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Common Preventable Defects of Childhoods
Evidence of inequitable use of chemotherapy in New Zealand colorectal cancer patients
Chunhuan Lao, Marion Kuper-Hommel, George Laking, Lynne Chepulis, Ross Lawrenson

The aim of this study was to explore variations in the use of and timeliness of chemotherapy in patients diagnosed with colorectal cancer in New Zealand. We linked cancer register data to the national prescribing dataset and to mortality data. We found 28% of colon cancer and 44% of rectal cancer patients were treated with chemotherapy. The use of chemotherapy is mainly related to the stage and location of the cancer but we have shown increasing age, female gender and ethnicity are all associated with less use of chemotherapy. Interestingly there are also regional variations in the use of chemotherapy.

Pneumocystis pneumonia in HIV-negative adults: missed opportunities for prevention
Nicholas Young, Stephen McBride, Susan Morpeth, Aliya Bryce, Ahsan Siddiqui, Hasan Bhally

Pneumocystis pneumonia is a life-threatening fungal chest infection that occurs in people with weakened immune systems, such as those with cancer or those receiving chemotherapy, prolonged courses of steroids or other immunosuppressive medications. Antibiotics are effective in preventing Pneumocystis pneumonia when prescribed to people at highest risk of contracting this infection. Our study found that many people who contracted Pneumocystis pneumonia in the Auckland region had not been prescribed preventive antibiotics. The number of people who contract Pneumocystis pneumonia could be reduced if preventive antibiotics were prescribed to those at highest risk, particularly to people with cancer who will be taking steroids for four weeks or longer.

Evaluating the implementation and outcomes of a sepsis pathway in the emergency department
Pourya Pouryahya, Natalie Guiney, Alastair Meyer, Neil Goldie

Early recognition and timely management, including prompt administration of antibiotics, has been fundamental in improving the mortality related to sepsis. We aimed to study the effect of the Sepsis Pathway Programme, a set of guidelines for sepsis, on the recognition, early investigation and management of septic patients in the emergency department. We demonstrated: 1) The implementation of the Sepsis Pathway improved time taken to perform investigations and manage patients with sepsis. 2) Although it had improved, there was still a delay in recognition of sepsis and initiation of investigations and management, demonstrating that further strategies need to be employed to reduce poor outcomes associated with sepsis. 3) However, it did not affect ICU admissions, length of stay or mortality.

Quality measures in cervical lymphadenectomy for cutaneous malignancy by head and neck trained general surgeons
Fouad Nahab, Sita Ollek, Richard Harman, Richard Martin

Cervical lymphadenectomy refers to the surgical removal of lymph nodes in the head and neck region. These are removed due to a high index of suspicion for harbouring malignancy which has spread from a primary skin source. Radiotherapy, a form of radiation used to treat an area of the body following surgical excision of cancer. Local or regional recurrence defined as the presence of the cancer within or near the original area of excision or recurrence within the lymph nodes responsible for that region of the body, respectively.
Combination budesonide/formoterol inhaler as sole reliever therapy in Māori and Pacific people with mild and moderate asthma

Jo Hardy, Jordan Tewhaiti-Smith, Christina Baggott, James Fingleton, Alex Semprini, Mark Holliday, Robert J Hancox, Mark Weatherall, Richard Beasley, Matire Harwood on behalf of the PRACTICAL Study Team

A ground-breaking Medical Research Institute of New Zealand (MRINZ) study published in the prestigious Lancet medical journal last year showed that a combination 2 in 1 inhaler, used as needed without the need for regular preventive treatment, cut the risk of severe asthma attacks by about one-third in all Kiwi patients studied, compared to regular scheduled preventive treatment together with a separate reliever inhaler. Now, a sub-analysis of that study, published today in the *New Zealand Medical Journal*, has shown that the benefit of this single 2 in 1 inhaler treatment regimen for Māori and Pacific patients is at least as great as in European and other ethnicities. These findings mean that the 2 in 1 Symbicort inhaler can be recommended as the optimal treatment for Māori and Pacific patients. In mild asthma it can be used simply as a reliever, and in moderate to severe asthma it can be used as both a regular maintenance and reliever inhaler, as recommended in the recent Asthma and Respiratory Foundation of New Zealand asthma guidelines.

A comparison of the clinical features and outcomes of Takotsubo syndrome across five metropolitan hospitals in New Zealand

Jen-Li Looi, Toby Verryt, Peter McLeod, Christina Chan, James Pemberton, Mark Webster, Andrew To, Mildred Lee, Andrew J Kerr

Takotsubo syndrome, TS (also known as broken heart syndrome) mimics the presentation of a heart attack. However, data on the characteristics between hospitals for homogeneity/heterogeneity in the presentation of TS patients and their outcomes in New Zealand are still lacking. In this large New Zealand TS cohort, we have shown that the clinical characteristics and presentation were similar among the five major hospitals. A subset of patients was critically unwell during the admission, but late deaths were almost all from non-cardiac (not related to heart disease) causes and recurrence was infrequent. The death rates post-discharge and recurrence were similar among the hospitals.

Assisted dying and evidence-based law-making: a critical analysis of an article’s role in New Zealand’s referendum

Ben P White, Lindy Willmott, Jocelyn Downie, Andrew Geddis, Colin Gavaghan

Debates about the referendum on the End of Life Choice Act should be based on reliable evidence. This article critically analyses an article written by Winnington and MacLeod which makes broad claims about potential risks for New Zealand society including “the potential for assisted dying becoming an expectation for others to pursue when unwell and possibly facing a life-threatening illness” and “that there may be the potential for such legislation to produce a contagion effect.” These claims are based on one interview with an individual who had a family member choose assisted dying in another country. A single interview with one person from a very different context cannot sustain the broad and significant claims made about how society in New Zealand might change as a result of assisted dying. We conclude—based on these flaws and others—that the article is not reliable evidence and should not be considered in debates leading up to the referendum.
The transition to a “virtual practice” in primary care during the COVID-19 pandemic: experience from one medical centre in New Zealand

Ibrahim S Al-Busaidi, Miriam Martin

The rapid spread of COVID-19 (Coronavirus disease 2019) across borders has driven fundamental transformations in the way patient care is delivered in hospitals and medical centres worldwide. As part of the response against COVID-19 across primary care in New Zealand, practices and medical centres have largely transitioned to telehealth (using email, texting, telephone and videoconferencing) over a short period of time while maintaining the traditional business model of in-person care on an as-required basis. To inform other practices and a likely second wave of COVID-19, we outline our experience at one general practice surgery and the challenges faced in the process of converting to telehealth in the middle of the COVID-19 pandemic.

Smoke-free cars legislation: it works but New Zealand should still rigorously evaluate its upcoming law

Nick Wilson, George Thomson, Richard Edwards

In this article we briefly review the evidence for smoke-free car legislation. We find that this legislation has been consistently associated with reduced secondhand exposure in cars with children/youth in all nine jurisdictions in which this has been studied, but there are still gaps in the scientific knowledge and so we argue that the New Zealand Ministry of Health should invest in a thorough evaluation of this important upcoming public health intervention. This is critical to help the country in further refining the design of the law (if necessary) to ensure it helps with achieving New Zealand's smokefree nation goal.

Saying it don't make it so: a response to Winnington and MacLeod

Eric Mathison

This paper responds to a previous paper's claims that legalising assisted death will have serious negative consequences for New Zealand. I show that none of the arguments the authors give support their conclusion. For instance, despite the authors' claim that legalising assisted death will invariably result in a slippery slope to an even worse outcome, the data from many jurisdictions shows that this is not the case.

Reflections on conducting research with healthcare users in a pandemic lockdown

Fiona Imlach

The COVID-19 lockdown period created both challenges and opportunities for health research. Research was facilitated by flexibility from funders and team members, support from networks and stakeholders and the willingness of individuals to participate. We could learn from the experience of lockdown research by improving institutional support for research processes and dissemination, investing in a nationwide online panel for public good research and ensuring that a planned database of health research can collect and monitor research proposals in times of rapid change and uncertainty.
A non-binding referendum on the legalisation of cannabis will be held in conjunction with the general election on 19 September 2020. Although many New Zealanders have consumed cannabis there is a much greater familiarity with alcohol as a recreational drug to the extent that a lot of people don’t even think of alcohol as a psychoactive drug. This paper seeks to provide comparative health information about two drugs: delta9-tetrahydrocannabinol (THC), the primary psychoactive drug in cannabis, and ethanol (ethyl alcohol) the psychoactive drug in alcoholic beverages.

We have been taught to consider cannabis a dangerous substance for 50 years through publicity aligned with the so-called “War on Drugs”, a global movement initiated by US President Nixon’s declaration in 1971 that drug abuse was “public enemy number one”. At the same time, alcohol has been promoted as relatively harmless and that it is not only entirely normal for people to consume alcohol most days of the year but that regular drinking is a sign of a successful and popular citizen. This marketing of alcohol by Big Business has been buttressed by backroom lobbying of successive governments to prevent stronger regulation of alcohol. The result of all of this propaganda and pressure is a strong tendency for us to think of alcohol as good and cannabis as bad.

Table 1 compares delta9-THC and ethanol according to 13 commonly discussed issues related to drugs and health. The descriptions of harm are in some cases based on

Table 1: A descriptive comparison of 13 harms to health related to two psychoactive drugs, delta9-THC and ethanol.

<table>
<thead>
<tr>
<th></th>
<th>Delta9-THC</th>
<th>Ethanol</th>
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<tbody>
<tr>
<td>1. Risk of death from overdose</td>
<td>virtually zero</td>
<td>relatively high**</td>
</tr>
<tr>
<td>2. Risk of aggressiveness during intoxication</td>
<td>low</td>
<td>moderate/high**</td>
</tr>
<tr>
<td>3. Risk of anxiety during intoxication</td>
<td>moderate</td>
<td>virtually zero</td>
</tr>
<tr>
<td>4. Risk of harm driving intoxicated</td>
<td>moderate/high</td>
<td>high*</td>
</tr>
<tr>
<td>5. Risk of irritability in withdrawal</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>6. Risk of death from severe withdrawal</td>
<td>virtually zero</td>
<td>relatively high**</td>
</tr>
<tr>
<td>7. Risk of brain damage from chronic heavy use</td>
<td>possible</td>
<td>definite**</td>
</tr>
<tr>
<td>8. Risk of fetal brain damage</td>
<td>probably low</td>
<td>definitely high**</td>
</tr>
<tr>
<td>9. Risk of liver and other organ damage</td>
<td>low</td>
<td>high**</td>
</tr>
<tr>
<td>10. Risk of addiction</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>11. Known to cause psychotic conditions</td>
<td>yes but fairly rare</td>
<td>yes but rare</td>
</tr>
<tr>
<td>12. Known to cause major depression</td>
<td>possibly</td>
<td>definitely*</td>
</tr>
<tr>
<td>13. Known to cause cancer</td>
<td>no evidence for THC</td>
<td>definite carcinogen**</td>
</tr>
<tr>
<td></td>
<td>possible for smoked cannabis</td>
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*Evidence that ethanol is more harmful than delta9-THC.

**Good evidence ethanol is distinctly more harmful than delta9-THC.
very solid information, such as the overdose and cancer risks of alcohol, whereas other aspects such as whether cannabis causes brain damage and depression are not clearly established by existing research.

Ethanol is more harmful than delta9-THC on nine of the 13 aspects considered. For two of these, motor vehicle injury and causation of depression, the evidence is indicative that alcohol is more harmful; but for seven of these there is good evidence that ethanol is distinctly more harmful as follows:

1. The safety ratio of delta9-THC is >1,000 indicating it is almost impossible to die from a cannabis overdose, whereas ethanol, with a safety ratio of 10, close to heroin which is six, makes death from alcohol poisoning a not infrequent event in New Zealand life and tragically associated at times with coming of age challenges to drink a potentially lethal dose of alcohol.

2. Ethanol directly causes aggression through a number of interacting mechanisms, including misinterpretation of visual cues and inducing sadism. The damage from drunken aggression can be observed every weekend and many weekdays in New Zealand’s ‘vibrant’ social life, and seen in the appalling alcohol-fueled family violence statistics that continue year after year, a phenomenon not observed for cannabis. In head-to-head research cannabis was found to decrease aggressive feelings following aggression exposure compared with alcohol, which enhanced aggressive feelings.

6. When severe, the withdrawal syndrome following neuroadaptation from ethanol is associated with complications that can pose a high potential for death in some patients. These complications include seizures and delirium as well as the risk of aspirating vomit. These complications are not a feature of delta9-THC withdrawal.

7. Chronic cognitive impairment is a well-known consequential risk for alcohol when consumed heavily for an extended period of time. The two main syndromes are alcoholic dementia (due to the direct toxic effect of alcohol on the brain and affecting frontal lobes in particular) and the Wernicke-Korsakoff syndrome (mediated by depletion of thiamine (Vitamin B1) in combination with the toxic effects of alcohol). The evidence for chronic cognitive impairment from heavy cannabis use is much less well established. Sensitive testing including electrophysiological measures have revealed long-term deficits in attention, although the clinical significance of this effect is considered subtle.

8. Fetal alcohol spectrum disorder (FASD) is the result of brain damage to unborn children when alcohol is consumed by their mothers during pregnancy resulting in a range of cognitive-behavioural problems in affected children. It has been estimated there could be as many as 3,000 children born with FASD every year in New Zealand. The same cannot be said for cannabis use by pregnant mothers. It has been shown that cannabis using mothers are at increased risk of producing low birth weight infants even after controlling for cigarette, alcohol and other drug use, but the existence of a fetal cannabis syndrome causing behavioural problems in affected children requires further research. In the meantime the best advice for women who are planning pregnancy or who find themselves pregnant is to discontinue all recreational drug use including both alcohol and cannabis.

9. Ethanol consumption is implicated in the causation of over 200 different medical conditions, whereas delta9-THC appears relatively non-toxic to the human body and has no such medical linkages. On the contrary, delta9-THC and other cannabinoids are the focus of a growing anecdotal literature as treatment for a range of medical conditions including glaucoma, nausea, AIDS-associated anorexia, chronic pain, inflammation, multiple sclerosis and epilepsy.
13. Alcohol is classified as a Group 1 carcinogen (definite carcinogen to humans) according to the World Health Organization's International Agency for Research on Cancer (IARC),12 which the alcohol industry goes out of its way to not warn its customers about.13 On the other hand, delta9-THC has not been classified by the IARC despite considerable research. While there remains doubt about whether smoking cannabis causes lung cancer, there is nevertheless good evidence of chronic obstructive pulmonary disease in heavy cannabis smokers,14 but this is likely the consequence of smoking dried plant matter in similar fashion to smoking tobacco rather than consuming the drug delta9-THC.

There is only one of the 13 health aspects, 3. Risk of anxiety during intoxication, where cannabis is distinctly more harmful than alcohol. Alcohol dissolves anxiety in most people, whereas cannabis can heighten feelings, including anxiety in some people. There will be a presentation to emergency departments most months of an inexperienced user of cannabis with a panic attack.

The one harm often pointed to as evidence of the danger of cannabis compared with alcohol is 11. known to cause psychotic conditions. In fact both cannabis and alcohol can cause psychotic conditions although these are rare events. They generally occur following chronic heavy use of potent forms of either drug, especially when there is a family history of psychosis. The main conditions are alcoholic hallucinosis and psychosis as part of delirium tremens in relation to alcohol, and cannabis-induced psychosis and schizophrenia where cannabis is considered an initiating factor. In terms of the latter, taking the extremes of people on a continuum of cannabis use there is a doubling of the risk of developing schizophrenia in people who are daily users of cannabis compared with people who have never used cannabis.15 Cannabis has been singled out as a psychotogen partly because it is known to change people's perceptions. Some researchers have labelled these perceptual changes “psychotic” when in fact the vast majority are “psychotic-like”. In addition to seeking a change in mood, users of cannabis generally enjoy changes in their perceptions as well as their accompanying thoughts; such as experiencing time going slower, having surprising new ideas or a deeper sense of meaning about normal routines or ordinary objects, or having a greater appreciation of music. A small minority of users view cannabis as a spiritual aid.

The differential harm profile described above demonstrates how irrational our drug laws are. A highly toxic, aggressigenic, carcinogen is sold by teenagers to the public through every supermarket in New Zealand, as well as via thousands of liquor stores, bars and restaurants, while the sale of a more benign substance is prohibited.

A rational ‘No’ vote in the upcoming referendum would not be based primarily on the potential health harm from cannabis, unless one is also advocating for the sale of alcohol to be made illegal.

On the other hand, to vote ‘Yes’ requires trust the door isn’t being opened to Big Business to ultimately control and exploit cannabis. The “unbridled commercialisation” that exists with Big Business’ involvement with alcohol, resulting in enormous harm and cost to the New Zealand public, would likely be similar if cannabis became a new product available for Big Business activity. However, societal harm can be predicted to be less overall if this occurred because cannabis is inherently safer than alcohol.
Competing interests:
Nil.

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Time for a sea change in our COVID-19 management

Des Gorman, Murray Horn

New Zealanders are confronted with a new reality: to learn to “live with COVID-19” until such time as we have herd immunity, hopefully by way of a vaccination in the next 18 months or so. This always was the reality, although 100 days with no community transmission tempted us to think it wasn’t true. The real question is “how best do we live with this virus”?

In our view, it makes no sense to continue to automatically resort to extensive social lockdowns because we are not well enough prepared to contain an outbreak without running unacceptable health risks if we don’t. Indeed, this strategy is unlikely to be sustainable, given that each time a lockdown is triggered it further undermines the twin foundations on which this approach rests: cheap public borrowing capacity and voluntary public compliance.

There is a better way: more disciplined border management, earlier detection through more testing along with faster contact tracing and isolation of cases, combined with approaches to social distancing (including masks) that are far more selective than full-scale Level Three or Four lockdowns.

The fact that we are still struggling to get the basic elements of this smarter approach right after so long suggests that we need a new approach. Einstein’s definition of insanity is doing the same thing over and over and expecting a different result.

Why haven’t we been able to shift our approach?

It is not a matter of cost. The financial cost of properly resourcing a smarter containment strategy must be small in comparison with locking down large sections of the economy for weeks. The health and other personal costs of lockdown are also significant and likely to fall disproportionately on those least well placed to weather them.

We have not been able to execute a smarter containment strategy because we have not planned well enough and because delivery has been patchy at best across the whole spectrum of activity that needs to be executed well for a smarter containment strategy to work.

First time around we were “caught with our pants down”. Our tendency to keep telling ourselves how well we had done left us poorly placed the second time around. So how do we avoid a third lockdown?

We need to be better prepared, better resourced and the execution of our pandemic plan needs to be better managed. It is not fair to ask a “policy shop” like the Ministry of Health, who have limited operational experience or capacity, to take up what is a complex operational command and control role. The Ministry needs to focus on the important job of maintaining a health system that faced considerable challenges well before COVID-19.

Being better prepared requires a best-practice plan that is informed and reformed by objective data and provides as much confidence as possible about what the ‘reaction’ will be in specific contexts. It requires clarity about the standards that have to be met for each of the key elements of the approach (ie, border management, testing, contact tracing and isolation, and social distancing).

Better resourcing requires a commitment from the government to resource the plan and, in particular, to provide the funds for the standards set out in the plan to be met.

Better governance and management is more complex because it requires a balancing of political, health and economic considerations. The primary focus needs to be on reducing health and economic risk and maintaining public trust and confidence, with political judgements reflected in the objectives given to the governance
group. Operational decisions need to be made independently, on the basis of expert health and economic opinion, as they are in many other areas of public provision. There would also be a need for governance skills to ensure that the right monitoring and auditing processes were in place so that the governors could be realistically held accountable for what goes on further down in their organisation.

We are suggesting that the key objective for such a group would be to ensure that we can contain the health and economic risks of the pandemic, without the need for Level Three or Four lockdowns. Other objectives, or operational constraints, would need to be as explicit as possible to allow operational independence.

We are suggesting that these objectives and constraints are decided on a bi-partisan basis, so they are widely “owned” and not subject to ongoing political contest. It would be desirable if all these objectives and constraints could be made explicit ex ante, so operational decisions could be made entirely independently, and the governance group populated by experts in health, economics and governance.

However, this may be trickier than in other areas where this model works well, such as the Reserve Bank. In our case, bipartisan representation in the governance group may be necessary to reflect those concerns that are harder to specify ex ante; for example, those actions that infringe on individual liberty and lifestyle. It may also be necessary to secure support for necessary regulatory or legislative changes. In this case, an independent chair would be desirable.

Ultimately, however, Government must be free to govern so, like most other areas of state operations, there needs to be an ability for Government to give explicit and transparent instructions to the governance group that certain things be done or not done.

The key to getting the balance between health, economic and wider political considerations right is to require transparency in the decision-making process. Some degree of direct public interaction would help. The point is that transparent decision making requires well-justified decisions that build public confidence and make it harder for partisan interests to prevail.

The most difficult element in the equation is the need to rapidly put in place the operational experience and expertise needed to deliver on the decisions of the governance group. Clearly, that would need to be seconded from across the public sector as well as contracted in from the private sector where specific expertise is needed. While this grouping may well evolve into something more permanent, the initial assignment should not need to last more than a couple of years. Departments are reluctant to release their best people and those on the “fast track” worry about being overtaken if they step off the ladder, even for a short assignment. This ‘problem’ will be a lot easier to solve if the State Services Commission is actively supportive.

It will take some time to establish a new operational framework, to identify and recruit necessary operational and logistical expertise, to align functions with existing public health units, and for the transfer of activities currently undertaken by the latter and the MOH. In the interim, it is essential that the resources and investment needed to secure the border and to improve levels of contact tracing and isolation are identified and made available. This investment needs to be seen in the context of the counterfactual, which is the cost of lockdowns.

Living with COVID-19 until such time as we have herd immunity will involve more constraints on our liberties and lifestyle than we would like. This can only be considered reasonable if governance and management of the pandemic is actually best practice. A publicly accountable and transparent process is essential for the restoration of trust and confidence, which in turn will underpin necessary community compliance with the hygiene and behavioral responses that are required.
Competing interests:
Nil.

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Evidence of inequitable use of chemotherapy in New Zealand colorectal cancer patients

Chunhuan Lao, Marion Kuper-Hommel, George Laking, Lynne Chepulis, Ross Lawrenson

ABSTRACT

AIMS: To explore variations in the use of and timeliness of chemotherapy in patients diagnosed with colorectal cancer in New Zealand.

METHODS: This study included patients diagnosed with colorectal cancer in New Zealand between 1 January 2006 and 31 December 2016. The first chemotherapy regime was identified from Pharmaceutical Collection dataset. Logistic regression model was used to estimate the adjusted odds ratio of having chemotherapy by subgroup after adjustment for other factors.

RESULTS: 27.8% (6,737/24,217) of colon cancer patients and 43.8% (3,582/8,170) of rectal cancer patients received publicly funded chemotherapy. The uptake and timeliness of chemotherapy has been improving over time. Pacific people were the least likely to receive chemotherapy, followed by Māori and Asian. Younger patients, New Zealand European, patients with metastatic disease and patients in the Southern Cancer Network were more likely to have chemotherapy in less than 10 weeks post-diagnosis. Over half of the advanced colorectal cancer patients who did not receive chemotherapy were aged 80+ years or had a short life expectancy.

CONCLUSIONS: Although the uptake and timeliness of chemotherapy for colorectal cancer has been improving, Māori, Pacific, Asian and older patients were less likely to receive chemotherapy and less likely to receive chemotherapy in a timely manner. There is a variation in use of chemotherapy by Region with patients in the Southern Cancer region appearing to be the most likely to receive chemotherapy and to receive it within a timely period.

New Zealand has one of the highest incidence rates of colorectal cancer in the world, and has higher colorectal cause-specific mortality than Australia.1,2 The most effective intervention to improve survival after diagnosis of colorectal cancer is surgery. For many patients, survival can be further increased when chemotherapy is added to surgery, so-called "adjuvant" treatment. It can reduce the risk of recurrence.3 Some patients also have neoadjuvant chemotherapy prior to surgery to shrink the tumour.4 For metastatic disease, surgery is used to prevent blockage and chemotherapy is given as palliative treatment to prolong survival but not as a cure.5 The publicly funded chemotherapy regimens for colorectal cancer in New Zealand included bolus / infusional 5-fluorouracil [5-FU] as monotherapy or combination chemotherapy including FOLFOX (5-FU, calcium folinate and oxaliplatin), FOLFIRI (5-FU, calcium folinate and irinotecan), FOLFOXIRI (5-FU, calcium folinate, oxaliplatin and irinotecan), capecitabine and the combination of capecitabine and oxaliplatin (CapOx).6–10 The timeliness of chemotherapy has become an increasingly important question in the management of colorectal cancer.11–13 The Standards of Service Provision for Bowel Cancer Patients in New Zealand recommends that patients’ post-operative
chemotherapy starts within four weeks of surgical resection. In a meta-analysis of 10 studies on time to start of chemotherapy, longer time to chemotherapy was shown to be associated with worse survival among patients with resected colorectal cancer. It showed that a four-week delay to chemotherapy could result in a significant decrease in both overall survival (Hazard ratio, 1.14; 95% confidence interval [CI], 1.10–1.17) and cancer-free survival (Hazard ratio, 1.14; 95% CI, 1.10–1.18).

New Zealand has a free-at-the-point-of-use public health service that purports to offer near universal coverage to all residents. There is an increasing body of evidence that access to diagnosis and treatment in New Zealand’s health service is inequitably distributed, with Māori at a particular disadvantage. To measure the quality of care and outcomes for people with colorectal cancer in New Zealand and to present opportunities for improving services or care pathways and reducing inequity, the Ministry of Health completed a bowel cancer quality improvement report in 2019. It investigated the diagnostic pathway, surgical treatment and radiation therapy, but did not audit the use of chemotherapy. Thus, this study aims to explore the use and timeliness of chemotherapy in patients diagnosed with colorectal cancer in New Zealand.

**Material and methods**

This study included patients diagnosed with colorectal cancer in New Zealand between 1 January 2006 and 31 December 2016, as recorded in the New Zealand Cancer Registry (NZCR). The NZCR was linked to the Pharmaceutical Collection (PHARMS) dataset by National Health Index (NHI) number to identify the publicly funded chemotherapy regimes in 2006–2017. The NHI number is a unique identifier for people who use publicly funded health and disability services in New Zealand. The PHARMS dataset stores claim and payment information from pharmacists for publicly subsidised dispensings. The combined dataset consisted of: 1) patient demographics: date of birth, gender and ethnicity; 2) tumour characteristics: date of diagnosis, cancer site, cancer extent and number of positive lymph nodes; and 3) medication dispensing information: chemical name, brand name, date of dispensing and quantity dispensed. The cancer extent recorded in the NZCR used the Surveillance Epidemiology and End Results (SEER) programme (A: localised within organ wall, B: limited to organ of origin, C: extension to adjacent organs, D: extension to regional lymph nodes and E: distant metastases). While the New Zealand Cancer Registry do have some T, N and M staging data, this is far from complete, while 81% of the colorectal cancer patients had SEER cancer extent information available. Consequently we have used the SEER cancer extent information in our analyses.

The publicly funded regimes of chemotherapy for colorectal cancer were grouped to FOLFOX, FOLFIRI, 5-FU with calcium folinate, capecitabine, CapOx and others. The first chemotherapy regime within 12 months post-colorectal cancer diagnosis was identified from the medication dispensing records as the primary chemotherapy regime. Because we could not ascertain whether the chemotherapy was for primary colorectal cancer or regional / distant recurrence, we used within one year post-diagnosis as time cut-off to identify the primary chemotherapy regime for the primary colorectal cancer. Timeliness of the chemotherapy was stratified into five groups: 1) less than five weeks after cancer diagnosis, 2) ≥5 weeks and <10 weeks, 3) ≥10 weeks and <15 weeks, 4) ≥15 weeks and <20 weeks, and 5) 20+ weeks post-diagnosis. Surgery dates were not available to examine the relationship of surgery with timeliness of chemotherapy.

Use of different chemotherapy regimes and timeliness of chemotherapy was described by gender, age group (<60, 60–64, 65–69, 70–74, 75–79, 80–84 and 85+ years), ethnicity (New Zealand European, Māori, Pacific, Asian and others), cancer extent, cancer grade (1–4), lymph node (had positive lymph nodes, no positive lymph node), year of diagnosis and cancer network (Northern, Mid Central, Midland and Southern Cancer Network). The analysis was stratified by site of cancer (colon cancer and rectal cancer). Subgroup differences were examined with Chi-square test. Logistic regression model was used to estimate the odds ratio of having chemotherapy by subgroup after adjustment for gender, age, ethnicity, deprivation quintile (NZDep2013), year of diagnosis, cancer...
extent, grade and cancer network. To identify possible reasons for not having chemotherapy, we examined patients diagnosed with advanced colorectal cancer who had no chemotherapy by age and follow-up time before death. Of the patients who had chemotherapy, we also estimated the adjusted odds ratio of having chemotherapy in less than 10 weeks post-diagnosis by subgroup after adjustment for gender, age, ethnicity, deprivation quintile, year of diagnosis, cancer extent, grade and cancer network.

All data analyses were performed in IBM SPSS statistics 25 (New York, US). The study is covered under ethics approval from the Health and Disability Ethics Committee (HDEC)—Approval Number: 17/NTB/156.

Results

During the study period 6,737/24,217 (27.8%) of patients diagnosed with colon cancer received publicly funded chemotherapy (Table 1) and 3,582/8,170 (43.8%) of patients with rectal cancer (Table 2). The proportion of patients having chemotherapy increased with cancer extent and grade. The use of chemotherapy decreased with increasing age, with only 4.4% of colon cancer patients aged 80+ years and 8.6% rectal cancer patients aged 80+ years receiving chemotherapy.

The pattern of chemotherapy regimes varied by subgroup. Older patients were more likely to receive Capecitabine and 5-FU, and younger patients were more likely to receive CapOx and FOLFOX. Patients with advanced cancer and patients with positive lymph nodes were more likely to have CapOx. The use of Capecitabine has been increasing over time, while the use of 5-FU has been reducing. CapOx were more commonly used in the Mid Central Cancer Network than in other cancer networks.

After adjustment for age, ethnicity, year of diagnosis, cancer extent, grade and cancer network (Table 3), men were more likely to have chemotherapy than women (OR1.19 for colon cancer; 1.31 for rectal cancer). There were also ethnic differences, with Pacific people being the least likely to receive chemotherapy after adjustment for gender, age, deprivation quintile, year of diagnosis, cancer extent, grade and cancer network (OR compared to Europeans: 0.47 for colon cancer; 0.63 for rectal cancer), followed by Māori (OR: 0.63 for colon cancer; 0.85 for rectal cancer) and Asian (OR: 0.69 for colon cancer; 0.79 for rectal cancer).

For patients with extent D and E colon cancer not receiving chemotherapy, 44.4% (2547/5734) were aged 80+ years, and another 15.9% (914/5,734) were aged less than 80 years but died within three months post-diagnosis. For extent D and E rectal cancer patients not receiving chemotherapy, 34.9% (390/1,116) of them were aged 80+ years, and another 16.2% (181/1,116) of patients were aged less than 80 years and died within three months post-diagnosis.

More than half of patients commenced their chemotherapy within the first 10 weeks post-diagnosis (Table 4 and 5), with around a quarter of the patients with metastatic disease starting chemotherapy within the first five weeks. The likelihood of starting chemotherapy in less than 10 weeks post-diagnosis has been increasing over time, with an adjusted odds ratio of 1.11 for colon cancer and 1.19 for rectal cancer (Table 6). Younger patients, New Zealand Europeans, patients with metastatic disease and patients in the Southern Cancer Network were more likely to have chemotherapy earlier.

Discussion

This study found that the use of chemotherapy in patients with colorectal cancer is not only influenced by the site and stage of disease but that there are also variations due to age, gender, ethnicity and the centre where treatment is provided. It is important to constantly review our management of cancer to ensure that New Zealand patients have equitable access to care. This study shows that despite the limitations of not having detailed individual clinical data, that routinely collected data can provide useful information when records are linked. In particular the comprehensive New Zealand Pharmaceutical data site provides valuable information on the use of chemotherapy for cancer patients in the absence of a prospectively collected registers of chemotherapy treatment. The findings from this study are consistent with those of the PIPER study—a retrospective study of 5,594 patients with colorectal cancer. Thus this study shows that overall 43.2% (2,836/6,559) of metastatic colorectal cancer patients received chemotherapy within one year after cancer.
Table 1: Use of publicly funded chemotherapy for colon cancer patients by subgroup.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Had chemotherapy</th>
<th>P-value</th>
<th>First chemotherapy regime after diagnosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Capecitabine, CapOx, 5-FU, FOLFIRI, FOLFOX, Others</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3,204</td>
<td>0.01</td>
<td>1,088, 28.5%, 914, 28.5%, 491, 15.3%, 149, 4.7%, 513, 16.0%, 49, 1.5%, 0.498</td>
<td>12,411</td>
</tr>
<tr>
<td>Male</td>
<td>3,533</td>
<td>0.001</td>
<td>1,110, 31.4%, 1,057, 29.9%, 570, 16.1%, 182, 5.2%, 553, 15.7%, 61, 1.7%</td>
<td>11,806</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>784</td>
<td>&lt;0.001</td>
<td>177, 22.6%, 296, 37.8%, 69, 8.8%, 35, 4.5%, 195, 24.9%, 12, 1.5%</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>1,207</td>
<td>0.001</td>
<td>289, 23.9%, 446, 36.5%, 137, 11.4%, 76, 6.3%, 243, 20.1%, 22, 1.8%</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>2,318</td>
<td>0.001</td>
<td>615, 26.5%, 608, 34.9%, 340, 14.7%, 129, 5.6%, 371, 16.0%, 55, 2.4%</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>2,124</td>
<td>0.001</td>
<td>932, 43.9%, 417, 19.6%, 428, 20.2%, 80, 3.8%, 246, 11.6%, 21, 1.0%</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>304</td>
<td>0.001</td>
<td>185, 60.9%, 10, 3.3%</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>221</td>
<td>&lt;0.001</td>
<td>68, 30.8%, 75, 33.9%, 24, 10.9%, 10, 4.5%</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>5,863</td>
<td>0.001</td>
<td>1,980, 33.8%, 1,671, 28.9%, 930, 15.9%, 290, 4.9%</td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>423</td>
<td>0.001</td>
<td>93, 22.0%, 139, 32.9%, 74, 17.5%</td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>131</td>
<td>0.001</td>
<td>26, 19.8%, 58, 44.3%</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>98</td>
<td>0.001</td>
<td>31, 31.6%</td>
<td>28, 28.6%</td>
</tr>
<tr>
<td>Cancer extent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: Limited to organ of origin</td>
<td>208</td>
<td>0.001</td>
<td>76, 36.5%, 40, 19.2%, 62, 29.8%, 8, 3.8%</td>
<td></td>
</tr>
<tr>
<td>C: Extension to adjacent organs</td>
<td>441</td>
<td>0.001</td>
<td>216, 49.0%, 53, 12.0%, 125, 28.3%</td>
<td></td>
</tr>
<tr>
<td>D: Extension to regional lymph nodes</td>
<td>3,457</td>
<td>0.001</td>
<td>1,182, 34.2%, 1,087, 31.4%, 593, 17.2%</td>
<td></td>
</tr>
<tr>
<td>E: Distant metastases</td>
<td>2,252</td>
<td>0.001</td>
<td>537, 23.8%, 724, 32.2%, 228, 10.1%</td>
<td></td>
</tr>
<tr>
<td>F: Unknown</td>
<td>375</td>
<td>0.001</td>
<td>187, 49.3%, 67, 17.7%, 53, 14.0%</td>
<td></td>
</tr>
<tr>
<td>Cancer grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>400</td>
<td>0.001</td>
<td>140, 35.0%, 96, 24.0%, 83, 20.8%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3,949</td>
<td>0.001</td>
<td>1,359, 34.4%, 1,227, 31.1%, 588, 14.9%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1,342</td>
<td>0.001</td>
<td>398, 29.7%, 393, 29.3%</td>
<td>224, 16.7%</td>
</tr>
<tr>
<td>4</td>
<td>157</td>
<td>0.001</td>
<td>67, 34.0%, 50, 25.4%</td>
<td>22, 11.2%</td>
</tr>
<tr>
<td>Unknown</td>
<td>849</td>
<td>0.001</td>
<td>234, 27.6%, 205, 24.1%</td>
<td>144, 17.0%</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No positive lymph node</td>
<td>938</td>
<td>0.001</td>
<td>387, 41.3%</td>
<td>177, 18.9%</td>
</tr>
<tr>
<td>Had positive lymph nodes</td>
<td>4,344</td>
<td>0.001</td>
<td>1,361, 31.3%, 1,426, 32.8%</td>
<td>670, 15.4%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1,455</td>
<td>0.001</td>
<td>450, 30.9%</td>
<td>368, 25.3%</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006–2009</td>
<td>2,047</td>
<td>0.001</td>
<td>624, 30.5%</td>
<td>488, 23.8%</td>
</tr>
<tr>
<td>2010–2013</td>
<td>2,677</td>
<td>0.001</td>
<td>879, 32.8%</td>
<td>497, 33.5%</td>
</tr>
<tr>
<td>2014–2016</td>
<td>2,013</td>
<td>0.001</td>
<td>695, 34.5%</td>
<td>586, 29.1%</td>
</tr>
<tr>
<td>Cancer network</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern</td>
<td>1,887</td>
<td>0.001</td>
<td>730, 38.7%</td>
<td>545, 28.9%</td>
</tr>
<tr>
<td>Mid Central</td>
<td>1,370</td>
<td>0.001</td>
<td>504, 36.8%</td>
<td>528, 45.8%</td>
</tr>
<tr>
<td>Midland</td>
<td>1,452</td>
<td>0.001</td>
<td>334, 23.0%</td>
<td>157, 10.8%</td>
</tr>
<tr>
<td>Southern</td>
<td>2,026</td>
<td>0.001</td>
<td>630, 31.1%</td>
<td>641, 31.6%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6,737</td>
<td>0.001</td>
<td>2,198, 32.6%</td>
<td>1,971, 29.3%</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Had chemotherapy</td>
<td>P-value</td>
<td>First chemotherapy regime after diagnosis</td>
<td>Total</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------</td>
<td>---------</td>
<td>------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Capcitabine, CapOx, 5-FU, FOLFIRI, FOLFOX, Others</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,255</td>
<td>0.01</td>
<td>709, 56.5%, 151, 12.0%, 271, 21.6%, 32, 2.5%, 81, 6.9%</td>
<td>3,126</td>
</tr>
<tr>
<td>Male</td>
<td>2,327</td>
<td>0.01</td>
<td>1,260, 54.1%, 296, 12.7%, 558, 24.0%, 63, 2.7%, 129, 5.5%</td>
<td>5,044</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>493</td>
<td>0.01</td>
<td>272, 54.5%, 80, 16.0%, 91, 18.2%, 8, 1.6%, 43, 8.6%</td>
<td>3,126</td>
</tr>
<tr>
<td>50–59</td>
<td>810</td>
<td>0.01</td>
<td>418, 53.6%, 117, 14.4%, 183, 22.6%, 25, 3.1%, 57, 7.0%</td>
<td>3,126</td>
</tr>
<tr>
<td>60–69</td>
<td>1,227</td>
<td>0.01</td>
<td>656, 53.5%, 185, 15.1%, 267, 21.8%, 35, 2.9%, 71, 5.8%</td>
<td>3,126</td>
</tr>
<tr>
<td>70–79</td>
<td>914</td>
<td>0.01</td>
<td>533, 58.3%, 64, 7.0%, 252, 27.6%, 25, 2.7%, 36, 3.9%</td>
<td>3,126</td>
</tr>
<tr>
<td>80+</td>
<td>132</td>
<td>0.01</td>
<td>90, 68.2%, 1, 0.8%, 36, 27.3%, 2, 1.5%, 3, 2.3%</td>
<td>1,154</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>149</td>
<td>0.01</td>
<td>90, 60.4%, 20, 13.4%, 26, 17.4%, 3, 2.0%, 9, 6.0%</td>
<td>323</td>
</tr>
<tr>
<td>European</td>
<td>2,938</td>
<td>0.01</td>
<td>1,623, 55.2%, 373, 12.7%, 689, 23.5%, 66, 2.2%, 161, 5.5%</td>
<td>6,873</td>
</tr>
<tr>
<td>Māori</td>
<td>294</td>
<td>0.01</td>
<td>139, 47.3%, 31, 10.5%, 78, 26.5%, 19, 6.5%, 24, 4.2%</td>
<td>562</td>
</tr>
<tr>
<td>Pacific</td>
<td>133</td>
<td>0.01</td>
<td>74, 55.6%, 14, 10.5%, 24, 18.0%, 5, 3.8%, 14, 10.5%</td>
<td>265</td>
</tr>
<tr>
<td>Others</td>
<td>68</td>
<td>0.01</td>
<td>43, 63.2%, 9, 13.2%, 12, 17.6%, 2, 2.9%, 2, 2.9%</td>
<td>147</td>
</tr>
<tr>
<td>Cancer extent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: Limited to organ of origin</td>
<td>83</td>
<td>0.01</td>
<td>145, 56.9%, 22, 8.6%, 65, 25.5%, 5, 2.0%, 16, 6.3%</td>
<td>1,660</td>
</tr>
<tr>
<td>C: Extension to adjacent organs</td>
<td>97</td>
<td>0.01</td>
<td>57, 58.8%, 8, 8.2%, 28, 28.9%, 1, 1.0%, 3, 3.1%</td>
<td>549</td>
</tr>
<tr>
<td>D: Extension to regional lymph nodes</td>
<td>845</td>
<td>0.01</td>
<td>380, 45.0%, 131, 22.6%, 186, 22.0%, 6, 0.7%, 68, 8.0%</td>
<td>1,380</td>
</tr>
<tr>
<td>E: Distant metastases</td>
<td>584</td>
<td>0.01</td>
<td>186, 31.8%, 147, 25.2%, 78, 13.4%, 44, 11.0%, 98, 16.8%</td>
<td>1,165</td>
</tr>
<tr>
<td>F: Unknown</td>
<td>1,973</td>
<td>0.01</td>
<td>1,310, 66.4%, 92, 4.7%, 510, 25.8%, 22, 1.1%, 34, 1.7%</td>
<td>3,416</td>
</tr>
<tr>
<td>Cancer grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>255</td>
<td>0.01</td>
<td>145, 56.9%, 22, 8.6%, 65, 25.5%, 5, 2.0%, 16, 6.3%</td>
<td>771</td>
</tr>
<tr>
<td>2</td>
<td>2,293</td>
<td>0.01</td>
<td>1,343, 58.6%, 281, 12.3%, 473, 20.6%, 51, 2.2%, 130, 5.7%</td>
<td>4,949</td>
</tr>
<tr>
<td>3</td>
<td>405</td>
<td>0.01</td>
<td>187, 46.2%, 66, 16.3%, 101, 24.9%, 16, 3.7%, 28, 6.9%</td>
<td>777</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>0.01</td>
<td>29, 67.6%, 2, 4.7%, 5, 11.6%, 1, 2.3%, 5, 11.6%</td>
<td>89</td>
</tr>
<tr>
<td>Unknown</td>
<td>588</td>
<td>0.01</td>
<td>265, 45.1%, 76, 12.9%, 185, 31.5%, 25, 3.9%, 31, 5.3%</td>
<td>1,584</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No positive lymph node</td>
<td>169</td>
<td>0.01</td>
<td>72, 42.6%, 25, 14.8%, 53, 31.4%, 3, 1.8%, 15, 9.9%</td>
<td>1,175</td>
</tr>
<tr>
<td>Had positive lymph nodes</td>
<td>678</td>
<td>0.01</td>
<td>252, 37.2%, 193, 28.5%, 145, 21.4%, 12, 1.8%, 63, 9.3%</td>
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<tr>
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<tr>
<td>Year of diagnosis</td>
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<td>2006–2009</td>
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<td>323, 30.6%, 147, 13.9%, 506, 48.0%, 16, 1.4%, 44, 4.2%</td>
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<td>816, 70.2%, 128, 11.0%, 73, 6.3%, 47, 4.0%, 94, 8.1%</td>
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<td>647, 64.1%, 131, 12.5%, 175, 16.6%, 9, 0.9%, 52, 4.9%</td>
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<td>740</td>
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<td>494, 66.8%, 134, 18.1%, 72, 9.7%, 13, 1.8%, 21, 2.8%</td>
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<tr>
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<td>726</td>
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<td>284, 39.1%, 24, 3.3%, 276, 38.0%, 69, 9.5%, 68, 9.4%</td>
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<tr>
<td>Southern</td>
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<td>0.01</td>
<td>516, 48.5%, 158, 14.9%, 306, 28.8%, 4, 0.4%, 69, 6.5%</td>
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<tr>
<td>Total</td>
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<td>1,969, 55.0%, 447, 12.5%, 829, 23.1%, 99, 2.7%, 210, 5.9%</td>
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Table 3: Adjusted odds ratio of having chemotherapy by logistic regression.

