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Medicinal cannabis: moving the debate forward

The benefits of constraining processed meat and red meat consumption in New Zealand: a public health perspective
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By D. COLQUHOUN, M.D., Otago University.
Should a CT Head be a standard part of the diagnostic process for dementia in New Zealand?
Matthew Croucher

The number of people in New Zealand with dementia is rapidly increasing. Improving access to timely diagnosis is a key part of how the health system aims to respond to this challenge. Computer-based “Cognitive Impairment Pathways” now exist in every District Health Board to help GP-based primary care clinicians to assess and diagnose dementia. There is as yet no agreement in New Zealand as to whether or not every person being assessed in this way should have access to a publically-funded “CT” x-ray scan of the brain. This study reviews all relevant international diagnostic criteria, guidelines and studies that shed light on this issue and concludes that a CT Head should be a standard part of the diagnostic process for dementia in New Zealand.

Changes in high sensitivity troponin T in incident haemodialysis patients
Tze Liang Goh, Stefanie Honegger, Caroline Chembo, David Semple, Karishma Sidhu, Ralph Stewart, Helen Pilmore

Troponin is used as a marker of heart injury. Previous studies had shown that stable patients on long-term haemodialysis has chronically elevated and stabilised troponin levels. This paper shows that troponin levels decrease after the initiation of haemodialysis after a period of two to four months.

Improving the use and timeliness of anticoagulation reversal for warfarin related intracranial haemorrhage
Carl Hanger, John Geddes, Tim Wilkinson, Michele Lee, Scott Pearson, Andrew Butler, Krishna Badami

Brain bleeds are a devastating form of stroke. If they occur while the person is taking anticoagulants, then this is a medical emergency. This paper reports the experience at Christchurch Hospital at changing the way, and the urgency that we reverse the bleeding tendency. The protocols developed have resulted in better (more complete) and faster reversal of the bleeding.

Implementation of fracture liaison service in a New Zealand public hospital: Waitemata district health board experience
David Kim, Denise Mackenzie, Rick Cutfield

Fracture (broken bone) is a common and burdensome problem in our community, and doing appropriate tests and starting appropriate treatment, referred to as secondary fracture prevention, in those at high risk of more fractures can hugely reduce future fractures. Secondary prevention of fractures is poorly done in New Zealand and globally. Our study showed that highly effective secondary fracture prevention programme (Fracture Liaison Service) can be established in a New Zealand public hospital setting.
Improving accessibility to intravitreal anti-vascular endothelial growth factor treatment for ophthalmic patients in a peripheral centre

Verona Botha, John Ah-Chan, Nishan Ramachandran

There has been an exponential rise in patients requiring treatment with intravitreal injections for macular conditions. This includes conditions such as the “wet form” of age-related macular degeneration and diabetic macular oedema. A senior nurse-led clinic was established in Palmerston North to monitor these macular diseases. Analysis has shown that this has allowed the accessibility to treatment and follow up for macular conditions to remain stable, despite a large increase in the number of patients requiring these treatments and associated follow-up appointments.

Detection of sudden death syndromes in New Zealand

Nikki Earle, Jackie Crawford, Kate Gibson, Donald Love, Ian Hayes, Katherine Neas, Martin Stiles, Mandy Graham, Tom Donoghue, Andrew Aitken, Jon Skinner

Sudden unexpected cardiac death in young people (aged 1–40) occurs at a rate of over 100 people per year in New Zealand. To date, we know that about one-third have a familial cause, and death can be prevented in these people, but they must first be detected in the community. This study shows that by screening family members of people who carry such a condition, with blood tests and heart tests, it is possible to detect large numbers of people at risk and offer them protection. It also shows that this is being done much better in the North Island than the South Island, because the South Island does not have anyone to coordinate the service and keep records. The authors argue that there is a pressing need for a South Island coordinator to address this inequity of service.

Hospital costs of Bordetella pertussis in New Zealand children

Anusha Ganeshalingham, Peter Reed, Cameron Grant, Brian Anderson, Emma Best, John Beca

Infants less than one year of age are more likely than older children to be admitted to hospital and the paediatric intensive care unit with whooping cough. This vulnerable group of children generate the bulk of hospitalisation costs. A revised focus on protecting this group of children include timely delivery of the primary immunisation schedule, booster doses of vaccination to adolescents and adults, maternal immunisation during pregnancy and providing a cocoon of protection around the baby by immunisation of immediate family and close relatives. This has the potential to reduce medical costs and improve health outcomes for infants with pertussis.

Asthma and Respiratory Foundation NZ adult asthma guidelines: a quick reference guide

Richard Beasley, Robert J Hancox, Matire Harwood, Kyle Perrin, Betty Poot, Janine Pilcher, Jim Reid, Api Talemaitoga, Darmiga Thayabaran

The New Zealand Adult Asthma Guidelines, published in the New Zealand Medical Journal, provide health professionals who deliver asthma care with simple, practical and evidence-based guidance for the diagnosis and treatment of asthma in adults. Prior to this project, New Zealand’s asthma guidelines had not been updated since 2002. The new guidelines align the latest research with specific information for the New Zealand context including valuable medications and relevant content for treating Māori and Pacific adults with asthma. Implementing the guidelines nationwide will mean all asthma patients will have the opportunity to receive the same level of care and up-to-date information.
Medicinal cannabis: moving the debate forward
Giles Newton-Howes, Sam McBride

There is an increase in the interest surrounding the application of cannabis for medical reasons, although doctors who would presumably prescribe are notably absent from this discussion to date. Cannabis has a long history of use by the medical fraternity and cannabis has clear psychoactive properties that could potentially be harnessed. The evidence of cannabis’ effectiveness are currently limited, however harms are well identified and this is a concern from a medical perspective. Doctors need to be engaged in the discussion of medical cannabis to move this debate forward.

A pioneer paediatrician in New Zealand—Geoffrey Bruton SWEET (1.9.1870–17.5.1939) MB ChM (Sydney 1893)
William J Sugrue, Patricia M Clarkson

An account of Dr Geoffrey Bruton Sweet, considered New Zealand’s first specialist paediatrician. He was a powerful advocate for children, well read and interested in clinical research, and realised the need to communicate with those directly involved in the care of children. For New Zealand, he was a man ahead of his time.

The benefits of constraining processed meat and red meat consumption in New Zealand: a public health perspective
Christine Cleghorn, Nick Wilson

There is now strong scientific evidence of an increased risk of colorectal cancer with processed meat consumption. There is also evidence of red meats being associated with colorectal cancer and some evidence of an association between red and processed meat and cardiovascular disease and type 2 diabetes. This is important, as these diseases are responsible for significant health loss for New Zealanders and also large costs on our publicly-funded health system. Other issues associated with some meat production that are important to consider include pollution of waterways and greenhouse gas (GHG) emissions that contribute to climate change. Fortunately, there are a range of plausible options for New Zealand agencies to consider if they decide to encourage reductions in the consumption of processed and red meat consumption in this country. These include agricultural GHG taxes, warning labels on processed meat products and promotional campaigns to improve New Zealand dietary patterns.
A cure for asthma

Lutz Beckert, Ying-Tung Liu

Currently there is no cure for asthma. Large research collaboratives like the Refractory Asthma Stratification Programme-UK and European Unbiased Biomarkers in Prediction of Respiratory Outcomes (U-BIOPRED) are keeping it on their agenda. However, the current treatment is affordable and works well. Despite this, we have good evidence from almost every country that patients do not necessarily adhere to treatment.1

Does it matter that patients do not take asthma treatments?

Well, it does. Asthma is a treatable disease with a peak onset at a young age. The findings of the recent Royal College of Physician’s inquiry into asthma deaths are tragic.2 Asthma still kills! Asthma killed 195 people in the UK in 2015 and at least half of these death were considered preventable. Particularly chilling are the findings that most children/youths who died of asthma were diagnosed with ‘mild or moderate’ asthma until they died.2 In 2012 there were eight deaths under the age of 45 in New Zealand due to asthma, with a total of 63 deaths throughout all age groups.1

Low-dose inhaled corticosteroids and as required salbutamol—it is that easy!

It’s that easy in most instances. This statement from the NZ Adult Asthma Quick Reference Guide is based on strong evidence.4 In this time of ‘super-sizing’, it is refreshing that this Reference Guide is reframing our thinking and making sure that the standard dose for the treatment of asthma should be a dose of inhaled corticosteroid (ICS) equivalent to beclomethasone 400–500mcg/day; 80–90% of the benefit of ICS can be achieved with the above dose.

Every patient who is using salbutamol more than twice a week is probably better off with regular inhaled corticosteroids. There is strong evidence of benefit for patients with fewer asthma symptoms.5 Certainly, an episode of asthma exacerbation needing oral steroids is an indication for regular ICS therapy.

If low dose steroids don’t work, should I increase the dose?

Yes, sometimes—however, it is here where we can probably have the biggest impact. The Reference Guide is helpful with links to the appropriate evidence, useful practice points and tables relevant for the New Zealand population. Given our propensity to prescribe Salbutamol, not everybody with a ‘blue inhaler’ has asthma. PHARMAC data show that we are prescribing one million salbutamol inhalers for a population of four million each year.6 The Reference Guide gives a useful list of features which makes the diagnosis of asthma more likely. This includes symptoms such as wheeze, breathlessness, chest tightness and cough. The guide also has the features that make asthma diagnosis less likely. This would include features such as lack of airways, reversibility or no response to a trial of treatment. In this situation, low dose inhaled corticosteroids may not work because the patient may not have asthma. In that case, an increase in inhaled corticosteroids would not work.

Patients may well have asthma, however, they may be using inhaled corticosteroids incorrectly or not at all. A recent review suggests that we have made little progress over the last 40 years in educating patients regarding inhaler techniques.7 Poor inhaler usage is a common reason for ‘poorly controlled’ asthma and increasing steroids will not help. It is here that we can make the biggest gain and the Reference Guide devotes a page to it based on the Global Initiative for Asthma.8 It is here,
as health care providers, where we can add real value by building therapeutic relationship with patients and whānau, while explaining the differences between symptom control, future risk and adjust therapy to the patient needs.

**Can we identify who is at risk of severe asthma exacerbation and/or mortality?**

Yes we can, and this has not really changed much over the years. A table in the guidelines list all the normal culprits like beta-agonist overuse, repeated courses of steroids, previous ICU admissions and comorbidities like major psychological illnesses, which the UK audit also identifies. The reference still lists Māori and Pacific ethnicity as a risk factor for adverse asthma outcome which is supported by New Zealand data, which identifies an increased burden of disease. The Reference Guide devotes a page with practical hints including an audit of our practice. Why is it that a population with a higher burden of disease, who have more hospital admissions and more asthma-related deaths receive less adequate education, fewer written asthma management plans and have fewer prescriptions of inhaled corticosteroids?

**Does the Reference Guide provide practical help?**

Yes, the quick reference guide has pre-formatted management plans, which can be printed in colour. All we need to do is to complete the patient specific details and drug doses. In the old days, one could imagine these action plans and flow charts on the office wall or the emergency department—in this modern area, it is up to us to show this in local Health Pathways or guidelines.

**Will this Asthma Quick Reference Guide make a difference?**

No, it won’t make a difference unless we actually use them. We are lucky to be practising at a time where we have treatments available to manage asthma successfully. We are working at a time where health providers work together and join forces to manage asthma. This reference guide is based on compelling evidence, written clearly and adjusted to the New Zealand population. However, none of this will make any difference if we do not apply this evidence to our practice, assess the adherence to low dose ICS and spend the time to up-skill ourselves. Will 2017 bring another year of high asthma mortality? Will the next census again show Māori and Pacific Islanders with an increased burden of this treatable disease?

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**Competing interests:**

Lutz Beckert has been on the advisory board for AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline and has provided independent medical education at symposia founded by AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline.

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The case for medicinal cannabis: where there is smoke there may well be fire
Chris Wilkins

In their informative article on medicinal cannabis, Newton-Howes and McBride (2016)1 rightly observe the introduction of medical cannabis regimes has largely been driven by political activism from patients and their families, and pro-recreational cannabis law reform organisations, such as NORML, rather than medical science. There are only a limited number of medicinal cannabis studies to start with and only a minority of these use the double-blind trial design which produces the standard of evidence sufficient to convince medical bodies.2 As Newton-Howes and McBride1 describe, one of the most recent systematic reviews (consisting of only 79 studies) found moderate-quality evidence to support use of cannabinoids for the treatment of chronic pain and spasticity, and low-quality evidence to support use of cannabinoids for nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders and Tourettes syndrome.3 Newton-Howes and McBride1 also rightly note the use of herbal cannabis as a medicine is inherently problematic due to the fact it is largely delivered via smoking, there is no standardisation of dose, and little direction concerning the required dosage, apart from the crude ‘use to effect’. Cannabis also has some well-documented adverse side effects including increased risk of psychosis, particularly among young and daily users, and dependency. The risk of cannabis dependency is being taken increasingly seriously and may be higher than commonly thought. Thirty-one percent of those who used cannabis in the last year in the US were assessed to have a DSM-IV cannabis use disorder in 2012/13.4

Cannabis users’ enthusiasm often muddies the medical debate
Newton-Howes and McBride (2016)1 also note the conflation of the debate over cannabis as a medicine versus cannabis as a recreational drug misdirects the discussion over the merits of cannabis as a medicine. Recreational drugs only have to create euphoria and other pleasant intoxication effects. As long as they do not create immediate serious health issues in the vast majority of users, in particular overdose and dependency, they can attract a large following of enthusiastic recreational users whose support for the drug may not be particularly critical due to their own controlled usage and positive experience. This applies to alcohol and tobacco as much as it does for cannabis. Medicines, on the other hand, must reach the much higher standard of positive therapeutic effect, including avoiding serious side effects, proven via a double-blind clinical trial. Support for recreational cannabis vs medicinal cannabis therefore represents two vastly different standards of debate and evidence. However, it should also be noted that the criminal prohibition of cannabis has had a chilling effect on the very medical research into cannabis that is now required to support the use of cannabis as a medicine. There are a number of novel aspects of cannabinoids as a chemical class which justify investigation of its therapeutic potential.5 Consequently, steps could be taken to remove barriers to
conducting medical cannabis research, such as permitting herbal cannabis to be used for medical research.

**Many cannabis users use cannabis as a medicine now**

Regardless of the lack of medical evidence supporting the effectiveness of cannabis as a medicine, many cannabis users believe they are using cannabis for medicinal reasons. Pledger, Martin and Cumming (2016) found 41% of those who reported using cannabis in the past year in New Zealand also reported they were using cannabis for medicinal reasons. Forty percent of these medicinal users were using cannabis to alleviate pain, followed by anxiety (27%), depression (26%) and nausea (11%).

A much larger study of cannabis cultivators conducted in Australia, Belgium, Denmark, Finland, Germany and the UK in 2012/13 (n=5,313) found 45% reported cultivating cannabis for medical purposes, either for themselves or others. The illnesses they reported using cannabis for included physical and mental illnesses. The most popularly reported were depression (43%, n=2,070), chronic pain (33%), anxiety (30%), headaches (24%), ADHD (15%), bowel problems (14%), arthritis (14%), PTSD (11%) and asthma (10%). This is a far broader list than conditions for which there is any medical evidence in relation to cannabis. More worryingly, there are also a number of mental health disorders (depression and other mood disorders) in this list for which the use of cannabis (at least herbal cannabis containing THC) may exacerbate the condition.

Seventy-six percent of those who reported cultivating cannabis for medicinal reasons said they had received a diagnosis for the condition from a doctor. This challenges the common perception that cannabis users only cite medical reasons to justify their recreational use. However, significantly, only a minority of those medical cannabis users with a diagnosis from a medical professional had discussed the use of cannabis as a medication with their doctors. Fifty-nine percent indicated their doctor had not recommended cannabis for their condition and they had not asked for it. Interestingly, 17% reported their doctor had suggested the use of cannabis. Alternatively, in 8% of cases the doctor had refused to recommend cannabis even though the respondent had asked for it, and in 9% of cases the doctor had advised the respondent against using cannabis.

**More informed debate and engagement needed**

Newton-Howes and McBride (2016) rightly call for doctors to become more engaged in the debate over the medical use of cannabis. This call could also be expanded to include politicians who currently appear to be reluctant to engage in such a highly polarised issue for fear of offending conservative elements among voters. The fact is change in regard to the legal status of cannabis, both for recreational and medical purposes, is gathering momentum around the world, to the point where New Zealand can no longer avoid serious debate. Polling in the US has shown that public support for the legalisation of cannabis has increased from 32% in favour in 2006, to 57% in favour in 2016.

Following the November elections in the US, another three States voted to legalise the recreational use of cannabis: California; Massachusetts and Nevada. The legalisation of recreational cannabis in California may well be a watershed moment for cannabis law reform. California is the largest US state by population, home to 38 million people, and is the fifth largest economy in the world. This guarantees a large impact both domestically in the US and on the international stage. The cannabis industry which develops in California will be an influential lobby group at both the federal level in the US and around the world.

In the same November elections in the US, Florida, Arkansas and North Dakota passed initiatives to establish medicinal cannabis regimes and joined 25 other US states who already have medical cannabis regimes. There are also legal medical cannabis regimes in Austria, Canada, the Czech Republic, Finland, Germany, Israel, Italy, the Netherlands, Portugal and Spain. The medical use of cannabis in Australia was also legalised at the federal level in November 2016.
As I have argued previously in this journal, it is important that New Zealand takes the opportunity to carefully examine the range of regulatory options available for a legal cannabis regime, rather than just adopting at the last minute the default commercial legal market option we are most familiar with from alcohol and tobacco, which also happens to be the most conducive to profit making by the related industry. Long experience with the commercial markets for alcohol and tobacco has shown they are associated with pricing cutting, marketing directed at young and heavy users, normalisation of use and industry opposition to stricter regulation.

The regulatory options for medicinal cannabis are narrower and can be structured around established prescription systems. An alternative approach is to accept that cannabis is more akin to a non-specific anxiolytic, and is in fact largely a dietary supplement. Dietary supplements elicit much less anxiety among regulators as they do not make any therapeutic claims. It could be argued that herbal cannabis has much more in common with common dietary supplements such as echinacea, ginkgo biloba and St. John's wort than modern medical pharmaceuticals. For example, the cannabis derived product Elixinol™ is sold as a ‘dietary supplement’ overseas, with its marketed benefits limited to the antioxidant properties of CBD. It is 18% cannabidiol (CBD) oil extract produced from pressing stalks and seeds of industrial hemp. It contains no THC and has no psychoactive properties. Although there is growing evidence supporting the therapeutic benefits of CBD, the US manufacturer of Elixinol™ does not make any therapeutic claims. Consequently, it could be easily classified and regulated as a dietary supplement in New Zealand.

Competing interests:
Nil.

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Should a CT Head be a standard part of the diagnostic process for dementia in New Zealand?

Matthew Croucher

**ABSTRACT**

Timely diagnosis of dementia is being encouraged in both primary and secondary care settings in New Zealand via the creation and promotion of internet-based dementia clinical pathways. There is no national consensus about the circumstances in which neuroimaging should be recommended and funded within these pathways. This lack of agreement is driven by uncertainty about the rationale for neuroimaging in the diagnosis of dementia as well as the costs involved. This paper summarises all relevant international guidelines to inform a recommendation that a CT Head should be routine in the dementia work up in the New Zealand setting.

Dementia is becoming increasingly common in primary and secondary care settings in New Zealand because of the phenomenon of our ageing population coupled with the strong effect of advancing age on dementia prevalence. The impact of the ageing population on dementia prevalence is particularly strong because it is not simply the result of ageing “baby boomers”; it also arises from increasing longevity. Unfortunately there are no New Zealand epidemiological data from which accurate estimates can be made of the numbers of people living with dementia. Alzheimer’s New Zealand commissioned estimates extrapolated from overseas data which indicate that over 50,000 people may currently be living with dementia in this country, with the number likely to nearly treble within thirty-five years.

Concerns about the relatively undeveloped state of services for people living with dementia and those that care about them have been rising in light of this unprecedented projected increase in dementia prevalence. The New Zealand Ministry of Health facilitated a stakeholder group process which generated the “New Zealand Framework for Dementia Care” in 2013 with an expectation that each District Health Board (DHB) must develop its own dementia care pathway, taking note of the recommendations set out in the framework document. Most DHBs responded initially by focusing on supporting clinicians, especially general practitioners, to make timely diagnoses of dementia and to initiate management plans. This support has largely revolved around producing or enhancing access to cognitive impairment diagnostic pathways via internet-based resources available in the clinic setting such as Health Pathways and the Map of Medicine.

Whether or not to carry out a routine Computed Tomography (CT) head scan is a question in respect of which each of these pathways must provide a recommendation. There is variation around the country with some pathways providing for more routine access and others suggesting limits on scanning relating to clinical criteria. One of the pressures on the system is the cost of this investigation, typically around $300 per CT Head, to some extent an additional cost not previously borne by the equivalent of the community radiology budget in each DHB. No current New Zealand dementia care pathway suggests routine use of a Magnetic Resonance Imaging (MRI) or any alternate imaging procedure other than CT.

This study reviews all relevant English language guidelines that deal with the issue of neuroimaging using CT in the dementia diagnostic process in order to inform New Zealand practice. The few guidelines published prior to the 21st century were all
predicated on the principle that the sole purpose of neuroimaging in the dementia work up is to exclude potentially reversible causes of a dementia-like syndrome such as brain tumours, sub-dural haematomas and Normal Pressure Hydrocephalus (NPH). Since these early guidelines were well summarised in a 2000 review and have been superseded by more modern clinical recommendations, they were not included in this study except where they remained the current statements of major guidelines groups.

**Method**

All relevant English language guidelines produced by neurology, psychiatry, governmental and NGO organisations as well as as translations of respected European Union sources were accessed via Google searching. A combined Medline, EMBASE and PsychInfo database search for relevant papers was also conducted using title and subject terms linking (“guideline” or “recommendation”) with (“neuroimaging” or “CT Head”), triangulated with various stems relating to (“dementia”). These searches were supplemented with a snowball approach to identify all relevant cited papers in each guideline or recommendation. The papers chosen for review were selected on the basis that they would be informative for weighing up the merits of CT scanning. “Guideline” status was imputed if a source made formal recommendations about neuroimaging in the dementia diagnostic process as opposed to critically appraising or otherwise analysing imaging options. These findings are discussed in light of the author’s clinical experience and knowledge of dementia pathway development in New Zealand in order that a considered suggestion for a national consensus might be made.

**Results**

**Diagnostic criteria for dementia**

The main international authorities that set out agreed criteria for the diagnosis of the dementia syndrome overall or for specific subtypes such as Alzheimer’s dementia vary in the importance they place on neuroimaging. The Diagnostic and Statistical Manual—Fifth Edition does not mandate neuroimaging in the diagnostic criteria for Major or Minor Neurocognitive Disorder but does outline imaging guidance in the “Diagnostic Features” notes within each dementia subtype. The National Institute of Aging and Alzheimer’s Association criteria for Alzheimer’s dementia implies the need for neuroimaging to rule out vascular lesions. The National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l’Enseignement en Neurosciences criteria for Vascular dementia give more primacy to neuroimaging as expected, especially in relation to the subtypes within this group of disorders. The dementia with Lewy Bodies Consortium criteria list neuroimaging findings as a supportive feature of diagnosis. The revised International Consensus Criteria for Fronto-Temporal Dementia request neuroimaging evidence for the diagnosis of the subtypes within this group of disorders.

**Dementia clinical guidelines**

Clinical guidelines published since 2000 covering the assessment and management of dementia ask for neuroimaging to varying degrees and for varying reasons. Table 1 summarises the key guidelines.

No guideline recommends the routine use of functional neuroimaging modalities such as Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET), although several list them as desirable options if required for diagnostic subtyping. No guideline states that structural neuroimaging using CT Head or MRI Brain should not be used. All guidelines have moved beyond simply using imaging to rule out potential reversible conditions in favour of assisting with diagnostic subtyping.

The American Association of Neurology, Scottish Intercollegial Guidelines Network and American Psychiatric Association guidelines all advise that CT or MRI should be used if possible, but stop short of saying either investigation should be routine. The Clinical Research Centre for Dementia of South Korea, the European Federation of Neurological Societies and an NHS England consortium all make statements that at least one modality of structural neuroimaging should be routine. The English guideline adds that lack of access to neuroimaging should not stop a GP from making the basic diagnosis of dementia.
The Canadian Consensus Conference on the Diagnosis and Treatment of Dementia has always taken an intermediate position and their most recent revision defines a complex ‘group of interest’ based on clinical indicators, simultaneously stating that this should result in structural neuroimaging being indicated for most patients. Notably, they prefer MRI. The characteristics of this ‘group of interest’ appear to be designed to detect cases of dementia likely to have less common neurological underpinnings such as people with early onset dementia, rapidly progressing dementia or clinical stigmata of tumours and NPH. The Australian Clinical Practice Guideline and the UK’s National Institute for Health and Care Excellence also take an intermediate position, stating that structural neuroimaging should be used except for a ‘group of no interest’ comprised of people with more advanced dementia for whom the diagnosis is reasonably certain (with the British preferring MRI).

Other key formal statements

The American College of Radiology’s Clinical Appropriateness Panel’s statement on dementia neuroimaging reviews various neuroimaging options in terms of their clinical utility but it is not a guideline per se. It implies that structural neuroimaging is routine and marginally favours MRI above CT in terms of being able to support diagnosis. The statement is in line with the guidelines above in its declaration that the purposes of neuroimaging are diagnostic subtyping as well as detecting potential reversible conditions. The International Psychogeriatric Association published a series on neuroimaging for dementia in 2011 including a review on the use of CT. Although this is based on older CT technology rather than modern helical scanning, the authors conclude that CT should be seen as a first-line tool before MRI to rule out rarer reversible causes of the syndrome and to assist with dementia subtyping. Health Quality Ontario produced a rigorous review of the clinical utility of neuroimaging for dementia concluding that rules-based criteria may not be reliable enough to use in clinical practice, CT compares favourably with MRI in real-world clinical settings, and that clinical utility is highest in cases where uncertainty about the diagnostic subtype is higher.

<table>
<thead>
<tr>
<th>Source</th>
<th>Structural imaging</th>
<th>Structural modality</th>
<th>Functional imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian CPG 2016</td>
<td>“Should usually be used … unless” Defines simple group of ‘no-interest’</td>
<td>CT or MRI</td>
<td>“Not recommended”</td>
</tr>
<tr>
<td>NICE 2014</td>
<td>“Should be used … unless” Defines a simple group of ‘no-interest’</td>
<td>MRI preferred over CT</td>
<td>SPECT or PET If required for subtyping</td>
</tr>
<tr>
<td>RCGP/NHS/ Dept Health 2014</td>
<td>Routine But do not withhold diagnosis if scan not available</td>
<td>CT Other scans likely to be specialist only</td>
<td>-</td>
</tr>
<tr>
<td>EFNS 2012</td>
<td>Routine “At least once”</td>
<td>MRI</td>
<td>-</td>
</tr>
<tr>
<td>CCCDTD 2012</td>
<td>“Indicated for most but not all” Defines a complex group of interest</td>
<td>MRI preferred over CT</td>
<td>-</td>
</tr>
<tr>
<td>CRDC S. Korea 2011</td>
<td>Routine</td>
<td>CT and MRI</td>
<td>SPECT or PET If required for subtyping</td>
</tr>
<tr>
<td>APA 2007</td>
<td>“Generally recommended”</td>
<td>CT or MRI</td>
<td>PET If required for subtyping</td>
</tr>
<tr>
<td>SIGN 2006</td>
<td>“Ideally”</td>
<td>CT or MRI</td>
<td>SPECT If required for subtyping</td>
</tr>
<tr>
<td>AAN 2001</td>
<td>“Appropriate” But optional</td>
<td>CT or MRI</td>
<td>-</td>
</tr>
</tbody>
</table>
Detecting potentially modifiable diseases

Health Quality Ontario have also produced an economic analysis\(^2\) of dementia neuroimaging but this restricted itself to examining the utility of neuroimaging to detect potentially reversible conditions rather than more modern clinical goals, in line with older iterations of the Canadian Consensus Committee (CCC) criteria. Within this restriction it preferred CT scanning being limited to people at higher prior probability of unusual causes of the dementia syndrome, however it highlights the strengths and weaknesses of all options including the CCC criteria and ultimately sat somewhat uncomfortably on the fence. The key review of the utility of different prediction rules for indicating neuroimaging prior to 2000\(^5\) focussed on screening for potentially reversible conditions in the dementia diagnostic process and concluded that none of the guidelines up to that point were sufficiently founded on scientific data nor very informative about the likely clinical effects of their recommendations. The authors also pointed out the tension between clinicians and patients wanting as high a sensitivity as possible but funders wanting as high a specificity as possible, and suggested that the Canadian Consensus Criteria of the time probably provided the best balance in the primary care setting based on the limited available evidence, but that all patients in specialist settings should be scanned because of the higher prior probability of finding rarer reversible causes in this population. A meta-analysis of this issue demonstrates that the base rates of potentially reversible conditions vary by clinical setting and are low in primary care, and that the true reversibility of these conditions is also low, especially in respect of cognitive impairment.\(^6\) Nonetheless, this aim is of extreme importance to the individuals involved.

Subtyping dementia to alter management

An early review\(^27\) suggested that structural neuroimaging should be recommended for the diagnosis of Alzheimer's disease in those settings where the diagnostic accuracy from clinical assessment is poorer, specifically in non-specialist settings and for early diagnosis, especially if aspects of the clinical situation such as a language barrier or specific learning deficits cloud the assessment of functional decline. Subsequent studies attempt to quantify the effectiveness of neuroimaging for altering diagnosis in the dementia assessment process. Condefer and colleagues\(^28\) demonstrated that CT changed diagnosis and occasionally management in a memory clinic setting but they pointed out that effects may be different in less specialist settings. Massoud and colleagues\(^29\) found that the validity of dementia diagnosis and diagnostic subtyping could be improved by adding neuroimaging and recommended MRI over CT because of the increased ability of MRI to discern more subtle cerebrovascular abnormalities. They found that diagnosis was most enhanced for younger patients, for whom clinical subtyping prior to scanning required revision more than half of the time. Tanev and colleagues\(^30\) found that structural imaging altered diagnosis in a third of patients in a dementia inpatient unit setting despite having a fairly unsophisticated scan report, and functional imaging was even better.

A relatively recent review of imaging access rules\(^31\) suggested that the key issue is not the effect of neuroimaging on diagnosis but on treatment. Because neurologically silent cerebrovascular disease is both common in the 'possible dementia' group and has growing treatment implications, they argue scanning is required in all patients with the exception of older people with more established dementia for whom cerebrovascular risk modifying treatment would not be offered. The authors compared imaging access rules from the guidelines extant to 2006 and concluded that none accounted for cerebrovascular disease because they were designed to detect traditional potentially reversible causes of dementia-like presentations. Even in this task, the authors found rules-based approaches wanting. Neurologically silent white matter disease and small strokes are now known to be common, associated with cognitive impairment\(^32\) and behavioural and psychological symptoms,\(^33\) and may generate different management strategies for cerebrovascular disease progression (such as whether or not to prescribe anti-platelet or antithrombotic agents) and for dementia symptoms (such as whether the
stroke risk of antipsychotics would be unacceptably high). It has certainly been argued that the diagnosis of a significant vascular component to dementia is unreliable without neuroimaging.34,35

CT versus MRI

The specific issue of CT versus MRI to assist with subtyping dementia was considered by several groups. A recent systematic review and meta-analysis36 concluded that MRI only just out-performed CT for subtyping in respect of vascular dementia, for which MRI should theoretically be the best modality. Since most studies on which the review was based pre-date the widespread availability of modern helical CT scanning, CT may perform even better now. A similar review specific to Alzheimer’s disease37 found that the specificity of both modalities was acceptable but was lower in both cases for less severe dementia; this is not what an ideal future system would provide with the advent of potentially disease-modifying treatments. Overall, both reviews agreed that imaging was reasonably able to distinguish Alzheimer’s dementia from normal ageing, Mild Cognitive Impairment and Vascular dementia cases, and that CT was comparable to MRI.

