the third most common type of cardiovascular disease. It is a major cause of mortality and morbidity among hospitalised patients, which may be fatal in the acute setting or lead to chronic disease and disability. Death, as the most serious consequence of large acute PE, is common, and two-thirds of such patients who succumb die within 2 h of presentation to hospital. In contrast, chronic PE can pose a mortality risk for up to 30 years and predispose to significant cardiovascular complications, such as chronic thromboembolic pulmonary hypertension and right heart failure.

The lack of specificity of the symptoms of PE does have diagnostic implications. The symptoms of dyspnoea, pleuritic chest pain, cough, fever, haemoptysis and syncope are non-discriminatory. Clinical decision tools have been developed using a combination of signs and symptoms to aid in analysing the pretest probability of PE in suspected cases. Examples of such validated tools include The Charlton Rule, Wells score, The Revised Geneva Score and Pulmonary Embolism Rule-Out Criteria.

Computed tomography pulmonary angiogram (CTPA), which allows high-resolution imaging of the pulmonary vasculature, is the current gold-standard investigation for the diagnosis of PE. When combined with Wells score, it has been shown to have a negative predictive value of 96% for low-risk and 89% for intermediate-risk
patients and a positive predictive value of 92–96% in patients with an intermediate or high clinical likelihood of PE.\textsuperscript{12} The drawbacks of CTPA, however, include the risks of contrast nephropathy and allergy, radiation exposure and the potential for incidental findings, which lack clinical implication but require further investigation. In addition, unnecessary ordering of CTPA is costly to healthcare systems.\textsuperscript{13}

Current evidence suggests that sensitive D-dimer testing can be combined with clinical findings and decision rules to exclude PE safely, thus circumventing some avoidable costs and unnecessary imaging.\textsuperscript{14,15} Despite this, there is an increasing use of CTPA in the assessment of patients with cardiorespiratory symptoms.\textsuperscript{16} The primary objective of this study was to establish if there was any association between the clinical parameters and biomarkers that influence the decision to order a CTPA and the presence or absence of PE on that test.

**Methods**

University Hospital Geelong is the only regional tertiary teaching hospital in Victoria, Australia with approximately 70,000 admissions per year. Approximately 60 CTPA scans are performed monthly at our institution.

CTPA studies performed between 21 December 2015 and 2 March 2016 were extracted from the Barwon Medical Imaging Synapse Application. Studies referred from external practitioners that did not result in an inpatient admission were excluded from analysis (no clinical signs, symptoms or biomarkers were available for collection), as were studies on patients who were known to have an existing PE based on a previous CTPA.

**Data collection**

Clinical data of patients who underwent CTPA were extracted from the patients’ Electronic Medical Records. The following variables were extracted: gender, age, CTPA result (positive or negative), presence of pleuritic chest pain, syncope, haemoptysis, previous history of venous thromboembolism (VTE), presence of risk factors for VTE (active malignancy, immobility, surgery within previous 3 months, inherited or acquired thrombophilia), presence of tachypnoea (respiratory rate > 20), hypoxia (peripheral pulse oximetry < 92% on room air or requiring supplementary oxygen), tachycardia (heart rate > 100 beats/min), hypotension (systolic blood pressure < 90 mmHg) and distended jugular venous pressure (> 5 cm of water or clinically documented) on presentation to the Emergency Department or at the time CTPA. Biochemical markers, including D-dimer and troponin, in the previous 72 h were recorded. A positive troponin was defined as a troponin I ≥ 0.045 ng/mL.

Where a historical clinical variable (such as chest pain or haemoptysis) was not recorded in the patient’s medical record, the assumption was made that the variable was not a feature of that patient’s presentation.

**Data analysis**

Study variables were entered into a spreadsheet (Microsoft Excel, Richmond, OR, USA), where all results were collated according to the pre-specified study parameters.

CTPA results were then subjected to further analysis according to the pre-specified variables using SPSS software (IBM, New York, NY, USA). The relationship between documented risk factors for VTE disease and the likelihood of CTPA demonstrating PE were analysed. As the data set was comprised of unpaired categorical variables, Pearson Chi-squared test was applied to establish the significance of associations between the variables for the CTPA-positive and CTPA-negative subgroups. Where subgroups contained less than five events, Fisher exact test was used.

**Ethics approval**

This project was approved by the Barwon Health Ethics Committee.

**Results**

The study included 150 CTPA. Thirty studies were excluded; six CTPA studies were ordered to review the progression of PE in patients already known to have a PE, and the remainder were performed on an outpatient basis and did not result in admission to hospital. There were 82 studies on female patients (55%), and 68 (45%) studies were performed on male patients. Of the 150 total CTPA included in the study, 25 were positive for the presence of PE disease (25/150, 17%) and 125 were negative.

With regards to age, the majority of patients were over 50 years of age. The proportion of positive CTPA according to age group varied from 10.6% in the 50–65 year age group to 64% (16/25) in patients older than 65 years. However, age was not significantly associated with a positive CTPA result (\(P = 0.19\)).

Clinical and biochemical variables and their association with CTPA results are depicted in Table 1.
Clinical features

When the presence of chest pain was examined, neither the presence of chest pain by itself nor the pre-specified character of pleuritic chest pain was significantly associated with a CTPA positive for PE. Extrapolating for the patients who did report chest pain, there was no significant relationship between the presence of pleuritic chest pain and a positive CTPA result ($P = 0.22$). Similarly, there was no statistically significant association found between multiple other clinical symptoms and signs and likelihood of a positive CTPA. In contrast, a past history of VTE and one or more risk factors for VTE were both significantly associated with a positive CTPA result. (Table 1).

Biomarkers

A positive troponin result was significantly associated with a positive CTPA result ($P \leq 0.002$). Only 42 of 150 patients (28%) had a D-dimer test performed. In nine patients, a CTPA was performed despite a negative D-dimer result, and all of these CTPA studies were negative. While 25 patients with a negative CTPA had a positive D-dimer, 8 patients with a positive CTPA result had a positive D-dimer.

Comorbid conditions among study patients

In 71 patients (47%), there was no relevant comorbid condition documented to explain their presentation. In the remaining 79 patients (53%), relevant comorbidities documented included: chronic obstructive pulmonary disease (COPD) (17), thoracic malignancy (14), non-thoracic malignancy (12), ischaemic heart disease/heart failure (10), previous PE (6) and pneumonia (3).

Alternative diagnoses on CTPA

Among the 125 patients with CTPA scans not showing PE, diagnoses found on CTPA included: pneumonia (21), pleural effusion (15), COPD (13), pulmonary atelectasis (9), malignancy (9), heart failure (8) and pericardial effusion (7).

Discussion

In this study, 17% of CTPA were positive for PE. This rate of positive CTPA is higher than other international studies of a similar inpatient tertiary centre demographic. This study established that many clinical variables that lead clinicians to order a CTPA (e.g. hypoxia, sinus tachycardia, pleuritic chest pain, tachyphoea) are not associated with the likelihood of a CTPA being positive.

Clinical findings

In this study, both the presence and character of chest pain (pleuritic vs non-pleuritic) was not associated with a positive CTPA study. This is different to traditional teaching that a pleuritic chest can be a marker of PE. Extrapolating for the patients who did report chest pain, there was no significant relationship between the presence of pleuritic chest pain and a positive CTPA result ($P = 0.22$). Similarly, there was no statistically significant association found between multiple other clinical symptoms and signs and likelihood of a positive CTPA. In contrast, a past history of VTE and one or more risk factors for VTE were both significantly associated with a positive CTPA result. (Table 1).

Table 1 Clinical and biochemical variables among patients who underwent CTPA

<table>
<thead>
<tr>
<th>Variable</th>
<th>CTPA positive, n (%)</th>
<th>CTPA negative, n (%)</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pleuritic chest pain</td>
<td>1/25 (4)</td>
<td>18/125 (14.4)</td>
<td>0.25 (0.01, 1.91)</td>
<td>0.20</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>11/25 (44)</td>
<td>56/125 (44.8)</td>
<td>0.97 (0.37, 2.49)</td>
<td>0.94</td>
</tr>
<tr>
<td>Syncope</td>
<td>2/25 (8)</td>
<td>4/125 (3.2)</td>
<td>2.63 (0.31, 18.25)</td>
<td>0.26</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1/25 (4)</td>
<td>6/125 (4.8)</td>
<td>0.83 (0.09, 7.18)</td>
<td>0.67</td>
</tr>
<tr>
<td>Elevated JVP</td>
<td>2/25 (8)</td>
<td>8/125 (6.4)</td>
<td>1.27 (0.25, 6.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>9/25 (36)</td>
<td>58/125 (46.4)</td>
<td>0.65 (0.24, 1.71)</td>
<td>0.34</td>
</tr>
<tr>
<td>Tachypnoea</td>
<td>10/25 (40)</td>
<td>44/125 (35.2)</td>
<td>1.23 (0.51, 2.96)</td>
<td>0.38</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>14/25 (56)</td>
<td>49/125 (39.2)</td>
<td>1.97 (0.77, 5.12)</td>
<td>0.12</td>
</tr>
<tr>
<td>Past history VTE</td>
<td>13/25 (52)</td>
<td>17/125 (13.6)</td>
<td>6.88 (2.45, 19.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive troponin</td>
<td>7/9 (77.8)</td>
<td>16/73 (21.9)</td>
<td>12.47 (2.1, 97.4)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Positive D-dimer</td>
<td>8/8 (100)</td>
<td>25/34 (73.5)</td>
<td>–</td>
<td>0.17</td>
</tr>
<tr>
<td>One or more RF for VTE</td>
<td>18/25 (72)</td>
<td>52/125 (41.6)</td>
<td>3.6 (1.41, 9.27)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CTPA, computed tomography pulmonary angiogram; JVP, jugular venous pressure; RF, risk factor; VTE, venous thromboembolism.
factors on history, such as recent immobility. The converse is also true, in that other medical conditions that exist among patients, such as COPD or heart failure, may be responsible for their presentation to hospital in cases where PE is suspected. In over half of patients in this study, a comorbid condition was present and could alone have explained the clinical presentation in many cases.

In this study, vital signs were not shown to be a useful predictor of a positive CTPA. In particular, there was no correlation between hypoxia and a subsequent positive CTPA result in this study. In our cohort, more than 50% of patients presented with normal peripheral oximetry. Only a small percentage of patients who had a CTPA were hypotensive. This is consistent with Ghani et al. who found that the Wells score and Medical Emergency Team activation indications of hypoxia, hypotension and tachycardia were not accurate in predicting the presence or extent of PE. Rather, these changes reflect the haemodynamic instability and physiological response to serious illnesses, a small subset of which could be due to PE. Although our results did not show a positive correlation between haemodynamic instability and a subsequent positive CTPA, studies have shown that haemodynamic instability at presentation is an adverse prognostic factor in confirmed cases of PE.

Biochemical predictors
Evidence suggests that a validated clinical prediction tool can be utilised to estimate the pretest probability of PE or DVT to guide further management. A low pretest probability of PE and a negative D-dimer is shown to be sufficient to exclude VTE. Our study results are consistent with prior literature, quoting an almost 100% negative predictive value of a negative D-dimer in low pretest probability patients. We found that none of the patients in our study with a negative D-dimer had a CTPA positive for PE. Likewise, our study also revealed that all of the positive CTPA studies had a concurrent D-dimer test that was positive, reinforcing the known high sensitivity of D-dimer for detecting VTE.

Risk stratification is an important part of management of patients with confirmed PE. Troponin elevation as a sign of right heart strain has been well demonstrated, and an elevated troponin is associated with an adverse prognosis in confirmed PE. Our results showed an association between raised serum troponin and a subsequent positive CTPA study. Whilst the serum troponin level may not be immediately available at presentation in the emergency department or during resuscitation of an acutely deteriorating patient, and a raised level might be difficult to interpret, our findings suggest that looking for PE may be useful and diagnostic if an alternative explanation for raised troponin has not been found. Moreover, concurrent troponin measurement with CTPA may add further prognostic value when massive PE is suspected.

Limitations
A large number of patients did not have clinical parameters documented adequately, which were assumed to be negative where absent (such as haemoptysis). In addition, given the large number of patients who did not have a troponin assay checked (45% of a study population of 150), the relationship between troponin and a positive CTPA may be subject to confounding. Moreover, values for both normal and abnormal clinical parameters vary significantly in the literature, indicating that rates of abnormal clinical signs in our patient population may not be generalisable to other populations. Finally, PE risk scores, such as the Wells score, were not calculated in this study given the retrospective methodology and the requirement for a determination about whether PE was the most likely diagnosis.

Conclusion
Our study confirmed the existing link of PE with the commonly appreciated risk factors for VTE and a previous history of VTE, and supports the utility of troponin testing and the negative predictive value of D-dimer testing in excluding PE. While patients over the age of 65 years accounted for two-thirds of all positive CTPA, age was not significantly associated with a positive CTPA result in this study. Furthermore, this study did not find a correlation between clinical parameters and the pretest probability of PE. This study does, however, highlight the importance of assessing the pretest probability of PE before ordering a CTPA. We support the use of clinical gestalt, taking into account alternative conditions that could explain a patient’s clinical presentation in combination with clinical decision-making tools, D-dimer and troponin measurement in determining the possibility of an underlying PE.

References


Do medical oncology patients and their support persons agree about end-of-life issues?

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Key words
Cancer, end of life, advance care planning, concordance, decision-making.

Abstract

Background: The perceptions of those called on to make decisions on behalf of patients who lack capacity at the end of life must accurately reflect patient preferences.

Aims: To establish the extent to which the views of medical oncology outpatients are understood by their support persons, specifically with regards to (i) preferred type and location of end-of-life care, (ii) preferred level of involvement in end-of-life decision-making and (iii) whether the patient has completed an advance care plan or appointed an enduring guardian.

Methods: Adults with a confirmed cancer diagnosis and their nominated support persons were approached between September 2015 and January 2016 in the waiting room of an Australian tertiary referral clinic. Consenting participants completed a pen-and-paper survey. Nominated support persons answered the same questions from the patient’s perspective.

Results: In total, 208 participants (39% of eligible dyads) participated. Observed agreement across the five outcomes ranged from 54% to 84%. Kappa values for concordance between patient–support person responses were fair to moderate (0.24–0.47) for enduring guardian, decision-making, advance care plan and care location outcomes. A slight level of concordance (κ = 0.15; 95% confidence interval: −0.02, 0.32) was found for the type of care outcome.

Conclusion: Relying on support persons’ views does not guarantee that patients’ actual preferences will be followed. Strategies that make patient preferences known to healthcare providers and support persons while they still have the capacity to do so is a critical next step in improving quality cancer care.

Introduction

It is estimated that up to 70% of people lack the capacity to make or communicate decisions at the end of life. In these situations, a family member or friend who can be trusted to act in the person’s best interests may be called on to make decisions on the patient’s behalf. Current policy recommends that these substitute decision makers (SDM) work together with the healthcare team to decide on the best options for the patient, basing this decision on the patient’s wishes and values as much as possible. This assumes that SDM perceptions of what a patient wants is consistent with the patient’s actual preference. When patient preferences have been clearly expressed and documented, those making end-of-life decisions on behalf of the patient often experience less burden and greater confidence. Inaccurate perceptions of patient preferences can result in conflict between different family members and/or the healthcare team, higher rates of electing unwanted invasive treatments and delays in referral to hospice.

Establishing concordance between patient and SDM views can identify those areas where improved communication may be needed. Discordance has been identified across multiple areas of cancer care, including estimates of patients’ symptoms and prognosis, unmet needs and fears concerning the future. However, concordance across the
broad range of end-of-life issues that people face is rarely examined. The few published studies are more than a decade old. A systematic review of 16 studies highlighted that SDM incorrectly predict patients’ end-of-life treatment preference in one third of cases.7 In the landmark Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) trial, the facilitated nurse-led intervention did not increase agreement between patients and SDM in relation to resuscitation preferences.6 Similarly, a study of elderly outpatients found that SDM predictions more closely resembled their own treatment wishes than they did the wishes of the patient.9,10 With the increasing emphasis on patient involvement in decision-making and achieving a good death, such findings may not reflect current circumstances. Some have looked at agreement between patient preferences and what the SDM wants for the patient (e.g. Bukki et al.11 and Phipps et al.12), while others focus on specific life-sustaining treatments or individual end-of-life domains.8,11,13,14 More recently, Fried et al.10 found that agreement about whether a living will had been completed was adequate (81%); however, only 68% of patient–SDM dyads agreed about whether a healthcare proxy had been completed. Furthermore, only two thirds agreed about whether they had communicated about life-sustaining treatment and quality versus quantity of life.10 These findings suggest that even if SDM awareness of patient wishes in one domain is high (e.g. whether patient wants a particular life-sustaining treatment), this does not ensure awareness in other domains (e.g. where patient wants to die). As choices at the end-of-life are complex and multi-layered, agreement across the range of domains that can influence quality of death and dying, such as involvement in decision-making, type and location of care, should be established.15

The aim of this study was to determine the extent to which the views of medical oncology outpatients are known or understood by their nominated support persons, with regards to (i) preferred type and location of end-of-life care, (ii) preferred level of involvement in end-of-life decision-making and (iii) whether the patient has completed an advance care plan or appointed an enduring guardian.