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<td>odds ratio 95% CI</td>
<td>p-value</td>
<td>odds ratio 95% CI</td>
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<tr>
<td>Female</td>
<td>Ref</td>
<td></td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Male</td>
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<td>1.19 1.11 1.28</td>
<td>&lt;0.001</td>
<td>1.31 1.17 1.47</td>
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<tr>
<td>Age (continuous)</td>
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<td>&lt;0.001</td>
<td>0.92 0.92 0.93</td>
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<td></td>
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<tr>
<td>European</td>
<td>Ref</td>
<td></td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>&lt;0.001</td>
<td>0.63 0.54 0.74</td>
<td>0.145</td>
<td>0.85 0.68 1.06</td>
</tr>
<tr>
<td>Pacific</td>
<td>&lt;0.001</td>
<td>0.47 0.36 0.62</td>
<td>0.004</td>
<td>0.63 0.46 0.87</td>
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<tr>
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<td>0.115</td>
<td>0.79 0.59 1.06</td>
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<tr>
<td>Others</td>
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<td>0.67 0.49 0.92</td>
<td>0.969</td>
<td>0.99 0.64 1.54</td>
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<tr>
<td>Year (continuous)</td>
<td>&lt;0.001</td>
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<td>&lt;0.001</td>
<td>1.06 1.04 1.08</td>
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<td><strong>Extent</strong></td>
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</tr>
<tr>
<td>B: Limited to organ of origin</td>
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<td></td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>C: Extension to adjacent organs</td>
<td>&lt;0.001</td>
<td>4.31 3.59 5.19</td>
<td>&lt;0.001</td>
<td>5.45 3.91 7.60</td>
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<td>D: Extension to regional lymph nodes</td>
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<td>64.90 54.96 76.63</td>
<td>&lt;0.001</td>
<td>47.71 36.53 62.31</td>
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<td>E: Distant metastases</td>
<td>&lt;0.001</td>
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<td>&lt;0.001</td>
<td>28.05 21.35 36.84</td>
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<td>&lt;0.001</td>
<td>0.55 0.47 0.63</td>
<td>&lt;0.001</td>
<td>0.62 0.50 0.77</td>
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<td>0.88 0.73 1.05</td>
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<td>0.82 0.50 1.36</td>
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<tr>
<td>Northern</td>
<td>Ref</td>
<td></td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Mid Central</td>
<td>0.018</td>
<td>1.14 1.02 1.27</td>
<td>0.148</td>
<td>1.13 0.96 1.32</td>
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<td>Midland</td>
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<td>0.007</td>
<td>1.25 1.06 1.47</td>
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<tr>
<td>Southern</td>
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<td>1.16 1.05 1.28</td>
<td>&lt;0.001</td>
<td>1.30 1.12 1.51</td>
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<td>0.99 0.83 1.20</td>
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<td>0.95 0.79 1.13</td>
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<td>0.87 0.78 0.98</td>
<td>0.067</td>
<td>0.85 0.71 1.01</td>
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<td>5</td>
<td>&lt;0.001</td>
<td>0.78 0.69 0.88</td>
<td>0.319</td>
<td>0.91 0.76 1.09</td>
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Table 4: Timing of chemotherapy for colon cancer.

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<th>&lt;5 weeks</th>
<th>≥5 weeks &amp; &lt;10 weeks</th>
<th>≥10 weeks &amp; &lt;15 weeks</th>
<th>≥15 weeks &amp; &lt;20 weeks</th>
<th>20+ weeks</th>
<th>P-value</th>
<th>Total having chemotherapy</th>
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<td>Female</td>
<td>417</td>
<td>1,375</td>
<td>812</td>
<td>296</td>
<td>304</td>
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<td>290</td>
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<td>106</td>
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<td>594</td>
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<td>75</td>
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<td>84</td>
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<td>120</td>
<td>48</td>
<td>49</td>
<td>11.6%</td>
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<td>11</td>
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<td>41</td>
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<td>11</td>
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<td>52</td>
<td>28</td>
<td>44</td>
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</tr>
<tr>
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<td>107</td>
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<tr>
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<td>1,072</td>
<td>401</td>
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<td>3,457</td>
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<tr>
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<td>1</td>
<td>32</td>
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<td>117</td>
<td>49</td>
<td>55</td>
<td>13.8%</td>
<td>400</td>
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<td>411</td>
<td>393</td>
<td>10.0%</td>
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<td>174</td>
<td>601</td>
<td>311</td>
<td>137</td>
<td>119</td>
<td>8.9%</td>
<td>1,342</td>
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<tr>
<td>4</td>
<td>23</td>
<td>99</td>
<td>56</td>
<td>16</td>
<td>3</td>
<td>1.5%</td>
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<td>134</td>
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<td>252</td>
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<td>521</td>
<td>118</td>
<td>170</td>
<td>18.1%</td>
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<td>136</td>
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<td>139</td>
<td>418</td>
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<td>1,732</td>
<td>666</td>
<td>650</td>
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Table 5: Timing of chemotherapy for rectal cancer.

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<th>≥5 weeks &amp; &lt;10 weeks</th>
<th>≥10 weeks &amp; &lt;15 weeks</th>
<th>≥15 weeks &amp; &lt;20 weeks</th>
<th>20+ weeks</th>
<th>P-value</th>
<th>Total having chemotherapy</th>
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<td>72</td>
<td>68</td>
<td>8.4%</td>
<td>810</td>
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<td>96</td>
<td>124</td>
<td>10.1%</td>
<td>1,227</td>
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<td>11.5%</td>
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<td>230</td>
<td>312</td>
<td>10.6%</td>
<td>2,938</td>
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<tr>
<td>Māori</td>
<td>37</td>
<td>141</td>
<td>57</td>
<td>27</td>
<td>32</td>
<td>10.9%</td>
<td>294</td>
</tr>
<tr>
<td>Pacific</td>
<td>7</td>
<td>69</td>
<td>27</td>
<td>16</td>
<td>14</td>
<td>10.5%</td>
<td>133</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
<td>34</td>
<td>11</td>
<td>10</td>
<td>2</td>
<td>2.9%</td>
<td>68</td>
</tr>
<tr>
<td><strong>Cancer extent</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>B: Limited to organ of origin</td>
<td>12</td>
<td>19</td>
<td>15</td>
<td>6</td>
<td>31</td>
<td>37.3%</td>
<td>83</td>
</tr>
<tr>
<td>C: Extension to adjacent organs</td>
<td>13</td>
<td>32</td>
<td>23</td>
<td>15</td>
<td>14</td>
<td>14.4%</td>
<td>97</td>
</tr>
<tr>
<td>D: Extension to regional lymph nodes</td>
<td>74</td>
<td>243</td>
<td>221</td>
<td>172</td>
<td>135</td>
<td>16.0%</td>
<td>845</td>
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<tr>
<td>E: Distant metastases</td>
<td>148</td>
<td>235</td>
<td>91</td>
<td>47</td>
<td>63</td>
<td>10.8%</td>
<td>584</td>
</tr>
<tr>
<td>F: Unknown</td>
<td>266</td>
<td>1,208</td>
<td>318</td>
<td>52</td>
<td>129</td>
<td>6.5%</td>
<td>1,973</td>
</tr>
<tr>
<td><strong>Cancer grade</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34</td>
<td>122</td>
<td>55</td>
<td>12</td>
<td>32</td>
<td>12.5%</td>
<td>&lt;0.001 255</td>
</tr>
<tr>
<td>2</td>
<td>298</td>
<td>1,133</td>
<td>437</td>
<td>194</td>
<td>229</td>
<td>10.0%</td>
<td>2,291</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>169</td>
<td>72</td>
<td>46</td>
<td>53</td>
<td>13.1%</td>
<td>405</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>21</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>14.0%</td>
<td>43</td>
</tr>
<tr>
<td>Unknown</td>
<td>113</td>
<td>292</td>
<td>96</td>
<td>35</td>
<td>52</td>
<td>8.8%</td>
<td>588</td>
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<tr>
<td><strong>Lymph nodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No positive lymph node</td>
<td>18</td>
<td>41</td>
<td>44</td>
<td>26</td>
<td>23</td>
<td>23.7%</td>
<td>&lt;0.001 169</td>
</tr>
<tr>
<td>Had positive lymph nodes</td>
<td>32</td>
<td>171</td>
<td>207</td>
<td>147</td>
<td>121</td>
<td>17.8%</td>
<td>678</td>
</tr>
<tr>
<td>Unknown</td>
<td>463</td>
<td>1,525</td>
<td>417</td>
<td>119</td>
<td>211</td>
<td>7.7%</td>
<td>2,735</td>
</tr>
<tr>
<td><strong>Year of diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006–2009</td>
<td>92</td>
<td>400</td>
<td>245</td>
<td>116</td>
<td>202</td>
<td>19.1%</td>
<td>&lt;0.001 1,055</td>
</tr>
<tr>
<td>2010–2013</td>
<td>210</td>
<td>709</td>
<td>250</td>
<td>95</td>
<td>101</td>
<td>7.4%</td>
<td>1,365</td>
</tr>
<tr>
<td>2014–2016</td>
<td>211</td>
<td>628</td>
<td>173</td>
<td>81</td>
<td>70</td>
<td>5.9%</td>
<td>1,162</td>
</tr>
<tr>
<td><strong>Cancer network</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern</td>
<td>500</td>
<td>211</td>
<td>101</td>
<td>132</td>
<td>108</td>
<td>10.3%</td>
<td>&lt;0.001 1,052</td>
</tr>
<tr>
<td>Mid Central</td>
<td>380</td>
<td>137</td>
<td>58</td>
<td>72</td>
<td>72</td>
<td>9.7%</td>
<td>740</td>
</tr>
<tr>
<td>Midland</td>
<td>355</td>
<td>149</td>
<td>62</td>
<td>77</td>
<td>83</td>
<td>11.4%</td>
<td>726</td>
</tr>
<tr>
<td>Southern</td>
<td>501</td>
<td>171</td>
<td>71</td>
<td>211</td>
<td>109</td>
<td>10.3%</td>
<td>1,063</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>513</td>
<td>1,737</td>
<td>668</td>
<td>292</td>
<td>372</td>
<td>10.4%</td>
<td>3,582</td>
</tr>
</tbody>
</table>
Table 6: Adjusted odds ratio of having chemotherapy in less than 10 weeks by logistic regression.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Colon cancer</th>
<th>Rectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>odds ratio</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.411</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Age (continuous)</strong></td>
<td>&lt;0.001</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>&lt;0.001</td>
<td>0.68</td>
</tr>
<tr>
<td>Pacific</td>
<td>0.005</td>
<td>0.58</td>
</tr>
<tr>
<td>Asian</td>
<td>&lt;0.001</td>
<td>0.61</td>
</tr>
<tr>
<td>Others</td>
<td>0.903</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Year (continuous)</strong></td>
<td>&lt;0.001</td>
<td>1.11</td>
</tr>
<tr>
<td><strong>Extent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: Limited to organ of origin</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>C: Extension to adjacent organs</td>
<td>0.650</td>
<td>1.08</td>
</tr>
<tr>
<td>D: Extension to regional lymph nodes</td>
<td>0.040</td>
<td>1.36</td>
</tr>
<tr>
<td>E: Distant metastases</td>
<td>&lt;0.001</td>
<td>2.28</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.892</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&lt;0.001</td>
<td>1.28</td>
</tr>
<tr>
<td>4</td>
<td>0.131</td>
<td>1.27</td>
</tr>
<tr>
<td><strong>Cancer network</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Mid Central</td>
<td>0.078</td>
<td>1.14</td>
</tr>
<tr>
<td>Midland</td>
<td>0.016</td>
<td>0.83</td>
</tr>
<tr>
<td>Southern</td>
<td>&lt;0.001</td>
<td>1.93</td>
</tr>
<tr>
<td><strong>Deprivation quintile</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.789</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>0.764</td>
<td>0.98</td>
</tr>
<tr>
<td>4</td>
<td>0.143</td>
<td>0.89</td>
</tr>
<tr>
<td>5</td>
<td>0.149</td>
<td>0.88</td>
</tr>
</tbody>
</table>
diagnosis compared to 49% (532/1,086) in the PIPER study. The 5% discrepancy in use of chemotherapy may be explained by the inclusion of privately funded chemotherapy agents in PIPER.

We have shown that the use of chemotherapy for patients with colorectal cancer has been increasing by 6% per year as well as showing improvements in the timeliness of treatment. The likelihood of colorectal cancer patients having chemotherapy decreased with increasing age, with only 5% of patients aged 80+ years receiving chemotherapy (10% if with extent D and 9% if extent E disease). It is well established that older cancer patients are less likely to receive chemotherapy. Older patients have more comorbidities and poorer performance status, and are at greater risk of toxicity from chemotherapy than younger patients.

A Denmark study showed that older patients were more frequently treated with single-agent therapy. This was also found in our study, with 89.5% of colon cancer patients aged 80+ years and 95.5% of rectal cancer patients aged 80+ years receiving 5-FU or capecitabine alone as the primary chemotherapy regime. More than half of the patients with advanced colorectal cancer (extent D and E) who did not receive chemotherapy were aged 80+ years or had a short life expectancy. Age was also a barrier in timely access to chemotherapy with an adjusted odds ratio of 0.98 per year for both colon cancer and rectal cancer.

Māori, Pacific and Asian patients were less likely to receive chemotherapy for colorectal cancer. We also have noted differences in the timing of chemotherapy for Māori, Pacific and Asian patients when compared to New Zealand Europeans. This finding is consistent with the results from a local cohort study that found Māori patients with stage III colon cancer were less likely to receive chemotherapy than non-Māori patients (relative risk: 0.69; 95% CI (0.53–0.91)). The findings that the variation in care applies to both colonic and rectal cancer and apply to pacific and Asian patients are of concern and suggest that the variations in care are not restricted just to the management of Māori with stage III colon cancer.

This study has also shown that there are variations in both the use and timing of chemotherapy depending on the Cancer Region where patients are treated. It seems that after adjustment for patient characteristics that patients in the Midland and Southern Region are more likely to be treated with chemotherapy. However, while patients in the Southern Region are more likely to be treated in a timely manner those in the Midland Region seem to be more likely to have delay before receiving treatment. These findings suggest that investigation of the regional variation in of surgery and radiotherapy as noted in the Bowel Cancer Quality Improvement Report can also extend to the use of chemotherapy.

One of the strengths of this study is that it was based on national datasets with 11 years data including 30,954 colorectal cancer patients. We have showed the most recent chemotherapy usage in New Zealand, and have demonstrated the changes over time. This study has its own limitations. Firstly the National Cancer Register does have missing data on staging on almost 20% of cases so matching chemotherapy regimens to both site and stage of disease would have missed some patients. On the other hand by including all cases of cancer we can have a better overall understanding of how chemotherapy is being used in New Zealand. The PHARMS dataset collects the dispensing records of pharmaceuticals that are publicly funded, but does not records data on pharmaceuticals that are privately funded. We used a long follow-up period of one year post-diagnosis as time cut-off to try and ensure a complete recording of chemotherapy. We recognise such a time is well outside the guidelines that post-operative chemotherapy starts within four weeks of surgical resection. We also did not have the data pertaining to other treatments including surgery and radiotherapy, and therefore could not discuss the relation of timeliness of chemotherapy with other treatments including surgery.
Conclusions
Chemotherapy is more likely to be used in younger patients with colorectal cancer and in men. Although the uptake and timeliness of chemotherapy for colorectal cancer has been improving, Māori, Pacific, Asian and older patients were less likely to receive chemotherapy and less likely to receive chemotherapy in less than 10 weeks post-diagnosis. There is a variation in use of chemotherapy by Region with patients in the Southern Cancer region appearing to be the most likely to receive chemotherapy and to receive it within a timely period.

Competing interests:
Dr Lawrenson reports grants from HRC during the conduct of the study; and Board Member of PHARMAC. Member of the Ministry of Health/Cancer Agency's Data Monitoring and Reporting Advisory Group.

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URL:

REFERENCES:
10. Boyne DJ, Cuthbert CA, O'Sullivan DE, Sajobi TT, Hillsden RJ, Friedenreich


Pneumocystis pneumonia in HIV-negative adults: missed opportunities for prevention
Nicholas Young, Stephen McBride, Susan Morpeth, Aliya Bryce, Ahsan Siddiqui, Hasan Bhally

ABSTRACT
AIM: Pneumocystis pneumonia (PCP) has a high mortality rate in HIV-negative immunocompromised patients, but is preventable with antimicrobial prophylaxis. We aimed to determine the incidence of PCP in three hospitals in Auckland, New Zealand that would have been potentially preventable if patients had been prescribed prophylaxis according to commonly proposed indications.

METHODS: We conducted a retrospective study of HIV-negative adults with PCP who were admitted to Middlemore, North Shore or Waitakere Hospitals between January 2011 and June 2017. We classified their PCP as potentially preventable if they had not been prescribed prophylaxis despite having a commonly proposed indication for this.

RESULTS: Of the 108 patients with PCP, 33/108 (30.6%) had potentially preventable infection. Of these, 14/33 (42.4%) died within 30 days of diagnosis of PCP. Most potentially preventable infections occurred in patients with solid organ or haematologic malignancies who were receiving high-dose corticosteroids for >4 weeks. We estimate that 28 cases of PCP and 12 deaths could have been prevented over the study duration if prophylaxis was prescribed to those with commonly proposed indications.

CONCLUSION: There is a substantial incidence of potentially preventable PCP and PCP-related mortality in the Auckland region. This could be reduced by greater clinician familiarity with commonly proposed indications for PCP prophylaxis, particularly for clinicians prescribing prolonged corticosteroid courses to patients with malignancies.

Pneumocystis pneumonia (PCP), caused by the opportunistic fungus Pneumocystis jirovecii, is almost exclusively a disease of the immunocompromised. While PCP is most recognised as an AIDS-defining condition, it also occurs in HIV-negative immunocompromised patients. In this population, PCP is associated with poorer outcomes compared to HIV-positive patients, with a higher rate of fulminant respiratory failure and mortality of approximately 30%.

Given the potential severity of PCP in HIV-negative immunocompromised patients, antimicrobial prophylaxis is crucial for those at highest risk. Trimethoprim-sulfamethoxazole (TMP-SMX) reduces the incidence of PCP by 85% and PCP-related mortality by 83% in this population, and is usually well tolerated. For patients with hypersensitivity to TMP-SMX, desensitisation or a graded challenge to this drug can be attempted in many instances. Alternatively, a second-line drug such as dapsone, atovaquone or nebulised pentamidine can be used, although their efficacy is inferior to TMP-SMX.

For HIV-negative adults, the benefits of TMP-SMX prophylaxis outweigh the risks of adverse events when the risk of PCP exceeds 3.5% for the period of the patient’s immunocompromise. For patients with malignancy, stem cell transplantation (SCT) and solid organ transplantation, guidelines for PCP prophylaxis have been published by several authoritative bodies. Guidelines have not been published for patients with rheumatologic diseases and other diseases requiring immunosuppressive drugs, although some authors have proposed indications for PCP prophylaxis for these patients. A summary of commonly proposed indications for PCP prophylaxis are presented in Table 1.
Polymerase chain reaction (PCR) is an important diagnostic tool for PCP in HIV-negative patients. PCR detects small amounts of *Pneumocystis* DNA in lower respiratory tract specimens and has far greater sensitivity in HIV-negative patients than immunofluorescent staining. However, PCR also detects asymptomatic airway colonisation with *Pneumocystis*; this is common in patients with chronic lung diseases but has not been definitively linked with risk of developing PCP. In the Auckland region, clinicians can request an Atypical Pneumonia PCR Panel on lower respiratory tract specimens that indiscriminately tests for multiple pathogens including *Pneumocystis*, and therefore a positive *Pneumocystis* result may be obtained in a patient who clinically does not have PCP. Consequently, a diagnosis of PCP requires a consistent clinical syndrome in addition to a positive PCR.

Cases of PCP have been described among patients who were not prescribed prophylaxis despite having a commonly proposed indication for this. For these patients, it is very likely that PCP would have been prevented if prophylaxis was prescribed. In our hospitals, there are no general policies for PCP prophylaxis outside of solid organ and stem cell transplantation and for specific chemotherapy regimens, and we therefore hypothesised that potentially preventable cases of PCP may be occurring. Our study aimed to determine the incidence of PCP among HIV-negative patients from three hospitals in Auckland, New Zealand that would have been potentially preventable if prophylaxis had been prescribed according to the commonly proposed indications in Table 1.

### Methods

We conducted a retrospective observational study of all HIV-negative patients aged ≥16 years old who were admitted to Middlemore Hospital (MMH), North Shore Hospital (NSH) or Waitakere Hospital (WTH)
between January 2011 and June 2017 and had a positive *Pneumocystis* PCR on lower respiratory tract specimens. Patients were identified by searching the laboratory database at MMH, where PCR testing for all study sites was performed using an 8-plex Atypical Pneumonia PCR panel (*AusDiagnostics*, Mascot NSW, Australia). Curves with a cycle threshold of <32 in step 2 of the *AusDiagnostics* assay were reported as positive.

Patients with a positive PCR were classified clinically into two groups: those with probable PCP, and those with probable asymptomatic *Pneumocystis* colonisation. This classification was determined by reviewing clinical records to ascertain the impression of the clinicians caring for the patient at the time. Patients were classified as probable PCP if their clinicians thought their presentation was consistent with PCP or if they were given PCP treatment. Patients were classified as probable asymptomatic colonisation if their clinicians thought their presentation was not consistent with PCP.

We collected data from clinical records on patient demographics and diagnoses of immunosuppressive conditions and chronic lung diseases (defined as bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease and lung cancer). We also collected laboratory data for immunofluorescent staining (with ≥5 cysts seen defined as positive). Dispensing records were reviewed for immunosuppressive drugs; for corticosteroids, we classified courses as either short (<4 weeks) or long (≥4 weeks). For long courses of corticosteroids, we calculated the average daily dose of prednisone during the month prior to the positive PCR; for patients receiving dexamethasone, we converted this to an equivalent prednisone dose using a ratio of 0.75mg of dexamethasone to 5mg of prednisone. Dispensing records were also reviewed for TMP-SMX, dapsone and atovaquone, and we assumed that these were prescribed for PCP prophylaxis if dispensed for ≥4 weeks. Medication charts were reviewed to identify patients receiving nebulised pentamidine.

For patients with PCP, we classified their infection as potentially preventable if they had a commonly proposed indication for prophylaxis in Table 1 but had not been prescribed this. For patients receiving chemotherapy regimens not listed in Table 1, we classified PCP as potentially preventable if the treating hospital's protocol for that chemotherapy regimen recommended PCP prophylaxis but this had not been prescribed.

Ethical approval was obtained from the research offices of the involved hospitals. Informed consent was not deemed necessary because our study was retrospective and no identifying characteristics were reported in our findings that could de-identify patients. Fisher's exact test was used for analysis of 2x2 contingency tables and a two-tailed t-test was used for comparison of means; a p-value <0.05 was deemed significant.

**Results**

A total of 217 patients with a positive *Pneumocystis* PCR were identified (Table 2). Of these, 108 patients (49.8%) had probable PCP and 109 patients (50.2%) had probable asymptomatic *Pneumocystis* colonisation. Those with probable PCP had a higher overall 30-day mortality than those classified as colonised (32.4% vs 16.5%, p=0.007). No patients classified as colonised subsequently developed PCP during the study period.

Of the 108 patients with PCP, 33/108 (30.6%) had a commonly proposed indication for prophylaxis as described in Table 1. No patient in this group had been prescribed prophylaxis, therefore all had potentially preventable infection. Of the patients with potentially preventable infection, 14/33 (42.4%) died within 30 days of the diagnosis of PCP. For no patient was it documented in the clinical record that prophylaxis was not prescribed due to a contraindication or concern about adverse effects.

The category of medical condition causing immunosuppression and/or requiring immunosuppressive drugs is shown in Table 3. Of the patients with solid organ malignancy, 17/26 (65.4%) had a commonly proposed indication for prophylaxis. This sub-group accounted for the majority of those with potentially preventable PCP (17/33, 51.5%). There were 22/26 patients (84.6%) with solid organ malignancy who had been prescribed long-course corticosteroids (average prednisone dose 42mg/day). In the three months prior to diagnosis of PCP, 8/26 patients (30.8%) had received.
chemotherapy and 12/26 patients (46.2%) had received radiotherapy.

Of the 24 patients with haematologic malignancy and/or SCT, 10/24 (41.7%) had a commonly proposed indication for prophylaxis. This sub-group accounted for the second largest group with potentially preventable PCP (10/33, 30.3%). There were 14/24 patients (58.3%) with haematologic malignancy and/or SCT who had been prescribed long-course corticosteroids (average prednisone dose 23mg/day), and 3/24 (12.5%) who had undergone SCT. One patient with hematologic malignancy developed PCP despite prophylaxis; this patient was receiving nebulised pentamidine but did not have a commonly proposed indication for prophylaxis.

Of the 108 patients with PCP, 75/108 (69.4%) did not have a commonly proposed indication for prophylaxis. Patients with rheumatologic disease were the largest contributor to this group (27/75, 36%), followed by patients with haematologic malignancy and/or SCT (14/75, 18.7%) and respiratory disease (12/75, 16%). Of those with rheumatologic disease, 12/30 (40%) had rheumatoid arthritis (RA). No patient with RA had a commonly proposed indication for prophylaxis and only 5/12 (41.7%) had been prescribed long-course corticosteroids (average prednisone dose 9mg/day). All patients with RA were prescribed non-corticosteroid immunosuppressive drugs, with a median of three drugs.

Of those with respiratory disease, most had interstitial lung disease (9/12, 75%), and most (8/12, 66.7%) had been prescribed long-course corticosteroids (average prednisone dose 23mg/day).

### Table 2: Characteristics of patients with PCP and patients with *Pneumocystis* colonisation.

<table>
<thead>
<tr>
<th></th>
<th>Patients with PCP (N=108)</th>
<th>Patients with <em>Pneumocystis</em> colonisation (N=109)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender – no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51 (47.2)</td>
<td>69 (63.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>57 (52.8)</td>
<td>40 (36.7)</td>
<td></td>
</tr>
<tr>
<td>Age in years – mean (range)</td>
<td>68.6 (36.9–93.8)</td>
<td>68.6 (17.2–94.9)</td>
<td>0.98</td>
</tr>
<tr>
<td>Overall 30-day mortality – no (%)</td>
<td>35 (32.4)</td>
<td>18 (16.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Immunosuppressive condition and/or immunosuppressive drugs – no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No immunosuppression</td>
<td>2 (1.9)</td>
<td>31 (28.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Short-course corticosteroids only</td>
<td>1 (0.9)</td>
<td>26 (23.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long-course corticosteroids only</td>
<td>13 (12)</td>
<td>14 (12.8)</td>
<td>1</td>
</tr>
<tr>
<td>Non-corticosteroid immunosuppression only</td>
<td>26 (24.1)</td>
<td>20 (18.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Long-course corticosteroids with at least one form of non-corticosteroid immunosuppression</td>
<td>66 (61.1)</td>
<td>18 (16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic lung disease – no (%)</td>
<td>37 (34.3)</td>
<td>77 (70.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive immunofluorescent staining – no (%)</td>
<td>23 (21.3)</td>
<td>1 (0.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*PCP* *Pneumocystis* pneumonia.
Discussion

Our study demonstrates that there is a substantial burden of potentially preventable PCP and PCP-related mortality among HIV-negative patients in the Auckland region. In our cohort, 33/108 patients (30.6%) had a commonly proposed indication for prophylaxis but had not been prescribed this, and 14/33 (42.4%) of these patients died within 30 days of their PCP diagnosis. Assuming that TMP-SMX prophylaxis reduces the incidence of PCP by 85% and PCP-related mortality by 83%, we estimate that 28 cases of PCP and 12 deaths could have been prevented over the 78-month duration of our study if TMP-SMX was prescribed according to the commonly proposed indications in Table 1.

For patients with solid organ or haematologic malignancies, consensus guidelines provide unambiguous indications for PCP prophylaxis. Despite this, the vast majority of potentially preventable PCP in our cohort occurred in patients with solid organ or haematologic malignancy (27/33, 81.8%). This finding suggests that suboptimal guideline adherence is a cause of poor outcomes among these patients. To improve outcomes, we firstly recommend that clinicians who care for patients with solid organ or haematologic malignancies familiarise themselves with guidelines for PCP prophylaxis, particularly if prescribing prolonged corticosteroid courses to these high-risk patients. Secondly, we recommend that clinicians should be aware of options for PCP prophylaxis in patients with hypersensitivity or other contraindications to TMP-SMX, including desensitisation or graded challenge to TMP-SMX or the use of second-line drugs such as dapsone, atovaquone and nebulised pentamidine. Thirdly, we recommend that departments develop local policies to assist clinicians in prescribing PCP prophylaxis and to raise awareness of potentially preventable PCP. This applies not only to oncology and haematology, but also to specialities such as general medicine, respiratory medicine and neurosurgery, who are often the first to diagnose malignancy and initiate corticosteroids prior to cancer specialists taking over care of the patient. Finally, when cases of potentially preventable PCP occur, we recommend that these events are critically reviewed for

Table 3: Condition causing immunosuppression and/or requiring immunosuppressive drugs in patients with PCP.

<table>
<thead>
<tr>
<th>Condition causing immunosuppression and/or requiring immunosuppressive drugs</th>
<th>Patients with PCP with an indication for prophylaxis (N=33)</th>
<th>Patients with PCP without an indication for prophylaxis (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients prescribed PCP prophylaxis – no (%)</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Solid organ malignancy – no (%)</td>
<td>17 (51.5)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Haematologic malignancy and/or stem cell transplantation – no (%)</td>
<td>10 (30.3)</td>
<td>14 (18.7)</td>
</tr>
<tr>
<td>Rheumatologic disease – no (%)</td>
<td>3 (9.1)</td>
<td>27 (36)</td>
</tr>
<tr>
<td>Dermatologic disease – no (%)</td>
<td>1 (3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Gastroenterological disease – no (%)</td>
<td>1 (3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Neurological disease – no (%)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory disease – no (%)</td>
<td>0</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Solid organ transplantation – no (%)</td>
<td>0</td>
<td>6 (8)</td>
</tr>
<tr>
<td>No known immunosuppressive condition or immunosuppressive drugs – no (%)</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Non-malignant haematologic disease – no (%)</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Renal disease – no (%)</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

PCP Pneumocystis pneumonia.
the purposes of clinician education and to identify changes that can be implemented to reduce risk to future patients.

Although we identified many cases of PCP in patients with rheumatologic disease, only 3/30 (10%) had a commonly proposed indication for prophylaxis. Assessing PCP risk in patients with rheumatologic disease is challenging, due to a complex interaction of risk factors including the specific rheumatologic disease, disease activity, age, lymphopaenia, current and past corticosteroid use and the use of non-corticosteroid immunosuppressive drugs, some of which pose a greater risk of PCP compared to others. While some authors have proposed approaches to PCP prophylaxis in patients with rheumatologic diseases, there is a pressing need for evidence-based guidelines to clearly define which patients with rheumatologic and other autoimmune diseases will benefit from prophylaxis.

To the best of our knowledge, this is the largest study of HIV-negative patients with PCP in New Zealand. However, our study has several limitations. Firstly, we did not have a control group of patients who had indications for PCP prophylaxis but did not develop PCP; therefore, we were unable to estimate the overall incidence of PCP in this population. This would have been helpful to confirm whether the indications in Table 1 accurately predict the threshold at which the benefits of prophylaxis outweigh the harms. Secondly, no specific diagnostic criteria were used to classify patients as having PCP or asymptomatic colonisation. While none of the colonised group developed PCP, it is possible that some colonised patients were incorrectly classified as having PCP. Finally, because we only identified patients with a positive PCR, we were not able to include those who were diagnosed with PCP on clinical grounds alone or those who died before diagnostic testing.

In conclusion, the incidence of potentially preventable PCP and PCP-related mortality in the Auckland region is considerable. These events are mostly occurring among patients with solid organ and haematologic malignancies receiving high-dose corticosteroids for ≥4 weeks, and could be substantially reduced by prescribing prophylaxis to these patients according to guidelines. Patients with rheumatologic diseases also account for a significant proportion of those with PCP in the Auckland region, but reducing the occurrence of PCP in this group will remain challenging until publication of rheumatology-specific guidelines for PCP prophylaxis.
Competing interests:
Nil.

Acknowledgements:
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URL:

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or not to prophylax (and when?); that is the question. Ann Rheum Dis. 2018; 77(5):631–3.


Evaluating the implementation and outcomes of a sepsis pathway in the emergency department

Pourya Pouryahya, Natalie Guiney, Alastair Meyer, Neil Goldie

ABSTRACT

AIM: Early recognition and timely management, including prompt administration of antibiotics, has been fundamental in improving the mortality related to sepsis. We aimed to study the effect of the Sepsis Pathway Programme, a set of guidelines for sepsis, on the recognition, early investigation and management of septic patients in the emergency department.

METHODS: We conducted a comparative prospective cohort study of patients who presented with suspected sepsis pre- and post-implementation of the Sepsis Pathway. Patients where the Sepsis Pathway was used were identified and followed prospectively to analyse outcomes. This group was compared to a pre-intervention control group who were identified retrospectively before the Sepsis Pathway was implemented to determine if there was any difference in outcomes.

RESULTS: A total of 109 patients were identified to be septic in the emergency department following the implementation of the Sepsis Pathway. Of these, 52 cases involved the initiation and completion of the Sepsis Pathway. One hundred and fifty-seven cases were identified in the pre-intervention group of which 18 cases were excluded. The time to antibiotic administration decreased from 182 to 75 minutes (p<0.00001). The proportion of cases where antibiotics were given within the hour was higher in the pathway group (36.5% vs 8.6%, OR 6.09, 95% CI 2.69–13.81, p<0.0001). Similarly, the time to lactate measurement decreased from 64 minutes to 54.5 minutes (p=0.0117) and the proportion of cases where lactate was measured improved from 64% to 92.3% (p=0.0005). Blood culture rates improved from 79.1% to 100%.

CONCLUSION: The implementation of the Sepsis Pathway improved time taken to perform investigations and manage patients with sepsis. Although it had improved, there was still a delay in recognition of sepsis and initiation of investigations and management, demonstrating that further strategies need to be employed to reduce poor outcomes associated with sepsis. However, it did not affect ICU admissions, length of stay or mortality.
Figure 1: Sepsis flowchart checklist.
SEPSIS PATHWAY – ADULT – EMERGENCY DEPARTMENT

SEPSIS RESUSCITATION GUIDELINE

Does the patient have an Advance Care Directive; are there any treatment limitations?