Discussion

Reviews of imaging in dementia published in the peer-reviewed literature increasingly assume MRI is the norm (if not PET) therefore CT-relevant articles have begun to vanish from the literature. While this may reflect the reality of academic centres in the US and Europe, it does not reflect the reality in the publically-funded health system in New Zealand. Indeed, it will not do so unless the clear superiority of MRI over CT is demonstrated in terms of changing management, something that has not yet occurred despite the agreed superiority of MRI in terms of ability to detect subtle and early brain changes, especially haemosiderin deposits indicative of amyloid angiopathy and associated with increased risk of intracerebral haemorrhages.38 Arguably, CT advantageously deletes many ‘incidentalomas’ that MRI would otherwise detect. Authors championing MRI’s superiority on the basis of better resolution frequently made no attempt to demonstrate that this matters in routine dementia assessment, certainly not to justify the approximately $900 price and restricted availability in this country.

The traditional rationale for neuroimaging in the dementia workup was clearly to rule out potentially reversible conditions, especially brain tumours and sub-dural haematomas. As outlined above, clinical screening rules to try to define a populations of increased risk for such conditions are unsatisfactory,44 cost-effectiveness of such neuroimaging for this purpose is difficult to quantify25 and these conditions are both uncommon and rarely truly reversible.26 Therefore, restricting an analysis of the place of neuroimaging for dementia assessment to this traditional clinical aim is unhelpful on clinical, scientific and economic grounds.

The more modern and now commonly espoused rationale for neuroimaging in the dementia workup is to assist with diagnostic subtyping of dementia. The strongest evidence in support of this is for the commonly occurring vascular dementias, in respect of which diagnosis is unreliable without imaging.34 The usefulness of assessing Alzheimer’s biomarkers such as markers of medial temporal lobe atrophy is less clear, however it is now generally accepted that, where present, positive findings help differentiate between Alzheimer’s disease and normal ageing or Mild Cognitive Impairment (MCI) but their absence is less informative. Fronto-temporal focal atrophy patterns are very helpful when present, but the diagnosis of dementia with Lewy Bodies is not advanced much by structural neuroimaging. There is little suggestion that MRI is superior to CT at detecting these more macroscopic diagnostic markers.

Subtyping is increasingly important because it alters management. The cholinesterase inhibitors are not equally effective in different subtypes, vascular risk factor modification is indicated to different degrees in the vascular subtypes especially in respect of whether or not stroke disease is present, and antipsychotic risks vary by subtype. It is to be expected that future medical technologies for dementia are likely to have even more differential effectiveness by subtype, and a core thrust of current dementia-prevention work is to detect specific disease types early so as to enable tailored treatment for high-risk individuals. That is why most
current guidelines highlight subtyping as the main reason structural neuroimaging is recommended, a contribution that will grow in importance in the future.

Another published reason to consider structural neuroimaging in the diagnostic process for dementia is that it may be useful to track progression, especially in the context of MCI, however prognosticating in this context is challenging. A baseline scan is especially useful for people with pre-existing neurocognitive impairment such as patients with learning disabilities, head injuries or long term major psychiatric illness who present with a suspicion of later-onset acquired cognitive impairment. Determining whether or not a neurodegenerative disease is superimposed on the pre-existing clinical picture is greatly assisted by comparing a baseline structural scan with subsequent imaging.

A final reason structural neuroimaging has been endorsed by clinicians that has not been discussed in the literature is to assist with patient education and motivation. Patients and their family/whanau/supporters are increasingly expecting a brain scan and a subtyped diagnosis. Discussing or ideally showing people their brain scan in-clinic is helpful for enhancing acceptance and for motivating participation in management. Being able to provide a subtyped diagnosis is also important for prognostication in terms of life expectancy, symptoms or complications to be aware of, and discussing heritability.

These arguments rely on the quality of scan reports being high and easy to understand by the referring clinician, and on the recipient being aware of the clinical significance of the results. This is a challenge that needs to be overcome in the New Zealand setting, given the complexity and rapid growth in this field. No international guidelines or studies have explicitly handled this issue, but one author has provided an algorithm for reading structural scans and several rating scales have also been proposed although none are widely used. Attempts are being made within some New Zealand clinical pathways to deal with this important part of the process, including standardising dementia scan reports, providing written information to guide clinical interpretation of findings in general and creating a ‘virtual clinic’ to provide specialist comment on CT Head results to referrers in light of other pertinent clinical data.

**Conclusion**

New Zealand dementia diagnostic pathways should align themselves with the guidelines and diagnostic statements made by the majority of our international peers by recommending and funding a CT Head at least once for every person being assessed for dementia. The express purposes would be to assist with subtyping, to assist with management planning if a diagnosis is made, to rule out potentially reversible conditions and to act as a piece of clinical baseline information should a diagnosis of dementia not be made. The only exclusion should be for people for whom the referrer judges subtyping would change neither management nor prognostication for them and for their family, for example some people of advanced age with established severe dementia. The availability of CT Head scans needs to be supported by accurate and consistent neuroimaging reporting, ideally with a mechanism to clearly convey the clinical significance of the neuroimaging findings to referring clinicians.
REFERENCES:


Changes in high sensitivity troponin T in incident haemodialysis patients

Tze Liang Goh, Stefanie Honegger, Caroline Chembo, David Semple, Karishma Sidhu, Ralph Stewart, Helen Pilmore

ABSTRACT

AIM: To characterise the changes in high sensitivity troponin T (hsTnT) in incident haemodialysis patients.

BACKGROUND: Previous studies had shown that stable chronic haemodialysis patients have elevated cardiac troponin compared to the general population. Cardiac troponin on incident haemodialysis patients had not been characterised.

METHODS: This prospective descriptive study included all patients who started haemodialysis in Auckland City Hospital over 18 months. A troponin level was measured prior to the commencement of their first haemodialysis session and regular pre-dialysis troponin levels are measured every two to four months. Each patient has two to four troponin measurements during the study with a minimum follow-up of six months.

RESULTS: A total of 91 patients started on haemodialysis during this period. Fifty-five patients had two troponin measurements and 40 of these patients had four troponin measurements. The baseline median troponin level prior to commencement of dialysis was 91ng/L (54–191ng/L) and declined with subsequent measurements. There was a significant decrease in the 3rd and 4th troponin measurements compared to baseline troponin. The baseline troponin levels were not independently associated with mortality. The decrease in troponin levels did not correlate with a decline in weight.

CONCLUSIONS: This is the first study to describe and show a decline in cardiac troponin post-initiation of haemodialysis. The baseline troponin measurements were not predictive of mortality.

Patients with end-stage renal failure have a high prevalence of cardiovascular disease and increased risk of myocardial infarction. Cardiac troponins had been used as sensitive markers for myocardial injury.

Multiple studies had shown that high sensitivity troponin T (hsTnT) is chronically elevated in stable and asymptomatic haemodialysis patients. Patients with chronically elevated troponin levels had been shown to have a worse prognosis with up to a two to five-fold increase in mortality rates over three years. The underlying pathophysiology of elevated troponin levels in stable haemodialysis patients may be due to underlying coronary artery disease, subclinical ischaemia, reduced renal clearance, myocardial stunning and left ventricular hypertrophy. In chronic haemodialysis patients, the level of troponin of each individual remains relatively stable over repeated measurements, with reported 99% of variance <0.06ug/L with older assays. With newer assays of hsTnT, with variation of <62ng/L over one month was reported previously by our own centre. Other smaller studies showed an intra-individual variability of 8.2% to 44%.

In contrast, the significance and stability of hsTnT levels in incident haemodialysis patients had not previously been evaluated. There are potential mechanisms which may lead to either an increase or decrease in cardiac troponin after the initiation of haemodialysis. Cardiac troponin may decline due to improvement in chronic fluid overload and hypertension. However, it may also increase due to factors including declining residual renal function, myocardial remodeling in the setting of left ventricular failure and recurrent myocardial stunning from haemodialysis. It remains
unclear if haemodialysis or haemodiafiltration removes troponin T. Our own centre showed a modest but statistically significant decrease in troponin T post dialysis compared to pre-dialysis levels but this finding is not a consistent finding in other studies. However, haemodiafiltration has previously been shown to have a small amount of albumin leakage, despite the larger molecular weight of 65kDa. It is also unclear if troponin levels measured prior to commencement of first haemodialysis and changes in subsequent troponin levels are prognostic of mortality.

This study aims to characterise and evaluate the significance of the changes in hsTnT in incident haemodialysis patients.

Methods

The procedures involved in this study were in accordance with the ethical standards of the committee on human experimentation of Auckland District Health Board.

Study sample

All patients who started haemodialysis between November 2012 and May 2014 (18 months) in our centre were eligible to be included in this study. This included all patients who started in in-centre haemodialysis, satellite units and home haemodialysis unit. The hsTnT levels of patients were measured prior to starting their first haemodialysis session and monitored for at least six months. The follow-up troponin levels were done prior to their mid-week dialysis session.

All hsTnT levels were measured with automated chemiluminescent immunoassay on a Roche Modular analyser using the Roche high sensitivity Troponin T assay (Roche Diagnostics, Mannheim, Germany). This assay has a detection limit of 5 ng/L and has a total imprecision of less than 10% at a level of 13 ng/L. In a sample of 616 healthy volunteers, the 99th centile was 13.5ng/L.

All the patients were started on Fresenius haemodialysis machines model 4008 or 5008. The patients uses Fresenius FX class high flux dialyzers (FX 60 or FX 100). The patients underwent haemodiafiltration as their chronic dialysis modality, with three times a week dialysis for four hours each session.

Demographic data collected at baseline included age, gender, ethnicity, body mass index, inpatient or outpatient start of haemodialysis, presence of ischaemic heart disease (previous myocardial infarction, angina, positive angiographic findings or stress imaging study), diabetes, left ventricular ejection fraction, smoking and atrial fibrillation.

The patients’ target weight was recorded monthly for the first four months, with the change in target weight as a surrogate for the extent of fluid overload on initiation of haemodialysis. The patients’ initial dialysis access and whether they started as inpatient or outpatient were recorded. Finally during the follow-up period, any acute coronary events, death and causes of deaths were recorded.

Statistical methods

In this study, continuous data are reported as medians with inter-quartile range (IQR) and categorical data are reported as frequencies with percentages.

The Wilcoxon rank-sum test was used to compare baseline troponin amounts between categories of patient demographic variables and patient clinical variables. Comparisons of change in troponin levels were made between inpatients and outpatients patients using the Wilcoxon rank-sum test. Univariate Cox proportional hazards regression was used to determine independent predictors of mortality, and results were reported with hazard ratios (HRs) with 95% confidence intervals (CI). Pearson Correlation Coefficients were calculated to indicate if change in weight and change in troponin correlated with each other. Bland-Altman plots were constructed to depict the changes between the troponin levels, in particular to highlight the wider variance in the change from baseline to subsequent troponin measurements. Statistical analyses were performed using the statistical package SAS version 9.3 (SAS Institute, Cary, NC). All p-values resulted from two-sided tests and a p-value of <0.05 was considered statistically significant.

Results

Patients and demographics

A total of 91 patients started haemodialysis during this period. Twenty-seven patients
Figure 1: Recruitment and follow-up of patients.

91 incident haemodialysis patients identified

65 patients having baseline troponin and accepted for ongoing follow-up

55 patients with 2nd troponin

50 patients with 3rd troponin

40 patients with 4th troponin

13 patients missing initial troponin
11 patients with acute kidney injury
1 patient undergoing cardiac transplant
1 patient with non-ST elevation myocardial infarct

5 patients died
2 patients transferred to other institutions
1 patient had a transplant
1 patient changed to peritoneal dialysis
1 patient recovered renal function

3 patients died
1 patient transfer to other institutions
1 patient reached end of follow-up

2 patients died
1 patient had a transplant
1 patient changed to peritoneal dialysis
1 patient recovered renal function
5 patients reached end of follow-up

Table 1: Baseline demographic data.

<table>
<thead>
<tr>
<th></th>
<th>Median (interquartile range) or number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 (50–70)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (46.15%)</td>
</tr>
<tr>
<td>Female</td>
<td>35 (53.85%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>24 (36.92%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>21 (32.31%)</td>
</tr>
<tr>
<td>Māori</td>
<td>9 (13.85%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (16.92%)</td>
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</table>
Table 1: Baseline demographic data (Continued).

<table>
<thead>
<tr>
<th>Table 1: Baseline demographic data (Continued).</th>
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<tbody>
<tr>
<td><strong>Smoker</strong></td>
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<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Ex-smoker</td>
</tr>
<tr>
<td>Never smoked</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Vascular access at initiation of first dialysis</strong></td>
</tr>
<tr>
<td>Arterio-venous fistula</td>
</tr>
<tr>
<td>Tunneled dialysis catheter</td>
</tr>
<tr>
<td>Temporary dialysis catheter</td>
</tr>
<tr>
<td>Systolic blood pressure prior to first dialysis (mmHg)</td>
</tr>
<tr>
<td>Diastolic blood pressure prior to first dialysis (mmHg)</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
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<td>Pre-existing coronary artery disease†</td>
</tr>
<tr>
<td><strong>Pre-existing left ventricular failure on echocardiogram</strong></td>
</tr>
<tr>
<td>Ejection fraction &lt;55%</td>
</tr>
<tr>
<td>Ejection fraction ≥55%</td>
</tr>
<tr>
<td>No previous echocardiogram</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>HbA1c</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
</tr>
<tr>
<td>Parathyroid hormone (pmol/L)</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
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<tr>
<td><strong>Cause of end-stage renal failure</strong></td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
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<tr>
<td>Vasculitis/anti-glomerular basement membrane disease</td>
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<td>Reno-vascular disease</td>
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<td>Adult polycystic kidney disease</td>
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<tr>
<td>Reflux nephropathy</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Other</td>
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</table>

†History of myocardial infarction, angina, angiogram proven coronary artery disease, positive dobutamine stress echocardiogram.
were excluded from the final analysis (Figure 1). Out of these 27 patients, 13 patients did not have their initial troponin measurement, 11 patients had acute kidney injury with subsequent recovery of renal function, one patient was undergoing heart transplant and one patient had myocardial infarction prior to first haemodialysis session. Sixty-five patients had their baseline hsTnT and had repeat measurement prior to a regular haemodialysis session every 2–4 months. Each patient was followed up for at least six months to a maximum of 18 months. The median follow-up period was 13.2 months. Forty patients had four hsTnT levels obtained at the end of the study period.

The baseline and demographic data for the 65 patients included in the final analysis is shown in Table 1. The mean age of the patients was 62 years, with Pacific Islanders making up about 37% of patients, followed by Caucasians (32%) and Māori (14%). Approximately 49% of the patients had diabetic nephropathy.

Troponin levels

The median baseline hsTnT was 91ng/L with an interquartile range (IQR) of 54–191 (Figure 2). Factors significantly associated with higher baseline troponin include non-Caucasian ethnicity, diabetes mellitus, pre-existing left ventricular dysfunction, albumin level less than 38g/L and CRP level more than 10 (Table 2).

There was a reduction in median hsTnT levels after the initiation of dialysis, with median 2\textsuperscript{nd} hsTnT of 77 (33–129), median 3\textsuperscript{rd} hsTnT of 63 (44–113) and median 4\textsuperscript{th} hsTnT of 71.5 (46–102) (Figure 2). The baseline troponin levels were significantly different to the 3\textsuperscript{rd} and 4\textsuperscript{th} troponin measurements. In comparison, there were no statistical significant differences between 2\textsuperscript{nd}, 3\textsuperscript{rd} and 4\textsuperscript{th} troponin. On subgroup analysis, patients with younger age (<65 years old), diabetes, non-smoker were associated with a statistically significant decrease in troponin levels (Table 3). There was no correlation between the changes in weight and troponin.

![Figure 2: Box plot of measurements high-sensitivity troponin T levels.](image)
## Table 2: Comparison of baseline troponin levels by selected clinical and biochemical variables.

<table>
<thead>
<tr>
<th></th>
<th>Number in each group</th>
<th>Median baseline troponin (ng/L)</th>
<th>Interquartile range (ng/L)</th>
<th>P-value</th>
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<td><strong>Age</strong></td>
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<td></td>
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<td></td>
</tr>
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<td>&lt;65</td>
<td>38</td>
<td>114</td>
<td>45 to 223</td>
<td>0.6223</td>
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<tr>
<td>≥65</td>
<td>27</td>
<td>86</td>
<td>58 to 139</td>
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<td><strong>Ethnicity</strong></td>
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<td>Caucasian</td>
<td>21</td>
<td>68</td>
<td>49 to 91</td>
<td>0.0362</td>
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<td>181.5</td>
<td>82 to 252</td>
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<td>Māori</td>
<td>9</td>
<td>119</td>
<td>71 to 240</td>
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<tr>
<td>Other</td>
<td>11</td>
<td>111</td>
<td>42 to 139</td>
<td></td>
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<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>28</td>
<td>54</td>
<td>38 to 91</td>
<td>&lt;0.0001</td>
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<tr>
<td>Yes</td>
<td>37</td>
<td>159</td>
<td>86 to 241</td>
<td></td>
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<tr>
<td><strong>History of ischaemic heart disease†</strong></td>
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<tr>
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<td>50</td>
<td>85.5</td>
<td>49 to 191</td>
<td>0.0812</td>
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<td>Yes</td>
<td>15</td>
<td>120</td>
<td>107 to 230</td>
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<td><strong>LV dysfunction ejection fraction &lt;55</strong></td>
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<td>14</td>
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<td>117 to 247</td>
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<tr>
<td>No</td>
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<td>Current</td>
<td>12</td>
<td>66.5</td>
<td>44.5 to 214</td>
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<td><strong>Albumin</strong></td>
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<td></td>
<td></td>
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<tr>
<td>&lt;38</td>
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<td>126</td>
<td>54 to 230</td>
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<tr>
<td>≥38</td>
<td>25</td>
<td>74</td>
<td>45 to 111</td>
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<tr>
<td><strong>C-reactive protein</strong></td>
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<td><strong>Body mass index</strong></td>
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<td>54 to 219</td>
<td>0.7521</td>
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<tr>
<td>≥35</td>
<td>22</td>
<td>88.5</td>
<td>44 to 178.5</td>
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</table>

†History of myocardial infarction, angina, angiogram proven coronary artery disease, positive dobutamine stress echocardiogram.
Table 3: Comparison of changes in baseline troponin to 2nd troponin level by selected clinical and biochemical variables.

<table>
<thead>
<tr>
<th></th>
<th>Number in each group</th>
<th>Change in baseline troponin to 2nd troponin (ng/L)</th>
<th>Interquartile range (ng/L)</th>
<th>P-value</th>
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<td>-103 to -5</td>
<td>0.0094</td>
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<tr>
<td>≥65</td>
<td>27</td>
<td>-5.5</td>
<td>-31 to 17</td>
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<td>Ethnicity</td>
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<td>13.5</td>
<td>-29 to 22</td>
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<td>Pacific Islander</td>
<td>24</td>
<td>-34</td>
<td>-116 to -6</td>
<td></td>
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<td>Māori</td>
<td>9</td>
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<td>-109 to 0</td>
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<tr>
<td>Other</td>
<td>11</td>
<td>-30</td>
<td>-41 to -17</td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>No</td>
<td>28</td>
<td>-8</td>
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<td>-37.5</td>
<td>-110 to -3.5</td>
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<tr>
<td>History of ischaemic heart disease†</td>
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<td>50</td>
<td>-19</td>
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<tr>
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<td>-109 to -6</td>
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<tr>
<td>Current</td>
<td>12</td>
<td>-17.5</td>
<td>-35 to -3</td>
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<tr>
<td>Albumin</td>
<td></td>
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<td>&lt;38</td>
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<tr>
<td>C-reactive protein</td>
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<td>&lt;10</td>
<td>13</td>
<td>-19</td>
<td>-41 to -5</td>
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<td>≥10</td>
<td>12</td>
<td>1</td>
<td>-29 to 18</td>
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<td>Body mass index</td>
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<td>&lt;35</td>
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<td>-46 to 1</td>
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<tr>
<td>≥35</td>
<td>22</td>
<td>-30</td>
<td>-68 to -10</td>
<td></td>
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</tbody>
</table>

†History of myocardial infarction, angina, angiogram proven coronary artery disease, positive dobutamine stress echocardiogram.
Figure 3a: Bland-Altman plot of second hsTnT compared to baseline hsTnT.

Figure 3b: Bland-Altman plot of fourth hsTnT compared to second hsTnT.
levels (p-value=0.30). Analysis of inpatient or outpatient start also did not reveal any statistical differences in all four troponin measurements.

There was a large variation in the change from baseline troponin to the subsequent troponin levels. In comparison, the 2nd, 3rd and 4th troponin levels had a lower variation (Figure 3a, 3b).

### Death

There were a total of 10 deaths during this period but only one resulted from cardiovascular death. There were three deaths from malignancy, three deaths from withdrawal of dialysis, one from respiratory arrest, one from calciphylaxis and one from infection. The hsTnT levels were not independently associated with mortality.

However, the study showed that the change from baseline to 2nd troponin level was associated with mortality. In contrast, the change from baseline to 3rd troponin was not associated with mortality. All patients who had four troponin T measurements were still alive at the end of study (Table 4).

Of the 10 deaths, five patients died prior to the second troponin level (Figure 1). Interestingly, out of the remaining five patients who died with follow-up troponin T levels, four had an increased second troponin level in comparison to the baseline troponin.

### Table 4: Independent predictors of death.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
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<tr>
<td>Baseline troponin</td>
<td>1</td>
<td>0.996–1.004</td>
<td>0.9749</td>
</tr>
<tr>
<td>2nd troponin</td>
<td>1.006</td>
<td>0.998–1.014</td>
<td>0.1257</td>
</tr>
<tr>
<td>3rd troponin</td>
<td>1.007</td>
<td>0.994–1.03</td>
<td>0.301</td>
</tr>
<tr>
<td>Change from baseline troponin to 2nd troponin</td>
<td>0.982</td>
<td>0.964–1.00</td>
<td>0.0474</td>
</tr>
<tr>
<td>Change from baseline troponin to 3rd troponin</td>
<td>0.97</td>
<td>0.926–1.017</td>
<td>0.2082</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>6.341</td>
<td>1.345–29.89</td>
<td>0.0196</td>
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<td>Ethnicity</td>
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<tr>
<td>Caucasian</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>0.26</td>
<td>0.052–2.914</td>
<td>0.099</td>
</tr>
<tr>
<td>Māori</td>
<td>0.35</td>
<td>0.042–2.914</td>
<td>0.3318</td>
</tr>
<tr>
<td>Other</td>
<td>0.287</td>
<td>0.035–2.384</td>
<td>0.2478</td>
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</tr>
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<td>Never smoked</td>
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<td></td>
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<tr>
<td>Ex-smoker</td>
<td>0.303</td>
<td>0.037–2.459</td>
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<td>Current</td>
<td>0.847</td>
<td>0.176–4.08</td>
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<tr>
<td>Albumin</td>
<td>0.901</td>
<td>0.812–0.999</td>
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<td>C-reactive protein</td>
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<td>0.99–1.014</td>
<td>0.0828</td>
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<td>Diabetes mellitus</td>
<td>1.857</td>
<td>0.48–7.181</td>
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</tr>
<tr>
<td>Body mass index</td>
<td></td>
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<td></td>
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<tr>
<td>≥35</td>
<td>1.093</td>
<td>0.114–10.521</td>
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<td>History of ischaemic heart disease</td>
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<td>0.361–5.399</td>
<td>0.6289</td>
</tr>
<tr>
<td>History of revascularisation</td>
<td>1.21</td>
<td>0.153–9.557</td>
<td>0.8562</td>
</tr>
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</table>
Other factors examined including diabetes, smoking, obesity and history of ischaemic heart disease did not correlate with an increase in mortality. A low albumin level and age over 65 years old were the only factors significantly associated with mortality (Table 4).

**Discussion**

To our knowledge, this is the first prospective study to describe the changes in troponin levels in a cohort of incident haemodialysis patients.

Troponin T decreases after initiation of dialysis, with a trend towards lower troponin levels evident even in the second measurement between two to four months, although not reaching statistical significance. Subsequent measurements of troponin levels remain relatively stable, consistent with previous studies. Baseline troponin levels may be helpful for evaluation of changes over time and assist in diagnosis of an acute event. An increase of troponin levels above baseline for each patient may assist in the diagnosis of an acute myocardial infarction. Although serial troponin performed over several hours during an acute presentation may be acquired to diagnose myocardial infarction, this may lead to a delay in diagnosis. There had been no clear guidelines to the ideal time in which baseline troponin should be obtained in patients newly started on haemodialysis. In this study, the results suggest that the initial baseline troponin T level may be obtained no earlier than two to four months after the initiation of haemodialysis.

We found that patients who were younger, diabetic and never smoked were significantly associated with a decrease in troponin after the initiation of dialysis. It is possible that these groups had a different underlying pathophysiology to their cause of initiation of haemodialysis but it is difficult to form firm conclusions. The decrease in troponin T levels could not be explained solely by removal of excess fluid, as the changes in weight of the patients did not correlate with the changes in troponin.

Analysis of inpatient or outpatient initiation of dialysis, acting as a surrogate for planned start dialysis versus urgent or acute start, also did not show any differences between these two groups.

High troponin levels had previously been shown to be associated with left ventricular hypertrophy. It is postulated that in uremic cardiac hypertrophy, the growth of myocyte outpace capillary growth, which lead to increase oxygenation distance, predisposing the heart to subclinical ischaemia. The initiation of dialysis could lead to improvement in left ventricular hypertrophy or improvement in hypertension, leading to decrease in troponin. It is possible that after the initiation of haemodialysis, a new steady state is formed between troponin production and removal.

In contrast to previous studies which have shown that high troponin T is associated with mortality, there was no significant independent association with the troponin T measurements at any of the time periods examined with mortality in this study. Patients with greater change from their baseline to 2nd troponin had a higher risk of mortality. However, half of the deaths reported in this study occurred early, prior to measurement of the second troponin levels, hence the significance of this finding is unclear.

The strengths of this study include inclusion of all patients initiated on haemodialysis irrespective of their site of initiation and the prospective follow-up of all patients. We also obtained significant observations including changes in weight during the course of the study. This study has a number of limitations. These include a small number of patients recruited, short follow-up time and low number of cardiovascular-related deaths, which limit our interpretation of the mortality associations. The analysis of left ventricular dysfunction is further impaired by the lack of previous echocardiogram in 35% of the patients. In previous studies, there is a variability of 8.2–44% on changes in hsTnT in prevalent haemodialysis patients, hence we cannot exclude the possibility that the changes we observed represent a natural variability of serial measurements. In conclusion, this is the first study to show that hsTnT levels decrease after the initiation of haemodialysis and remained relatively stable with subsequent measurements. The baseline hsTnT measured prior to commencement of haemodialysis did not correlate with mortality. The cause of change of the hsTnT is unclear but is not solely explained by initial fluid overload or urgent start haemodialysis.
Competing interests: Nil.

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URL:

REFERENCES:


Improving the use and timeliness of anticoagulation reversal for warfarin related intracranial haemorrhage

Carl Hanger, John Geddes, Tim Wilkinson, Michele Lee, Scott Pearson, Andrew Butler, Krishna Badami

ABSTRACT

BACKGROUND: Warfarin-related intracranial haemorrhage (WRICH) is a life-threatening complication of warfarin use. Rapid and complete reversal of the coagulopathy is required. Reversal protocols which include prothrombin complex concentrates (PCC) are now recommended. We report on a quality improvement project to implement and refine such a protocol.

METHODS: Retrospective and then prospective audits of all WRICH patients presenting to a single centre. The protocol development and subsequent refinements are described. Outcomes included times to scanning, treatment and overall door-needle times, as well as use of PCC.

RESULTS: Across the three cohorts, use of PCC increased over time from 15% to 100% of eligible patients (p<0.001). There were significant improvements in median time to scanning (1.9 to 1.5 to 1.3 hours, p=0.03) and median door-needle times (4.5 to 2.9 to 1.9 hours, p=0.018). Key steps in the change process included (1) identifying need for change, (2) utilising senior clinical opinion leaders, (3) using “Plan-do-study-act” cycles, (4) involvement of all relevant stakeholders, (5) having a broad implementation and education plan, (6) a “change friendly” environment and (7) collaborating across departments.

CONCLUSION: The introduction (and revisions) of an anticoagulation reversal strategy for WRICH has led to increased PCC use and reduced times to both diagnosis and treatment. Further work is required to improve door-needle times and monitoring.

Warfarin is commonly used to prevent thromboembolism in conditions such as atrial fibrillation. Haemorrhages are potential complications of warfarin therapy and warfarin related intracranial haemorrhage (WRICH) is one of the most devastating of these. WRICH constitute between 10–15% of all intracerebral haemorrhage (ICH). The 40–68% early mortality in WRICH is higher than primary ICH and there is severe disability in many survivors. Prolonged bleeding due to the coagulopathy leads to haemorrhagic expansion (HE) and increased final volume of the ICH. Both HE and volume of bleed are independent predictors of poor outcomes.

While guidelines recommend urgent reversal of anticoagulation in WRICH, there are still a range of strategies suggested, possibly reflecting the paucity of randomised controlled data available. The main therapeutic options include vitamin K, fresh frozen plasma (FFP), recombinant factor VIIa and prothrombin complex concentrates (PCC) or combinations of these. Historically, FFP together with Vitamin K has been the mainstay of reversal in the US, whereas treatment that includes PCC has become more commonly used elsewhere. Reversal with FFP is readily available, but takes time to prepare and administer, and requires larger plasma volumes for adequate reversal. Reversal of the coagulopathy is often incomplete in the first few hours after FFP. In comparison, PCCs are quick to administer, correct the international
normalised ratio (INR) rapidly and are lower volume infusions. The use of PCC is recommended in many haematological reversal guidelines but has been less consistent in stroke literature until recently.\(^1,9\)

We recently showed an improved survival in WRICH with PCC use, and a trend to better outcomes with earlier reversal.\(^12\) While the time window for reversal is uncertain, it is assumed to be as soon as possible to minimise HE.\(^13\) In the stroke thrombolysis literature, door-to-needle times are closely monitored and minimised. Despite the mantra of “time is brain” equally applying to WRICH treatments, there has been less emphasis placed on the urgency of reversal of bleeding. Many studies report door-to-treatment times of many hours,\(^14,15\) which seem too slow for a life threatening situation. Thus both timing and completeness of reversal with treatment should be focused on.

An initial audit of anticoagulation reversal in WRICH at our institution (1996–2006) revealed very poor use of reversal strategies, with little standardisation of practice. Doses of vitamin K and FFP varied markedly and PCC was not used at all. Because of the inadequacy of our anticoagulation reversal, we developed a local protocol to emphasise the importance of both adequacy and urgency of reversal. There was a specific intent of increasing the use of PCC.\(^11\) A variety of strategies were employed over time to introduce this protocol and then refine it. A repeat audit showed that while there was a successful uptake of the PCC based protocol, with improved patient outcomes, there remained significant delays (median 2.7 hours from CT to PCC). In response to these audit findings, further refinements in both protocol and service delivery have been made.