**Methods**

**Design**

This study was a cross-sectional survey of medical oncology outpatients recruited from a single tertiary referral centre in New South Wales, Australia.

**Participants**

Eligible patients had a confirmed cancer diagnosis (any type), were attending at least their second appointment at the clinic (to ensure that patients had experienced cancer care), were aged ≥18 years, were able to read and understand English and were deemed by clinical staff to be physically and mentally able to give informed consent to complete the survey. Patients were included regardless of their stage of disease or estimated life expectancy.

**Procedure**

Clinic staff identified eligible patients from daily clinic lists. Informed consent was obtained by a trained research assistant (RA) by consecutively approaching eligible patients while they waited for their appointment. Consenting patients were asked to nominate a support person. If the support person was present in the clinic, the RA approached them for consent. If they were not present, the patient was given a recruitment package to pass on to their support person. To assess consent bias, those who withheld consent were asked to provide their age and gender. Given the potentially sensitive nature of the items, consenting participants were asked to complete a pen-and-paper survey at home and return it directly to the research team in a reply paid envelope. Non-responders were sent reminder letters 2 and 4 weeks after recruitment.

**Development of survey**

A literature review of studies conducted with the target population identified important components of end-of-life care, including type of end-of-life care, location of care and involvement of others in end-of-life decision-making. Potential items were reviewed by a panel, including behavioural scientists, medical oncologists, a surgeon, a respiratory physician and a supportive care expert, until consensus on the content and format of items was reached. Thirteen cancer care providers and two medical oncology outpatients participated in 20–30-min individual interviews to elicit their views about the type and location of care available at the end of life; the manner in which end-of-life care should be discussed and decided and the acceptability, relevance and clarity of the proposed items.

Items were modified and tested with a convenience sample of 25 medical oncology outpatients and their support persons before refinement.

**Outcome measures**

**Preferred type of end-of-life care**

It was measured using the single-item question: ‘If you could choose, would you prefer care that focuses: (i) on
extending life as much as possible, even if it meant more pain and discomfort; (ii) relieving pain and discomfort as much as possible, even if it meant not living as long; or (iii) Unsure’. The item has content validity and clinical sensibility in similar populations. Support persons were asked to indicate what they thought the patient would prefer, using the same response options.

**Preferred location of end-of-life care (1 item)**

Participants were asked ‘If you had a choice, where would you prefer to be cared for at the end of life?’. Four response options were provided: (i) in your own home; (ii) in relative’s home; (iii) in a hospital or (iv) in a hospice/palliative care unit. Support persons were asked to indicate what they thought the patient would prefer using these same response options. The response options for location of care were combined in order to create the following two categories: ‘in your own home or a relative’s home’ and ‘in a hospital, hospice or palliative care unit’.

**Involvement in end-of-life decision-making**

Participants were asked to respond to the statement: ‘If you were unable to make decisions yourself, would you prefer your end-of-life care decided by:’. Response options were ‘my doctor and family/friends’, ‘my doctor only’ or ‘a care plan’. Support persons were asked to indicate what they thought the patient would prefer using these same response options.

**Completion of advance care planning instruments**

Patients were asked whether they had already: (i) written down their EOL wishes (i.e. in an advance care directive or care plan) and/or (ii) appointed an enduring guardian. Response options for each item were ‘yes’ or ‘no’. Support persons were asked whether they thought the patient had completed an advance directive or appointed an enduring guardian.

**Independent variables assessed**

Variables were obtained from patient and support person self-reports. Patient and support person sociodemographic items included: gender, age and country of birth. Support person demographics included: relationship to the patient, whether they currently live with the patient and an estimation of how many hours per week they spent caring. Clinical items included the patient’s self-reported cancer type and cancer status.

Both patients and support persons were asked to estimate the life expectancy of the patient.

**Statistical analysis**

STATA v11 (StataCorp LP, TX, USA) was used for all statistical analyses. Consent bias (age, gender) was assessed with chi-squared analyses. Frequency and percentages were used to describe patient and support person preferences, including type of end-of-life care, location of end-of-life care, involvement in end-of-life care decisions and participation in advance care planning, including completion of an advanced directive or care plan and appointment of an enduring guardian. The response options for location of care were combined in order to create the following two categories: ‘in your own home or a relative’s home’ and ‘in a hospital, hospice or palliative care unit’ (i.e. institution) to allow for an adequately powered comparison. The response options for involvement in decision-making were combined in order to create the following two categories: ‘others’ and ‘a care plan,’ also to allow for an adequate sample size. Agreement between patient and support person responses to each of the outcomes were analysed using the Cohen’s Kappa statistic. The interpreted strength of agreement was based on categories for Cohen’s Kappa, with ≤0 = poor, 0.01–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial and 0.81 to 1 = almost perfect.

**Ethics approvals**

The University of Newcastle Human Research Ethics Committee (H-2014-0411) and the ethics committee of the participating health service approved the study (14/11/19/4.04).

**Results**

**Sample**

In total, 441 eligible patients were identified, of whom 268 were recorded as having an eligible support person. Of the 268 eligible patient–support person dyads recorded, 104 returned a completed survey (39% participation rate). Table 1 presents the characteristics of participating patients and support persons. There was a significant association between patients’ perceived cancer stage and what was recorded in their clinical records ($X^2 = 38.67, \text{df}(1), P < 0.001$). Most patients accurately estimated their cancer status as curable (45%) or palliative (36%). Only a minority inaccurately identified their cancer status as curable (14%) or palliative (5.2%).
Dyad agreement on end-of-life care

Table 1 Sociodemographic and clinical characteristics of patients (n = 104) and support persons (n = 104) who returned a completed survey

<table>
<thead>
<tr>
<th>Patient sample n (%)</th>
<th>SP sample n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (47%)</td>
</tr>
<tr>
<td>Female</td>
<td>55 (53%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Younger than 60 years</td>
<td>30 (29%)</td>
</tr>
<tr>
<td>60 years and over</td>
<td>74 (71%)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>34 (33%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>22 (21%)</td>
</tr>
<tr>
<td>Other</td>
<td>35 (34%)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Clinician estimation of cancer status (obtained from medical record)</td>
<td></td>
</tr>
<tr>
<td>Curable</td>
<td>49 (47%)</td>
</tr>
<tr>
<td>Incurable</td>
<td>50 (48%)</td>
</tr>
<tr>
<td>Missing</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>SP relationship to patient</td>
<td></td>
</tr>
<tr>
<td>Spouse/partner</td>
<td>N/A</td>
</tr>
<tr>
<td>Other (including parent, sibling, offspring and other)</td>
<td>N/A</td>
</tr>
<tr>
<td>Missing</td>
<td>N/A</td>
</tr>
<tr>
<td>SP living with patient</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Missing</td>
<td>N/A</td>
</tr>
<tr>
<td>SP time spent caring per week</td>
<td></td>
</tr>
<tr>
<td>&lt;20 h</td>
<td>N/A</td>
</tr>
<tr>
<td>20–40 h</td>
<td>N/A</td>
</tr>
<tr>
<td>&gt;40 h</td>
<td>N/A</td>
</tr>
<tr>
<td>Unsure/do not provide any care</td>
<td>N/A</td>
</tr>
<tr>
<td>Missing</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient’s own estimation of their life expectancy</td>
<td></td>
</tr>
<tr>
<td>2 years or less</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>More than 2 years</td>
<td>38 (36%)</td>
</tr>
<tr>
<td>Don’t know</td>
<td>54 (52%)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

SP, support person.

**Are support persons able to predict patients’ end-of-life care preferences?**

Table 2 presents the number and percentage of patients and support persons responding to each of the main outcomes assessed for this study. The observed percentage agreement for the five outcomes ranged from 54% to 84%. Based on the Cohen’s Kappa statistic, the level of agreement between patients and support persons was moderate on their reporting of ‘whether an enduring guardian had already been appointed’ and ‘the patient’s preferred location of care’. Agreement was fair between patient and support person reporting of ‘how patients would like their end-of-life decisions made’ and ‘whether patients have already completed an advanced care directive or care plan’. However, agreement was only slight between patients and their support person’s perceptions for the type of end-of-life care patients prefer.

**Discussion**

This is the first Australian study to demonstrate quantitatively the degree of concordance between the end-of-life views of patients with a life-threatening cancer diagnosis and the views of their support persons. The degree of concordance between patient and support person responses was variable, ranging from slight to moderate across the five end-of-life outcomes.

These findings highlight the importance of patient and support person involvement in end-of-life discussions. End-of-life discussions should cover a range of topics, and the outcomes should be recorded where possible. While discussions about end-of-life issues will rarely be able to cover all eventualities, they can provide a framework on which to base decisions.21–23

General values and goals of care should be elicited first,21,23 followed by relevant specific treatment scenarios.24,25 This is important as agreement between patients and support persons was lacking even when views on end-of-life care were sought in a general way (i.e. quality vs quantity of life). In contrast to previous studies where support persons chose more invasive care than patients, a higher percentage of support persons in this study perceived that the patient would prefer comfort care compared to patients themselves. In fact, almost one fifth of patients surveyed were unsure of the care they would prefer. This uncertainty may reflect the heterogeneous sample (i.e. not all facing end of life) or the general nature of the question.

In addition to the type of care people want to receive, the location in which they want to be cared for should be discussed. Dying in the location of their choice is important to patients, and the majority are willing to discuss this topic. Support persons in our study overestimated patients’ preferences for home care and underestimated preferences for institutional care (i.e. hospital/hospice). Perceptions about the potential impact on the health and well-being of the other member of the dyad may influence views. For instance, patients may not choose home care as they perceive this would be too great a burden on the family/carer. Support persons need to be involved in discussions to ascertain agreement between both parties and establish the feasibility of achieving preferences. Improved communication about patients’ preferred place of death may significantly increase the likelihood that preferences are achieved.26,27
Some people prefer an active role in all aspects of end-of-life decision-making (i.e. personal control), while others prefer a more passive role, relying on providers and/or support persons to decide (i.e. doctor/family control). This variability highlights the significant demands placed on providers with respect to facilitating a decision-making model that is in accordance with people’s wishes. In our study, agreement in relation to the preferred decision-making model was fair. However, some support persons perceived that patients preferred a model where doctors decided in consultation with families, even though patients indicated a preference for care to be guided by a care plan. The proportion of patients who wanted personal control over decisions (i.e. a care plan) was higher than previous studies with seriously ill older people. This difference may be a consequence of the patient group being surveyed (i.e. only 50% incurable disease in our study) as people’s preferred model may change as their condition worsens. It may also be that those with more advanced disease have had more experience with, and therefore have greater trust in, their treating doctor.

Finally, end-of-life discussions should include a process for summarising and documenting what has been discussed. This can increase the likelihood that understanding is consistent across patients, providers and support persons. Despite many patients in this study expressing a desire for decisions to be made by a care plan (40%), few had written down their end-of-life wishes or appointed an enduring guardian. Where multi-disciplinary teams are involved in care, such as in cancer, documentation may support consistent communication about patient wishes. While not explored here, previously identified barriers include patient or support person uncertainty about prognosis or the potential risks and benefits of life-sustaining treatments. Support persons and providers may be concerned that patients will be unnecessarily distressed if end-of-life issues are raised and may perceive that they lack the skills necessary to discuss these issues or be apprehensive of legal issues. These findings emphasise the need for strategies that allow patients to make their preferences known to support persons and healthcare providers while they still have the capacity to do so. Interventions have typically focused on increasing the uptake of advance directives as a means of achieving patient end-of-life preferences. These interventions are rarely effective.

<table>
<thead>
<tr>
<th>Written down wishes (advance directive/care plan)</th>
<th>SP Yes</th>
<th>SP No</th>
<th>Total</th>
<th>Observed % agree</th>
<th>Cohen’s Kappa (k)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Yes</td>
<td>6 (6.3%)</td>
<td>3 (3.1%)</td>
<td>9 (9%)</td>
<td>84</td>
<td>0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient No</td>
<td>12 (13%)</td>
<td>75 (78%)</td>
<td>87 (91%)</td>
<td>73</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>18 (19%)</td>
<td>78 (81%)</td>
<td>96 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enduring guardian appointed</th>
<th>SP Yes</th>
<th>SP No</th>
<th>Total</th>
<th>Observed % agree</th>
<th>Cohen’s Kappa (k)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Yes</td>
<td>36 (36%)</td>
<td>14 (14%)</td>
<td>50 (50%)</td>
<td>73</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient No</td>
<td>13 (13%)</td>
<td>38 (38%)</td>
<td>51 (51%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>49 (49%)</td>
<td>52 (51%)</td>
<td>101 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of care</th>
<th>SP home</th>
<th>SP hospice/hospital</th>
<th>Total</th>
<th>Observed % agree</th>
<th>Cohen’s Kappa (k)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient home</td>
<td>41 (44%)</td>
<td>7 (7.5%)</td>
<td>48 (52%)</td>
<td>72</td>
<td>0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient hospice/hospital</td>
<td>19 (20%)</td>
<td>26 (28%)</td>
<td>45 (48%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60 (65%)</td>
<td>33 (35%)</td>
<td>93 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decision-making</th>
<th>SP care plan</th>
<th>SP doctor/family</th>
<th>Total</th>
<th>Observed % agree</th>
<th>Cohen’s Kappa (k)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient – care plan</td>
<td>26 (27%)</td>
<td>15 (15%)</td>
<td>41 (42%)</td>
<td>62</td>
<td>0.24</td>
<td>0.009</td>
</tr>
<tr>
<td>Patient – doctor/family</td>
<td>22 (23%)</td>
<td>34 (35%)</td>
<td>56 (58%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>48 (49%)</td>
<td>49 (51%)</td>
<td>97 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of end-of-life care</th>
<th>SP extend life</th>
<th>SP relieve symptoms</th>
<th>SP unsure</th>
<th>Total</th>
<th>Observed % agree</th>
<th>Cohen’s Kappa (k)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient – extend life</td>
<td>2 (2.6%)</td>
<td>4 (5.1%)</td>
<td>4 (5.1%)</td>
<td>10 (13%)</td>
<td>54</td>
<td>0.15</td>
<td>0.04</td>
</tr>
<tr>
<td>Patient – relieve symptoms</td>
<td>1 (1.3%)</td>
<td>34 (44%)</td>
<td>8 (10%)</td>
<td>43 (55%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient – unsure</td>
<td>5 (6.4%)</td>
<td>14 (18%)</td>
<td>6 (7.7%)</td>
<td>25 (32%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8 (10%)</td>
<td>52 (67%)</td>
<td>18 (23%)</td>
<td>78 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SP, support person.
Rather than relying solely on advance directives, increasing the frequency with which end-of-life discussions occur between patients, support persons and healthcare providers is recommended. Clinicians should routinely ask patients who they want involved in decisions and then actively involve those people if requested. Strategies for facilitating consensus decision-making and supporting patients and families to identify and decide on realistic goals of care might include: patient–support person-directed interventions, such as question prompt lists and coaching, provider-directed education and training interventions; family meetings and decision support strategies, such as decision aids.

Strengths and limitations

This study is the first Australian and one of few studies internationally to quantify the agreement between patient and support persons’ views about end-of-life issues across multiple domains, including preferred type of end-of-life care, location of care and involvement in end-of-life decision-making. Findings must be interpreted with caution given the low response rates. Respondents may have been more interested in end-of-life issues. Thus, results may be biased towards greater reported participation in end-of-life care discussions. The low response rate also meant that categories needed to be combined, which may have excluded meaningful data if those categories were left as they were originally intended. It may be that patients who did not consent to the study had a support person who was not recorded, which would mean the number of eligible dyads was greater than reported, and thus, the participant rate is an overestimation. Like most studies in this field, this study included those for whom end-of-life scenarios did not reflect their current circumstance. The inclusion of heterogeneous participants may have biased responses depending on the patient’s ability to project themselves into that situation. A systematic review found that SDM made more accurate judgments when considering situations relevant to real-life circumstances. As preferences may change, longitudinal data are needed to establish the extent to which agreement between patient and support person perceptions improves or decreases over time.

Conclusions

Many support persons are unaware of patient preferences across a broad range of end-of-life domains. Relying on support persons’ views does not guarantee that patients’ true preferences will be achieved. Strategies that allow patients to make their preferences known to support persons and healthcare providers while they still have the capacity to do so are a desirable component of quality cancer care. End-of-life discussions should incorporate scenarios that cover a range of topics, and preferences should be recorded where possible as this can serve as a basis for the decisions at the end of life.

Acknowledgements

The authors acknowledge research support from Ms Lucy Boyd, Ms Judy Hollingworth and Ms Natalie Dodd. Our thanks to hospital staff, patients and families for their contribution to this research.

References

11 Bukki J, Unterpauly T, Nubling G, Jo XJ, Lorenzo S. Decision making at the end of life--cancer patients’ and their caregivers’ views on artificial
Type 2 diabetes in young adults in Central Auckland: demography and complications

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Key words
type 2 diabetes, young adults, retinopathy, albuminuria.

Abstract

Background: Type 2 diabetes (T2D) in young adults is associated with a high risk of diabetes complications.

Aims: To investigated the demography and the emergence of complications of young adults with T2D in the central Auckland region where there has been substantial immigration.

Methods: In total, 310 young adults with T2D (<40 years) were registered with the Auckland Diabetes Centre in 2015. We documented demographic, anthropometric and metabolic variables and prevalence and the emergence of complications.