A
Maintain patent airway

B
Give oxygen
Aim SpO₂ > 95% (or 88-92% for COPD & chronic type II respiratory failure)

C
Large bore intravenous access, collect and check results:
- Lactate
- Blood gas
- Blood cultures x 2 (separate sites)
- EUC
- Coags
- CRP or procalcitonin if available
- FBC
- LFTs
- Glucose

IV fluid resuscitation
Give initial 20mL/kg 0.9% sodium chloride bolus STAT; aim for MAP of > 65mmHg or SBP > 100mmHg. If no response, repeat 20mL/kg 0.9% sodium chloride bolus unless there are signs of pulmonary oedema
If no response commence inotropes as per local protocol and in consultation with senior doctor

PRESCRIBE and ADMINISTER ANTIBIOTICS WITHIN 60 MINUTES
from diagnosis of sepsis or within 30 MINUTES if haematology/oncology patient (Please refer to Neutropenic Fever pathway from Prompt)

Do not delay for investigations or results

D
Assess level of consciousness (LOC) using Alert, Voice, Pain, Unresponsive (AVPU)
If P or U re-assess Airway, Breathing and Circulation

E
Examine patient for source of sepsis
Collect appropriate swabs, cultures, ECG, chest X-ray if indicated

F
Fluid balance
Monitor and document fluid input & output - consider IDC
Maintain urine output ≥ 0.5 mL/kg/hour

G
Check Blood Glucose Level: if > 12mmol/L, consider glycaemic control

MONITOR & REASSESS
Continue monitoring and assess for signs of deterioration:
- Respiratory rate in the Red or Yellow Zone
- SBP < 100mmHg
- Decreased or no improvement in level of consciousness
- Urine output < 0.5mL/kg/hour
- Increasing or no improvement in serum lactate
Commence Sepsis 48 Hour Management Plan

IF NO IMPROVEMENT INTENSIVE CARE MAY BE REQUIRED

- Reassess suitability to continue resuscitation
- Request review by ICU doctor to occur within 30 minutes
- Discuss with ICU/ARV 1300 368 661
- Discuss management plan with patient and their family/carers
Victorian sepsis pathway was developed by the Monash health multidisciplinary sepsis group. Monash Health is the largest health network in the state of Victoria, Australia, with an annual emergency department network census of about 200,000 presentations. It comprises of three hospitals: Monash Medical Centre (tertiary referral), Dandenong and Casey hospitals (district hospitals).

To assist with the recognition of sepsis, the guideline includes a checklist of vital sign parameters, which vary slightly from the well-known Systemic Inflammatory Response Criteria, but are aligned with Australian Observation and Response Charts. The Guideline suggests responding to patients with two or more observations that fall within the set criteria with a review by a senior clinician within 30 minutes.

The pathway advises collection of blood for multiple tests including two sets of blood cultures, a venous blood gas and a lactate level. However, it also emphasises that administration of empirical antibiotics for sepsis should not be delayed by investigations or results (Figure 2).

The Sepsis Pathway was introduced as part of a Sepsis Pack, designed to support clinicians in performing the steps outlined in the guideline. The Sepsis Pack includes equipment for intravenous cannulation and intravenous fluids, as well as for collection of blood for culture and lactate measurement.

This article evaluates the impact of the implementation of the Sepsis Pathway Programme on the recognition, early investigation and management of septic patients in the emergency department.

Methods

The aim of this pathway was to improve recognition of patients with sepsis (RECOGNISE) and to initiate early management with intravenous fluid and antimicrobial therapy (REACT). The Sepsis Pathway was designed with broad inclusion criteria to identify sepsis as well as risk stratify potential septic patients. There are a set of risk factors based on history and physical examination to identify high-risk patients:

- Immunocompromised/chronic illness/chemotherapy/radiotherapy
- Abdominal pain/distension/peritonism
- Indwelling medical device
- Cough/sputum/breathlessness
- Recent surgery/invasive procedure
- New onset of confusion/altered LOC/neck stiffness/headache
- History of fever or rigors
- Re-presentation within 48 hours
- Wound infection cellulitis
- Fall not related to mechanism of injury
- Dysuria/frequency/odour
- Age >65yo

This, in conjunction with the analysis of the patients’ vital signs can be used to risk stratify patients. Vital signs triggering the initiation of Sepsis Pathway are as follows:

- Respirations ≤10 or ≥25 per minute
- SpO2 ≤95%
- Systolic blood pressure ≤100mmHg
- Heart rate ≤50 or ≥120 per minute
- Altered LOC or new onset of confusion
- Temp <35.5 °C or >38.5 °C

High-risk patients are identified if:

- Lactate ≥4mmol/L
- Immunocompromised
- SBP ≤90mmHg
- Base excess <-5.0

After identification of a septic or potentially septic patient, the pathway is strictly followed.

An explicit Sepsis Data Collection Form to assess the effect of the Sepsis Pathway was added to Sepsis Packs at Casey Hospital, a district hospital with mixed emergency department (adults and paediatrics) with about 60,000 presentations annually. A comparative prospective cohort study of patients presenting with suspected sepsis pre- and post-implementation of the Sepsis Pathway was then conducted. This was in conjunction with multidisciplinary Monash Health sepsis pathway development programme, which was approved by the ethics committee. From June to December 2015, data was collected prospectively for patients who were identified in the emergency department to have potential sepsis. The outcomes were measured for groups where the Sepsis Pathway was used and...
**Figure 2:** Sepsis management plan.

### Sepsis Assessment

<table>
<thead>
<tr>
<th>Time:</th>
<th>Date:</th>
</tr>
</thead>
</table>

### Tick the relevant risk factors, signs or symptoms of infection

- Immunocompromised
- Indwelling medical device
- Recent surgery/invasive procedure
- History of fever and/or rigors
- Re-presentation within 48 hours
- Fall not related to mechanism of injury

- Abdomen: pain, peritonism
- Lung: cough, SOB
- Neuro: altered LOC, new onset of confusion, neck stiffness, headache
- Skin: cellulitis, wound
- Urine: dysuria, frequency, odour

**Does the patient have any YELLOW criteria?**

- Respiration ≤ 10 or ≥ 25/min
- SpO2 < 95%
- SBP ≤ 100 mmHg
- Heart rate ≤ 50 or ≥ 120/min
- Altered LOC or new onset of confusion
- Temp < 35.5 or > 38.5

**If any risk factor, sign or symptom of infection**

**PLUS** two yellow criteria

**THE PATIENT MAY HAVE SEPSIS**

- Obtain senior clinician review within 30 minutes
- Look for other causes of deterioration
- Commence SEPSIS SIX

If fewer than 2 yellow criteria present, treat and re-assess simultaneously. SEPSIS may still be a concern.

**In addition does the patient have any RED criteria?**

- SBP < 90 mmHg
- First Lactate ≥ 4 mmol/L
- Base excess < -5.0
- Age > 65 years
- Immunocompromised

**If one or more red criteria present**

**THE PATIENT HAS SEVERE SEPSIS or SEPTIC SHOCK until proven otherwise**

- Obtain immediate senior clinician review
- Expedite transfer to resuscitation area or equivalent
- Commence resuscitation as per SEPSIS SIX

### Triage Category (1-5)

(ED Only)

Does the patient have an Advance Care Directive; are there any treatment limitations?

- No ☐
- Yes ☐ If YES, consider how this may impact ongoing management of sepsis.
# Sepsis Management: Sepsis Six

1. **Oxygen**
   - Maintain $\text{SpO}_2 > 95$
   - If increased oxygen is required, seek senior medical review
   - **Oxygen administration:** [ ] litres/minute

2. **Blood Cultures**
   - Blood cultures (2 aerobic, 2 anaerobic)
     - FBC, UECs, LFTs, coags, glucose, +/- wound, urine, sputum, or other cultures
   - **Blood cultures** [ ] FBC [ ] Coags [ ] Other cultures [ ] UEC [ ] BGL [ ] Swabs [ ] LFTs

3. **Lactate**
   - Take blood for formal lactate or VBG
   - [ ] mmol/L

4. **IV Fluids**
   - Give 20mL/kg 0.9% sodium chloride fluid challenge **STAT**
   - Aim to achieve MAP of > 65mmHg or SBP > 100mmHg
   - If no response, repeat 20mL/kg 0.9% sodium chloride unless there are signs of pulmonary oedema
   - If no response commence inotropes as per local protocol and in consultation with senior medical officer
   - **FLUID RESUSCITATION**
     - Second litre IV fluid commenced:
     - YES: Time: [ ] [ ] [ ] Date: [ ] [ ] / [ ] / [ ]
     - NO: [ ] Not prescribed [ ] Fluid restricted

5. **IV Antibiotics**
   - Prescribe and commence within 60 minutes from triage/time of diagnosis
   - or within 30 MINUTES if haematology/oncology patient
   - (refer to local guidelines and seek specialist advice)
   - **Do not wait for results of investigations**
   - **ANTIBIOTIC ADMINISTRATION**
     - First IV antibiotic commenced:
     - Time: [ ] [ ] [ ] Date: [ ] [ ] / [ ] / [ ]
     - Frequency of observations required over next six hours
     - Every [ ] minutes

6. **Monitoring**
   - Monitor respiratory rate, $\text{SpO}_2$, blood pressure, heart rate, temperature, LOC, fluid balance, urinary output, consider urinary catheter
   - Review antibiotics when blood/specimen results available
   - Management plan (discuss with senior medical officer)

## Presumptive Source of Sepsis
- [ ] Abdomen
- [ ] CNS
- [ ] Lung
- [ ] Orthopaedic
- [ ] Skin/soft tissue
- [ ] Urinary tract
- [ ] Vascular device
- [ ] Other
- [ ] Unknown

## Disposition
- [ ] Unchanged
- [ ] Home
- [ ] Ward
- [ ] Other hospital
- [ ] HDU/ICU
- [ ] Death
- Date of death: [ ] [ ] / [ ] / [ ]
not used. Cases where a diagnosis of sepsis was missed in the emergency department were identified through a search of electronic medical records (EMR) looking for all patients subsequently diagnosed with sepsis as well as those that had documented positive blood cultures during admission. Those with growth on blood culture of a gram-positive coccii were excluded from this group as they were considered false positives due to likely contamination.

These groups were compared to a control group which included patients with suspected sepsis who presented to the same emergency department from June to December 2014, a year prior to the implementation of the Sepsis Pathway. These patients were identified through a search of EMR looking for patients who were diagnosed with sepsis in the emergency department. Those cases that were missed in the emergency department were also included. They were identified through a search of the EMR looking for patients diagnosed with sepsis throughout their admission or those that had positive blood cultures during admission. Similar to above, false positives were duly accounted for and excluded as any growth of gram-positive cocci were considered most likely contaminated samples. We compared the control group (2014) to the group of patients specifically placed on the Sepsis Pathway (2015), as well as those that were missed and later identified through EMR during the intervention period. Patients <18 years old, those who were already taking a course of antibiotics as an outpatient prior to their presentation and those that were transferred to other hospitals during admission were excluded from the study.

The following data was collected:

- Date of birth
- Triage time and date
- Triage category
- Presenting problem at triage
- Time to antibiotic from time of triage
- Time to lactate measurement from time of triage
- Number of cases where blood cultures were taken
- Number of intensive care admissions
- Length of intensive care admission
- Length of hospital admission
- In-hospital mortality

Analysis included the calculation of odds ratios with 95% confidence intervals according to Altman and p-values using Fisher's exact and t-test. Statistical significance was defined as p<0.05.

**Results**

Following the introduction of the Sepsis Pathway, a total of 109 patients were identified to be septic, either at presentation in the emergency department or throughout admission during the study period of 15 June to 31 December 2015. Of these, 52 cases were identified prospectively to be septic through the initiation and completion of the Sepsis Pathway Collection Form. This group will be referred to as the ‘Sepsis Pathway’ Group. It also includes patients who were identified and treated as septic, and subsequently transferred to intensive care unit from the emergency department. The remaining cases were either those identified with sepsis in the emergency department but were not treated with the Sepsis Pathway or those that were missed and identified to be septic throughout their admission. These groups were identified to have sepsis through a retrospective search of the EMR using positive blood cultures collected on presentation or during their admission. The missed cases that had gram-positive coccii grown on blood culture were excluded as they were presumed to be contaminated samples and could bias the data. This group will be referred to as the ‘Missed Cases Group’. The pre-intervention control group included 139 patients who presented from 15 June to 31 December 2014. They were either identified in the emergency department to be septic, were documented as septic during their admission or had a true positive blood culture, again excluding any cases that could be contaminated (gram positive coccii growth on blood culture).

The Pre-intervention Control Group (2014) had a median age of 78 (IQR 56–91). Patients in the ‘Sepsis Pathway Group (2015)’ and the ‘Missed Cases Group (2015)’ had a median age of 67 (IQR 53.75–81) and 69 (IQR 50–84), respectively.
In the study period prior to the implementation of the Sepsis Pathway, there was a significantly lower proportion of septic patients who were triaged as Category 1 according to the Australasian Triage Scale (ATS) from no cases in the pre-intervention period to three cases in the Sepsis Pathway Group (0% vs 5.8%, p=0.0193).\(^5\)

The three most common presenting problems in all groups were ‘febrile/PUO’ (17.8% of all cases), ‘shortness of breath’ (13.9% of all cases) and ‘generally unwell’ (15.4% of all cases).

The median time to antibiotic administration in the Sepsis Pathway Group improved significantly compared to the Control Group (75 minutes vs 182 minutes, p<0.00001). The proportion of patients who received antibiotics within 60 minutes of triage was greater in the Sepsis Pathway Group than in the pre-intervention group (36.5% vs 8.6%, OR 6.09–13.81, p<0.0001).

Similarly, the median time to lactate measurement was significantly shorter in the Sepsis Pathway Group compared to the pre-intervention group (54.5 minutes vs. 64 minutes, p=0.0117). A greater proportion of patients had their lactate measured within 60 minutes of triage in the Sepsis Pathway Group than in the pre-intervention group and this was statistically significant (53.8% vs 27.3%, OR 2.86, 95% CI 1.49–5.49, p=0.0016).

Serum lactate levels were tested more often in the Sepsis Pathway Group than in the Control Group (92.3% vs 64.0%, OR 2.51–11.90, p=0.005). Blood cultures were sent in all of the cases that utilised the Sepsis Pathway; 20.9% of the cases in the pre-implementation group did not have blood cultures taken during their admission.

There was an increase in the rate of ICU admission in the Sepsis Pathway group when compared to the pre-intervention group; however, this was not statistically significant (28.8% vs 16.5%, OR 1.94, 95% CI 0.92–4.09, p=0.0823).

No significant differences were seen between the groups when looking at the median length of stay in ICU, length of hospital admission or mortality.
Figure 4: Comparison of the triage categories.

![Chart showing comparison of triage categories for Pre-intervention (2014), Sepsis Pathway (2015), and Missed Cases (2015).]

Table 1: The three most common presenting problems.

<table>
<thead>
<tr>
<th>Three most common presenting problems</th>
<th>Pre-intervention (2014) n=139</th>
<th>Sepsis Pathway (2015) n=52</th>
<th>Missed cases (2015) n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia of unknown origin: n (%)</td>
<td>20 (14.4%)</td>
<td>11 (21.2%)</td>
<td>6 (35.3%)</td>
</tr>
<tr>
<td>Shortness of breath: n (%)</td>
<td>19 (13.7%)</td>
<td>8 (15.4%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Generally unwell: n (%)</td>
<td>19 (13.7%)</td>
<td>11 (21.2%)</td>
<td>2 (11.8%)</td>
</tr>
</tbody>
</table>

Figure 5: Antibiotics administered within the hour.

![Chart showing antibiotics administration for Pre-intervention (2014), Sepsis Pathway (2015), and Missed Cases (2015).]
Table 2: Median time to antibiotics administration and lactate measurement.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to antibiotic: minutes (IQR)</td>
<td>182 (110–337)</td>
<td>75 (46.25–115.5)</td>
<td>154 (100–301.5)</td>
</tr>
<tr>
<td>Median time to lactate measurement: minutes (IQR)</td>
<td>64 (30.25–187.75)</td>
<td>54.5 (27.25–89)</td>
<td>58 (43–74.5)</td>
</tr>
</tbody>
</table>

Table 3: Number of blood culture and lactate done in each group.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate level measured</td>
<td>89 (64.0%)</td>
<td>48 (92.3%)</td>
<td>9 (52.9%)</td>
</tr>
<tr>
<td>Blood cultures taken</td>
<td>112 (80.1%)</td>
<td>52 (100%)</td>
<td>17 (100%)</td>
</tr>
</tbody>
</table>

Table 4: ICU admission rates and length of stay, hospital length of stay and mortality comparison.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission: n (%)</td>
<td>23 (16.5%)</td>
<td>15 (28.8%)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>Median ICU LOS: days (IQR)</td>
<td>3 (2–6)</td>
<td>4 (2–7)</td>
<td>3</td>
</tr>
<tr>
<td>Median Hospital LOS: days (IQR)</td>
<td>6 (4–10)</td>
<td>6.5 (4–9)</td>
<td>7 (5–12.5)</td>
</tr>
<tr>
<td>Mortality: n (%)</td>
<td>9 (6.5%)</td>
<td>7 (13.5%)</td>
<td>2 (11.8%)</td>
</tr>
</tbody>
</table>
Discussion

Recognition of sepsis and the importance of prompt management appear to have improved following the introduction of the Sepsis Pathway Flowchart. This is demonstrated by the reduction of missed cases in the emergency department following the implementation of the Sepsis Pathway when compared to the pre-implementation phase (69.1% vs 20.5%). This decrease could be due to the guideline being presented as a checklist to medical staff, allowing doctors to follow it easily even when they are unsure. Though there is a decrease in the number of missed cases after the implementation of the Sepsis Pathway, there is still room for improvement. False negatives remain with non-specific presentations or early presenting features not covered by the checklist. Additionally, in 2015, more patients were triaged as Category 1 and 2 compared to prior to the implementation of the Sepsis Pathway (38.5% vs 22.3%). Being classified in a more urgent Triage Category, these patients are more likely to be seen by a clinician earlier and subsequently, investigation and management may be initiated earlier. Previous sepsis quality improvement programmes have also resulted in increases in the number of patients in higher urgency triage categories, such as ATS 1 or 2, and there were also reciprocal reductions in less urgent triage categories.5

In sepsis, delay in administration of appropriate antibiotics is associated with increased mortality. Commencing appropriate antibiotic therapy as soon as possible in septic patients is ideal, with international guidelines recommending one hour as a reasonable minimal target.3,7 The median time to antibiotic administration was shorter in the Sepsis Pathway Group with significantly more patients receiving antibiotics within 60 minutes of being triaged. However, the median time remained suboptimal even after the introduction of the Sepsis Pathway with 64.5% of antibiotic administration times exceeding the target of 60 minutes.

There has been a recent change in the classification of sepsis, with the introduction of the sepsis 3 criteria. Lactate levels are included in the clinical criteria for septic shock as they an important indicator of illness severity and therapeutic response.8 Not only was there a significant increase in the rate of lactate measurement in the Sepsis Pathway Group compared to the Control Group (92.3% vs 64%, OR 6.74, 95% CI 2.30–19.80, p=0.0005), but the time to lactate measurement was also shorter; the median time to lactate measurement was 54.5 minutes in the Sepsis Pathway Group compared to 64 minutes in the control group. Also, the proportion of patients who had their lactate measured within the target of 60 minutes after triage almost doubled from 27.3% prior to the pathway to 53.8% in the Sepsis Pathway Group (OR 2.86, 95% CI 1.49–5.49, p=0.0016). Blood culture collection rates were also significantly higher in the Sepsis Pathway Group with blood cultures performed on all patients in the group. This indicates that staff may have been prompted to perform lactate levels and blood cultures by the complementary Sepsis Pack, which included equipment for intravenous cannulation, lactate measurement and blood cultures.

The initial investigation and management with antibiotics of septic patients improved when the Sepsis Pathway was used. However, this did not have a significant effect on outcomes such as duration of ICU admission and length of hospital stay. There was also an increase in mortality and ICU admission rates in septic patients where the Sepsis Pathway was used; however, this was not statistically significant.

The predominant presenting problems both pre- and post-protocol were non-specific, including fever/pyrexia of unknown origin, shortness of breath and generally unwell. More timely recognition of potential sepsis in these patients may lead to further improvements in time to antibiotic and investigation, with subsequent improvements in ICU rates and mortality.1,2

The moment a patient presents to the emergency department, they are classified into a Triage Category, which affects how quickly they are seen by a clinician in the department. A greater index of suspicion that patients are potentially septic, especially in those with non-specific presenting problems, may lead to expedition of their investigation and management, including allocation to more urgent triage categories. This has a flow-on effect as these patients are likely to be seen by a clinician earlier,
have investigations performed more promptly and receive empirical antibiotics earlier. This effect should be further evaluated to see whether the introduction of the Sepsis Pathway and its effect on the Triage Category has a causational effect on antibiotic administration times and time to investigations. Further work is required to examine the confounding effect of a generally higher triage category on time to antibiotics and investigations.

Additionally, the Sepsis Pathway, as aforementioned should risk stratify patients. This will ensure that cases that are more severe are prioritised. Although patients that were septic were identified, further investigations should be explored in future studies to assess the degree of organ dysfunction that has occurred as a result of sepsis. Markers of organ and tissue dysfunction such as those included in the SOFA score (e.g., serum creatinine, bilirubin and platelet count) may be useful in determining the risk of adverse outcomes. This could be included in future studies9 (Table 5).

Table 5: Summary.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triage category: n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0%)</td>
<td>3 (5.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>2</td>
<td>31 (22.3%)</td>
<td>17 (33%)</td>
<td>5 (29.4%)</td>
</tr>
<tr>
<td>3</td>
<td>89 (64.0%)</td>
<td>30 (58%)</td>
<td>11 (64.7%)</td>
</tr>
<tr>
<td>4</td>
<td>19 (13.7%)</td>
<td>2 (3.8%)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Most common presenting problems: n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia of unknown origin n=37 (17.8%)</td>
<td>20 (14.4%)</td>
<td>11 (21.2%)</td>
<td>6 (35.3%)</td>
</tr>
<tr>
<td>Shortness of breath n=29 (13.9%)</td>
<td>19 (13.7%)</td>
<td>8 (15.4%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Generally unwell n=32 (15.4%)</td>
<td>19 (13.7%)</td>
<td>11 (21.2%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Median time to antibiotic: minutes (IQR)</td>
<td>182 (110–337)</td>
<td>75 (46.25–115.5)</td>
<td>154 (100–301.5)</td>
</tr>
<tr>
<td>Antibiotics administered in ≤1 hour from triage: n (%)</td>
<td>12 (8.6%)</td>
<td>19 (36.5%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Median time to lactate measurement: minutes (IQR)</td>
<td>64 (30.25–187.75)</td>
<td>54.5 (27.25–89)</td>
<td>58 (43–74.5)</td>
</tr>
<tr>
<td>Lactate measured in ≤1 hour from triage: n (%)</td>
<td>38 (27.3%)</td>
<td>28 (53.8%)</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>Lactate level measured</td>
<td>89 (64.0%)</td>
<td>48 (92.3%)</td>
<td>9 (52.9%)</td>
</tr>
<tr>
<td>Blood cultures taken</td>
<td>112 (80.1%)</td>
<td>52 (100%)</td>
<td>17 (100%)</td>
</tr>
<tr>
<td>ICU admission: n (%)</td>
<td>23 (16.5%)</td>
<td>15 (28.8%)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>Median length of stay in ICU: days (IQR)</td>
<td>3 (2–6)</td>
<td>4 (2–7)</td>
<td>3</td>
</tr>
<tr>
<td>Median length of stay in hospital: days (IQR)</td>
<td>6 (4–10)</td>
<td>6.5 (4–9)</td>
<td>7 (5–12.5)</td>
</tr>
<tr>
<td>Mortality: n (%)</td>
<td>9 (6.5%)</td>
<td>7 (13.5%)</td>
<td>2 (11.8%)</td>
</tr>
</tbody>
</table>
Limitations

This study was conducted at a single health service across three sites and is subsequently limited by a small study size. As with other quality improvement programmes and especially in the emergency department where staff turnover is high, the improved outcomes may also be related to other factors. Staff experience, knowledge of sepsis and the recent sepsis recognition awareness training within the hospital are potential confounders. Moreover, this study was conducted after the Monash Health Sepsis Pathway Project was established. Naturally as a result of this, there was some delay in publishing the results obtained.

Our data collection involved the time antibiotics were given but did not include the time antibiotics were prescribed. Without knowing the time a decision was made to give antibiotics, it is difficult to identify the cause of the delay in antibiotic administration. This could be due to the antibiotics not being prescribed early enough or due to a delay in administration. Additionally, data collection did not include time from onset of symptoms to presentation to the emergency department as this was not always documented. Ideally, this should be considered as this will impact on results. Similarly, the origin of sepsis was also not often known and therefore could not be analysed as a variable that may affect outcomes.

Septic patients were also not separated in terms of antibiotic protocol used, however this can be considered in further study.

As the selection of patients in the control group is retrospective in nature, identification of patients is subject to selection bias. This is demonstrated by a slight difference in age between the pre-intervention group and Sepsis Pathway and Missed Cases groups. We recognise that age could be a confounder as a result. We attempted to reduce this bias, however by ensuring that all cases that were identified through blood cultures were not false positives.

Due to the importance of quick biomarker results in this critically unwell septic cohort, venous blood gas lactate was used in this study. The accuracy of lactate measurement might vary based on the sample site, however strong correlation between arterial, central vein and peripheral vein lactate as well as other parameter with laboratory blood tests was demonstrated in previous studies.10,11

Conclusions

Implementation of the Sepsis Pathway led to earlier recognition, the lactate being measured more often and earlier administration of antibiotics in patients presenting to the emergency department with suspected sepsis. Nonetheless, this did not influence frequency of ICU admission or hospital length of stay.

There are still delays in the recognition of sepsis and initiation of investigation and management. Further evaluation of the Sepsis Pathway in a larger multi-centre study, also evaluating duration from the time a patient is first seen by a clinician rather than from triage, is warranted.
Competing interests: Nil.

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URL:

REFERENCES:


Quality measures in cervical lymphadenectomy for cutaneous malignancy by head and neck trained general surgeons

Fouad Nahab, Sita Ollek, Richard Harman, Richard Martin

ABSTRACT

AIM: Therapeutic lymphadenectomy remains the gold standard for surgical management of clinically evident regional cervical disease for cutaneous malignancy. However, international consensus on adequate lymphadenectomy is lacking. Attempts have been made to establish quality measures; suggested benchmarks for minimum and average nodal yield, as well as recurrence and complication rates have been quoted. We aim to compare our key performance indicators to those benchmarks published in the literature.

METHODS: This is a retrospective observational study conducted with prospectively maintained data, over an 11-year period (2007–2018).

RESULTS: Of 91 cervical lymphadenectomies included, mean nodal yield for ≤3 and ≥4 dissection levels were 19.7 and 38.7 respectively. We observed a combined locoregional recurrence rate of 25%. Subgroup analysis for melanoma (60) and cSCC (28) revealing regional nodal recurrence of 15% and 11%, respectively. We observed a 38.5% complication rate; however, less than 5.5% was considered grade IIIb/IIIb(d) [Clavein-Dindo]. Median follow-up of 19.3 months, five-year survival rate of 38% and 32% for melanoma and cSCC, respectively.

CONCLUSION: Our data indicates that we are meeting quality measures, set by higher volume centres. We believe that any surgeon with subspecialty training in head and neck surgery can meet quality measures with regards to cervical lymphadenopathy for cutaneous malignancy.
The LNR may therefore prove useful in prognostication following TLND. While it has been shown that a complete lymphadenectomy does not impart a significant survival benefit compared to clinical observation in those patients with SLNB positive disease; it is still valuable in providing prognostic information, improving regional nodal control and allowing access to new adjuvant systemic treatment options.\textsuperscript{13,14}

To standardise surgical care and establish quality standards, key performance indicators (KPIs) have been proposed by high volume centres where benchmarks for nodal dissection have been reported. The Sydney Melanoma Unit (now Melanoma Institute Australia—MIA) has demonstrated that in their centre, the 90\textsuperscript{th} percentile for nodal yield of ≤3 and ≥4 level neck dissections were ≥6 and ≥20 lymph nodes, respectively.\textsuperscript{9} The literature further supports the benefit of achieving a minimum nodal yield and highlights the staging information it provides. For example, Rossi et al (2014) demonstrated that a higher number of excised lymph nodes was associated with better prognosis and recommended a minimum nodal yield of 7 and 14 nodes for ≤3 and ≥4 level cervical lymphadenectomies respectively, in order to more accurately stage patients using the American Joint Committee on Cancer (AJCC) guidelines.\textsuperscript{10}

A regional lymphadenectomy is a standardised dissection, the extent of which is determined by pre-defined anatomic boundaries, node levels at risk and radiological imaging. The American Academy of Otolaryngology—Head and Neck Surgery provide standardised anatomical boundaries to determine the level of dissection, for both therapeutic lymphadenectomy and selective lymph node dissections.\textsuperscript{15} Although cadaveric and radiological studies have demonstrated that on average there are at least 28 lymph nodes on each side of the neck,\textsuperscript{16,17} variation exists in the extent of nodal dissection and the resulting nodal yield. Factors contributing to this variation include modifications based on an anatomic area, patient anatomy, surgical technique and thoroughness of histopathologic analysis.\textsuperscript{18,19} In addition, surgeon experience and clinical judgment based on the individual clinical scenario is an important factor in determining the volume of tissue harvested and from which levels, as is done with a selective nodal dissection in the head and neck region. This is well demonstrated by recent research which reinforces the trend to safely omit level 1 and 4 when operating on patients with clinically apparent parotid melanoma metastases, allowing the surgeon to take ≤3 levels of lymph nodes in their neck dissection.\textsuperscript{20}

With data published from MSLT-II, a positive SLNB is no longer an indication for an immediate lymphadenectomy.\textsuperscript{12} However, at the present time a therapeutic lymphadenectomy remains the standard of care for clinically evident regional disease.\textsuperscript{4,12} Previous literature on cervical nodes from the MIA has also demonstrated the significance of nodal positivity as one of the most important factors (alongside Breslow thickness) in determining survival in melanoma patients with nodal metastases in the head and neck region.\textsuperscript{21} Lymphadenectomy is not without risk and carries potential morbidity. The frequency and severity of postoperative complications is another important metric for quality assurance. The complication rate following cervical lymphadenectomy is reported in the literature to be between 8\% to 39\%; and included wound complications (bleeding, seroma, infection) in addition to transient and permanent nerve damage.\textsuperscript{22,23} Striving to minimise morbidity following cervical lymphadenectomy is an important part of maintaining high-quality care.

Melanoma and non-melanoma skin cancer (NMSC), mainly cSCC, are cutaneous malignancies for which cervical lymphadenectomies are commonly performed.\textsuperscript{24,25} New Zealand has the highest rate of cutaneous melanoma in the world (51.8 per 100,000) and Auckland has the highest incidence of NMSC (1,906 per 100,000). International research has indicated that incidence of melanoma in New Zealand is projected to rise within the next decade, and we still carry the highest age-standardised melanoma mortality rates.\textsuperscript{26–28} Waitematā District Health Board (WDHB) is located in Auckland City, and is the largest district health board in New Zealand; servicing more than 620,000 people.\textsuperscript{29} Given the high volume of disease being treated within our district health board, we wished to assess the quality of cervical lymphadenectomies being
performed. We aimed to evaluate outcomes including nodal yield, complications, recurrence and all-cause mortality in patients undergoing cervical lymphadenectomies for melanoma and NMSC over an 11-year period by general surgeons with subspecialty training in head and neck surgery.

**Method**

**Objectives**

Our primary objective was to determine the mean and minimum nodal yield obtained with cervical lymphadenectomies and to compare this to published literature. Secondary objectives were to assess quality standards including overall survival, complication rate, in addition to local, regional nodal and distant recurrence rates.

**Patients and methods**

This retrospective observational study is based on a prospectively maintained database from the WDHB and Melanoma Unit. We included patients who underwent a cervical lymphadenectomy between 2007–2018 for cutaneous malignancies with regional cervical metastases. Neck dissections involving parotidectomy were identified and provided a ‘parotid nodal’ category. Dissections included patients with clinically occult (ie, identified on SLNB) or clinically evident (ie, palpable or radiographically detected) regional nodal disease. Operations were performed by one of two general surgeons with subspecialty training and experience in head and neck surgery. All cases were discussed through a regional multidisciplinary meeting. Patients underwent routine postoperative follow-up at two weeks following surgery, then intermittently for 3–4 months. This research was approved by institution locality process (Awhina).

**Statistics**

We analysed data points of interest using descriptive statistics; and included age, gender, date of surgery, date of death where applicable, primary diagnosis, type of procedure, primary tumour site, Breslow thickness, nodal yield, number of positive lymph nodes, extracapsular spread, postoperative complications, adjuvant radiotherapy, as well as local, regional and distant recurrence. Oncologic outcomes including mortality and recurrence rate were analysed separately for melanoma and cSCC. Lymphadenectomies were categorised as ≤3 dissection levels versus ≥4 dissection levels. We compared the nodal yield from both ≤3 and ≥4 level dissections to the findings by the Spillane group, who demonstrated that their 90th percentile nodal yield for ≤3 and ≥4 level dissections were ≥6 and ≥20 lymph nodes, respectively. Flow charts and tables were created using Google documents and Lucidchart. Chi-squared test was conducted to assess statistical significance using Graph-Pad Prism 8.3.1 software. Melanoma stage was assigned based on the AJCC (8th edition).

**Results**

Ninety-one cervical lymphadenectomies were performed in patients with metastatic disease to cervical lymph nodes, with all but one being unilateral dissections. For the bilateral case, we treated nodal yield from each side separately. The median age at time of surgery was 72 years (mean: 71 years, SD 13.8, range 21–94); there was a male predominance with 74 males (81%), compared with 17 females (19%) (Table 2). Melanoma was the most common primary malignancy, accounting for 66% (60/91) of patients. cSCC was the second most common

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>n</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>60</td>
<td>66%</td>
</tr>
<tr>
<td>SCC</td>
<td>28</td>
<td>31%</td>
</tr>
<tr>
<td>MCC</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>Cutaneous mucinous carcinoma</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>Adnexal tumour</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Breakdown of primary tumour diagnoses.

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primary malignancy at 31% (28/91). There were three other primary malignancies: Merkel cell carcinoma (MCC), primary cutaneous mucinous carcinoma, and one case of an adnexal tumour (Table 1). Patients with melanoma were categorised as stage IIIA, IIIB, IIIC and IIID in 10%, 24%, 54% and 7% of cases respectively, according to the AJCC. There were three patients (5%) with stage IV melanoma (Figure 1). The stage IV melanoma cases were two palliative dissections in the context of non-regional metastatic disease, and one curative dissection having previously had an axillary dissection with now palpable cervical metastases.

### Table 2: Demographics for patients undergoing cervical lymphadenectomy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (mean)</th>
<th>Proportion</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>73 (71.3)</td>
<td>-</td>
<td>21-94</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74</td>
<td>81%</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>19%</td>
<td>-</td>
</tr>
<tr>
<td>Primary tumour site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head + neck</td>
<td>64</td>
<td>70%</td>
<td>-</td>
</tr>
<tr>
<td>Torso</td>
<td>15</td>
<td>16.5%</td>
<td>-</td>
</tr>
<tr>
<td>Upper limb</td>
<td>5</td>
<td>5.5%</td>
<td>-</td>
</tr>
<tr>
<td>Unknown primary site</td>
<td>7</td>
<td>8%</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 1: Proportion of melanoma by stage (%)—based on AJCC 8th Edition.
Thirty-two cases included cervical dissection of ≤3 levels, and 59 cases were dissection of ≥4 levels (Figure 2). The median nodal yield in ≤3 dissection levels was 27 (mean: 19.7, SD 17.1, range 6–48). The median nodal yield in ≥4 dissection levels was 35 (mean: 38.7, SD 17.4 range 15–76). All patients who underwent a ≤3 dissection had a nodal yield of six or more lymph nodes. Among those who underwent ≥4 dissection levels, 88% (52/59) had ≥20 lymph nodes removed. The overall mean and median LNR for all patients were 12% (SD 0.15) and 6% respectively. The mean LNR was lower for patients with melanoma (10%) when compared to those with SCC (14%). Of the 91 neck dissections, 31% included superficial or complete parotidectomy. The median number parotid lymph nodes dissected was 1 (Mean: 2.6, SD 2.2, range 1–8). 90% of our ≤3 level dissections, and ≥4 level dissections contained ≥8 and ≥19 lymph nodes, respectively.

With a median follow-up duration of 19.4 months (mean 29 months, SD 30.9, range 0.5–130), locoregional recurrence occurred in 25% of patients (23/91). Of the 91 lymphadenectomies included in the study, 13% had regional nodal recurrence. The overall complication rate was 38.5%, with a total of 35 complications. Transient neuropraxia was the most common complication, occurring in 13 patients (14%), of which 11 involved a branch of the facial nerve (CNVII), and two involved the spinal accessory nerve (CNXI). Formation of a seroma or hematoma occurred in 11 patients (12%). Other complications included wound breakdown or infection, chyle leak and permanent nerve palsy (Table 3). Of these five patients; one developed a postoperative pneumomediastinum which was self-limiting. Most complications were managed in an outpatient setting and did not require operative intervention. A total of five patients (5.5%) patients experienced complications considered as Grade IIIb/IIIb(d) Clavien-Dindo classification. Of these five patients; one developed a postoperative haematoma requiring evacuation in theatre; another a suppurative wound infection requiring operative drainage and washout. 3.3% had permanent cranial nerve palsy (3/91), two cases of facial nerve (CNVII) and one of accessory nerve (CNXI) impairment. No postoperative deaths were observed. During the follow-up period, all-cause mortality rate was 56% (51/91).
Melanoma patients

In those patients who underwent a cervical lymphadenectomy for regional metastatic melanoma, 16 patients (26.7%) developed some form of disease relapse; locoregional recurrence. However, the rate of nodal recurrence alone was 15% (9/60) in the melanoma group overall. All patients who developed a local and/or regional nodal recurrence also eventually developed distant metastatic disease. Overall, 38 patients (63%) developed distant metastatic disease, with 22 (58%) of these patients developing distant metastatic disease without evidence of locoregional recurrence. Twenty-six (36.7%) patients remained disease free at the time of last follow up.

From this group, 55% (33/60) received postoperative radiotherapy. We observed a regional nodal recurrence rate of 15.2% (5/33) in those receiving radiotherapy. This is compared to 14.8% (4/27) recurrence rate in the no-radiation group. There was a statistically significant higher rate of extra-capsular spread in the radiotherapy group compared to the no-radiotherapy group, 66% vs 30% (p=0.043, Chi square 8.148), respectively. In addition, there was a greater mean positive node in those undergoing radiotherapy vs no-radiotherapy, 4.0 (SD 4.59, 0–21) vs. 1.6 (SD 4.73, 1–4). Regional nodal recurrence rate for clinically occult and clinically detectable disease was 6% and 19% respectively; and reflect a completion lymph node dissection (CLND) in 33.3% of cases (20), compared to TLND in 66.7% of cases (40).

The all-cause mortality rate of patients with melanoma was 50% (30/60), within the follow-up period of the study; with a five-year overall survival rate of 38% (Figure 3). The mortality rate did not differ significantly between those with clinically occult (47%) versus clinically detected (51%) regional disease (p=0.71, Chi-squared = 0.1372).

Table 3: Complications by type.