We wish to share this process of change in order to help others also implement change. The aims of this quality improvement project are to (1) describe the protocol changes made, (2) describe the strategies used to change clinical behaviour and (3) to assess the effectiveness of strategies in reversing anticoagulation in WRICH, using key outcome measures.

**Methods**

**Context**

Christchurch, New Zealand is a city with one acute hospital and two rehabilitation hospitals (population catchment of 520,000), to which all ICH patients are admitted. The acute site has all the acute services expected in a tertiary referral hospital, including a neurosurgical unit and an acute stroke unit (ASU) established in 2004.\(^16\) WRICH is a relatively uncommon but serious condition (approximately 20/year) presenting to an Emergency Department (ED) with annual attendances of 90,000.

**Figure 1:** Timeline.
Study timeline

This paper reports on a series of retrospective and then prospective audits of the adequacy of coagulopathy reversal in all patients presenting with WRICH to Christchurch (Figure 1). An initial audit from 1996 to 2006 inclusive (data not shown) showed inadequate reversal and no PCC use. As a result of that audit, a protocol for WRICH reversal was developed and the results re-audited (2nd audit) and published. Further refinements of the protocol were required and a prospective 3rd audit of all WRICH was completed for July 2010–Oct 2013.

The results presented here are a combination of the previously published data for 2004–2011 and subsequent data (until Oct 31, 2013) with an emphasis on treatment protocols in place at the time (no protocol [< 1/2/09], after first protocol [1/2/09–31/12 inclusive] or post Emergency Department (ED) protocol [1/2/12–31/10/13]), with a view to documenting and explaining any changed practice over time.

Case finding

ICH patients were identified from discharge coding data, using international classification of diseases (ICD-10) coding of ICH (I61 or I62.9). These data were cross-checked with the prospective stroke register in ASU. The electronic and laboratory records for each person with an ICH were then reviewed to identify those with a WRICH. A WRICH was defined if there was (1) an ICH confirmed on imaging or post-mortem studies (includes those with intraventricular haemorrhage alone) and (2) an elevated INR >1.2 on admission and (3) patient taking warfarin at the time of stroke. The clinical notes of each of these WRICH patients were reviewed to collect data on treatments given.

Exclusions were: ICH secondary to trauma or thrombocytopenia, thrombolyis or heparin-related ICH, haemorrhagic transformation of an infarct, subdural and subarachnoid bleeding, asymptomatic micro-bleeds and patients presenting to hospital late (>24 h of onset). Some patients were clearly dying from the outset and were given palliative cares only. Patients whose clinical notes stated palliative intent at outset were not included in the analyses of treatments or timeliness.

Outcome measures

‘ED arrival-scan’ times measure time to obtain a diagnosis, whereas ‘scan-treatment’ times reflect the urgency of reversal. The combined ED arrival-treatment times reflect the overall efficiency of both diagnosis and treatment, equivalent to “door-to-needle time” for thrombolysis.

The volume of ICH was calculated using standard ABC/2 formula from acute CT scans.

Times of presentation to ED, scanning and blood tests were taken from ED clinical records and from times recorded on the images or blood test results. For each reversal agent given, the administration time as recorded by the administering nurse was used, rather than when it was prescribed.

The local ethics committee considered these studies as audits and did not require formal ethics committee review (URB/10/EXP/016).

Statistics

Between group comparisons for continuous variables were undertaken with ANOVA and for categorical variables were undertaken with the Chi-square test.

Results

Stages of protocol development

Development of first protocol

Immediately following the initial audit (unpublished) which showed inadequate reversal of the coagulopathy in WRICH patients, a group involving haematologists, general and stroke physicians was convened to develop the first WRICH reversal protocol (Appendix). This was based on general haemostasis guidelines and emphasised the urgent use of PCC and reduced the role of FFP. This advice differed from some ICH specific guidelines at the time, which did not specify which agents should be used. This protocol was widely disseminated through resident medical officer (RMO) teaching sessions, discussion with General Medicine senior medical officers (SMO) and inclusion in local handbooks (both paper and electronic versions). There was a grand round presentation to a broad audience of physicians, RMOs and other clinical staff within the hospital.
During the implementation phases of the first protocol the group identified several potential issues which might contribute to delays. These included: (1) clinicians attitudes (“nothing will alter outcome”), (2) procedural (delays in access to CT scanning, a requirement to contact on call haematologist or blood transfusion specialist and to have INR result before being able to access PCC) and (3) educational (staff unsure how to access or give PCC, or how fast to give it).

Development of ED protocol

In response to the results of an audit of the first protocol, a different approach, with wider clinical representation, was deemed appropriate. A presentation to all ED physicians and discussion with the blood transfusion service resulted in the convening of a group focused on urgent reversal within ED. There was representation from stroke physicians, ED and the blood transfusion service. Similarities to the thrombolysis pathway for ischaemic stroke, where minimising delays is crucial, were made. Initial thoughts were to develop a “reversal kit” to accompany the patient to CT scanning, similar to the thrombolysis kit.

At that time, perceived critical barriers causing delays included: (1) the location where reversal occurs (ED or ASU) and who delivers it, (2) need for INR result before PCC released by New Zealand Blood Service (NZBS), (3) perception of less urgency for scanning by ED staff for some patients (eg less unwell with higher Glasgow coma scale (GCS)), (4) need to telephone on call haematology or NZBS specialist for permission to use PCC, (5) delivery of PCC to ED from NZBS and (6) practical issues with administering PCC to patient. It was apparent that these predominantly ED-based issues were different from those addressed in our first protocol when the focus was on ASU staff.

The revised protocol took several iterations to get to its final form (Appendix). Steps which were important in the protocol development included the following.

- An urgent CT scan should be considered for any patient who presents with a stroke syndrome and is taking warfarin.
- If ICH is seen on this urgent CT, the ED transit nurse with the patient immediately activates the “urgent reversal” pathway by faxing a blood bank request form (with “URGENT warfarin reversal haemorrhage” sticker attached to it) to NZBS and phoning ED to prepare for the reversal. For practical reasons, it was not deemed feasible to start the infusion in the scanning room and the consensus was for patient to immediately return to ED for this. Thus, the urgent reversal “kit” became a flow chart with the appropriate fax and phone numbers included and a blood bank request form (marked “URGENT warfarin reversal haemorrhage”).
- Because WRICH is life threatening, it was unanimously agreed that urgency was paramount and systemic barriers such as the requirements for a raised INR result and a phone call to the blood specialist were removed. On return to ED, nurses give PCC, then Vitamin K, before starting FFP infusion (FFP needs time to thaw). There were some concerns about the duration of PCC infusion, with some existing protocols stating maximum infusion rate of 3ml/minute. After deliberation, the ED protocol allows for an initial slow push, followed by an increased rate of infusion up to 10ml/minute. This enabled the entire PCC dose to be delivered in 10–15 minutes via syringe pump.
- To minimise time spent in ED, the ASU would prepare a bed during the PCC infusion and then “pull” the patient from ED as soon as possible after this. This might occur before FFP was given.

Practical implementation of ED protocol

Our initial discussions for the ED protocol did not involve the radiologists, and the first few patients presenting with a stroke syndrome and on warfarin exposed this oversight. However, it was quickly rectified...
Table 1: Demographic variables of the three cohorts.

<table>
<thead>
<tr>
<th></th>
<th>No protocol (n=59)</th>
<th>First protocol (n=53)</th>
<th>ED protocol (n=25)</th>
<th>Between group comparisons (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean, years) (IQR)</strong></td>
<td>77.9 (75–84)</td>
<td>77.8 (73–83)</td>
<td>75.3 (69–84)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Gender (% female)</strong></td>
<td>49%</td>
<td>38%</td>
<td>28%</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Indication for warfarin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>47 (80%)</td>
<td>42 (79%)</td>
<td>15 (60%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>3 (5%)</td>
<td>6 (11%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Venous thrombo-emboli</td>
<td>4 (7%)</td>
<td>3 (6%)</td>
<td>4 (16%)</td>
<td></td>
</tr>
<tr>
<td>Systemic emboli</td>
<td>2 (3%)</td>
<td>0</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (5%)</td>
<td>2 (4%)</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean INR on presentation (range)</strong></td>
<td>2.8 (1.6– 8.8)</td>
<td>2.8 (1.6–6.1)</td>
<td>3.4 (1.3– 11.9)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>ICH volume - mean (ml) Median</strong></td>
<td>24.1</td>
<td>29.4</td>
<td>37.5</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>ICH volume</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (&lt;5ml)</td>
<td>15 (25%)</td>
<td>12 (23%)</td>
<td>4 (16%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Medium (5–30ml)</td>
<td>24 (41%)</td>
<td>21 (40%)</td>
<td>7 (28%)</td>
<td></td>
</tr>
<tr>
<td>Large(&gt;30ml)</td>
<td>15 (25%)</td>
<td>18 (34%)</td>
<td>12 (48%)</td>
<td></td>
</tr>
<tr>
<td><strong>Location of ICH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>0</td>
<td>2 (4%)</td>
<td>0</td>
<td>0.30</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>11 (19%)</td>
<td>4 (7%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Deep</td>
<td>22 (37%)</td>
<td>24 (45%)</td>
<td>11 (44%)</td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>21 (36%)</td>
<td>21 (40%)</td>
<td>11 (44%)</td>
<td></td>
</tr>
<tr>
<td>IVH alone</td>
<td>5 (8%)</td>
<td>2 (4%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td><strong>ICH score mean (median)</strong></td>
<td>2.0 (2)</td>
<td>1.8 (2)</td>
<td>2.0 (2)</td>
<td>0.80</td>
</tr>
<tr>
<td>Initial GCS mean (median)</td>
<td>11.8 (14)</td>
<td>12.0 (14)</td>
<td>12.0 (14)</td>
<td>0.95</td>
</tr>
<tr>
<td>Palliated from onset in ED</td>
<td>13 (22%)</td>
<td>18 (34%)</td>
<td>2 (8%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with intraventricular extension</td>
<td>30 (51%)</td>
<td>29 (55%)</td>
<td>14 (56%)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Acute hospital length of stay (mean, days)</strong></td>
<td>7.3</td>
<td>5.8</td>
<td>6.4</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Total hospital length of stay (includes rehab LOS)(mean, days)</strong></td>
<td>22.2</td>
<td>19.4</td>
<td>19.5</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Admitted from</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>56 (95%)</td>
<td>47 (89%)</td>
<td>25 (100%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Residential care</td>
<td>3 (5%)</td>
<td>6 (11%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Deaths in hospital</td>
<td>30 (51%)</td>
<td>23 (43%)</td>
<td>11 (44%)</td>
<td>0.70</td>
</tr>
</tbody>
</table>
through direct discussions between ED and radiology specialists. There was added value for the radiologists, as the protocol ensured a rapid “pull” of the patient from the scanner back to ED, thus reducing delays in the scanner.

Education about the revised protocol was achieved in several different ways. There were teaching sessions for the following groups: ED nurses, ASU staff (medical and nursing) and general physicians. It has been incorporated into local acute medicine, ED and stroke guidelines. There has been a further grand round presentation. ED nurses developed a one-page practical guide for PCC administration, which includes preparation and infusion rates. Discussions between clinicians about cases where there had been delays raised awareness of the protocol, highlighted the urgency of treatment and contributed to the success of the protocol.

**Table 2: Key outcomes for the three cohorts.**

<table>
<thead>
<tr>
<th>Treatments given</th>
<th>No protocol</th>
<th>First protocol</th>
<th>ED protocol</th>
<th>Difference between cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>43 (93%)</td>
<td>34 (97%)</td>
<td>21 (91%)</td>
<td>P=0.62</td>
</tr>
<tr>
<td>Prothrombin Complex Concentrates (PCC)</td>
<td>7 (15%)</td>
<td>30 (86%)</td>
<td>23 (100%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Fresh Frozen Plasma (FFP)</td>
<td>30 (65%)</td>
<td>18 (51%)</td>
<td>16 (70%)</td>
<td>P=0.30</td>
</tr>
<tr>
<td>Median number of units FFP given (IQR)</td>
<td>2 (2–4)</td>
<td>1 (1.0–1.8)</td>
<td>1 (1.0–2.0)</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Median number of treatment agents given (IQR)</td>
<td>2 (1–2)</td>
<td>2 (1–3)</td>
<td>3 (2–3)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median time in hours (IQR)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ED arrival to scan</td>
<td>1.9 (1.3–4.0)</td>
<td>1.5 (0.9–2.6)</td>
<td>1.3 (0.8–1.9)</td>
<td>P=0.03</td>
</tr>
<tr>
<td>Scan to Vitamin K</td>
<td>1.4 (0.8–3.3)</td>
<td>1.3 (0.6–1.8)</td>
<td>0.8 (0.4–1.3)</td>
<td>P=0.08</td>
</tr>
<tr>
<td>Scan to FFP</td>
<td>2.4 (1.9–3.7)</td>
<td>2.4 (1.1–3.6)</td>
<td>2.8 (1.7–4.5)</td>
<td>P=0.89</td>
</tr>
<tr>
<td>Scan to PCC</td>
<td>3.0 (2.2–4.2)</td>
<td>2.4 (1.6–3.1)</td>
<td>1.5 (0.9–2.4)</td>
<td>P=0.14</td>
</tr>
<tr>
<td>Scan to first (any) treatment</td>
<td>1.3 (0.7–3.1)</td>
<td>1.2 (0.6–1.7)</td>
<td>0.7 (0.5–1.1)</td>
<td>P=0.03</td>
</tr>
<tr>
<td>ED arrival to first (any) treatment</td>
<td>4.5 (2.2–7.2)</td>
<td>2.9 (1.7–4.9)</td>
<td>1.9 (1.5–2.4)</td>
<td>P=0.018</td>
</tr>
<tr>
<td>ED arrival to PCC</td>
<td>5.6 (3.9–7.0)</td>
<td>4.4 (2.5–9.2)</td>
<td>2.8 (1.8–4.2)</td>
<td>P=0.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monitoring of INR</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time (hours) from PCC (or FFP) to first INR monitoring</td>
<td>9.8 (3.7–17.8)</td>
<td>6.1 (2.5–12.2)</td>
<td>3.3 (1.4–5.1)</td>
<td>P=0.001</td>
</tr>
<tr>
<td>INR checked at some time</td>
<td>32 (70%)</td>
<td>27 (77%)</td>
<td>16 (80%)</td>
<td>P=0.60</td>
</tr>
<tr>
<td>INR normal (&lt;1.3) on first testing</td>
<td>16 (50%)</td>
<td>23 (85%)</td>
<td>14 (88%)</td>
<td>P=0.003</td>
</tr>
</tbody>
</table>
Outcomes

There were no demographic differences between the three cohorts (Table 1), except that in the ED cohort, fewer were treated as palliative from outset.

The number of patients given PCC increased following the first protocol and again following the ED protocol (p<0.001) (Table 2). Compliance with protocol dosing of PCC (all given 25–50 IU/kg, most given 50 IU/kg) was complete in all patients (latter two cohorts). The only exceptions were in patients in whom active treatment was changed to palliation.

FFP dosing was higher in the no-protocol cohort (expected as PCC generally not used), whereas subsequent FFP use was 1–2 units, in accordance with protocol (one patient given three units due to difficulty accessing PCC), (p<0.001).

The development of the first and then ED protocols not only improved the use of PCC, but also reduced variation in time to treatment. ED to scan times were significantly faster over time (p=0.03) with greater consistency.

Time from diagnosis (scan) to treatment with individual agents showed nonsignificant trends toward faster treatments with Vitamin K and PCC, whereas FFP was given at similar times throughout. The time from scan to first treatment (any agent, but usually PCC or Vitamin K) was significantly faster with marked reduction in variability.

The combined time (door-needle) was faster, with significant improvements in ‘ED to first reversal (any agent)’ and a trend for ‘ED to PCC reversal’ times.

The number of patients who had some monitoring of the adequacy of reversal did not significantly alter. However, both the timeliness and the completeness of reversal (INR <1.3) did improve significantly.

Discussion

Our implementation and then refinement of a WRICH anticoagulation reversal strategy was successful in changing several components of clinical practice for this emergency condition. The most obvious success was in the increased and sustained use of PCC for anticoagulation reversal. Timeliness of scanning (diagnosis) and time to reversal also improved significantly, with much less variation in response times. Both the use of PCC and the speed of reversal have been shown to be associated with better outcomes after WRICH.12

The improvements in overall ‘ED arrival to treatment’ times reflect more efficient diagnosis and treatment, equivalent to the ‘door-needle time’ for thrombolysis.17 These improvements fit with the ‘time is brain (lost)’ concept and while the times have improved and are better than some reports,21,22 there is no room for complacency. Earlier and complete reversal is likely to be better12 and ongoing quality improvements to reduce door-needle times are needed. Systemic barriers to sourcing PCC from the blood bank have been reduced, similar to other studies.20,21 To minimise any delays and to keep it simple, our protocol deliberately did not depend on determining the INR, in contrast to a recent guideline.22

Point of care INR testing in the ED is an alternative approach to minimise delays21 but was not used here. The protocol also encouraged that PCC reversal should be given as soon as possible in ED, rather than deferred until the patient is in the ASU. ED delivery may be associated with better patient outcomes.23

Not only did reversal with PCC increase, but prescribing of Vitamin K and FFP was maintained with better compliance with dosing. It is important that PCC is not used in isolation from other agents, as it is the combination of PCC, Vitamin K and small doses of FFP that reverses most rapidly, completely and with lasting effect.11 Combined treatment options may be associated with lower mortality,24 although value of low dose FFP in addition to PCC is debated.25 Some recommend the use of combination of a 4-factor PCC (contains factors II, VII, IX and X) and Vitamin K without FFP.26 In the development of the ED protocol, this was discussed. We chose to keep low dose FFP in the protocol because of (1) the PCC available was a 3-factor PCC and does not have reliable amounts of factor VII and (2) the need for complete, rapid and sustained reversal and (3) the extreme mortality and morbidity of WRICH. Removal of FFP from the protocol would certainly simplify the protocol and is a future consideration.
Checking the INR after reversal did not improve and may reflect a failure of the protocol or failure in the transfer of information between clinical areas. Others have noted similar delays. Post-reversal checks were indicated when the patients reached the ASU, rather than while still in the ED. This suggests that while the protocol is effective within the ED, its reach into ASU was less effective. The educational efforts for the ED protocol were primarily directed to ED staff, but need to include ASU. Point of care INR testing might also assist with more timely checking of reversal.

The protocol wording about monitoring reversal may be ambiguous and has been revised (Appendix). It is reassuring that despite a lack of increase in INR checks, those that were checked were done earlier and were more likely to have normalised, reflecting improved reversal strategies. While warfarin use may change with the introduction of direct-acting oral anticoagulants (DOACs), many patients will still require warfarin, such as those with prosthetic heart valves or renal impairment and those already stabilised on warfarin. Thus there is a continued need both for protocols such as this, as well as for the urgent reversal of DOACs.

Translating guidelines into routine clinical practice is often a slow process and was the focus of this study. The introduction of our protocols reflects many aspects of a successful change process. We suggest some key elements of success were: (1) identifying a need for change, (2) utilising senior clinical opinion leaders, (3) using “Plan-do-study-act (PDSA)” cycles, (4) involvement of all relevant stakeholders, (5) having a broad implementation and education plan, (6) working within a “change friendly” environment and (7) collaborating across departments with common goal of improving patient and systems outcomes. These are each explored below.

The initial poor audit results provoked strong discussions, stimulated key senior clinicians to take action and created a desire for change. This desire for change overcomes the inertia encountered in an “unfreeze-transition-refreeze” sequence. Guidelines alone are poor effectors of change, but when guidelines are combined with key clinical opinion leaders who see a need to change because of local data showing poor performance, it is more likely changes will occur. Following the first protocol implementation, PCC use improved, yet delays in reversal were common. When ED physicians saw these delays, they then became the key drivers in promoting further changes, which resulted in the development of the ED protocol.

Use of the PDSA audit cycle provides the ability to progressively enhance systems and provides a method of feedback to stakeholders. Identification of a need for change then initiates development of new standards (first protocol). However, completion of the full audit cycle with ongoing data collection, analysis and refining the processes is essential to achieve persisting change. Repeated audit cycles have kept this relatively uncommon, but serious, condition in clinicians’ minds and allowed both consolidation and then further changes of the protocols. At the time of writing, we are just completing a fourth audit (data not shown) and further refinement of the protocol (Appendix).

We were able to resolve conflicting advice from different guidelines (stroke specific versus haematology) through involving stakeholders from a range of professions. Involvement of all stakeholders is a key aspect of achieving practice change. There needed to be a consultation phase before implementation. The lack of initial involvement of one critical group (radiologists) was promptly corrected with discussions between key players. The initial protocol failed to deliver the impact we had hoped for, largely because it missed the ED physicians. ED physicians identified further barriers to change and were critical in championing the ED protocol.

Implementation and education was achieved through a variety of means. These included teaching grand rounds, local paper and online versions of the protocol in different locations (The Bluebook, Stroke and ED guidelines). Translating guidelines into practice may be most effective using multifaceted strategies including audit, opinion leaders and reminder systems. While we did not have reminders, our use of multiple methods and ensuring our guideline was easily accessible via local intranet may have helped embed our
change. Senior nurses and nurse educators helped disseminate the protocol to all ED staff. ED staff could see added value of the protocol for other patient groups with life threatening bleeding such as GI bleeds while on warfarin. A particularly important and ongoing method of embedding the protocol has been rapid critical incident feedback and discussion between relevant senior clinicians when a protocol violation has occurred. This helps to reinforce both the presence and importance of the protocol and identifies further barriers.

While our protocol introduction appears to have been successful, there may be alternative explanations for our results. The introduction of guidelines alone may have worked, irrespective of the advocacy, implementation and education. However, this is unlikely based on slow or poor uptake of guidelines alone. A government mandated ‘six-hour rule’ for ED discharges may have increased urgency regardless of our protocol. While this six-hour rule creates a sense of urgency, it nearly thwarted our ED protocol. There was initial hesitancy to bring the patient back from scanning to ED because of this rule. However the ED clinicians advocated for this using a “best for patient-best for system” argument. Collaboration between departments ensured ASU “pulled” the patient from ED as soon as the PCC infusion finished. As with any new agent, knowledge of PCC may have been incidentally learnt, leading to improved uptake. However, it is more likely that the introduction of a dedicated protocol containing PCC increased awareness. One aspect of change strategy that we did not employ, but is promoted in many models, is employing a dedicated change agent. A change agent may have achieved successful implementation of the protocols sooner. Our use of local opinion leaders may have been slower, but their longer tenure promotes sustained change beyond the temporary employment of a change agent.

We have outlined the successful introduction of an improved WRICH anticoagulation reversal strategy, which over time has led to improved clinical urgency, but there is still room for improvement of door-needle times.

**Competing interests:**
Nil.

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REFERENCES:


Appendix

First reversal guidelines for warfarin-related intracerebral haemorrhage

All patients with a warfarin-related ICH and an elevated INR (>1.2) should have rapid reversal of the coagulopathy. Do ALL of the following:

- Cease warfarin.
- Give 5–10mg Vitamin K intravenously.
- Prothrombin complex concentrate (Prothrombinex-HT is available in New Zealand) 25–50IU/kg intravenously.
- Fresh frozen plasma (150–300ml) IV.

Notes:

- Vitamin K takes 6–24 hours to be effective.
- Fresh frozen plasma contains all the relevant clotting factors but requires large volumes (two or more litres) to adequately replace clotting factors.
- Prothrombin complex concentrate acts rapidly (within 15 minutes) and is accessed through contacting New Zealand Blood Service doctor on call.
- Prothrombinex™-HT used in New Zealand may not contain sufficient factor VII, hence concurrent use of a small amount of FFP as well.
- Monitoring:
  - INR alone is not useful for monitoring the effectiveness of clotting factor replacement. It is only useful for monitoring warfarin use in steady state situations.
  - Monitoring should be done immediately after treatment using a coagulation screen (INR, APTT, thrombin time and fibrinogen). If still abnormal, more coagulation factors should be given immediately.
  - If normal recheck in 4–6 hours (reflecting shortest half life of factor VII and Vitamin K onset of action).
  - If normal again, then recheck at 24 hours or sooner if patient clinically unstable.
- The risk of thrombotic events during this short-term reversal appears very low, even in patients with prosthetic heart valves.


Revised (ed protocol) guidelines for intracerebral haemorrhage while on warfarin: reversal of the warfarin-related coagulopathy 2012

Background

- ICH while taking warfarin is life threatening medical emergency with a mortality of between 43–70% at 30 days.
- Initial ICH volume and further haemorrhagic expansion are both independent predictors of mortality.
- ICH volume is not maximal at the outset but can continue to increase for several hours or up to 24–48 hours if taking warfarin.
- Most warfarin-related ICHs occur with the INR within the “therapeutic” range.
- Warfarin causes functional deficiencies of several different clotting factors which need immediate replacement in the setting of ICH while taking warfarin.

Reversal guidelines

- Any patient with both (1) an acute intracerebral haemorrhage and (2) taking warfarin should have immediate intravenous reversal of the coagulopathy. This includes:
- Stop warfarin.
- Give Vitamin K 5–10mg intravenously immediately.
• Give Prothrombin complex concentrate (PCC) 50 units/kg intravenously immediately.
• Give Fresh Frozen Plasma (150–300ml) (1–2 units).

Notes:
• Vitamin K takes 6–24 hours to be effective.
• Prothrombin complex concentrate (PCC) rapidly reverses the coagulopathy within 15 minutes. It is accessed by either
  • Following “life-threatening bleed on warfarin” protocol in Emergency Department (warfarin reversal pack to accompany patient to CT scanner from ED) or
  • contacting New Zealand Blood Service Doctor on call.
• If PCC is NOT available, Vitamin K (as above) and larger doses of Fresh Frozen Plasma (FFP) can be given (at a dose of 15–30ml/kg) but produces suboptimal anticoagulation reversal.
• Monitoring:
  • INR is not useful for monitoring the effectiveness of clotting factor replacement. It is only useful for monitoring warfarin use in steady state situations.
  • Monitoring should be done immediately after treatment using a coagulation screen (INR, APPT, Thrombin time and fibrinogen). If still abnormal, more coagulation factors should be given immediately.
  • If normal recheck in 4–6 hours (reflecting shortest half life of factor VII and vitamin K onset of action).
  • If normal again, then recheck at 24 hours or sooner if patient clinically unstable.
• The risk of thrombotic events during this short-term reversal appears very low, even in patients with prosthetic heart valves.
• Oral thrombin inhibitors (Dabigatran) related ICH
  Like warfarin related ICH, these patients need urgent reversal of the coagulopathy. See notes in * section for dabigatran reversal Blue Book Section 14.8.5 (Haematology).
• Longer-term management
  This requires an individual assessment of the risks and benefits of restarting warfarin or not. Most should not restart warfarin, but it is dependent on indications for anticoagulation, location and severity of bleed, comorbidities, age and concurrent medications.

Intracranial haemorrhage on warfarin

This pathway covers reversal of warfarin-related coagulopathy in patients with intracranial haemorrhage while on warfarin.

There is a different process for patients with:

• Oral thrombin inhibitors (dabigatran) related intracranial haemorrhage
• Patients with oral thrombin inhibitors (dabigatran) related intracranial haemorrhage
• Other life-threatening bleeds while on warfarin
  • Reversal of warfarin coagulopathy for other life threatening bleeds eg, upper gastrointestinal bleeds or trauma, might have specific clinical criteria for reversal eg, endoscopic findings or clinical manifestations of shock. Seek advice from relevant senior medical staff.
  • The process of reversal using prothrombinex, FFP and Vitamin K is the same as this pathway describes and can be used for any life-threatening bleeds where reversal is deemed appropriate.

About intracranial haemorrhage in patients on warfarin

Medical emergency urgently

Assessment

1. Arrange Urgent CT Head.
   • Fax a CT request to 81504, and
   • Page the Radiology Registrar on 8911, or
   • Use E-request when this becomes available, but phone to make sure an urgent CT is being organised.

2. To prevent any delays in administering intravenous reversal of coagulopathy:
   • Do not wait for the results of an INR. Reversal is required even if INR is in the sub-therapeutic range (INR 1.5 or above).
   • Before CT Head, arrange Prothrombinex VF and Fresh Frozen Plasma (FFP).

Prothrombinex VF and Fresh Frozen Plasma (FFP)

Obtain Prothrombinex and Fresh Frozen Plasma for patients on warfarin with life-threatening bleeding (including intracranial bleeding):

1. Complete the Blood Components Form (QMR022B) and clearly write “Life-threatening bleed in patient on warfarin”.
2. Include required dose of Prothrombinex, based on the patient's estimated weight (50 units/kg).
3. Request 1 unit (approximately 300mL) Fresh Frozen Plasma (FFP). On the form, write “on telephone confirmation of bleed”.
4. Send in the Lamson tube, or arrange sample delivery, to the Blood Bank and inform them via phone.
5. When reconstituting prothrombinex do not shake the vials. For full reconstitution instructions see the blood resource folder G.

Nursing guidance Note: Prosthetic heart valves are not a contraindication to reversal in this situation as the risk of thrombotic events during this short term reversal appears very low.

3. Reversal should not be given until CT confirmation of intracranial bleed. In the rare circumstances that a CT cannot be done and reversal is deemed appropriate and urgent, discuss with the consultant.
Management
1. As soon as intracranial haemorrhage is confirmed by CT Head, call the ED, ward or ICU staff and ask them to:
   • Reconstitute the required dose of Prothrombinex VF, which should have arrived by now, in preparation for administration. If the CT is normal, the Prothrombinex can be returned unused.
   • Tell the Blood Bank to prepare and send the FFP.
   • Draw up 5mg of Vitamin K for IV administration.
2. Immediately return with the patient to Emergency Department, ward or ICU.
3. Administer reversal as quickly as possible:
   • Stop warfarin.
   • Give Prothrombinex VF 50 units/kg IV, immediately on its arrival from the Blood Bank.
   • Give 5mg Vitamin K IV immediately. Vitamin K takes 6–24 hours to be effective.
   Monitoring:
   • Monitoring after reversal is essential and should include blood testing 15–30 minutes after administering Prothrombinex + FFP, then at 4–6 hours, and at 24 hours at least.
   • Send a coagulation screen (INR, APTT, thrombin time and fibrinogen) immediately after treatment.
   • If still abnormal, contact the Transfusion Medicine Specialist via the Blood Bank or seek acute haematology advice.
   • If normal, recheck in 4–6 hours (reflecting shortest half-life of factor VII and Vitamin K onset of action).
   • If normal again, recheck at 24 hours or sooner if the patient is clinically unstable.
5. Longer-term management:
   • Requires an individual assessment of the risks and benefits of restarting warfarin or not.
   • Most should not restart warfarin. However, it is dependent on indications for anticoagulation, location and severity of bleed, comorbidities, age and concurrent medications.
Implementation of fracture liaison service in a New Zealand public hospital: Waitemata district health board experience

David Kim, Denise Mackenzie, Rick Cutfield

ABSTRACT

AIM: To analyse the performance of a Fracture Liaison Service (FLS) at Waitemata District Health Board (WDHB), and to detail how systematic secondary fracture prevention can be delivered in a secondary healthcare setting in New Zealand.