Results: Three demographic groups accounted for 243 participants (78%): 135 (44%) were migrants of Asian or Pacific Island origin, diagnosed a median 9 years after migration at a mean age of 28 years; 88 (29%) were New Zealand-born Pasifikans, with a high prevalence of morbid obesity and 37 (12%) had major mental illness or intellectual disability. At diagnosis, the median HbA1c was 80 mmol/mol, and in 28%, it was ≥100 mmol/mol. A median 6 years after diagnosis, 56% had some degree of retinopathy, with the prevalence related both to the duration of diabetes and glycaemic control ($P = 0.001$). Forty-four percent of subjects had abnormal albuminuria at diagnosis (12% with macroalbuminuria). Increased albuminuria was strongly associated with obesity ($P = 0.002$). The development of CKD stages 4–5 was related both to the severity of retinopathy and degree of albuminuria at diagnosis ($P = 0.0001$). Major cardiovascular events were related to the severity of retinopathy at diagnosis ($P = 0.0001$).

Conclusions: New migrants, New Zealand-born Pasifikans and patients with mental illness or an intellectual disability comprise the bulk of young onset T2D. The disease is aggressive, and by the age of 40, patients are already developing advanced complications.

Introduction

The prevalence of type 2 diabetes (T2D) continues to rise. The New Zealand Ministry of Health Virtual Diabetes Register shows that between 2010 and 2015, the number of people with diabetes in Aotearoa-New Zealand increased by nearly 23% (to 260 458). Over the same period, the number of people with diabetes in the Auckland District Health Board (ADHB) region increased by 40% to 27 484. This region is home to one in four of New Zealand’s Asian population and almost one in five of its Pasifikans. Migration, which can be a significant risk factor for diabetes, has fuelled the increasing ethnic diversity of Auckland and also contributes to the relative youth of the region (e.g. 33% of the ADHB population are in the 25–44 age group, compared with 26% nationally).

The rising prevalence of T2D has been accompanied by a reduction in its average age at onset. Thus, T2D, formerly a disorder of middle or old age, is increasingly found in adolescents and young adults. Recent publications from several countries have highlighted the ‘aggressive’ course of young-onset T2D. Poor glycaemic control is common, and the rates of both diabetic microvascular complications and cardiovascular disease are high. In this paper, we describe the demographic features and the emergence of complications in young adults with T2D on the Auckland Diabetes Centre (ADC) registry.
Methods

Data on the study population were extracted from the registry at the Diabetes Centre at Greenlane Clinical Centre. It includes patients referred from general practitioners or hospital specialists for diabetes management, education or retinal screening. We identified clinical records of 310 young adults with T2D who were aged 18–39 years and were registered in our clinical electronic record as of 2015.

We recorded the year and the patients’ age at diagnosis; gender, ethnicity, country of birth and year of migration – the latter information was obtained from ADHB registration documents, which are included in the electronic record. We calculated body mass index (BMI kg/m²) at diagnosis and from the latest recorded weight. We also noted major comorbidities. Irrespective of whether management was undertaken primarily at the ADC or in general practice, we were able, through the TestSafe network in the greater Auckland region, to access data from local laboratories (Hba1c, lipids profile, estimated glomerular filtration rate [eGFR] and urine albumin/creatinine ratio) and pharmacies (prescriptions collected).

Glycaemic control was assessed by Hba1c measurement. We recorded the value at diagnosis and also as the average in the 2 years up to December 2015. Albuminuria and chronic kidney disease (CKD) were graded as per the National Foundation of Kidney Disease Outcomes Quality Initiative (NFK KDOQI) guidelines. Albuminuria was assessed by the ratio of urine albumin to creatinine in random urine specimens and was classified as either normoalbuminuria (<3 g/mol), microalbuminuria (3–30 g/mol) or macroalbuminuria (>30 g/mol).

Retinal status was assessed independently by photographic screening. The photographs were graded initially by trained retinal photographers as abnormal or normal. Abnormal photographs were then classified as minimal, mild, moderate or severe retinopathy by trained graders and opticians, with verification by ophthalmologists. The number of patients undergoing laser treatment for retinopathy was also recorded, but we do not have reliable data on the number treated with intravitreal therapy. Retinopathy and albuminuria status are reported both at the time of diagnosis and on the most recent assessment. In those without retinopathy and albuminuria data at the time of diagnosis, the earliest subsequent assessments were included in the analysis. Data on peripheral neuropathy were not collected routinely. We also recorded cardiovascular events (myocardial infarction, stroke and peripheral vascular disease) and renal events, particularly advanced CKD stage 4 or 5 – eGFR 15–29 or <15 mL/min, respectively – or the need for renal replacement treatment.

Statistical analysis

Categorical variables were expressed as a percentage. Median values are expressed with interquartile range (IQR). The χ² test was used for comparing proportions in categorical variables. Student’s t-test, one-way ANOVA and the Mann–Whitney test were used where appropriate to evaluate between-group differences. Statistical analyses were undertaken with PRISM Graph pad 7 and SPSS version 23.

The study was approved by the Auckland District Health Board Ethics Committee (A+7475).

Results

At presentation

In total, 310 patients with T2D who were <40 years old were registered with the ADC in 2015. Close to the time of diagnosis, 298 (96%) had height and 262 (85%) had weight measurements; 261(84%) had Hba1c; 306 (99%) had albuminuria, and 281(91%) had retinal screening data recorded. Of the participants, 140 (45%) were of Pasifika descent, 42 (14%) Māori, 49 (16%) South Asian, 35 (11%) European and 29 (9%) South East or East Asian. Of the participants, 145 (47%) were male and 163 (52%) female; there were two transgender subjects. The mean age of T2D diagnosis was 26 ± 7 years, and the median duration of diabetes at the end of 2015 was 6 years (IQR 4–9). As measured by BMI, the majority of subjects were obese at diagnosis, with 42% in the morbidly obese category (defined as BMI >40 kg/m² or, for Asian populations, >32.5 kg/m²). The proportion with morbid obesity was the greatest in the Pasifika population (54%) and the least in those of South Asian descent (23%); 160 (52%) had a parent or sibling with diabetes (Table 1).

Of the patients, 243 (78%) fell into one of three major demographic categories: new migrants (n = 135), New Zealand-born people of Pasifika descent (n = 88) and people with major psychiatric illness or an intellectual disability (n = 37). There was some minor overlap between the latter two categories.

More than 90% of those of South, South East or East Asian descent were new migrants; their mean BMI was 30 ± 7 kg/m² at the time of diagnosis. Only 20 of the new migrants were known to have T2D prior to arrival. The median interval between migration and diagnosis of T2D was 9 years (IQR 3–14) but was the shortest for subjects of South Asian descent, although these subjects were, on average, older at the time of migration (Table 1).
The people of Pasifika descent who were New Zealand-born had a mean age at diagnosis of 24.7 years, and the subjects were markedly overweight, with a mean BMI of 41.11 kg/m².

Of the participants, 37 subjects (12% of the total) had significant mental health problems: 22 (7% overall, but 13% of the New Zealand-born subjects) had severe mental illness (schizophrenia, schizoaffective disorder or bipolar disorder) and were being treated with 'atypical' antipsychotic agents (olanzapine, risperidone, clozapine or quetiapine).

There were two male-to-female transgender subjects and five patients with intellectual disability. Seventy-four (24%) were current smokers. Smoking was most prevalent in Māori (43%) and in those with severe mental illness (51%).

At diagnosis, the median HbA1c was 80 mmol/mol, with 87 (28%) having values ≥100 mmol/mol; 85 (27%) patients were without assessment of retinopathy, and 70 (22%) were without assessment of albuminuria. For these patients, we included their earliest subsequent assessment in the analysis. Some degree of diabetic retinopathy and abnormal albuminuria was detected in 136 (37%) and 134 (44%) subjects respectively. Macroalbuminuria (ACR >30 g/mol) was present in 38 (12%) subjects. The presence of micro- and macroalbuminuria was unrelated to HbA1c or eGFR but was associated with a high BMI (Fig. 1).

At follow up, updated BMI, HbA1c, retinal and albuminuria status was available for 234 (75%), 214 (69%), 249 (80%) and 274 (88%) of subjects respectively. Only 19 subjects (6%) were managing their diabetes with

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**Table 1** Characteristics of young adults with type 2 diabetes at diagnosis

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>All subjects, n = 310</th>
<th>European, n = 35 (11%)</th>
<th>Māori, n = 42 (14%)</th>
<th>Pasifika, n = 140 (45%)</th>
<th>South Asian, n = 49 (16%)</th>
<th>SE/East Asian, n = 29 (9%)</th>
<th>Other, n = 15 (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis ± SD (years)</td>
<td>26 ± 7</td>
<td>29 ± 5</td>
<td>26 ± 7</td>
<td>25 ± 7</td>
<td>27 ± 6</td>
<td>26 ± 6</td>
<td>29 ± 6</td>
</tr>
<tr>
<td>Gender (M/F), %</td>
<td>47/52†</td>
<td>48.5/48.5†</td>
<td>50/50</td>
<td>37/63</td>
<td>55/43†</td>
<td>62/38</td>
<td>67/33</td>
</tr>
<tr>
<td>First-degree relative with T2D, n (%)</td>
<td>160 (52)</td>
<td>9 (26)</td>
<td>18 (43)</td>
<td>81 (58)</td>
<td>33 (67)</td>
<td>14 (48)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>New migrants, n (%)</td>
<td>135 (44)</td>
<td>2 (6)</td>
<td>-</td>
<td>49 (36)</td>
<td>45 (92)</td>
<td>27 (93)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Age (years) at migration, median (IQR)</td>
<td>20 (15–25)</td>
<td>30 (27–33)</td>
<td>–</td>
<td>18 (12–22)</td>
<td>25.5 (16–29)</td>
<td>17.5 (15–22)</td>
<td>21 (14–23)</td>
</tr>
<tr>
<td>Migration to T2D diagnosis interval, median (IQR)</td>
<td>9 (3–14)</td>
<td>–</td>
<td>–</td>
<td>12 (9–17)</td>
<td>4 (2–8)</td>
<td>9 (4–14)</td>
<td>7 (3–12)</td>
</tr>
<tr>
<td>T2D before or at the time of migration, n (%)</td>
<td>20 (6)</td>
<td>2 (6)</td>
<td>-</td>
<td>6 (13)</td>
<td>9 (18)</td>
<td>2 (7)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Major psychiatric disorder/ID, n (%)</td>
<td>37 (12)</td>
<td>8 (23)</td>
<td>12 (29)</td>
<td>14 (10)</td>
<td>2 (4)</td>
<td>-</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>74 (24)</td>
<td>7 (20)</td>
<td>18 (43)</td>
<td>33 (24)</td>
<td>7 (14)</td>
<td>6 (21)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>38 ± 11</td>
<td>39 ± 8</td>
<td>40 ± 7</td>
<td>42 ± 12</td>
<td>30 ± 7</td>
<td>33 ± 9</td>
<td>37 ± 9</td>
</tr>
<tr>
<td>Proportion with morbid obesity‡ (%)</td>
<td>42</td>
<td>39</td>
<td>39</td>
<td>54</td>
<td>23</td>
<td>34</td>
<td>11</td>
</tr>
<tr>
<td>HbA1c (mmol/mol), median (IQR)</td>
<td>80 (61–103)</td>
<td>80 (56–99)</td>
<td>79 (54–102)</td>
<td>75 (59–100)</td>
<td>86 (63–109)</td>
<td>89 (66–108)</td>
<td>86 (62–95)</td>
</tr>
<tr>
<td>ACR (g/mol), n = 203, median (IQR)</td>
<td>2.1 (1.0–9.9)</td>
<td>1.0 (1.3–8.9)</td>
<td>2.5 (1–20)</td>
<td>5.2 (1–15)</td>
<td>1.0 (0.8–4.5)</td>
<td>1.1 (1–3)</td>
<td>1.8 (0.5–4)</td>
</tr>
<tr>
<td>Macroalbuminuria, n (%)</td>
<td>38 (12)</td>
<td>-</td>
<td>7 (17)</td>
<td>27 (19)</td>
<td>1 (2)</td>
<td>2 (7)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Retinopathy, n (%)</td>
<td>88 (31)</td>
<td>15 (43)</td>
<td>10 (28)</td>
<td>42 (33)</td>
<td>11 (24)</td>
<td>6 (22)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Minimal to moderate</td>
<td>18 (6)</td>
<td>-</td>
<td>4 (11)</td>
<td>12 (9)</td>
<td>2 (4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

† Transgender subjects make up the 100%. ‡ Morbid obesity defined as a BMI >40 kg/m² or (for Asian populations) >32.5 kg/m². ACR, urine albumin/creatinine ratio; BMI, body mass index; ID, intellectual disability; IQR, Interquartile range; SD, standard deviation. Available data for albuminuria, n = 306; for retinopathy, n = 281.
dietary measures alone. Metformin was prescribed in 247 (85%) subjects and in 106 (36%) in combination with a sulphonylurea. Of the patients, 135 (44%) were being treated with insulin, 34 of whom had received insulin since diagnosis. Anti-GAD antibodies were measured in 24 of the latter and were negative in all cases.

Antihypertensive and lipid-lowering medications were prescribed for 44% and 38% respectively. The mean BMI was 1.1 kg/m² lower, and the mean HbAlc 6 mmol/mol was lower than at diagnosis.

Over a median follow up of 6 years (IQR 4–9 years), the proportion of any retinopathy increased from 37% to 56% (Table 2). In subjects with diabetes duration >10 years, 41 (77%) subjects had some degree of retinopathy – severe in 16 (30%). The prevalence of retinopathy was related both to duration of diabetes and glycemic control, as assessed by average HbAlc over the past 2 years (P = 0.001; Fig. 2). Eighteen patients had severe retinopathy at diagnosis; of these, four (22%), progressed to end-stage renal disease, and four had a cardiovascular event during follow up (Table 3).

Over the same period, the increase in the proportion of subjects with an elevated ACR was relatively small (Table 2), but after >10 years of diabetes, 21% had macroalbuminuria (ACR >30 mg/mmol). Four subjects with presumed diabetic nephropathy had to start dialysis, and six others with proteinuric renal disease had other, biopsy-proven, renal pathology. Seven of these ten subjects had macroalbuminuria at the time of diagnosis of T2D (Table 3). There were 13 major cardiovascular events (including two sudden deaths) in 12 patients.

### Discussion

We found that known T2D was present in ~0.2% of the 18–39-year-old age group in the ADHB area. The mean age at diagnosis was 26 years, but a high proportion had some degree of retinopathy at diagnosis, indicating an even earlier onset. We identified groups that appeared to be particularly vulnerable: new migrants, New Zealand-born people of Pasifika descent and patients with major mental illness or an intellectual disability made up 78% of this cohort. More than half the patients had a first-degree relative with T2D, suggesting a possible familial predisposition. Obesity was the rule rather than exception, with 42% in the morbidly obese category. We documented a high rate of complications: after a median 6 years of follow up, 3% of subjects had advanced renal disease and 15% had severe retinopathy.

A high proportion of the subjects (44%) were first-generation migrants – the majority (54%) from various parts of eastern and southern Asia or from the Pacific Islands (36%). The former had relatively low BMI compared to the latter (even considering the differing BMI cut-off value for morbid obesity). It is well recognised that T2D develops at lower BMI levels in people of Asian descent and patients with major mental illness or an intellectual disability made up 78% of this cohort.
Studies from many parts of the world have demonstrated that the incidence of T2D was higher in migrants than in those of European descent because of a tendency to accumulate visceral fat. Migrants to New Zealand have to undergo some form of screening for diabetes as part of their immigration medical examination. Few were identified as having diabetes before arrival, but the screening process may have missed some cases. Before 2009, a fasting laboratory blood glucose or HbA1c was required only in subjects over 15 years of age with either hypertension or glycosuria or a high BMI or waist circumference. Subsequently, a fasting laboratory blood glucose test became mandatory, regardless of associated risk factors. Since 2012, HbA1c has been routinely tested in all subjects over 15 years of age. Nonetheless, with the median interval from migration to diagnosis being 9 years, it is probable that the great majority acquired T2D after arrival.

The Tokelau Island Migrant study was among the first to demonstrate that the incidence of T2D was higher in migrants to New Zealand than in those remaining in their homeland. Studies from many parts of the world have shown that the prevalence of diabetes is high in migrants. Migration involves losses, disruption to usual life habits, exposure to new experiences and challenges that can impact adiposity and T2D through nutrition transition to high-caloric diets, physical inactivity, stress and neighbourhood deprivation. Pacific people (40%), Māori (27%) and Asian (20%) people are more likely to reside in the poorest areas (NZ Dep 13 Quintile 5 areas) than people of European descent. Several studies have shown a strong association between disadvantaged neighbourhood environments and the increased risk of developing T2D. The potential mediating factors include reduced employment and income opportunities, the purchase of calorie-dense food, limited psychosocial resources, language barriers and poor coping strategies resulting in chronic high stress.

Eighty-eight (29%) of the patients were of Pasifika descent but were born in New Zealand. These patients were diagnosed at a mean age of 24 ± 7 years and were strikingly obese, with a mean BMI of 41 ± 11 kg/m², with 46% in the morbidly obese category, reflecting the very high rates of severe obesity reported in Pasifika children in New Zealand. Pasifika people were disproportionately represented in those developing renal disease (9 of 10) and macrovascular complications (7 of 10), a finding consistent with previous reports of a high prevalence of nephropathy and cardiovascular events in Pasifika people.