<table>
<thead>
<tr>
<th>Complication</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chyle leak</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nerve injury (transient)</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Permanent palsy</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Seroma/haematoma</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Wound infection</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3: Kaplan-Meier Survival Curve: melanoma by stage IIIA, B, C, D and IV.

5-YR: five-year survival rate (%). Staged according to AJCC 8th Edition.
Squamous cell carcinoma

Among the 28 patients with a primary cSCC, postoperative disease relapse (locoregional recurrence) occurred in seven patients (25%). However, the rate of regional nodal recurrence alone in this group was 11% (3/28) overall. One quarter of these patients (25%) with local or regional nodal recurrence also developed distant metastases.

Of the cSCC group, 82% (23/28) underwent postoperative adjuvant radiation therapy. We observed a statistically significant reduction in regional nodal recurrence rate with the use of adjuvant radiotherapy (4% with radiotherapy vs 40% without radiotherapy) (p=0.02, Chi square = 5.46). The distant metastatic rate was 28.5%, and all-cause mortality for those undergoing cervical lymphadenectomy for metastatic cSCC was 67.9% (19/28); we observed a five-year survival rate of 32% in this group.

Discussion

Surgery continues to play a key role in the treatment of patients with lymph node metastases from cutaneous malignancies and remains the gold-standard in those with clinically evident disease. While a thorough surgical dissection is imperative, this must be balanced against the potential for morbidity and risk of complication. It is important that standards are set and followed to ensure provision of adequate surgical resection while minimising morbidity during such a procedure.

While what constitutes an adequate regional cervical lymphadenectomy remains undefined, a proposed measure of quality assessment is the minimum nodal yield. The nodal yield is a combined surgical and pathology key performance indicator. The MIA has suggested a benchmark nodal yield average of 19.5 lymph nodes (median 18.5) for cervical lymphadenectomies with ≤3 dissection levels or an average 38.9 (median 36) for ≥4 dissection levels. Moreover, a minimum nodal yield of ≥6 lymph nodes for ≤3 cervical dissection levels, and ≥20 lymph nodes for cervical lymphadenectomy dissection of ≥4 levels has been proposed, using the 10th percentile as a cut-off metric. Our series has met this standard of quality assurance, reaching a median nodal yield of 27 (mean 19.7, SD 17.08, range 6–48) for ≤3 dissection levels and 35 (mean 38.7, SD 17.42 range 15–76) for ≥4 dissection levels. We have also met the recommended benchmarks for minimum nodal yield, in 100% of our cervical lymphadenectomies involving ≤3 dissection levels, and in 88% of those involving ≥4 or more dissection levels. Although our data would suggest a minimum recommended nodal yield of ≥8 nodes, and ≥20 nodes for ≤3 and ≥4 level dissections, respectively and is based on the 10th percentile metric. We have aligned our minimum nodal yield metric of the 10th percentile with previously published research, as this metric is reproducible across institutions, and accounts for minimal nodal yield with respect to the extent of surgery within each nodal field.

Use of this 90% threshold helps to identify those cases of inadequate lymph node retrieval and ensures institutions continue to achieve a high benchmark. Although, previously published literature on minimal nodal yield has also been based on expert opinion, with a figure of minimum 15 nodes for cervical neck dissections published by the Bilimoria group which include ≤3 and ≥4 dissection levels.

Previous research has reinforced the importance of LNR as an independent prognostication tool, highlighting the improved survival in those cases with LNR ≤10%. Our overall mean LNR was 12%, with a difference in mean LNR for melanoma and SCC, 10% and 14%, respectively. Furthermore, it has been shown specifically for head and neck regional metastatic melanoma, that the most important factors predicting survival were nodal positivity in addition to Breslow thickness. Published cervical lymphadenectomy complication rate ranges from 8.3 to 39.0%. Our complication rate of 38.5% reflects all complications, including those which did not require readmission or re-operation and lines up with the type of complications encountered in the literature. The majority were temporary cranial nerve neuropraxias followed by operative site seroma. Less than 5% of our complications are considered Grade IIIb/IIIb(d). There were no complications grade IV or higher. Only 3.3% (3/91) had permanent neuropraxia. Our findings are in keeping with previously published benchmarks on acceptable complication rates from the MIA, which quotes an acceptable rate of less than 5% for re-intervention for wound complications following
cervical lymphadenectomy; and <50% and <20% temporary and permanent cranial nerve palsy rate, respectively.34

Another important aspect of quality assurance is regional disease control following lymphadenectomy. The Chan group reported a regional recurrence rate of 56% (86/153) following cervical lymphadenectomies for metastatic melanoma.35 And previous work by the Geltzeiler group has demonstrated a regional recurrence rate of 29% in cervical lymphadenectomy for metastatic melanoma.21,24 In work by another National unit, combined local and regional recurrence rates have been reported as 30% for cervical TLND of stage III melanoma.11 Data from the Martin group (2012) has demonstrated a combined locoregional recurrence rate of 27.6% following cervical TLND in head and neck melanoma; further breakdown revealed a lymph node recurrence of 8.5%.21 We have identified an overall disease relapse (locoregional recurrence) rate of 25%; however, this was further analysed to account for differences in disease characteristics for melanoma compared to SCC, with emphasis on regional nodal recurrence. Subgroup analyses of our regional nodal recurrence revealed a rate of 15.0% and 10.7% for melanoma and SCC, respectively. Overall this reflects an accurate and reproducible surgical practice and is comparable to rates previously reported in the literature.11,21,24,35

Our observed regional nodal recurrence rates following radiation therapy differed between the SCC and melanoma groups. There was a significant reduction in nodal recurrence following radiation therapy in the cSCC group (4%), compared to 40% recurrence in those not undergoing postoperative radiation therapy. This result is based on a small dataset and requires a larger sample size to see a true effect. In the melanoma group, the radiotherapy vs no-radiotherapy group had similar nodal recurrence rates (15.2% vs. 14.8%, respectively). The patients in these two groups cannot be directly compared due the higher risk of nodal recurrence carried in the radiotherapy group, seen with a greater rate of ECS and greater mean positive nodes, compared to the no-radiotherapy group. This result highlights the effect of radiotherapy at reducing risk of nodal recurrence, as seen in the high risk (radiotherapy group) sustaining similar rates of recurrence in the lower risk group (no-radiotherapy).

This result aligns with well-established evidence that radiotherapy has an approximately 10% reduction in nodal recurrence for melanoma patients following therapeutic lymphadenectomy.14

Our centre provides head and neck oncological resection services to the WDHB which is expected to serve a projected population of 628,970 by 2019. Of this demographic, a large proportion of the population (31.7%) are aged 50 years or older.29 Although there is a lack of consensus in regional and international guidelines on the minimum recommended nodal yield for cervical lymphadenectomies performed for cutaneous metastases, we can still assess quality standards against those recommended by higher volume centres.6,7 Here we have demonstrated that the nodal yield for cervical lymphadenectomies in our centre is in keeping with the proposed benchmarked quoted in the literature.5,18 Furthermore, our complication rate is similar to that which has previously been published.

Quality measures or KPIs are an important metric when dealing with low-volume surgical procedures. The number of nodal dissections for melanoma has dramatically reduced since the practice changing results from MSLT-II.13 If KPIs are not met then node dissection cases should be referred to tertiary referral centres that are meeting KPIs, but who also have the appropriate perioperative support; for example, nurse specialists, and lymphoedema physiotherapists. Our results show a 42% survival at 19.3-month median follow-up based on surgical treatment only. We are now entering a very interesting period with adjuvant and neoadjuvant anti-PD1 or BRAF/MEK systemic treatment which will no doubt improve survival in these high-risk melanoma patients.36–39

We recommend a minimum nodal yield of 8 for ≤3 level and 19 for ≥4 level dissections for cutaneous malignancies, using the 10th percentile cut-off metric. We believe that any surgeon with subspecialty training in head and neck surgery can meet quality assurance standards with regards to cervical lymphadenectomy for cutaneous malignancy. Until a consensus is reached on the accepted quality standards for regional lymphadenectomies, we must routinely audit and compare our performance to the currently published recommendations to ensure we are providing the best possible care.33

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Competing interests: Nil.

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REFERENCES:


Combination budesonide/formoterol inhaler as sole reliever therapy in Māori and Pacific people with mild and moderate asthma

Jo Hardy, Jordan Tewhaiti-Smith, Christina Baggott, James Fingleton, Alex Semprini, Mark Holliday, Robert J Hancox, Mark Weatherall, Richard Beasley, Matire Harwood on behalf of the PRACTICAL Study Team

Asthma is a major public health problem in New Zealand. The prevalence rate is among the highest in the world, particularly in adults identifying as Māori, the indigenous people of New Zealand, and Pacific people. Furthermore, substantial morbidity and mortality persist despite efforts to improve management, with disparities in health outcomes for Māori and Pacific peoples across the severities of asthma.

Systemic issues such as institutional racism and socioeconomic disadvantage are core drivers to these disparities. Lower socioeconomic status results in barriers to healthcare access and is associated with worse health literacy and poor adherence to maintenance inhaled corticosteroid (ICS).

When healthcare is accessed, despite the burden of asthma being greater among Māori and Pacific people, they are more likely to remain on the lowest steps of asthma treatment.6–7

Over the past decade a number of strategies including community-based education programmes and asthma action plans have contributed to improving outcomes for Māori and Pacific people with asthma, but novel strategies may be required if further progress is to be made.6–10 One strategy has been the combination ICS/fast-onset long-acting beta-agonist (LABA) used as both maintenance and reliever therapy, an approach which reduces the risk of severe exacerbations compared with maintenance ICS/LABA and short-acting beta2-agonist

ABSTRACT

AIM: In the PRACTICAL study, as-needed budesonide/formoterol reduced the rate of severe exacerbations compared with maintenance budesonide plus as-needed terbutaline. In a pre-specified analysis we analysed the efficacy in Māori and Pacific peoples, populations with worse asthma outcomes.

METHOD: The PRACTICAL study was a 52-week, open-label, parallel group, randomised controlled trial of 890 adults with mild to moderate asthma, who were randomised to budesonide/formoterol Turbuhaler 200/6mcg one actuation as required or budesonide Turbuhaler 200mcg one actuation twice daily and terbutaline Turbuhaler 250mcg two actuations as required. The primary outcome was rate of severe exacerbations. The analysis strategy was to test an ethnicity-treatment interaction term for each outcome variable.

RESULTS: Seventy-two participants (8%) identified as Māori, 36 participants (4%) as Pacific ethnicity. There was no evidence that ethnicity was an effect modifier for severe exacerbations (P interaction 0.70).

CONCLUSION: The reduction in severe exacerbation risk with budesonide-formoterol reliever compared with maintenance budesonide was similar in Māori and Pacific adults compared with New Zealand European/Other.
(SABA) reliever therapy in children and adults.11 This efficacy benefit has been shown in Māori adults with asthma,12 and has been recommended for use in Māori in local guidelines.13

An extension to this strategy is the use of combination ICS (budesonide)/fast-onset LABA (formoterol) used solely as needed in mild asthma, as an alternative to either SABA as sole reliever therapy or ICS maintenance and SABA reliever therapy. Four clinical trials have demonstrated that as-required budesonide/formoterol is non-inferior or superior14,15 to regular budesonide plus as needed SABA, and superior to SABA alone,14,16 in reducing severe exacerbation risk. One of these clinical trials, the PRACTICAL study, only recruited patients in New Zealand, which provided the opportunity to investigate whether this novel regimen is effective and safe in Māori and Pacific peoples. In this manuscript, we report a subgroup analyses of the influence of ethnicity on the efficacy of as-needed budesonide-formoterol vs maintenance budesonide and as-needed terbutaline in adults with mild to moderate asthma.

Methods

The PRACTICAL study was a 52-week, open label, parallel group, multicentre, phase III, randomised controlled trial to compare the efficacy and safety of two asthma treatment regimens; budesonide-formoterol Turbuhaler [Symbicort] 200/6mcg, one inhalation for relief of symptoms as required (budesonide-formoterol group), or budesonide Turbuhaler [Pulmicort] 200mcg, one inhalation twice daily and terbutaline Turbuhaler [Bricanyl] 250mcg, two inhalations for relief of symptoms as required (budesonide maintenance group). The PRACTICAL study was funded by the Health Research Council of New Zealand and was undertaken independently of the pharmaceutical industry.

Eight hundred and ninety adult patients, aged 18 to 75, with doctor-diagnosed asthma were recruited from 15 primary care facilities and research centres across New Zealand. Patients taking SABA reliever therapy alone or together with low to moderate doses of inhaled corticosteroid in the 12 weeks prior to randomisation were eligible. This pragmatic study was designed to more closely reflect real-world clinical practice.18 Smokers were only excluded if they had a greater than 20-pack year smoking history or respiratory symptoms that began after the age of 40 in participants with at least a 10-pack year smoking history. Additional key exclusion criteria included self-reported use of LABA or leukotriene receptor antagonist as maintenance therapy in the 12 weeks before potential study entry or the diagnosis of other lung disease.

All participants provided written informed consent and the study was approved by the Northern B ethics committee (15/NTB/178/AM01). Each site sought local Māori research committee approval. Participants and investigators were not masked to group assignment which allowed any real-world advantage of the as-needed ICS/formoterol regimen, that is, the use of a single medication and no requirement for regular inhaler use, to be studied.

Written asthma management plans were provided and inhaler technique was checked at each study visit. Questions on housing conditions and physical residential address, for calculation of deprivation score, were collected at week 0. Validated housing questions were adapted from the New Zealand heating study and Building Research Institute of New Zealand (BRANZ) house condition study.19,20 Detailed trial methodology has been reported elsewhere.21 Patients remained under the care of their primary care physician throughout the trial.

A Kaupapa Māori approach was utilised in some capacity, to increase the number of Māori participants.22 This involved the development of recruitment strategies, including recruiting through Māori providers and clinics, with the support of Kaupapa Māori trained asthma health workers. Participants self-reported their ethnicity at the first study visit. New Zealand national guidelines were used to classify ethnicity for participants reporting more than one ethnicity by a standard system.23

Outcome measures

The primary outcome was the number of severe exacerbations per patient per year. Severe exacerbations were defined as ii) the use of systemic steroids for at least three days because of asthma or ii) hospitalisation or ED visit because of asthma requiring systemic steroids, as recommended by ATS/ERS Task Force.24
Secondary outcomes were rate of asthma exacerbations per patient per year defined as worsening asthma resulting in unplanned medical review or use of systemic glucocorticoids of any duration, asthma control questionnaire 5 (ACQ-5) score, the mean of five questions about asthma symptoms during the previous week, each scored on a 7-point scale between 0 (no impairment) and 6 (maximum impairment), on-treatment FEV1 and fractional exhaled nitric oxide (FeNO).

**Statistical analysis**

The statistical analysis was an intention to treat superiority analysis. The general analysis strategy was to test an ethnicity-treatment interaction term for each outcome variable. In the event, none of the interaction terms was statistically significant. For illustration purposes only, the estimates of treatment differences and 95% confidence intervals are shown for each ethnicity from these interaction models and these are not accompanied by P values as there was no evidence that the effects within ethnic groups were different from the Overall rate in models that did not have ethnicity. The Overall rate is accompanied by a confidence interval and associated P value testing the hypotheses that the values of these outcome variables was different depending on treatments. These analyses have not been adjusted for multiple comparisons.

The recognised ethnicities within the PRACTICAL study are Māori, Pacific, Asian, New Zealand European and Other. Given the small number of participants within the Asian and Other ethnicity groups, Asian, New Zealand European and Other ethnicities were analysed together.

Categorical data are presented as the number and proportion expressed as a percentage and continuous data summaries including mean (SD) and median (IQR).

Analysis of the number of severe exacerbations per patient per year and combined rate of exacerbations and severe exacerbation per year was by Poisson regression with an offset for time of observation.

Differences in ACQ-5 and FEV1 were estimated by ANCOVA with the baseline measurement as a continuous co-variate. Spirometry was performed on treatment, ie, without withholding of usual inhaled therapy. Normality assumptions for FeNO were not well met on an untransformed scale but were met on a logarithm transformed scale. ANOVA was used on this scale and the exponent of the difference in logarithm FeNO is interpreted as the ratio of geometric means FeNO. In the models with ethnicity as a potential effect modifier interaction terms were used.

New Zealand deprivation score was calculated by geocoding the address of each participant to a meshblock, merging this geocoded dataset with the NZdep2013 file using meshblock number and linking each geocoded address with its area deprivation score. It is scaled to have mean 1,000 index points and standard deviation 100 index points.

The Māori subgroup analysis was pre-specified and is exploratory as we did not recruit sufficient Māori participants to detect a difference in the main outcome. We have not adjusted for multiplicity of analysis.

SAS version 9.4 was used for all analyses.

The trial was registered with the Australian and New Zealand Clinical Trials Registry ACTRN12616000377437.

**Results**

Eight hundred and ninety participants were enrolled between 4 May 2016 and 22 December 2017 of whom 72 (8%) were Māori, 36 (4%) were Pacific and 777 (88%) were New Zealand European/Other (Figure 1).

The intention to treat data set included 885 eligible participants and no follow-up data was available in five participants of New Zealand European/Other ethnicity.

At baseline, Māori and Pacific participants had higher (worse) average ACQ-5 scores than New Zealand European/Other participants (mean ACQ-5 1.5, 1.6 and 1.1 respectively) and lower FEV1 values (83% predicted, 84% predicted and 88% predicted respectively). Inhaled corticosteroids were used at baseline by 49 (68%) Māori participants, 21 (58%) Pacific people and 551 (71%) New Zealand European/Other participants.

Median (IQR) baseline FeNO was higher in Pacific participants than either Māori or New Zealand European/Other ethnicity; 45.5 ppB, (18–80.5); 26.5 (12.5–50); and 28 (17–56), respectively (Table 1).
Figure 1: Consort diagram.

Smoking status was that 19 (26%) Māori participants were current smokers compared to three (8%) Pacific participants and 41 (5%) New Zealand European/Other participants. Māori and Pacific participants lived in more deprived areas than New Zealand European/Other participants as demonstrated by higher mean New Zealand deprivation scores: 1,006.3, 1,021.7 and 961.3 respectively (Table 1).

The proportion of Māori and Pacific participants who reported living in cold, damp and musty smelling housing was higher than that reported by New Zealand European/Other participants. The proportion of participants reporting that their home smelt damp or musty was 38% for Māori participants, 42% for Pacific participants and 25% for New Zealand European/Other participants. The proportion of participants reporting that their house was so cold that they could see their breath in the previous winter was 42% for Māori participants, 44% for Pacific participants and 28% for New Zealand European/Other participants (Table 2).
Table 1: Characteristics of participants by ethnicity.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Māori (N=72)</th>
<th>Pacific (N=36)</th>
<th>NZ European/Other (N=777)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr</td>
<td>41.6 (14.8)</td>
<td>35.5 (13.4)</td>
<td>43.5 (16.1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>32.8 (8.6)</td>
<td>34.4 (8.1)</td>
<td>28.0 (5.9)</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>41 (56.9)</td>
<td>19 (52.8)</td>
<td>425 (54.7)</td>
</tr>
<tr>
<td>Smoking status – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>19 (26.4)</td>
<td>3 (8.3)</td>
<td>41 (5.3)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>25 (34.7)</td>
<td>14 (38.9)</td>
<td>196 (25.2)</td>
</tr>
<tr>
<td>Never smokers</td>
<td>28 (38.9)</td>
<td>19 (52.8)</td>
<td>540 (69.5)</td>
</tr>
<tr>
<td>Age at diagnosis – yr</td>
<td>16.4 (15.6)</td>
<td>14.9 (14.3)</td>
<td>19.6 (18.2)</td>
</tr>
<tr>
<td>Randomised to budesonide/formoterol as needed (%)</td>
<td>41 (56.9)</td>
<td>20 (55.6)</td>
<td>376 (48.4)</td>
</tr>
<tr>
<td>Patient reported adherence to inhaled corticosteroids in the four weeks before enrolment (percentage of prescribed dose)</td>
<td>49.8 (45.4, n=49)</td>
<td>56.5 (97.4, n=21)</td>
<td>57.3 (38.8, n=549)</td>
</tr>
<tr>
<td>Patient-reported inhaled glucocorticoid use ever – no. (%)</td>
<td>64 (88.9)</td>
<td>24 (66.7)</td>
<td>683 (87.9)</td>
</tr>
</tbody>
</table>

Patient-reported SABA use in the four weeks prior to enrolment

<table>
<thead>
<tr>
<th>No. of occasions per week</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>5.5 (6.4)</td>
<td>6.8 (6.8)</td>
<td>4.4 (6.9)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3 (1–7)</td>
<td>4.5 (2–11)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Range</td>
<td>0–28</td>
<td>0–21</td>
<td>0–84</td>
</tr>
<tr>
<td>No. of hospital admissions for asthma during lifetime – number per patient</td>
<td>0.8 (2.1)</td>
<td>0.8 (2.7)</td>
<td>0.6 (4)</td>
</tr>
<tr>
<td>One or more severe exacerbation in the previous 12 months - no. (%)</td>
<td>13 (18.1)</td>
<td>6 (16.7)</td>
<td>86 (11.1)</td>
</tr>
<tr>
<td>ACQ-5 score†</td>
<td>1.5 (1)</td>
<td>1.6 (0.9)</td>
<td>1.1 (0.8)</td>
</tr>
</tbody>
</table>

GINA symptom control – no. (%)

| Well controlled                          | 8 (11.1)     | 3 (8.3)        | 193 (24.8)               |
| Partly controlled                        | 4. (55.6)    | 11 (30.6)      | 384 (49.4)               |
| Uncontrolled                             | 24 (33.3)    | 22 (62.1)      | 200 (25.7)               |
| On-treatment FEV₁, % of predicted value‡ | 82.6 (14.2)  | 83.6 (19.7)    | 88.3 (16.3)              |
| Median FeNO (IQR) – ppb                  | 26.5 (12.5–50)| 45.5 (18–80.5)| 28 (17–56)               |
| Mean log FeNO (SD) – ppb                 | 3.3 (0.9)    | 3.7 (0.9)      | 3.4 (0.9)                |
| Blood eosinophil count – x10⁸ per liter  | 0.3 (0.2)    | 0.3 (0.2)      | 0.3 (0.2)                |
| NZ deprivation score‡                    | 1,006.3 (106.0)| 1,021.7 (104.5)| 961.3 (76.0)            |
| Highest level of education               | (n=60)       | (n=29)         | (n=705)                   |
| College                                  | 19 (31.7)    | 12 (41.4)      | 174 (24.7)               |
| High school                              | 12 (20)      | 4 (13.8)       | 111 (15.7)               |
| Middle/Intermediate School               | 2 (3.3)      | 4 (13.8)       | 15 (2.1)                 |
| Three or more years of College/University| 27 (45)      | 9 (31)         | 404 (57.3)               |
| Unknown                                  | 0 (0)        | 0 (0)          | 1 (0.1)                  |

Self-reported housing condition (%)

| Very poor                                | 1 (1.4)      | 0 (0)          | 8 (1.0)                  |
| Poor                                     | 3 (4.2)      | 3 (8.3)        | 23 (3.0)                 |
| Average                                  | 17 (23.6)    | 10 (27.8)      | 131 (16.9)               |
| Good                                     | 25 (34.7)    | 13 (36.1)      | 311 (40.0)               |
| Excellent                                | 26 (36.1)    | 10 (27.8)      | 304 (39.1)               |

*Values are means, bracketed values are ±SD unless otherwise stated. Patients in the budesonide maintenance group received budesonide (Pulmicort Turbuhaler, AstraZeneca), 200mcg, one inhalation twice daily, plus terbutaline (Bricanyl), 250mcg, two inhalations as needed for symptom relief. Patients in the budesonide–formoterol group received budesonide–formoterol (Symbicort Turbuhaler, AstraZeneca), 200mcg of budesonide and 6mcg of formoterol, one inhalation as needed for symptom relief. FeNO denotes fraction of exhaled nitric oxide, FEV₁, forced expiratory volume in one second, IQR interquartile range, ppb parts per billion, and SABA short-acting beta-2-agonist.

†The Asthma Control Questionnaire–5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week, each of which is scored on a 7-point scale that ranges from 0 (no impairment) to 6 (maximum impairment), in which a 0.5-unit change represents the minimal clinically important difference.

‡Patients received no specific instruction to withhold use of their bronchodilator before measurement of FEV₁.

$The NZ deprivation score is a measure of socioeconomic deprivation. It is scaled to have mean 1000 index points and standard deviation 100 index points.
Table 2: Housing questionnaire.

<table>
<thead>
<tr>
<th>Housing questions</th>
<th>Māori (n=72) (%)</th>
<th>Pacific (n=36) (%)</th>
<th>NZ European/Other (n=777) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you ever have the house colder than you would have liked during the last winter (June to September)?</td>
<td>42 (58.3)</td>
<td>30 (83.3)</td>
<td>480 (61.8)</td>
</tr>
<tr>
<td>Does your home smell damp or musty?</td>
<td>27 (37.5)</td>
<td>15 (41.7)</td>
<td>195 (25.1)</td>
</tr>
<tr>
<td>Are there damp walls in the living areas of your home, bedrooms, kitchen or lounge?</td>
<td>25 (34.7)</td>
<td>14 (38.9)</td>
<td>297 (38.2)</td>
</tr>
<tr>
<td>Was your house ever so cold that you could see your breath inside during the last winter (June to September)?</td>
<td>30 (41.7)</td>
<td>16 (44.4)</td>
<td>215 (27.7)</td>
</tr>
<tr>
<td>Was your house ever so cold that you shivered inside during the last winter (June to September)?</td>
<td>36 (50.0)</td>
<td>21 (58.3)</td>
<td>287 (36.9)</td>
</tr>
</tbody>
</table>

Budesonide-formoterol as needed versus budesonide maintenance and terbutaline as needed and ethnicity
Table 3 shows the interaction analyses with ethnicity. There was no evidence that ethnicity was an effect modifier for either severe exacerbations or total exacerbations; P=0.70 and 0.43 for the ethnicity-treatment interaction terms respectively. Although the estimates for the difference between treatments within each ethnic group were consistent with Pacific people having more benefit, this lack of a statistically significant interaction term means that the relative rate of severe exacerbations was the same, 0.69 (0.48–1.0), P=0.049, regardless of ethnicity. A similar pattern was seen for any exacerbations, namely that although the point estimates were consistent with more benefit for Māori and Pacific people the lack of a statistically significant interaction term means there was no evidence that the relative rate of exacerbation, 0.70 (0.51–0.95), P=0.024, was different in relation to ethnicity.

There was no evidence that ethnicity was an effect modifier for asthma control as measured by ACQ-5, forced expiratory volume in one second (FEV₁) or fractional exhaled nitric oxide (FeNO).

Discussion
This randomised controlled trial of as-needed budesonide-formoterol therapy in adults with mild and moderate asthma found no evidence that the regimen was more or less efficacious and safe in Māori and Pacific peoples compared to a New Zealand European/Other population. In other words, the as-needed budesonide-formoterol regimen achieved a clinically important reduction in risk of severe exacerbations compared with maintenance budesonide and terbutaline reliever therapy that did not differ by ethnicity. Similarly, there was no evidence that the treatment effect on ACQ or FEV₁ was higher in those randomised to as required Budesonide.
Table 3: Severe asthma exacerbations, asthma control, lung function and FeNO.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Māori</th>
<th>Pacific</th>
<th>NZ European/Other</th>
<th>Overall rate</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Budesonide-formoterol as required N=41</td>
<td>Budesonide maintenance and terbutaline reliever N=31</td>
<td>Budesonide-formoterol as required N=20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe exacerbation rate per participant per year</td>
<td>0.16 (0.20–2.00)</td>
<td>0.28 (0.03–2.71)</td>
<td>0.71 (0.48–1.06)</td>
<td>0.69 (0.48–1.0)</td>
<td>P=0.049</td>
</tr>
<tr>
<td>Relative rate of severe exacerbation (95% CI)</td>
<td>0.65 (0.20–2.00)</td>
<td>0.28 (0.03–2.71)</td>
<td>0.71 (0.48–1.06)</td>
<td>0.69 (0.48–1.0)</td>
<td>P=0.049</td>
</tr>
<tr>
<td>Moderate and severe exacerbation rate</td>
<td>0.43 (0.15–1.21)</td>
<td>0.28 (0.03–2.71)</td>
<td>0.75 (0.54–1.04)</td>
<td>0.70 (0.51–0.95)</td>
<td>P=0.024</td>
</tr>
<tr>
<td>Exacerbation rate per participant per year</td>
<td>0.16</td>
<td>0.37</td>
<td>0.06</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Relative rate of exacerbation (95% CI)</td>
<td>0.43 (0.15–1.21)</td>
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<td>0.70 (0.51–0.95)</td>
<td>P=0.024</td>
</tr>
<tr>
<td>ACQ-5</td>
<td>1.29 [1.06, n=41]</td>
<td>1.68 [0.80, n=31]</td>
<td>0.90 [0.26, n=20]</td>
<td>1.8 [1.0, n=16]</td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>1.09 [0.81, n=376]</td>
<td>1.11 [0.82, n=401]</td>
<td>0.75 [0.54–1.04]</td>
<td>0.70 (0.51–0.95)</td>
<td>P=0.024</td>
</tr>
<tr>
<td>Visit 6</td>
<td>1.01 [0.83, n=36]</td>
<td>1.14 [1.0, n=25]</td>
<td>0.71 [0.57, n=15]</td>
<td>0.67 [0.72, n=14]</td>
<td></td>
</tr>
<tr>
<td>FEV1 adjusted for baseline (95% CI)</td>
<td>0.03 [-0.35–0.41]</td>
<td>0.19 [-0.35–0.72]</td>
<td>0.06 [-0.04–0.17]</td>
<td>-0.01 [-0.05–0.03]</td>
<td>-0.001 [-0.04–0.04]</td>
</tr>
<tr>
<td>Difference in ACQ-5 adjusted for baseline (95% CI)</td>
<td>0.03 [-0.35–0.41]</td>
<td>0.19 [-0.35–0.72]</td>
<td>0.06 [-0.04–0.17]</td>
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<td>-0.001 [-0.04–0.04]</td>
</tr>
</tbody>
</table>
At randomisation, Māori and Pacific subgroups had worse asthma control and higher exacerbation rates despite similar rates of prescription of ICS and self-reported adherence to ICS therapy. This suggests that other factors such as environmental and socioeconomic factors related to housing status and deprivation may play a role in the worse asthma outcomes. Many studies have demonstrated that damp and cold homes have a deleterious effect on respiratory health. This study provides evidence of greater disparities in environmental risk factors, as a higher proportion of Māori and Pacific participants reported that they live in cold and damp housing as compared to New Zealand European/Other participants. There is an ongoing need for implementation of effective policies to reduce inequalities in this area.\textsuperscript{27,28} The higher rates of current smoking in Māori also reinforce the requirement for measures to reduce smoking to be particularly focused on Māori. The study was not designed to specifically explore the effect of deprivation, eg, by stratification by deprivation; however, an analysis (not reported here) found little evidence of an association between exacerbations and New Zealand Deprivation scores.

This analysis has a number of limitations. Assessment of housing conditions was by self-report, which is associated with the risk of responder bias. Analysis of whether treatment group had a differential effect depending on ethnicity was pre-specified, although the trial was not specifically designed to detect differences between Māori, Pacific and New Zealand European/Other ethnicities, and may therefore lack power to detect important differences by ethnicity. For completeness the individual difference within each level of ethnicity is shown, however if the interaction p value is not statistically significant there is no evidence that the treatment differences are different by ethnicity. The P value given for the Overall rate tests if there is a difference between treatments in models that just have the effect of treatment.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
 & Log FeNO & & & & \\
 & Visit 1 & Visit 6 & Difference in Log FeNO adjusted for baseline (95\% CI) & Ratio of geometric mean FENO (95\% CI) & \\
 & 3.29 (0.92, n=41) & 3.41 (0.66, n=34) & 0.27 (0.0–0.53) & 1.30 (1.0–1.70) & \\
 & 3.34 (0.95, n=31) & 3.12 (0.73, n=25) & -0.23 (-0.61–0.15) & 0.80 (0.54–1.17) & \\
 & 3.69 (0.89, n=20) & 3.64 (0.89, n=14) & 0.12 (0.05–0.20) & 1.13 (1.05–1.22) & \\
 & 3.73 (0.85, n=16) & 3.69 (0.83, n=14) & & 1.13 (1.05–1.21) & \\
 & 3.32 (0.81, n=376) & 3.27 (0.75, n=353) & & & \\
 & 3.46 (0.90, n=401) & 3.27 (0.73, n=366) & & & \\
\hline
\end{tabular}
\caption{Severe asthma exacerbations, asthma control, lung function and FeNO (continued).}
\end{table}

* Differences in ACQ-5, FEV\textsubscript{1}, and FeNO are given for budesonide/formoterol as needed minus budesonide maintenance and terbutaline reliever. The p interaction tests if the difference between budesonide/formoterol and budesonide maintenance and terbutaline reliever differs by ethnicity. For completeness the individual difference within each level of ethnicity is shown, however if the interaction p value is not statistically significant there is no evidence that the treatment differences are different by ethnicity. The P value given for the Overall rate tests if there is a difference between treatments in models that just have the effect of treatment.
with and without maintenance ICS/LABA therapy, regardless of ethnicity. As Māori and Pacific peoples have higher morbidity from asthma, the absolute benefit from a reduction in exacerbations is likely to be greater, even though the relative reduction in risk with this regimen is similar.

An important consideration is whether the efficacy of the budesonide-formoterol reliever therapy regimen observed in Māori and Pacific adults with asthma in this study may be internationally transferable and apply to other at-risk populations defined by ethnicity, including Aboriginal Australian and African American people with asthma. Many of the barriers to healthcare, inequity in treatment received, and socioeconomic determinants of health outcomes in asthma observed in Māori and Pacific peoples in this study are also present in other indigenous groups. As a result, it is likely that our findings are generalisable, although the demonstration of differences in response to LABA therapy in African Americans emphasises the importance of investigating the impact of ethnicity on outcome in clinical trials.30

In conclusion, this trial has demonstrated that the greater reduction in the risk of severe exacerbations achieved with as-needed budesonide-formoterol compared with maintenance budesonide plus as-needed terbutaline was similar in Māori and Pacific adults as with European/other ethnicities. Implementation of the pragmatic budesonide-formoterol reliever therapy regimen in Māori and Pacific peoples has major potential to improve asthma outcomes and reduce their disproportionate burden from asthma.
Competing interests:
Dr Baggott reports grants from Health Research Council of New Zealand during the conduct of the study; personal fees from Astra Zeneca, personal fees from Novartis, outside the submitted work. Dr Fingleton reports grants, personal fees and non-financial support from AstraZeneca, grants from Genentech, grants, personal fees and non-financial support from GlaxoSmithKline, personal fees and non-financial support from Boheringer Ingelheim, outside the submitted work. Dr Beasley reports grants from Health Research Council of New Zealand during the conduct of the study; grants and personal fees from Astra Zeneca, personal fees from Avillion, grants from Cephalon, grants from Chiesi, grants and personal fees from Genentech, grants from GlaxoSmithKline, personal fees from Theravance, grants, from Novartis, outside the submitted work; Dr Hancox reports grants from Health Research Council of New Zealand, during the conduct of the study; other from Astra Zeneca, other from Menarini, other from Boehringer Ingelheim, outside the submitted work. Dr Hardy reports grants from AstraZeneca, grants from Health Research Council of New Zealand, during the conduct of the study; other from Astra Zeneca, outside the submitted work. Mr Holliday and Dr Harwood report grants from Health Research Council New Zealand during the conduct of the study.

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URL:
REFERENCES:


A comparison of the clinical features and outcomes of Takotsubo syndrome across five metropolitan hospitals in New Zealand

Jen-Li Looi, Toby Verryt, Peter McLeod, Christina Chan, James Pemberton, Mark Webster, Andrew To, Mildred Lee, Andrew J Kerr

ABSTRACT

AIM: Takotsubo syndrome (TS) mimics acute coronary syndrome but has a distinct pathophysiology. This study aimed to compare and contrast the clinical presentation, management and outcomes of patients with TS in five large New Zealand hospitals.

METHODS: We identified 632 consecutive patients presenting to the five major tertiary hospitals in New Zealand (Middlemore Hospital, Auckland City Hospital, North Shore Hospital, Christchurch Hospital and Dunedin Hospital) between January 2006 and June 2018 and obtained clinical, laboratory, electrocardiography, echocardiography, coronary angiography and long-term follow-up data.

RESULTS: Six hundred and thirty-two consecutive patients with TS (606 women, mean age 65.0±11.1 years) were included. An associated stressor was identified in two-thirds of patients, and emotional triggers were more frequent than physical triggers (62.9% and 37.1%, respectively). Overall, 12.7% of patient had depression and 11.7% anxiety but this was more common in patients from Christchurch Hospital (20.4%) and 23.4%, respectively). The in-hospital mortality among the five hospitals ranges between 0 to 2.0%. The mean follow-up was 4.9±3.4 years (median 4.4 years). Fifty-four people died post-discharge, all but one from a non-cardiac cause. Forty patients had recurrent TS. Mortality post-discharge (p=0.63) and TS recurrence (p=0.38) did not differ significantly among the five hospitals.

CONCLUSION: In this large New Zealand TS cohort, the clinical characteristics and presentation were similar among the five hospitals. A subset of patients had a complicated in-hospital course, but late deaths were almost all from non-cardiac causes and recurrence was infrequent. Mortality post-discharge and recurrence was similar between the hospitals.

Takotsubo syndrome (TS) (also known as apical ballooning syndrome) is an acute heart failure condition characterised by acute but rapidly reversible left ventricular (LV) dysfunction with distinct wall motion abnormalities subtending more than one coronary artery territory. The prevalence of TS is 1.0–2.5% in patients presenting with an acute coronary syndrome (ACS), and 12% in women presenting with an apparent anterior ST-elevation myocardial infarction (STEMI). The condition tends to occur in postmenopausal women after a stressful event. The aetiology of TS remains unknown but is likely to be complex with evidence for a role of the brain-heart axis in its pathogenesis. Since the initial report by Japanese cardiologists 25 years ago, TS has been increasingly recognised internationally.
We have previously reported the clinical characteristics and outcomes of 100 patients with TS in the Auckland region.\textsuperscript{9} Christchurch has reported 21 cases of TS triggered by the February 2011 Christchurch earthquake.\textsuperscript{10} However, data on the characteristics between hospitals for homogeneity/heterogeneity in the presentation of TS patients and their outcomes in New Zealand are still lacking. Therefore, this study aims to describe the clinical features and outcomes of patients with TS in a large New Zealand cohort.

**Methods**

**Study population**

The study population was prospectively identified between January 2006 and June 2018 from the three major public hospitals in the Auckland region (Middlemore Hospital, Auckland City Hospital and North Shore Hospital) and Christchurch Hospital except Dunedin Hospital where the study population was retrospectively identified. Only patients who underwent angiography (either cardiac CT angiography or invasive coronary angiography) were included in the study.

TS was initially defined using the diagnostic criteria proposed by the Mayo Clinic group\textsuperscript{11} until 2018 when the International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)\textsuperscript{12} was being proposed.

Patients’ data including baseline characteristics, triggering factors (categorised as emotional or physical), cardiovascular risk factors, psychiatric illnesses, electrocardiography (ECG), echocardiography and angiography data were obtained at the time of the index admission.

**In-hospital outcomes**

We recorded in-hospital complications, including acute pulmonary oedema, cardiogenic shock, use of invasive or non-invasive ventilation or intra-aortic balloon pump insertion and death. A composite endpoint was defined which included at least one of the above complications.

Late follow-up data was obtained by reviewing the medical records of each patient.