METHOD: Clinical details of patients supervised by the WDHB FLS during the calendar year 2014 were reviewed and analysed. Additional information including treatment compliance and re-fracture rates were sought a year after initial intervention.

RESULTS: During the 12-month period, 301 patients with fragility fracture were seen by the WDHB FLS. All patients had clinical and laboratory assessment, one-to-one education by the FLS co-ordinator. One hundred and twenty-one patients had dual energy x-ray absorptiometry (DEXA) performed. One hundred and thirty-four of 226 treatment naive patients were started or recommended to be started on a bone protection therapy, bisphosphonate in almost all cases, and another 25 of 75 patients had adjustment made to their current therapy. Of those who were started or continued on treatment, adherence rate was 70% at a mean follow-up of 12 months.

CONCLUSION: An effective secondary fracture prevention programme, such as a FLS, can be successfully implemented in a New Zealand district hospital setting.

Secondary fracture prevention is a well-recognised care gap globally. Fracture liaison service (FLS) is a growing and popular concept for systematic secondary fracture prevention, and has been reported to be cost-effective in a number of studies.1–4 FLS exists and operates in various forms throughout the world but the core essence of FLS is having a FLS co-ordinator. This co-ordinator role is to systematically identify patients with a fragility fracture, complete patient assessment and appropriate investigations, and to initiate treatment or provide recommendations to GPs to initiate appropriate bone protection treatment.5,6

Waitemata District Health Board (WDHB) is the largest district health board in New Zealand, serving a population of over half a million in Auckland. The WDHB FLS was established in 2012 as one of the first secondary fracture prevention services in New Zealand. As well as FLS co-ordinator, the service has two FLS clinicians (endocrinologists) who provide regular clinical oversight. On the basis of its 2013 work, WDHB FLS has attained ‘bronze’ status on the International Osteoporosis Federation’s ‘FLS Map of Excellence’.

After encountering various short-comings in the first two years of its service delivery, a number of significant amendments were made to our FLS protocol, and this new protocol was implemented from January 2014. We present results of the 12 months’ work for the calendar year 2014.
Method

FLS study population
As an initial step, we sought to identify those patients over the age of 50 years who presented to a WDHB hospital (inpatient or outpatient) with a fragility fracture—defined as a fracture sustained from falling from standing height or less. Those patients with fracture of the rib, sternum, clavicle, any bone of head and neck, hands or feet were excluded.

FLS personnel
We had a dedicated 0.5 full-time equivalent (FTE) FLS nurse co-ordinator who actively screened for and identified relevant cases and implemented appropriate care. Regular weekly meetings took place with FLS co-ordinator and FLS clinician discussing each case and making management decisions.

Case detection, assessment and record keeping
The FLS co-ordinator identified cases through screening outpatient fracture clinic lists and orthopaedic inpatient lists. Relevant demographic and clinical details of identified patients were prospectively kept in an electronic database and included type of fracture, past fracture history and current or previous bone-protection treatment. Adequate ‘bone-protection treatment’ was considered to be one or more of the following: current bisphosphonate treatment or being on ‘bisphosphonate drug holiday’ for less than two years, teriparatide, hormone replacement therapy (HRT), raloxifene or an osteoporosis clinical trial drug. Calcium and/or vitamin D supplements were not considered ‘bone-protection treatment’ in this analysis. The medical history, including current medications, smoking status and alcohol consumption was routinely reviewed.

Investigation protocol
All patients routinely had serum calcium and renal function test. Those found to have raised serum calcium had serum PTH measured. Those under the age of 60 were also screened for C-reactive protein, TSH and coeliac antibodies. Men under the age of 70 had morning serum total testosterone levels measured. Dual energy x-ray absorptiometry (DEXA) was routinely performed in those under the age of 75 years and in some patients over 75 years where the DEXA result might alter a management decision or patient compliance with recommended treatment. All DEXA scans were performed by a private DEXA provider contracted by WDHB, at no cost to the patient. All DEXA scans were performed on General Electric Lunar Prodigy densitometers.

Intervention and its implementation
All identified patients received either ‘face-to-face’ or ‘over-the-phone’ education from the FLS co-ordinator regarding what osteoporosis is and its implications. Those over the age of 75 were routinely recommended to start on a bisphosphonate therapy. Those under the age of 75 whose fracture risk, after incorporating the DEXA result, was assessed to be high (>3% hip fracture risk in 10 years using FRAX and/or Garvan fracture risk calculator) were recommended to commence on bisphosphonate therapy. Alternative therapy and/or specialist clinic follow-up was arranged for those already on bisphosphonate therapy, with multiple or recurrent fractures or with secondary causes of osteoporosis needing specialist review, or patients with severe osteoporosis at the discretion of the FLS clinician. Assessment results, treatment and follow-up recommendations were communicated directly to the patient, and a formal letter detailing these was routinely sent to the patients’ general practitioner (GP). Whenever feasible and deemed appropriate, zoledronic acid infusion was delivered either while inpatient or arranged to be delivered as outpatient at one of WDHB hospitals.

Follow-up: compliance review
Electronic medication dispensing records (TestSafe) were reviewed to ascertain adherence to treatment in those who were recommended to start or were started on treatment by the WDHB FLS. If dispensing of the relevant treatment agent was not evident on the electronic system, the patient’s general practice was called to ascertain current treatment. This compliance screening was performed at a mean of 12 months after the treatment initiation (range 6–18 months).
Re-fracture detection

Patients were screened for re-fracture at a mean of 14 months (range 8–20 months) after the initial FLS input by screening electronic records for new fracture encounters at WDHB.

Ethical approval

Ethical approval was not sought because assessment, treatment and follow-up, as outlined above, is delivery of standard clinical care for FLS.

Results

Patient demographics

Three hundred and one patients were identified and reviewed. The general characteristics at the time of patient identification are summarised in Table 1. Mean age was 72 years with 86 patients between the age 50 and 65 years. The majority of patients were female of European descent.

Past history

At the time of initial assessment, 37% (112) of patients had history of at least one fragility fracture [e fracture(s) preceding index fracture], and only 53 of these 112 patients were on pre-existing bone protection treatment. An additional 22 patients were on pre-existing bone protection treatment without a past history of fragility fracture(s). The majority (63/75) of the pre-existing bone protection treatment used was alendronate or zoledronic acid. There were a small number of patients on a ‘drug holiday’ after a course of bisphosphonate, while a similar number were on HRT or a clinical trial drug, and one patient was on teriparatide (Table 1).

Types of index fractures

One hundred and thirty-eight (46%) of our cohort had a wrist fracture as their index event, with another 79 (26%) with a fractured femur, 34 (11%) humerus, and the remaining 50 (17%) with a mixture of fracture sites, mostly pelvis and ankle.

DEXA scan

One hundred and twenty-four (41%) patients were offered a DEXA scan performed, and three patients either refused or did not attend the DEXA appointment. Of 121 patients who had DEXA, 36 (30%) patients were found to have osteoporosis (lowest T score -2.5 or below) and 56 (46%) had osteopenia (lowest T score between -1.0 and -2.5). The remaining 29 (24%) patients had normal DEXA indices.

Intervention/treatment

Of 226 treatment-naive patients, 131 (58%) were either treated with zoledronic acid or recommended to start zoledronic acid or an oral bisphosphonate. Seventy-six patients had education with or without vitamin D supplementation only, and the remaining 19 patients either declined FLS, DEXA and/or the treatment or died prior to treatment recommendation (Figure 1).

Of 75 patients who were on bone protection treatment prior to the index

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n=301)</th>
<th>(%)</th>
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</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>271</td>
<td>(90)</td>
</tr>
<tr>
<td>Mean age (+/- SD)</td>
<td>72</td>
<td>(+/-11)</td>
</tr>
<tr>
<td>Ethnicity (Pakeha/ other European)</td>
<td>267</td>
<td>(89)</td>
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<tr>
<td>Past history of fracture</td>
<td>112</td>
<td>(37)</td>
</tr>
<tr>
<td>Pre-existing treatment with past fracture</td>
<td>53</td>
<td>(25)</td>
</tr>
<tr>
<td>Pre-existing treatment used</td>
<td>(n=75)</td>
<td>(%)</td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>63</td>
<td>(84)</td>
</tr>
<tr>
<td>Bisphosphonate drug holiday</td>
<td>4</td>
<td>(5.3)</td>
</tr>
<tr>
<td>HRT</td>
<td>4</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Trial drug</td>
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<td>(4.0)</td>
</tr>
<tr>
<td>Teriparatide</td>
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</table>
fracture, 25 (33%) had their treatment changed by the FLS. Two died and the remaining 48 had no change to their pre-existing treatment.

Overall, of the 292 patients alive at the time of treatment recommendation, 205 were either on, or started or had been recommended to start bone protection treatment by the FLS.

Significantly abnormal laboratory test results were detected in only three patients. Thirteen patients were referred to bone/endocrine clinic either owing to these laboratory abnormalities or due to multiple and/or recurrent fractures while on treatment. One patient had treatment for hyperparathyroidism and another patient for hypogonadism. Two patients were initiated on teriparatide therapy.

Compliance
At a mean follow-up of 12 months, 136 of 193 (70%) patients who were alive and were expected to be on bone protection treatment were compliant with therapy.

Re-fracture
At a mean follow-up of 14 months, 22 of 282 (7.8%) patients who were alive were found to have had a re-fracture since the index fracture.

Discussion
Our study illustrates that a highly effective FLS can be implemented in a secondary healthcare setting in New Zealand. Even with 0.5 FTE FLS co-ordinator time, we have intervened in over 300 patients with fragility fractures in a 12-month period. 40% of these patients had a DEXA scan, and over 50% were either started or recommended to start on bone protection treatment or had an alteration to pre-existing therapy. Additionally, essentially all patients received one-to-one education about their condition and non-pharmacologic intervention advice for fracture prevention. A clinical summary was routinely sent to the patient's GP, detailing assessment results and management recommendations. This has the potential not only to improve patients' care but to raise awareness about osteoporosis with the general practice.

A large proportion (37%) of our patients have had a past history of fragility fracture, with less than half of them having been established on adequate bone protection treatment, highlighting that both ‘fracture begets fracture’ and that there is a large unmet need for those suffering a fragility fracture. Significantly, more patients were osteopenic (46%) than osteoporotic (30%) on our DEXA assessment. This is consistent with the literature that more fragility fractures occur in the osteopenic group, although individual fracture risk is still substantially higher in those with osteoporosis.7 Significant laboratory abnormalities in our cohort were uncommon, indicating underlying conditions such as coeliac disease, hyperparathyroidism or thyrotoxicosis were uncommon. We have observed reasonable compliance rate of 70%
at 12 months. This compares favourably to previous compliance studies for bisphosphonate therapy,8,9 and is at least in part due to frequent use of zoledronic acid infusion in our cohort (50 of 193 treated cases). However, our crude method of confirming ‘prescription fill-rate’ may have over-estimated compliance in those on oral agents. Our compliance rates are not dissimilar to those reported by other FLS.10,11 It is difficult to draw direct comparisons of re-fracture rates with other studies due to inherent differences in population characteristics as well as the short duration of our study. Additionally, a few re-fracture cases may have been missed, as we relied on WDHB hospital electronic records for detection. Nonetheless a re-fracture rate of 7.8% (22/282) at 14 months is in line with observed rates in other FLS studies.4,11

We believe the most important success factor for a well-performing FLS is having a dedicated FLS co-ordinator. Oversight from a clinician with appropriate expertise and interest who is regularly available for discussion of patient management is equally important. These core components have been advocated by various international clinical standards guidelines,5,12,13 and adopted by most FLS around the world. Funding and logistical support at an operational level is equally important. Other success factors include having a systematic method of case identification and having a rational and practical FLS protocol for assessment, investigation and treatment, with ready access to DEXA scans.

Although the WDHB FLS has identified and intervened on over 300 patients in a year, this is estimated to represent less than a quarter of total number of fragility fracture cases presenting to WDHB hospitals in 2014. Limiting factor is the time needed for education, assessment and intervention by the FLS co-ordinator and not with difficulty in identifying appropriate fracture cases. To resolve this issue we are in the process of attaining extra funding from the DHB to increase FLS co-ordinator time. Clinical areas in our DHB where fragility fracture cases are currently potentially being largely missed by FLS include emergency departments and general medical wards. We are also aware that a large number of vertebral compression fractures are being detected on chest x-rays but without appropriate intervention and follow-up. Other challenges that our FLS initially encountered include finding reliable and less time-consuming ways to identify appropriate cases, and not having a clinic space for patient consultation. We also found face-to-face contact with patients and accurate database record keeping time-consuming. Another current care gap is the lack of a streamlined falls prevention programme for those at high risk of falls, though this vital aspect is being reviewed urgently.

In conclusion, we believe that nationwide implementation of a secondary fracture prevention programme, such as FLS, is feasible and timely in New Zealand. While individual district health boards may plan and fund their own programme, funding and strategic support at a government level would enable and expedite smoother implementation of secondary fracture prevention programmes throughout New Zealand, which in-turn will reduce individual suffering and healthcare costs.

Competing interests: Nil.

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Improving accessibility to intravitreal anti-vascular endothelial growth factor treatment for ophthalmic patients in a peripheral centre

Verona Botha, John Ah-Chan, Nishan Ramachandran

ABSTRACT

AIM: An exponential rise in patients requiring intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment has occurred over recent years. We addressed this in Palmerston North by establishing a senior nurse-led macular review clinic. We aimed to determine the current intravitreal service accessibility and compared it to results from 2012.

METHODS: Chart analysis.

RESULTS: Planned follow-up was aimed for 42 days, near the end of the anti-VEGF therapeutic effect. It occurred on average at 45.05 (12 to 127) days after initial treatment induction and 40.7 (14 to 77) days for subsequent follow-ups. Treatment was started on average 29.8 (0 to 139) days after the decision was made. Further injections occurred on average 25.7 (0 to 104) days after the retreatment decision. These findings were similar to 2012 where initial follow-up occurred on average 42 (29 to 89) days following treatment, initial treatment 30 (0 to 78) days after treatment decision and retreatment at 34 (6 to 89) days.

CONCLUSION: Instituting the senior nurse-led macular review clinic has enabled timely review of patients despite significant increases in those requiring treatment and surveillance. The average follow-up appointment delay is within the four week guideline set by NICE.

The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents heralded an exciting new era in Ophthalmology, thanks to its improved visual outcomes in conditions where there were previously limited treatment options available.\(^1\) Bevacizumab (Avastin) is the agent most commonly used in the New Zealand public health sector due to its cost efficacy.\(^2\) There has been a reported three to five-fold increase in the number of intravitreal Bevacizumab procedures performed in New Zealand over the last five years.\(^2\) This is attributable to increasing treatment indications, the ongoing need for injections by current patients and the constant addition of treatment naive patients.

Unfortunately, the follow-up appointments associated with these procedures have quickly outstripped budgeted outpatient targets, reduced an already fragile capacity, and created a significant impact on an already overburdened public ophthalmic service.\(^3\) With an ageing population, increasing options to manage ophthalmic chronic disease and ophthalmology workforce shortages,\(^4\) the current ophthalmic strategies and resourcing is failing to adequately meet this need. Innovative and creative changes in service design and delivery are essential to provide timely access and optimal care in the management of sight-threatening conditions such as exudative age-related macular degeneration (AMD).\(^3\)

The prevalence of AMD affected patients are forecast to continue to rise due to the ageing population and the chronic nature.
of the disease.\textsuperscript{3,5,6} Worsley et al suggests that the prevalence of late AMD in New Zealand is likely to increase by 13.6\% by 2026.\textsuperscript{6} Exudative AMD, which requires intravitreal anti-VEGF treatment to prevent devastating visual outcomes, represents a small, but significant proportion of patients with late AMD.\textsuperscript{6} Once started on treatment, patients require ongoing monitoring and treatment for years and possibly the rest of their lives to maintain good visual outcomes.\textsuperscript{6,7}

Frequent monitoring and prompt treatment are essential, as studies have shown that significant losses in visual acuity occur while awaiting intravitreal anti-VEGF treatment, especially in exudative AMD.\textsuperscript{8–10} Furthermore, the expansion of indications for intravitreal treatment, including diabetic macular oedema, retinal vein occlusions and many others,\textsuperscript{3,11–14} has reduced accessibility, timely surveillance and re-treatment. In the resource limited environment we must be faithful stewards of the resources entrusted to us and develop innovative and creative service provision models to address this crisis. The senior nurse-led macular review clinic (MRC) supervised, credentialed and audited by consultant ophthalmologists is the model adopted here.

The macular review clinic (MRC)

Consistent with international experience, Palmerston North Eye clinic has felt the impact of the vanguard of the chronic ophthalmic disease, where the increasing demand for initial assessments and subsequent follow-ups vastly exceeded the department’s clinical capacity to meet this demand. This resulted in unacceptable delays to both existing follow-ups and urgent first specialist assessments (FSA).

The intravitreal service was identified as a key area that needed to be addressed to ensure ongoing service accessibility while expanding to meet the increasing clinical need. The number of intravitreal injections performed at the Palmerston North Eye Clinic has increased by more than 67\% between 2012 and 2014 and this dramatic rise is expected to continue.

Modelling exercises have shown that the bottleneck in service delivery for patients requiring intravitreal injections is the provision of clinical review follow-up appointments, where clinical details are reviewed and the treatment plan refined, rather than the injection appointments only.\textsuperscript{2} In response, a senior nurse-led macular review clinic (MRC) was established in an attempt to manage the growing “follow-up” waiting list and free up FSAs with consultants for more complex cases and new referrals.

All patients referred to the macular service at Palmerston North Hospital are initially assessed in a senior medical officer (SMO) clinic where the decision to start intravitreal treatment is made and discussed with the patient. In our current service it is not possible to perform injections on the day the decision to treat is made, due to time, space and staffing constraints. Instead patients are placed on a waiting list and receive injections at the next available date. Most commonly, patients receive an induction series of three injections, with further treatment on an as needed (prn) basis as determined at the MRC appointments.

During visits to the MRC, best-corrected visual acuity (BCVA) is assessed, macular photographs, autofluorescence and optical coherence tomography (OCT) scans are taken. Such visits also provide opportunity for patient education on diet, dietary supplementation, smoking cessation and Amsler grid monitoring. Clinical oversight in the form of regular meetings between the nurses involved in the clinic and the patient’s consultant ophthalmologist occur, during which the clinical notes, photos and OCT images of patients that may require intervention are reviewed.

Aims

This retrospective analysis identified patients that were started on intravitreal treatment in 2013 and 2014 at the Palmerston North Eye Clinic. The primary aim was to determine the length of time between receiving intravitreal injections and patient follow-up appointments. These results were compared to a previous audit performed in 2012 in order to assess the impact of the introduction of the Macular Review Clinic. Secondary aims were to determine the length of time between the decision to treat and the initial intravitreal injection, the delay between later decisions to retreat and receiving treatment as well as the percentage of patients that had a stabili-
sation or improvement of their vision while undergoing intravitreal treatment.

Methods

Study population
A retrospective analysis of the clinical records of patients that were treated with intravitreal injections was undertaken. Patients newly started on intravitreal treatment between January 2013 and December 2014 were identified. We excluded all patients that commenced treatment in other centres, received intravitreal injections in combination with other surgical procedures and those that had not yet completed their induction series or had their first follow-up appointment following their induction series at the time of study completion. Eighty-five patients met the inclusion criteria for this study.

Data collection
Data was collected from the clinical records and entered into an Excel spreadsheet. For the initial appointment the following data was entered:
- Date of birth
- Overseeing consultant
- Diagnosis
- Ocular co-morbidities
- Date of diagnosis
- Best-corrected visual acuity (BCVA)
- Central retinal thickness determined on optical coherence tomography (OCT)
- Phakic/pseudophakic
- Intraocular pressures

For each follow-up appointment the following data was entered:
- Date
- Whether they were seen by a consultant, registrar or senior nurse
- BCVA
- Central retinal thickness on OCT

Following each appointment the treatment (if any), as well as date of intravitreal injection was included. Any complications that occurred as a result of the treatment were also recorded.

Data analysis
We determined the initial follow-up delay, as measured from the final injection of the induction series to the first clinic
follow-up appointment. We also looked at subsequent clinic delays, as measured from subsequent intravitreal injections to follow-up clinic appointments. To assess the treatment delay we assessed the time between the initial listing date and first intravitreal injection as well as the delay between listing for further injections and the treatment date. Further analysis was also done to compare these results with a previous audit performed in 2012.

The change in BCVA was determined after the initial injection of intravitreal bevacizumab, after three injections (typically an induction series), as well as one year and at final follow-up appointment at the time of conclusion of this study. The number of intravitreal injections required were also determined. A further analysis was done to determine the percentage of patients that had a stabilisation or improvement of vision.

Results

Patients ranged in age between 43 and 94 years, with a mean age of 77.32 years, and 50.6% were male. Figure 2 illustrates the conditions treated with intravitreal injections. 48.24% of patients included were receiving intravitreal treatment for exudative AMD, 29.41% for macular oedema due to retinal vein occlusions (RVO), 20% for diabetic macular oedema (DME) and 2.35% for macular oedema due to other causes.

Follow-up delay

After the initial injection or induction series of intravitreal bevacizumab the aim was to see patients in 42 days (six weeks), towards the end of the anti-VEGF therapeutic effect. We found that patients were seen on average 45.05 (range 12–127) days after the final injection of the induction series. Almost half of patients were seen in the aimed 42 days (49.4%). 77.1% of patients

Figure 2: Conditions treated with intravitreal injections. 48% of patients were treated for exudative AMD, 30% for macular oedema due to RVO, 20% for diabetic macular oedema and 2% for other conditions.
were seen in 50 days or less. Of those patients that were delayed, 47.6% were seen within a week (seven days) of the aimed follow-up date, 61.9% within two weeks (14 days) and more than 80% within four weeks (28 days).

After undergoing further intravitreal treatment, beyond the initial induction series, we found that subsequent follow-up appointments occurred on average at 40.7 days with a range of 14 to 77 days. The average was well within the aimed 42 days (six weeks). 56.9% of these follow-up appointments occurred within the aimed 42 days. 87.9% of follow-up appointments occurred in 50 days or less. Of those patients that were delayed 60% were seen within a week (seven days) of the aimed follow-up date, 82% within two weeks (14 days) and more than 98% within four weeks (28 days).

**Treatment delays**

Figure 5 illustrates the initial treatment delay. Patients waited on average 29.78 (range 0 to 139) days for initiation of intravitreal treatment following the decision to treat. This was similar to the results in 2012 where the mean delay was 30 (range 0 to 78) days. 57.6% of patients waited less than
25 days and 84.7% less than 50 days for the initiation of treatment.

Once the decision was made to retreat, patients waited on average 25.72 (range 0 to 104) days for a further intravitreal injection. This was an improvement from 2012 when the mean delay was 34 (six to 80) days. 62% of patients received their injection less than 25 days after listing and 88% in less than 50 days. These findings are illustrated in Figure 6.

Comparison to previous results
Table 1 compares the results of this study with an audit performed in 2012.

Treatment results
During the course of the study period 48 eyes were started on intravitreal treatment for exudative AMD. The mean age of these...
patients was 80.9 (range 59 to 96) years and 47.7% were male. Follow-up duration ranged from six to 28.5 months at the conclusion of this study (with a mean of 15.5 months). The starting BCVA ranged from -0.053 to 2 LogMAR (or 6/5 part to 6/600 Snellen) with a mean of 0.63 LogMAR (or 6/24 Snellen). BCVA was stable, as defined by a loss of visual acuity of less than 0.3 LogMAR (or less than three lines on Snellen testing), in 93.1% after one injection, 90.9% after three injections, 81.5% at one year and 81.3% at final follow-up (mean 15.5 months). An improvement in vision occurred in 51.7% after one injection, 57.6% after three injections, 55.6% at one year and 50% at final follow-up. An improvement of more than -0.3 LogMAR (or more than three lines on Snellen testing) occurred in 13.8% after one injection, 24.2% after three injections, 33.3% at one year and 25% at final follow-up. These results are demonstrated in Figure 8. Patients received one to five injections per year with a mean of 3.7 injections per year.

Discussion
There has been a dramatic increase in the number of patients requiring intravitreal treatment over recent years, with a rise of 67% in the number of intravitreal procedures being performed in Palmerston North from 2012 to 2014. This is due to the ongoing treatment needs of the existing patient cohort, continual addition of new patients requiring treatment and the ever expanding indications for intravitreal treatment.14 In order to improve intravitreal service availability and hence efficacy, we need to reduce both the treatment and follow-up delay.

Table 1: Comparison of current study results to a similar audit performed in 2012.

<table>
<thead>
<tr>
<th></th>
<th>Initial follow-up delay</th>
<th>Decision to treat to first injection</th>
<th>Decision to retreat to next injection</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>28</td>
<td>83</td>
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<tr>
<td>Avg time (days)</td>
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<tr>
<td>Range (days)</td>
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<td>12–127</td>
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Figure 7: BCVA at the start of treatment, after one injection, after three injections, at one year and at final follow-up.
Follow-up appointment delay

Following intravitreal treatment patients require frequent ongoing clinic follow-up appointments. Access to these follow-up appointments has been shown in modelling exercises to drive the need for increased capacity in an intravitreal service. Previ-ously, all patients receiving intravitreal treatment at the Palmerston North Eye Clinic were seen on a regular basis by a consultant ophthalmologist.

However, expanding the roles of non-con-sultant clinical staff, such as nurses, in a multidisciplinary approach to patient management allows for consultants time to be used more efficiently. Furthermore, advanced nursing has been advocated internationally as a cost-effective service resource to assist in overcoming workforce shortages, with ophthalmic nurses leading AMD triage clinics and wet AMD review clinics in the UK. In Palmerston North we adopted a similar approach, instituting the senior nurse-led MRC. This has allowed us to increase the number of available follow-up appointments and also freed up consultant appointments in order to see new patients requiring intravitreal treatment in a more timely manner.

We generally aim to see patients within 42 days following an intravitreal injection, towards the end of the anti-VEGF therapeu-tic effect. We found that the average wait for an initial follow-up appointment during the current study period was 45 days, slightly longer than the 2012 result of 42 days on average. However it is important to note that 77.1% of patients were being seen in 50 days or less with 47.6% of those overdue delayed with less than a week.

Subsequent follow-up appointments occurred more promptly, on average at 40.7 days, within the aimed 42 days. It is encouraging to note that 56.9% of patients were seen in the aimed time frame, with 87.9% of patients following up within a week of their desired appointment.

The institution of the MRC has thus allowed us to keep our follow-up appointment availability stable, despite the exponential increase in patients receiving intravitreal treatment. Increasing the frequency of the MRC in the future will aim to reduce this delay further.

Treatment and re-treatment delay

A significant vision reduction can occur while awaiting intravitreal injec-tions. The longer the delay, the greater the vision loss and the less improvement following treatment in patients requiring treatment for exudative AMD, which includes the majority of our intravitreal treatment patients. We aim for patients to receive intravitreal injections as soon as possible following the decision to treat. Same-day treatment would be the gold standard, unfortunately due to resource constraints, in particular staff and space,
it is seldom possible. Over recent years we have increased the number of intravitreal injection lists in order to improve treatment availability. Unfortunately, the mean waiting time of 29.78 days to initial injection is still longer than the NICE recommended ideal goal of less than two weeks (14 days). However, we have stabilised and reduced the waiting time delay (compared to 2012), despite a dramatic increase in the number of patients requiring intravitreal injections. Furthermore, more than two-thirds of NHS trusts have been unable to comply with the NICE guidelines.

Our time to re-treatment has improved with a mean waiting time of 25.72 days, compared to 34 days in 2012.

Treatment results
At one year 81.5% of patients in our study started on prn bevacizumab for exudative AMD had a stabilisation of vision, with a mean of 3.7 injections. In the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)\textsuperscript{18} 91.5% of patients that received prn intravitreal bevacizumab had a stabilisation of vision with an average of 7.7 injections. This result demonstrates that Palmerston North is currently underperforming in the number of injections per patient being given over a year and as a result in our intended visual acuity outcomes. However, two important factors should be taken into consideration with regards to these results. Firstly, at the Palmerston North Eye Clinic, visual acuities are taken at the time of patients being listed for intravitreal injections and not on the day of injection. As discussed earlier there is commonly a delay in receiving injections, on average 29.8 days for initial injections and 25.7 days for subsequent injections. Studies have shown that significant losses in visual acuity occurs while awaiting intravitreal anti-VEGF treatment, especially in exudative AMD.\textsuperscript{8–10} We can thus assume that visual acuities prior to injections were in fact worse than those recorded and stabilisation and improvement rates are likely higher than found in this analysis. Secondly, patients were not excluded from this study if their BCVAs did not meet a predetermined standard, in a hope to emulate real world clinical situations. In the CATT study\textsuperscript{18} only patients with visions between 6/7.5 and 6/96 on Snellen testing were included, however in our study, patients with visual acuities ranging from 6/5 part to 6/600 were included. Patients with very good starting visual acuities are less likely to have an improvement in vision due to the ceiling effect, while patients with very low starting visual acuities are likely to have presented with a degree of scarring and would be less likely to improve also.

Future directions
The institution of the senior nurse-led MRC in combination with the expansion of intravitreal injection lists has allowed us to maintain intravitreal service accessibility, despite the ever-increasing intravitreal treatment demand. However, the results do suggest additional innovative solutions need to be sought.

To that end we are currently investigating the adoption of a proactive “Treat and extend regime” to reduce frequency of follow-up visits and improve visual prognosis.\textsuperscript{19,20} We are also evaluating further avenues, including redesigning the eye clinic “space” and addressing staff resourcing to perform immediate same-day intravitreal injections, improving IT audit, tracking and management systems.

We are also currently investigating the feasibility of nurses or other allied personnel performing intravitreal injections in the future. This has been adopted by several institutions in New Zealand and abroad with reports demonstrating this to be a safe and efficient method of improving accessibility in an intravitreal service.\textsuperscript{21–23}

Lastly, the introduction of a fast-track patient referral system from primary health services to allow earlier intervention in conditions requiring intravitreal treatment is also being evaluated for future implementation. However, such a system requires a robust receiving system (of prompt assessment, treatment, monitoring and re-treatment) to manage the additional detected need.

Limitations
The patients of three different ophthalmologists were included. Slight variances in treatment decisions naturally occurred.
Competing interests:
Nil.

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Detection of sudden death syndromes in New Zealand

Nikki Earle, Jackie Crawford, Kate Gibson, Donald Love, Ian Hayes, Katherine Neas, Martin Stiles, Mandy Graham, Tom Donoghue, Andrew Aitken, Jonathan R Skinner

ABSTRACT

AIM: To investigate regional variations in the detection of sudden death syndromes across New Zealand by assessing registrations in the national Cardiac Inherited Diseases Registry New Zealand (CIDRNZ).

METHODS: The CIDRNZ has been a national entity since 2009, with a hub in Auckland and locally funded regional coordinators (Midland, Central) linked with multidisciplinary cardiac genetic teams. Registration is consent-based and voluntary, and involves the collection of clinical/genetic information and permits genetic testing and research. Registry data were extracted from the CIDRNZ in October 2015 and results are expressed as registrations per 100,000 people by district health board area.

RESULTS: The CIDRNZ has 1,940 registrants from 712 families, 46% of whom are definitely or probably affected by cardiac inherited disease. There are clear regional differences in registration frequencies between regions and between the North and South Islands, both for overall registrations (56/100,000 and 14/100,000, respectively; p<0.001) and for long QT syndrome registrations (15/100,000 and 6/100,000, respectively; p<0.001). Regions with local coordinators have the highest number of registrations.