Patients with serious mental illness or an intellectual disability comprised 12% of the group. These are both recognised risk factors for obesity. T2D is two to four times more common in patients with severe mental health illness than the general population. Chronic hypercortisolism, appetite increase and weight gain with antipsychotic medication use, unhealthy lifestyle and poor self-care are the main diabetogenic risk factors in such patients, although some agents, such as clozapine, may also directly affect β-cell function. The high prevalence of smoking in patients with severe mental illness also contributes to reduced life expectancy.

At follow up, a median 6 years after diagnosis, most patients were taking metformin, and nearly half were being treated with insulin, in keeping with the ‘aggressive’ nature of T2D in this age group reported by others. We also observed a substantial complication rate in terms of retinopathy and the emergence of cardiovascular disease. Most concerning was the high prevalence of renal disease. Macroalbuminuria at the time of diagnosis was prevalent, and a substantial proportion of these subjects went on to develop advanced renal disease and/or cardiovascular disease. Albuminuria has been recognised to predict the risk of end-stage renal disease and cardiovascular events in many previous studies. Not all the renal disease was attributable to diabetic nephropathy – other renal diseases, particularly focal segmental glomerulosclerosis, were prominent. This pattern of non-diabetic renal pathology in Pasifika people has been noted recently by Tan et al. We also observed a high burden of ESRD and cardiovascular events in patients with severe-to-advanced retinopathy at diagnosis. This finding is also consistent with previous reports.

The strengths of this study are the completeness of our data, through access to comprehensive records for biochemical tests and community dispensing through the TestSafe network within the greater Auckland region, and the good length of follow up. The diabetes registry includes patients who were managed within primary care as long as they had been referred for retinal screening, so it is likely that it is reasonably complete.

This study has certain limitations. The rate of undiagnosed T2D in young adults (<40 years) is of course unknown but could be substantial (37% had some degree of retinopathy at diagnosis). Our survey involved only those between the ages of 18 and 39 in 2015. Neither people with T2D ≥40 years of age who had diabetes onset at a young age nor those who were still <18 years of age in 2015 were included, so we cannot estimate the incidence of young onset T2D and its complications from these data. We cannot be sure how many were identified as having diabetes in primary care but not referred for retinal screening.

**Conclusion**

We have identified particular groups at high risk of early-onset T2D: new migrants, New Zealand-born Pasifika people and those with major psychiatric illness or an intellectual disability. We observed high rates of...
complications, particularly renal disease, despite an aggressive approach to treatment with insulin. Early onset T2D is a serious public health challenge given its associated morbidity and mortality.

References


3 Demographic summary. Auckland District Health Board 2016.


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**BRIEF COMMUNICATIONS**

**Non-immediate heparin and heparinoid cutaneous allergic reactions: a role for fondaparinux**

Elina Tan,1 Grace Thompson,1,2 Charlotta Ekstrom1 and Michaela Lucas1,3,4,5

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**Key words**

hypersensitivity, unfractionated heparin, low molecular weight heparin, anticoagulation, venous thromboembolism, immunology.

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**Abstract**

Non-immediate allergic cutaneous reactions to heparins have been increasingly reported, typically manifesting as large, eczematous plaques at sites of subcutaneous injection. Patients may demonstrate cross-reactivity between unfractionated heparin, low molecular weight heparin and semi-synthetic heparinoids, making finding an alternative difficult. Fondaparinux has been identified as a useful alternative in such patients; here we present the first two documented cases in Australia and a literature review.

**Funding:** None.

**Conflict of interest:** None.
Non-immediate allergic reactions to unfractionated heparin (UFH) and low molecular weight heparin (LMWH) have been increasingly reported, with more than 75 cases documented in the literature. Typical presentations include painful, erythematous plaques at injection sites, generalised rashes and heparin-induced thrombocytopenia Type II, with incidence likely underreported. Finding alternatives can be challenging due to anticoagulant cross-reactivity. More recently, the anticoagulant fondaparinux has been identified as an alternative. Here we describe two cases which are, to the authors’ knowledge, the first documented Australian cases of non-immediate, severe allergic cutaneous reactions to heparins and heparinoids, where fondaparinux was successfully used as an alternative anticoagulant. Additionally, a review of the literature regarding fondaparinux as an alternative anticoagulant in the setting of non-immediate hypersensitivity to heparins and heparinoids has been performed, to provide clinicians with an overview of the field.

Two patients were referred to clinical immunology outpatient clinics with a history of pruritic, erythematous plaques at abdominal injection sites, 12–48 h after administration of heparins. Patient 1, a 64-year-old woman (height, 1.63 m; weight, 120 kg; body mass index (BMI), 45.2) on warfarin for recurrent deep vein thrombosis (DVT) and pulmonary embolism, presented with previous reactions to subcutaneous LMWHs enoxaparin and dalteparin during periods of subtherapeutic international normalised ratio levels. Subsequent subcutaneous challenge to heparin (5000 units) and graded subcutaneous challenge to semi-synthetic heparin danaparoid at 1:10 and full doses (150 and 1500 units) resulted in severe local eczematous reactions within 24 h. Patient 2, a 41-year-old woman (height, 1.69 m; weight, 160 kg; BMI, 56.0), also developed non-immediate severe local eczematous allergic reactions to UFH given for DVT prophylaxis and later against enoxaparin, given for DVT treatment. Intracutaneous delayed readings (7 days; 1:100; 1:10) to heparin (50 and 500 units), enoxaparin (0.2 and 2 mg), dalteparin (50 and 500 units), danaparoid (7.5 and 75 units) and fondaparinux (0.025 and 0.25 mg) revealed positive reactions 6 days post-challenge to all except danaparoid and fondaparinux. Subsequent subcutaneous danaparoid challenge was unsuccessful. Subcutaneous challenge performed with both patients against fondaparinux at 1:10 and full doses (0.25 and 2.5 mg) resulted in no evidence of non-immediate cutaneous reactions. Rechallenge with fondaparinux in Patient 1 was successful (2.5 mg) (Fig. 1).

Discussion

Heparins are mucopolysaccharides derived from bovine or porcine tissues, commonly used for prophylaxis and treatment of thromboembolism. Non-immediate hypersensitivity cutaneous reactions to heparins usually present as erythematous and tender lesions at the site of injection. These reactions are not infrequent and are likely an underreported phenomenon. Highlighting this, in a prospective study in Germany which investigated non-immediate reactions to subcutaneous heparins in patients under care of internal medicine, 24 of 320 patients showed signs of non-immediate reactions to heparins (incidence 7.5%).1 Significant risk factors identified for such reactions include treatment duration >9 days (odds ratio (OR) 5.9), obesity (BMI > 25; OR 4.6) and female sex (OR 3.0).1 For diagnosis, subcutaneous testing is considered the gold standard as false negative results are seen with intracutaneous and patch testing.2,3 Typical histological findings from biopsies of cutaneous reaction sites exhibit dermal oedema and mixed perivascular infiltrate with increased eosinophils.3

Identification of an alternative anticoagulant in cases of non-immediate cutaneous hypersensitivity can be challenging (Box 1). Substitution of one LMWH with another without testing is not recommended due to high rates of cross-reactivity.3 Alternatives to LMWH include heparinoids, hirudins and fondaparinux. Heparinoids (e.g. danaparoid) are semi-synthetic mixtures of porcine-derived glycosaminoglycans. Cross-reactivity between heparinoids and heparins is less common, therefore testing
is reasonable. Hirudins (e.g. desirudin) are peptides that are usually produced in the salivary glands of leeches; their mode of action is through thrombin inhibition. For medical use, recombinant hirudins are produced from yeasts. Cross-reactivity between hirudins and UFH and LMWH is observed less frequently, however significant allergic reactions, including severe eczematous reactions, fatal anaphylaxis and bleeding have been described, making this class a less appealing option.

**Box 1 Non-immediate cutaneous hypersensitivity to heparins**
- Non-immediate hypersensitivity reactions to heparins include localised skin reactions, generalised rashes and heparin-induced thrombocytopenia.
- Non-immediate cutaneous hypersensitivity reactions to heparins typically present as large erythematous, eczematous, painful and pruritic lesions at the site of subcutaneous injection.
- Subcutaneous challenge is the gold standard for diagnosis.
- Significant risk factors identified include treatment duration >9 days, obesity and female sex.
- Fondaparinux, a subcutaneous anticoagulant that potentiates the activity of anti-thrombin, is a useful alternative.
- Non-immediate cutaneous allergic reactions to fondaparinux are rare, with an incidence of 0.4%.

Fondaparinux is the first in a new class of anticoagulants, comprising of a fully synthetic pentasaccharide sequence which binds to anti-thrombin and enhances its ability to inactivate factor Xa by 300-fold. Fondaparinux can be given for thromboembolism treatment and prophylaxis and is administered once daily subcutaneously with dose based on weight.

Based on the current literature, fondaparinux has been a useful alternative in at least 40 cases of non-immediate cutaneous reactions from heparins and heparinoids. Various studies and case reports from centres in Germany, Austria and Spain demonstrated that cross-reactivity is not uncommon between various types of UFH and LMWH and between heparins and heparinoids. In a total of 48 cases where patients with confirmed non-immediate reactions to heparins or heparinoids were challenged with fondaparinux, 43 did not demonstrate any non-immediate cutaneous reaction to fondaparinux. There are only five cases of cross-reactivity to fondaparinux reported, with three of these reactions occurring only after rechallenge. All five reactions were localised cutaneous reactions with no reports of anaphylaxis. Findings based on the current literature are presented in Table 1.

In a prospective study by Schindewolf (2010), of 231 patients administered fondaparinux and observed for subsequent cutaneous reactions, the incidence of cutaneous reaction was 0.4%. The primary aim of this study was to assess the incidence and types of skin reactions to fondaparinux. The one patient who reacted to fondaparinux was a 44-year-old female with BMI of 35 who had not previously been exposed to heparins. Of the 231 patients administered fondaparinux, five had a history of previous non-immediate cutaneous reactions to heparins or heparinoids; however none of these patients demonstrated cross-reactivity to fondaparinux. Phan et al. (2014) identified patients with positive skin test(s) to at least one heparin, then tested for reactivity to heparins, hirudins and fondaparinux by intracutaneous challenge. All 11 patients tested against fondaparinux had negative readings. However on subsequent subcutaneous administration, two of seven patients followed up developed localised reactions, highlighting importance of re-challenge. Another three case reports from Germany also document reactions to fondaparinux. The first describes a 64-year-old female who reacted to UFH, LMWH and danaparoid also reacted to fondaparinux. The second case involves a 39-year-old female who had a documented history of non-immediate cutaneous hypersensitivity to several LMWHs. On initial subcutaneous exposure to fondaparinux, there was no documented reaction. However on subsequent exposure a localised eczematous reaction developed, again highlighting importance of re-challenge to confirm. Finally, the third case describes a 59-year-old female who developed non-immediate cutaneous reactions to nadroparin. On testing with various LMWH, hirudins and fondaparinux, initially no reaction was demonstrated on intracutaneous testing. However following subcutaneous administration of fondaparinux, a non-immediate hypersensitivity cutaneous reaction developed. BMI was not documented for these latter three case reports.

The basis for cross-reactivity between heparins, heparinoids and factor Xa inhibitors (such as fondaparinux) is likely attributable to shared epitopes between these classes. Fondaparinux has potential to cross-react, because it represents the shortest sequence within the heparin molecule that is required to interact with factor Xa. The difference between these classes of anticoagulants in regards to their antigenicity and ability to induce non-immediate cutaneous reactions has been postulated to be related to their molecular heterogeneity, with heparins comprising large molecular weight structures (Mr 3000–58 000 Da) of high heterogeneity. This heterogeneity is not surprising given they are naturally occurring molecules sourced from various tissues of different species (porcine and bovine). In contrast, fondaparinux is a fully synthetic pentasaccharide structure (Mr 1700 Da), which is therefore homogenous in terms of its molecular structure and thus has fewer potential epitopes.
To the authors’ knowledge, the two female patients described in our clinical record represent the first two reported cases of non-immediate cutaneous hypersensitivity reaction due to heparins from Australia, in whom fondaparinux has been identified as an alternative. The two patients both share the risk factors for non-immediate cutaneous hypersensitivity reactions to heparins; namely female sex, BMI > 35 and prolonged therapy. In summary, considering these two Australian cases and following a review of the international literature, cross-reactivity between UFH, LMWH and heparinoids is common and likely under-reported, and fondaparinux is a useful alternative. We recommend that in patients who demonstrate non-immediate cutaneous allergic reactions to heparin or LMWH, subcutaneous testing with heparinoids and fondaparinux should be performed if the patient has access to an allergy clinic with ability to perform such testing. Importantly, a negative result should be confirmed with a subsequent subcutaneous rechallenge. In the absence of availability of subcutaneous testing, and if an alternative to heparin or heparinoids is required imminently, fondaparinux can be substituted as it has a very low potential to cross-react. Closer monitoring for cutaneous reactions after subcutaneous administration of heparins should be

Table 1 Overview of studies testing cross-reactivity to fondaparinux

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study features</th>
<th>Anticoagulant confirmed to cause non-immediate cutaneous reactions (route)</th>
<th>Time frame until positive reaction</th>
<th>Patients tested with fondaparinux (successful/unsuccessful)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phan et al., 2014 (n = 19)</td>
<td>Retrospective study. Patients with history of reaction to heparins</td>
<td>UFH (IC) LMWH (IC) Heparinoid (IC) Hirudin (IC) Fondaparinux (IC)</td>
<td>(ND)</td>
<td>9/21</td>
</tr>
<tr>
<td>Schindewolf et al., 2010 (n = 231)</td>
<td>Prospective study. Primary outcome was to determine incidence and causes of skin reactions after administration of fondaparinux. Five patients had history of non-immediate reactions to LMWH or heparinoid, but did not cross-react with fondaparinux.</td>
<td>LMWH (ND) Heparinoid (ND)</td>
<td>(ND)</td>
<td>5/0</td>
</tr>
<tr>
<td>Pföhler et al., 2008 (n = 15)</td>
<td>Single centre case series. Patients with history of reaction to LMWH</td>
<td>UFH (IC, SC, patch, IV) LMWH (IC, SC, patch) Danaparoid (IC, SC)</td>
<td>20 min to more than 120 h (time frames for individual agents not specified)</td>
<td>14/0</td>
</tr>
<tr>
<td>Grims et al. 2007 (n = 8)</td>
<td>Single centre case series. Patients with history of reaction to LMWH</td>
<td>LMWH (SC) Danaparoid (SC)</td>
<td>24–72 h (ND)</td>
<td>8/0</td>
</tr>
<tr>
<td>Jappe et al., 2004 (n = 7)</td>
<td>Single centre case series. Patients with history of reaction to heparins and heparinoids</td>
<td>UFH (IC) LMWH (IC) Heparinoids (IC) Fondaparinux (IC, SC) LMWH (SC)</td>
<td>48 h</td>
<td>5/1</td>
</tr>
<tr>
<td>Parody et al., 2003 (n = 1)</td>
<td>Case report. Patient with history of reaction to LMWH</td>
<td>UFH (IC, SC, patch) LMWH (IC, SC, patch)</td>
<td>5 days</td>
<td>1/0</td>
</tr>
<tr>
<td>Santiago Sánchez-Mateos et al., 2010 (n = 1)</td>
<td>Case report. Patient with history of reaction to heparins</td>
<td>UFH (IC, SC, patch) LMWH (IC, SC, patch)</td>
<td>7 days</td>
<td>1/0</td>
</tr>
<tr>
<td>Hirsch et al., 2004 (n = 1)</td>
<td>Case report. Patient with history of reactions to heparins</td>
<td>UFH (IC) LMWH (IC, SC) Fondaparinux (IC, SC)</td>
<td>4 days</td>
<td>0/1</td>
</tr>
<tr>
<td>Maetzke et al., 2005 (n = 1)</td>
<td>Case report. Patient with history of reactions to heparins</td>
<td>UFH (IC, patch) LMWH (IC, patch) Heparinoid (patch) Fondaparinux (IC, SC)</td>
<td>48 h</td>
<td>0/1</td>
</tr>
</tbody>
</table>

†Reaction only on rechallenge.
IC, intracutaneous; IV, intravenous; LMWH, low molecular weight heparin; ND, not documented. SC, subcutaneous; UFH, unfractionated heparin.
Table 2: Overview of test doses of anticoagulants used in our cases and in the literature

<table>
<thead>
<tr>
<th>Drug tested</th>
<th>Range of doses used (concentration)</th>
<th>Usual prophylactic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intradermal testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>50 units (1:100), 500 units (1:10)</td>
<td>5000 units twice daily</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>0.2 mg (1:100), 2 mg (1:10)</td>
<td>20–40 mg once daily</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>50 units (1:100), 500 units (1:10)</td>
<td>2500–5000 units once daily</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>7.5 units (1:100), 75 units (1:10)</td>
<td>750–1500 units twice daily</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>0.025 mg (1:100), 0.25 mg (1:10)</td>
<td>2.5 mg once daily</td>
</tr>
<tr>
<td><strong>Subcutaneous challenge</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>500 units (1:10), 5000 units (neat)</td>
<td>5000 units twice daily</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>1250 units (neat)</td>
<td>2500–5000 units once daily</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>7.5 units, (1:100) 75 units (1:10)</td>
<td>750–1500 units twice daily</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>150 units (1:10), 375 units (neat), 1500 units (neat) 0.25 mg (1:10), 1.5 mg (neat), 2.5 mg (neat), 5 mg (neat), 7.5 mg (neat), 10 mg (neat)</td>
<td>2.5 mg once daily</td>
</tr>
</tbody>
</table>

Doses used in our cases are in bold. UFH, unfractionated heparin.

performed in those with risk factors of obesity, female sex and prolonged therapy. Fondaparinux is an anticoagulant with low allergic potential, likely owing to its fully synthetic pentasaccharide structure which has fewer potential epitopes compared to the heterogeneous mix of glycosaminoglycans that constitute heparins and heparinoids. It has emerged as a useful alternative for subjects with non-immediate cutaneous reactions to heparins, which can be used for both prevention and treatment of venous thromboembolism.