**Post-discharge outcomes**

The primary outcome was post-discharge mortality in those patients discharged alive. Each death was classified as due to a cardiac or non-cardiac cause. We also report rehospitalisation for recurrence of TS, obtained by reviewing the medical records of each patient, or telephone interview with patients’ general practitioners. Recurrent TS was defined using the Mayo Clinic/InterTAK Diagnostic criteria, except that in most cases coronary angiography was not repeated.

The study was approved by the Health and Disability Ethics Committees as a clinical Audit (NTX/11/EXP/288).

**Statistical analysis**

Categorical data were summarised as frequency and percentage while continuous data were reported as mean and standard deviation (SD), or median and inter-quartile range (IQR). Comparison of categorical data between groups was performed by Chi-square test or Fisher exact test where appropriate. For continuous data, comparison between groups were performed by the non-parametric Kruskal-Wallis test due to data were not normally distributed.

Log-rank tests were used to compare the Kaplan-Meier estimates of event rates of all-cause mortality and TS recurrence for the whole cohort.

All P-values reported were two tailed and P-value <0.05 was considered significant.

Data were analysed using SAS statistical package, version 9.4 (SAS Institute, Cary, NC). Survival plots were created using RStudio version 1.1.442.

**Results**

**Total cohort**

**Patients characteristics (Table 1)**

Of the 632 consecutive patients with TS included in this study, 606 (95.9%) were women and the mean age at presentation was 65.0±11.1 years. More than 80% were European, 10% were Maori, 4% were Pacific Islanders and 3.5% were Asian. Almost half of the patients had hypertension. Only 8.5%
Table 1: Clinical characteristics of Takotsubo patients.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=632)</th>
<th>MMH (n=151)</th>
<th>ACH (n=130)</th>
<th>NSH (n=82)</th>
<th>Christchurch (n=201)</th>
<th>Dunedin (n=68)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>606 (95.9)</td>
<td>143 (94.7)</td>
<td>123 (94.6)</td>
<td>79 (96.3)</td>
<td>197 (98.0)</td>
<td>64 (94.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>65.0 (11.1)</td>
<td>61.4 (12.2)</td>
<td>65.6 (10.5)</td>
<td>66.1 (11.1)</td>
<td>66.5 (10.5)</td>
<td>66.5 (10.0)</td>
<td></td>
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<tr>
<td>Ethnicity</td>
<td></td>
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<tr>
<td>European</td>
<td>516 (81.6)</td>
<td>90 (59.6)</td>
<td>99 (76.2)</td>
<td>70 (85.4)</td>
<td>197 (98.0)</td>
<td>60 (88.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NZ Māori</td>
<td>63 (10.0)</td>
<td>35 (23.2)</td>
<td>14 (10.8)</td>
<td>7 (8.5)</td>
<td>2 (1.0)</td>
<td>5 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Pacific Islanders</td>
<td>25 (4.0)</td>
<td>15 (9.9)</td>
<td>6 (4.6)</td>
<td>3 (3.7)</td>
<td>1 (0.5)</td>
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</tr>
<tr>
<td>Asian</td>
<td>22 (3.5)</td>
<td>7 (4.6)</td>
<td>11 (8.5)</td>
<td>2 (2.4)</td>
<td>1 (0.5)</td>
<td>1 (1.5)</td>
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</tr>
<tr>
<td>Other</td>
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<td>4 (2.6)</td>
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<td>0 (0)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>292 (46.2)</td>
<td>72 (47.7)</td>
<td>58 (44.6)</td>
<td>27 (32.9)</td>
<td>90 (44.8)</td>
<td>45 (66.2)</td>
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<tr>
<td>Dyslipidaemia</td>
<td>220 (34.8)</td>
<td>49 (32.5)</td>
<td>36 (27.7)</td>
<td>19 (23.2)</td>
<td>79 (39.3)</td>
<td>37 (54.4)</td>
<td>&lt;.001</td>
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<tr>
<td>Diabetes mellitus</td>
<td>72 (11.4)</td>
<td>27 (17.9)</td>
<td>18 (13.8)</td>
<td>7 (8.5)</td>
<td>16 (8.0)</td>
<td>4 (5.9)</td>
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<td></td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>69 (10.9)</td>
<td>21 (13.9)</td>
<td>16 (12.3)</td>
<td>9 (11.0)</td>
<td>18 (9.0)</td>
<td>5 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Previous CVD</td>
<td>54 (8.5)</td>
<td>8 (5.3)</td>
<td>8 (6.2)</td>
<td>6 (7.3)</td>
<td>28 (13.9)</td>
<td>4 (5.9)</td>
<td>0.02</td>
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<tr>
<td>Depression</td>
<td>80 (12.7)</td>
<td>12 (7.9)</td>
<td>9 (6.9)</td>
<td>7 (8.5)</td>
<td>41 (20.4)</td>
<td>11 (16.2)</td>
<td>0.001</td>
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<tr>
<td>Psychosis</td>
<td>7 (1.1)</td>
<td>2 (1.3)</td>
<td>3 (2.3)</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td>1 (1.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>4 (0.6)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>1 (1.2)</td>
<td>2 (1.0)</td>
<td>0 (0)</td>
<td>0.77</td>
</tr>
<tr>
<td>Anxiety</td>
<td>74 (11.7)</td>
<td>6 (4.0)</td>
<td>8 (6.2)</td>
<td>8 (9.8)</td>
<td>47 (23.4)</td>
<td>5 (7.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ACH, Auckland City Hospital; MMH, Middlemore Hospital; NSH, Northshore Hospital; CVD, cardiovascular disease.

patients were known to have prior cardiovascular diseases.

12.7% and 11.7% of patients had a prior history of depression or anxiety, and 12.2% and 4.3% were taking antidepressants/antipsychotics or benzodiazepines on admission.

Clinical presentation (Table 2)

The predominant symptom on admission was chest pain (80.2%), followed by dyspnoea (19%). 6.3% patients presented with new atrial arrhythmia (atrial fibrillation, n=34) and 2.5% patients presented with ventricular arrhythmias (ventricular tachycardia, n=8). Seventy-three patients had radiological evidence of pulmonary oedema on admission. A stressful trigger (defined as an unusual emotional or physical stress occurring before symptom onset) was identified in 73.7% patients. Emotional triggers were more frequent than physical triggers (62.9% and 37.1%, respectively). In 26.3% of patients, TS occurred without any evident trigger.

One-third of patients had ST-segment elevation on their admission ECG. ST-depression occurred only in 3.3% of patients with TS. More than half of the patients with TS had a significant reduction in left ventricular (LV) systolic function either on transthoracic echocardiography or left ventriculogram during the acute phase: 17.4% had low-normal LV function, 27.5% had mild LV impairment, and 55.1% had moderate/severe LV systolic impairment. Apical TS was identified in 84.7% of patients, whereas the midventricular form was found in 7.7%, and basal and focal forms were diagnosed in 2.4% and 5.3%, respectively. Right ventricular involvement was seen in only 17.1% of patients with TS. All patients
## Table 2: Clinical presentation.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=632)</th>
<th>MMH (n=151)</th>
<th>ACH (n=130)</th>
<th>NSH (n=82)</th>
<th>Christchurch (n=201)</th>
<th>Dunedin (n=68)</th>
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<td>Dyspnoea</td>
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<td>Moderate/severe</td>
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<td>97 (64.2)</td>
<td>61 (46.9)</td>
<td>37 (45.1)</td>
<td>123 (61.2)</td>
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<td>Apical type</td>
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<td>109 (83.9)</td>
<td>73 (89.0)</td>
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<td>Mid ventricular type</td>
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<td>Basal/reverse type</td>
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<td>Focal type</td>
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<td>54 (26.9)</td>
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<td>No</td>
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<td>Length of stay (days)</td>
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<td>Median (IQR)</td>
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<td>Pulmonary oedema on admission</td>
<td>76 (12.0)</td>
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<td>Cardiogenic shock</td>
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<td>IABP insertion</td>
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<td>CPAP ventilation</td>
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<td>3 (1.5)</td>
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<tr>
<td>In-hospital death</td>
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<td>1 (0.8)</td>
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<td>2 (1.0)</td>
<td>0 (0)</td>
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<tr>
<td>In-hospital complications (at least one of the following: acute pulmonary oedema, cardiogenic shock, use of invasive or non-invasive ventilation or intra-aortic balloon pump insertion, or death)</td>
<td>92 (14.6)</td>
<td>24 (15.9)</td>
<td>22 (16.9)</td>
<td>12 (14.6)</td>
<td>28 (13.9)</td>
<td>6 (8.8)</td>
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</table>

Values are n (%) unless otherwise stated.
*P-value excluded missing category
ACH, Auckland City Hospital; MMH, Middlemore Hospital; NSH, Northshore Hospital; CVD, cardiovascular disease IABP, intra-aortic balloon pump; CPAP, continuous positive airway pressure.
underwent either invasive coronary angiography (n=603) or CT coronary angiography (n=29) during the acute admission: 55.5% of patients had normal coronary arteries.

On admission, 15.2% of the patients were taking beta-blockers, and 30.7% were taking either angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers. The rates of use of these two classes of drugs had increased at discharge (to 74.8% and 67.4%, respectively, Table 3).

Of the 626 patients discharged alive, 91.4% underwent follow-up transthoracic echocardiography. Three died before having a follow-up transthoracic echocardiography appointment. Eight percent of patients did not attend the follow-up echocardiography appointment. The median time of recovery imaging was 56 days (range 2–2,256 days, mean 105±198 days) from the day of index hospitalisation. Ninety-three percent of those who had echo (534/572) had full recovery of wall motion abnormalities and left ventricular function on echocardiography. One patient had worsening left ventricular function as a result of embolisation of ventricular thrombus into coronary artery. The remaining patients had persistent regional wall motion abnormalities and impaired left ventricular function but all had improved markedly compared to baseline studies.

### In-hospital outcomes (Table 2)

During the index hospitalisation, 12% of patients had radiological evidence of pulmonary oedema on admission. Thirty patients were intubated, of whom three required intra-aortic balloon pump (IABP) insertion. Eight patients required continuous positive pressure airway (CPAP) ventilation. Fifteen patients with TS (2.4%) were in cardiogenic shock during the index admission. Six patients (1.0%) died during the index admission. Ninety-two patients (14.6%) had at least one of the in-hospital

### Table 3: Medications on admission and on discharge.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=632)</th>
<th>MMH (n=151)</th>
<th>ACH (n=130)</th>
<th>NSH (n=82)</th>
<th>Christchurch (n=201)</th>
<th>Dunedin (n=68)</th>
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<td><strong>Admission medications</strong></td>
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<td>Aspirin</td>
<td>141 (22.3)</td>
<td>36 (23.8)</td>
<td>17 (13.1)</td>
<td>22 (26.8)</td>
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<td>Clopidogrel</td>
<td>10 (1.6)</td>
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<td>Warfarin</td>
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<td>NOAC</td>
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<td>Statins</td>
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<td>Beta-blockers</td>
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<td>Antidepressants/antipsychotics</td>
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<td>Benzodiazepines</td>
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</table>

ACH, Auckland City Hospital; MMH, Middlemore Hospital; NSH, Northshore Hospital; NOAC, non-vitamin K antagonist oral anticoagulants; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers.

† Discharge medication for those patients discharged alive from index admission.
complications (defined as acute pulmonary oedema, cardiogenic shock, use of invasive or non-invasive ventilation or intra-aortic balloon pump insertion, or death).

Post-discharge outcomes (Figure 1 and 2, Table 4)

Six hundred and twenty-six patients were discharged alive after the index hospitalisation. The mean follow-up time was 4.9±3.4 years (median 4.4 years). 8.6% of the patients (54/626) died after hospital discharge, only one from cardiac causes. One patient developed heart failure as a result of embolisation of ventricular thrombus into coronary artery.

6.4% (40/626) of patients, all women, experienced recurrent TS, none of which were fatal. In 26 of the 40 patients with TS recurrence, the subsequent events involved stress triggers (physical triggers, n=5; emotional triggers, n=21).

Figure 1: Kaplan-Meier curves showing post-discharge survival in Takotsubo patients.

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<th>Strata</th>
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<tr>
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<tr>
<td>A1</td>
<td>626</td>
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</table>

Figure 2: Recurrence of Takotsubo syndrome post-discharge.
triggers, n=21). These 26 patients had their first recurrence of TS 23 days to 3,323 days after the initial event.

Comparison between hospitals

Demographic (Table 1)
The majority of TS cases were females in all hospitals and there were only minor differences in the mean age of patients. The distribution of patients by ethnicity was representative of New Zealand population without predominance of a particular ethnic group.

Cardiovascular risk factors
There were some relatively minor differences in the risk factors between the hospitals. There were more diabetes and smokers in Middlemore and Auckland whereas dyslipidaemia and hypertension were more common in Dunedin.

Psychiatric disorders
12.7% and 11.7% of patients had a prior history of depression or anxiety but this was more common in Christchurch patients (20.4% and 23.4%, respectively). The high prevalence of psychiatric disorders in Christchurch was also reflected by the fact that a substantial number of patients were taking antidepressants/antipsychotics (n=29) and benzodiazepines (n=11) on admission.

Clinical presentation (Table 2)
Chest pain was the predominant symptom on admission in all hospitals. The rates of preceding stressor, ST-elevation on admission ECG, clinical heart failure and moderate/severe LV systolic impairment were similar. The distribution of the type of TS was also similar among the hospitals.

Compared with pre-admission, there was a similar increase in prescribing of aspirin, beta-blocker, ACE inhibitors and statins on discharge in all hospitals (Table 3).

In-hospital outcomes (Table 2)
The rates of in-hospital complications among the hospitals did not differ significantly (p=0.37). The in-hospital mortality rate for TS patients is comparable among the five hospitals (p=0.73).

Post-discharge outcomes (Table 4)
There were no differences in the mortality (p=0.63) and recurrence risks (p=0.38) in TS patients after discharged among the five hospitals.

Discussion
To our knowledge, this cohort is the largest series of TS patients published to date in Australasia and one of the largest internationally. Our series was similar to prior published series in terms of characteristics of the patient population. The distribution of patients by ethnicity was similar to that of New Zealand patient presenting with ACS without predominance of a particular ethnic group. There were no significant differences in the baseline demographics in TS patients among the five hospitals.

There was a high prevalence of depression and anxiety in our TS cohort. Of interest, the prevalence of depression and anxiety were higher in Christchurch. Following the major Christchurch and Kaikoura earthquakes, Christchurch Hospital has seen unprecedented case clusters of TS. Two extensive overviews of American TS cohorts found that anxiety and chronic stress were both associated with significantly higher odds of developing TS. Depression has also been reported to be associated with higher odds of developing TS. The increased prevalence of premorbid psychiatric diagnoses, particularly anxiety disorders and depression

Table 4: Post-discharge outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=632)</th>
<th>MMH (n=151)</th>
<th>ACH (n=130)</th>
<th>NSH (n=82)</th>
<th>Christchurch (n=201)</th>
<th>Dunedin (n=68)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total death</td>
<td>54 (8.6)</td>
<td>14 (9.5)</td>
<td>11 (8.5)</td>
<td>10 (12.2)</td>
<td>13 (6.5)</td>
<td>6 (8.8)</td>
<td>0.63</td>
</tr>
<tr>
<td>Death (non-cardiac)</td>
<td>53 (8.5)</td>
<td>13 (8.8)</td>
<td>11 (8.5)</td>
<td>10 (12.2)</td>
<td>13 (6.5)</td>
<td>6 (8.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>Death (cardiac)</td>
<td>1 (0.2)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.68</td>
</tr>
<tr>
<td>TS recurrence</td>
<td>40 (6.4)</td>
<td>12 (8.1)</td>
<td>8 (6.2)</td>
<td>7 (8.5)</td>
<td>12 (6.0)</td>
<td>1 (1.5)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

ACH, Auckland City Hospital; MMH, Middlemore Hospital; NSH, Northshore Hospital; TS, Takotsubo syndrome.
in TS patients suggests a potential link between neuropsychiatric disorders and TS. In particular, the Canterbury earthquakes had significant adverse impact on mental health, which could account for the high incidence observed.

A unique feature of TC is a preceding emotional or physical stressor, although in some cases, precipitant stressors have not been identified. Presentation was preceded by a physical or emotional stressor in two-thirds of our patients, but in the remaining third there was no identifiable pre-event stressor despite specific enquiry after the diagnosis was made. Emotional triggers were more frequent than physical triggers (62.9% and 37.1% respectively). Reassuringly, the rates of preceding stressor were similar among the five hospitals.

Patients with TS have an in-hospital mortality rate similar to that of patients with an MI. In addition, adverse events due to haemodynamic instability (eg, acute heart failure or cardiogenic shock) may occur in up to one-fourth of patients, even during the first hours after clinical onset. Almost 12% of our patients had pulmonary oedema at admission and there was a subset of patients who were critically ill at presentation requiring inotropic support, intubation and/or intra-aortic balloon pump. This finding was similar to the North American and European cohorts, illustrating the previously underestimated risk of complications during the acute phase of TS and highlights the need for concise clinical evaluation, monitoring and management. Despite the relatively high adverse events reported during the acute phase, the rates of in-hospital complications did not differ significant among the five hospitals.

Of the patients with TS discharged alive, 8.6% died during follow-up, with all but one of the 54 deaths from non-cardiac causes. This is consistent with other local and international studies which have reported that late mortality after TS is largely due to non-cardiac causes and appears to be related to the presence of comorbid disease rather than the TS event itself. Forty of our surviving patients experienced recurrent and remarkably similar TS episodes. There were no significant differences in the late mortality and recurrence rates for TS patients in our cohorts among the five hospitals, albeit with only small event rates. There was no clear consensus about the appropriate treatment of patients with TS. New Zealand guidelines recommend routine post-discharge use of dual antiplatelet therapy, either clopidogrel or ticagrelor, statins, ACE inhibitors or ARB and beta blockers in patients without contraindications or intolerance after ACS presentations, with the aim of reducing further events. Because TS patients are frequently started on the same therapy on the basis of suspected ACS, there was marked increase in prescribing aspirin, beta-blocker, ACE inhibitors and statins on discharge among the five hospitals. To our knowledge, there are no data to support the use of particular medication regimens in patients with TS.

Study limitations

Despite prospectively capturing all patients presenting with TS in four major hospitals in New Zealand over 12 years, it is possible that some TS cases in the participating hospitals were not diagnosed, were hospitalised in other specialty departments, did not undergo catheterisation, which would imply underestimation of the true number of TS cases that occurred over the study period. However, it is likely that such cohort will continue to form an important source for research on TS in the future. In addition, we were unable to provide results of cardiac biomarkers such as troponin because of the different assays used in the different centres.

Conclusion

This study represents the largest TS cohort published to date in Australasia and also one of the largest internationally. Our clinical findings support previously published series. A subset of patients had a complicated in-hospital course but the in-hospital mortality for patients diagnosed with TS was similar among the five major hospitals. The late mortality and recurrence rates for TS patients who survived the index event also did not differ significantly among the hospitals. TS is a relatively recently described condition, its aetiology is poorly understood and it is probably still underdiagnosed. This cohort reassures us that TS presentations are similar across New Zealand and comparable to international experience. Establishment of this cohort will allow further investigation of this novel condition.
Competing interests: Nil.

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Assisted dying and evidence-based law-making: a critical analysis of an article’s role in New Zealand’s referendum

Ben P White, Lindy Willmott, Jocelyn Downie, Andrew Geddis, Colin Gavaghan

ABSTRACT

AIM: To critically analyse the reliability of an article which claims to be evidence that the End of Life Choice Act 2019 provides a “potential hotspot for family, community and social discord that may not be easily remedied” should the legislation receive public support in New Zealand’s September 2020 referendum.

METHODS: The subject article was reviewed multiple times by all authors and critiqued against three criteria: a reliability pyramid developed to weigh evidence about assisted dying; principles that guide the conduct of social science research; and the use of reliable and current social science literature to support factual claims.

RESULTS: The study being analysed involved a single interview and so is located at the second bottom row of the reliability pyramid. Its research design is also unable to support the broad findings that are asserted. Other flaws in method included findings being extended beyond the data, and failure to state appropriate limitations in the research method. Further, claims are made that are unsupported by the weight of reliable social science literature.

CONCLUSION: The subject article is methodologically and factually flawed so is unreliable as evidence. It should not be considered in the assisted dying debates preceding the forthcoming referendum.

Assisted dying (AD) is a significant social policy issue, so reliable evidence to inform law-making is critical. Society expects health policy and health-care to be evidence-based. This expectation should extend to law-making.

In September 2020, New Zealanders will participate in a binding referendum to determine whether the End of Life Choice Act 2019 (EOLCA)—legislation permitting AD already passed by Parliament—will come into force. A recent article published in the New Zealand Medical Journal by Winnington and MacLeod (WM article) raised concerns about the potential impact of this law. Further, the WM article proposed that the “evidence from this study must be factored into the New Zealand debate before the referendum on the [EOLCA]” (p21).

This article responds to the suggestion that the WM article be evidence in this debate. Our goal is to undertake a critical analysis of the evidence it purports to contribute, to determine its reliability and therefore probative value. We conclude that a combination of the nature of the study, flaws in its research design, its use of data to draw conclusions, a failure to outline limitations and inadequate engagement with social science literature make the WM article unreliable. It should not be considered as evidence in deliberations about the EOLCA.
Methods
Criteria to assess reliability
We applied three criteria to assess reliability. The first is a pyramid of evidence developed by one of the authors (JD). This pyramid draws on existing models for assessing evidence and graphically depicts how reliability increases as it ascends the pyramid, but is adapted for the evidence most commonly used when making law about AD and the sort of external review that can occur (Figure 1). Reliability is assessed both by determining the level of the pyramid at which particular evidence sits, and by considering whether it has been externally tested and the nature of that testing—whether by peer review or review by courts, non-partisan parliamentary committees or expert panels.

The second criterion is the principles that guide the conduct of social science research. We are conscious of different approaches in quantitative and qualitative research but there is broad acceptance across different research traditions of the following principles: study design (including data collection and analysis) that is appropriate to research aims; rigorous use of selected research methods; and fair presentation of results including only conclusions sustained by data and acknowledging appropriate limitations.

The third criterion for reliability was whether factual claims made in the WM article were defensible in light of available social science literature. We inquired whether factual claims were based on literature that was reliable (informed by some of the above considerations), up to date and fairly represented the field’s state of knowledge.

Review process
Two authors (BW and LW) reviewed the WM article multiple times and compiled a list of possible failures to meet the reliability criteria. These were grouped according to issue type and written up. These critiques were reviewed by other authors with an invitation to add new areas, revise or remove existing ones. All authors endorse the critical analysis below.

Results
Summary of Winnington and MacLeod article
The stated aim of the WM article was to consider “the possibility of consequences ... for families left behind, communities and society as a whole” should New Zealand legalise AD (p18). To address this aim, a

![Figure 1: Adapted reliability pyramid of evidence for assisted dying.](image-url)
single semi-structured interview was undertaken with a person who had experience with AD in a country where AD is lawful. The interviewee’s perspective was from being married to a sibling of the person who chose AD. Thematic analysis of this interview identified three key themes: potential expectations that people would seek AD when unwell and possibly facing a life-threatening illness; stigma for individuals using AD and their families; and the potential for AD legislation to produce contagion (not defined in the article but we understand refers to the notion that AD may activate others to seek AD who would not otherwise do so) (p18).

The article calls for further research including “to investigate whether a contagion effect of AD is possible (or even probable)” (p22).

Criterion 1: reliability pyramid
As research based on a single case study, this study falls into the second bottom row of the pyramid (Figure 1). On this basis alone, the reliability of such evidence is limited. In addition, some conclusions or claims are not based on the data or go beyond what the data could support (see examples below), and would fall to the bottom row: anecdotes and opinion.

Although the nature of the study means it is of limited reliability, some external testing adds reliability; the article is published in the peer-reviewed New Zealand Medical Journal.

Criterion 2: reliability in terms of principles of social science research

Study design not appropriate for aims
The article’s aim was to consider “the possibility of consequences ... for families left behind, communities and society as a whole” should New Zealand legalise AD (p18). In terms of study design, a single interview is not capable of meeting this ambitious aim, even with the qualifier “possibility”. This is particularly so in relation to consequences for the wider communities and society as a whole. Such a method might shed light on family experiences, albeit in a very limited way with only one interview, but it cannot reliably inform about broader community perspectives.

Results extended beyond what data reasonably supports
The WM article’s analysis identified three key themes (abstract, p18):

- “the potential for assisted dying becoming an expectation for others to pursue when unwell and possibly facing a life-threatening illness;”
- “the notion of stigma being associated with the individual using assisted dying legislation and the family left behind;” and
- “that there may be the potential for such legislation to produce a contagion effect.”

We accept the interviewee discussed these three issues. But a threshold concern is whether all themes are supported by the data. It is possible that an interview with a member of an extended family with an experience of AD could, with relevant limitations articulated, produce findings about stigma within a family.

However, it is not justifiable to present the other themes as results from these data. Both relate to wider, societal-level trends rather than individual experience. The experience of one person could not, from a scientific perspective, be reliable evidence of wider community views or experiences. Determining the existence of these phenomena would require quite different research methods such as community surveys or, in the case of the contagion argument, quantitative studies about use of AD.

A second concern is how these results are extended and transformed into substantive potential problems for society. In other words, an issue is raised in the data and unjustifiably elevated to a level beyond which can be safely done from the data. We provide three examples.

Example 1: Fracturing society. The WM article expresses “concern that the legislation for AD in New Zealand has potential to fracture family and community structures” (p21). This statement is followed by the interviewee suggesting that “fractured families” make it more likely, without “support of their family”, to seek AD (p21). The first problem is that there is no evidence in the quote that the interviewee was basing his comment on experience within
his family (as opposed to speculation about what might happen). The second problem is that the authors’ claim—that AD legislation could fracture family and community structures—is different from the interviewee’s point, namely that those without family support (i.e., in already fractured families) may be more likely to seek AD. Yet, the segue is made from one to the other. The third problem is the shift from families (as stated by the interviewee), to the “potential to fracture family and community structures” (emphasis added) (p21), and then to the even broader claim of “potential of fracturing of our New Zealand communities and broader social settings” (emphasis added) (p21). This progression involves a significant shift from the data (a family perspective) to the wider community level.

Example 2: AD contagion. The article itself noted that the interviewee only “hinted” (p21) at this issue. This was based on the interviewee having known “three extended family members use the [AD] legislation over a short period of time” as well as AD being chosen by two of his father’s friends. However, nothing about contagion can be drawn from his quotes—there is no evidence that the three extended family members or two friends of his father who had AD knew each other or knew that each other had had AD. Furthermore, the interviewee worries that AD may be “infectious” (p21) but does not link this to the experience of his extended family member receiving AD (essential for the case study method). Even more concerning is that this discussion of contagion, which comprised only three paragraphs in the Results section, was transformed into a substantive concern. The shift during the article is noteworthy: from the interviewee hinting at the issue, to the conclusion calling for further research to investigate “whether a contagion effect of AD is possible”, and then “(or even probable)” (emphasis added) (p22).

Example 3: “Slippery slopes”. The WM article claims the data support slippery-slope arguments. Because of this claim’s significance, two key sentences are extracted in full here: “In conducting this study, it was anticipated that social consequences of AD legislation may be present in terms of the slippery-slope discourse. However, it was unexpected to obtain data that painted a distinct picture of how the slippery-slope effect was unfolding in a country where AD was legal” (p21, endnotes omitted). The interviewee noted a view that there may be an expectation on people to use AD, and we understand this to be the sense in which the term slippery slope is used. (We note, however, that this is not what the “slippery-slope effect” in the “slippery-slope discourse” generally means—even in the literature the authors reference for this claim).

Claims that a “distinct picture” (p21) of this occurring (an expectation that people use AD) are unsustainable. We note the many empirical studies which rebut the common slippery-slope claim that the vulnerable are more likely to seek AD. These studies include large meta-analyses or population-level studies (and so are at or towards the top of the reliability pyramid). They have been peer reviewed, and many have also been the subject of further external testing by courts, expert panels and non-partisan parliamentary committees. When this sort of research is placed beside the WM article, it is not reasonable to consider this single interview as reliable evidence of the “slippery-slope effect” (p21).

Appropriate statements of limitations of research

The WM article does not have a sufficiently robust statement of limitations. It acknowledges that it is based on a single interview, and that this interview was conducted in a country other than New Zealand (where AD is legal). However, the implications of this latter point are not identified, namely that findings from this single interview are not generalisable to other countries with different healthcare, social welfare, and legal systems and AD models. To illustrate, it is unclear if AD in the case study would have been available under the EOLCA, as no mention is made of an eligible terminal illness (indeed, the description at p19 makes it highly unlikely). The WM article also fails to note that a person’s pre-existing views about AD may affect their assessment of their experience. But perhaps the most significant limitation omitted was to make clear that views expressed in a single interview cannot support claims about wider societal effects.
such as community expectations to die and AD contagion. Indeed, instead of noting such limitations, these data from a single interview were explicitly used to ground such claims.

‘Generation’ of evidence through discussion of issues on which no data is reported

Finally, conclusions were drawn where there were no data to support such findings. While consideration of related issues may occur in an article, particularly in Background or Discussion sections, a study's results and conclusions must be grounded in data.

The WM article at times identifies a concern about AD raised in literature (often without mentioning conflicting literature: see below). It then discusses that issue as a concern of substance, but this occurs without supporting data from the interview. One example is the claim that AD will be shaped by financial drivers. The article notes a potential consequence of AD legislation that it “reduces our future existence to being considered only through the practical lens relating to the cost of care and reduces our life to having a dollar value” (p21). This is revisited in the Conclusion: “... this case study offers insight into some elements associated with slippage [reference to slippery slope in sentence preceding] in terms of family members being expected to die when their care becomes too difficult or expensive” (p22). This significant (and very controversial) issue was not present in the data reported so its inclusion in the article's Conclusion is not justifiable.

Criterion 3: Reliability evidenced by factual claims being defensible in light of literature

Authors must ensure that factual claims are defensible having regard to the weight of reliable literature and the field's current state of knowledge. Some claims in the WM article cannot be defended in this way. We are not able to comprehensively catalogue all such concerns here. However, we provide one example of a claim that is not defensible and is also presented in a misleading way. The relevant passage appears in Background: “Despite the potential for those using AD legislation to be judged or stigmatised, there is further concern that AD may produce a contagion effect.” Jones and Paton observed that unlike some studies that perceived AD as providing a suicide-inhibiting effect, their results suggested that any inhibitory mechanisms were counteracted by ‘equal or larger opposite effects’ (p19, WM endnotes in Figure 2).

A preliminary point is why, when the article claims to focus on AD contagion (ie, cases of AD leading to more AD cases), it shifts to engage with literature on the different issue of suicide contagion (ie, legalising AD leading to an increased suicide rate). Further, its suggestion that suicide contagion is a credible concern (later leveraged in potential concerns about AD contagion) is not supported by the literature, nor does the article engage with the current state of knowledge.

For instance, there is a later article by Lowe and Downie which critically analyses the primary source relied upon for suicide contagion (Jones and Paton), but this was not considered or even acknowledged in the WM article. Lowe and Downie identify significant errors in the Jones and Paton methodology and concerns about how the results were presented, and urge caution in relation to its findings. While not all literature can be cited, it is concerning that an article which has been the subject of a detailed critical analysis is presented without qualification. Also missing was the report from a major review of the state of evidence in relation to various aspects of AD undertaken by the Council of Canadian Academies (comprised of experts both in favour of AD and opposed). It concluded, including after considering the two papers above: “There is no evidence of any association between the legal status of assisted dying in a country and its suicide rate”. In short, there is no reliable evidence that suicide contagion will occur if AD is legalised.

A further concern is that the WM article references (Figure 2) are misleading, creating the perception that six references support the suicide contagion proposition in some way. In fact, only one study purports to consider suicide contagion (Jones and Paton: reference 16, although
as noted above, Lowe and Downie argue it does not address this concept and should not be relied upon\(^{17}\)). References 13 and 14 address potential stigma of AD (presumably a reference for the first half of the sentence), while reference 17 is Posner's book, which includes a claim that AD may reduce rates of suicide (contrary to suicide contagion). Reference 18 appears to be to Hansard (not a study but rather a statement in parliament) although incomplete citation details mean we cannot locate what the parliamentarian said. Reference 15 refers to suicide contagion (incorrectly according to Lowe and Downie\(^{17}\)) but is not an independent study, rather just a commentary on the Jones and Paton article.

There are other concerns about engagement with literature that could be raised. One is using literature which draws on anecdotal evidence (at the bottom of the reliability pyramid): both the Kheriaty (reference 15) and Hendin and Foley (reference 27) articles are relied upon by the WM article but they are in turn merely reporting on single cases they read about in newspaper reports. Another is not engaging with the large body of social science literature (and findings of expert panels, non-partisan parliamentary committees and courts) about “slippery slopes” (discussed above), and also being unclear about what is meant by this concept. However, as mentioned, there is not scope to include these more detailed analyses here.

**Discussion**

The New Zealand public will shortly decide whether AD should become lawful. Evidence-based law-making, including through a referendum, is critical, especially for significant social policy reform such as AD. This requires critical review of evidence proffered to inform public debates and public decision-making about AD.

The WM article proposed it be considered as evidence in the deliberations about AD in New Zealand. Our analysis has concluded, however, that the article is not reliable evidence and should not form part of these deliberations. It is based on a single interview with a person (the brother-in-law of a person who accessed AD) from an unidentified country where AD is legal (not New Zealand). This methodology is not capable of supporting the article's significant claims, in particular about potential expectations that people when unwell and facing a life-threatening illness should use AD and the potential of AD contagion. In addition, the WM article presents assertions beyond what its very limited data can sustain and

**Figure 2:** Selected references as cited by Winnington and MacLeod article.

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<th>Reference</th>
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indeed, makes claims for which there is no data in support. Further, the study fails to appropriately limit the scope of its findings; indeed, it makes claims beyond what is justified. Finally, its reliability can also be questioned as not all of its factual claims can be supported by the social science literature.

We conclude by repeating our call for evidence-making law-making on the critical social policy issue of AD.1


Competing interests:
This research did not receive any specific funding. Ben White and Lindy Willmott were engaged by the Victorian Government (Australia) to design and provide the legislatively mandated training for doctors involved in assisted dying. Both have also developed a model Bill for assisted dying for parliaments to consider. Ben White is a recipient of an Australian Research Council Future Fellowship (project number FT190100410: Enhancing End-of-Life Decision-Making: Optimal Regulation of Voluntary Assisted Dying) funded by the Australian Government. Lindy Willmott is a member of the board of Palliative Care Australia, but states this article only represents her views. Jocelyn Downie was a member of the pro bono legal team in Carter v Canada, the Royal Society of Canada Expert Panel on End-of-Life Decision Making, the Provincial-Territorial Expert Advisory Group on Physician-Assisted Dying, and the Council of Canadian Academies Expert Panel on Medical Assistance in Dying. Andrew Geddis is a member of ‘Lawyers for End of Life Choice’ and ‘Yes for Compassion’. Colin Gavaghan is a member of ‘Lawyers for End of Life Choice’ and a board member of ‘Yes for Compassion’. He was an expert witness for the plaintiff in Seales v Attorney General.

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The transition to a “virtual practice” in primary care during the COVID-19 pandemic: experience from one medical centre in New Zealand

Ibrahim S Al-Busaidi, Miriam Martin

ABSTRACT
Coronavirus disease 2019 (COVID-19) has rapidly spread across the globe, driving radical transformation in the way patient care is delivered in primary and secondary care. As part of the response against COVID-19 across primary care in New Zealand, practices and medical centres have largely transitioned to telehealth over a short period of time while maintaining the traditional business model of in-person care on an as-required basis. To inform other primary care services and future practice, we describe our experience at one general practice and the challenges faced in the process of converting to telehealth in the midst of the COVID-19 pandemic.
largely “switched” to telehealth over a short period of time while maintaining the traditional business model of in-person care on an as-required basis. To inform other practices and a likely second wave of COVID-19, we describe our experience in the process of converting to telehealth at one urban medical centre, the challenges faced, and our plans for the weeks and months to come.

Our practice is run by eight general practitioners (GPs) and four practice nurses serving a population of 5,000 patients (54% female; 14% ≥ 65 years; 69% European, 11% Māori and 6% Pacific Peoples; 34% New Zealand deprivation quintiles 4 and 5).

Before COVID-19
Before the COVID-19 pandemic, we relied heavily on the traditional model of in-person consultations, and telehealth played a minor role in patient care. All of our GPs actively utilise ManageMyHealth™ patient portal (an online tool that allows direct patient-to-doctor communication via messaging, online booking, access to investigations and repeat prescription requests). However, its uptake is low in our patient population. Only two GPs in our practice utilised phone consultations before COVID-19 but did so on only a few occasions throughout the year and mainly for medication adjustment and mental health follow-up reviews. None of us had used video consultations nor were we planning or in the process of integrating telehealth/virtual consultations into routine patient care.

Early preparation
For us February 2020 was a month of anticipation. As for the rest of world, we were increasingly familiar with reports of the novel coronavirus, later typed SARS-CoV-2, spreading outside of its epicentre to other countries including Iran and Europe. Early in February, we held weekly meetings to update ourselves with the ever-growing knowledge of COVID-19; its epidemiology, symptomatology, management and outcomes. As we learned more about its basic reproduction number, R0 (an indicator of the transmissibility of the virus), the mild clinical course in children, and the high mortality rate among older adults, immunosuppressed, and those with comorbidities, it became increasingly important for us to understand what this would mean for our staff and patient population.

We deliberated on how we would respond to COVID-19 if it arrived on our shores. As February progressed, our meetings became more frequent (from two to three meetings a week to our daily 08:30am ‘huddle’) and we shifted our focus into exploring new approaches and implementing policies aimed at protecting staff and vulnerable patients including new organisational models of care provision. In addition to the regularly updated Ministry of Health information for primary care services, we received regular guidance and support from our primary health organisation and district health board, and exchanged ideas with other local medical centres on how to best deal with the growing COVID-19 crisis including the transition to telehealth.

The transition to telehealth
It is important to note that the process of transitioning to telehealth was gradual for our practice. We adopted a policy that guarantees provision of care utilising several methods (in-person and remote consultations via email, texting, telephone and videoconferencing) and regulated access to our practice building for in-person visits. Our goal was to protect staff and vulnerable patients by minimising the number of patients in our practice building. Measures undertaken early-mid March 2020 to achieve this goal included:

- Reduce working hours
- Reduce the number of healthcare professionals on-site
- Suspend acute services
- Suspend the ManageMyHealth™ online booking function to allow for phone triage prior to being seen (patients were still able to request repeat prescriptions and communicate with their GPs)
- Firstly triaging all ‘acute’ consultations over the phone
- Establishing “infectious phone calls and clinic” work streams
- Introduce virtual/remote consultations as appropriate
- Placing signs by our medical centre entrance (Figure 1) and notifications on our website and social media accounts to inform patients of our new policies related to COVID-19
On 9 March 2020, we made the decision to integrate telehealth into our daily practice. We also identified a list of presentations that can be safely managed remotely using email, telephone or videoconferencing. These included repeat prescriptions, follow-up visits for stable chronic conditions including hypertension, asthma, chronic obstructive pulmonary disease, heart failure, depression and diabetes, and acute simple presentations including uncomplicated urinary tract infection and osteoarthritis flares. Later in mid-March, work capacity medical certificates and ACC continuation of work certificates were permitted to be issued following a remote consultation. We started by reviewing already booked appointments for the week and called some patients informing them of our plan to transition to virtual consultations. Many times, the triage phone call was sufficient and resolved patients’ requests. Some appointments were deferred/cancelled and others were scheduled as in-person or virtual consultations. Telephone was the main modality to conduct virtual consultations. The fact that some of our GPs were themselves in home self-isolation (quarantine) facilitated the early uptake of virtual consultations.