CONCLUSION: The detection of sudden death syndromes in New Zealand through a cardiac genetic registry is possible but much work is needed to improve regional variation in the detection/reporting of these conditions across the country.

The sudden cardiac death (SCD) of a young person is a devastating event, with the incidence estimated at between one to seven deaths per 100,000 people per year in 1–35 year olds.1–3 This equates to about 150 deaths per year in New Zealand. Many studies have shown that 20–50% of SCD in 1–35 year olds are due to inherited heart conditions such as cardiomyopathies and ion channelopathies.4–6 Since death is largely preventable in these conditions through avoidance of triggers, regular beta blockers, left cardiac sympathectomy or implantable cardiac defibrillators, there is an imperative to find and protect those at risk.7

Community-based electrocardiogram (ECG) screening programs for inherited heart conditions are controversial, mostly due to the poor sensitivity and specificity of the ECG.8,9 However, there is now abundant evidence that pre-symptomatic individuals can be identified through cascade clinical cardiac and genetic screening of relatives of affected individuals, including the investigation and management of families of young sudden cardiac death victims.10–12

Since 2009, New Zealand has had a national cardiac inherited disease registry that coordinates the cardiac and genetic investigation of sudden unexplained deaths with the national coronial and forensic services, and undertakes family cascade screening of people diagnosed with inherited heart conditions and in those resuscitated in the community for which no cause can be identified.13 The effectiveness of the registry is proven by the high level of detection of individuals with long QT syndrome in Auckland City where the registry is based and was initially established; approximately one in 4,000 have already been identified, with an anticipated population prevalence of one in 2,000.10,11

The national registry coordinator is based in Auckland and works predominantly across Auckland, Waitemata, Counties Manukau and Northland district health boards. National funding for the registry has been sought from the Ministry of Health on a number of occasions over the last ten years but has been denied. Regional coordinators, with local funding, were appointed...
in the Midland area (Waikato, Taranaki, Bay of Plenty, Lakes District and Tairawhiti district health boards) and Central (Capital and Coast, Hutt Valley, Hawke’s Bay, MidCentral, Wairarapa, Whanganui and Nelson Marlborough district health boards) in 2012 after initial charitable support from Cure Kids. There is no registry coordinator based in the South Island, though referrals including sudden deaths in the South Island are handled through the national office.

The aim of the study reported here was to investigate regional variations in the detection of sudden death syndromes across New Zealand by assessing registrations in the national cardiac inherited disease registry across district health board areas, and to study the detected prevalence of one particular cardiac inherited disease, long QT syndrome, across the country.

Methods

The national registry is known as the Cardiac Inherited Diseases Registry New Zealand (CIDRNZ), which is maintained by the Cardiac Inherited Diseases Group New Zealand. Demographic, clinical and genetic data are stored on a secure web-based database, from which the data for these analyses was extracted on October 1st 2015. Population data of each district health board area was obtained from Statistics New Zealand. Results are expressed as registrations per 100,000 people by district health board area, based on the residential address given at the time of enrolment in the registry.

Registration with the cardiac inherited disease registry

Registration is consent-based and voluntary. When giving consent, each patient, guardian or next-of-kin (for deceased probands), permits the maintenance of clinical and genetic information, genetic testing where appropriate and research into their condition. The information sheets and consent forms have been approved by the multi-regional ethics committee (AKX/02/00/107/AM3).

Referrals to the Cardiac Inherited Diseases Group are received from paediatric/cardiology services or a pathologist in the case of sudden death, and the registry coordinator gathers the relevant clinical information needed for a multidisciplinary case discussion (Figure 1). Each registry coordinator is linked to a cardiac genetic team, with specialist cardiology and clinical genetics. Consent is usually obtained via the registry coordinator or by the lead clinician. Once an affected proband has been identified, most cascade testing of family members is arranged via regional cardiac genetic clinics, with joint counselling by specialist cardiologists and genetic consultants or associates.

There is also a national hub based in Auckland, which includes additional specialist molecular genetics, cardiac electrophysiology, paediatric cardiology and pathology representation. This multidisciplinary team meets fortnightly with the regional coordinators. The whole national team meets by video conference bi-monthly.

Prior to the national registry being established in 2009, a local registry was established in the Northern region in 2006 and these patients were incorporated into the national registry upon its formation.

Initial funding of the cardiac inherited disease registry

Cure Kids provided the initial funding for a prospective evaluation of long QT syndrome molecular autopsy for sudden unexplained death in 2006. The diagnostic success of this program (30% when including family cardiac testing) led, in 2008, to the Ministry of Justice funding ongoing testing for such cases through the then Chief Coroner for New Zealand (Judge Neil Maclean). The National Forensic Pathology Service and the Cardiac Inherited Diseases Group manage this national budget for molecular autopsy of sudden unexplained death in young people.

Results

There were 1,940 registrants in the national cardiac inherited disease registry from 712 families (Table 1) since 2006 when the registry was established. These registrants originate from 133 sudden death investigations, 290 families with a proband with a cardiac ion channelopathy (238 Long QT syndrome, 36 Brugada syndrome, 13 catecholaminergic polymorphic ventricular tachycardia, three progressive cardiac conduction disorder), 257 families with
a cardiomyopathy (202 hypertrophic cardiomyopathy, 28 arrhythmogenic right ventricular cardiomyopathy, 27 dilated cardiomyopathy) and 32 resuscitated sudden death investigations. Forty-six percent of registrants were classified as being definitely or probably clinically affected by an inherited cardiac disease, regardless of genetic testing status. 1,206 (62%) registrants underwent genetic screening, with a disease-causing mutation confirmed in 40% of those tested.

The distribution of registrations per 100,000 residents in each district health board area varies widely throughout the country, ranging from 0/100,000 in West Coast to 104/100,000 in Auckland (Figure 2). Notably, the average number of registrations for the North Island and South Island differ significantly (56/100,000 and 14/100,000, respectively; p<0.001).

Registrations have markedly increased in the past 2.5 years in regions with coordinators in place. The Midland and Central coordinators were employed late 2012, and a coordinator has been in place in the Northern region since 2006. From January 2013 until the current data from October 2015, in the Midland region, the numbers of registered patients increased by 28/100,000 resident population (from 31/100,000 to 59/100,000). In the Central area, registrations increased 12/100,000 (16/100,000 to 28/100,000), and in the Northern region, the registrations increased 24/100,000 (43/100,000 to 67/100,000). In the remainder of the South Island, where there has been no registry coordinator, registrations have increased only 6/100,000 (7/100,000 to 13/100,000).

Long QT syndrome is the inherited cardiac disease with the highest number of registrants in the New Zealand registry (41%). The numbers of registrants with clinically diagnosed long QT syndrome varies widely between different district health board areas, and again there is significant disparity in the number of registered patients between the North and South Islands (15/100,000 and 6/100,000, respectively; p<0.001) (Figure 3).
**Table 1**: Demographic and clinical characteristics of patients enrolled in the national Cardiac Inherited Diseases Registry New Zealand since 2006.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total n = 1940</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>959 (49)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>1050 (54)</td>
</tr>
<tr>
<td>Māori</td>
<td>277 (14)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>106 (5)</td>
</tr>
<tr>
<td>Asian</td>
<td>40 (2)</td>
</tr>
<tr>
<td>Indian</td>
<td>29 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (1)</td>
</tr>
<tr>
<td>Not stated or Unknown</td>
<td>421 (22)</td>
</tr>
<tr>
<td>Probands, n (%)</td>
<td>712 (37)</td>
</tr>
<tr>
<td>Age, med (IQR)</td>
<td>36 (19–54)</td>
</tr>
<tr>
<td>Deceased, n (%)</td>
<td>206 (11)</td>
</tr>
<tr>
<td>Presenting condition, n (n probands)*</td>
<td></td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>795 (238 probands)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>436 (202 probands)</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>364 (133 probands)</td>
</tr>
<tr>
<td>Resuscitated SCD/syncope</td>
<td>65 (32 probands)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>104 (27 probands)</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>52 (36 probands)</td>
</tr>
<tr>
<td>Catecholaminergic polymorphic ventricular tachycardia</td>
<td>35 (13 probands)</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>80 (28 probands)</td>
</tr>
<tr>
<td>Progressive cardiac conduction disorder</td>
<td>9 (3 probands)</td>
</tr>
<tr>
<td>Clinical status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Definitely affected</td>
<td>607 (31)</td>
</tr>
<tr>
<td>Probably affected</td>
<td>283 (15)</td>
</tr>
<tr>
<td>Possibly affected</td>
<td>332 (17)</td>
</tr>
<tr>
<td>Unlikely to be/not affected</td>
<td>260 (13)</td>
</tr>
<tr>
<td>Clinical status undetermined**</td>
<td>458 (24)</td>
</tr>
<tr>
<td>Genetic status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Genotype positive</td>
<td>487 (25)</td>
</tr>
<tr>
<td>Genotype negative</td>
<td>293 (15)</td>
</tr>
<tr>
<td>Testing uninformative</td>
<td>325 (17)</td>
</tr>
<tr>
<td>Unclassified variant</td>
<td>101 (5)</td>
</tr>
<tr>
<td>Genetic testing not undertaken</td>
<td>734 (38)</td>
</tr>
</tbody>
</table>

NZ = New Zealand; IQR = interquartile range; SCD = sudden cardiac death.
* Classification is according to their categorisation at presentation.
** This includes victims of SCD and their families where no inherited heart disease diagnosis has yet been made.
A key measure of the success of a screening program is the number of family members being investigated with genetic testing for a genetic mutation of proven pathogenicity (cascade genetic tests), allowing pre-symptomatic treatment to reduce the risk of sudden death. The numbers of cascade genetic tests performed for long QT syndrome per 100,000 residents by district health board area are shown in Figure 4. These data are dependent on whether a pathogenic mutation has been identified in a family, and the number of family members who are available and have consented for testing. Nevertheless, the variation across regions is clear.

Discussion

These data demonstrate the success of the registry in the identification of individuals at risk of inherited heart conditions across New Zealand. There is a clear difference between regions in the numbers of individuals registered with the national cardiac inherited disease registry.

A limitation of the data presented here is that it only includes people registered with CIDRNZ and does not represent every case of inherited heart disease, nor every patient who has undergone a cardiac genetic test in New Zealand. The Northern hub of Genetic Health Service New Zealand (GHSNZ), based in...
in Auckland, performs all of its tests for inherited heart disease through CIDRNZ (this does not include Marfan syndrome or other dysmorphic syndromes such as Noonan syndrome, nor familial hypercholesterolaemia). The Central and South Island hubs of GHSNZ, while performing some testing through CIDRNZ, also carry out cardiac genetic assessment and testing outside of the registry; this may relate to ease-of-access to the collaborative service through the regional coordinator. Neither hub has an additional database which enables this additional genetic testing or the diagnostic rate for cardiac conditions to be collated efficiently at this stage. The South Island hub of GHSNZ, as the most recently established hub of GHSNZ, has had a small number of referrals with cardiac inherited disease, so the data presented here is likely to be representative of the total for the region. The Central hub of GHSNZ based in Wellington has had a more active program, which started before CIDRNZ existed, and manages some large long QT syndrome pedigrees. Total numbers detected may be significantly higher in that region than what is reported here. There is a possibility that management and genetic testing of families with cardiac inherited disease might also occur through district health board cardiology departments, general practice or in the private sector although genetic testing is likely to be limited by cost.

The data demonstrate that in regions with registry coordinators, the frequencies of registration and detection are higher, and the data also reflect the length of time the coordinators have been in place. Prior to the appointment of the Midland coordinator, relative proximity to the original single Auckland coordinator permitted the referral and investigation of many families, and this has accelerated following the appointment of the local coordinator. The variability within the Northern region with high rates in central Auckland is due to historical reasons (the registry began in central Auckland), and because tertiary paediatric cardiology services are located at Starship Hospital. Given it is known that death can be prevented in these conditions and that many sudden deaths or cardiac arrests occur as the first presentation of disease, this raises the possibility that death from these conditions has been more likely in regions where registrations are fewer, particularly in the South Island. The recent agreement to fund a coordinator in the South Island is likely to increase registration and detection and reduce the likelihood of deaths from these conditions in this region.

The establishment of a regional registry coordinator, with cardiology and genetics

Figure 4: Cascade genetic tests carried out for families with a definitive genetic diagnosis of long QT syndrome per 100,000 residents.
supervision, has a number of positive effects locally. The profile of cardiac inherited disease is raised, and local education to medical, nursing and paramedical staff leads to increased referral of appropriate cases. Obtaining a three-generation family history alone has a high diagnostic hit-rate in resuscitated sudden cardiac death, and dilated cardiomyopathy in particular.\textsuperscript{17} A registry coordinator increases the outreach of services: specialist cardiologists and clinical geneticists may be inadequately resourced to recruit family members to the registry or to offer cascade screening. A coordinator can work with the family and tests can be organised for review by a specialised cardiac genetic team. Forensic pathologists benefit from a local team with whom they can discuss cases which might benefit from a molecular autopsy and family cardiac investigation.\textsuperscript{18–20}

Funding for the regional coordinators must still be found from within the regions, and no additional funding is available for genetic testing; some district health boards are more reluctant than others to permit such testing, which can have high initial costs. The Ministry of Health has been resistant to requests for national funding of cardiac inherited disease services despite its own investigation in 2008 (under the National Service and Technology Review process) finding that “a national registry of inherited heart diseases is essential”. On the plus side, however, we have recently been advised that from July 2016, the Ministry of Health will fund one day a week of national clinical leadership, together with full funding for a national registry coordinator and a database administrator.

New Zealand’s national cardiac inherited disease registry and clinical service network was established as one of the first in the world, and such a program potentially obviates the need for controversial and expensive national ECG screening programs advocated by some European countries and Japan.\textsuperscript{8,9} Unfortunately, published population-level international data on the investigation and detection of inherited heart disease are scarce, meaning comparison with the New Zealand rates of registration and detection is not currently possible. The data presented here show that the registry is effective in facilitating the detection of these conditions, but there is still much to be done to improve regional variation in the detection of inherited heart conditions across the country, most particularly in the South Island. The registry and its associated clinical program require further investment to permit equity of access across New Zealand.

\textbf{Competing interests:}

Nil.

\textbf{Acknowledgements:}

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Hospital costs of *Bordetella pertussis* in New Zealand children

Anusha Ganeshalingham, Peter Reed, Cameron Grant, Brian Anderson, Emma Best, John Beca

**ABSTRACT**

**AIM:** To estimate hospitalisation costs for children with pertussis in New Zealand.

**METHOD:** All children less than 16 years of age and hospitalised with pertussis between 01/01/2003 and 31/12/2013 were identified from the National Minimum Data Set and the National Paediatric Intensive Care Unit database. The cost of hospital care was estimated by multiplying the diagnosis-related group cost-weight by the national price and inflating to 2013/2014 values.

**RESULTS:** There were 1,456 children with pertussis admitted to hospital including 65 admissions to the paediatric intensive care unit. Infants (<1 year) accounted for 78% of hospital admissions, 98% of paediatric intensive care admissions and 87% of hospitalisation costs. The total inflation-adjusted cost of the 11-year cohort was estimated at $8.3 million and the mean cost of hospital ward and paediatric intensive care was $4,242 and $42,016 respectively, per child. The 2011–2013 epidemic accounted for 39% of all hospital admissions and the cost estimated at $4.2 million. Peak annual hospitalisation costs during epidemic years increased from under $800,000 in 2004 and 2009 to over $2 million in 2012.

**CONCLUSION:** Infants with pertussis are more likely than older children to be admitted to hospital and to the paediatric intensive care unit and generate the majority of hospitalisation costs. A revised focus on protecting vulnerable newborns and infants has the potential to both improve health outcomes for infants with pertussis and reduce medical costs.

Pertussis, caused by infection with the Gram-negative bacterium *Bordetella pertussis*, is a highly contagious respiratory illness. Pertussis, which can cause severe and sometimes fatal disease in infants has proved more difficult to control than other vaccine preventable diseases included in national childhood immunisation schedules. Circulation of *B. pertussis* remains endemic. Epidemics continue to be reported from many countries, including Australia, England and the US.

Pertussis affects people of all ages but is more prevalent and severe in children. In New Zealand, in 2014, children comprised 31% of notified cases and 62% of hospitalised cases. Infants (less than one year of age) accounted for 8% of all cases (an incidence six times greater than adults) and 43% of hospitalised cases. Pertussis epidemics occur in New Zealand every three-to-five years and last two-to-three years. In recent times there have been epidemics in 1999–2000, 2004–2005, 2008–2009 and most recently 2011–2013.

The most recent epidemic resulted in the largest number of admissions (38 children) and deaths (two children) in the paediatric intensive care unit (PICU) at Starship Children’s Hospital in Auckland, since the national unit was established in 1991. While the health burden of pertussis in New Zealand has been described, the economic burden has not. Documentation of these costs will inform decision-making around new strategies aimed at reducing pertussis disease burden. Our aim was to quantify the medical costs associated with hospital ward and PICU admissions for children with pertussis in New Zealand.

**Methods**

We completed a retrospective review of all children less than 15 years of age and hospitalised with pertussis between 1999–2010.
January 2003 and 31st December 2013. The regional hospital ethics committee approved the study.

Identification of cases

Pertussis is a notifiable disease in New Zealand and all notified cases are referred to the communicable disease centre at the Institute of Environmental Science and Research (ESR) Limited. The dataset held by ESR was cross-referenced with the National Minimum Data Set (NMDS) held by the Ministry of Health to identify children with pertussis admitted to hospital. The dataset included patient demographics, prioritised ethnicity, district health board, length of hospital stay and cost-weight. All children with severe pertussis are referred to and managed by the national PICU at Starship Children's Hospital in Auckland. Children with pertussis that required paediatric intensive care were identified using the PICU database. The PICU dataset included patient demographics, transport to intensive care and length of intensive care stay.

Hospitalisation costs

Hospitalisation costs were defined as those costs generated by hospital resource utilisation. Diagnosis-related group (DRG) cost-weights for all pertussis hospital admissions were obtained from the NMDS using the Weighted Inlier Equivalent Separations (WIES) methodology. The cost of each admission was calculated by multiplying the WIES cost-weight by the national price for the corresponding financial year. The annual cost was then inflated to 2013/14 values using the Consumer Price Index.

Transportation costs

Referral centres around New Zealand are invoiced directly by the transport providers for the cost of transporting critically ill children with pertussis to the PICU. Fixed wing or rotary wing aircraft are used to transport children from centres outside the Auckland region. An ambulance service is used for road transportation from hospitals within the Auckland region and from

Figure 1: Age of children hospitalised with pertussis (2003–2013).

Figure 2: Ethnicity of children hospitalised with pertussis (2003–2013).
Auckland airport for fixed wing transports, at a set cost per journey. The transport costs incurred by children with severe pertussis during the study period were made available by the transport providers.

Statistics
Data were analysed using JMP version 11.1 (SAS Inc., Wellington, NZ). The proportion of patients requiring intensive care was compared across patient demographics using odds ratios (OR) provided with 95% confidence intervals (95% CI).

Results
There were 9,812 pertussis notifications in children made between 1st January 2003 and 31st December 2013. During this time there were 1,456 (15%) admissions to hospital including 65 children admitted to the PICU (4.5%).

Demographics of children hospitalised with pertussis
There were 1,456 children hospitalised with pertussis and 747 (51%) were female. The majority (78%) were less than 12 months of age at presentation (Figure 1). Of children who were admitted to the PICU, 98% (64/65) were infants. In comparison with older children hospitalised with pertussis, the odds of an infant hospitalised with pertussis requiring admission to PICU were increased (OR=18.9, 95% CI 2.6–136.7, p<0.001).

Of children hospitalised with pertussis, 567 (39%) were European, 566 (39%) Māori, 254 (17%) Pacific Island and 41 (3%) Asian (Figure 2). Pacific children hospitalised with pertussis had increased odds of PICU admission compared to European (OR=4.2, 95% CI 1.9–9.4, p<0.001) or Māori children (OR=2.0, 95% CI 1.0–3.7, p=0.03).

Children with pertussis were hospitalised in all 21 New Zealand district health boards (DHB) (Figure 3). The greatest number of admissions was at the three Auckland DHBs and Canterbury DHB, which provide care for New Zealand's largest and second largest metropolitan areas, respectively: Counties-Manukau, 254 (17%) children; Canterbury, 145 (10%) children; Waitemata, 130 (9%) children and Auckland, 112 (8%) children. New Zealand's least populated area, serviced by the West Coast DHB had the least number of admissions (four children, 0.3%). Counties-Manukau had the largest proportion of hospital admissions requiring PICU admission (14%, 95% CI 10–20%).

Length of hospital and PICU stay
The mean length of hospital stay for all children was 5.2 days. The mean length of hospital ward stay for the 1,391 children whose illness did not require intensive care was 4.4 days (range, one to 98 days). The mean length of hospital stay for the 65 infants whose illness required intensive care was 22.6 days (range two to 81 days), with an average 12.9 days in the PICU.

Figure 3: Admitting district health board of children hospitalised with pertussis (2003–2013).
Transportation costs
There were 17 children who were admitted to the PICU directly from the paediatric ward (eight children) or the Children’s Emergency Department (nine children) at Starship Children’s Hospital and therefore incurred no transport costs. Table 1 details the mode of transport and the costs associated with transporting the remaining 48 children to the PICU. The mean transportation cost was $6,879 (Table 1).

Hospitalisation costs
The total inflation-adjusted cost of the entire 11-year cohort was $8,631,542 (Table 2). The total inflation-adjusted cost of children admitted to a hospital ward but not requiring PICU care was $5,900,530 and the mean cost per child was $4,242 (Table 2). The total cost of children admitted to PICU (including hospital ward stay before and after intensive care admission) was $2,400,826 and the mean cost per child was $36,936 (Table 2). The total intensive care cost including transportation was $2,731,012 and the mean cost per child was $42,016 (Table 2).

Annual costs
The mean annual cost was $785,000. Annual hospitalisation costs rose and fell in line with the epidemics, ranging from $176,000 in non-epidemic 2006 to over $2 million in 2012 at the height of the most recent epidemic (Figure 4). The other epidemics in this study period had peak annual costs of $784,000 (2004) and $759,000 (2009).

Costs by age group
Infants accounted for 87% of the hospitalisation costs at a mean cost of $6,571 per infant (Figure 5). For children aged one to four years (12% of admissions) and five to 10 years (7% of admissions), the mean hospitalisation costs were $2,693 and $3,582 per child respectively. For children greater than 10 years of age, the mean costs per child were greater ($8,219) but they accounted for only 3% of pertussis admissions.

Costs of the 2011–2013 pertussis epidemic
There were 572 children admitted to hospital during the most recent pertussis epidemic that began in August 2011 and ended in December 2013. Admissions during the epidemic accounted for 39% of all pertussis hospitalisations during the 11-year study period and 49% ($4.2 million) of the total costs.

There were 38 children (37 infants and one three year-old) who were admitted to the PICU during the epidemic, accounting for

Table 1: Cost of transportation to the paediatric intensive care unit (2003–2013).

<table>
<thead>
<tr>
<th>Transport mode</th>
<th>Number of children</th>
<th>Total cost (NZD)</th>
<th>Mean cost per child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Road</td>
<td>32</td>
<td>$4,640</td>
<td>$145</td>
</tr>
<tr>
<td>Helicopter</td>
<td>7</td>
<td>$65,055</td>
<td>$9,294</td>
</tr>
<tr>
<td>Fixed wing aircraft</td>
<td>9</td>
<td>$260,491</td>
<td>$28,943</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>$330,186</td>
<td>$6,879</td>
</tr>
</tbody>
</table>

Legend: NZD, New Zealand Dollar in 2013/14 values.

Table 2: Hospital and paediatric intensive care unit length of stay costs for children with pertussis (2003–2013).

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of children</th>
<th>Total cost (NZD)</th>
<th>Mean cost per child (NZD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital ward</td>
<td>1391</td>
<td>$5,900,530</td>
<td>$4,242</td>
</tr>
<tr>
<td>Paediatric intensive care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transportation costs</td>
<td>65</td>
<td>$2,400,826</td>
<td>$36,936</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>$330,186</td>
<td>$6,879</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>$2,731,012</td>
<td>$42,016</td>
</tr>
<tr>
<td>Total</td>
<td>1456</td>
<td>$8,631,542</td>
<td>$5,928</td>
</tr>
</tbody>
</table>

Legend: NZD, New Zealand Dollar in 2013/14 values.
58% of all PICU pertussis admissions during the 11-year study period. The mean length of stay was 15.9 days. The total hospitalisation cost for those PICU patients during the epidemic was $1.7 million, 20% of the total cost of all pertussis hospital admissions in the 11-year study period.

Discussion

This study has a number of important findings related to estimating hospitalisation costs for children with pertussis in New Zealand. Firstly, total inflation-adjusted costs over the 11-year study period were estimated at $8.3 million and the mean cost of hospital ward and PICU care was $4,242 and $42,016 respectively per child. Secondly, infants accounted for 78% of hospital admissions, 98% of paediatric intensive care admissions and 87% of hospitalisation costs. Thirdly, the most recent epidemic lasting less than 2.5 years accounted for 39% of all hospital admissions and 49% of total costs. Finally, the peak annual hospitalisation costs during epidemic years increased from under $800,000 in 2004 and 2009 to over $2 million in 2012 (inflation-adjusted to 2013/14 values).

The medical costs of pertussis have not previously been reported at a national level for any country. A national estimate was possible for New Zealand because: (i) all pertussis notifications are reported to a single national institute for disease control.

Figure 4: Annual hospitalisation costs of children with pertussis (2003–2013).

Figure 5: Hospitalisation costs of children with pertussis by age (2003–2013).
surveillance; (ii) one government agency collates and stores information on all patients hospitalised nationally; (iii) all hospital care is delivered by public hospitals funded by the New Zealand government and; (iv) all children with severe pertussis infection are referred to a single PICU.

We estimated the cost of children with pertussis that required hospital ward care to be $4,242 per child. Cost estimation studies have been published in Europe\textsuperscript{11}, South America\textsuperscript{12} and the US.\textsuperscript{13–15} The mean length of hospital stay upon which our estimates were based (5.2 days) is comparable to those used in an estimate of length of stay for pertussis in Germany in the 1990s (6.5 days).\textsuperscript{11} Our estimate of average direct medical costs per admission were comparable to those estimated in the US from 1996 to 1999 from approximately 1,000 hospitals in California, Florida, Maryland and Massachusetts (mean cost per child of $9,130 USD ($11,500 NZD).\textsuperscript{14} In this study, mean length of stay was 6.0 days and 13% were admitted to a PICU. The inpatient hospital costs of pertussis in three hospitals in Argentina from 2010 to 2012 were estimated at $2,130 USD.\textsuperscript{12} The cost of providing paediatric intensive care services to infants with pertussis has not previously been reported. Our study estimated mean costs per infant of $42,016 NZD, including the cost of transportation to the PICU.

Direct comparisons of health care costs are difficult to make because of differences in the cost of health care between countries. However, with infant pertussis hospitalisation rates in New Zealand (2000s: 196/100,000)\textsuperscript{16} being three times higher than those in Australia (2001: 56/100,000)\textsuperscript{17} or the US (2003: 65/100,000)\textsuperscript{14}, the direct medical costs of pertussis in New Zealand remain unacceptably high.

Our study confirms that infants account for the majority of hospital ward and paediatric intensive care admissions and the burden of cost. With the majority of direct medical costs for pertussis being generated by infants, New Zealand must continue to seek to improve the prevention of pertussis in this age group. Current immunisation coverage rates are at the highest that New Zealand has ever achieved.\textsuperscript{19} However, immunisation timeliness remains suboptimal. In the 12 months to September 2015, although 94% of infants in New Zealand had received the complete three-dose primary immunisation series (due at six weeks, three months and five months) by 12 months of age, only 80% had completed the series by age six months.\textsuperscript{19} Delay in receipt of any of the three infant doses of pertussis vaccine is associated with a five-fold increased risk of an infant being hospitalised with pertussis.\textsuperscript{20}

Because the majority of infants with severe and life-threatening pertussis are less than three months old, improving the timely delivery of the infant pertussis vaccine series will, on its own, be insufficient to prevent disease in those with the greatest risk of death and disability and for whom health care costs are highest. Better protection of those most likely to transmit pertussis to young infants is necessary. Mothers are a well-documented source of pertussis transmission to infants. Immunisation of pregnant women withacellular pertussis vaccine has been shown to be highly effective at preventing pertussis in infants less than three months old.\textsuperscript{21}

In response to the most recent epidemic in New Zealand, all pregnant women between 28–38 weeks gestation who had not received a booster dose of pertussis vaccine in the last 10 years were encouraged to undergo publicly funded immunisation.\textsuperscript{22} However the uptake of pertussis pregnancy vaccination is low. For this strategy to be effective, it will be necessary for pregnancy coverage rates to be as high as those now achieved with the infant immunisation series.

Our study has several important limitations. DRG-based cost-weights are used by the Ministry of Health to calculate revenue paid to each of the DHBs for providing health care services. These cost-weights are based on historical average expenditure per diagnostic group and do not necessarily reflect the true cost at the individual patient level. Cost-weights also exclude the cost of adjusters paid to DHBs in recognition of complexity of services, rural location, overseas visitors, Māori health and the Starship adjuster. In addition, it is likely that some infants with severe pertussis may have been managed in an adult intensive care unit at their referring DHB prior to transfer to the PICU. Our estimates of intensive care cost are therefore likely to be conservative.
Our study focused on costs associated with hospital resource provision to children, and therefore describes only a proportion of the total health care costs incurred by pertussis. Our cost estimates are an approximation and underestimate the full economic burden generated by general practitioner visits, public health involvement and the provision of antibiotics to close and household contacts. Direct non-medical costs such as travel expenses incurred for medical consultations and additional childcare provision were beyond the scope of this study as were indirect non-medical costs including lack of parental sleep and the effect on productivity, absenteeism from work and the effect on siblings and other family members.\textsuperscript{13,23}

The periodicity of pertussis epidemics in New Zealand is unlikely to change despite the recent improvements in infant immunisation coverage. Given the severity of the most recent epidemic there is an urgent need to better protect our infants from this severe and expensive disease. A clear focus on improved timeliness and high coverage of the infant immunisation series together with a pregnancy dose of pertussis vaccine are key components of this strategy. To be cost-effective, both of these immunisation strategies must make the prevention of pertussis in population groups at highest risk of disease a priority. In New Zealand these groups include children of Māori or Pacific ethnicity.\textsuperscript{24}

\textbf{Competing interests:} Nil.

\textbf{Acknowledgements:}
We wish to acknowledge Dale Robison at the Ministry of Health for providing the NMDS and staff at the Institute of Environmental Science and Research Ltd (ESR) for providing and matching data for this analysis. At Auckland District Health Board, we wish to thank Sue Ashley, PICU Clinical Administrator for providing PICU data; Kris Caton, PICU Transport Nurse Co-ordinator for assisting in accessing transport costs and Patrick Horan, Costing Manager who provided costing advice.