References

Current lung cancer screening practice amongst general practitioners in Western Australia: a cross-sectional study

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1Midland Physician Service, St John of God Public and Private Hospital, 2School of Primary, Aboriginal and Rural Health Care, University of Western Australia, 3Department of Respiratory Medicine, Fiona Stanley Hospital, 4Department of Respiratory Medicine, Sir Charles Gairdner Hospital, and 5Curtin Medical School, Curtin University, Perth, Western Australia, Australia

Abstract

Lung cancer screening with low dose computed tomography (LDCT) is recommended in the USA and Canada for high-risk smokers but not in Australia. We administered a cross-sectional survey to Western Australian general practitioners (GP). The majority (64/93, 69%) reported requesting a screening chest X-ray (42/93, 45%) and/or LDCT (38/93, 41%) in the past year. LDCT screening was more common if the GP had received education from radiology practices (odds ratio (OR) 2.81, \(P = 0.03\)) or if they believed screening is funded by the Medical Benefits Scheme (OR 3.57, \(P = 0.02\)). Lung cancer screening with LDCT is occurring outside a coordinated programme, contrary to Australian guidelines.

Lung cancer screening for high-risk individuals with low dose computed tomography (LDCT) of the chest is recommended practice in the USA and Canada for high-risk individuals only.1,2 In Australia, however, both the Federal Department of Health and the Royal Australian College of General Practitioners (RACGP) currently do not recommend screening.3,4 Issues requiring resolution prior to implementation of coordinated population-based screening in Australia include: identification and recruitment of high-risk eligible participants, local economic cost analysis, establishment of nodule management protocols and strategies to minimise harm from benign screen-detected abnormalities.5,6 There is concern that opportunistic screening with LDCT may be occurring in the community without the infrastructure, protocols and quality assurance required for a formal screening programme. This study aimed to describe current lung cancer screening practices by general practitioners (GP) in Western Australia (WA).

GP in WA were invited to complete the survey online through an email invitation distributed by the RACGP WA Faculty between September 2015 and January 2016 or at GP education sessions attended by the authors. The survey (Supporting Information Appendix SI) comprised respondent demographics, self-reported screening practices, a series of short case vignettes, knowledge of current recommendations and recent education about screening. Statistical analysis, including logistic regression, was performed using SAS University Edition version 3.5 (SAS Institute, Cary, NC, USA). Ethics approval was provided by the University of Western Australia Human Research Ethics Committee (RA/4/1/7712).

The survey was attempted by 103 individuals, 10 were excluded from the analysis (5 did not complete it and 5 were not practising GP). The demographics of the respondents are described in Table 1. The majority were female (52/93, 56%), working more than six sessions per week (70/93, 75%) and based at metropolitan (65/93, 70%) and group practices (69/93, 74%).

In the last 12 months, the majority of GP (64/93, 69%) reported requesting a screening chest X-ray (CXR) (42/93, 45%) and/or LDCT (38/93, 41%) for one or more of their high-risk asymptomatic patients. Nine GP (10%) reported that the most recent CT chest they requested was for lung cancer screening.

Figure 1 describes the case vignettes and responses. Based on the vignettes, the majority of GP would recommend LDCT or CXR screening to asymptomatic current smokers (LDCT: 58/93, 62%; CXR 26/93, 30%) or former smokers (LDCT: 50/93, 54%; CXR 26/93, 30%) who would meet current USA or Canadian guidelines (Cases 4 and 5).

A significant proportion of GP would recommend screening for case vignettes where the lung cancer risk
fell outside current international guidelines: Case 3 – a distant ex-smoker who quit 20 years ago, 56% would recommend either LDCT (23/93, 25%) or CXR (29/93, 31%); Case 2 – a never smoker who had been exposed to second-hand smoke, 44% would recommend either LDCT (14/93, 15%) or CXR (27/93, 29%).

Over half (57%) of GP reported that at least one patient had asked if they could or should be screened for lung cancer within the last year, suggesting significant community demand. A quarter (23/93, 25%) of GP believed that LDCT for lung cancer screening was funded by the Medical Benefits Schedule (MBS). The remainder either did not believe it was funded by the MBS (35/93, 38%) or did not know (35/93, 38%). Only 9% (8/93) believed screening is recommended by Australian professional societies. The majority knew that screening was not recommended (57/93, 61%). The remaining respondents were not sure (28/93 30%).

In the last 12 months, 44% (41/93) of GP reported receiving education about screening from radiology providers. Such education was associated with less reported CXR screening (odds ratio (OR) 0.30, 95% confidence interval (CI) 0.13–0.72, \( P = 0.007 \)). Using univariate analysis, the factors associated with ordering LDCT screening were: education from radiology providers (OR 3.83, 95% CI 1.60–9.17; \( P < 0.01 \)) and believing that screening was funded by the MBS (Yes vs No: OR 4.99, 95% CI 1.60–15.6; \( P < 0.01 \)). When the two risk factors were included in a multivariate analysis, the adjusted-OR remained significant (radiology education adj-OR 2.85, 95% CI 1.12–7.24; \( P = 0.03 \), MBS funded adj-OR 3.80, 95% CI 1.16–12.41; \( P = 0.02 \)).

**Discussion**

This small survey has shown that screening for lung cancer is occurring against local recommendations and outside of a coordinated programme in WA. A previous survey of Australian GP prior to the advent of LDCT screening reported that 22.5% recommended screening CXR, notably less than the reported rate of screening with CXR or LDCT in this study of 69%.\(^7\) A more recent US study performed before LDCT screening was recommended reported that 57% of primary care physicians

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**Table 1** Participant characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
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<tbody>
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GP, general practitioner.

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have ordered at least one lung cancer screening test in the last 12 months, similar to this study.8 There is discordance between Australian screening recommendations and self-reported practices. Similar discordant practices have been reported in a French study that showed that 94% of GP used inappropriate screening tests.7 While Australian recommendations against CXR screening are clear, LDCT guidelines recommend against screening despite acknowledging evidence of efficacy.3 This apparently contradictory message may be contributing to the practices identified in this study.

It appears that increasing community awareness of LDCT screening for lung cancer, promotion of LDCT screening by radiology practices and perhaps a lack of a coordinated screening programme are contributing to the development of opportunistic screening in the WA community. Education from radiology practices was independently associated with more self-reported LDCT screening and less CXR screening. It is not clear if this practice has increased overall opportunistic screening, but it appears that it has changed GP pre-existing screening practices from CXR to LDCT.

This study is limited by a small sample size, very low participation rate and the likelihood of both selection and recall bias. Given there are 2900 GP registered with the RACGP WA Faculty, the estimated participation rate was only 3.2%. The results may not be generalisable to other parts of Australia. The quantity of screening performed by GP is not known, nor whether LDCT is being offered appropriately to high-risk individuals.

In WA, lung cancer screening with LDCT is occurring outside a coordinated programme and there is discordance between reported screening practice and local recommendations. This highlights an urgent need for clearer guidance from national and professional bodies and improved education for healthcare professionals about current screening recommendations.

References

Supporting Information
Additional supporting information may be found in the online version of this article at the publisher’s web-site:

Appendix S1. Survey.
Pneumocystis jirovecii pneumonia in patients with acute myeloid leukaemia

Hung Chang,1,2,3 Ming-Chung Kuo,1,2 Tung-Liang Lin,1 Jin-Hou Wu1 and Po-Nan Wang1

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Key words acute myeloid leukaemia, Pneumocystis jiroveci, pneumonia, neutropaenia.

Abstract

The association of Pneumocystis jirovecii pneumonia (PJP) and acute myeloid leukaemia (AML) is not clearly defined. In our experience of 291 patients with AML, 20 (14 males and 6 females, median age 56) developed PJP (incidence 6.8%). Thirteen patients (65%) survived until discharge from hospital. We conclude that PJP is not uncommon among patients with AML. In clinical care of AML, awareness of PJP should be heightened and prophylaxis should be considered.

Patients with leukaemia are subject to various infections. Pneumocystis jirovecii pneumonia (PJP) is an opportunistic infection that often occurs in immunocompromised subjects.1,2 Although PJP may occur in a myriad of haematological malignancies, there are only a few scattered reports of PJP in patients with acute myeloid leukaemia (AML).3,4 Its incidence, outcome and clinical significance have not been well described.5 Whether prophylaxis is indicated in AML patients receiving chemotherapy is unclear. Data from a complete cohort may contribute to the understanding of disease characteristics and improvement of clinical management. Therefore, we retrospectively collected consecutive patient data in our institute from 2009 to 2012, including patients receiving chemotherapy or only supportive treatment. The diagnosis of AML was made according to the 2008 version of World Health Organization diagnostic criteria.6 Diagnosis of PJP was made according to clinical symptoms and features of radiographs or computed tomography (CT) scans. Diagnosis of PJP was subdivided into definite and possible, according to definition of Robert-Gangneux et al.7 Laboratory detection of PJP DNA with polymerase chain reaction (PCR) assays was available in late 2011. Demographic data, such as age and gender and clinical information, such as symptoms, anti-leukaemia treatment modalities, status of leukaemia (i.e. remission, refractory or relapse), neutropaenia, use of antibiotics and results of image studies (i.e. chest radiographs and CT scans) were collected and the findings reviewed. Severe neutropaenia was defined as an absolute neutrophil count less than 0.5 x 10^9/L. Survival at discharge from hospital was the clinical endpoint in this study. For comparison of numerical variables, the non-parametric Mann-Whitney U-test was used. For comparison of categorial variables, the Chi square test with Yate’s correction was used. In all analyses, P < 0.05 was considered significant statistically.

Two hundred and ninety-one patients with AML were analysed. In total, 1051 chemotherapy sessions were administered. According to review of medical records, 26 patients were suspected. After reviewing radiographic findings, six patients were excluded in the absence of typical pulmonary infiltrations. Twenty patients (14 males and 6 females) were diagnosed with PJP (incidence 6.8%) and one had recurrence. Based on the definition of Robert-Gangneux et al.,7 14 patients were considered definite PJP and 6 were possible PJP cases. Their median age was 55.5 (range 20–67). There was no significant difference in gender distribution between patients with or without PJP (P = 0.24). However, compared to patients without PJP (median age 58.0, range 16–90), patients with PJP were significantly younger (median age 55.5, range 20–67, P = 0.03, one-tail analysis). Eleven patients had their AML in complete remission prior to development of PJP. Two had a new diagnosis and the remaining seven patients had relapsed or refractory leukaemia. Two patients had undergone allogeneic stem cell transplantation before PJP, one receiving re-induction therapy for relapse and the other developing PJP during

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immunosuppression for treatment of graft versus host disease. Eighteen patients experienced severe neutropenia before PJP. All patients had fever and all received antibiotics before specific PJP treatment was begun. CT scans showed typical diffuse ground-glass infiltrations in 19 patients. In one patient without CT scanning, diffuse interstitial infiltrates were shown by chest radiographs. PCR studies were carried out in 11 patients with PJP (4 bronchoalveolar lavage and 7 sputum samples). PJP DNA was detected in nine cases. During the same period, sputum samples of 13 patients were tested by PCR and two had positive results. As a number, the analysis showed no difference of age (\(P = 0.87\)) or status of complete remission (\(P = 0.77\), gender (\(P = 0.87\)) or status of complete remission (\(P = 0.88\)).

In the present study, we have described the epidemiological data of a relatively large and complete cohort of AML (Table 1). While PJP has been well known among patients with haematological malignancies, PJP in association with AML is uncommonly reported, except in the setting of allogeneic stem cell transplantation.2,8,9 The most common haematological malignancy associated with PJP is non-Hodgkin lymphoma.2,9,11 As treatment of lymphoma often includes steroids, it is not surprising that such patients are susceptible to PJP infections. Addition of rituximab in treatment may lead to more severe immunosuppression and prophylaxis has been advocated.5,12,13 On the other hand, treatment of AML does not involve steroids. Therefore, PJP has not been known to be a common complication of AML.2,8 However, in the present study, we found an incidence of 6.8% for AML and an average risk of 2% for each chemotherapy received. PJP occurred in induction as well as consolidation chemotherapies, regardless of their age, gender and remission status. Although patients with PJP infections were significantly younger in our study, it is difficult to define age as a risk factor for PJP with a small case number. In addition, young patients may likely receive more intensive treatment, including stem cell transplantation and therefore susceptible to opportunistic infections. Further large-scale studies are needed to establish true risk factors.

None of the patients who developed PJP had received prophylaxis at the time of chemotherapy. In previous studies, the risk of PJP in AML or patients receiving high dose cytarabine is unclear.2 The guideline of European Conference on Infections in Leukaemia recommended prophylaxis in paediatric but not adult patients with AML.13 In a meta-analysis, Green et al. recommend prophylaxis when the risk of PJP is greater than 3.5%.2 In view of the

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Table 1: Demographic and clinical characteristics of acute myeloid leukaemia (AML) patients developing *Pneumocystis jiroveci* pneumonia

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>AML status</th>
<th>SCT</th>
<th>Chemotherapy</th>
<th>Severe neutropenia</th>
<th>Outcome</th>
<th>PCR</th>
<th>PJP diagnosis subdivision</th>
</tr>
</thead>
<tbody>
<tr>
<td>55/M</td>
<td>CR</td>
<td>N</td>
<td>HDAC</td>
<td>Y</td>
<td>Death</td>
<td>ND</td>
<td>Definite</td>
</tr>
<tr>
<td>45/M</td>
<td>CR</td>
<td>N</td>
<td>HDAC</td>
<td>Y</td>
<td>Survival</td>
<td>ND</td>
<td>Definite</td>
</tr>
<tr>
<td>54/M</td>
<td>New diagnosis</td>
<td>N</td>
<td>D</td>
<td>Y</td>
<td>Survival</td>
<td>ND</td>
<td>Definite</td>
</tr>
<tr>
<td>48/M</td>
<td>CR</td>
<td>N</td>
<td>HDAC</td>
<td>Y</td>
<td>Death</td>
<td>ND</td>
<td>Definite</td>
</tr>
<tr>
<td>56/F</td>
<td>CR</td>
<td>N</td>
<td>HDAC</td>
<td>Y</td>
<td>Death</td>
<td>ND</td>
<td>Possible</td>
</tr>
<tr>
<td>58/F</td>
<td>Relapse</td>
<td>N</td>
<td>M,E,C</td>
<td>Y</td>
<td>Survival</td>
<td>Positive</td>
<td>Definite</td>
</tr>
<tr>
<td>60/M</td>
<td>Refractory</td>
<td>N</td>
<td>C</td>
<td>Y</td>
<td>Death</td>
<td>ND</td>
<td>Definite</td>
</tr>
<tr>
<td>24/F</td>
<td>Relapse</td>
<td>Y</td>
<td>FLAG</td>
<td>Y</td>
<td>Death</td>
<td>None</td>
<td>Possible</td>
</tr>
<tr>
<td>67/M</td>
<td>CR</td>
<td>N</td>
<td>HDAC</td>
<td>Y</td>
<td>Survival</td>
<td>Positive</td>
<td>Definite</td>
</tr>
<tr>
<td>30/M</td>
<td>CR</td>
<td>N</td>
<td>D</td>
<td>N</td>
<td>Survival</td>
<td>ND</td>
<td>Definite</td>
</tr>
<tr>
<td>31/M</td>
<td>CR</td>
<td>N</td>
<td>HDAC</td>
<td>Y</td>
<td>Survival</td>
<td>Positive</td>
<td>Possible</td>
</tr>
<tr>
<td>63/M</td>
<td>CR</td>
<td>N</td>
<td>HDAC</td>
<td>Y</td>
<td>Survival</td>
<td>ND</td>
<td>Definite</td>
</tr>
<tr>
<td>64/M</td>
<td>Relapse</td>
<td>N</td>
<td>FLAG</td>
<td>Y</td>
<td>Death</td>
<td>Positive</td>
<td>Possible</td>
</tr>
<tr>
<td>20/M</td>
<td>New diagnosis</td>
<td>N</td>
<td>I3A7</td>
<td>Y</td>
<td>Survival</td>
<td>Positive</td>
<td>Possible</td>
</tr>
<tr>
<td>51/M</td>
<td>Refractory</td>
<td>N</td>
<td>FLAG</td>
<td>Y</td>
<td>Survival</td>
<td>ND</td>
<td>Definite</td>
</tr>
<tr>
<td>20/F</td>
<td>Refractory</td>
<td>Y</td>
<td>None†</td>
<td>N</td>
<td>Survival</td>
<td>Negative</td>
<td>Definite</td>
</tr>
<tr>
<td>67/F</td>
<td>Refractory</td>
<td>N</td>
<td>E,C</td>
<td>Y</td>
<td>Survival</td>
<td>Positive</td>
<td>Possible</td>
</tr>
<tr>
<td>56/F</td>
<td>CR</td>
<td>N</td>
<td>HDAC</td>
<td>Y</td>
<td>Survival</td>
<td>Positive</td>
<td>Definite</td>
</tr>
<tr>
<td>61/F</td>
<td>CR</td>
<td>N</td>
<td>HDAC</td>
<td>Y</td>
<td>Survival</td>
<td>Positive</td>
<td>Definite</td>
</tr>
</tbody>
</table>

CR, complete remission; F, female; M, male; ND, not done; PCR, polymerase chain reaction; SCT, stem cell transplantation. Chemotherapy: C, cytarabine; D, daunomycin; E, etoposide; FLAG, fludarabine, cytarabine and granulocyte-stimulating factor; HDAC, high dose cytarabine; I3A7, idarubicin (3 days) + cytarabine (7 days); M, mitoxantrone. †During treatment of graft versus host disease.
relatively high incidence in our clinical experience, PJP prophylaxis may be warranted in adult AML patients when they receive chemotherapy. However, the present study was limited by its retrospective nature and lack of adequate pathological diagnosis. Such findings should be further validated by other large-scale researches.