We developed policies and protocols for our front desk staff on (1) how to screen appointment requests for COVID-19 (ie, fever, cough, sore throat, flu-like symptoms, recent overseas travel, contact with confirmed or probable COVID-19 case—see Appendix), (2) which requests can be booked directly into the GP (eg, mental health review for adults and work capacity certification) or nurse (eg, six-week immunisation, flu vaccination) appointment template, (3) which should be deferred for several months (eg, annual general check-ups), and (4) which should be triaged by a clinician first (ie, almost all other requests). We allocated a daily slot of 30–60 minutes at the beginning of the morning session for GPs to phone-triage presentations/requests. Some patients were asked to come in for an examination provided that they had no COVID-19-related symptoms or contact with confirmed/probable cases (eg, fall at home with a swollen painful knee and partial weight-bearing). Blood tests were only ordered if absolutely necessary. Our newly developed polices and protocols and their level of implementation have evolved over time.

We also implemented a policy that laboratory/imaging request forms, prescrip-
tions, medical off-work certificates and other forms were not to be collected directly from our reception. All prescriptions were faxed to an onsite pharmacy or to a pharmacy nominated by the patient for pick-up. Blood request forms and medical certificates were emailed directly to patients or their relatives with their consent. Emailing of forms was facilitated by the email functionality on the Medtech Evolution practice management system9 or using practice email address. Invoices were either emailed or text messaged to patients on the same day of consultation.

By the week of Monday 9 March 2020, we established a daily morning session ‘infectious phone call list’ where patients with flu-like symptoms, coryza, sore throat and other established symptoms of COVID-19 were phone-triaged. Patients who required further assessment were invited in for a video or ‘drive through consultation’. Patients were asked to park in our ambulance area and remain in their car for an in-person assessment conducted by a team of one GP and two nurses in full personal protective equipment. Provided sufficient nasopharyngeal swabs in our stock, patients who met the current criteria for COVID-19 testing were swabbed and advised to self-isolate as per Ministry of Health advice. If no swabs were available on the day, we referred patients to our local community-based assessment centres (CBACs) for testing.

“Go hard, go early”

Driven primarily by information received from Italy10 pertaining to the significant contribution of practice waiting rooms in the spread of COVID-19, the Royal New Zealand College of General Practitioners circulated an email on 21 March 2020 titled “Call to action: Go Hard, Go Early” urging all of its members to immediately switch to virtual consultations (eg, phone, email or video consultations) with the goal of reducing in-person visits by 70% starting on 23 March (less than 48 hours later). This was followed by a webinar hosted by the College on the following day detailing and explaining these recommendations.11 This is also the day New Zealand went into Level 3 before transitioning into Level 4 (lockdown) 48 hours later.

Figure 2: In-person and virtual consultations at one medical practice.
Switching to telehealth

We made the decision to switch to predominantly remote consultations following the College’s recommendation. By this time around 15–55% of our daily consults were virtual, all of which were conducted by telephone (Figure 2). We thought it would be relatively easier for us to make the “switch” given that we had already (but not uniformly) integrated telehealth into our routine patient care. Despite this, 23 March 2020 was a day to be remembered. It was the day when general practice was forced to make a giant leap toward telehealth.

We rushed to ring patients who had already been booked in for in-person consultations on that Monday and the rest of the week and advised them of the switch. As the day progressed, we began to find it difficult to reach patients using landlines or even our personal mobile phones due to significant countrywide congestion. We resorted to other communication modalities including text messaging using Medtech. Our already established protocols and policies were immediately and strictly reinforced. We managed to reduce in-person consultations significantly on the first week of the lockdown (in-person consults constituted 22% of total consults on the Monday and remained <20% for the rest of the week).

We had already invested in telehealth by acquiring webcams and headsets early in the process, which allowed the use of other communication platforms/applications such as Zoom and doxy.me. Telephone was the mainstay modality in our practice, constituting 99% of telehealth consultations over the first three weeks of lockdown (355 phone, 124 in-person, and 5 video consults). Photos were used as adjunct to virtual consultations in specific complaints (eg, skin lesions, wounds and rashes) and all were uploaded to the patient’s portal.

The total number of appointments dropped significantly by 40–60% compared to pre-COVID-19. Reasons for this were several and include the regulated access to the practice building under Levels 3 and 4, significantly reduced staff on-site, patients’ perceptions that practices were overwhelmed by COVID-19 related work, and fears of becoming infected with the COVID-19 virus. This resulted in significant reductions in total revenue by approximately 55%. Our consultation billing scheme also contributed to the downfall in revenue; we billed phone/video consultations that were followed by in-person examination only once and reduced the charge significantly for phone consultations lasting less than five minutes.

Summary of our experience

With the lifting of social and public health measures across the globe, resurgence and future second waves of COVID-19 are possible. Newly established organisational models of patient care that integrate telehealth need to be sustainable in the medium to long term. Our goals for the weeks and months to come are to strengthen our telehealth infrastructure, fine-tune our virtual triage and consultation systems, and increase patients’ uptake of online portals such as ManageMyHealth™.

Although we have not systematically examined patients’ views and acceptability of telehealth as a modality of care during the COVID-19 pandemic, informal feedback and our experience suggest that most patients embraced telehealth especially those with access barriers related to proximity, transport, cost and child care. We are hopeful that the increased uptake by GPs and patients may result in reduced health inequities through improving access to care.

Some patients, particularly older adults, expressed resistance to telehealth in general for several reasons including their preference of in-person visits, resistance to technology and perceived low value for cost. Additionally, most patients found video consultations problematic primarily due to technical issues. Zoom videoconferencing, however, was the platform of choice for our GP semi-daily virtual meeting as it facilitated physical distancing.

On reflection, the early preparation for the pandemic before it arrived on our shores allowed us to plan, introduce and modify protocols and policies related to COVID-19. The relatively gradual introduction of telehealth before the College call for immediate “virtualisation” in late March provided us and our patients with additional time to familiarise ourselves with these new modalities (ie, e-mail, phone and videoconferencing). Technical barriers,
however, resulted in a low uptake of video consultations in our practice. In addition, triage/infectious phone calls and the daily infectious clinic were very helpful measures in reducing in-person visits. To address deficiencies and mitigate challenges faced by patients and GPs during this pandemic, we are currently developing protocols and policies to guide our response in the event of future similar challenges (eg, pandemics/national disasters) including compulsory telehealth training.

To facilitate virtual triage and management of common presentations/conditions in general practice, we will ensure that/encourage our patients (especially those with high-risk chronic medical conditions) to obtain home monitoring medical devices such as blood pressure monitors, oxygen saturation monitors, temperature probes, peak flow meters and glucometers. Although the role of, and outcomes associated with home-based monitoring in the management of chronic conditions such as hypertension, heart failure and chronic obstructive pulmonary disease have been studied, research is needed to examine the cost-effectiveness of the use of home monitoring devices among the general primary care patient population.

The suitability of presentations for virtual consultations may be contingent on several factors including acuity (ie, acute mental health distress with suicidal ideation versus follow-up review for chronic treated depression), severity of presentations (eg, mild versus moderate/severe asthma exacerbation), the necessity for a physical examination (eg, a 75-year man with weeks history of abdominal pain, altered bowel habit and weight loss). Likewise, several patient-related factors may influence doctors’ ability to conduct virtual consultations (eg, access to phone/internet connection).

**Conclusion**

Telehealth has enabled many of us to continue providing care to our patients while maintaining the necessary public health measures adopted in the fight against COVID-19. However, the rapid transformation in the way patient care is delivered has created increased uncertainty over the future of general practice. Is this “switch” to telehealth going to be sustainable in the long-term? What will be the level and degree of telehealth adoption beyond COVID-19? What is the role of the New Zealand Medical Council, the Royal New Zealand College of General Practitioners and primary health organisations in providing further support and guidance on the appropriateness of telehealth in various presentations and clinical circumstances? How is the situation created by COVID-19 going to affect practices and medical centres in the medium to long term? Many questions remain to be answered.
Appendix

Flow for phone calls into booked appointments

Reception triages phone call:

*Use triage phone script to screen for infectious symptoms (1 & 2)*

1. Have you recently (in the last two weeks) travelled overseas or been in close contact with a confirmed or probable COVID-19 case?
2. Have you got cold-like/respiratory symptoms? Fever, cough, runny nose, sore throat, diarrhea or vomiting, earache

**If YES to 1 or 2 above:**

What they want to see a doctor for?

1. Self-isolation questions/advice → ring Healthline 0800 358 5453
2. Medical certificate for self-isolation → nurse telephone consultation
3. Viral illness/fever/respiratory symptoms/diarrhoea or vomiting and want a medical appointment → put onto the acute doctor/infectious phone call list for a phone call and annotate next to their name. It would be helpful if they can get a temperature and pulse rate at home.

**If NO to both:**

1. Other acute symptoms (eg, urinary symptoms, chest pain, etc) → acute nurse template screen
2. All other patients → put onto the doctor's triage phone template* for an initial phone call. The doctor will decide if patient needs to come in for examination. If non-urgent complaint, put onto phone triage list for another suitable day.

*A two-minute phone call from the doctor or nurse to decide what kind of appointment the patient needs.

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**Competing interests:**

Dr Miriam Martin is the owner and medical director of Village Health.

Dr Ibrahim S Al-Busaidi reports no conflicts of interest.

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Smoke-free cars legislation: it works but New Zealand should still rigorously evaluate its upcoming law

Nick Wilson, George Thomson, Richard Edwards

ABSTRACT

In this viewpoint we briefly review the evidence for smoke-free car legislation. We find that this legislation has been consistently associated with reduced secondhand exposure in cars with children/youth in all nine jurisdictions studied. Despite this, there are various aspects of this intervention that warrant further study—especially determining its impact on reducing tobacco-related ethnic inequalities. So we argue that the New Zealand Ministry of Health should invest in a thorough evaluation of this important upcoming public health intervention. This could both help the country in further refining the design of the law (if necessary) and would also be a valuable contribution to advancing the knowledge base for international tobacco control.

A systematic review has reported that smoking in cars leads to extremely high exposure to secondhand smoke (SHS), “even in the presence of air-conditioning or increased airflow from open windows”. Many jurisdictions have responded to this hazard by legislating against smoking in cars (particularly in Canada, Australia and the US). However, the latest Cochrane systematic review on the impact of smoke-free legislation does not specifically consider the impact of such laws on youth exposure to SHS in cars. We therefore aimed to examine the relevant literature to determine the impact of such legislation and to help policymakers decide if further evaluation is worthwhile around the planned smoke-free cars legislation for New Zealand.

Methods for the literature review

Searches of the peer-reviewed literature were conducted using PubMed and Google Scholar on 9 February 2020 using a range of search terms (eg, smoke AND cars/vehicles AND ban/law). In these searches we aimed to identify studies where the impact of a smoke-free car law was estimated from survey data on smoking in cars containing children/youth. The bibliographies of these identified studies were also searched for additional relevant studies.

Results of the literature review

From publications identified by the searches (n=136 in PubMed; the first n=100 items in Google Scholar), we identified five relevant peer-reviewed studies. These studies covered nine different jurisdictions with smoke-free car laws (England, California and seven Canadian provinces) (Table 1). In all these jurisdictions there was evidence of declines in youth exposure to SHS after implementing the law, and in jurisdictions where it was assessed these declines persisted in all the subsequent survey waves.
Table 1: Studies identified in the peer-reviewed journal literature on the impact of smoke-free cars legislation on smoking in cars containing children/youth.

<table>
<thead>
<tr>
<th>Setting (publication year)</th>
<th>Summary of impact</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian provinces (2013)</td>
<td>Reduction in youth SHS exposure (using two different analytical methods) of 26% and 39% for one dataset; and 10% and 12% for another dataset.</td>
<td>This study used a quasi-experimental design (before and after law implementation and with control provinces). It used two different analytical methods and also two different survey datasets—though both with self-reporting. There were up to seven provinces in the intervention group depending on the analytical method.</td>
</tr>
<tr>
<td>Canadian provinces (2015)</td>
<td>Lower odds of exposure to SHS in children (aged 11–14 years) of between 0.45 and 0.98 (first wave post-implementation) and between 0.51 to 0.91 in subsequent survey waves</td>
<td>This study of smoke-free car laws in seven Canadian provinces used repeated cross-sectional surveys (involving self-reporting) with a quasi-experimental design. The results for exposure to SHS in cars for the first survey wave post-law (compared to the control provinces) were: Ontario with odds ratio [OR] = 0.45; Newfoundland (OR = 0.53); Nova Scotia (0.59); Saskatchewan (0.68); Prince Edward Island (0.73); British Colombia (0.96); and Manitoba (0.98). There were also lower odds in all subsequent survey waves (n=8 results).</td>
</tr>
<tr>
<td>California (2018)</td>
<td>Large post-implementation reductions in SHS exposure (12% annually) in middle and high school students</td>
<td>This study involved a before and after design with comparison with the rest of the US (of which only 5% of the population was covered by such smoke-free car laws). It reported that the proportion of Californian students self-reporting exposure to smoking in cars in the last seven days declined &lt;1% annually from 2001 through 2005, but declined 12% annually from 2007 to 2011 (ie, after the law in 2007). There was a 37% reduction in the odds of exposure to smoking in cars in 2011 compared with 2001 (OR = 0.63; 95%CI: 0.57–0.70). The national trends (for the US) did not show comparable declines after 2006.</td>
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<tr>
<td>England (2019)</td>
<td>A 23% reduction in SHS exposure for children aged 8–15 years</td>
<td>This study involved interrupted time series logistic or ordinal regression analyses using national survey data, albeit also relying on self-reporting. Compared to pre-legislation, the odds ratio of self-reported exposure to smoking in cars post legislation was 0.77 (95%CI: 0.51–1.17; p=0.222). Exposure in the pre-legislation period (2011-14) was 9.4–12.8%, and post-legislation (2016–17) was 5.0–5.8%. Of note is that we consider that this study (along with the second Canadian one above), seemed to pay excessive attention to arbitrary indicators of statistical significance—as opposed to commenting on the overall pattern of the results and how they compare to previous studies. That is we agree with the arguments in Amrhein et al which explain the problem of dismissing results as “non-significant” despite them being similar to the findings in other studies.</td>
</tr>
<tr>
<td>England (2020)</td>
<td>A 72% relative reduction or a -4.1% absolute reduction in SHS exposure in children aged 13–15 years</td>
<td>This study used logistic regression within a difference-in-differences framework with survey data for three different years for the two jurisdictions of England and Scotland. It found that “among children aged 13–15 years, self-reported levels of regular exposure to smoke in cars for Scotland were 3.4% in 2012, 2.2% in 2014 and 1.3% in 2016 and for England 6.3%, 5.9% and 1.6%.” The ban in England was associated with a -4.1% (95%CI: -4.9% to -3.3%) absolute reduction (72% relative reduction) in exposure to tobacco smoke among children.</td>
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</table>
Putting the evidence in context

The findings of this review indicate that smoke-free car legislation was consistently associated with reduced SHS exposure in cars with children/youth in all nine jurisdictions studied. This finding is consistent with other types of evidence, eg, a study in Quebec where smoking in cars with children was lower among smokers who mistakenly believed Quebec had such a law.9 Similarly, it is consistent with spill-over benefits of reduced smoking/SHS exposure in cars from other smoke-free legislation for public places (eg, in England,10 in the three other UK jurisdictions,11 Canada12 and the US for adopting smoke-free car rules13). It is also consistent with international evidence from a Cochrane systematic review on smoke-free legislation being effective in many other settings,7 and with what is known about the effectiveness of public health laws in general from a major systematic review.14

What evaluation of the upcoming law should New Zealand do?

From a health protection perspective, there appears to be enough real-world evidence for policy-makers to introduce smoke-free car legislation. However, there are still major knowledge gaps. For example, there is a need to evaluate the equity impacts of such laws (eg, the relative size of Māori vs non-Māori benefits in the New Zealand context) and to evaluate the impact of any laws that prohibit vaping in cars. It also seems desirable to determine the value of co-interventions to enhance the law, such as mass media campaigns around the SHS hazard. Finally, evaluation of the impact by level of enforcement, would also provide useful information, as has been argued by others.15

New Zealand, with its upcoming law to prohibit smoking in cars with youth (<18 years), is well positioned to do this work. This is because past New Zealand research has refined methods for on-street observing smoking in cars (in these studies;16–18) and has an ongoing national annual survey of around 30,000 14–15-year-old school students (Year 10 survey) which collects relevant data (eg, as in a study19 which considered inequalities by ethnicity and school-based socioeconomic position). Indeed, this survey of school students has been running annually since 1999 and so it could provide enough time points for a time-series analysis. There are also data from a cohort of adults about self-reported smoking in cars with children from the New Zealand arm of the International Tobacco Control (ITC) Survey, which will allow for repeat cross-sectional, and possibly within-cohort analyses. It is conceivable that a time-series analysis of smoking prevalence among adults in their 20s and 30s (ie, those who are most likely to have young children) from the New Zealand Health Survey might show a differential impact relative to other age-groups. But this is probably unlikely given the law is more likely to result in a change of where smoking occurs (ie, not in vehicles) as opposed to quitting.

Evaluation work using biomarkers (cotinine and nicotine levels) would be more expensive but is also probably justified to verify changes in self-reported exposures and to assess whether total exposure to SHS for children from all sources has decreased (ie, a reduction in SHS exposure from inside vehicles has not been replaced by more smoking in the home, albeit a remote possibility given available international data from other smoke-free laws). The “Growing up in New Zealand” longitudinal study20 could potentially adopt biomarker assessment of SHS exposure in children in conjunction with other routine assessments.

Such research should ideally be commissioned by the government agency which developed the law: the Ministry of Health. It could be tendered for by relevant university based researchers, consultancies doing research or non-governmental agencies (eg, the organisation ASH runs the Year 10 Survey). Such an approach was taken by the Ministry when it commissioned evaluation work21 of the new smoke-free environments law implemented in 2004 (covering smoke-free bars and restaurants), including an additional evaluation of the impacts on Māori health.22 The Ministry has also recently commissioned evaluation work on tobacco taxes.23 Unfortunately however, the Ministry has failed to evaluate other recent major national tobacco control policy interventions, including: the initial introduction of pictorial health warnings, the point-of-sale display ban for tobacco and (most recently) standardised packs with enhanced pictorial health warnings.
The results from evaluating the new smoke-free cars law would be potentially very useful for New Zealand in refining the design of the law or adjusting the level of media promotion or enforcement. It would also make a valuable contribution to advancing the knowledge base for international tobacco control.

Competing interests:
Nil.

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Saying it don’t make it so: a response to Winnington and MacLeod

Eric Mathison

In their recent article ‘Social consequences of assisted dying: a case study’, Rhona Winnington and Roderick MacLeod raise concerns about the societal implications of legalising assisted dying (AD) in New Zealand. They present the results of an interview they conducted with an individual whose family member had an assisted death in a country where it is legal. Based on this interview and other evidence, they argue that there is the possibility for broad “community and social discord”:

“…we must also consider the potential of fracturing of our New Zealand communities and broader social settings. Even if we can ‘fix’ such fractures after AD is legislated and implemented, we may not be able to return them to their former status, thereby changing the supportive and intimate nature of the New Zealand social landscape.”

Though they say little about what practical outcomes should follow from their paper, they say that “evidence from this study must be factored into the New Zealand debate before the referendum on the End of Life Choice Act in 2020”. Since voters can only vote yes or no in the referendum, and since the specific legislation being voted on cannot be changed before then, the authors seem to believe that evidence from the study should serve as at least partial justification for voting against the motion to legalise AD.

The authors are correct that social consequences are important. No medical decision occurs in a vacuum, and just as in other end-of-life situations, AD will affect healthcare providers, families and others. Therefore, it is worth considering what these effects might be in case AD becomes legal in New Zealand. I encounter these effects regularly in my role as a clinical ethicist in Canada, where AD has been legal for five years. Winnington and MacLeod focus on three concepts to make their case: that legalising AD will lead to a “slippery slope” in which, among other effects, essential restrictions on accessing AD will be lifted over time; that there is stigma surrounding AD that will affect patients, families and providers; and that AD has the potential to cause what the authors refer to as a ‘contagion effect’. Despite the strong language the authors employ, they fail to provide compelling evidence for their conclusions. In what follows, I consider each of their points in turn.

Slippery slope

Winnington and MacLeod argue that legalising AD will result in a “slippery slope”, a term typically used to mean that something is acceptable in the beginning but, over time, leads to unacceptable results. The authors have two slopes in mind. The first is that patients will feel pressured to die:

“Despite the prevalence of right-to-die narratives that support those who are concerned about loss of dignity and quality of life, medicine (in collaboration with law) has maintained an unwavering stance that the right-to-die produces a ‘slippery slope’ effect, whereby some patients may be obligated to terminate their lives.”

The claim that either medicine or the law maintain an ‘unwavering’ belief in the slippery slope is false. Demonstrating the falsity of this claim requires looking no further than the conclusion of their own paper, where they say “There remains ongoing debate with regard to the slippery-slope effect”. Though the authors give no citations here, a cursory look at the literature shows that there is considerable debate about the existence of any slope and what effect its potential existence should have on policy.
The claim that the law has maintained a similar unwavering stance is also false. The slippery slope concern is explicitly discussed in *Carter v Canada*, the unanimous Supreme Court of Canada decision that struck down the prohibition on AD:

“The trial judge, after an exhaustive review of the evidence, rejected the argument that adoption of a regulatory regime would initiate a descent down a slippery slope into homicide. We should not lightly assume that the regulatory regime will function defectively, nor should we assume that other criminal sanctions against the taking of lives will prove impotent against abuse.”

In other words, the trial judge who originally heard the case found no compelling evidence that a well-regulated AD policy would lead to a slippery slope. After surveying the evidence for themselves, all nine Supreme Court justices agreed with her. Therefore, it is far from being the case that medicine and the law are unwavering in their belief that a slippery slope is inevitable.

The evidence that Winnington and MacLeod present to bolster their claim that patients may be obligated to terminate their lives is the following: “[Evidence for the slippery slope] can be seen in the Netherlands, where one in 30 individuals died by euthanasia in 2012 compared with one in 90 in 2002”. The authors say that this increase “could suggest” that death is becoming a duty for some people. This is true. However, there is no reason to favour this explanation over the explanation that more people are receiving assisted deaths because more people are aware of it and believe that it is the right choice for them. It is an unjustified leap to a negative conclusion. As the Supreme Court of Canada justices admonish, “We should not lightly assume that the regulatory regime will function defectively.” In order to conclude that widespread coercion is taking place, we need some real evidence. When we look for it, we find empirical research showing that no slippery slope has occurred in the Netherlands.

The second type of slippery slope Winnington and MacLeod are concerned with is the more traditional one in AD discussions: that, over time, stringent eligibility criteria will be loosened to the detriment of the vulnerable. They say that “Research suggests that globally, similar bills have initially restricted eligibility to those with terminal illnesses to make AD more palatable, but the eligibility criteria subsequently became more flexible”.

As a factual claim, this is correct. While increased flexibility is not inevitable—Oregon’s criteria have not changed since 1997—as Canada shows, some jurisdictions do change their eligibility criteria. Following the *Carter* ruling that a complete prohibition on AD was unconstitutional, parliament passed a bill permitting AD in certain circumstances. (That bill is similar in many ways to the one being voted on in New Zealand.) For reasons having to do with the *Carter* decision, instead of following the Oregon model, which requires that patients must be likely to die of their illness within six months, the parliament of Canada required that death must be “reasonably foreseeable”. Last year, the Superior Court of Quebec (a Canadian province) ruled that the reasonable foreseeability criterion is unconstitutional, and the Minister of Justice and Attorney General of Canada introduced a bill to amend the criminal code to get rid of the unconstitutional criterion.

The details of Canada’s legislation are less important here than the justification for the changes. Winnington and MacLeod take removal of the terminal illness criterion to be evidence of a slippery slope (ie, an unwelcome result). However, a superior court judge and the government of Canada take a different view. The case against a terminal illness condition is that an arbitrary time frame means that people who are experiencing the same level of unbearable suffering due to a medical condition will not qualify for relief from that suffering simply because their death is too far away. Far from this being a justified standard, it means that those people will suffer more. Since the point of AD is to ameliorate unbearable suffering, a terminal illness condition is at odds with a just system, not in line with it. Of course, one person’s good outcome can be another’s slippery slope, but we need to see the argument that removing the terminal illness condition constitutes slippage. The ethical argument points the other way.
Stigma

The second key concept Winnington and MacLeod discuss is stigma. One of their concerns is that patients seeking AD will either disclose to their families their intention to have an assisted death and experience a negative response (pressure to stop, guilt, judgement, abandonment). Another is that physicians and other healthcare workers will be stigmatised for participating in AD.

The authors are correct about the existence of AD stigma. As they note, stigma has been documented in research, and, anecdotally, I have seen instances of AD stigma directed at both patients (by families and healthcare staff) and providers. However, the authors once again paint a dire picture that is not warranted by the evidence they provide. Most importantly, they give no evidence that “communities and broader social settings” will be threatened by AD. Even if we grant that some families will be significantly strained by a family member getting an assisted death, the authors give no clear causal path from a fractured family to communities and the fabric of society being irreparably torn. Oregon is not falling apart. Canada is not falling apart. Switzerland is doing fine. Of course, the legalisation of AD in each of these places has required them to undergo significant change, but the burden of proof is on the authors either to produce evidence of social upheaval in these places or to explain why New Zealand is different enough to warrant a different outcome.

The are many prescriptions for stigma. Even if we grant the assertion that stigma will cause fractured families and communities, it does not mean that AD should be prohibited. Consider the stigma around being gay. Unfortunately, coming out as gay can come with many negative consequences, so, as a result, some gay people keep it a secret from their family. Others come out to their family and community only to experience ostracism, judgement, abandonment and, in the worst cases, threats to their safety. No doubt, the result is fractured families and maybe even communities. Nevertheless, the best prescription is not to try to stop the thing that is causing the stigma, but instead to address the source of the stigma and attempt to reduce it.

The same is true of AD. While many patients I have met are open with their families about their plans for AD, some have kept it a secret. (Of course, this is not unique to AD.) Unfortunately, the health system where I work has had to enact policies to protect patients and staff from the stigma around AD. I have seen no evidence that this stigma is threatening communities (and the authors offer none), but even if such evidence exists, it still would not be grounds for prohibiting AD. It might be grounds, but making that case would require an argument that the correct course of action is to restrict the act instead of addressing the stigma. In either case, since patients and doctors are aware of the stigma, there is no reason why people should not be allowed to decide what is best for themselves.

Winnington and MacLeod describe New Zealand as being at a tipping point from which there might be no going back, and they use stigma as potential grounds for continuing the prohibition of AD. They are wrong about both the facts and the values.

Contagion effect

The final concept Winnington and MacLeod discuss is what they refer to as a ‘contagion effect’. What they seem to have in mind is that increased exposure or awareness of AD will lead to more people using AD. For example, they say that “the provision of positive role modelling of AD practices may normalise or even promote this means of death unless assisted deaths are protected by rigorous legislation that supports those involved” before adding that AD is “now becoming the most prevalent mode of death for patients with cancer” in the Netherlands.

Suppose that by ‘contagion effect’ the authors simply mean a rise in the number of assisted deaths. If so, then using the negative term ‘contagion’ is poorly chosen. (Regardless of their aims, to describe AD in such terms during a global pandemic is irresponsible.) Instead, they clearly have something negative in mind. After all, if a restaurant opens and gets more popular over time, it would be strange to claim that the increase in popularity was evidence of ‘contagion’. Instead, the increase in popularity should be described as a value-neutral increase in use.
That more people are getting an assisted death in the Netherlands is only evidence that more people are using it. Similarly, the authors give the assisted deaths of three extended family members of the research participant as evidence of a contagion effect. But, once again, this does not support the ‘contagion’ hypothesis (where that means something negative) over the value-neutral explanation that people are finding out about AD and deciding to use it. Especially in a jurisdiction where AD was recently legalised, a year-over-year increase should be expected. This negative view of AD is also evidenced by the authors’ endorsement of the participant’s framing of AD as infectious. Since the authors give no indication that the participant’s relatives were coerced or manipulated, the contagion claim is unjustified.

They repeat the error: “[The participant’s concern] was consistent with Kheriaty, who observed that exposure to the idea of AD can lead others to seek such assistance”¹. Yet again, instead of evidence of ‘contagion’, this is only evidence of increased use. If the authors have an objection to AD on ethical grounds, they should say so and provide the argument. Otherwise, evidence that people are accessing AD, even after they find out about it from friends and relatives, does not constitute ‘contagion’.

This move is problematic because the authors immediately switch from discussing increased AD to describing their belief that society is at risk of being fractured. But, as we have seen, the fracture thesis is not justified by the evidence Winnington and MacLeod provide.

Finally, the authors directly undercut their justified concern about stigma with their claim about contagion. Imagine telling your loved ones that you were seeking an assisted death, only to be told that doing so is the equivalent of spreading a disease. If the authors are genuine in their concern about stigma, they should abandon their stigmatising language.

Conclusion

I have shown that none of the points made by Winnington and MacLeod support their conclusions of social discord and fracturing. This is not to say that the transition to legalised AD is pain free. Stigma exists. Providers have to figure out how to navigate the new landscape. Families are affected. These will be important topics of research for many years, and we will surely continue to figure out how to do it better. Some problems will occur, but dystopic claims require strong evidence. Winnington and MacLeod fail to provide it.

Competing interests:
Nil.

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Reflections on conducting research with healthcare users in a pandemic lockdown

Fiona Imlach

ABSTRACT
The COVID-19 lockdown period created both challenges and opportunities to undertake research. Research was facilitated by flexibility from funders and team members, support from networks and stakeholders and the willingness of individuals to participate. We could learn from the experience of lockdown research by improving institutional support for research processes and dissemination, investing in a nationwide online panel for public good research and ensuring that a planned database of health research can collect and monitor research proposals in times of rapid change and uncertainty.

For most of us, the COVID-19 pandemic and lockdown is and was an unforeseen and unprecedented experience. It changed the way we worked, shopped and engaged with each other. It also changed the way we did research.

On 29 February 2020, the first case of COVID-19 was confirmed in Aotearoa/New Zealand. At that time, I was writing an ethics application for a research project to explore how service users experienced primary healthcare delivered by practices adopting the Health Care Home (HCH) model in Wellington as part of a Health Research Council programme grant.

Our research team submitted an application to the University Human Ethics Committee (HEC) on 12 March 2020, the day after the World Health Organization declared that there was, in fact, a pandemic. The public health calamity became apparent over the next few weeks, with travellers to New Zealand required to self-isolate for 14 days—and a $12.1 billion COVID-19 business package announced. By 19 March, borders and ports were closed to all but the country’s citizens and their dependents and our research team had our first (online) conversation about whether or how to continue with our extant project. During the next week, we were introduced to the new pandemic Alert Levels, and moved rapidly from Level 2, through Level 3 to Level 4 at midnight of 25 March, the equivalent of a nationwide lockdown.

It was now obvious that our research could not be conducted as intended, as it needed the assistance of primary care providers to recruit service users for in-person interviews. I withdrew our ethics committee application. The next day, a university directive was issued which provided guidelines for all organisations doing research: “There is an ethical imperative to ensure that you do not put others at risk of infection through your research. If your proposed project involves face-to-face interviews or focus groups you must either adopt other methods for data collection or delay the research.” Also at the time, primary care staff were undertaking a massive change in service delivery from in-person to ‘tele-health’ (remote consultations by telephone, video, email, etc) wherever possible, as required by the shift to Alert Levels 3 and 4. They were also managing the fear of exposing themselves and others to a virus that was yet poorly understood. This
milieu of stress and uncertainty meant that a research project based in primary care that had no direct relationship to the COVID-19 event was at best inopportune (and at worst, unacceptable). Seeking service users' views on healthcare in HCH practices was rendered an irrelevant question, as healthcare delivery was completely upended by the crisis. Implementing services which were considered staples in HCH practices, such as telephone triage and consultations, patient portals and email contacts, became a priority in the lockdown, where telehealth became mandatory as a first port of call, almost overnight.

In this context, our only option was to pivot, and swiftly. Our research team had wanted to explore service users' experiences of HCH—the obvious corollary was to shift to exploring their experience of healthcare in the pandemic, particularly the lockdown period. Essentially, a nationwide change programme had been forced upon general practice, after years of inconsistency in embracing new technologies and new ways of engaging healthcare service users to fit the people-centred direction of the New Zealand Health Strategy. We expected that many researchers would be looking at these changes from the perspective of clinicians, but the consumer's voice was in danger of being overlooked. The Health Quality and Safety Commission runs a regular survey that records patient experiences of primary care, but through unfortunate timing, this was in abeyance due to a change of research provider and a review of the content, so would not be in the field during lockdown. The New Zealand Health Survey, which also collects detailed information about patients and their experiences of healthcare, was on hold during this period, since it was administered in-person. It was replaced by a weekly telephone survey from March. This focused on health and wellbeing and included some questions on access to healthcare but did not ask in detail about experiences of telehealth.

This seemed to be a gap. Would people like the new telehealth approaches or not? Did telehealth meet their needs or not? Would the exposure to telehealth during lockdown mean they wanted these types of services in the future? When did they work well, and for whom, and when did they not work, and why?

After a Zoom research team meeting on 24 March, this new project commenced and an online survey of healthcare service users about their experiences of telehealth, health and wellbeing during lockdown was developed, to be supplemented with in-depth interviews. The next steps were as follows:

- 1 April: First draft of an ethics application sent to the research team
- 2 April: Ethics application, survey questionnaire and associated documents submitted (under extremity) for consideration at University HEC meeting on 7 April
- 6 April: Social media posts drafted and plans on how to disseminate the survey developed
- 15 April: Received review and comments from University HEC
- 16 April: Submitted revised ethics application
- 17 April: Received approval for the project from University HEC
- 20 April: Online survey went 'live' and dissemination activities began
- 4 May: First in-depth qualitative interview completed
- 13 May: Online survey closed, as Aotearoa moved down to Alert Level 2 (1,010 usable responses)
- 28 May: Final in-depth qualitative interview completed (38 in total with 6 Māori and 3 Pacific participants)

It was a whirlwind experience. In the span of two months, we went from research project conception to completion of data collection, which in normal circumstances might take twice as long. There were some critical elements that enabled this to happen.

**Flexibility from the research funders**

This was a Health Research Council (HRC) funded project. The HRC were exceptionally accommodating about the change in focus of our project, demonstrating both their appreciation of the extraordinary circumstances and the value of relevant research in such circumstances.
Flexibility from the research team

The team adopted and adapted rapidly to the change in focus and we were also able to co-opt others from our wider research group to help with elements we had not expected in our previous project (such as survey data analysis).

Support from our networks and communities

Given the physical distancing and ‘stay at home’ constraints, we had to use online methods to reach out to survey participants. We used ‘snowball recruitment’, starting with personal and professional contacts and social media platforms, a method that had reported success during COVID-19. Many organisations and individuals went out of their way to disseminate the survey, even when I approached them cold, with no pre-existing connection. I do not even know who to thank for helping us achieve our target of 1,000 survey responses.

Telecommunications

With the restrictions on in-person meetings, more conversations with research team members happened on the phone (and by Zoom), which was more efficient than email. We conducted our participant interviews mostly by Zoom, with a few by telephone. While not typical practice for in-depth qualitative interviews, and for some researchers initially an unfamiliar and awkward method, this quickly became normal and comfortable. As a researcher in lockdown, the Zoom interviews provided a welcome means of meeting and talking to new people and feeling connected to society, a sentiment echoed by many participants. Other researchers have also found that online interviews can be a comfortable, safe and convenient way to engage with participants, even on a sensitive topic.

Willing participants

We could not have completed this research without the contribution of the survey and interview participants, who generously gave us their time and openly shared their stories and experiences. The research team was overwhelmed with the number of people (436) who gave us their contact details to follow up after the survey with an interview. Researchers were warmly welcomed by participants into their worlds with notably little social warm-up needed to start the interview. With little prompting, participants opened up about deeply personal and stressful health and social experiences. Participants visually showed researchers aspects of their lives and lockdown activities through the webcams and followed up with messages.

Alongside the positives, however, there were things that could be done better, the next time we are confronted with an unprecedented disruption to our research, at a research institutional level and at a national level. At the institutional level, my experience was that institutions varied in their responses to COVID-19 and the lockdown and this inconsistency highlighted areas that could be improved in the future.

Ethics Committee processes

On 25 March, the Health and Disability Ethics Committees issued emergency ethical review standard operating procedures, outlining the intent for COVID-19-related (or affected) research to have an expedited five-day review, by a committee that was established on 5 April. The University HEC, however, did not follow this precedent or respond to requests for flexibility or increased timeliness in reviewing research projects that were related to COVID-19. Only by pure luck and dogged drafting was I able to submit our ethics application to meet the deadline for the pre-set HEC meeting. If I had missed this deadline, and had to wait another two to three weeks for the next meeting, I would have lost the moment. I appreciated the prompt acceptance of our revision of the application, but it was a significant, and potentially avoidable, cause of stress that the University HEC did not consider expediting their processes in a time of crisis, when the timeframe for undertaking this research was precariously narrow.

Institutional support for research dissemination

Members of the research team were affiliated with several universities across Aotearoa. One university disseminated the survey widely through their social media platforms and communication networks but another university provided very little support for dissemination. Which begs the question, if a university will not use its connections to promote research, who
will? Similarly, despite having a university communications and marketing team, I was unable to find anyone to help with designing a social media advertisement for our research. With no experience and without even having a Facebook account, I undertook a self-directed crash course on Facebook posts, which might have been a pleasant learning experience if I hadn’t also been pulling together an ethics application under duress.

At a national level, the ability to conduct flexible and robust research, both in times of disruption and in usual circumstances, could be improved in several ways.

**Researcher collaboration for online research panels**

The pandemic starkly highlighted the need for a way to access a representative sample of New Zealanders online. COMPASS and the Public Policy Institute have been investigating a nationwide probabilistic online panel for years, that academics and government researchers could access for ‘public good’ research. The only other alternative is the commercial online panels (eg, Colmar Brunton), but these are convenience samples, often lack adequate representation of Pacific peoples especially, and of Māori, and are expensive to use. My research group could not afford to use one of these panels, and had to resort to the social media dissemination strategy, which has its own biases. If there was ever a time to commit to funding a representative online panel that could be accessed rapidly for socially beneficially research, it is now.

**Health research database**

At the time of lockdown, there was limited information about what research was being undertaken or planned with respect to COVID-19 or the response to the pandemic. Subsequently, a collection of such research projects was started, and is now online. This demonstrates what is possible, in a relatively short timeframe, when there is an urgent need for co-ordination and collaboration in research and funding. A regularly updated repository of all types of health research would also help avoid duplication and encourage collaboration and would be a useful way to map out existing health research, gaps and opportunities. The New Zealand Research Information System, which is an online hub about research and innovation being developed over the next four years by the Ministry of Business, Innovation and Employment, may be able to fill this gap and provide critical information for our next health emergency. This new system will need to be rigorously tested and evaluated to ensure it is fit for this purpose.

From a research perspective, the pandemic provided both an obstruction to existing research and an opportunity for new research. What did I learn from this experience? It was all about whether people could work together, putting aside differences and unnecessary rules. Some people and organisations rise to the occasion with prescience and agility. People you don’t even know, but who believe in the value of your work and the ultimate benefit for Aotearoa and the primary care system, will come forward to help you. There are changes we can make now, that will make doing research during a pandemic, a lockdown or a similar crisis much easier next time. And even if we keep COVID-19 beaten, there will be a next time.
Competing interests:
Nil.