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REFERENCES:


Asthma and Respiratory Foundation NZ
adult asthma guidelines:
a quick reference guide

Richard Beasley, Robert J Hancox, Matire Harwood, Kyle Perrin, Betty Poot, Janine Pilcher, Jim Reid, Api Talemaidaga, Darmiga Thayabaran

ABSTRACT
The purpose of the Asthma and Respiratory Foundation NZ Adult Asthma Guidelines is to provide simple, practical and evidence-based recommendations for the diagnosis, assessment and management of asthma in adults (aged 16 and over) in a quick reference format. The intended users are health professionals responsible for delivering asthma care in the community and hospital Emergency Department settings, and those responsible for the training of such health professionals.

Abbreviations:
ABG Arterial Blood Gas
ACT Asthma Control Test
ACOS Asthma/COPD overlap syndrome
COPD Chronic obstructive pulmonary disease
CXR Chest X-Ray
DHB District Health Board
DPI Dry-powder inhaler
ED Emergency Department
FeNO Fraction of expired nitric oxide
FEV₁ Forced expiratory volume in one second
FVC Forced vital capacity
HDU High Dependency Unit
ICS Inhaled corticosteroid
ICU Intensive Care Unit
LABA Long-acting beta-2 agonist
LAMA Long-acting muscarinic antagonist
MDI Pressurised Metered Dose Inhaler
NIV Non-invasive ventilation
NSAID Non-steroidal anti-inflammatory drug
PaO₂, PaCO₂ Arterial oxygen and carbon dioxide tension
PEF Peak expiratory flow
PHO Primary Health Organisation
SABA Short-acting beta-2 agonist
SpO₂ Oxygen saturation measured by pulse oximetry
U + E Urea and Electrolytes
Context

Providing health professionals with current best practice guidance sits within the Asthma and Respiratory Foundation NZ's work programme, as a priority action towards reducing New Zealand's significant respiratory health burden. Three important documents were released by the Foundation in 2015; Te Ha Ora: The National Respiratory Strategy, The Impact of Respiratory Disease in New Zealand: 2014 update and He Maratanga huangō: Asthma health literacy for Māori children in New Zealand. These set the context of the growing incidence and impact of asthma in New Zealand, the inequalities suffered by Māori, Pacific peoples and low income families, and the holistic approach needed to tackle the issues.

Guidelines review

The following documents were reviewed to formulate these Adult Asthma Guidelines: The New Zealand Guidelines Group 2002, ‘The Diagnosis and Treatment of Adult Asthma Best Practice Evidence-Based Guideline’, the National Asthma Council of Australia 2015 ‘Australian Asthma Handbook Quick Reference Guide’, the Global Initiative for Asthma 2016 ‘Asthma Management and Prevention’ including the companion ‘Pocket Guide’ and the SIGN 2014 British Guidelines on the Management of Asthma including the ‘Quick Reference Guide’. A systematic review was not performed, although relevant references were reviewed where necessary to formulate this guideline version, and referenced as required to clarify differences in recommendations made between guidelines. Readers are referred to the above published guidelines and handbooks for the more comprehensive detail that they provide.

Grading

No levels of evidence grades are provided due to the format of the Adult Asthma Guidelines which is based on related Quick Reference Guides. Readers are referred to the above published guidelines and handbooks for the level of evidence for the recommendations on which the guidelines are based.

Guideline development group

This group included representatives from a range of professions and disciplines relevant to the scope of the guidelines. The first draft was written by Richard Beasley.

Development of the Adult Asthma Guidelines was funded by the Asthma and Respiratory Foundation NZ. No funding was sought or obtained from pharmaceutical companies.

Peer review

The draft guidelines were peer-reviewed by a wide range of respiratory health experts and key professional organisations, including the New Zealand Nurses Organisation Te Rūnanga o Aotearoa and Respiratory sections, the Pasifikā GP Network, PHARMAC, the Royal New Zealand College of General Practitioners, the Thoracic Society of Australia and New Zealand, and the Internal Medicine Society of Australia and New Zealand.

Presentation

The guidelines are primarily presented through tables and figures with the intention to provide an electronic format which can be used in clinical practice. Key references are provided where necessary to support recommendations that may differ from previous guidelines or current clinical practice.

Dissemination plan

The guidelines will be translated into tools for practical use by health professionals, and used to update existing consumer resources. They will be published in the New Zealand Medical Journal and the Asthma and Respiratory Foundation NZ website, and disseminated widely via a range of publications, training opportunities and other communication channels, to health professionals, nursing and medical schools, PHOs and DHBs.

Implementation

The implementation of the guidelines by organisations will require communication, education and training strategies.

Expiry date

2019
Diagnosis

• The diagnosis of asthma starts with the recognition of a characteristic pattern of symptoms and signs, in the absence of an alternative explanation.
• The key to making the diagnosis of asthma is to take a careful clinical history and then to undertake a clinical examination, document variable expiratory airflow limitation and assess response to inhaled bronchodilator and/or inhaled cortico-steroid (ICS) treatment (Table 1, Figure 1). There is no reliable single ‘gold standard’ diagnostic test.

Practice points

• An increase in FEV₁ ≥12% and ≥200ml from baseline after bronchodilator therapy are traditionally considered as diagnostic criteria for asthma. However, most people with asthma will not exhibit this degree of reversibility at any one assessment. There is a substantial overlap in bronchodilator reversibility between individuals with asthma, chronic obstructive pulmonary disease (COPD) and those with no respiratory disease, and as a result, no clear-cut divisions can be suggested.⁸

A. Asthma more likely

• Two or more of these symptoms:
  - Wheeze (most sensitive and specific symptom of asthma)
  - Breathlessness
  - Chest tightness
  - Cough.

• Symptom pattern:
  - Typically worse at night or in the early morning
  - Provoked by exercise, cold air, allergen exposure, irritants, viral infections, beta blockers, aspirin or other NSAIDs
  - Recurrent or seasonal
  - Began in childhood.

• History of atopic disorder or family history of asthma
• Widespread wheeze heard on chest auscultation
• Symptoms rapidly relieved by inhaled short-acting beta-2 agonist (SABA)
• Airflow obstruction on spirometry (FEV₁/FVC<0.7)
• Increase in FEV₁ following bronchodilator, >10%; the greater the increase, the greater the probability
• Variability in PEF over time (highest-lowest PEF/mean), >15%; the greater the variability, the greater the probability.

B. Asthma less likely

• Chronic productive cough in absence of wheeze or breathlessness
• No wheeze when symptomatic
• Normal spirometry or PEF when symptomatic
• Symptoms beginning later in life, particularly in people who smoke
• Increase in FEV₁ following bronchodilator, <10%; the lesser the increase, the lower the probability
• Variability in PEF over time, <15%; the lesser the variability, the lower the probability
• No response to trial of asthma treatment.

Measurement of bronchial responsiveness, blood eosinophils and FeNO may be informative.
Alternative methods to identify variable airflow obstruction include repeat measures of spirometry with bronchodilator reversibility, peak flow variability with repeat measures at different times of the day and other specialist tests such as measures of bronchial hyper-responsiveness to exercise, methacholine or other provoking agents.

In most patients, observing a symptomatic response to treatment may help confirm the diagnosis, but a limited response to bronchodilator or ICS does not rule out asthma.

It may be difficult to distinguish between a diagnosis of asthma and COPD, particularly in adults with a smoking history, as they may have clinical features of both disorders. This has led to the term ACOS (Asthma COPD Overlap Syndrome).

The possibility of an occupational cause should be considered in all cases of adult onset asthma. If occupational asthma is suspected, it needs to be formally investigated, and this may require specialist referral.

Assessing asthma severity, control and future risk

Evaluation of asthma severity, the level of control and the risk of future events are all important components of the assessment of individuals with asthma.

Severity of asthma is defined by the treatment needed to maintain good control.

Figure 1:

GUIDELINES
Practice points:

• For symptomatic patients, asthma severity can be determined only after a therapeutic trial of ICS for at least eight weeks. Start the therapeutic trial and book the follow-up appointment for eight weeks later.

• Severe asthma is asthma that remains uncontrolled despite optimal treatment, taken correctly. Patients who initially present with frequent symptoms often have mild asthma, which can be well controlled with ICS therapy.

Asthma symptom control is defined by the frequency of symptoms, the degree to which symptoms affect sleep and activity, and the need for reliever medication.

Practice point:

• Many patients under-report their asthma symptoms on general enquiry. Different methods for assessing asthma symptom control are available including:

  i) **Asthma Control Test (Figure 2)**
  
  This test has been widely validated\(^9,10\) and is recommended with the following cut points:

<table>
<thead>
<tr>
<th>ACT scores</th>
<th>Symptom control</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25</td>
<td>Well controlled</td>
</tr>
<tr>
<td>16–19</td>
<td>Partly controlled</td>
</tr>
<tr>
<td>5–15</td>
<td>Poorly controlled</td>
</tr>
</tbody>
</table>

  The latest version of the test can be accessed via [http://www.asthmacontrol.co.nz/](http://www.asthmacontrol.co.nz/).

ii) **Australian Asthma Handbook**

This provides useful alternative questions that might be used to assess control (Table 2).\(^5\)

Assessment of the risk of adverse outcomes including severe exacerbations, mortality and treatment-related adverse effects is also required (Table 3).

Practice point:

• High-risk patients can be identified by monitoring health care use (such as hospital admissions, ED and emergency and/or unplanned doctor visits) and medication requirements (such as courses of steroids, frequency of SABA prescriptions and more prescriptions for SABA than ICS).

### Identifying management goals in collaboration with the patient

Managing asthma requires a partnership between the patient, their whānau and their healthcare team. This involves agreeing on management goals and a cycle based on repeated assessment, adjustment of treatment and review of responses as outlined in Figure 3.\(^11\)

Practice points:

• Check adherence and inhaler technique (and instruct patients using

---

**Table 2**: Definition of levels of asthma symptom control, regardless of current treatment.

<table>
<thead>
<tr>
<th>Good control</th>
<th>Partial control</th>
<th>Poor control</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of:</td>
<td>One or two of:</td>
<td>Three or more of:</td>
</tr>
<tr>
<td>• Daytime symptoms ≤ 2 days per week</td>
<td>• Daytime symptoms &gt; 2 days per week</td>
<td>• Daytime symptoms &gt; 2 days per week</td>
</tr>
<tr>
<td>• Need for reliever ≤ 2 days per week(^1)</td>
<td>• Need for reliever &gt; 2 days per week(^1)</td>
<td>• Need for reliever &gt; 2 days per week(^1)</td>
</tr>
<tr>
<td>• No limitation of activities</td>
<td>• Any limitation of activities</td>
<td>• Any limitation of activities</td>
</tr>
<tr>
<td>• No symptoms during night or on waking</td>
<td>• Any symptoms during night or on waking</td>
<td>• Any symptoms during night or on waking</td>
</tr>
</tbody>
</table>

\(^1\) Not including SABA taken prophylactically before exercise. (Record this separately and take into account when assessing management.)

Note: Recent asthma symptom control is based on symptoms over the previous four weeks.

Figure 2: The Asthma Control Test.

The first step is achieving control over your asthma, so you know where you’ll be right now. That way, your health care professional (doctor, nurse or pharmacist) can help you reach the best asthma control possible.

This test is a way of working out your present level of asthma control. Take five minutes now and do this simple test.

**STEP 1** Answer these simple questions.

**Q1.** In the past four weeks, how often did your asthma prevent you from getting as much done as usual, such as work or school?

<table>
<thead>
<tr>
<th>Score</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

**Q2.** During the past four weeks, how often have you had shortness of breath?

<table>
<thead>
<tr>
<th>Score</th>
<th>None of the time</th>
<th>Less than half the time</th>
<th>Half of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

**Q3.** During the past four weeks, how often have you had asthma symptoms such as wheezing, coughing, shortness of breath, chest tightness or shortness of breath that lasted more than a few minutes?

<table>
<thead>
<tr>
<th>Score</th>
<th>Less than half the time</th>
<th>Half of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Q4.** During the past four weeks, how often have you used rescue medication such as your blue inhaler or rescue inhaler?

<table>
<thead>
<tr>
<th>Score</th>
<th>None of the time</th>
<th>Less than half the time</th>
<th>Half of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

**Q5.** How would you rate your asthma controlling the past four weeks?

<table>
<thead>
<tr>
<th>Score</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

**STEP 2** Add up each score to get the total.

**STEP 3** Turn this leaflet over to find out how well your asthma is controlled.

---

**He pai tō whakahaere i tō mate huango?**

Ke te hokio tawhitu kia maa ariki huango kia te mātaurua kia bekeke kia maa tō huango inianian tinou. I eke, ka tawhiti kia agora kia haua kia takuta, mātou tō te kaihakahakauana kia te ohiora a ko maa kia bekeke ai tō tiki pai raua kia tō huango. Kia tō te kaihakahakauana he huarangi ki tō tiki mai kia te tauawhuiro tō te kaihakahakauana. Kia wire te mātaurua inianian kia te mātaurua nga whakawhakatanga.

**PAE 1** Whakautaua ēnei pātai nga whakawhakatanga

<table>
<thead>
<tr>
<th>Score</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

**PAE 2** Tāpiritia nga kaiti kia e tē tapelo

Hunaitia tō pānui na kia te kaimakaperahia kia tō te whakahaere o tō huango.

---

**He aha te tikanga o te putanga o tō Whakamātau Mau Huango?**

He aromatia tō putanga whakamātau o te kūkū o tō whakahaere i tō mate huango. He tō kūkū kia tō te kūkū o tō whakahaere i tō mate huango. He tō kūkū kia tō te kūkū o tō whakahaere i tō mate huango. He tō kūkū kia tō te kūkū o tō whakahaere i tō mate huango.

**Kauta: 20-25**

Tūnga, Asthma kia rino tō huango. He tūnga, ka heke ke tō whakamātau o te whakahaere i tō mate huango. He tō kūkū kia tō te kūkū o tō whakamātau o te whakahaere i tō mate huango.

**Kauta: 19, ihi iho rānei**

Te kūkū kia tō te kūkū o tō whakamātau, ka heke ke tō kūkū o tō whakamātau o te whakahaere i tō mate huango.

---

Asthma Control Test (ACT™) © 2002, 2007 Quality Metric Inc. All rights reserved. ACT™ is a trademark of QualityMetric Incorporated.
Table 3: Clinical features associated with increased risk of severe exacerbations and/or mortality.

A. **Asthma**
- Poor symptom control
- Hospitalisation or ED visit in the last year
- High SABA use (>1 canister per month)
- Home nebuliser
- History of sudden asthma attacks
- Impaired lung function (FEV<sub>1</sub> < 60% predicted)
- Raised blood eosinophil count
- ICU admission or intubation (ever)
- Requirement for long-term or repeated courses of oral corticosteroids.

B. **Comorbidity**
- Psychotropic medications
- Major psychosocial problems
- Smoking
- Alcohol and drug abuse
- Aspirin or other NSAID sensitivity.

C. **Other factors**
- Underuse or poor adherence to ICS treatment
- Discontinuity of medical care
- Socioeconomic disadvantage
- Māori and Pacific ethnicity
- Occupational asthma.

Figure 3: The control-based asthma management cycle.

Adapted from reference 6.
a physical demonstration of correct technique) at every visit.
• Consider alternative inhaler devices if persistent difficulty with technique.
• It is strongly recommended that a spacer is used with the pressurised metered dose inhaler (MDI) for the regular administration of ICS, ICS/long acting beta-2 agonist (LABA) and the administration of SABA in the setting of an acute attack. The two preferred methods are: one deep slow inhalation and a 10 second breath-hold, or 5–6 tidal breaths.

**Initial treatment choices (when to add ICS)**

- At initial diagnosis, all patients with asthma should be provided with a SABA to take as required for relief of symptoms.
- The key issue is when to start ICS therapy. There are proven benefits from the early introduction of ICS therapy in patients with mild or intermittent asthma and very few symptoms but the adherence to ICS therapy in real world studies is generally poor. This has led to uncertainty in determining the right stage at which to start ICS. It is recommended that ICS therapy is introduced if patients have symptoms ≥2 times in the last week, with evidence of benefit in patients with less frequent symptoms.
- An exacerbation requiring oral corticosteroids in the previous year is widely regarded as a requirement for regular ICS therapy to reduce the risk of further exacerbations.
- The daily doses of ICS which achieve 80–90% of maximum obtainable efficacy are shown in Table 4. These can be considered ‘standard’ doses for ICS, rather than ‘low’ doses as previously suggested.
- It is recommended that treatment with ICS is started at these standard doses. There is no greater benefit with initiation of ICS therapy at daily doses two to four times higher than these doses.
- Higher doses may be used in patients in whom adequate control is not achieved, or the patient may be switched to ICS/LABA combination therapy.
- ICS and ICS/LABA are best administered from an MDI with spacer or from a dry-powder inhaler (DPI).

**Step up to ICS/LABA therapy**

- Combination ICS/LABA single-inhaler treatment may either be prescribed at a fixed maintenance dose with a SABA as reliever therapy or, only for budesonide/formoterol, as Single ICS/LABA Maintenance and Reliever Therapy (SMART regimen).
- The SMART regimen involves using the budesonide/formoterol combination inhaler for both regular maintenance use (once or twice daily), and for relief of symptoms (one actuation as required). Patients should not be prescribed a SABA reliever when taking the SMART regimen.
- The SMART regimen is more effective at reducing severe exacerbations than maintenance ICS/LABA with SABA reliever therapy. It is the preferred ICS/LABA regimen for treating patients at risk of severe exacerbations.
- Currently in New Zealand the SMART

**Table 4**: The recommended standard daily dose of ICS in adult asthma.

<table>
<thead>
<tr>
<th>ICS/Propionate</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>400–500 µg/day</td>
</tr>
<tr>
<td>Beclomethasone dipropionate extrafine</td>
<td>200 µg/day</td>
</tr>
<tr>
<td>Budesonide</td>
<td>400 µg/day</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>200–250 µg/day</td>
</tr>
</tbody>
</table>
A regimen is only approved for use with the budesonide/formoterol DPI.

- LABA monotherapy is unsafe in patients with asthma and is a risk if patients are poorly adherent with ICS therapy. LABAs should not be prescribed in a separate inhaler from ICS in patients with asthma.

Figure 4: The stepwise approach to asthma treatment.

**STEP UP** to achieve control and reduce risk of exacerbations

**STEP DOWN** after a period of prolonged control to find and maintain lowest required step

At every step consider treatable traits, including overlapping disorders, comorbidities, environmental and behavioural factors

**STEP 1**
SABA reliever therapy

**STEP 2**
Maintenance standard dose ICS and SABA reliever therapy

**STEP 3**
Maintenance standard dose ICS/LABA and SABA reliever therapy

**STEP 4**
Maintenance high dose (not standard) ICS/LABA and SABA reliever therapy
Or
High dose (not standard) Single ICS/LABA Maintenance and Reliever Therapy (SMART regimen)

**STEP 5**
Maintenance high dose (not standard) ICS/LABA and SABA reliever therapy
Or
High dose (not standard) Single ICS/LABA Maintenance and Reliever Therapy (SMART regimen)

Consider add on treatment and seek specialist advice

**Recommended ICS/LABA doses in adult asthma**

<table>
<thead>
<tr>
<th>Step 3</th>
<th>Step 4 + 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP/Salm 50/25 2 inh BD + SABA for relief</td>
<td>FP/Salm 125/25 2 inh BD + SABA for relief</td>
</tr>
<tr>
<td>FP/Salm 100/50 1 inh BD + SABA for relief</td>
<td>FP/Salm 250/50 1 inh BD + SABA for relief</td>
</tr>
<tr>
<td>Bud/Form 100/6 2 inh BD + SABA for relief</td>
<td>Bud/Form 200/6 2 inh BD + SABA for relief</td>
</tr>
<tr>
<td>Bud/Form 200/6 1 inh BD + SABA for relief</td>
<td>FF/Vilanterol 100/25 1 inh OD + SABA for relief</td>
</tr>
<tr>
<td>Or</td>
<td>[FF/Vilanterol 200/25 currently not funded]</td>
</tr>
<tr>
<td>SMART regimen</td>
<td>[SMART regimen]</td>
</tr>
<tr>
<td>Bud/Form 100/6 2 inh BD + 1 inh for relief</td>
<td>Bud/Form 200/6 2 inh BD + 1 inh for relief</td>
</tr>
<tr>
<td>Bud/Form 200/6 1 inh BD + 1 inh for relief</td>
<td>[Bud/Form 400/12 is not recommended]</td>
</tr>
</tbody>
</table>

FP/Salm: Fluticasone Propionate/Salmeterol; Bud/Form: Budesonide/Formoterol; FF/Vilanterol: Fluticasone Furoate/Vilanterol; OD: once daily; BD: twice daily; SMART: Single ICS/LABA Maintenance and Reliever Therapy.
Practice points:

- Consider stepping up if uncontrolled symptoms, exacerbations or at increased risk, but check diagnosis, adherence, inhaler technique and modifiable risk factors first.
- Consider stepping down if symptoms are controlled for three months and low risk for exacerbations.20 Ceasing ICS is not advised.
- At step 5, additional high dose ICS, oral steroids, monoclonal antibody therapy (IgE) and oral theophylline may be considered as add on treatment, with specialist review. The provision of a home nebuliser is not recommended.
- Alternative therapies such as sodium cromoglycate, nedocromil or montelukast may be considered in some patients at the lower steps.
- In asthma patients with features of COPD, long acting muscarinic antagonists (LAMA) may be considered.21
- At each step check inhaler technique, adherence to treatment, understanding of self-management plan and barriers to self-care.

Non-pharmacological measures

- The key non-pharmacological measures to improve asthma outcomes include smoking cessation, weight loss and breathing exercise programmes.
- Avoiding triggers which have been identified to provoke or precipitate attacks such as aspirin and other NSAIDs or attacks associated with features of anaphylaxis.
- Currently available house dust mite avoidance measures are not effective.22
- Modifications to diet are unlikely to improve asthma control. Food avoidance should not be recommended unless an allergy or sensitivity has been confirmed.
- Exercise should be encouraged. If exercise provokes asthma it is a marker of poor control and should lead to a review of treatment.
- Limitation of exposure or removal from the workplace is crucial in the management of occupational asthma.
- Asthma control may be improved by a warm, dry domestic environment.23
- Unflued gas heaters may make asthma symptoms worse.

Self-management

Self-management education based on a written, personalised, action plan improves health outcomes and should be offered to all people with asthma.11,24,25

Practice points:

- Asthma action plans may be based on symptoms with or without peak flow measurements and comprise either three or four stages depending on patient and health professional preference.
- Asthma and Respiratory Foundation NZ asthma action plans (Figures 5A, 5B, 5C) can be downloaded from their website http://asthmafoundation.org.nz/:
  - ICS and SABA (three and four stage plan)
  - ICS/LABA and SABA (three stage plan)
  - Single ICS/LABA Maintenance and Reliever Therapy (SMART regimen)
- The peak flow level at which patients are guided to recognise worsening asthma is around 80% (of best), severe asthma at 60 to 70% (of best) and an asthma emergency at around 50% (of best).
- The four-stage plan has been shown to be effective in the management of asthma. In this plan there is an extra step giving patients the option of increasing the dose of ICS, up to four-fold, through increasing the frequency of use, and/or the dose at each use, when they recognise worsening asthma symptoms. Patients should be advised to return to their normal ICS dose once asthma symptoms have improved.
- The recommended action plans can be modified as required depending on patient and practitioner preference.
**Figure 5A:** Maintenance ICS and SABA reliever four-stage asthma action plan.

**Figure 5B:** Maintenance ICS/LABA and SABA reliever three-stage asthma action plan or maintenance ICS and SABA reliever three-stage asthma action plan.
**Figure 5C:** Single ICS/LABA Maintenance and Reliever Therapy (SMART) asthma action plan.

### YOUR SMART™ ASThma ACTION PLAN

**“Single Maintenance and Reliever Therapy”**

<table>
<thead>
<tr>
<th>Know your asthma symptoms</th>
<th>Know when and how to take your medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feeling good</strong></td>
<td><strong>Symbicort</strong></td>
</tr>
<tr>
<td>- you don’t have asthma symptoms most days ( wheeze, tight chest, a cough or feeling breathless)</td>
<td></td>
</tr>
<tr>
<td>- you have no cough or wheeze at night</td>
<td></td>
</tr>
<tr>
<td>- you can do all your usual activities and exercise freely</td>
<td></td>
</tr>
<tr>
<td>- Most days you don’t need your Symbicort inhaler</td>
<td></td>
</tr>
<tr>
<td>Your peak flow reading is above</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Severe</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- your symptoms are getting severe (wheeze, tight chest, a cough or feeling breathless)</td>
</tr>
<tr>
<td>- your Symbicort is only helping for 2-3 hours, or you are using more than 8 doses a day in total (regular + reliever use)</td>
</tr>
<tr>
<td>- you feel you need to see your doctor</td>
</tr>
<tr>
<td>Your peak flow reading is below</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Emergency</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- your symptoms are getting more severe quickly</td>
</tr>
<tr>
<td>- you are finding it hard to speak or breathe</td>
</tr>
<tr>
<td>- your Symbicort is not helping much</td>
</tr>
<tr>
<td>- you are using your Symbicort every 1-2 hours</td>
</tr>
<tr>
<td>Your peak flow reading is below</td>
</tr>
</tbody>
</table>

### Caution - your asthma is getting severe when

- your symptoms are getting severe (wheeze, tight chest, a cough or feeling breathless)
- your Symbicort is only helping for 2-3 hours, or you are using more than 8 doses a day in total (regular + reliever use)
- you feel you need to see your doctor

<table>
<thead>
<tr>
<th>Let’s take action…</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Continue your regular Symbicort PLUS 1 dose of your Symbicort when needed to relieve symptoms</td>
</tr>
<tr>
<td>- Start prednisone if you have it:</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>and then</td>
</tr>
</tbody>
</table>

**Other instructions:**

- Important: You need to see your doctor today

### Treatable traits

- The standard regimen for a course of prednisone in the situation of severe asthma is 40mg daily for five days. An alternative regimen is 40mg daily until definite improvement, and then 20mg daily for the same number of days.

Adherence to treatment should be routinely assessed and encouragement provided as part of the self-management education. For example, encourage patients to link their inhaler use with some other activity such as cleaning their teeth (and then rinsing their mouth).

Inhaler technique should be routinely assessed at consultations and training provided as part of self-management education. It is preferable to administer ICS and ICS/LABA MDIs via a spacer, or to use a DPI.

The four-step adult asthma consultation, which includes guidance for writing an asthma action plan, is provided in the appendix.

**Treatable traits**

A key feature of the management of adult asthma is the recognition and treatment of overlapping disorders, comorbidities, environmental and behavioural factors, recently referred to as ‘treatable traits’. The assessment and management of some of the treatable traits may require specialist referral. One schema to consider is outlined in Table 5.
Asthma in Māori\textsuperscript{1–3,27,28}

Māori rights in regards to health, recognised in Te Tiriti of Waitangi and other national and international declarations, promote both Māori participation in health-related decision making as well as equity of health outcomes for all New Zealanders. Currently Māori with asthma are more likely to be hospitalised or die due to asthma. Despite this, Māori with asthma are less likely to be prescribed ICS, have an action plan or receive adequate education. Major barriers to good asthma management for Māori include access to care, discontinuity and poor quality care, and reduced health literacy. Māori whānau have greater exposure to environmental triggers for asthma, such as smoking and poor housing. It is recommended that for Māori with asthma:

- Asthma providers should undertake clinical audit or other similar quality-improvement activities to monitor and improve asthma care and outcomes for Māori. The asthma action plan system of care,\textsuperscript{24} including the SMART regimen have been shown to improve outcomes in Māori.\textsuperscript{29}
- A systematic approach to health literacy and asthma education for Māori whānau is required. The evidence of the health literacy demands, the barriers and facilitators, and steps to delivering excellent asthma management with Māori which are described in He maramatanga huango: Asthma health literacy for Māori children in New Zealand also apply to adults.
- Asthma providers should support staff to develop cultural competency skills for engaging Māori with asthma and their whanau, in line with professional requirements. Information about the role of respiratory nurses working with Māori can be found on the New Zealand Nurses Organisation: http://www.nzno.org.nz/groups/colleges_sections/sections/respiratory_nurses.
- Māori leadership is required in the development of asthma management programmes that improve access to asthma care and facilitate 'wrap around' services to address the wider determinants (such as housing or financial factors) for Māori with asthma.

Asthma in Pacific peoples

Similar considerations are likely to apply to asthma in Pacific peoples who also have a disproportionate burden of asthma, including high rates of hospital admission, and should be considered a high-risk group requiring targeted care. Inclusive in this targeted approach is addressing risk factors such as poor housing, overcrowding, health literacy, obesity, smoking and poor access to health care services.

<table>
<thead>
<tr>
<th>Overlapping disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>Dysfunctional breathing including vocal cord dysfunction.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidities:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux disease</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Depression/anxiety.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Occupational exposures</td>
</tr>
<tr>
<td>Provoking factors including aspirin, other NSAIDs and beta blockers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behavioural:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
</tr>
<tr>
<td>Inhaler technique.</td>
</tr>
</tbody>
</table>

Table 5: Treatable traits in asthma.
Asthma in pregnancy

Pregnancy can affect the course of asthma and women should be advised of the importance of maintaining good asthma control during pregnancy to avoid risk to both mother and baby.

- SABAs, ICS and LABAs should be used as normal during pregnancy.
- The risks to the baby of poor asthma control in pregnancy outweigh any theoretical risks associated with asthma medications.
- Oral steroids should be used as normal when indicated during pregnancy for women with severe asthma.
- Acute severe asthma in pregnancy is a medical emergency and should be treated in hospital.

Management of acute severe asthma (primary care, afterhours or ED)

Acute asthma management is based on:

- objective measurement of severity (Table 6)
- assessment of the need for referral to hospital and/or hospital admission (Table 7)
- administering treatment appropriate for the degree of severity and
- repeatedly reassessing the response to treatment.

Table 6: Levels of severity of acute asthma exacerbation.

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate asthma exacerbation</td>
<td>Increasing symptoms, FEV₁ or PEF &gt;50% best or predicted, No features of acute severe asthma.</td>
</tr>
<tr>
<td>Severe asthma</td>
<td>Any one of: FEV₁ or PEF 30–50% best or predicted, Respiratory rate ≥25/min, Heart rate ≥110/min, Inability to complete sentences in one breath.</td>
</tr>
<tr>
<td>Life-threatening asthma</td>
<td>Any one of the following in a patient with severe asthma: FEV₁ or PEF &lt;30% best or predicted, SpO₂ &lt;92% or PaO₂ &lt;60mmHg, PaCO₂ ≥45mmHg, Inability to talk#, Silent chest#, Cyanosis#, Feeble respiratory effort, exhaustion#, Hypotension or bradycardia#.</td>
</tr>
</tbody>
</table>

# These are very late manifestations and reflect a patient at risk of imminent respiratory arrest.

Direct measurement of airflow obstruction is the best and most objective marker of asthma severity. This can be based on either the measurement of peak expiratory flow (PEF) or preferably FEV₁, if available, with both measures expressed as percent of the previous best or predicted normal values.

The levels of FEV₁ or PEF to signify severe and life-threatening asthma in these situations differ from (and are lower than) those used by patients in action plans in a non-health care setting.

Key priorities include identification of a life-threatening attack requiring urgent admission to an ICU or HDU, and a severe asthma attack requiring hospital admission (Table 7).

An evidence-based algorithm for the management of severe asthma can be used to guide treatment (Figure 6).