It should be noted that PJP is often overlooked in management of febrile neutropenia. As PJP often results in hypoxaemia, failure to recognise such infections may lead to delayed management and poor prognosis. The present study illustrated the possible risk of PJP for patients with AML. Therefore, if patients are not provided with prophylaxis, physicians should raise their awareness of PJP in order to administer timely treatment. Future guidelines of supportive care should take PJP into account in patients with AML.

References

Acceptability of opt-out consent in a hospital patient population

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Key words
informed consent, research ethics, opt-out, recruitment.

Abstract
Research has been slow to leverage digitalised medical records as a data resource. Our study assessed patient acceptability of opt-out consent for secondary use of digital patient data. A questionnaire was distributed to patients in multiple languages and with an interpreter. Of 919 completed surveys, 33% were of non-English speaking background, 15% self-reported cognitive impairment and 3% were refugees. Opt-out consent was accepted in this diverse population; 87% of participants approved, or were indifferent to opt-out consent. Gender, employment and cognition status were not significant determinants of acceptability.

‘Big data’ has had a significant impact in a variety of disciplines, such as transportation,1 economics and politics.2 Healthcare has been slow to leverage the growth of ‘big data’, such as patient information routinely collected through digitalised medical records.3 Secondary use of routinely collected electronic medical record (EMR) data could improve sample size, study efficiency, data quality and reduce selection bias in clinical research, which is often limited by traditional opt-in consent processes.4 For example, despite representing more than 28% of the Australian population,5 foreign-born and ‘vulnerable’ populations,6 such as those of non-English speaking background (NESB), refugees and the cognitively impaired, are often excluded from research investigations.7 This may limit generalisability of results as these subpopulations vary in several health domains.8 The potential benefits of ‘opt-out’ consent have been recognised and included in the Australian National Health and Medical Research Council (NHMRC) statement on conduct in human research (2007)9 as an acceptable alternative if representative sampling is desired.

An opt-out consent approach has been utilised by several national and global registries to improve generalisability of research,10 and small studies have shown opt-out is acceptable with benefits readily apparent to participants.11,12 In this study, we investigated the acceptability of opt-out consent in a large cohort of patients characterised by high ethnic and socioeconomic diversity.

This multi-centre study was performed on inpatients and outpatients of Monash Health (MH) and approved by the Monash Health Human Research Ethics Committee. MH is the second-largest healthcare network in Australia and services a large and ethnically diverse population.

Patients admitted between April and June 2016 were invited to complete an 18-item questionnaire to measure their understanding of, and attitude towards, implementation of opt-out consent for the collection of de-identified data for research. Trained research assistants were present to answer questions or assist in questionnaire completion if requested. The survey was available in the five most common languages spoken in Australia other than English (simplified Chinese, Italian, Vietnamese, Greek and Arabic) and an interpreter was provided for subjects who did not speak one of the aforementioned languages or were illiterate in their primary language.

A study was performed in 75 patients to evaluate understanding of the survey aims, wording and questions skipped. Feedback from this process was utilised in the construction of the final questionnaire which collected demographic data, presence of cognitive impairment, and prior research experience (Supporting Information Appendix SI). Level of education and employment status were compared to age-matched, national census data. Participants were asked to respond on a 5-point Likert scale to questions regarding their attitude towards participating in research activities, the
acceptability of an opt-out approach, their preferred consent method, and methods of indicating their withdrawal of consent. An explanation of the proposed use of de-identified clinical data for research and key terms was described in a cover letter.

Analysis was performed using IBM SPSS Grad Pack version 24.0 (Chicago, IL, USA). Ordinal data were summarised as absolute numbers and frequencies. Fisher exact text and ordinal logistic regression were used to compare patient characteristics and acceptability of opt-out consent. A two-tailed $P$-value $\leq 0.05$ was regarded as statistically significant.

Of the 1013 patients approached, 94 declined to participate, with a response rate of 91%. The baseline characteristics of the 919 participants are summarised in Table 1. A total of 303 (33%) patients listed English as a non-preferred language, with 98 (11%) of patients unable to communicate in English. Twenty-five (3%) participants were refugees and spoke a language other than those supplied (‘Other’). The study population had a lower level of education compared to age-matched population rates, with only 473 (51%) completing a post-secondary school qualification, compared to a population rate of 67% ($P < 0.001$). The prevalence of self-reported cognitive impairment in the study population was 15% ($n = 137$), which was significantly higher than expected age-matched prevalence rates of 5% ($P < 0.001$).

A total of 813 (88%) patients approved of or were indifferent to their medical data being collected for treatment purposes, a frequency almost identical to the 810 (88%) that approved of, or were indifferent to having the same information re-used for research purposes. A total of 421 (46%) patients assumed their medical data was already being used for research in the absence of explicit consent.

When asked about their level of support for a proposed opt-out consent model, 800 (87%) approved or were indifferent (Fig. 1). Refugees, those who were illiterate and those with prior research experience demonstrated greatest support for an opt-out model (Table 2).

When asked to nominate a preferred consent model, 494 (54%) chose an ‘opt-out’ approach as their consent method of choice, whilst 172 (19%) had no preference and 253 (28%) chose the traditional ‘opt-in’. There was no significant effect of gender, age, employment status or cognitive status on the preferred consent method.

Patients of a NESB were significantly more likely to favour an opt-out model compared to English speaking participants (64%, 95% confidence interval (CI) 56–72% vs 52%, 95% CI 48–55%; $P < 0.01$). Among NESB participants, the greatest support for an opt-out model came from those who were illiterate in their primary language (92%) and refugees (93%).

When asked about the preferred method of communicating withdrawal of consent, 431 (40%) of participants preferred a telephone voicemail message, whilst 330 (30%) favoured email correspondence.

### Discussion

Translational research requires large amounts of high quality data to generate results generalisable to healthcare practice. Strategies to improve recruitment of
patients into studies are continually being sought. The EMR creates opportunities for large scale clinical research that existing opt-in consent methods render infeasible. The clinical utility of translational research requires that research data be as representative as possible of the cohort in which the research outcome will be applied. A recent Cochrane review has suggested opt-out consent as a potential technique to improve patient numbers in research studies. Here, we investigated the acceptability of opt-out consent by studying patients of a large health service to examine the contribution of demographic, ethnic, and socioeconomic factors to this question.

The high survey completion rate (91%) is consistent with the idea that patients recognise the benefits of medical research and are keen to engage with the research community as reported by Moorcraft et al. A key finding of our study was that almost half the participants assumed their medical data were already being used for research purposes without prior consent, a finding which supports previous smaller studies. In a study by Kaufman et al., 451 veterans were surveyed to assess their acceptability of an opt-out database. However, whilst an opt-out model was supported by most veterans, the level of support expressed by our participants was significantly higher.

A key strength of this study is the sample size, which is the largest reported in this field, and the diversity and potential generalisability of its sample population. Thirty-three percent of participants in this study were of European descent, higher than that of the Moorcraft (n = 276) and Kaufman (n = 451) studies (14% and 20% respectively). More than half the participants preferred an opt-out approach compared to the conventional opt-in method and support for an opt-out model was comparable between different age groups, genders, employment status and cognitive ability. Participants with prior research involvement were more likely to support an opt-out approach which may reflect positive past experiences with research.

Given the possibility that opt-out consent may undermine patient autonomy, particularly in those with cognitive impairment or do not speak English, every effort was made to ensure these communities were studied. These subpopulations are often overlooked in medical research due to perceptions regarding consent and yet their inclusion in medical research datasets may improve not only the generalisability of research findings, but also potentially unveil important research issues within these subgroups. That opt-out consent for low-risk medical research is supported by these complex and vulnerable populations represents a novel research finding.

This was paralleled by support in those who were illiterate, a cohort which has not been explored in previous studies. These findings are in contrast to the findings in a much smaller study of Woodward-Kron et al., who analysed attitudes towards medical research in 21 older Italian-Australians and found ‘few indicated willingness to participate in medical research’. This study has several limitations. Possible response bias, with those completing the survey demonstrating a willingness to participate in research, cannot be excluded; however, a completion rate of 91% suggests this may be minor. We cannot exclude higher levels of support from NESB populations and refugees is due to a perception by the respondent of linkage to care. The investigators made all attempts to minimise this bias, with those completing the survey demonstrating a willingness to participate in research, cannot be excluded; however, a completion rate of 91% suggests this may be minor. We cannot exclude higher levels of support from NESB populations and refugees is due to a perception by the respondent of linkage to care. The investigators made all attempts to minimise this bias.

Opt-out consent has high acceptability and is the preferred consent methodology among a diverse hospital patient population. Subpopulations traditionally considered as ‘vulnerable’ in research were the strongest...
supporters of opt-out consent. Opt-out consent should be further explored as a potential mechanism to redress current inequalities in patient recruitment for clinical research and the generalisability of evidence based care.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher’s web-site:

Appendix S1. Acceptability of opt-out consent questionnaire.
Southcare Geriatric Flying Squad: an innovative Australian model providing acute care in residential aged care facilities
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Key words
residential aged care facilities, Geriatric Flying Squad, hospitalisation, nurse practitioner, emergency avoidance.

Abstract
This study reviews the outcomes of a model developed to improve the quality of care of residents living within residential aged care facilities (RACF). The Southcare Geriatric Flying Squad saw a total of 640 acutely unwell RACF residents over an 18-month period. Of these, 578 (90.3%) were managed in the RACF avoiding emergency department. Only 35 (5.5%) patients required emergency department transfer and 27 (4.2%) were directly admitted to a medical ward. The service may have reduced emergency presentations by offering rapid assessment and management, choice in place of treatment and level of interventions.

Frail older persons living in residential aged care facilities (RACF) are vulnerable to frequent episodes of acute deterioration with transfer to emergency department (ED) often the default procedure. In general, frail older people admitted to hospital from RACF may be better cared for in the facility itself and improved patient outcomes have been demonstrated when they are treated in their own environment by reducing complications, such as delirium, falls and infections. Studies have shown that up to 1 in 2 emergency presentations from RACF are avoidable and can be safely managed in the facility. Reducing avoidable admissions has an impact on reducing hospital burden and healthcare-related expenditure. Access to intravenous therapy and rapid laboratory results within the RACF reduces avoidable admissions. Other potential solutions include education of RACF nursing staff to improve skills, better communication with general practitioners (GP), improved advance care planning and palliative care services in RACF. The Geriatric Flying Squad (GFS) model has been developed to address these key factors.

The GFS is a rapid response outreach service of Southcare, Aged and Extended Care, a division of The Sutherland Hospital and Community Health Service located in the Sydney South metropolitan area. The GFS service started in November 2011 with a geriatrician as the only service provider. The GFS currently comprises a team of geriatrician, nurse practitioners/nurse practitioner candidates and clinical nurse consultant providing a 7-day service.

Referral to GFS can be made for residents living in RACF with an acute deterioration in condition, where emergency hospital transfer is being considered (Fig. 1). Referrals can be made by GP, geriatricians or RACF-registered nurse after obtaining GP consent.

The GFS team provides a comprehensive assessment within 2–4 h of referral. Diagnostic testing and management is provided in the RACF with close follow-up and monitoring until the acute episode is resolved. Facilitated direct admission either to public or private hospital is arranged if deemed necessary.

Exclusion criteria for GFS include conditions requiring urgent investigations or if the patient is critically unwell and cannot wait 2–4 h, for example shock, suspected cardiac chest pain, neurological events including stroke or seizures and an acute bleeding episode. Also excluded are major injuries or suspected fracture post-fall and surgical conditions, such as an acute abdomen, needing urgent imaging and surgical consultation. In the event that the patient or family do not want hospital transfer and wishes for a palliative approach to care, they may be referred to the service for symptom management regardless of the GFS exclusion criteria.

There were 21 RACF in the catchment area at commencement of the service in 2011. The number had increased to 26 by the study period (1 April 2015 to 30 September 2016). The service was promoted through multiple visits to all RACF and presentations to GP meetings to raise awareness and clarify the service referral
process. All RACF in the area utilised the service during the study period.

Portable equipment was purchased over time to enable the GFS team to perform point-of-care testing, including blood pathology lab, bladder scanner and electrocardiograph machine. Subcutaneous drug delivery pumps/syringe drivers were used for palliative care. The GFS team utilised private pathology home collection services as well as mobile x-ray service for additional investigations.

Data collection was undertaken for the patients referred to GFS, including: mean age, name of referring RACF, reason for referral, service response time, diagnosis, interventions and length of stay, for that acute episode. The patients who required emergency transfer or facilitated hospital admission after GFS review were recorded.

Data were retrospectively analysed from 1 April 2015 to 30 September 2016 inclusive. This period was selected as GFS offered a 7-day extended hour service and was well established by this time. The referrals not seen by GFS after phone triage were also recorded from 1 July 2015 to 31 October 2015.

The data collection was exempted from Human Research Ethics Committee review as it was meeting the criteria for a quality activity/programme evaluation.

Over the 18-month period, GFS saw 640 patients, of which 578 (90.3%) were managed at the RACF and did not require emergency transfer for that acute episode. Without GFS involvement, all of these patients would have been sent to ED.

Only 35 (5.5%) of patients required transfer to ED (Fig. 2) after being seen by GFS. For the other 27 (4.2%) GFS facilitated direct admission to a medical ward at either the public or private hospital depending upon bed availability, the patient’s level of insurance cover and the patient or family’s preferences. Terminal palliative care

Figure 1 Geriatric Flying Squad (GFS) referral flowchart.

Figure 2 Geriatric Flying Squad (GFS) referral outcomes from 1 April 2015 to 30 September 2016. RACF, residential aged care facilities.
was provided to 116 (18%) patients. The median number of days patients stayed on the service was 4 days (range 1–22 days).

The mean age was 86 years with a female preponderance (male 257; female 383). The five most common reasons for referral were respiratory symptoms, delirium, sepsis, dehydration and acute symptom management in a palliative/terminal care setting. The median response time was 103 min from the time of referral (range 5–390 min). The GFS nurse attended the initial assessment in 67% (n = 429) of cases with the majority of these assessments occurring on the weekend in consultation with the public hospital on-call geriatrician. Where the GFS nurse attended the initial assessment, a follow-up review by the GFS geriatrician was provided in 40% of cases (n = 172). The geriatrician did not review the remaining 60% patients as they had either improved significantly or died.

The interventions provided included intravenous fluids and antibiotics (25%, n = 160), subcutaneous fluids (32%, n = 203), oral antibiotics, analgesia, medication review, catheter/device care and palliative symptom management. Most patients required multiple interventions simultaneously. The GFS team managed insertion and maintenance of intravenous cannulae. All intravenous drugs, fluids and equipment/consumables were obtained from the local public hospital.

The treatment provided in the RACF was well tolerated with less than 1% intervention-related complications, such as local swelling, erythema infusion site or skin rash post-intravenous antibiotic administration. No patients required transfer to hospital for treatment-related complications.

An additional 77 referrals were declined during 1 July 2015 to 31 October 2015 (Table 1). The GFS reviewed 13 of the 77 patients within 2 weeks of initially declining the referral. The reasons for review included abnormalities on investigations done by the GP or ongoing concerns from the nursing staff or GP.

**Discussion**

There are several models of care nationally and internationally, which aim to reduce hospitalisation for older adults or focus on their early discharge from hospital. Most of the models have a clinical nurse consultant or nurse practitioner as the team leader and focus on chronic issues of community dwelling older adults. The GFS is led by a geriatrician and focuses on improving quality of acute care of patients in RACF. These patients are extremely frail with significant multi-morbidities requiring repeated hospitalisations and are especially prone to hospital-acquired complications. This indicates significant cohort benefits from interventions aimed at managing their acute problems in the RACF avoiding hospital transfer where possible. A service led by a specialist geriatrician, who is trained in acute geriatric medicine, is an effective way to deliver this model of care and may reduce hospital presentations.