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Transparency in the year of COVID-19 means tracking and publishing performance in the whole health system: progress on the public reporting of acute coronary syndrome data in New Zealand

Andrew Kerr, Carl Shuker, Gerry Devlin

As previously reported in this Journal, the Ombudsman has called for greater transparency around data relating to healthcare performance in Aotearoa New Zealand.1 In his ruling, the Ombudsman noted that “New Zealand lags behind [international] developments” in the “proactive disclosure of performance and outcome information”.

Daily and very public reports from the Ministry of Health of coronavirus cases in New Zealand—their locations, origins, treatments and outcomes—have become our new norm and this transparency has contributed greatly to New Zealand’s collective acceptance of strong government measures to limit community spread. Proactive pursuit of intelligent policies and practices of transparency works. Despite the massive and emergent challenges of COVID-19 and the knock-on effects of our responses, it remains crucial to track performance in the rest of the health system and make that information transparent to New Zealanders in intelligent and evidence-based ways.

Acute coronary syndrome and transparency

Since 2016 the Health Quality & Safety Commission (the Commission) has undertaken work alongside the Ministry of Health (the Ministry) to increase transparency of healthcare data in New Zealand through a co-design process with consumers and clinicians using existing, robust registry data that clinicians trust, on the premise that data would be circulated internally first to providers to assist in quality improvement work, and then subsequently published in ways the New Zealand public want and can understand. This work began with the All New Zealand Acute Coronary Syndrome Quality Improvement programme (ANZACS-QI).

ANZACS-QI is a clinician-led initiative from the New Zealand National Cardiac Network that was implemented in 2012 with funding from the Ministry. Its primary aim is to support appropriate, evidence-based management for all New Zealand patients with acute coronary syndromes (ACS), congestive heart failure and those who receive cardiac procedures. Governance of the ANZACS-QI programme is by the ANZACS-QI governance group on behalf of the New Zealand branch of the Cardiac Society of Australia and New Zealand (CSANZ) and includes regional clinical, Ministry and consumer representatives.2 The detailed ANZACS-QI registry is complemented by parallel analyses of, and individual linkage to, New Zealand’s multiple routine health information datasets. ANZACS-QI has been successfully
implemented in all the 41 public hospitals across New Zealand where acute cardiac patients are admitted. By December 2019 there were 60,471 patient admissions with an ACS and 120,380 coronary angiogram procedures captured in the ANZACS-QI registry: each with a comprehensive and complete dataset. The ANZACS-QI Governance Group uses the ANZACS-QI data to develop and recommend clinical indicators and national performance targets to the Cardiac Network and the Ministry. Performance against these indicators is then reported to district health board (DHB) management and secondary care clinicians, and to the Ministry, via monthly and quarterly reporting. To date, much of this performance data has been reported via peer-reviewed publications3–7 with no mechanism established until now to routinely report the indicators in a format designed specifically for and accessible to the public.

Co-design workshop findings and transparency of data—internal circulation

Transparency of data within the cardiology community is a key goal for ANZACS-QI. However, as ANZACS-QI reporting matured, the sheer volume and complexity and frequency of the detailed reports generated threatened to overwhelm the DHB clinician and management audiences.

The evidence for the effects of publication of performance data is large and still growing, yet uneven. Early reviews suggested improved performance by individuals in response to publication of data by named individual, though much of this evidence was informed by heavily studied work in New York state around coronary artery bypass surgery.8 More recent studies and reviews conclude that there is evidence that public reporting at team, unit or institutional level (as advocated by the Commission’s 2016 position paper9) generates quality improvement,8,10,11 with growing acceptance that the mechanism is via institutional reputation, rather than changes in patient choice of provider in response to publicly available information on provider quality.10,11 This latter point is particularly relevant within the context of the New Zealand public health service.

ANZACS-QI clinicians, Commission and Ministry staff engaged with consumers directly in 2017 via the Open Heart transparency co-design workshop.14 Findings from this workshop spurred support for development and completion of a standardised discharge tool and establishment of a process to publicly share DHB performance data.

In 2017 the ANZACS-QI Governance group partnered with the Commission to develop a dashboard of ACS care quality indicators derived from registry data for DHB clinical and managerial audiences. The initial focus on these groups was for two reasons—establishing comprehension, buy-in, and a sense of the utility of easily graspable graphical displays of variation, and to give those audiences time to understand, engage and begin addressing inappropriate variation ahead of public-facing reporting.

This dashboard is now maintained and updated by ANZACS-QI and has been shared with the Cardiac Network and DHBs since 2018 (Figure 1).

Transparency of data—public presentation how and where?

How to present consumer-facing data?

In general, consumers have low comprehension of measures of quality in healthcare or in some cases that there is indeed variation in quality of care.15–17 Thinkers in patient activation and educational theory posit a need for a graspable organising framework to aid understanding of granular data points of performance.18,19 The Italian performance evaluation system (PES), for example, uses stave charts, presenting performance indicators from a patient perspective, ie, as pathways, rather than siloes.20

The stave presents five bands of performance horizontally, divided into phases of the care pathway with indicators clustered in each phase (see Figure 2). This view “allows users to focus on strengths and weaknesses characterising the healthcare service delivery in the different pathway phases”.21 Performance of the regional unit is presented as a dot higher or lower on the “stave”—dark green being best performance, red being worst. In this example from the Italian PES work on quality of
maternity care, the indicators progress from left to right with a cluster of antenatal care indicators on the left, progressing into perinatal care, and then into postpartum care.

Nuti and colleagues tested the comprehensibility of stave charts versus dartboard and radar visualisations (see Figure 3), finding stave charts rated highest for perceived understanding (ie, “the graph was clear”) and objective understanding (ie, most correct identifications of best performance) (n=903 health professionals).²²

Figure 2: Five-band stave graphs showing the multidimensional performance evaluation measurement of the maternal care pathway of a Tuscany local health unit, from the Italian PES.
ANZACS-QI’s initial set of internally circulated acute coronary syndrome indicators have now been adapted to a consumer-facing version for publication using the stave visualisation, showing the patient journey from admission to hospital care to discharge and medication adherence post-discharge. Users can click on their region on the map of New Zealand to the right to show their own DHB’s latest performance, and control-click to show comparative performance against other DHBs and the New Zealand national average (see Figure 4) and, indeed, national targets for performance.

Figure 3: Five-band stave graphs showing the multidimensional performance evaluation measurement of the maternal care pathway of a Tuscany local health unit, from the Italian PES.

Figure 4: Dashboard of ACS care quality indicators—consumer-facing version.
Where to put consumer-facing data?

When considering the most appropriate forum for presentation of this data for the public, the Ministry, Commission and ANZACS-QI governance again sought the views of consumers. Consumer consultation unanimously showed the Heart Foundation was a trusted source of information on heart health in New Zealand.

The Heart Foundation has a unique role in shining a light and helping the sector. A partnership with the Heart Foundation to provide public access to an interactive consumer-facing version of the dashboard of care quality indicators was proposed and agreed. These indicators are updated at six-month intervals, and the set can be expanded upon as new, more granular indicators are validated, pass through internal circulation processes, and prepared for publication. Access to the dashboard via the Heart Foundation website was made available on 7 July 2020. It can be accessed here: http://www.heartfoundation.org.nz/your-heart.

What the new dashboard presently shows—variation, reasons for this and opportunities

The dashboard is a checklist for DHB performance across the different phases of ACS management, from initial symptoms to one year post-discharge. At each phase patients are cared for by a different, albeit overlapping, team of clinicians. All the indicators are “process” measures supported by compelling international clinical trial evidence that optimal performance is associated with improved clinical outcomes.3–7,23,24 On the dashboard red lines indicate national targets where these are in place. The national targets are not always 100%. This is because some patients require delayed or different treatment, depending on their needs, so reaching 100% is not in fact optimal performance. Generally a level of over 80% would be considered appropriate. Any performance below this is likely to be an opportunity for that DHB to improve care and outcomes for their patients and there is currently wide variation between DHBs on most indicators.

The reasons for variation, and therefore the solutions, are indicator specific. For example, the time taken to deliver acute reperfusion treatment with fibrinolysis or percutaneous coronary intervention for ST-segment elevation myocardial infarction is dependent on a seamless process by the ambulance, emergency departments and acute cardiac interventional teams. In contrast, for DHB hospitals without on-site coronary angiography the time taken to arrange and achieve transport to an intervention-capable centre is an important reason for variation in the three-day target. Reducing these delays is therefore an important target for quality improvement for those DHBs.

Conclusion

The sector faces continued rapid and unpredictable change in the coming months and indeed years. The national response to COVID-19 has shown us the New Zealand public responds well to positive and proactive policies of transparency. We face challenges across our system and it is crucial that we track performance, act on that information and make it available to those whom we serve.
Competing interests:
Nil.

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Spontaneous atraumatic lingual haematoma presenting with threatened airway obstruction
Cheerag B Patel, Lina Benamira, John Chaplin

ABSTRACT
Spontaneous bleeding in the head and neck region is exceedingly rare, particularly in the absence of trauma or an underlying disorder. We describe a case of an atraumatic lingual haematoma in an 88-year-old male presenting with threatened airway obstruction. The only risk factor our patient had was Aspirin use. Our patient was able to be managed conservatively with observation in the hospital's high dependency unit (HDU) and intravenous steroid (Dexamethasone) and antibiotic (Amoxicillin + Clavulanic acid) therapy. We discuss this case to highlight the importance of recognising an impending airway emergency in the setting of deep space bleeding or swelling.

Spontaneous bleeding in the head and neck region in the absence of trauma, use of anticoagulant medication or an intrinsic bleeding disorder is a rare medical entity. There is little published on this subject to date. Spontaneous lingual haematoma has more commonly been described in patients on antiocoagulation medications.\textsuperscript{1,2} The main blood supply to the tongue is the lingual artery and its branches on each side. The lingual artery emerges from the external carotid artery and supplies the ipsilateral half of the tongue by its four branches; the suprahypoid and dorsal lingual branches, the sublingual artery and the deep artery of the tongue (the terminal continuation of the lingual artery).\textsuperscript{3} The rich vascular supply to the tongue has dichotomous consequences like other tissues in the head and neck region—reduced infection risk and faster healing time is counter-balanced with more profuse bleeding. Bleeding within the tongue may result in postero-superior displacement of the tongue and life-threatening airway obstruction.\textsuperscript{4} While traumatic lingual or sublingual bleeding is frequently reported in the literature, spontaneous lingual haematoma formation in the absence of an underlying anatomical abnormality or systemic condition is exceedingly rare. Potential anatomical abnormalities include arteriovenous malformations (AVMs) and tumours. Systemic conditions may include clotting function disorders, antiplatelet or anticoagulant medication use and vessel-wall fragility conditions.

Case report
Our case involves an 88-year-old male with a background medical history significant for:
- Previous bilateral subdural haemorrhage requiring dual burr hole drainage while on Dabigatran for paroxysmal atrial fibrillation;
- Ischaemic heart disease with a four-vessel coronary artery bypass grafting surgery completed in 2004;
- Paroxysmal atrial fibrillation—not anti-coagulated at time of presentation;
- Dyslipidaemia;
• Hypertension;
• Cerebrovascular disease with previous transient ischaemic attack in 2015;
• Asthma;
• Previously raised prothrombin ratio (PR) despite stopping Rivaroxaban and Dabigatran in August 2018—currently normalised with PR of 1.1 on presentation;
• Chronic kidney disease Currently on Aspirin 100mg once daily
• Other medications include Doxazosin, Colecalciferol, Zinc, Frusemide
• No family history or other personal history of excessive bleeding

This 88-year-old male woke up one morning with massive painless swelling of his tongue. He presented to his local general practitioner (GP) with severe dysphagia and dysarthria secondary to the tongue swelling.

He was subsequently sent to the nearest hospital’s emergency department. At the emergency department, he was taken to the resuscitation (RESUS) area. On history, the patient had gone to sleep the night before after eating his usual dinner (egg sandwich) with no issues. The following morning he woke to find his tongue was severely swollen (with a bluish-purple discoloration). He had significant impairment of speech as well as dysphagia.

He denied pain, fevers, preceding trauma (including tongue biting, insect bite, falling) and difficulty in breathing.

There was no stridor or laboured breathing, only mild dysarthria. Vital signs including respiratory rate, oxygen saturation and temperature were all within acceptable limits.

Oral examination revealed marked lingual swelling and blue/black discolouration with only the hard palate being visible superiorly. The tongue was soft and non-tender with very limited movement; there were no signs of traumatic injury such as bite marks or external bleeding. The floor of mouth was soft and non-tender. Native dentition was healthy with no signs of acute dental or periodontal infection.

Examination of the neck including the submental and submandibular region was unremarkable, full range of neck movement was preserved.

Flexible nasendoscopy revealed a similarly discoloured and swollen base of tongue with mild supraglottic oedema and pooling of secretions. There was no supraglottic erythema or evidence of infection. Vocal fold motion was normal. The airway was patent.

Laboratory investigations were essentially normal.

A computed tomography (CT) scan of the neck with intravenous contrast showed

**Figure 1:** CT scan demonstrates swelling of tongue including base of tongue with no underlying collection, mass, vascular malformation or active bleeding. No obvious underlying cause for the lingual haematoma was found.
only swelling of the tongue. The internal structures of the tongue (including intrinsic musculature and midline raphe) were normal. No underlying collection, mass, tumour or vascular malformation was seen. The lingual arteries also looked unremarkable with no evidence of active or recent bleeding.

A decision was made not to secure the airway with endotracheal intubation or tracheostomy. The patient was admitted to HDU overnight for observation to ensure there was no further airway compromise and was started on empiric steroid therapy (Dexamethasone IV 8mg Q8H) and antibiotic therapy (Amoxicillin and Clavulanic acid IV 1.2g Q8H).

On the following day, the patient was stepped down to a dedicated ORL ward for further monitoring as the tongue swelling had reduced. He was continued on antibiotic therapy while the steroid therapy was weaned down.

Haematology advice was sought, and additional blood tests (Factor VIII assay, Von Willebrand Factor antigen, Ristocetin factor, Collagen binding assay and Factor XIII assay) were within acceptable limits.

No further input from their service was required.

The patient remained in hospital for a further two days as the tongue swelling continued to reduce. He was eventually discharged on the third day of his admission once his speech and swallowing function was back to baseline. He was prescribed a further five-day course of oral antibiotic therapy.

**Discussion**

Spontaneous atraumatic lingual haematoma causing airway compromise is an exceedingly rare clinical entity. It is usually associated with bleeding disorders or underlying structural abnormalities. The only risk factor this patient had for his lingual haematoma was Aspirin.

Trauma is an important cause of lingual or sublingual haematoma, it typically occurs in a patient who is using an anticoagulant medication such as Warfarin or Dabigatran. There was no evidence of this in our patient, with no history of injury, and no laceration, scratch, bite mark or external bleeding seen. Another important group of underlying abnormalities to consider in a patient such as ours is structural abnormalities such as tumour or vascular malformation. Again there was no evidence of either of these from the patient's CT scan.

Definitive management of a case like ours can vary depending on the underlying cause (i.e., medical correction of an underlying haematological disorder vs surgical management of an underlying tumour), but the most important issue is airway management.
Airway risk in a case like ours is similar to that seen in Ludwig’s angina, where progressive swelling of the sublingual soft tissue results in postero-superior displacement of the oral tongue causing obstruction to the oropharyngeal airway.\(^4\)

Intubation was ultimately not required as the patient’s airway was deemed safe enough for close observation in HDU with an explicit understanding that any further increase in lingual swelling would necessitate immediate and definitive airway management.

This case highlights the importance for all healthcare professionals to recognise the risk that any lingual, sublingual or external neck swelling can put on a patient’s airway.

\textbf{Figure 3:} Photograph of patient’s tongue 55 days after initial presentation with no persisting swelling or discolouration.
Competing interests:
Nil.

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REFERENCES:
Necrotising fasciitis (NF) is a severe and rapidly fulminating septic process, primarily involving subcutaneous and fascial tissues. It has the potential to spread precipitously to involve an entire limb resulting in significant soft tissue defects and in some cases amputation and death. The upper extremity is less commonly affected (6–27%) compared with other anatomical sites and the diagnosis is often challenging. Early surgical debridement is the single most important factor in determining outcome and delay in treatment adversely impacts mortality.

Due to the rarity of upper extremity NF, its description in the literature has been limited to case reports, small studies or large studies of mixed anatomical sites which included the upper limb. Mortality rates for the upper extremity have been reported as high as 36%. Factors predicting mortality for NF of the upper extremity include altered level of consciousness and respiratory distress on presentation as well as more proximal involvement of a limb. NF has been shown to be twice as prevalent in the South Auckland population compared with the rest of the developed world. Investigation into these factors of the upper extremity is yet to be done on an Australasian population.

This study aimed to comment on the incidence and outcomes of NF of the upper limb in Auckland, New Zealand. It looked at the characteristics of patients with upper limb NF to assess whether any characteristics could be correlated with outcomes. The hypothesis was that an older age, history of immunosuppression and delay until first debridement would result in higher rates of morbidity and mortality.

Methods

A retrospective review of all patients treated with necrotising fasciitis of the upper limb at the Auckland Regional Centre for Plastic, Reconstructive and Hand Surgery between 1 January 2006 and 1 December 2015 was performed. Diagnosis was made intraoperatively by the surgical team with the presence of necrotic fascia removed easily with blunt dissection in conjunction with purulence resembling a ‘dishwater’ appearance (Figure 2, 3). Patient demographics, clinical features, laboratory and radiological investigations, surgical parameters, reconstruction methods and immediate and long-term outcomes were investigated. QuickDASH (Disabilities of Arm, Shoulder and Hand) and Patient Evaluation Measure (PEM) questionnaires (Figure 1) were used to evaluate subjective outcomes. Tests of association was carried out between each of the clinical characteristics and mortality, using Fisher exact test for the categorical variables and non-parametric test for the continuous variables.

Results

Fifteen patients were identified. Mean follow-up time was 24 (standard deviation [SD]21) months. Mean age at admission was 54 (SD:21) years (Table 1). Forty-seven percent were NZ European, 40% Polynesian and 13% Māori. Positive smoking history was recorded in 40% of patients. The most common comorbidity seen was type 2 diabetes (40%). Only one case had a history of intravenous drug usage (IVDU). The most common initial site of symptomatology was the hand (60%) followed by the elbow (20%), forearm (13%) and chest.
wall (7%). Ninety-three percent of cases had positive tissue cultures of which the most frequently isolated organism was *Streptococcus pyogenes* (73%). Polymicrobial cultures were seen in 57%. The majority of patients initially received an antibiotic regime of intravenous Penicillin, Clindamycin and Gentamicin until a specific organism(s) was isolated. Mean time to the operating room from admission was 47 (SD: 84) hours. Patients underwent a mean of 3.4 debridements and 12 cases underwent reconstruction (11 split skin graft, one anterolateral thigh free flap). Reconstruction did not occur in three cases; two due to mortality and one healed satisfactorily by secondary intention. Mean length of hospital admission was 17.6 (SD:12.4) days.

Three patients (20%) died in our study, all due to disease specific causes. Two deceased cases were complicated by multi-organ dysfunction secondary to sepsicaemia. One deceased case was complicated by hospital-acquired pneumonia and sepsicaemia-induced arrhythmia with subsequent cardiac dysfunction.

Univariate analysis (Table 1) demonstrated older age (p=0.017), hypertensive disease (p=0.044) and the need for amputation (p=0.029) were significantly associated with mortality. Requirement for amputation in the two cases indicated the difficulty in controlling the infection; correlating with more severe disease course as opposed to a lack of reconstructive options. Ethnicity, diabetes, smoking history, history of IVDU, more proximal involvement of the upper limb, time between presentation and first debridement, pyrexia, dyspnoea and hypotension were not significantly associated with an increased risk of mortality.

Of the survivors, mean QuickDASH score was 21.1. A QuickDASH score of 0 indicates no disability, while a score of 100 indicates complete disability. PEM Hand Health score was 77% and PEM Overall Assessment score was 87%, with a higher percentage demonstrating a higher level of satisfaction (Figure 4).

### Table 1: Univariate analysis.

<table>
<thead>
<tr>
<th></th>
<th>Survived</th>
<th>Deceased</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years(SD)</td>
<td>47.7 (17.9)</td>
<td>80.3 (9.5)</td>
<td>0.017</td>
</tr>
<tr>
<td>Type II diabetes (%)</td>
<td>33.3</td>
<td>66.6</td>
<td>0.525</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>25</td>
<td>100</td>
<td>0.044</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>50</td>
<td>0</td>
<td>0.229</td>
</tr>
<tr>
<td>IVDU* (%)</td>
<td>1</td>
<td>0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Time to debridement, hours (SD)</td>
<td>30 (48.9)</td>
<td>110 (163.2)</td>
<td>0.276</td>
</tr>
<tr>
<td>Amputation (%)</td>
<td>0</td>
<td>66.6</td>
<td>0.029</td>
</tr>
<tr>
<td>Length of stay, mean days(SD)</td>
<td>19 (12.5)</td>
<td>12 (12.8)</td>
<td>0.391</td>
</tr>
<tr>
<td>Number of debridements, mean (SD)</td>
<td>3.9 (2.2)</td>
<td>1.7 (1.2)</td>
<td>0.089</td>
</tr>
</tbody>
</table>

*Vital signs on presentation

<table>
<thead>
<tr>
<th></th>
<th>Survived</th>
<th>Deceased</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever* (%)</td>
<td>66.7</td>
<td>100</td>
<td>0.73</td>
</tr>
<tr>
<td>Dyspnoea* (%)</td>
<td>22.2</td>
<td>33.3</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hypotension* (%)</td>
<td>22.2</td>
<td>33.3</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

*IVDU—Intravenous drug usage. Fever defined as >38°C. Dyspnoea defined as a respiratory rate ≥20 breaths/minute. Hypotension defined as a systolic blood pressure ≤90mmHg.
Discussion

This study has shown that NF of the upper limb poses a significant mortality risk, particularly in the elderly. The foundation of treatment for NF is early and aggressive surgical debridement, initiation of broad spectrum antibiotics and intensive care support.\(^{10-14}\) The results presented here demonstrate of those that survive and obtain aggressive treatment, sound quality of life outcomes can be achieved.

Diagnosis is often delayed resulting in poor outcomes with a mortality rate in the upper limb in the range of 9–36%.\(^{2,15}\) Distinguishing NF from a simple soft tissue infection can be problematic and relies on a high index of suspicion. Early in the disease process, patients can appear relatively well, without features of systemic toxicity such as high-grade pyrexia and hypotension. Early findings of low-grade pyrexia, oedema, erythema and pain are present. Crepitus, suggesting gas formation in the deeper tissues as a result of anaerobic metabolism, is a classical but infrequent sign.\(^2\) Pain out of proportion to the clinical picture in conjunction with clinical acumen is a reliable sign assisting diagnosis.\(^2,9\)

NF of the upper extremity is uncommon, affecting 10% of cases in a large 11-year retrospective review of all anatomical sites in a New Zealand based study.\(^{10}\) Given the paucity of published cases specifically of the upper limb, no convincing prognostic indicators have been identified. Cheng and colleagues demonstrated an altered level of consciousness on arrival to hospital as well as signs of respiratory distress were significant predictors of mortality in their retrospective review.\(^2\) Schecter and colleagues demonstrated a significant reduction in the length of hospital admission and number of debridements needed in patients undergoing radical debridement within 24 hours.\(^{15}\) No significant predictors of mortality were noted.

The results of this study have demonstrated significantly worse outcomes for older patients (48 [SD: 18] years in survivors and 80 [SD: 10] years in deceased) and those with hypertensive disease. Type 2 diabetes, although the most commonly encountered comorbidity in the current study population, was not significantly associated

Figure 1: Patient Evaluation Measure (PEM) questionnaire sections 2 and 3 utilised for this study.
Figure 2: Prior to first debridement, 43 hours after presentation. ‘Dishwater appearance noted with gentle blunt debridement’.

Figure 3: Dorsal forearm fascia during first debridement.
Figure 4: Seven months post-operatively after split skin graft reconstruction demonstrating satisfactory cosmetic appearance and function.
with mortality in this study. It is possible, however, with a larger sample size this trend would have likely lead to significance. Numerous authors have demonstrated risk factors significantly associated with mortality in studies of NF of all anatomical sites. Type 2 diabetes,16 heart disease,17 pre-existing renal impairment and gout11 have all been demonstrated as predictors of mortality in NF of all anatomical sites. McHenry et al showed that the average time from admission to operation in those who survived was 25 h versus 90 h in the non-survivors (both clinically and statistically significant).18 Tang and colleagues found significantly worse mortality with individuals suffering from more proximal involvement of a limb compared with distal sites such as the hand and foot.9

Three cases (20%) in the current study underwent radiological investigations (ultrasonography, USS ± computed tomography, CT/magnetic resonance imaging, MRI) ordered prior to first debridement. USS aided in excluding subcutaneous collections, however CT/MRI proved inconclusive. Although time to the operating room from presentation was longer in patients requiring radiology (79 hours) compared with those who did not (38 hours), this trend was not significant. No significant relationship was found between ordering of radiology, number of debridements or length of stay. Foreign bodies, abscesses and fluid collections can be easily demonstrated using sonography,19–21 however these features are not always present in NF. CT allows detection of subcutaneous and fascial oedema, gas formation, abscesses and foreign bodies.22 In cases of massive fluid collections along the fascia seen on CT or USS, NF can be suspected. Compared with MRI,23,24 USS and CT do not have as high accuracy for differentiation between cellulitis and NF because of their lower sensitivity in detecting deep fascial fluid. Although the treatment of choice due to its high sensitivity (100%), MRI is costly, not entirely specific (86%) and often unavailable in a timely manner allowing prompt diagnosis.25 Clinical acumen must remain to allow timely diagnosis and recognition of the need for surgical debridement.

Despite variation in reconstructive procedures that took place patients who retained their affected limb had generally satisfactory outcomes in terms of QuickDASH and PEM. As there were no survivors who underwent amputation (two cases) the functional outcome of these patients cannot be assessed and plausibly could have reduced the mean score.

The study is by its small sample size and retrospective nature, highlighting the scarcity of NF. Although a high proportion of our study, only three patients died limiting statistical analysis. Risk factors such as type 2 diabetes and a delay in time to first surgical debridement may have had an association with mortality as demonstrated by authors on other populations.

In conclusion, NF of the upper limb is an uncommon condition with significant mortality, especially in the elderly, requiring prompt recognition and early surgical management. Diagnosis remains clinical and an element of diagnostic acumen will allow prompt appropriate treatment to be initiated. This study has demonstrated sound outcomes in survivors of NF of the upper limb and high levels of patient satisfaction with treatment.
Competing interests:
Nil.

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Fistula-in-ano is a very common surgical condition, caused by anal cryptoglandular inflammation. Most cases are idiopathic. Other causes such as Crohn's disease, trauma and malignancy are well known. Management of fistula-in-ano is largely surgical, especially if the patient is symptomatic. The goal of surgical therapy is sepsis drainage, delineate anatomy and eradicate the fistula while preserving faecal continence. Establishing the aetiology is also crucial as often a combination of specialist medical therapy is required, for example, in Crohn's disease. We report an extremely unusual case of fistula-in-ano on an elderly man with chronic lymphocytic leukaemia (CLL). Histology from the fistula track demonstrated CLL infiltration. This case, not previously reported on PubMed search, illustrates a good example of joint specialist medical (a haematologist) and surgical effort in successfully treating this symptomatic fistula-in-ano.

ABSTRACT

Fistula-in-ano is a very common surgical condition, caused by anal cryptoglandular inflammation. Most cases are idiopathic. Other causes such as Crohn's disease, trauma and malignancy are well known. Management of fistula-in-ano is largely surgical, especially if the patient is symptomatic. The goal of surgical therapy is sepsis drainage, delineate anatomy and eradicate the fistula while preserving faecal continence. Establishing the aetiology is also crucial as often a combination of specialist medical therapy is required, for example, in Crohn's disease. We report a case of a 79-year-old man with a history of CLL for over 40 years, who presented with a fistula-in-ano. The reactivation or development of the fistula is thought to be due to CLL. The patient journey and management are discussed.

Case report

A 79-year-old Caucasian man was admitted as an emergency with perianal pain. He had a background of chronic lymphocytic leukaemia for over 40 years. After five years, he received brief treatment with chlorambucil and prednisolone for constitutional symptoms. Seventeen years later after his initial diagnosis of CLL, the patient had an ischiorectal abscess, which was incised and drained. His white cell count was consistently around 70x10^9 cells/litre at that time. The wound healed and there were no further consequences until he presented with another abscess from the same area 15 years later: it was again incised and drained successfully and he was discharged from surgical follow-up. Between the two episodes of the ischiorectal abscesses, the patient was not on any treatment for his CLL.

Another eight years later, his white cell count was maintained with his normal levels between 50 and 60x10^9 cells/litre. The patient underwent examination under anaesthesia and an abscess was found at 5 o'clock position, where there was evidence of previous incisions. Further incision and drainage took place but this time he was to be followed up with an MRI scan six weeks later.

T1 weighted MRI of his perineum showed complex high intersphincteric ischiorectal fistula draining out onto the surface at 5 o'clock position with an internal opening just at left medial to 12 o'clock position. T2 weighted images showed a small abscess intersphincterically (Figure 1). The patient was electively brought back to theatre for another examination of anorectum under anaesthesia. The external opening was identified at 4cm from anal verge at 5 o'clock position and this opening was dilated. The fistula track was curetted to remove the granulation tissue and obtaining histology specimen. A seton was placed to improve drainage.
Clinical follow-up around two months later was arranged with both the surgeon and his haematologist. The seton was felt to be comfortable with minimal drainage. Histology of the fistula showed significant leukemic infiltration into the epithelial lining of the fistula (Figure 2). The opinion with the haematologist was that given his age and his stable CLL, no acute therapy was required.

Figure 2 shows a low and high-power haematoxylin and eosin view of the CLL deposits. These are irregular lymphocytic deposits, composed of a monotonous population of small and round dark cells. The deposits are surrounded by a fibrotic stroma and adipose tissue. The absence of a mixed population of lymphocytes suggests this is not simply a reactive process. Further immunohistochemical staining (not shown here) illustrated that the lymphocytes expressed were CD20 and CD23 and CD5 antigens positive, which is characteristic for CLL.

Discussion
Fistula-in-ano is considered a result of anal cryptoglandular inflammation. Most cases are idiopathic but occasionally can be consequent to a chronic inflammatory condition such as Crohn’s disease or tuberculosis. Seldomly, it results from invasion of local malignancy. Therefore, recurrent ischiorectal abscesses need to have a fistula, especially possible complex fistulae, either confirmed or excluded.
This gentleman had his first abscess drained in 1996. A possible recurrence was not until 2011. It would not have been unreasonable to consider the episode in 2011 to be a de novo abscess. Furthermore, the patient may not recall the event some 15 years earlier. CLL does have immunocompromising effect and the consequent development of an ischiorectal abscess would not be an unreasonable causative assumption similar to those with poorly controlled diabetes. This theory is nowadays challenged. The diagnosis of an underlying pathology should be established as it affects management of ischiorectal fistula.

The principle management of an ischiorectal fistula is to treat any sepsis, delineate the anatomy and eradication of the fistula. As with any chronic inflammatory conditions such as Crohn's disease or tuberculosis, eradication of the fistula often requires joint assistance of a medical specialist. In the case of Crohn's disease, once the sepsis is drained, gastroenterologists often commence on immunotherapy. Biopsies of the fistula track occasionally can help with establishing the diagnosis, assuring the medical specialists prior to commencement of these toxic medications.

Perianal complications resulting from haematological malignancy are seldomly reported. All the reported cases claimed the attribution to immunosuppression from either the primary disease or chemotherapy for the disease. Biopsies of our patient suggests leukaemic infiltration of the epithelial lining of the fistula. It is almost certainly unlikely that this recurrent or de novo fistula was directly caused by CLL. The more plausible theory is the immunosuppressive effects of CLL predispose to the activation or development of existing cryptoglandular inflammation. Furthermore, the presence of neoplastic tissue may have been all a while responsible for preventing healing of the fistula.

The opinion of the haematologist was to continue the watch and wait regime rather than commencement of immunotherapy such as Ibrutinib (tyrosine kinase inhibitor) and chemotherapy. In the case of mild CLL, watch and wait regime has demonstrated equivocal survival outcome for those considered asymptomatic. The debate from this case, which was controversial at the haematology multidisciplinary meeting, was that the patient had developed a fistula possibly consequent to or exacerbated by CLL. The consensus eventually was that given his age, free of symptoms and a maintained white cell count, risk of medical intervention may outweigh benefits. Radiotherapy of the anorectum was discussed. However, the patient is elderly with good fistula controlled of drainage, radiotherapy may worsen symptoms and, worse still, further prevent successful healing of the fistula.
Conclusion

Leukaemic infiltration within a fistula-in-ano has not been previously reported. The general principles of management of fistula in ano still applied. Importantly, this case illustrated that successful treatment of secondary complex ischiorectal fistula requires specialist multidisciplinary approach.

**Competing interests:**
Nil.

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**REFERENCES:**

A severely injured person in New Zealand is entitled to lump sum compensation under the Accident Compensation Act 2001; that compensation being legislatively linked to the level of ‘Whole Person Impairment’ (WPI) as assessed by a medical practitioner using the American Medical Association Guides to the Evaluation of Permanent Impairment (the AMA guide), currently employing the 4th Edition1 first published in 1993.

In 2018, of 2,895 claims that were active 12 months after lodgement, none of those who were potentially disabled were assessed as reaching the 10% disability ‘threshold’. Our opinion is that the Accident Compensation Corporation (ACC) is using an outdated edition of the AMA Guide and that this is disadvantaging claimants.

The Guides are not entirely evidence-based being described as “not a scientific document based on demographic or epidemiological data, but rather is a ‘Delphi’ panel of informed experts who have formed a relative consensus”.2 As in any other area of medicine, best practice is essential and each edition of the Guides, first published in 1958 and now in their 6th Edition (2007),3 corrects failings in the previous edition and modifies the mechanisms of assessment in light of modern medicine, particularly with respect to modern imaging techniques. Each edition is accepted as being notably superior to its predecessor,4 particularly with respect to Lumbar and upper limb impairment,5 the latter acknowledged by Accident Compensation Corporation (ACC)6 in their implementation handbook.

The use of the almost 30-year-old 4th edition in New Zealand benefits neither the assessor nor the injured. In particular, this edition inadequately accounts for a number of conditions such as low back injuries where it evaluates two factors: “Loss of Motion Segment Integrity” and “Diagnosis Related Estimates” (DRE). ACC has further restricted their application by not allowing WPI based on Loss of Motion Segment Integrity. The 4th Edition DRE for lumbar injury requires clinical signs of radiculopathy (rather than symptoms and identification of appropriate pathology),7 a difficult and often clinically subjective barrier to achieve in most cases even where there is obvious impairment.

By contrast the 5th edition (published 2000), although still flawed, allows for a cautious assessment of the impact of lumbar disc injury on impairment and function. Most importantly, it refines the concept of DRE to include lumbar disc injury reducing the clinical subjectivity of that assessment.

To estimate this disadvantage to the claimant the authors carried out an Official Information Request of ACC of the READ8 codes associated with low back disorder excluding lumbar body vertebral fracture and spinal cord injury. These were stratified and classified as to chronicity and work-relation. The number deemed eligible (WPI >10%) for lump sum compensation are shown in Table 1.

Over the six-year data collection period, the number of claimants with sufficiently severe low back injury to exceed a 10% WPI ranged from 0–10 cases per year. This finding appears implausible given the fact that there were 37,804–42,680 work-related low-back injury claims accepted per year during this period.

Our argument is that the use of the 4th edition does not take advantage of the increased utility that arises in the later 5th edition that incorporates of modern imaging techniques. This may reduce the ACC’s outstanding claims liability and constrain levy growth but it does so at the expense of New Zealand workers and as such is iniquitous.

We have focused on work-related back injuries to illustrate the need for ACC to abandon an outdated and demonstrably flawed version of the AMA Guide, but our argument is that Low Back injury is not an isolated anomaly in the 4th edition.
We acknowledge the ongoing use of the 4th edition in some states of America (seven states) but note the adoption of the 5th and 6th editions by the majority (31 states or districts). In New South Wales the 5th edition is used to determine WorkCover (the NSW equivalent of ACC) impairment assessments but the 4th Edition for the assessment of WPI arising from motor vehicle assessments.

It is our opinion that If a guide is to be used to assess New Zealand workers, it needs to be the best available and not one that serves purposes other than the best interests of those workers.

Amending which edition is used is relatively simple and can be made by a recommendation of the Minister, by Order in Council, to make a change to the appropriate Regulations.

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**Table 1**: New Zealand Accident Compensation Corporation low back injury lump sum incidence.

<table>
<thead>
<tr>
<th>Calendar year of claim lodgement¹</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of claims lodged with one or more of the specified READ codes</td>
<td>232,448</td>
<td>241,721</td>
<td>252,098</td>
<td>261,430</td>
<td>263,629</td>
<td>271,308</td>
</tr>
<tr>
<td>Number of lodged claims accepted</td>
<td>225,277</td>
<td>235,084</td>
<td>245,242</td>
<td>254,498</td>
<td>256,114</td>
<td>262,148</td>
</tr>
<tr>
<td>Number of accepted claims that are work-related</td>
<td>37,804</td>
<td>38,361</td>
<td>39,493</td>
<td>39,792</td>
<td>40,901</td>
<td>42,680</td>
</tr>
<tr>
<td>Number of accepted work-related claims that were active at any point 12 months after lodgement</td>
<td>2,979</td>
<td>2,979</td>
<td>3,075</td>
<td>3,114</td>
<td>3,557</td>
<td>2,895</td>
</tr>
<tr>
<td>Number of accepted work-related claims where a READ code contains “fracture” or “spinal cord injury”</td>
<td>78</td>
<td>94</td>
<td>115</td>
<td>88</td>
<td>113</td>
<td>109</td>
</tr>
<tr>
<td>Number of work accepted work-related claims secondary to soft tissue injury, possibly disc injury</td>
<td>2901</td>
<td>2885</td>
<td>2960</td>
<td>3026</td>
<td>3444</td>
<td>2786</td>
</tr>
<tr>
<td>Number of accepted work-related claims where a READ code does not contain “fracture” or “spinal cord injury” and were still active 12 months after lodgement where the claimant has received a lump sum payment</td>
<td>16</td>
<td>19</td>
<td>13</td>
<td>16</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Percentage of claims receiving lump sum entitlement where WPI &gt;10%</td>
<td>0.55%</td>
<td>0.65%</td>
<td>0.44%</td>
<td>0.53%</td>
<td>0.12%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Competing interests:
Nil.

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www.nzma.org.nz/journal-articles/time-for-a-change

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On the epistemology of case studies of social phenomena in healthcare

Dylan Mordaunt

Winnington and MacLeod recently reported in NZMJ a case study related to voluntary assisted dying (VAD). In this study, the authors used a semi-structured interview of a single participant's experience of VAD in a family member, in a foreign country. This was analysed and reported in the form of a case study, with the stated intent to explore the individual's experience of VAD in this foreign country and their perception of how this may relate to the upcoming End of Life Choice Act (EoLCA) referendum, scheduled for September 2020. There are significant challenges with the study from a methodological and analytical perspective. What follows is an evaluation of these challenges and a reflection on the nature of this research.

In the introduction, the authors state, “medicine (in collaboration with law) has maintained an unwavering stance that the right-to-die produces a ‘slippery slope’ effect, whereby some patients may be obligated to terminate their lives prematurely”. Using the current state of law as support for this claim is circular logic and unhelpful for addressing the current issues of whether VAD should be legalised in New Zealand, how health and social outcomes can be maximised, nor do the authors present evidence that supports law being maintained specifically to address the ‘slippery slope’ premise. Similarly, the data cited on uptake in the Netherlands do not support the assertion of a ‘duty to die’ premise, they reflect uptake.