Practice points:

- A lack of response to initial bronchodilator treatment and/or a requirement for repeat doses indicates the likely requirement for referral to hospital and/or admission.
- For most patients, initial treatment with a SABA via a spacer and oral steroids is likely to be sufficient. Reserve nebulised bronchodilators for those with severe asthma who do not respond to initial inhaled therapy.
- Magnesium sulphate is the preferred intravenous bronchodilator to be administered in life-threatening situations.

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asthma. There is no role for intravenous beta-2 agonists, unless inhaled treatment cannot be given. Similarly, there is no role for intravenous aminophylline.

- There is no role for adrenaline (epinephrine) unless asthma is accompanied by anaphylaxis or angioedema.
- There is insufficient evidence to support the use of non-invasive ventilation (NIV) in life-threatening asthma, outside an ICU or HDU setting, and as a result it is not recommended in other settings.

For patients who are treated in primary care or discharged from the Afterhours or ED, long term management should be reviewed and an early follow-up appointment with their primary healthcare team should be arranged. All patients not taking ICS should be started on ICS before going home (Table 8).

**Table 7:** Criteria for referral to hospital and/or hospital admission.

- Patients with any feature of life-threatening asthma
- Patients with any feature of severe attack persisting after initial treatment
- Patients in whom other considerations suggest that admission may be appropriate:
  - Still have significant symptoms
  - Living alone/socially isolated
  - Psychosocial problems
  - Physical disability or learning difficulties
  - Previous near fatal attack
  - Exacerbation despite adequate dose of oral steroids pre-presentation
  - Presentation at night
  - Pregnancy.

**Algorithm for Management of Severe Asthma**

1. **IMMEDIATELY**
   - **MILD/MODERATE FEV1/PEF >50%**
     - Give 6x100µg salbutamol via MDI and spacer*
   - **SEVERE FEV1/PEF 30-50%**
     - Give 6x100µg salbutamol via MDI and spacer* or salbutamol 2.5mg via nebulisation, prednisone 40mg, oxygen if required to keep sats > 92%
   - **LIFE-THREATENING FEV1/PEF <30%**
     - Give continuous salbutamol via nebulisation, ipratropium bromide 500µg via nebulisation, IV hydrocortisone 100mg or prednisone 40mg, oxygen if required to keep sats > 92%
   - **ARRANGE URGENT TRANSFER TO HOSPITAL BY AMBULANCE**
     - All patients will require hospital admission
   - **REFER TO ICU/HDU**
     - Give salbutamol 2.5mg via nebulisation, frequency determined by response, up to continuously; Ipratropium bromide 500µg via nebulisation, up to hourly, consider IV magnesium sulphate 1.2-2.0g over 20 min, oxygen if required to keep sats 92-96%

2. **15-60 MIN**
   - **FEV1/PEF >70%**
     - Consider oral prednisone 40mg, if not given above, and ICS
   - **FEV1/PEF 50-70%**
     - Give prednisone 40mg if not given above
     - Repeat salbutamol 6x100µg via MDI and spacer*
   - **FEV1/PEF <50%**
     - Give 6x100µg salbutamol via MDI and spacer* or salbutamol 2.5mg via nebulisation, up to 3 times over 1st hour
     - Ipratropium bromide 6x200µg via MDI and spacer* or 500µg via nebulisation, oxygen if required to keep sats 92-96%

3. **1-2 HR**
   - **STABLE**
     - No signs of severe asthma and FEV1/PEF > 70%
     - DISCHARGE
     - Once pre-discharge conditions are met
   - **UNSTABLE**
     - Signs of severe asthma or FEV1/PEF <50-70%
     - ADMIT
     - Once pre-discharge conditions are met

*Administered in individual doses

For practical purposes, the FEV1 and PEF are considered interchangeable when expressed as % predicted for the purpose of assessment of acute asthma severity.
Table 8: Pre-discharge considerations.

1. Most patients presenting with acute exacerbations of asthma should have a course of oral prednisone, 40mg daily for at least five days.
2. All patients should have an ICS started, or current use reinforced.
3. It is recommended that patients have prednisone and ICS dispensed prior to discharge to ensure there are no barriers to taking medication.
4. Before the patient goes home, ensure that the patient:
   • Understands treatment prescribed and the signs of worsening asthma
   • Has a peak flow meter and knows at what level to contact emergency medical help if worsens
   • Can use their inhalers correctly and has a supply of their medication
   • Arranges an early follow-up appointment with their primary healthcare team for review
   • Consider referral to a specialist respiratory service.

Appendix

The four-step adult asthma consultation

<table>
<thead>
<tr>
<th>1. Assess asthma control</th>
<th>2. Consider other relevant clinical issues</th>
<th>3. Decide if increase or decrease in maintenance therapy required</th>
<th>4. Complete the asthma action plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete the Asthma Control Test (ACT) score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–25: well controlled</td>
<td>Ask about compliance with maintenance treatment</td>
<td>Is a step up in the level of treatment required if asthma is not adequately controlled, poor lung function or recent severe exacerbation?</td>
<td>Decide which plan to use:</td>
</tr>
<tr>
<td>16–19: partly controlled</td>
<td>Check inhaler technique</td>
<td></td>
<td>• Three stage maintenance ICS + SABA reliever</td>
</tr>
<tr>
<td>5–15: poorly controlled</td>
<td>Enquire about clinical features associated with an increased risk</td>
<td>Is a step down in the level of treatment possible if there has been a sustained period of good control?</td>
<td>• Four stage maintenance ICS + SABA reliever</td>
</tr>
<tr>
<td>Review lung function tests</td>
<td>Consider treatable traits</td>
<td></td>
<td>[This includes the instruction to increase dose and frequency of ICS in worsening asthma]</td>
</tr>
<tr>
<td>Peak flow monitoring and/or Spirometry</td>
<td>Decide whether peak flow monitoring is indicated</td>
<td>Is a change to the SMART regimen required in patients prescribed ICS/LABA treatment who have had a recent severe exacerbation?</td>
<td>• Three stage ICS/LABA + SABA reliever</td>
</tr>
<tr>
<td>Review history of severe asthma attacks in last 12 months (requiring urgent medical review, oral steroids or bronchodilator nebuliser use)</td>
<td></td>
<td></td>
<td>• Single ICS/LABA Maintenance and Reliever Therapy [SMART]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For those with peak flow instructions, enter personal best recent peak flow and peak flow at each level in the plan. The recommended cut points of &lt;80% for getting worse, &lt;60 to 70% for severe asthma and &lt;50% for an emergency are a reference guide only and can be adjusted according to clinical judgement depending on the patient.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enter the prednisone regimen. The standard regimen in severe asthma is 40mg daily for five days. An alternative regimen is 40mg daily until there is definite improvement and then 20mg daily for the same number of days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enter additional instructions in the box provided. This may include avoidance of provoking factors such as aspirin.</td>
</tr>
</tbody>
</table>
Figure 7A: Completing the maintenance ICS and SABA reliever four-stage asthma action plan.

- Write name of preventer - eg Beclometasone
- Write number of puffs
- Ensure that the patient's inhaler and spacer technique is checked
- Any special instructions here

Figure 7B: Completing the maintenance ICS/LABA and SABA reliever or maintenance ICS and SABA reliever three-stage asthma action plan.

- Write name of preventer - eg Seretide; Beclometasone
- Write name of reliever - eg Ventolin
- Write number of puffs
- Any special instructions here

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Figure 7C: Completing the Single ICS/LABA Maintenance and Reliever Therapy (SMART) asthma action plan.

Competing interests:
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Medicinal cannabis: moving the debate forward
Giles Newton-Howes, Sam McBride

ABSTRACT
There has been increased interest in cannabis as a medicine both nationally and internationally. Internationally, cannabis is accepted as a medication for a variety of purposes in a variety of legal guises and this, associated with anecdotes of the utility of cannabis as medication has led for calls for it to be ‘medicalised’ in New Zealand. This viewpoint discusses the issues associated with this approach to accessing cannabis and some of the difficulties that may be associated with it. It is important doctors are at the forefront of the debate surrounding medicalised cannabis. Recommendations as to the ongoing debate are offered.

Recent debate on medicinal cannabis has occurred with doctors, those expected to prescribe, largely silent. The use of medicinal cannabis in some overseas jurisdictions has seen the introduction of a product as a medicine outside of usual criteria and driven by legislation and popular demand rather than strong evidence for efficacy. The lines between recreational use and that of cannabis for medicinal reasons are blurred. These factors have the potential for prescribers to become either the gatekeepers for recreational use or to prescribe in situations in which diagnostic categories become meaningless. The medical profession needs to not only contribute to but also lead any debate on medicinal cannabis. This viewpoint aims to encourage this debate by outlining the context of medicinal cannabis, surrounding issues and providing a framework for consideration of medicinal cannabis in New Zealand.

The context
Cannabis is one of the first recorded medications with prescriptions for its use dating back to 1500BC. The introduction of cannabis into Western medicine occurred via physicians exposed to its use in India with reported use as an analgesic, appetite stimulant, anti-emetic, muscle relaxant and anticonvulsant. Use was not just restricted to the most impoverished as, potentially, an escape from the hardship of life. Dr J Reynolds, Queen Victoria’s personal physician, described 30 years of use in a range of conditions. In the US, cannabis was included in the US Pharmacopoeia from 1850 through to 1937. Prohibition in the first half of the twentieth century reflected less the harms of cannabis than the socio-political prejudices of the day. One profound consequence of prohibition was to confound research into the medical potential of cannabis, a situation that is only just being addressed in some jurisdictions today.

Levels of cannabis restriction vary from minimal restraints as found in countries such as the Netherlands to a strict prohibitionist approach such as occurs at a US Federal level, New Zealand being more closely aligned to the latter. Despite the criminal liability associated with cannabis, its use in New Zealand is widespread. The reported annual prevalence of use of 10.2% is high by international standards and cannabis remains the most widely used illicit drug in New Zealand. The high levels of cannabis use suggest a degree of acceptance of use within New Zealand and imply a ready population of people who may wish to access cannabis should it be available medically.

Greater acceptance of cannabis has contributed to the increasing advocacy for medicinal use of cannabis. Medical regimes are more likely to be introduced where use in general is higher and medicinal cannabis has largely been a consumer-led initiative. This dynamic is reflected in New Zealand. Public figures have spoken about their use in New Zealand typically in the context of serious illness. The New Zealand Drug Foundation and the New Zealand Law Commission have argued for increased
access to medicinal cannabis. Advocacy groups such as Green Cross, United in Compassion and NORML campaign vigorously. Industry is also calling for development of a legal market extolling the potential economic benefits.

This local support occurs against a backdrop of increasing international use of cannabis in health settings, though models of use vary widely from use of cannabinoid medications, removal of criminal sanctions for patients using cannabis for medical purposes to access to ‘medical grade’ herbal cannabis. Use of herbal cannabis is authorised or legislated for in some jurisdictions in the US, Netherlands, Canada, Israel, Finland, Denmark, Uruguay and the Czech republic. Australia has recently passed amendments into their Narcotics Drugs Act 1967 allowing cultivation of cannabis for medical and scientific purposes, and paving the way for trials into and the potential use of herbal cannabis for medical purposes.

What is cannabis?
The leaves and flowers of cannabis contain over 400 distinct compounds and contain at least 100 different phytocannabinoid compounds (cannabinoids occurring naturally within the cannabis plant). The two major constituents are ∆9-tetrahydrocannabinol (∆9THC or THC) and cannabidiol (CBD). THC is responsible for most of the psychoactive properties of cannabis, including effects sought by recreational users. Cannabidiol has anxiolytic and anti-psychotic properties and may moderate some of the psychoactive effects of THC. Emphasis has been placed upon isolating individual components of cannabis to use as therapeutic compounds, such as the use of cannabidiol for childhood epilepsy. However, the approach has had limited success and it is postulated that the efficacy of cannabis-based medications relies upon synergy between the compounds or the ‘entourage effect’.

Cannabinoids interact with the endocannabinoid system, which is made up of the cannabinoid receptors (CB1 and CB2) and endogenous cannabinoids of which anandamide and 2-arachidonoyl glycerol have been isolated. CB1 is the most common G-protein-coupled receptor in the brain. It is widely distributed with high levels in the hippocampus, cerebellum, basal ganglia and neocortex in addition to peripheral nerve terminals. CB2 receptors are found largely within peripheral areas, including cells of the immune system. The endocannabinoid system is believed to be involved in a large range of bodily functions, including analgesia, vomiting, immune system regulation, appetite, cognitive processes and motor control, providing biological plausibility to the use of cannabis as a medicine and potential targets.

The argument for the use of cannabis as a medicine
Despite the hiatus in the investigation of cannabis, largely related to prohibition, sufficient data has been accumulated to allow formal review. A systematic review into the use of cannabis for treatment of chronic non-cancer pain concluded that there was evidence for moderate efficacy of cannabinoids in neurological pain with preliminary evidence for fibromyalgia and rheumatoid arthritis. A recent systematic review and meta-analysis concluded that there was moderate-quality evidence to support the use of cannabinoids for treatment of chronic pain and spasticity with low-quality evidence to support cannabinoids being useful in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders and Tourette syndrome.

Other evidence for the utility of cannabis as a medicine is limited. Trials of other neurological conditions including: levodopa induced dyskinesia in patients with Parkinson’s disease, non-chorea-related symptoms of Huntington’s disease, Tourette syndrome, cervical dystonia and epilepsy have occurred. Despite enthusiasm for cannabinoids in epilepsy, a 2012 Cochrane Review concluded “No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy” with similar results published by expert systematic reviews.

Outside of this limited range of conditions there is little current evidence to suggest that cannabis has any medical role. However, there is increased adoption of medicinal cannabis internationally for conditions that include hepatitis C, Parkinson’s disease, PTSD, glaucoma, Crohn’s disease and Alzheimer’s disease. This slippage into other diagnostic categories is, unfortunately, not uncommon in medicine but does raise
concerns as to who cannabis would be prescribed for. The introduction of cannabis by accord, rather than evidence, has led to the invidious situation of doctors being asked “to authorise our patients’ access to a product with little evidence to support its use”. This creates ethical and practical problems for physicians, who may be asked for an intervention with little or no evidence over a treatment that is well evidenced.

Cannabis and cannabinoids: medication or flower?

Complicating any debate about medicinal cannabis is that it may refer to herbal cannabis or standardised cannabis extracts and synthetic cannabinoids used in regulated doses.

The Ministry of Health (MOH) allows potential access to pharmaceutical grade products that have consent for distribution in New Zealand, pharmaceutical grade products that do not have consent for distribution in New Zealand and non-pharmaceutical grade products.

Only one pharmaceutical grade product, Nabiximols (marketed as Sativex®), an extract of cannabis, is licensed for use in New Zealand. It is approved by Medsafe for add-on treatment for symptom improvement in patients with moderate to severe spasticity due to Multiple Sclerosis where response to anti-spasticity medication has not occurred and who respond to initial trials of therapy. Ministerial approval may also be made for non-approved authorisations such as cachexia, neuropathic and chronic pain. Unlike other drugs whose access is restricted, Ministerial approval is required for use due to concerns about risks of diversion and dependence. The utility of this is questionable considering the expense associated with Nabiximols compared to illicit cannabis, making diversion highly unlikely. The level of scrutiny is also inconsistent with other drugs such as methadone or methylphenidate, where ‘home production’ is virtually impossible and the expense is low (as these drugs are funded), making diversion considerably more likely. This appears to be a conflation of the illegal status of recreational cannabis and the use of cannabinoids as pharmacotherapy.

Synthetic preparations of THC available for medicinal use, though not licensed within New Zealand, include Drobinol (Marinol®), marketed as treatment for nausea/vomiting associated with chemotherapy and acquired immune deficiency syndrome (AIDS) associated anorexia and weight loss. Nabilone (Cesamet®) is marketed for nausea and vomiting associated with chemotherapy. Both products contain synthetic THC alone.

The application criteria for access to non-pharmaceutical grade products are more stringent including restriction of use to a severe or life threatening condition, evidence that conventional products have been trialed without adequately controlling symptoms, that the risk benefit analysis of medications has been adequately considered by a qualified clinical specialist, application to be made by appropriate specialist or chief medical officer of a district health board, provision of a certificate of analysis and informed consent from either parent or guardian for minors. This allows the potential to access cannabis-based products for compassionate purposes in conditions such as terminal illness where conventional products have failed to control symptoms or forms of childhood epilepsy such as Dravet syndrome.

However, guidance for use for these products is lacking with no clear pathway as to how patients or practitioners may access appropriate information. Given the public interest in medicinal cannabis it is inevitable that doctors will be asked about products and at present most are operating in a vacuum. There is an urgent need for doctors to take a lead in determining what products may be appropriate and both monitoring and disseminating response to their use. Neurologists, palliative care and pain specialists have a particular role in this regard.

A case for herbal cannabis?

Importantly, patients prefer herbal cannabis. Herbal preparations are variously available as standardised cigarettes, loose herb, food and drinks. Unsurprisingly however, the bulk of herbal cannabis use is smoked, the form in which cannabis is typically used recreationally. Compared to oral use, smoking cannabis results in rapid uptake and avoids first pass metabolism with resulting faster onset of action, not to mention the significant health hazards associated with smoking. Preference for herbal cannabis may also reflect the unantagonised THC in synthetic compounds.
Dosage is also problematic, in contrast to some prescribing practices in which medicines are provided in regulated doses, instructions to patients are essentially to smoke to effect. This may be because the amount of psychoactive ingredients in botanical cannabis can vary and be further altered by mode of preparation and method of smoking. Although ‘use to effect’ regimes may exist for the short term control of pain (eg with nitrous oxide or methoxyflurane), they are rare for chronic conditions and non-existent where the ‘medication’ is smoked and the dose is not known to the prescriber. This is further complicated by the lipophilic properties of cannabinoids and second order kinetics of metabolism, leading to prolonged release from fat in chronic users.

Prescribing considerations

As with any medication, for cannabis to be considered as a pharmacotherapy requires conformity with other regulated medications. This is the process undertaken for the licensing of Nabimixols and herbal cannabis would need to fulfil the same licensing regulations. This requires at minimum a consistent reproducible medication delivering the same dose of drug, evidence of efficacy and ideally effectiveness, indications as to which disorder(s) the pharmacotherapy is licensed for and symptom targets. All this requires strong evidence, provided for in stage II and III randomised controlled trials (RCTs). A structure by which herbal cannabis could be introduced to Australia and the complexities involved is outlined by Martin and Bonomo and should be given consideration in New Zealand.

Risks relating the use of medicinal cannabis are wide ranging, though often overstated, and need to be held in context with commonly used medications such as anti-convulsants. The effects of regularly smoked cannabis seem to be largely associated with symptoms of bronchitis and inflammation, although an association with respiratory cancer remains unclear. These risks may be reduced by the use of vaporizers, though evidence is lacking and complicated by the range of devices available and variable sophistication.

Prescription of cannabis in adolescence or early adulthood is associated with an increased risk of psychosis and reduced educational outcomes in a dose-dependent fashion. Recent use of cannabis is associated with impairment of executive function including memory, and heavy use may be associated with deficits in decision making and concept formation that may not resolve with abstinence. While cannabis has been associated with increased rates of motor vehicle accidents, early evidence from Colorado where cannabis is legal has not substantiated concerns. Use disorders are also a significant consideration. New Zealand surveys suggest that there is a 1.4% prevalence of abuse and dependence related to illicit use of cannabis; this is of note given that many of the indications for which medicinal cannabis is suggested are chronic conditions for which on-going medication is likely to be required.

The implications of such findings for widespread use of medicinal cannabis are complex and need to be weighed against the side-effect profile of other medications. In this regard, proponents of medicinal cannabis note that concerns about the risks associated with medicinal cannabis are inconsistent with those associated with opioid analgesia, with a lower risk of dependence and toxicity. However, the uncertainty in relation to the effectiveness and side-effects prevents clear conceptualisation that would allow prescribers and patients to make fully informed decisions about their pharmacotherapy.

The intersect between medicinal cannabinoids and recreational cannabis

What is the threshold for which cannabis might be used? While public debate often concentrates upon the role of cannabis in terminal illness, studies suggest that cannabis is largely used for a variety of conditions, not all of which might meet criteria for disorder, including: pain, insomnia and anxiety. A study reporting data from Te Rau Hinengaro: the New Zealand Mental Health Survey, in contrast to expectations of those with chronic disease, cannabis users were predominantly young, with 45% under the age of 34. These results suggest that the effects of cannabis across a range of disorders may be a non-specific anxiolytic effect reinforcing the confluence between recreational and medicinal use.
The similarity between recreational and medicinal users of cannabis is also shown in other ways. Often smoked preparations are preferred and medicinal users of cannabis typically have a history of recreational use. A recent study examining recreation and reported medicinal users of cannabis found a significant crossover with 86% of those reporting medicinal use also using cannabis recreationally. The availability of medicinal cannabis does not preclude either continuing to grow supplies or purchase outside pharmaceutical supplies. The use of cannabis and use disorders is higher in settings where medical use is approved, and it is speculated that this reflects more positive attitudes to cannabis use. It is possible that this relationship is bi-directional where the introduction of medical cannabis leads to normalisation of use. Advocacy for medical cannabis may in part reflect a desire for change of the prohibitive approach to cannabis in general. That cannabis is certain to have a greater safety profile than alcohol despite the latter drugs' highly commercial status and the similar aims of users is likely to add to the level of perceived injustice among advocates and confound informed debate. However, the authors argue that medicinal use of cannabis and re-consideration of prohibition must be considered separately, on their own merits and within appropriate frameworks.

A pathway forward for medicinal cannabinoid?

There is the possibility that medicinal cannabinoids will prove of value to New Zealanders as pharmacotherapy. This may be of particular value as the likely conditions treated are vulnerable populations with chronic conditions. It will be important, however, to have a framework moving forward that allows for rational discussion. We propose the following as a general framework for this discussion:

1. The discussion between the legal framework of cannabis and the medicinal framework of cannabinoids be kept separate. As much as possible the licensing of medicinal cannabinoids needs to conform to the framework for all medications. This is to prevent the ‘decriminalisation’ of cannabis via a medical route.

2. In fact however, current legislation allows for the use of cannabis in some medical circumstances. Doctors need to be engaged in this debate and the use of cannabis for the management of disease. This is akin to medical professional providing advice about non-pharmaceutical products for the treatment of medical disorders such as fish oil for mood disorders.

3. The use of medicinal cannabinoids needs a dialogue that clearly differentiates it from the dialogue about the legal status of cannabis. To this end we would suggest, if discussion about cannabinoids as a medicine occurs, it is referred to as medicinal cannabinoids, not cannabis.

4. The use of cannabinoids as therapies may be beset with possible risks, both individual and societal, however these need to be considered in a similar light to other medications rather than used carte blanche to suggest there is no place for cannabinoids in medicine.

5. It is hard to justify a place for a smoked medication, in light of the serious public health harms related to smoking and availability of other methods of delivery. For this reason the authors would not recommend continuing a debate about the use of smoked medicinal cannabinoids.

6. As with any medication, there needs to be sufficient evidence for effectiveness to warrant prescription. This is a central component of the medicinal cannabinoid debate and currently lacking.

7. There is recognition of the use of regulatory systems already in place in New Zealand, such as the special authority forms for funded medication, that could be put to good effect should medicinal cannabinoids be licensed and publically funded. This avoids the conflation of a medicine with a prohibited substance.

It is important that all areas of society engage in the medicinal cannabis debate, and the authors of this paper encourage ongoing robust discussion.
Competing interests:
Dr Newton-Howes reports that he sits on PTAC.

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A pioneer paediatrician in New Zealand
Geoffrey Bruton SWEET
(1.9.1870–17.5.1939) MB ChM (Sydney 1893)

William J Sugrue, Patricia M Clarkson

ABSTRACT

Paediatrics as a specialty was slow to emerge in New Zealand where Geoffrey Bruton Sweet was a pioneer full-time paediatrician from 1907 to 1939. Although there had been appointments as paediatric lecturers to the Otago Medical School, the early appointees were not restricted to paediatric practice. Dr Sweet, an Australian graduate, came to New Zealand and made a major contribution to the development of pathology services before embarking on a career devoted to paediatrics. He was a powerful advocate for children, well read and interested in clinical research, and realised the need to communicate with those directly involved in the care of children. For New Zealand, he was a man ahead of his time.

Figure 1: Napier Doctors 1894. In front Dr E Menzies. Back from left Drs TC Moore, FL deLisle, JA Jarvis, G Bruton Sweet, A Milne-Thomson.
Geoffrey Bruton Sweet is thought to be New Zealand’s first specialist paediatrician.¹ He was born in Newton Abbot, Devonshire, England and went to Australia at the age of 12 years.² He continued his education in Australia and took his medical degree at Sydney University. There he would have come under the influence of Professor Thomas Anderson Stuart (Dean) who demanded a high standard from his students.³ After graduation he took up a position as resident medical officer at Little Bay Hospital on North Head of Botany Bay, but within a year came to New Zealand to a full time hospital post in Napier,⁴ where he was registered on 24th May 1894.⁵ He was the resident medical officer (a post akin to medical superintendent) at Napier Hospital 1894–96.⁶

His arrival there started a remarkable development in which Napier led the field for many years. At a local meeting of the British Medical Association (BMA), Dr Sweet moved that “a pathology sub-committee be formed to examine microscopically and bacteriologically if necessary, and report on morbid specimens forwarded to them by any member of this branch”, that “such a committee be composed of three local doctors and the mover” and further, that “the Pathology sub-committee meet at an early date to draw up a set of rules to be submitted to the next general meeting”.⁷ What was being set up was a district laboratory service.⁷

He moved to practice in Whangarei where he was appointed public vaccinator in May 1897,⁸ port health officer in June 1901⁹ and medical attendant at the new local hospital.¹⁰ In 1901 he married Kathleen Mary Louise Thompson, daughter of the local member of parliament.¹¹

In 1906 he sold his practice in Whangarei¹² and went to England, arriving in London in September.¹³ There he spent time as a clinical assistant at the Hospital for Sick Children in Great Ormond Street,¹⁴ and it was probably also during this time that he took advantage to learn from Professor Still who occupied the first chair of paediatrics in England at King’s College Hospital.¹⁵ By November 1907 he had returned to Auckland¹⁶ and set up in paediatric practice in the city.¹⁷ In 1908 he was appointed as physician to the Auckland Hospital and at the time was noted to be an authority on children’s diseases.¹⁸ He was honorary consulting and medical advisor at St Mary’s Home, Otahuhu until 1921¹⁹ and also attended infants at the Door of Hope.²⁰

He volunteered to serve in WW1, was appointed Captain NZMC, November 1916 and soon left for England where he was based at Codford and later at Walton-on-Thames.²¹ On return to Auckland he resumed paediatric practice.

In 1923 he spent time in England in hospitals primarily noted for their work among children²² and attended the annual meeting of the BMA.²³ He took time to visit a specialist hospital in Hampshire which dealt with conditions such as bone and joint tuberculosis and the post-acute effects of poliomyelitis that required long term hospitalisation.²⁴ On returning to Auckland in 1924 he became senior physician at the Princess Mary Children’s Hospital,²⁵ taking over from Dr WE Williams, a Remuera General Practitioner who was the first physician in charge of the children’s medical wards in the Princess Mary Hospital for Children.²⁶ In 1927 he was granted three months leave of absence by the Auckland Hospital Board²⁷ and travelled to the US by way of Sydney and Vancouver to attend a national conference in Kansas City.

Colleagues associated in the care of hospitalised children would have included Drs WE Williams who was an honorary physician up to the time of his death,²⁸ SL Ludbrook who was appointed in 1926,²⁹ EH Roche who held a temporary appointment 1932–35,³⁰ and also E Hughes³¹ and E Sayers.³²

In addition to his medical practice, Dr Sweet was involved throughout his career in a variety of activities aimed at improving the health of the wider community. Life-saving instruction was undertaken at the local swimming club.³³ He was a strong advocate for pasteurised milk and ran advertisements in the local newspaper exhorting its adoption.³⁴ Injury prompted a “good Samaritan” response.³⁵ He also showed—at significant risk to himself—no hesitation in going to the aid of a young man being attacked by a shark.³⁶ He spoke out for better treatment for returned servicemen suffering from tuberculosis.³⁷ There was involvement in the organisation and care of
children made ill, uncared for or orphaned by the influenza epidemic. He spoke out against overcrowding in schools, was concerned about the dietary habits of school children and became an advocate for free milk in schools.

He was aware of the deficiencies in the training of those to whom infant care was entrusted. In 1920 he published a book entitled “Lectures on the Management of Infants in Health and Sickness” which was based on a short series of lectures delivered to the nurses at St Mary’s Home for infants. In it he acknowledged the work of the Plunket Society in improving the health of infants, but felt it his bounden duty to criticise the teaching of Dr Truby King on infant feeding. Although the book received a favourable review in the Nursing Journal, it generated an unwarranted, irascible response from Dr Truby King. A telegram was sent to the New Zealand branch of the BMA protesting against the attitude taken up by Dr Sweet in the book and asking its council to take action in the matter. There followed an article to the local medical journal denigrating Sweet’s approach and advice regarding the feeding of infants which was at variance (rightly) with his own, which was promulgated by the Plunket Society. There was a measured reasoned response from Dr Sweet in a paper he read before the Auckland Division of the New Zealand BMA, which was subsequently published.

As a practising physician, he was actively involved in the local branch of the BMA, attending meetings, annual national congresses and served as president of the Auckland branch. In addition to presenting papers at annual BMA congresses, there were also presentations at conferences of Child Welfare and the National Council of Women. He was an early member of the Auckland Clinical Society and contributed to its meetings.

He published articles in scientific medical journals and was on the advisory board of the Archives of Disease in Childhood. In addition to the book, which was published in 1921 and dedicated to Dr GF Still “…as a slight recognition of the benefits derived from his personal teaching”, he left an unpublished manuscript, which reflected his long-standing interest in infant welfare. This would have been the basis for a book about some of the health problems of infancy directed towards senior medical students and general practitioners. In it he clearly outlines the features and management of problems commonly encountered in the first year of life. The text reflects the best practice of the time presented in an uncomplicated manner.
In Dunedin, Dr Isiah De Zouche had been registered in 1877. There was a hospital appointment as a physician and an account of the times notes there were no specialists. He had an appointment as lecturer in Diseases of Children at the Otago Medical School 1886–1893. Dr Ernest Harry Williams MB ChB New Zealand graduated in 1899 and then spent several years in Britain including time at Great Ormond Street. He returned to Dunedin where he was registered in 1908 and practised as a general physician with clinical responsibility for the children’s ward in Dunedin Hospital. In 1914 there was a medical school appointment as lecturer in Diseases of Children—a position he held for several decades.

Dr Sweet limited his private and hospital practice to paediatrics from the time he returned to New Zealand in 1907. His successor, Dr Ludbrook, although having had several years of experience in paediatrics in England and being appointed to a paediatric position at Auckland Hospital in 1926, did not limit his practice to paediatrics until 1940.

In 1937 Dr Sweet came into conflict with the Auckland Hospital Board because of the replacement of honorary surgeons by others whom he considered less well qualified. His appointment was discontinued as he preferred to remain free to criticise the Hospital Board and its officers when warranted. He died suddenly on 17th May 1939.

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The benefits of constraining processed meat and red meat consumption in New Zealand: a public health perspective
Christine Cleghorn, Nick Wilson

ABSTRACT
There is now strong scientific evidence of an increased risk of colorectal cancer with processed meat consumption, some evidence of red meats being associated with colorectal cancer and some evidence of an association between red and processed meat and cardiovascular disease and type 2 diabetes. This is important as these diseases collectively impose substantial health loss for New Zealanders and also large costs on publicly-funded health systems. There are also other indirect health issues involved with meat production including pollution of waterways and greenhouse gas (GHG) emissions from ruminant agriculture that contribute to climate change. Fortunately, there are a range of plausible options for New Zealand agencies to consider (such as GHG taxes applied to agriculture and health warning labels), if they decide to encourage reductions in the consumption of processed and red meat consumption in this country.