Multiple factors impact on decisions to transfer patients from RACF to hospital. Shortage of skilled registered nurses, poor advance care planning, GP availability and preferences for treatment and inability of nursing staff to recognise early signs of deterioration are among the factors that influence decisions. The GFS aims to address these factors by providing rapid assessment and management plan within and after hours, ongoing education to nursing staff and engaging families and RACF in advance care planning.

Studies suggest that 25–46% of RACF residents present to hospital frequently in the last 6–12 months of their life. Almost 50% of these hospitalisations are

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**Table 1 Referrals initially declined by GFS and their outcomes**

<table>
<thead>
<tr>
<th>Number of referrals not seen</th>
<th>Reasons for not seeing referred residents</th>
<th>Advised action plan</th>
<th>Sent to hospital post-GFS referral</th>
<th>Seen by GFS within 14 days of initial referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>Sub-acute or chronic problem and does not require urgent review</td>
<td>Refer to usual GP or after hours</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>20</td>
<td>Palliative care plan already in place</td>
<td>Refer to GP</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Follow-up requested post-ED presentation</td>
<td>Refer to GP as management plan already in place from ED</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Too acutely unwell – need hospital-based management</td>
<td>Transfer resident to emergency/direct admission</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>GP unable to source medications/ consumables required to manage patient at RACF</td>
<td>Medication/consumables supplied by GFS allowing GP to continue management</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ED, emergency department; GFS, Geriatric Flying Squad; GP, general practitioners; RACF, residential aged care facilities.
potentially avoidable.11 Of all the patients seen by the GFS, 18% received palliative care either after a trial of treatment or as the first line management following an acute deterioration. This reduced unnecessary transfer of these patients to hospital for terminal care and enabled them to stay in familiar surroundings during their last days of life.

Limitations of this study include the lack of a control group as it is unknown whether the patients that were managed in the RACF would have had different outcomes in the hospital setting. The regional focus of the study in an area with a high Caucasian (90%) population12 may impact on the transferability of the model to other culturally diverse or rural populations. This study only captured data related to a geriatrician-led model and whether a similar model led by nurse practitioner or GP would achieve comparable outcomes could be a focus for further study.

In summary, the study found that the service may have diverted emergency presentations for 90.3% of the referred acutely unwell patients by offering rapid assessment and management, choice in place of treatment and level of interventions.

Key factors impacting on service uptake and utilisation included establishing relationships with all stakeholders (patient/family/RACF/GP/hospital), effective communication, flexible/individualised patient management plans and availability of point-of-care equipment and consumables. This model of care can be successfully transferred to other area health networks with comparable outcomes if these key factors are addressed.

References

PERSONAL VIEWPOINT

Looking to tomorrow’s healthcare today: a participatory health perspective
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Key words
health system, patient participation, health reform, M (mobile) health, telehealth.

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Abstract
Health systems around the world face the issue of financial and workforce sustainability. Mobile health technologies – those devices which connect health professionals, patients, payers and the many other contributors who make up the health system offer some solutions – not just as ‘add ons’ but as enablers of real system change. This paper presents a vision for what the health system of the future could be like and emphasises the opportunities for real patient participation in clinical decision-making if the professions can engage the technologies and patients/community in a meaningful way. Predicting the future is never easy but many of the technologies are here now – but how we will use them to make the system more patient friendly, more productive and sustainable is still for discussion. This paper should start that conversation.

Introduction
In a recent issue of the Internal Medicine Journal O’Shea et al.1 provide a review of the different modalities of mobile health and their uses. The authors primarily discuss the opportunities for these technologies to improve connectivity between health professionals and patients whether it be for virtual consultations, delivery of educational messages, personal prompts or for remote monitoring. Use of mobile technologies is clearly a significant step forward in improving communications with patients and enhancing convenience. However, an exciting opportunity exists to take a step back and reimagine how the health system could be, rather than how it currently is.

We suggest that mobile health could mean much more and that we need to look more broadly at this new virtual health world. This means not just incremental additions to the current system but exploring how we might use technologies to raise the health system to another level – to one that really does engage patients and health professionals in a more seamless way.

The quandary facing healthcare is hardly a surprise. The perfect storm of factors that combine to make healthcare unaffordable and unsustainable are all well-known and mostly well understood.2 Economic, epidemiologic and demographic shifts mean that ‘more of the same’ fails to deal with the many difficult problems facing 21st century healthcare.3 Rising costs, consumer expectations, new technologies and increasing globalisation place intense pressure on the health sector to align better with economic constraints. Long-established systems of primary, secondary and tertiary care are increasingly unsuited to deliver responses to challenges arising from ageing populations and as the burden of disease shifts to chronic conditions, such as diabetes, musculoskeletal disease and cardiovascular disease.4 What is more, how care is organised and delivered is being re-shaped by changes in the broader environment, including innovative technologies, social networks and a cultural shift towards sharing and participation.

To balance access, quality and equity alongside economic considerations, contemporary thinking in health policy targets three essential shifts from volume to value,5 greater patient engagement,6 and a shift in the organisational structures of delivery.7 Many reforms focus on the supply-side of healthcare, such as performance and payment, few consider demand-side disruption.

We have developed a forward view of an aspect of healthcare, Health reimagined: a new participatory health paradigm.8 In this, we explore the potential for an engaged consumer to re-shape healthcare. Our vision is an idea about a possible future and an exploration of

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something that we consider inevitable. Intended to be challenging, we hope to stimulate a conversation as to how to facilitate ‘big’ and most likely disruptive solutions in healthcare. An expanding and participatory health ecosystem is envisioned, one based around the individual. In this, the consumer acts as an active participant in their own digital health ecosystem or ‘digisphere’. The ‘digisphere’ as a complex, borderless, interconnected community (virtual as well as real) that forms around an individual and advances lifelong health. We hypothesise that a participatory ecosystem, shared decision-making, patient activation, patient-centred and consumer-directed care. Increasing engagement has long been part of the health industry’s rhetoric but participatory health is more than just better patient inclusion and a transformed patient–provider relationship – both are foundational to any respectful interactions. Participatory health is reflective of a deep and profound shift in perspective towards wellbeing and wellness, convenience, flexibility, self-direction and personalised experiences. This goes beyond ‘sick care’ to ‘healthfulness’ inspiring, encouraging and teaching individuals to make positive care and lifestyle choices and be engaged in and accountable for lifelong health.

This shift posits a very different perspective of healthcare, where the patient becomes the central focus. It is one where the person navigates their health and care as an equal partner, or at least a better partner, with their health professional, to the extent that they wish to be involved. We note Gawande’s observation that the exercise of autonomy means being able to relinquish it. Participation in shared decision-making is defined as a process by which both patient and healthcare professional make a joint decision, considering the best evidence of available options and the patient’s values and preferences. The Society for Participatory Medicine describes this interaction as a cooperative and active relationship between ‘patients, professionals, caregivers and others along the continuum of care on all issues related to an individual’s health’. Advocate and cancer survivor Dave deBronkart or ‘e-patient Dave’ considers that best practice care is a combination of a professional’s essential clinical knowledge and experience with a patient’s life experience and intimate knowledge of their own needs.

### Why this is important

Digital and personal health technologies are the bridge between the pre-internet world to that of e-patients. These opened doors to information and avenues for collaboration and partnerships that were previously not possible. Smartphones, digital health technologies and devices, big data and analytics, and personal support from peer and social networks are the tools of engagement that drive and support participatory health. Three enablers will redefine how individuals manage their health and engage with care systems (Fig. 1).

- **Social 2.0** – Interactive and dynamically changing web-based platforms support social networks that link consumers to others and rich information resources on health and lifestyle. A future challenge will be to deliver evidence-based information that consumers can curate and critically evaluate.
- **Technology** – Consumer-grade personal technologies are fundamental to participatory health. Wearables, devices, sensors and apps with functionalities ranging from supporting health and fitness to clinical condition management are growing rapidly. The extent to which these function as digital therapeutics to deliver clinical impact, enhance the patient–provider relationship, and address payment, ethical and privacy issues, will determine how quickly these technologies influence or shape the health system.
- **Maturing consumerism** – Individuals increasingly adopt health technologies and seek better outcomes, value, connectivity and the tools for self-direction. Unlike other industries, healthcare has not taken full advantage of the digital revolution. Health literacy or being able to understand information well enough to make informed decisions is foundational to healthcare consumerism.

We think of the new ecosystem as a ‘digisphere’ (Fig. 2). A functional ‘digisphere’ requires a participatory patient–provider relationship and a personal health cloud anchored around and controlled by the individual. In a ‘digisphere’:

- **Individuals**
  - Actively manage lifelong health and wellness and curate health experiences through their personal health cloud. This is a network of connected personal devices that capture and share personal health data in addition to the integrated electronic health record.
• Share experiences, peer-to-peer and motivational information through social networking channels
• For many, the relationship between the individual and health professional shifts to that of partners or co-producers, with professionals acting as expert advisors. Others will seek a more traditional relationship

**Services**

• Clinical decision-making algorithms, artificial intelligence (AI) diagnostics, case management and care delivery pathways systematise systems and processes efficiently and effectively
• New entrants (telecommunications and technology companies, retailers and entrepreneurs) remake clinical delivery systems, population health management, back-end operations, business models and consumer engagement
• Existing players, such as life-sciences businesses and insurers seek to align better with the end-consumer developing new social partnerships and mining customer insights

**Systems**

• Building blocks include navigation (to deliver the right care at the right time to the right person at the right price), curation (of personalised care and personal data) and integration (AI and analytics turn complex information into usable insights and new solutions)
Privacy and security of personal health information
A digital backbone underpins and shapes an intelligent healthcare system

The way that we interact with the world is altering and participatory health echoes complex social changes towards sharing and participation. In parallel, health systems must respond to changing epidemiologic and demographic trends. Challenges also arise to progress health systems towards a sustainable footing, improved competitiveness, productivity and quality. We contend that shifts in the design, delivery and financing of healthcare and to the consumer experience necessary to deliver participatory health are long overdue. We continue to seek to understand the changes necessary to embed participatory health and the digisphere within the core business of healthcare.

As indicated, our hope is to stimulate a conversation around the disruptive potential of an engaged consumer. At best, we think that participatory health can re-shape the demand for healthcare by giving people the right tools to manage their health and lifestyle choices with better care models, manage chronic conditions in vastly different ways and ultimately drive a healthier population through prevention and wellness. At a minimum, we think that participatory health will go some way towards engaging individuals on their terms. Helping people to help themselves strengthens an individual’s capacity to self-manage, make smarter choices and moderate health consumption and expectations. The challenge will be to ensure some degree of equity as this transition occurs.

O’Shea and colleagues have shown us what might be available – but the important question is surely –
will we use this knowledge really to challenge the way we do things – and use this to create a new health system? One that is ‘fit for purpose’ and somewhat more sustaining. The opportunity exists to look at new directions in healthcare, bringing together ALL the partners in the complex system and developing a new approach. The digital revolution in healthcare described by Topol\textsuperscript{15} and the promise of connected health\textsuperscript{16} offer untold opportunities to deliver care and connect with consumers in unique ways. Our view of a ‘digisphere’ is not just following the latest fashion for all things digital. Rather, it is a recognition the core business of healthcare will ultimately be transformed as technologies mature and disruptive solutions succeed. These demand new ways of thinking and inspired business models to foster innovation and shift from legacy ways of delivering and paying for care.

References
LETTERS TO THE EDITOR

Clinical-scientific notes

Localisation of occult extra-pancreatic insulinoma using glucagon-like peptide-1 receptor molecular imaging

We report a case of an occult insulinoma and the use of glucagon-like peptide-1 (GLP1) receptor molecular imaging for tumour localisation.

A 64-year-old woman with type 2 diabetes mellitus presented to emergency with frequent symptomatic hypoglycaemia. Her local doctor had previously advised cessation of metformin monotherapy and home blood glucose level (BGL) monitoring in the context of hypoglycaemia and improved glycaemic control (HbA1c 5.4%) despite 20 kg weight gain. However, she recommenced monitoring due to transient impaired conscious state and noted hypoglycaemia (1.7 mmol/L) prompting this admission.

On examination the patient was obese (132 kg) with central adiposity (body mass index (BMI) 52 kg/m²), Glasgow Coma Score 15 and BGL 9.4 mmol/L. She became diaphoretic and anxious 5 h after presentation. Investigations confirmed hypoglycaemia (2.0 mmol/L) concurrent with inappropriately elevated insulin (46 mIU/L), pro-insulin (99.9 pmol/L, reference range (RR) <13.3) and c-peptide (2.54 nmol/L, RR 0.30–2.30) with a suppressed β-hydroxybutyrate (0.3 mmol/L, RR <0.5), negative insulin antibodies and a negative sulfonylurea screen consistent with insulinoma. HbA1c was 4.4%, other biochemistry were normal.

Contrast-enhanced abdominal computed tomography (CT) demonstrated a normal pancreas with a 1-cm splenic hilum nodule consistent with a splenunculus. The patient’s abdominal girth precluded further investigation with magnetic resonance imaging (MRI). 68Ga-exendin-4 positron emission tomography (PET)/CT clearly identified a solitary insulinoma at the site of the reported splenunculus (Fig. 1). The patient underwent laparoscopic resection and histology revealed a 15×10×10 mm neuroendocrine tumour abutting the pancreatic margin. Immunohistochemistry stained positive for synaptophysin, chromogranin, insulin and Ki-67 proliferation index was <1%. Postoperative hyperglycaemia (15 mmol/L) was managed with metformin 2 g plus gliclazide MR 60 mg daily.

Hypoglycaemia due to insulinoma in patients with diabetes is rare.1 The majority of insulinomas are solitary and intra-pancreatic (<1%) are ectopic and <10% are malignant or multifocal.2 Surgical resection is required for cure and preoperative localisation is preferable, but limited by small tumour size. Reported accuracy varies widely, but a contemporary study3 demonstrates sensitivity of abdominal CT (64%) and MRI (75%). Endoscopic ultrasound (65%) and intra-arterial calcium stimulation testing (IACST, 63%) are highly operator dependent and the latter particularly invasive. Extra-pancreatic location and typical enhancement pattern of the apparent ‘splenunculus’ in this case confounds localisation by conventional imaging and IACST likely would have been misleading. Notably a similar insulinoma masquerading as a splenunculus was identified post-mortem in a patient who died despite multiple localisation attempts by conventional imaging, venous sampling and repeat laparotomy.4

Sensitivity of somatostatin receptor (SSTR) imaging is limited by SSTR type 2 expression in 69% of insulinomas. However, dense GLP1 receptor expression is present in nearly all insulinomas5 and rapidly emerging experience with 68Ga-exendin-4 PET/CT demonstrates confident localisation of up to 97.7% insulinomas.6 GLP1 negative cases are typically avid on SSTR imaging.5,6 Halo reconstruction artefact (i.e. suppression of background activity adjacent to regions of intense uptake) is a known limitation of PET ‘scatter correction’ algorithms.

Figure 1 Contrast-enhanced computed tomography (CT) (A) demonstrates typical enhancing appearance of apparent ‘splenunculus’ (arrow), subsequently clearly characterised as extra-pancreatic insulinoma with focal intense uptake on fused 68Ga-exendin-4 positron emission tomography (PET/CT) (B) and PET maximum intensity projection (C). Note reduced background tracer uptake adjacent to intensely avid kidneys due to ‘halo’ reconstruction artefact.
Whilst this may theoretically limit detection of small lesions in the pancreatic tail, it does not appear to have reduced the high sensitivity of $^{68}$Ga-exendin-4 PET/CT in this case or published trials. Recently updated scatter correction protocols have reduced this problem, but if observed it can be resolved through re-processing PET data without use of ‘scatter correction’.

In our patient initially reported to have a normal pancreas on CT, $^{68}$Ga-exendin-4 PET/CT effectively localised an insulinoma at the splenic hilum enabling a curative laparoscopic resection. This case highlights the role of functional imaging with $^{68}$Ga-exendin-4 PET/CT for preoperative insulinoma localisation.

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Delayed-onset heparin-induced thrombocytopenia complicated by arterial and venous thromboses

Heparin-induced thrombocytopenia (HIT) is an immune mediated adverse reaction caused by platelet-activating immunoglobulin G (IgG) antibodies reacting against platelet factor 4 (PF4) bound to heparin. A more recently recognised atypical form, delayed-onset HIT, is due to high titre PF4/heparin antibodies which activate platelets even in the absence of heparin and cause thrombocytopenia and thrombosis weeks after heparin cessation.

A 73-year-old female was diagnosed with delayed-onset HIT 24-h after admission to our facility critically unwell with bilateral pulmonary emboli (PE). She was initially treated with tenecteplase followed by intravenous unfractionated heparin (IV UFH). Her platelet count prior to thrombolysis was $70 \times 10^9/L$. A haematological consultation suggested the diagnosis of HIT syndrome, prompting her heparin infusion to be replaced with danaparoid. A screening test for antibodies to heparin/PF4 was positive. Over the next 4 days her platelet count fell to a nadir of $25 \times 10^9/L$ before gradually normalising over 2 weeks after heparin cessation. Her slow platelet count recovery caused the diagnosis of HIT to be questioned, but alternative diagnoses were excluded and serologic evidence of persisting high levels of antibodies supported the diagnosis of HIT. A functional whole blood impedance aggregometry assay was subsequently performed. Platelet aggregation occurred in the presence of low dose (0.5 IU/mL) heparin, but was abolished with high dose (100 IU/mL) thus demonstrating the platelet activating nature of the anti-PF4/heparin antibodies and confirming the diagnosis of HIT. After 7 days of danaparoid therapy and confirmation of the diagnosis of HIT she was changed to rivaroxaban.