The ‘slippery slope’ argument has been covered extensively elsewhere, ie, the premise that legalisation of VAD will eventually lead down a slippery slope where euthanasia in all its forms is accepted. Empirical data on experience of VAD can be interpreted to provide conflicting viewpoints of experiences in countries such as the Netherlands and Belgium.

The authors’ suggestion that there is consensus about this within the medical profession is inaccurate, and indeed that countries have legalised VAD with the support of medical and health professionals, demonstrates that this is not correct. Unfortunately, attempts by groups in New Zealand purporting to represent the entirety of the medical profession have been misleading, as they do not represent the entire profession and indeed by their nature do not represent all health professions. That the ‘slippery slope’ premise is raised in the introduction to this study raises the question of what steps were taken to prevent and address “leakage” of the prior views of the authors, into the study—an issue linked with ascertaining that is raised later in this response.

Moving onto the study method, the authors cite the Yin case study method as the basis for their approach. The methodology section gives very little detail on this, the theoretical/epistemological basis underlying the approach, whether the interview questions were developed a priori and whether the protocol was submitted for review prior to progressing with the interview. Most notable in its absence is the process by which the individual was ascertained specifically to address the ‘slippery slope’ premise. Similarly, the data cited on uptake in the Netherlands do not support the assertion of a ‘duty to die’ premise, they reflect uptake.
synthesis. Related to the ascertainment is that the interview itself is semi-structured, clearly linked with prior knowledge of the individual. The relationship between the authors and the participant, prior conversation and formation of the questions, was not clearly described in the report, further raising the possibility of data leakage and of bias. Additional challenges with the method are that the authors reference thematic analysis but do not describe the method that was undertaken, nor the tools used to assist with the analysis, such as computer-assisted qualitative data analysis software (CAQDAS). Finally, although disclosure of no conflicts is made, from a meta-research perspective, the lack of financial disclosure is problematic and not consistent with many models of research quality assessment in healthcare.

In reporting the findings of the study, baseline characteristics were omitted from the report, including age category, gender, country of origin (which is an important factor in understanding the individual's experience of said health system), prior beliefs about VAD, the quality of the relationship to the deceased family member and specific details under which that individual undertook VAD, we are unable to assess elements of external validity such as directness and generalisability. Indeed, given that this was a case study involving a single person, rather than a number of people from the family, the lack of description of the individual's own physical and mental wellbeing leaves questions about the internal validity of the case study.

The authors describe three key themes that emerged from interviewing this individual, “expectation of VAD”, “stigma” and “VAD as contagion”. The participant disclosed what sounds like strong views and interesting beliefs around VAD relating to a perceived expectation that the individual themselves would be forced to use VAD. This seems related to the ‘slippery slope’ argument and though they perhaps may be distinct, the lack of exploration of this and tying in with prior literature about this is noteworthy.

An observation was made in the thematic reporting about the stigma that could occur on both “sides”. A point of clarification is that the critical difference is that, in the presence of legal prohibition, stigma is reflected in law. In relation to this theme of stigma, the study subject's reflection on individuals potentially not informing their family members, it seems critical that this should have been explored with relation to this individual's connection with their own family member and perhaps as a reflection the impact of how that disclosure or non-disclosure had affected them or their family.

“[V]AD as contagion” appears to have been raised in the context of this individual experiencing multiple family members undergo VAD. This is mentioned twice within a short period of the discussion. That this individual has had three family members undergo VAD is a feature of the subject's personal circumstances that is clearly critically important to this person's narrative, the analysis and interpretation of their experience and perhaps part of their perception of contagion. This concept of ‘contagion’ is also not a new finding with there being a variety of value-laden literature and news media exploring and touting this.5

In their discussion, the authors' characterisation of the themes from the analysis of the interview suggests that generalisable phenomena were identified in this study, rather than the purpose of a case study, which was to find themes for further exploration, such as quantitation. While a single person's experience of a major event in a foreign health system is interesting and in the presence of new findings could potentially be valuable, the authors appear to have mischaracterised the themes from this case study as evidence of the ‘slippery slope’ phenomena. As a literal “n of 1”, these observations are inductive and not generalisable to the entire population.

That the authors further assert that, “evidence from this study must be factored into the New Zealand debate before the referendum on the End of Life Choice Act in 2020” is doubtful. Reflecting on the study method, findings and synthesis, there is nothing new that this article adds to the literature, either in terms of broader themes identified globally, nor specific findings to the New Zealand healthcare or broader community. Since these themes are not new additions, this raises the possibility that this report has been engineered as a form of social activism to leverage the NZMJ platform to legitimise poorly conducted qualitative research from a single interviewee. The authors appear...
to have overreached in their assertion that “This study clearly showed how experiencing [V]AD through a relative’s lens and by partial engagement with [V]AD can impact broader family and friend networks”. At best this should be prefaced by “might” impact.

Later in their discussion the authors leave behind the premise of using the themes identified through the interview by asserting “This potential consequence of [V]AD legislation reduces our future existence to being considered only through the practical lens relating to the cost of care and reduces our life to having a dollar value, as opposed to [V]AD alleviating the fear of indignity, pain and suffering at end-of-life”, a statement not backed by the themes identified in their research, by other evidence nor citations.

In asserting “The results highlighted how [V]AD remains contentious, irrespective of legality...” the authors have further gone beyond what little is described in their methods and results. That contentiousness of an issue could be conclusively identified from thematic analysis of interviewing a single person and then omitted from the results section of a publication before being raised in the discussion of a report, raises critical quality issues about the study. At this point in the discussion, the text deteriorates into impassioned narrative and further evaluation of the discussion adds little.

Case studies are useful for exploring issues in depth in an inductive fashion, ie, developing new areas that need to be explored. VAD is far from a new issue, either in New Zealand or abroad. All of the issues that were raised in this case study have been explored in great depth elsewhere. A systematic review of these issues may be of value, particularly with respect to generalisability of the findings to the New Zealand context, but also for exploring whether these issues became a significant issue following implementation of the law (in countries where it has been implemented) or are thought experiments that go no further in practice.

It is not the purpose of case studies to identify broadly generalisable phenomena, but to identify themes or findings for further investigation. Case studies are a method used extensively in healthcare and in some ways the most fundamental form of empirical research we have. In Yin’s text on case study methodology, he describes a framework for assessing the design of case studies by addressing construct validity, internal validity, external validity and reliability. If this study’s intent was to draw out the assertions made in the discussion, the study design cannot answer these.

Finally, the past two decades has seen a steady shift to open models of publication. These include openness in terms of maximising access to articles, which the NZMJ and many other healthcare journals have engaged in. More recently, this model has extended to include an increase in the sharing of source data, inclusion of increasing supplementary items and open peer review, in which we can better understand the peer review and editorial process that led to an article being published. In this particular instance, it would be useful to understand the process that led to a journal which commonly publishes high-quality case studies, allowing one through peer review with such critical weaknesses as this.

Competing interests:
Nil.

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Ischaemic cardiomyopathy: management strategies and patient outcomes

Bernard Wong, Charles Yao-Cheng Ho

Ischaemic heart disease is the leading cause of death worldwide. Surviv...
statistical significance ($p=0.072$). However, improvement in LVEF was seen across all groups on follow-up echocardiography (Figure 1).

Table 1: Baseline characteristics of study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study population (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD years</td>
<td>65.7±11.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>89 (80.2)</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>65 (58.6)</td>
</tr>
<tr>
<td>New Zealand Māori</td>
<td>17 (15.3)</td>
</tr>
<tr>
<td>Pacific</td>
<td>19 (17.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (5.4)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>78 (70.3)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>50 (45.0)</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>89 (80.2)</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>70 (63.0)</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>32 (28.8)</td>
</tr>
<tr>
<td>Previous CABG (%)</td>
<td>22 (19.8)</td>
</tr>
<tr>
<td>Previous PCI (%)</td>
<td>13 (11.7)</td>
</tr>
<tr>
<td>eGFR, mean ± SD ml/min/1.73m²</td>
<td>61.4±25.6</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass grafting, eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention, SD = standard deviation.

Major adverse cardiovascular events (MACE) was a composite of all-cause mortality, myocardial infarction (MI), hospitalisation with congestive heart failure.

Figure 1: Mean left ventricular ejection fraction on echocardiography at baseline and at first follow-up.
(CHF) and unplanned revascularisation. At a maximum follow-up of five years (mean two years), MACE occurred in 58 patients (52.3%). The rates of each component of MACE at end of follow-up were: 32.4% hospitalisation with CHF, 27.0% all-cause mortality, 9.9% recurrent MI and 6.3% unplanned revascularisation. Patients who underwent CABG were four times less likely to experience MACE compared to those who received OMT alone (OR 0.25, 95%CI: 0.08–0.80, p=0.02). There was no difference in rates of MACE between the PCI and OMT groups (OR 0.81, 95%CI: 0.43–1.51, p=0.51). MACE-free survival curves are shown in Figure 2.

Although this study was not propensity matched, the superiority of CABG in ischaemic cardiomyopathy is consistent with current registry data and international guidelines. Studies such as the REVIVED-BCIS2 trial investigating the efficacy of PCI compared to OMT in ischaemic cardiomyopathy are ongoing.6 With the current available evidence, CABG should be the first-line treatment for ischaemic cardiomyopathy in patients with acceptable surgical risk. PCI can be considered as an alternative to CABG in ischaemic cardiomyopathy taking into consideration patient comorbidities, coronary anatomy and expected completeness of revascularisation.
Competing interests:
Nil.

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Intensive care in New Zealand: time for a national network

Toby Betteridge, Seton Henderson

The COVID-19 worldwide pandemic seems fortunately to have left New Zealand relatively unscathed in comparison to many countries throughout the world. There have been to date a total of 1,556 cases (1,206 confirmed and 350 probable) with 22 deaths. The national implementation of movement restrictions, border closures and business constraints have been well documented, effective and generally well perceived on the world stage. The resurgence of cases worldwide in recent weeks, including in countries previously felt to be managing well, has illustrated the importance of maintaining ongoing vigilance and management to keep the disease burden down.

In New Zealand, there are approximately 4.6 critical care beds per 100,000 population. These are distributed throughout 29 ICUs/HDUs (adult and mixed), one PICU. This number has declined over the last 10 years and compares poorly to other OECD countries with similar healthcare systems, eg, UK 6.4/100,000, Australia 8.9/100,000. The recently published New Zealand Health and Disability System Review sets out the vision for New Zealand health services over the coming years. There is much emphasis on integration of health services across the country with collaboration both within and across specialties. This encompasses, among other aspects, the more efficient sharing of digital information to allow equity of healthcare to all residents.

Within the medical sphere there has been an immense amount of work carried out in hospitals and intensive care units throughout the country in preparation for a possible influx of patients. This planning has had multiple facets; many units have rearranged rosters, produced whole new teams incorporating both ICU and non-ICU staff, produced new protocols and undertaken hours of meetings and teaching events to train theirs and other specialties’ staff. There has been rapid cataloguing of equipment and identification of deficiencies, planning for expansion into non-critical care areas and conversion and upgrading of existing facilities. During this time period New Zealand has seen the development of an electronic intensive care dashboard through the work of the South Island Alliance. This has been invaluable in allowing clinicians around the South Island to visualise the status of other ICUs within the region on a daily basis, thus allowing for planning of inter-district flow of patients and the likelihood thereof. Similar systems are already in place in Australia (eg, REACH information systems network in Victoria) and the UK (Critical Care Networks) with multiple others worldwide. Indeed, during the 2009 H1N1 avian flu pandemic, a similar system was in situ for a period in New Zealand.

Throughout the world, the importance of collaboration, and the sharing of information and resources by the intensive care community has been shown to be invaluable in trying to stem the tide of admissions and adopt new treatment strategies on the run. In New Zealand, and in many other countries, there has in consequence been an immense amount of knowledge generated in a very short space of time.

Lessons learnt from this global crisis should help inform future strategies in dealing with large-scale disasters. To maximise these benefits I would propose the creation of two entities; the first, in line with recent recommendations, a New Zealand-wide ICU strategic network. This would incorporate aspects of intensive care medicine from standards and protocols of care, through to staffing, training and equipment procurement. Further, it would

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contain the pooled knowledge gained from this current crisis and previous as well as that from ‘routine’ ICU work and would be made freely available and easily accessible to all intensive care units in New Zealand. The aim being to provide equitable access for all patients to ICU- and HDU-level care in both tertiary and smaller regional centres.

The second entity would be an electronic ICU dashboard. This would allow ICUs countrywide to share up-to-date information about, among other aspects; bed capacity, patient acuity and available resources in all HDU and ICU facilities throughout the North and South Islands. A real time indication of surge capacity in the event of a localised or national disaster would be readily available to help guide patient movements and resource allocation.

The COVID-19 pandemic undoubtedly represents one of the greatest healthcare crises of modern times, but it also offers the chance for us to gain from it and move our specialty forward—we should embrace the opportunity.

Competing interests:
Nil.

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Get up, get dressed, get moving! Preventing functional decline is everyone’s business

Katherine Bloomfield, Keith Colvine, Martin J Connolly, Kirsten Ter Braak

Getting up, dressed and moving is important for older inpatients, who are known to rapidly succumb to skeletal muscle loss and mobility/functional decline while in hospital.1 This is not a new concept, with physician Dr Richard Asher writing in a BMJ article in 1947 “Get people up and we may save patients from an early grave”.

In modern times, those active on social media may have seen the global #endpjparalysis movement, where likeminded health professionals tweet their support for this message. Within our own institution there has been, over the last two years, visible education of both staff and public on the evils of bed rest. A Google search establishes that many other district health boards also promote this concept, with educational videos of physiotherapists and images of staff grouped together in their pyjamas.

Yet is this enough? We recently reviewed the bedside environment of our patients when seen on consultant-led ward rounds. From within a DHB with a strong ‘get up’ message, we were interested in exploring whether our patients were out of bed and dressed, and what physical obstacles may limit getting up and moving. One geriatrician and one general physician reviewed 100 patients aged 75 years or over seen on their respective consultant-led ward rounds, teaching sessions or other opportune moments in September–October 2019. Each patient/environment was only assessed once. Patients seen on post-acute ward rounds were not assessed, due to time constraints. As well as documenting the physical space around the patient, physicians gave an opinion on whether the patient was able to get up and out of bed themselves, and if not, what was limiting them: physical (determined by physical limitation on mobility, provided by bedside mobility-status boards) or environmental factors (subjectively determined and based on whether each individual patient was thought to be able to navigate potential barriers such as tables, or distance from walking aids), or a mixture of both.

The median age was 82 years (range 75–98), 38 were seen on a rehabilitation ward, 62 on general medical ward and 42 had documented cognitive impairment (CI). Seventy-two patients were in bed (18 [25%] had rails up, 13 [18%] had table over the bed), 26 in a chair (16 [62%] with table in front of chair) and two were actively mobilising at time of physician visit. Seventy-three required some form of mobility aid and 26 (36%) had their aid within reach. Twenty-nine patients were in their own clothes and the call bell was accessible for 71 patients. Physicians thought 48 patients were able to mobilise themselves at time of visit. Of the 52 remaining, 11 (21%) were unable to mobilise for physical reasons, 15 (29%) had environmental obstacles, and 26 (50%) had a combination of both physical and environmental factors.

T test or chi-square tests were used to examine differences between those with CI and those without, and those on rehabilitation ward and those on non-rehab wards. While there were no differences in age, ward, gender, being in bed or not, or being in their own clothes, those with CI were more likely to have bed rails elevated (15/30 vs 3/42, p<0.005) and were less likely to be thought of as being able to mobilise at the time of review than those without CI (11/42 vs 37/58, p<0.005).
No differences in age, gender, CI, call-bell accessibility or physicians' opinion on patients' ability to mobilise at time of review were seen between wards; however, patients on rehab wards had greater mobility dependency (independent 5/38 (13%) vs 22/62 (35%), supervision 18/38 (47%) vs 23/62 (37%), assistance needed 15/38 (39%) vs 17/62 (27%), p=0.049). Despite this, they were less likely to be in bed (18/38 (47%) vs 54/62 (87%), p<0.005), and more likely to be in their own clothes (21/38 [55%] vs 8/62 [13%], p<0.005).

In summary, a concerning number of older adults were in bed, in hospital clothes and with environmental obstacles present. Differences were seen in those with and without CI, and between rehab/general wards. This was a rapid, small, uncontrolled snapshot of daily ward life with significant limitations, including subjective environmental assessment; however, lessons can be learned. Those with CI are potentially more limited and harmed by their environment (eg, bed rails up, chairs placed in front of bed/chair4–6), so it is concerning that there is evidence of environmental restraint. While those on general wards are probably more unwell, they are likely to be mostly medically stable (not seen on post-acute rounds), and it is likely that much of their medical care can still be delivered while they are out of bed. While there is great enthusiasm for falls prevention, this should not come at the expense of maintaining mobility.7 Deconditioning in older adults is a factor in delayed discharge.8,9 We acknowledge that in the modern ward environment, sometimes bed rails can be enablers to patients, and the importance of table proximity for maintaining hydration. Our findings require further study and will be used to inform future research.

Patients interact with multiple people over the time of their admission, from cleaning and kitchen staff to allied health and medical specialists. Each one of us has a responsibility to leave our patients as enabled and primed for mobility as possible. We can all make a difference by small actions, such as ensuring our patients have mobility aids close by, their bell close, and in considering aspects of the environment that essentially act as restraints. Even better, we could take our patients for a brief walk around the ward during daily rounds. The wider hospital may benefit from the rehabilitation ward philosophy, where the culture is one of enablement and maintaining independence. For those senior staff members working on non-rehabilitation wards, your leadership in encouraging patients to get dressed, sit out of bed, eat meals in a chair, is an excellent place to start role-modelling for the wider ward teams. Work from our Australian colleagues provides guidance to improve in this area.10 This is everyone's business.
Competing interests: Nil.

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Pandemic control: getting to the heart of unintended consequences

Bernard Wong, Seif El-Jack, Guy Armstrong

In December 2019, a cluster of pneumonia of unknown cause was reported in Wuhan, China. This was later identified to be caused by a novel coronavirus from the same family of viruses that caused previous outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The virus is now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease it causes is called coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020 after rapid spread of the disease worldwide.

The first case of COVID-19 in New Zealand was reported on 28 February 2020. Two weeks following the announcement of a global pandemic, New Zealand closed its borders and entered a nationwide “alert level 4 lockdown”: all non-essential travel is restricted (including border closure), only essential services allowed to operate, people instructed to work from home, public gatherings banned, physical distancing of 2m applied and “stay home” adopted as the default instruction. A parallel COVID-19 national hospital response framework, which reflects the pandemic’s potential impact on hospitals, was designed with escalating levels of preparedness providing a nationally consistent and managed approach to clinical service delivery. Public hospitals in New Zealand reached a response level 2 (out of 4), which includes deferral of non-urgent elective investigations and procedures. This also entailed suspension of all face-to-face elective clinical encounters and instruction of patients to only seek medical care for serious symptoms and engage with their family doctors as a first step. This particularly applied to patients aged 70 years and above who are at high risk from COVID-19.

Cardiovascular disease (CVD) is one of the major causes of mortality and morbidity in New Zealand. Hospitalisation is often required for acute presentations of CVD such as acute coronary syndromes (ACS), cardiac arrhythmias or decompensated heart failure. In May 2007, there were over 1,000 admissions of suspected or confirmed ACS in New Zealand over a two-week period. In the year 2016/17, approximately 5% of all hospital admissions were due to CVD in New Zealand. During the nationwide alert level 4 period, we have observed a dramatic decrease in admissions related to CVD in our department; our district health board is one of 20 in New Zealand and it has a catchment of approximately 629,000 out of a population of five million. In this observational study, we compare the trends of hospital admissions due to CVD between the levels 4 and 3 lockdown periods and non-pandemic times and discuss some possible contributing factors to this variation.

Methods

This study focused on hospital admissions related to CVD at Waitemata District Health Board (WDHB). Common presentations of CVD were identified using ICD-10 codes from electronic records. The CVD presentations being investigated in this study are ACS, decompensated heart failure, cardiac arrhythmias and cardiac arrest. The study period is the seven-week period comprising of alert level 4 (25 March to 27 April 2020) and level 3 (28 April to 13 May 2020). The controls used were the identical dates in 2018 and 2019. These were chosen as controls to adjust for seasonal impact on various cardiac conditions. Ethics approval was not required due to the retrospective observational nature of the study, with patient data anonymised. Standard statistical analysis was performed with IBM SPSS.
Results

A total of 321 patients had 347 CVD presentations at WDHB during the seven-week lockdown period (26 patients had multiple admissions). This comprised 182 admissions for decompensated heart failure (52.4%), 152 ACS (43.8%), 11 non-fatal cardiac arrhythmias (3.2%) and two cardiac arrests (0.6%). The mean age was 74.5±14.7 years and 44.5% were women. There was no significant difference between the age or gender of patients admitted during the COVID-19 lockdown and control periods. The number of combined CVD admissions were significantly less than the control periods in 2018 (526 admissions, 467 patients) and 2019 (479 admissions, 436 patients).

The combined number of weekly CVD admissions during the lockdown period are compared to corresponding controls in Figure 1. The weekly variation in CVD admissions during the lockdown period were significant when compared to the controls. During the first three weeks of lockdown, the mean number of CVD admissions per week was 42 compared to 69 in 2018 and 65 in 2019. Admissions peaked during weeks four and five of the lockdown, followed by a decrease in the final two weeks. The weekly admission numbers for decompensated heart failure and ACS are shown in Figures 2A and 2B respectively. Although both admissions for decompensated heart failure and ACS increased during weeks four and five of lockdown, this rebound was more dramatic for ACS as it exceeded the admission numbers of the corresponding control periods. The combined number of ACS admissions in weeks four and five of lockdown were 63, compared to 59 in 2018 and 52 in 2019. We did not observe an age variation in the likelihood of presenting to hospital during the study period.

Discussion

The unprecedented national lockdown period due to COVID-19 had significant impact on the numbers and pattern of CVD presentations to hospital. A decline in ACS admissions have similarly been described in European countries.7,8 There are several patient-related, healthcare-related and environmental hypotheses which may explain the findings of our study. The strict stay-home message, especially for those aged over 70 years, announced by the government and escalating cases of COVID-19 in the early phase of the lockdown likely caused a degree of apprehension for people with cardiac symptoms to seek medical care. A total of 15 COVID-19 cases (confirmed plus probable) were admitted to hospital at WDHB during the lockdown period, which could have been

![Figure 1: Number of combined cardiology admissions (heart failure, acute coronary syndrome, arrhythmia and cardiac arrest) during 2020 alert levels 4 and 3 lockdown compared with control years.](image)
a further deterrent for patients presenting to hospital. Additionally, staying at home during lockdown would have resulted in a more sedentary lifestyle for the majority of people which may mask exertional angina or dyspnoea due to ACS or heart failure. The use of non-contact telephone consultations by general practitioners and specialists during lockdown may have resulted in limitations or delay in diagnosis of patients with CVD. The lack of physical examination performed in usual face-to-face consultations have taken away the ability of clinicians to identify subtle signs of heart failure such as pitting oedema or elevated jugular venous pressure.

The effects of air pollution on cardiovascular disease and in particular heart failure has been well established. The benefit of air pollution reduction on non-COVID-19 mortality during pandemic has been described in China. The reduction of CO2 emissions in New Zealand during lockdown was 41.1% compared to the same time in 2019, the second largest relative decrease in the world. This dramatic change is likely to be temporary and reflects the reduction in CO2 emissions from transport and relatively aggressive lockdown measures implemented by the New Zealand government compared to other countries. It may have indirectly positively impacted heart failure admissions.

Our analysis has its limitations. Hospital mortality and serious morbidity during medium and long-term follow up was not

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**Figure 2:** (A) Number of heart failure admissions during 2020 lockdown compared to controls. (B) Number of acute coronary syndrome admissions during 2020 lockdown compared to controls.
assessed. Our catchment population may not reflect the national demographic in age, morbidity, geographic density and access to various health services. Some moderately sick patients that traditionally were referred to hospital may have been successfully managed in the community by their family doctors. Finally, community mortality was not collated.

In conclusion, we have observed an overall reduction in CVD admissions and rebound in weeks four and five during the COVID-19 lockdown. Although our study does not assess adverse outcomes, it raises the concern that the delay in CVD presentations may have been an unintended consequence of pandemic control measures.

Competing interests:
Nil.

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Common Preventable Defects of Childhoods

By E. H. WILKINS, M.B., Dub., Superintendent of the School Medical Services, N.Z.

To medical men in private practice the poor physical condition of present-day children is not likely to be so obvious as to one engaged in examining large numbers in the schools. The extreme rarity of a complete sound set of teeth and the great prevalence of deformity of the chest are indices of serious errors in their upbringing. The most serious and widespread physical defects found in New Zealand schoolchildren are dental caries, faulty development of the jaws and palate, nasal obstruction, adenoids and enlarged tonsils, and rachitic deformity of the chest. I am confident that these defects are due to the same fundamental causes, that these causes can be easily removed, and that, therefore, the vast majority of the diseases and defects from which children suffer are readily preventable. The causes are, I maintain, errors in nutrition, and consist in (1) the unnatural softness of foods, (2) deficiency of vitamines, and (3) deficiency of salts.

Let us consider faulty development of the jaws. It shows itself in crowding and irregularity of the teeth and malocclusion. Insufficient expansion of the upper jaw results in a narrow high arching of the palate, which is of necessity accompanied by narrow, poorly-expanded nostrils and deflection of the septum. The consequent tendency to nasal obstruction results in deficient ventilation and a moist, catarrhal state of the nasal passages. The catarrhal condition is increased by the irritation of mouth-breathing. Both these factors cause an unnaturally moist and sodden state of the nasal and post-nasal mucous membrane. This is admittedly a cause of chronic enlargement—analogous to exuberant granulations in a discharging wound—hence the polypoid overgrowth of the pharangeal tonsil which we call adenoids. Or the adenoid enlargement may be compensatory, to cope with the bacteria which inevitably accompany catarrh. Another theory is that the adenoids are primary and are in some way due to disturbance of the internal secretions; and that the adenoids lead to poor expansion of the nostrils, palate, and so on.

It is a clinical, fact that removal of adenoids and the establishment of nasal breathing tends to rectify under-development of the jaw, but I am confident of this—that under-development of the jaw due to deficient masticatory exercise is the primary condition.

Just as poor development of the upper jaw results consecutively in narrow nostrils, nasal obstruction, and adenoids, so also the resulting mouth-breathing, by irritating the respiratory passages, tends to increase the nasal obstruction, and the open mouth by traction on the cheeks tends to increase the narrowing of the jaws.

Again, irregularity of the teeth increases the tendency to the retention of food in the inter-dental crevices, and, therefore, increases the tendency to dental caries. Mouthbreathing, by causing dryness of the gums and teeth and putting into abeyance the cleansing action of the saliva, also increases dental caries. Faulty development of the jaws, being the cause of both dental irregularity and mouth-breathing, is, therefore, in these two ways a cause of dental caries. Also, the septic state resulting from dental caries undoubtedly contributes to a septic enlargement of the tonsils. Here, then, are many vicious circles reacting upon each other.

If, therefore, poor jaw development is directly and indirectly the cause or one of the causes of these evils, what is the cause of the poor jaw development? I believe
that it is due chiefly to the first of the three dietetic deficiencies mentioned above—the unnatural softness of food. Lack of vigorous mastication, especially in the early growing years of childhood, results in poor development of the muscles of mastication, with consequent poor development of the bones to which they are attached. The pull of the masseter muscles in vigorous mastication undoubtedly has a widening effect on the lower jaw, and the actual biting force of mastication must tend to spread and widen the arch of the maxilla and palate. The pterygoid muscles of mastication are attached to the external pterygoid plate of the ethmoid, which is in close relation to the lateral wall of the naso-pharynx and to the palate bones which form the outer walls of the posterior part of the nostrils. The outward pull of the pterygoids, therefore, would seem to have a widening effect upon the naso-pharynx and on the posterior part of the nose, the parts which are so frequently narrowed and obstructed. Therefore, vigorous exercise of the jaws in masticating hard food contributes, in more ways than one, to well-developed jaws, a wide arch of the palate, and wide and roomy nostrils and naso-pharynx.

We are all familiar with the close association of narrow jaws, crowding of teeth, narrow, highly-arched palate, nasal obstruction and adenoids, but there is no general recognition of the lack of mastication and under-development of the jaws as the primary cause. We can bring a few additional arguments to bear on the problem.

The softness of modern food, especially of children's food, is one of the most obvious departures from the natural in modern diet. It operates from about twelve months of age and continues throughout the whole period of growth. Surely the lack of this most natural exercise, for which every young child shows such an obvious craving, during a period most sensitive to habit and environment, is likely to have some marked developmental effect upon the structures concerned.

The undue sucking in bottle-feeding as contrasted with the munching of breast-feeding has also been shown to lead to a narrowing of the jaws. Dummies and thumb-sucking to, a much greater extent have the same effect, as well as being media for bacterial infection.

When we consider the massiveness of the muscles of mastication in comparison to the size of the bones to which they are attached, it is natural to expect that their vigorous exercise would have an important effect upon the circulation to, and development of, the jaws. Again, the greatest under-development is not in the upper but in the lower jaw, where one would expect it to be, as it is to it that the masticatory muscles are attached, the upper being stationary and passive. Owing to the peculiar interlocking of the teeth, I believe that dentists find the lower jaw is the primary one in which to correct deformity, as to a great extent it controls the shape of the upper.

Further, the actual size of the palate and the actual size of the nasal septum do not appear to be affected. Both these structures retain their natural dimensions, but through lack of space are compelled to undergo unnatural curvature. The primary developmental error seems to be, not in the nose and not in the palate, but in the jaws. The jaws are undersized; no part of the nasal structure is undersized, it is simply expanded. Surely this proves indisputably that the jaw condition is primary, and if this is not due to lack of hard food—lack of exercise of the jaw—what is it due to? There is a serious developmental flaw in the modern child's jaw which fails to bring the individual teeth of the second set into their proper positions.

Now, I am not claiming to have discovered anything. Attention has been called to these matters by others whose opinions are worth more than mine—by Dr. Pickerill, Sim Wallace, Harry Campbell, and many others. I am merely reviewing the facts with a view to obtaining for them greater general recognition as the causes of these very far-reaching and widespread defects. If insufficient exercise of the jaws is causing these serious defects in children, surely the medical and dental professions should be in a position to recommend the remedy.

I might draw attention here to the close association between deformity of the jaw and adenoids on the one hand, and pigeon-breast and depression of the ribs on the other. While softness of bone makes these deformities possible, the resistance to inspiration caused by adenoids certainly contributes to depression of the chest-wall.
And, conversely, the diminished respiratory power resulting from poor development of the chest renders the overcoming of nasal obstruction more difficult.

Passing on to the subject of dental caries, although there may be some doubt as to its immediate cause, I think there can be no doubt that a great predisposing cause is the poor quality and defective structure of the teeth themselves, so that they are unable to withstand the strain of modern oral conditions. Defective structure of the teeth has been shown by experiments on animals to result from diets deficient in vitamins, and, as teeth are composed chiefly of lime, the metabolism of mineral salts is a factor of great importance. In referring to mineral salts I mean their organic combinations in food, not inorganic mineral. The latter is comparatively unimportant and can in no way replace the former.

Most of our common foods are deficient in vitamins and mineral salts. Meat contains practically no lime: 99 per cent. of the lime in an animal is contained in the bones; and carnivorous animals, who depend altogether on animal food, eat the bones as well as the flesh. Wheat, whole rice, maize, and barley are valuable sources of vitamins and salts, but in the artificially refined and partial state in which they are now eaten—as white flour, polished rice, cornflour, and pearl barley—they are deprived of their germ and outer layers, and so lose all their vitamins and about 50 per cent. of their salts. In the common method of boiling vegetables an average of 40 per cent. of their potash and other salts is thrown down the sink. By carelessness in allowing vegetables to cook for an unduly long time, their vitamins are to a great extent destroyed. Sago, tapioca, and arrowroot consist of chemically or mechanically separated starch, and are deficient in vitamins and salts. The vitamins of the fruit in jam are completely devitalised by the prolonged cooking to which they are subject. The same applies to sugar, which is chemically pure, and therefore a highly deficient and unbalanced food. All the common foods have been mentioned except oatmeal, milk and its products, fruit and honey, all of which are valuable for their vitamins and salts.

It is obvious, therefore, that the bulk of our diet is very deficient in these important constituents. Enough has been said by those who have done original work regarding the effects of deficiency of vitamins to indicate that their artificial removal is a dangerous procedure, and that it is impossible at present to estimate how much ill-health and lowered vitality are directly due to it.

With regard to mineral nutriment, Bunge says that lime and iron salts are those which are likely to be insufficient in ordinary diets. Sherman, of Columbia University, says that the usual diet is frequently deficient in lime. These deficiencies are calculated in terms of the adult requirement of calcium, but the growing child, whose bones and teeth are in process of calcification, requires more calcium in proportion to its weight than the adult. Hence to the child this deficiency is more serious.

The deficiency of lime would be serious enough in itself, but is rendered more so by the concurrent deficiency of other alkaline salts, as will be shown.

As a result of metabolism, acid substances are produced which have to be neutralised in the body. They are neutralised by the alkaline bases derived from food. Hence the great value of the alkaline salts of potassium and sodium, and of the vegetable and fruit acids, which are oxidised into alkaline carbonates.

Meat is relatively poor in basic salts. Meat contains sulphur and phosphorous compounds which by oxidation in the body form sulphuric and phosphoric acids. According to Sherman, meat and eggs yield a considerable excess of acids. A diet in which the acid-forming elements greatly predominate must result in a withdrawal of fixed alkalies from the blood and tissues.

Now, in cooking vegetables we throw away 40 per cent. of these vegetable alkalies; and in New Zealand we eat an absurd excess of meat. What seems to be a matter of immense importance is this—that, under these circumstances, calcium, which is on its way to the building of bones and teeth, may be diverted into the neutralising of these acids, and in this way the calcification of bones and of dental enamel may be interfered with.

Not only is it possible by the depletion of the alkaline reserves of the body to divert calcium from bone construction, but,
according to Voit, bone takes some part in the daily metabolism, and it is possible, on a diet deficient in mineral, for the lime in the bones to be withdrawn to neutralise the acids of metabolism. Bunge says that calcium more than any other inorganic element is likely to be deficient as a result of the change from mother’s milk to other food. It has been shown that the majority of American diets even for the adult are dangerously deficient in lime, and also in phosphorus—and what applies to American applies also to New Zealand diets, for they are practically the same.

It is now definitely established that in anaemia medicinal inorganic iron is not itself built into haemoglobin, but acts only as a stimulant to blood-formation from the organic iron compounds of food. The iron content of food, which according to Abderhalden is also dangerously low in the average diet, is therefore a matter of great importance. Everything points to the necessity of giving serious consideration to the mineral content of our diet, especially as degeneration in the structure and rapid decay of the teeth—one of the chief mineral-built organs in the body—has become such a veritable menace to national health.

I will quote a passage from Von Noorden, one of the strongest advocates of a liberal use of meat in the adult diet. He says: “The necessity of a generous supply of vegetables and fruits must be particularly emphasised. They are of the greatest importance for the normal development of the body and of all its functions. As far as children are concerned, we believe we could do better by following the diet of the most rigid vegetarians than by feeding the children as though they were carnivora, according to the bad custom which is still prevalent. If we limit the most important sources of iron—vegetables and fruits—we cause a certain sluggishness of blood formations and an entire lack of reserve iron such as is normally found in the liver, spleen, and bone marrow of healthy well-nourished individuals.”

In Sherman’s “Chemistry of Food and Nutrition” we find: “In an experimental dietary study in New York it was found that the free use of vegetables, whole wheat bread, and the cheaper sorts of fruit, with milk, but without meat, resulted in a gain of 30 per cent. in the iron content of the diet, while the protein, fuel value, and cost remained the same as in the ordinary mixed diet.” I make these quotations to emphasise the importance of the salts of vegetable foods as constituents of our diet.

The consideration of the causes of dental caries is not complete without reference to the effects of modern diet upon the flow of saliva and upon acid fermentation in the mouth. This subject has been fully dealt with by Dr. Pickerill, and I believe it to be of very great importance. I will confine myself to the observation that the same artificialities in diet which contribute to poorly-built teeth also have a depressing effect upon the flow of saliva. The lack of hard food, the undue moisture and pastiness of food, the lack of fibre, of raw vegetable juices and raw fruit, the excessive consumption of sugar and tea and sweet confectionery—all these factors depress the flow of saliva and contribute to the retention of food about the teeth. The high milling of cereals, the removal of so much mineral matter and flavour from vegetables by cooking, and the use of so many artificially separated and soft foods, not only produce badly-formed teeth and jaws, but also increase the virulence of the conditions they have to contend with in the mouth.

There may be some difference of opinion as to the exact modus operandi of how these defects of childhood are brought about, and I do not wish to insist too much on any particular theory. My main contention is that it is the artificial nature of the foods we eat—something in the food, or something which is not in it—that is responsible for these evidences of malnutrition. No one, I think, will disagree on this point—the fate of the Māori’s teeth in the course of about two generations is a clear proof of it.

I think you will agree with me, however, that we have very definite scientific reasons for urging the most radical dietetic reform. We know that the mineral and vitamine contents of foods are reduced by artificial processes. We know—if we know anything—that these deficiencies cause poor nutrition and poor development of bones and teeth; and at the same time these very defects are assuming gigantic proportions and threatening to undermine our national welfare. If the British Empire is to successfully withstand the storms of the future we must possess that indispensable foundation of
national greatness, the health of the people. Food, of all matters, is the basis of health. We must have hard food, that we may learn the salutary virtue of mastication; we must have whole cereals—wheatmeal bread and unpolished rice; we must eat less meat; learn the value of fruits and vegetables, and above all, learn how to cook them; we must appreciate the value of uncooked foods—we must look after the salts and the vitamins. I do not know of any matter of more urgent and vital importance to the health of the country than this one of food.

Now, in this paper I have called your attention to matters which have already been written about by others, but which, from my experience in the medical inspection of school-children, I am very strongly of opinion deserve more serious consideration than they have up to the present received. As Superintendent of the School Medical Services I am concerned with the health of the rising generation. The medical inspectors of schools are apostles of health, endeavouring to educate the public in how to rear healthy, robust, and vigorous children. At the recent conference of our staff in Wellington a committee was formed to decide upon a uniform code of recommendations regarding children's health, most of which are embodied in what I have already said. If any of our fraternity in private practice have other theories as to the causes of these defects, or can in any way assist us, we shall be very much indebted to them. It is our aim to lay the foundations of a healthier, a happier, and a more prosperous New Zealand; we want your help and co-operation in this great work.

P.S.—As a result of talking over some of these matters at the Medical Conference, I have modified my views slightly regarding the causes of maldevelopment of the jaws. While I still maintain that vigorous mastication has a very important effect upon the size and general growth of the jaws, I believe now that the actual shape of the jaw is controlled more by the moulding action of the lips and tongue. The muscles of mastication are attached to the posterior part of the jaws, whereas it is the anterior part of the alveoler arch which is so commonly narrowed and mis-shaped. I am inclined to think that the first factor in the vicious series is bottle-feeding and the dummy. These tend to push up the centre of the palate and to narrow the jaws by the constant sucking, thus producing the tendency to nasal obstruction. The resulting open mouth brings further narrowing pressure on the jaws, and the open relaxed lips allow the incisor teeth to be pressed forward. These forces, though slight, are acting constantly, and—like the ivy spray which pushes its way through a stone wall—would have a considerable effect upon the soft developing jawbone. Decay and early extraction of the temporary teeth are other important causes of undersized jaws.
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