It seems timely to consider the issue of processed and red meat consumption in New Zealand given a recent International Agency for Research on Cancer (IARC) monograph on the related cancer risk. Furthermore, there are growing concerns around the need to make dietary patterns more sustainable, including around agricultural greenhouse gas (GHG) emissions and the threat of climate change. Here we briefly look at this topic from a public health perspective and give consideration to the possible options for New Zealand moving forward.

Meat consumption and risk of chronic disease
In September 2015 the cancer agency of the World Health Organization, IARC, published a monograph on the carcinogenicity of consuming red and processed meat. Over 400 different epidemiological studies on cancer in humans provided data on processed meat and over 700 provided data on red meat. IARC defines processed meat as “meat that has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation. Most processed meats contain pork or beef, but processed meats may also contain other red meats, poultry, offal or meat by-products such as blood”. Examples of processed meat include hot dogs, ham, sausages, corned beef, beef jerky, canned meat and meat-based preparations and sauces.

In this monograph, IARC classified processed meat as being carcinogenic to humans, based on “sufficient evidence” in humans that the consumption of processed meat causes colorectal cancer. An association with stomach cancer was also seen, but the evidence is described as “not conclusive”.

In the IARC monograph, red meat refers to unprocessed mammalian muscle meat, including beef, veal, pork, lamb, mutton, horse and goat. Red meat was classified by IARC as probably carcinogenic to humans, based on limited evidence that the consumption of red meat causes colorectal cancer in humans and strong mechanistic evidence supporting a carcinogenic effect.
Evidence of associations with pancreatic cancer and prostate cancer were also reported.\(^4\)

IARC has categorised the association of processed meat with cancer in the highest category of strength of evidence, but how strongly is processed meat actually associated with cancer? IARC reported that a 50g portion (e.g., 1–2 rashers of bacon) of processed meat eaten daily increases the risk of colorectal cancer by 18%. Only 12.7% of the New Zealand adult population ‘never consumed (or not consumed in past four weeks)’ processed meat,\(^5\) and the average total consumption of processed meat (a narrower definition, ignoring corned beef, canned meat and meat-based preparations and sauces) ranged from 24g per day in non-Māori females to 56g per day in Māori males in the last New Zealand adult nutrition survey (unpublished data supplied by Otago University Life in New Zealand staff (Charlie Blakey, Claire Smith, Winsome Parnell)). So this increased risk is relevant to the average New Zealander and equates to 9% to 20% increased risk compared to an equivalent New Zealander who did not consume processed meat.

The risks of cardiovascular disease (CVD) and diabetes are also likely to be relevant. A recently published meta-analysis found that those in the highest category of consumption of processed meat and red meat had an increased risk of dying from CVD compared to those in the lowest category of consumption\(^6\) (see Table 1). Similarly, the risk of type 2 diabetes was between 9% and 35% higher per 100g consumption of red meat and between 24% and 105% higher for 50g consumption of processed meat.\(^7\)

While the results from such meta-analyses should be interpreted with caution due to the potential of residual confounding, the overall evidence from systematic reviews in recent years (Table 1) seems enough to justify concern from a public health perspective.

Some indication of the likely scale of the impact of such risks comes from the Global Burden of Disease study. It has been estimated that approximately 841,000 global deaths per year, due to colorectal cancer, coronary heart disease and diabetes, are attributable to diets high in processed meat\(^8\) (ranked the 14\(^{th}\) most important risk factor for health loss in Australasia). This study estimates that 13% of the disability-adjusted life-years lost from coronary heart disease globally are attributable to processed meat consumption. Furthermore, an estimated 38,000 deaths per year, due to colorectal cancer and diabetes, were attributed to (non-processed) red meat consumption globally each year.\(^8\)

**Other nutritional issues**

Red meat is a good source of protein and certain micronutrients such as iron, zinc and B12.\(^9,10\) But such nutrients can be obtained from plant-based foods with the partial exception of B12 which can be obtained from eggs, dairy and some fortified plant foods, fermented soy products such as tempeh\(^11\) and nori\(^12\) (the seaweed commonly used to wrap sushi). Furthermore, these alternatives may provide a healthier source given the lower associated risks of various diseases. For example, nuts are a good source of protein and micronutrients and the evidence favouring nut consumption for reduction in CVD deaths, cancer deaths and all-cause mortality is relatively strong (see these systematic reviews\(^13,14\)).

**Environmental impacts of meat production and consumption**

Last December 195 nations, including New Zealand, agreed to a goal of limiting global warming to well below 2°C above pre-industrial levels at the COP 21: UN Climate Change Conference in Paris. In order for this to happen, global emissions need to peak as soon as possible and then rapidly reduce. It has been estimated that by the year 2050, with current global dietary trends (if unchecked), diets high in red meat would be a major contributor to an estimated 80 percent increase in global agricultural GHG emissions from food production and global land clearing.\(^2\) Yet alternative diets “could, if widely adopted, reduce global agricultural GHG emissions, reduce land clearing and resultant species extinctions.”\(^2\)

More specifically, a review has reported that life cycle analyses of animal foods in OECD countries yield consistent results for their impacts on use of land, energy and climate change impacts.\(^15\) The production of beef uses the most land and energy, and has the greatest potential to impact global warming, followed by the production of
pork and chicken (when considering per kg of product and also per kg of protein from these products). The use of such metrics (eg, impact per weight of protein) is likely to be more appropriate than the metrics used in some other studies (eg, impact per caloric intake used by in a recent study by Tom et al16). This is because protein is one of the main non-taste reasons as to why people consume meat products.

An estimated 49% of New Zealand’s GHG emissions (in CO₂ equivalents) comes from agriculture, which is well ahead of the next largest source: the energy sector at 40%. Work carried out in New Zealand suggests the potential for major reductions in GHG emissions from a shift to different dietary patterns that involve less red meat (eg, towards an Asian-style diet, Mediterranean style diet and vegetarian diets).18 Such diets were also estimated to be lower cost than the traditional New Zealand diet.18

Another concern for the New Zealand context is water pollution caused by livestock. New Zealand research on river catchments has reported “high level of ruminant faecal contamination was detected all over the farming areas”. Cattle grazing in wetland areas may be a particularly important contributor to this problem. A report by the Parliamentary Commissioner for the Environment has noted that there is high public concern and vigorous debate on water quality in New Zealand. Furthermore, that most of the nitrogen that is present in fresh water has come from animal urine. While this report did indicate growing land use for dairy farming in New Zealand, there were still over five times higher land use dedicated to sheep and beef farming (see Figure 3.4, p29 in the Report).

### Livestock production and microbes

Antibiotic resistance development and spread is linked with animal production, and of 51 antibiotics commonly used in aquaculture and agriculture, 76% are also of importance in human medicine. One part of this global problem is with intensive pig production. Indeed, in New Zealand pig offal isolates of *Campylobacter* have been found to be highly erythromycin resistant, and other New Zealand research has found that for: “commercial pig farms which used antimicrobial agents, there was a higher level of antimicrobial resistance in the E.

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**Table 1:** Relative risks (95% confidence intervals) of processed and red meat consumption with chronic disease from recently published systematic reviews in the years 2013 to June 2016.

<table>
<thead>
<tr>
<th>Systematic review</th>
<th>Health outcome</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red meat (for each additional 100g/day consumed)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IARC 2015*</td>
<td>Colorectal cancer (incidence)</td>
<td>1.17 (1.05–1.31)</td>
</tr>
<tr>
<td>GBD 2015*</td>
<td>Colorectal cancer (incidence)</td>
<td>1.18 (1.05–1.31)</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes (incidence)</td>
<td>1.09 (1.06–1.12) to 1.35 (1.09–1.68)*</td>
</tr>
<tr>
<td>Abete et al 2014**</td>
<td>All-cause mortality</td>
<td>1.04 (0.92–1.17)</td>
</tr>
<tr>
<td></td>
<td>CVD (mortality)</td>
<td>1.15 (1.05–1.26)</td>
</tr>
</tbody>
</table>

| **Processed meat (for each additional 50g/day consumed)** | | |
| IARC 2015*         | Colorectal cancer (incidence) | 1.18 (1.10–1.28)                         |
| GBD 2015*          | Colorectal cancer (incidence) | 1.18 (1.10–1.28)                         |
|                     | Type 2 diabetes (incidence)   | 1.24 (1.19–1.29) to 2.05 (1.49–2.78)*   |
|                     | CHD (incidence)               | 1.21 (1.13–1.29) to 1.94 (1.16–3.19)*   |
| Abete et al 2014** | All-cause mortality           | 1.25 (1.07–1.45)                         |
|                     | CVD (mortality)               | 1.24 (1.09–1.40)                         |

*Range presented, varies depending on age group.
**We did a Medline search with the term “meat” and “mortality” for the period from January 2013 to June 2016. This was limited to ‘human’ and ‘meta-analyses’. The most recent meta-analyses that reported dose response analyses are reported in this table.
coli" and Enterococcus spp cultured from the faeces of pigs compared with an organic farm which used no antibiotics."

Mass pig production also contributes to the global risk of pandemic influenza in humans, along with poultry production. Indeed, the “swine flu” pandemic arose in 2009 from influenza virus infection in US pigs. While New Zealand pig farming is likely to be a tiny part of the risk of new influenza pandemics internationally—there is arguably a global public health rationale for minimising factory farms for pigs in all countries.

Alternative perspectives
This article uses a public health perspective but we recognise that a range of other perspectives could be taken. For example, if the size of the New Zealand economy was a dominant consideration, then the Government may wish to move cautiously on anything that might impede the export-orientated red meat production sector. But this is a complex issue as this sector could conceivably benefit in the long-term if its production levels were somewhat lower but were at the same time more sustainable (ie, New Zealand meat exports became more favoured by environmentally-concerned overseas customers). Furthermore, the government needs to consider all costs and benefits to society and so should balance economic considerations with health and environmental ones (including the health costs from chronic diseases). Indeed, as tourism is a larger contributor to the New Zealand economy than meat exports, such issues as protecting the New Zealand environment (including avoiding the pollution of waterways) become an even more important consideration.

Another perspective is around the ethics of killing animals for food and around animal welfare. While there is a vast philosophical literature on such topics, there is likely to be fairly widespread public agreement that animal welfare does matter and that farmed animals should not suffer unnecessary pain and deprivations. Unfortunately there is evidence that modern factory-farming practice causes animal suffering in various forms, see these two systematic reviews on pain in farmed piglets.

Potential responses by New Zealand agencies
Individuals can make their own decisions about reducing food-related risks to health and the trade-offs (eg, taste preferences, food costs etc). But New Zealand health agencies have specific responsibilities and should be concerned about reducing disease burdens and also reducing the costs of such chronic diseases to the taxpayer-funded health system. For example, there could be large savings to the health sector from reducing CVD (eg, up to 211,000 quality-adjusted life-years gained for reducing CVD by changing levels of dietary salt, as per New Zealand modelling work). Similarly, the cost associated with treating colorectal cancer in this country is large at around $130 million per year ($43,000 per case).

While there is probably enough information for health agencies to be concerned about processed and red meat consumption, they may also need to commission more research into the health consequences of dietary changes. For example, can the health gains be quantified and are there any risks (eg, some people replacing meat products by increasing intake of ultra-processed foods).

Government agencies concerned with meeting New Zealand’s international commitments around reducing GHGs should have an interest in lowering these emissions from the agricultural sector. Local government should also have interests in water quality improvements through reductions of livestock-based agriculture. So what then could be done if these New Zealand agencies decided to act on this topic? One place they could start is to promote the inclusion of agricultural GHGs in New Zealand’s system for pricing carbon. At present the Emissions Trading System in New Zealand (which has multiple design problems) does not include such gases and so the agricultural sector is currently getting a free ride while the rest of New Zealand pays for carbon emissions. Agricultural GHG taxes (such as methane and nitrogen taxes) are internationally regarded as potential instruments to help achieve emissions reductions, though clear gaps exist in the evidence-base around the potential co-benefits for health. These taxes could work in New Zealand by taxing each ruminant animal arriving...
at the freezing works with the likely result being the increase in processed and red meat prices. Additional taxes for GHG emissions from manure would increase the price of pork (pigs would be exempt from the tax on methane as they are not ruminants). These higher prices are then likely to reduce consumption of these meat products (as per basic economic theory and as seen with taxes on tobacco,\textsuperscript{33} alcohol\textsuperscript{44,45} and soft drinks\textsuperscript{46}). Research into the health, environmental and welfare implications of consumers switching their consumption from red and processed meat onto poultry, fish or plant-based protein as a result of these taxes may be useful for guiding further policies.

Other options that could be assessed and then evaluated in trials include the following:

- Regulations to limit the portion size and use of processed and red meat in government-funded institutions (eg, schools, hospitals and military camps). Indeed, the National Health Service (NHS) Carbon Reduction Strategy for England has recommended the NHS reduce its reliance on meat in hospital food.\textsuperscript{47} Such institutions could even test out having regular days with only vegetarian options.
- Regulations to require warning labels on processed meat products (eg, on the cancer risk or other aspects such as the high salt levels in some of these products).
- Ministry of Health funded promotional campaigns to improve New Zealand dietary patterns. For example, themes for campaigns could be based on a report published by the global food security programme on ‘How to eat well for a healthy planet’. It suggests eating meat in smaller portion sizes, making dishes with less meat by incorporating other plant sources of protein and using small quantities of meat as a garnish to add flavour to dishes.\textsuperscript{48} Myths that vegetarian diets are inadequate or unhealthy could also be addressed.

**Conclusions**

There is strong scientific evidence of an increased risk of colorectal cancer with processed meat consumption in addition to some evidence of red meats being associated with colorectal cancer and red and processed meat being associated with cardiovascular disease and type 2 diabetes. These diseases collectively impose substantial health loss on New Zealanders and large costs on the publicly-funded health system. Additionally, meat production adds to the pollution of waterways and increases GHG emissions which contribute to climate change. Fortunately, there are a range of options for New Zealand agencies to consider if they decide to encourage reductions in processed and red meat consumption in this country, including agricultural GHG taxes, health warning labels and promotional campaigns.

**Competing interests:**

Nil.

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Mitral stenosis with smoking mitral valve

Animesh Mishra, Manish Kapoor, Tony Ete, Gaurav Kavi, Pravin Jha, Rondeep Nath Sivam

A 39 year-old female was admitted with complaints of dyspnoea on exertion (NYHA-II) for one year. The patient also had history of orthopnoea and paroxysmal nocturnal dyspnoea. She was in atrial fibrillation with a heart murmur consistent with mitral stenosis. TTE showed a dilated left atrium with severe rheumatic mitral stenosis (MVA 0.8 sq cm). Marked spontaneous echocardiographic contrast in the left atrium flowing through a stenotic mitral valve was seen, giving the appearance of a “smoking mitral valve” (Figure 1 and 2). Transoesophageal echocardiography (TEE) corroborated the finding of TTE including spontaneous echocardiographic contrast (SEC) in left ventricle. In conditions with slow blood-flow or stasis, spontaneous echocardiographic contrast is seen, which is a characteristic echocardiographic phenomenon with a very distinct smoke-like swirling pattern. SEC is an indicator of increased thromboembolic risk.

Figure 1: Apical four-chamber view showing thickened calcified rheumatic mitral leaflets with dilated left atrium and spontaneous echocardiographic contrast (smoking mitral valve).
Figure 2: Parasternal long-axis view showing thickened calcified rheumatic mitral leaflets with dilated left atrium, hockey stick shaped anterior mitral leaflet and “smoking mitral valve”.

Competing interests:
Nil.

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Life threatening torsades de pointes due to abiraterone-induced hypokaelemia in a patient with metastatic prostate cancer

Afrasyab Khan, Barry Kneale

ABSTRACT

We present a case of a 77 year-old gentleman with previous coronary artery bypass grafting, admitted to hospital with recurrent torsades de pointes (TdP) due to abiraterone-induced hypokalaemia and prolonged QTc. The patient was on abiraterone and prednisone for metastatic prostate cancer. He required multiple defibrillations for recurrent TdP. Abiraterone is a relatively novel drug used in metastatic prostate cancer and we discuss this potential adverse effect and its management in this unusual presentation.

Abiraterone acetate is an inhibitor of CYP17 and is used in metastatic prostate cancer with mineralocorticoid excess and resultant hypokalaemia as a known side effect. We present a case of recurrent torsades de pointes (TdP) due to abiraterone-induced hypokalaemia. This is a relatively novel drug and we discuss this potential adverse effect and its management in this unusual presentation.

Case report

A 77 year-old gentleman with ischaemic heart disease (IHD), previous coronary artery bypass grafting (CABG) and atrial fibrillation was brought to the emergency department (ED) after a syncopal event. He had metastatic castrate-resistant prostate cancer treated with prednisone and abiraterone. At the scene he was noted to have runs of ventricular tachycardia—subsequently diagnosed as TdP. Intravenous (IV) amiodarone (300mg) was administered before transport to the emergency department (ED). On arrival in ED his heart rate was 70 beats/min and BP was 150/85mmHg. Physical examination revealed minimal crackles at lung bases but was otherwise unremarkable. An electrocardiogram (ECG) showed a prolonged corrected QT interval (QTc) of 650ms which was new compared to a previous ECG (Figure 1). Chest x-ray showed a left lower lobe infiltrate suggestive of atelectasis or infection.

He had three episodes of TdP in ED, resulting in syncope and requiring defibrillation (200 joules biphasic). His regular medications were abiraterone (started six months ago) 250mg four times a day, prednisone 10mg once a day, goserelin injections 10.8mg three-monthly (last dose three months ago) and warfarin 4mg once a day. He had been compliant with his medications. Serum electrolyte levels were as follows (normal ranges in brackets): sodium 135mmol/L (135–145), potassium 2.7mmol/L (3.5–5.2), magnesium 0.84 mmol/L (0.7–1.0) and calcium 2.17 mmol/L (2.10–2.55). IV replacement of potassium and magnesium were started. Liver and renal function tests were normal. He had four further episodes of TdP requiring defibrillation as well as multiple episodes of non-sustained TdP (Figure 2 and 3). He was commenced on isoprenaline by IV infusion to increase the heart rate and thus trying to decrease his QT interval. This was weaned off during hospital day 2.

Over the first 24 hours he received a total of 160mmol of potassium. His QTc interval improved significantly after potassium replacement.
replacement. A transthoracic echocardiogram showed mild left ventricular impairment with previously known inferior wall motion abnormalities (WMA). He was discharged home after remaining stable off abiraterone without any further arrhythmias. His QTc on discharge and at clinic follow-up one month later was 460ms (Figure 1). His electrolytes remained normal at clinic follow-up. Our discharge diagnosis was abiraterone-induced hypokalaemia initiating TdP in a patient with known IHD.

Discussion

Abiraterone acetate is an inhibitor of CYP17, which is an important enzyme in testosterone and oestrogen synthesis and is currently used for metastatic castration-resistant prostate cancer.1 Its effectiveness was studied in a trial but patients with clinically significant heart disease were excluded.2 In the abiraterone arm of the study, cardiac disorders as adverse events were reported in 126 (23.2%) versus 96 (17.7%) patients

Figure 1: ECG from old records (a); on arrival in the emergency department showing prolonged QTc (b); and after discharge from the hospital (c).

Figure 2: Episode of non-sustained TdP with R-on-T phenomenon.
taking placebo without any mention of statistical significance. QTc interval was not measured in this study. Abiraterone is not known to cause a prolonged QTc and certainly did not result in any QTc prolongation in one study with 33 participants. The patient was not on any medications known to cause QTc prolongation. There is no causal relationship between goserelin and QTc prolongation.

The cytochrome P450 enzyme involved in the metabolism of abiraterone is CYP3A4. The patient was not on any medications known to affect the metabolism of abiraterone. Mineralocorticoid excess and hypokalaemia are known side effects of abiraterone due to CYP17 inhibition. Inhibition of CYP17 by abiraterone results in reduction of cortisol. This in turn leads to an increase in adrenocorticotropic hormone (ACTH). ACTH drives the biosynthesis pathway of steroids and hence results in increased levels of corticosterone (by a median 40-fold) and deoxycorticosterone (by a median 10-fold) as a result of CYP17 inhibition. Prednisone is added with abiraterone to enhance its anti-tumour activity by lowering ACTH and supress steroids upstream of CYP17 as well as to prevent mineralocorticoid excess associated with CYP17 inhibition. This reduces hypokalaemia in patients on abiraterone. Mineralocorticoid excess can also manifest as hypertension and oedema. Potassium levels are frequently monitored during treatment with abiraterone. In a phase III study, potassium levels were checked at initiation of abiraterone, then every two weeks for three months and then monthly as long as the treatment was continued. We recommend similar frequency of monitoring as long as potassium levels are satisfactory.

Hypokalaemia occurred in 17 percent of patients treated with abiraterone even while being on prednisone. Hypokalaemia is well known to cause prolongation of the QTc interval and this can lead to torsades de pointes. There is limited or no data regarding abiraterone treatment in patient with known structural heart disease or prior cardiac surgery. By calculating the Naranjo probability score, the likelihood of an adverse effect due to a drug can be scored as definite, probable, possible or doubtful. The score for abiraterone causing hypokalaemia in this case was 7 deriving from hypokalaemia being a known side effect of abiraterone, occurred after drug administration, potassium level remained normal at follow-up after withdrawal of suspected drug, no alternative cause was evident and it was confirmed with objective evidence of a low potassium level. The score of 7 indicates a probable adverse drug reaction.

**Conclusion**

This report describes a potentially fatal adverse consequence of a relatively novel agent having predictable metabolic side effects. To our knowledge there is one other reported case of TdP and hypokalaemia in the setting of abiraterone treatment. The hypokalaemia is easily treated and QTc prolongation can be prevented. We recommend that clinicians be alerted to this serious adverse event both as a possible emergency presentation and when prescribing this therapy.
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Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease

Few data are available for the efficacy of “triple therapy” with two long-acting bronchodilators and an inhaled corticosteroid in chronic obstructive pulmonary disease (COPD). This study was designed to assess efficacy of single-inhaler combination of an extra fine formulation of beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide (BDP/FF/GB) in COPD compared with beclometasone dipropionate and formoterol fumarate (BDP/FF) treatment.

1,368 patients with COPD were randomised to either BDP/FF/GB or BDP/FF. After 26 weeks treatment there was a significant improvement in the forced expiratory volume in the triple therapy group compared with BDP/FF group. Moderate to severe exacerbation frequencies were also reduced in the triple therapy group.

The authors conclude that they have provided evidence for the clinical benefits of stepping up patients with COPD from an inhaled corticosteroid/long-acting β2-agonist combination treatment to triple therapy using a single inhaler.

Lancet 2016;388: 963–73

Ticagrelor versus aspirin in acute stroke or transient ischaemic attack

Ticagrelor may be a more effective antiplatelet therapy than aspirin for the prevention of recurrent stroke and cardiovascular events in patients with acute cerebral ischaemia. Aspirin currently holds pride of place in the prevention of recurrent strokes but its performance is far from perfect. Hence this trial comparing aspirin and ticagrelor.

This international randomised trial involved over 13,000 appropriate patients who were treated for 90 days with either aspirin or ticagrelor. The primary end point was the occurrence of stroke or a significant cardiovascular event. This occurred in 6.7% of the ticagrelor patients and in 7.5% of those on aspirin, a non-significant difference. Major bleeding occurred in 0.5% (ticagrelor) and 0.6% (aspirin) patients respectively.

The researchers concluded that in their trial involving patients with acute ischaemic stroke or transient ischaemic attack, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction or death at 90 days.


Vascular risks associated with combined oral contraceptives

What are the risks of pulmonary embolism, ischaemic stroke and myocardial infarction associated with combined oral contraceptives according to dose of oestrogen (ethinylestradiol) and progestogen?

This important issue is addressed in this observational cohort study in which the authors use data from the French national health insurance and hospital databases. A total of nearly five million women taking one of eight combined oral contraceptives were included in the study. After adjustment for risk factors and for the same dose of oestrogen, desogestrel and gestodene compared with levonorgestrel were associated with 2.2-fold and 1.6-fold statistically significantly higher risk of pulmonary embolism. They also note that an oestrogen dose of 20µg compared with 30–40µg was associated with a lower risk of pulmonary embolism and serious cardiovascular problems.

The results suggest that levonorgestrel with 20µg of oestrogen is the combination associated with the overall lowest risk of pulmonary embolism and arterial thromboembolism.

BMJ 2016;353: i2002

URL:
Several students of the New Zealand Medical School, who served in Egypt and Gallipoli, at my request, have written the accounts of their experiences, which are subjoined. These do not need any comment from me beyond the statement that I think they illustrate a side of the war problem which is generally neglected in more pretentious histories.

Mr. A. E. O'Sullivan writes—

The New Zealand Main Body was in numbers as large as the population of a fair-sized inland town, and therefore one would only naturally expect that otherwise healthy men would fall victims to the minor ailments that a medical man daily meets with in course of practice in such places.

By far the commonest ailments that an army medical officer has to treat are constipation and diarrhoea. In any local military encampment it would be looked upon as abnormal if one did not see a long line of sufferers on sick parade each morning—this one demanding a pill No. viii. to cure his looseness of bowels, and that one a No. ix. to move his bowels. In passing there occurs to me an amusing incident that happened in an Otago encampment some two years ago; there was a medical student on duty in the hospital tent, and a forlorn soldier suffering from constipation came in and meekly asked for a No. ix.; the No. ix. pill-box was empty, but the budding young medico was not to be outdone, and got over the difficulty by prescribing a No. iv. along with a No. v.

I have often heard men in such camps say that before they came to camp they had never experienced diarrhoea or constipation; they all used to associate these troubles, and rightly so too, with the change of diet and the way in which it was cooked and served up. Certainly, before the introduction into the camps by the military authorities of cookers and cookhouses, there was much left to be desired: the regimental cooks were generally chosen from amongst the slackers at drill, and cooking was looked upon more or less as a form of punishment. Seeing that these men often did not have the slightest idea of preparing a meal, and generally being sluggards, were not particular as regards the cleanliness of utensils, one can easily
imagine what disgusting conglomerations were often served up. The eternal military stew was made from the meat and vegetables available; these were cut up in huge lumps and thrown haphazard into a large boiler; the boiler may have been previously wiped out with a dirty greasy rag that had been used to clean every other utensil in the place as well as to dry the dirty hands of the various cooks in the place. Then there used to be a number of men in the regiment who had no idea of cleanliness; they would bring along to the cookhouse their little mess-tins rinsed out with some stale tea that had been left in it from the previous meal perhaps.

It was no wonder at all that attempts to eat such huge pieces of half-cooked meat was the causation of constipation in some individuals; and the greasy utensils used for cooking and eating out of undoubtedly led to numbers of the men suffering from diarrhoea.

But all this is now-a-days remedied to a great extent; each regiment has its cooker installed in a roomy cook-house; and, moreover, the cooks are mostly men who have undergone a special course of training in Trentham; each regiment is now well supplied with cooks, for many individuals are keen on the extra pay attached to the position; and then there is the element of competition, for each private cook can rise to be a sergeant-cook by examination, and, again, all Territorial officers that attain the rank of captain have to have a knowledge of military hygiene, and they are constantly impressing on their men the necessity of being scrupulously clean in camps.

All such difficulties as mentioned had to be contended with in the various concentration camps for the Main Body; a number of these men had no previous Territorial training; indeed a great number had no previous military training at all.

In these camps the latrine accommodation was of the usual military character: in the Auckland camp an acre of ground was enclosed with galvanised iron.

Trenches, 3 feet long, 1 foot wide, and 1 foot deep, were dug, with intervening spaces, a width of 2 feet; the trenches for one day were in alignment. The first day’s trenches were dug right at the back of the enclosed area; the following morning these were closed in and a fresh lot opened up immediately in front; and so on from day to day. In the corner was a urine pit; each night urine tins were placed at the ends of tent lines on lime-besprinkled area of ground; and these were removed each morning by a sanitary fatigue. The enclosed ground was sprinkled daily with lime. But there was room for improvement; in spite of the strict watch kept by the camp police, a number of men would persist in sitting at the side of a trench instead of astride it. The result was that the ground intervening between two trenches became fouled and saturated with urine, and with the constant passage of boots the whole place became contaminated and men carried the befouled mud on their boots to the tents. This was not at all desirable. And, again, every man did not cover up his excreta as he was supposed to do; this only served the purpose of attracting flies from the kitchen, which was not more than 50 yards away.

Kitchen Slop.—Water was disposed of in pits covered with brushwood to retain the grease; this brushwood was subsequently used as fuel in the kitchen fires.

Horse-dung was often left lying for too long in the horse lines; it is the natural breeding place of flies, and to keep camps free from flies they must be kept free from accumulations of horse-dung and stable litter.

The general rule followed, as to disposal of refuse, was—Burn all you can, and bury what you cannot burn.

The officers’ quarters on board the transports were luxuriously fitted up; water-closets, urinals, and other hygienic arrangements were modern. There was no lack of fresh water in their bathrooms, even though the men frequently had their drinking allowance cut down to satisfy the wants of some inconsiderate officers whilst journeying through the tropics. The men’s bathrooms were supplied with salt water only. This difficulty was easily surmounted as most individuals purchased a large supply of salt-water soap before embarking, and one could easily heat the bath in a few minutes by turning on the steam. One of the great difficulties of the sanitary sergeant was to keep men from washing their dirty clothes in the baths, and extra police had to be supplied to check this objectionable habit; a similar duty of these police was to
keep men from washing their dirty sox in the wash-basins, for this was a favourite practice seeing that this was the only place where fresh water could be obtained for washing purposes.

Latrine accommodation for the men was of the poorest. The latrines were long zinc trough-like arrangements, through which there was supposed to be a continuous flow of salt water; the water was more often turned off than on. The result was that the trough often become full of excrement and then, when the water was actually turned on, no amount of water would force the contents down the soil pipe, the place simply overflowed and nieces floated about the floor of the latrine. Then the Ambulance Corps would have to set to work and shovel out the contents over the side of the ship. During the process a considerable amount of deck space was soiled, and the cleaning of this involved considerable labour. The position of night-soil man for a medical student was not looked upon as a particularly happy one. An objectionable practice of some men was that, being too lazy to walk to the urinal at the stern of the ship, they simply strolled into the nearest latrine and micturated all over the rail that served the purpose of a seat; men who subsequently came in to defaecate had perforce to stand on the rail, and this act combined with the lurching of the ship in a heavy sea resulted in the painting of the back wall of the latrine. All this added greatly to the already heavy burdens of the sanitary fatigue, which was generally chosen from amongst the medical students of the Ambulance Corps owing to the affection of a certain fond sergeant-major and that of a gallant captain, who more than once declared that it was his misfortune to be in command of “the scum of the medical school.”

On arrival at the various ports of call, the water was always turned off from the latrines according to shipping regulations, but some individuals, who always thought themselves funny, would succeed in turning on the water and flushing out the contents of the latrines on to the wares and fancy goods of some poor Cingalese or Arab salesman in a boat below. Whilst in port some officers actually attempted to prevent men from using latrines altogether as the water was not turned on. I do not know if such people expected the men to improvise latrines out of their breeches.