She had three hospital admissions in the 2 months prior to presentation with PE and eventual HIT diagnosis. The first, a 5-day hospitalisation due to small-bowel obstruction, featured a normal platelet count while receiving daily enoxaparin as thromboprophylaxis. Five weeks later, she had a 2-day admission for elective shoulder replacement at which time she had a normal
platelet count and received no thromboprophylaxis. One week after her orthopaedic surgery and 6 weeks after enoxaparin therapy she re-presented with an inferior ST-elevation myocardial infarction. Despite being thrombocytopenic on presentation with platelets of $76 \times 10^9$/L she was treated with tenecteplase and enoxaparin. Twenty-four hours later, coronary angioplasty was performed with accompanying IV UFH. Following this, progressive thrombocytopenia developed with a nadir platelet count of $41 \times 10^9$/L. A positive immunoassay for heparin antibodies was considered a false positive for HIT both due to the late development of thrombocytopenia after heparin exposure and the stabilisation of her platelet count at $70 \times 10^9$/L despite ongoing enoxaparin. At the time of discharge her platelet count was $70 \times 10^9$/L and it was unchanged when she was readmitted with extensive bilateral PE 1 day later. Figure 1 shows the patient’s platelet counts and key clinical events during her four hospitalisations.

Most patients with HIT develop thrombocytopenia within 5–14 days after commencing heparin and it is typically of moderate severity with median platelet counts at the time of diagnosis being $50–80 \times 10^9$/L. The platelet count usually continues to fall if heparin administration is continued although severe thrombocytopenia ($<20 \times 10^9$/L) is unusual.

Delayed-onset HIT is a potentially fatal immune-mediated disorder that characteristically begins several days to weeks after heparin has been discontinued. Many patients with delayed-onset HIT have been exposed to heparin during an initial period of hospitalisation and only develop HIT after hospital discharge. On readmission, they are found to have thrombocytopenia in association with thrombosis. The diagnosis of HIT may not be immediately considered in the absence of ongoing heparin exposure which may result in continued heparin exposure with potentially fatal consequences.
Letters to the Editor

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Intra-abdominal sepsis following a Papanicolaou test

A previously well 28-year old woman presented to the emergency department with abdominal pain, nausea, vomiting, diarrhoea and fever for 48 h. Her symptoms developed 5 h after an otherwise uncomplicated screening Papanicolaou (Pap) test. The initial assessment revealed fever, tachypnoea, tachycardia and hypotension. She had a tender abdomen, but an otherwise unremarkable pelvic examination with no intrauterine device or tampon in situ. She had a single long-term male sexual partner and her only medication was the oral contraceptive pill.

Abnormal investigations included a venous lactate of 8.4 mmol/L, creatinine of 126 μmol/L and C-reactive protein of 613 μg/mL. A contrast-enhanced abdominal computed tomography (CT) scan demonstrated a large volume of intraperitoneal free fluid with thickening and enhancement of the peritoneum, thickening of the wall of the rectum and sigmoid colon and no free gas. The radiologist favoured a diagnosis of pelvic inflammatory disease causing peritonitis and reactive colitis.

She was admitted to the intensive care unit and treated empirically with piperacillin–tazobactam and azithromycin. Diagnostic laparoscopy found purulent peritonitis thought to be arising from the pelvis. There was no appendicitis. The uterus, fallopian tubes and ovaries appeared inflamed, but there was no abscess. An operative peritoneal sample yielded group A streptococcus (GAS) only. A flexible sigmoidoscopy revealed no gross colitis and biopsies were normal on histopathological examination and negative on molecular testing for cytomegalovirus. Multiple blood cultures drawn prior to and after antibiotic administration as well as testing for chlamydia, gonorrhoea, syphilis and HIV were negative and a vaginal swab grew normal flora only.

After an initial clinical improvement she developed an ileus and signs of ongoing sepsis and a repeat CT on day 10 showed enhancing, loculated presacral fluid that was drained percutaneously with improvement of her symptoms. The fluid was culture-negative and she made slow clinical improvement over the following weeks and was discharged home on day 36.

We hypothesise that this patient developed bacterial peritonitis secondary to pelvic inflammation caused by the Pap test. To our knowledge this is the first reported case. Two cases of endocarditis and one of septic arthritis have previously been reported in association with Pap testing, all involving Group B streptococci.1–3

GAS is known to colonise vaginal mucosa and may cause a diverse spectrum of clinical disease, including peritonitis.4 The clinician who performed the Pap test reported grossly normal vaginal and cervical epithelium with no clinical lesions and the smear was negative for abnormal cells. As with any procedure, there is a risk of translocation of potentially pathogenic bacteria and, as we were unable to find an alternative explanation, we hypothesise that this was the mechanism by which she developed invasive GAS infection.

Pap testing is generally a very safe procedure and does not require antibiotic prophylaxis.5 Nevertheless, clinicians should take a history of prior procedures when assessing patients with sepsis and remind patients of the possibility of infection inherent in any medical procedure.
An increasing incidence of syphilis among young women in Japan

Syphilis is caused by infection with Treponema pallidum subsp. pallidum, and it remains an important public health problem commonly seen in low-income and middle-income countries. However, the rates have begun to increase dramatically in Western Europe and the USA, especially among men who have sex with men. Although Japan has also an increasing incidence of syphilis in recent years, the rates are also getting higher not only among men but also among young women.1

In the past few decades, the number of syphilis cases reported to the government peaked at 2928 in 1988, and had decreased to 509 (males, 388; females, 121) in 2003. However, the number has turned to rise until today, as high as 4559 (males, 3174; females, 1385) in 2016.2 The underlying causes are still unclear but some possible reasons include changes of sexual behaviour and engagement in prostitution due to increasing poverty and unemployment rates among younger generations, alterations of business styles, such as adoption of oral sex in the commercial sex industry. Unfortunately, sexually transmitted diseases (STD) among at risk and vulnerable Japanese population remain a neglected field for public health intervention as well as for research, and no reliable statistical data are available to reveal the underlying causes.

To counter the current trend of increasing incidence of syphilis, we would like to raise several issues to be considered. First, although uncomplicated syphilis is curable with standard therapy using a single dose of intramuscular benzathine penicillin G injection, the drug has not been available in Japan, because of the market withdrawal after a fatal anaphylactic shock accident in the past. The drug is as important as included in the World Health Organization Model Lists of Essential Medicines.3 It should be reintroduced into the Japanese market as early as possible, as alternative drugs that require multiple visits often lead to poor adherence of patients. Second, the Japanese government has been squeamish about sex education, and it has been criticised that the government creates a vacuum of useful information about sex and STD, resulting in unreliable media as the only source of such information for young generations.4 More medically underpinned information and open discussion should be offered for adolescents to prevent a further increase of STD, including syphilis.

Last but not least, now is the right time for the Japanese health authorities and medical professionals to engage in more effective research and control measures for STD because the Japanese government promotes to increase foreign visitors towards the 2020 Tokyo Olympic Games. Japan should learn from a few countries that have specialised national programmes for prevention and control of syphilis; in the USA, the Centers for Disease Control and Prevention launched the Syphilis Elimination Effort with the release in 1999 of the National Plan to Eliminate Syphilis from the United States; the Chinese Government also officially launched the National Program for Prevention and Control of Syphilis in China (2010–2020).5 In the highly connected general correspondence

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Letters to the Editor

21st century, we should note that STD, including syphilis, can spread easily beyond borders. More international concerted efforts should be explored including awareness raising that encourages the use of latex condoms, such as a super-thin Japanese brand, in cases of a sexual exposure even through oral route for Japanese people as well as for international travellers.

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The strength of evidence: low dose morphine for chronic breathlessness

Smallwood et al.1 are to be commended for their online survey of the beliefs and behaviours of basic physician trainees about using low dose opioids for the symptomatic relief of chronic breathlessness.2 It is important to understand how the practices of the next generation of clinicians evolve in response to new knowledge.

In relation to the excellent discussion of the net clinical benefit of low dose opioids for breathlessness, we would like to comment on the cited Cochrane meta-analysis by Barnes et al.3 It is likely that this meta-analysis understated the benefits attributed to regular, low dose morphine for the relief of chronic breathlessness due to methodological issues. Although 11 of 12 included studies were cross-over trials, the meta-analysis did not account for cross-over data and analysed only the first randomisation for each participant in each study as though they were parallel arm studies, yielding confidence intervals that were unnecessarily wide and almost crossed zero. In addition, using a fixed effects model rather than a random effects model, the Barnes et al. Cochrane review does not account for any variations in the true between-study effects. This is of concern given the heterogeneity in time frames and designs of the included studies. Further, their addition of a criterion relating to sample size, but without taking study design or power into consideration, caused them to rate the risk of bias as ‘high’ and the quality of evidence to ‘low’ or ‘very low’, in contrast to previous meta-analyses.

When reanalysed using standard methods,4 the findings in favour of regular, low dose morphine are far stronger with evidence of clinical and statistical significance that should directly inform clinical practice.5 Ensuring the most robust methods are used consistently is crucial as clinicians rely on meta-analyses in a world where the number of individual studies is now overwhelming.6

It is encouraging to see that such a significant proportion of survey respondents are willing to prescribe low dose opioids for the relief of breathlessness. However, Smallwood et al. rightly draw attention to apparent education needs for prescribers. It is notable that unfounded fears of respiratory depression persist, but yet the importance of excellent monitoring for and management of the well-known common opioid-related harms seems less recognised. This risks a reduction in net benefit. Lastly, it is concerning that there does not appear to be an appreciation that the best evidence for the greatest benefit is seen with steady state morphine rather than pro re nata administration of immediate release preparations.

Regular, low dose morphine has an important role in palliating the distressing impact of chronic breathlessness. It is good to see improved uptake, but a posology rather than an algorithm that should directly inform clinical practice.5 Ensuring the most robust methods are used consistently is crucial as clinicians rely on meta-analyses in a world where the number of individual studies is now overwhelming.6

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Increasing awareness of addiction in palliative care: applying best practice in an area of limited management guidance

In their article, Pinkerton and Hardy note that with evolving cancer management and survivorship, cancer may now be considered a chronic disease. Similarly, the Society for Addiction Medicine Annual Meeting identified that, ’Intravenous drug (IV) addiction is a potentially life limiting condition. It therefore meets the World Health Organization definition of a Palliative Condition’. In Australia, the 2013 National Drugs Strategy Household Survey found that despite rates of some illegal drug use decreasing (heroin for example), rates of prescription medication abuse have increased by 0.5% between the 2010 and 2013 surveys. It stands to reason then, that those of us working in the field of palliative care appear to be seeing an increasing cohort of patients in whom cancer and addiction co-exist.

The relative inefficacy of opioids in the treatment of chronic, non-malignant pain and the risks of medication diversion are well established; however, in the context of malignant pain the restriction of opiates in patients with addiction is considered neither achievable nor desirable.

My own interest was sparked by the presentation of a 37-year-old homeless man referred to the palliative care team in which I was a registrar. His struggles with addiction since his young-adult years had resulted in the breakdown of relationships with his family and friends. When he subsequently developed metastatic clear-cell sarcoma his dependence on heroin increased, at least in part to manage pain. The level of his opiate divergence became clear when he was transferred to a hospice and drug-taking paraphernalia was found in his room. Multidisciplinary team meetings often reflected the difficult ethical considerations we faced in treating this young man.

Analogous to this case, Pinkerton and Hardy also highlight evidence that adolescents and young adults with cancer are a high-risk group for aberrant drug use and consider the use of various screening tools including the Opioid Risk Tool. Despite the range of screening tools available, however, none is validated in a palliative care setting. Further research is needed to ascertain which, if any, tools may be useful in discriminating high-risk patients with cancer-related pain. Similarly, once identified as high-risk, guidance on how to manage such patients is limited. Gourlay et al. advocate an approach of ‘universal precautions’. This standardised approach to prescribing references: risk stratification, identification of psychological conditions, appropriate opioid prescribing, and monitoring and documentation. The 4A’s approach to monitoring (analgesia, activities of daily living, adverse effects and aberrant behaviours) has also been advocated, although this too has been investigated only in patients with non-malignant chronic pain.

Pinkerton and Hardy’s article serves to remind us that palliative care patients may not have been as immune to the issues of addiction as first thought and with increasing cancer survivorship and prescription-opioid
addiction, this iceberg of illness appears to be growing. Despite the increasing recognition of this challenging patient-group, further research is needed to inform screening and management of addiction in patients with cancer-related pain.

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Does obesity reduce risk for osteoporosis and fractures in older adults?

We read with interest the review by Cheung and colleagues and agree that existing evidence for the obesity paradox is weak.1 However, we contend that benefits of excessive adiposity for osteoporotic fractures are not supported by the literature, despite the authors’ conclusion that obesity protects against fractures.

While obesity defined by body mass index (BMI) is generally associated with lower fracture incidence, fracture rate at specific sites may be increased. In the Global Longitudinal Osteoporosis in Women study, fracture prevalence and incidence were similar for obese and non-obese women, and risk of incident ankle and upper leg fractures were significantly higher in obese.2 Cheung et al. note that BMI is a better indicator of lean than fat mass1 and in over 43 000 Canadian older adults, higher lean mass was positively associated with femoral neck bone mineral density (BMD), whereas fat mass had no effect on BMD and adversely affected femoral strength index.3 Thus, higher lean mass, not fat mass, likely explains positive associations of higher BMI with BMD in older adults.

The authors identified that body fat distribution is more predictive of clinical outcomes than BMI,1 and this may be true for osteoporotic fractures. Men with higher levels of visceral adipose tissue have poorer bone mechanical properties, despite having similar BMD compared with those with low visceral adipose tissue.4 A recent meta-analysis also demonstrated that high waist circumference, a measure of abdominal adiposity, was associated with almost 60% increased relative risk of hip fracture.5

Finally, while we agree that weight loss in obese older adults is beneficial for cardiometabolic health, clinicians should be aware that weight loss results in declines in muscle and bone mass that may increase falls and fracture risk. Incorporating exercise, particularly resistance training, into weight loss programmes can significantly reduce the loss of muscle and bone mass,6 and is therefore strongly recommended for obese older adults.

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General practitioners require more support to prescribe direct acting antiviral therapy for hepatitis C

Kaan et al.’s recent survey predicted that current treatment centres could treat between two and five times the number of patients with chronic hepatitis C virus (HCV) infection using direct acting antiviral (DAA) therapy, compared with previous interferon-based treatments. Despite this, the number of patients being treated (up to 10 000 per year) would remain significantly below the total numbers needed (at least 13 500 per year) to prevent an increasing burden of HCV-related liver disease complications and deaths.

New models of care such as general practitioner (GP) initiated treatment are required to increase treatment uptake to the desired levels. The Pharmaceutical Benefits Scheme (PBS) listing of DAA therapy enables GP who are experienced in the treatment of HCV to prescribe independently, or otherwise in consultation with a specialist. Only patients with cirrhosis, complex comorbidities, or in whom first-line treatment has failed require referral to specialist care. The majority of patients with HCV in Australia have mild to moderate liver fibrosis and may be suitable for GP-led treatment. GP are also in a better position to treat injecting drug users, who were under-represented in the survey, as they do not access tertiary care unless extremely unwell.

In the first 6 months of PBS funded DAA therapy commencing 1 March 2016, 213 patients were treated through our tertiary centre. Only six (2.8%) of these patients had GP-initiated treatment through remote consultation with our centre. The majority of the remaining 207 patients who attended our liver clinics were non-cirrhotic (78.7%) and treatment naive (82.6%), and may have been suitable for GP-led treatment.

Data on Australian GP perspectives on prescribing DAA therapy are lacking. We anonymously surveyed 131 GP (78 females, 53 males) with a median duration of practice of 21 years (range 1–56 years) in the Central and Eastern Sydney Primary Health Network. Only 5% of GP had prescribed DAA therapy, 29% felt up-to-date with current hepatitis C management guidelines for non-cirrhotic patients, and 28% indicated that they are likely to prescribe DAA therapy. The 117 GP who had not yet prescribed DAA therapy cited significant barriers to doing so, including unfamiliarity with the drugs (88%), uncertainty if treatment was indicated (45%), uncertainty if local pharmacies dispense DAA regimens (28%), and concerns about non-compliance (22%). Only 51% of GP knew the rate of cure with current DAA therapies was greater than 90%, 21% of GP were not aware that DAA therapy was oral medications, and 45% of GP felt injecting drug users were ineligible for treatment.

Our findings show that GP were not initiating DAA therapy and instead relying on referral to specialist care. The survey identified significant barriers GP face to prescribing DAA therapy. Further studies on identifying the best approaches to support GP initiating DAA therapy are needed. It is likely that further educational programmes, increased availability of simple tools for liver fibrosis assessment in the community, and increased links with specialists will be required to increase GP-led treatment that will allow HCV to be eliminated as a major public health issue in Australia.

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